Stereotactic Radiosurgery for the Treatment of Central Nervous System Meningiomas

Michele Longhi
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Foreword

No other neurosurgical condition is able of such a diversity. Being a slow-growing tumour that forms from the meninges, these extra-nevraxic tumours are supposed to be easy to cure for a neurosurgeon. However, meningiomas are meeting with considerable challenges. Quite easy to resect extensively at the level of the convexity, skull base meningiomas are frequently impossible to resect with the surrounding dura and underlying bone without disabling neurological consequences [1]. Consequently, the microsurgical resection of meningiomas is at risk for functional deterioration and carries a high risk of recurrences in the middle long term [2]. Radiotherapy has been demonstrated to dramatically reduce the incidence of long-term recurrences but at the price of the risk of long-term complications, frequently in young patients with a long life expectancy, including tumour genesis, cancer genesis, radionecrosis and cognitive decline [3].

Thus, the introduction of stereotactic radiosurgery (SRS) in the neurosurgical management of meningiomas has been of utmost importance [4]. It has been demonstrated that the GKR of small/middle-size skull base meningiomas provides a long-term tumour control equivalent to complete tumour resection with surrounding dura and underlying bone resection [5, 6]. However, numerous critical pending issues still persist:

How to define best the target in critical skull base area?

Is it at the benefit of the patients to wait for a demonstration of tumour growth?

Why the biological response of midline meningiomas to SRS is so different from the response of skull base one?

What is the best management of para-optic meningiomas encasing the visual pathways and is hypofractionation making the visual outcome better?

What is the role of radiosurgery in malignant or aggressive meningiomas?

How to assess the efficacy of SRS on these tumours, which are generally keeping stable in size in the long run?

How to manage the large one when combined approach is not an option?

And numerous others …

Finally, I would like to pay a tribute to the "Italian network of radiosurgery centres" that have achieved a fantastic work by summarizing the state of the art of SRS in intracranial and spinal meningiomas. This complex pathology is an approach in all its nuances. No doubt that this unique work will remain for long years a milestone reference and a precious companion for those facing this condition in their everyday practice.

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Preface

Treatment of meningiomas (MNs) of the central nervous system (CNS) has always been a particular challenge for the neurosurgeon. In 1895, Italian physician Francesco Durante (1844–1934) was the first to remove an intracranial meningioma, at which time he also introduced the osteoplastic flap. Since then, both the other international pioneers of neurosurgery—H.W. Cushing (1869–1939), W. Dandy (1886–1946) and H. Olivecrona (1891–1980)—and all the neurosurgeons around the world that followed have tried their hand at the treatment of meningeal cancers. This challenge became even more fascinating after the Second World War, with the advent of M.G. Yaşargil's operating microscope in the 1970s, which marked the beginning of modern neurosurgery. Since then, the introduction of sophisticated imaging technologies, modern computer neuronavigation systems and methods of intraoperative monitoring, not to mention increasingly powerful and effective antibiotics, modern anaesthesia and resuscitation procedures, have led to a far more complex neurosurgical approach to MNs of the cranial base.

Thousands of articles and books dedicated to the neurosurgical treatment of MNs have naturally accompanied all these exciting developments, and the editors of this volume offer here their contribution to the scientific literature—an up-to-date monograph on stereotactic radiosurgery (SRS) for MN. Indeed, since its advent in the 1970s and 1980s, SRS, or neuroradiosurgery, has completely revolutionized the approach to and treatment of many CNS pathologies, spreading and evolving, largely thanks to its relatively non-invasive nature. SRS enables the treatment of a range of brain and spinal pathologies, even in highly critical areas, with considerable effectiveness and safety. As a result, by the end of 2018, more than 1,213,000 patients worldwide had been treated via Gamma Knife radiosurgery, and a few hundred thousand more had been treated using other technologies and radiosurgery procedures (LINAC, proton beam, CyberKnife, etc.). Over 200,000 of these patients exhibited MN in the CNS.

This massive number of patients has been matched by a steady growth in work published on this issue. However, it is very rare to find in the scientific literature volumes dedicated exclusively to the neuroradiosurgical management of CNS MNs. Hence, we considered it timely to propose this volume, drawing on the expertise of the Italian Neuroradiosurgery Group—a study group of the Italian Society of Hospital Neurological Sciences (SNO) and the neuroradiosurgery arm of the Italian Society of Neurosurgery (SINch). This association enabled us to distil the clinical experiences of the majority of active Italian treatment centres, and therefore the leading Italian

experts in neuroradiosurgery, who for years have been occupied in the multidisciplinary management of these patients. Indeed, since its very origins, Italy has strived for excellence and advancement of neurosurgery, in particular neuroradiosurgery. It is currently home to nine Gamma Knife centres dedicated to SRS treatment of brain pathologies and numerous other LINAC and CyberKnife centres that are particularly active in the treatment of CNS pathologies via SRS. As a consequence, it has a high ratio of neuroradiosurgery centres to population density, with more than 40,000 patients having been treated by the end of 2018.

In order to provide a comprehensive overview of the neuroradiosurgical treatment of CNS MNs, and to highlight in particular the role of SRS in this field, we have divided this volume into chapters that each addresses different modalities and problems that can arise as part of a neuroradiosurgical approach to these patients. The outcomes of SRS in the treatment of MNs located in different areas of the CNS—both intracranial and spinal—are analysed and described, with a special focus on highly critical and deep locations, such as the cranial base, cavernous sinus and posterior cranial fossa. Then, we go on to analyse and discuss other interesting and problematic aspects of SRS, with chapters dedicated to the treatment of aggressive forms of CNS MN, and fractionated SRS—an innovative neuroradiosurgical approach for larger MNs and/or those that arise in proximity to critical and highly radiosensitive encephalic structures such as the anterior optic pathways. In addition, since neuroradiosurgery has from the outset relied on the convergence of different skills and specializations, we felt that it would be appropriate to emphasize this fact, dedicating several chapters of the book specifically to the multidisciplinary approach to SRS treatment of MNs, shining a light on the respective roles of the neurosurgeon, neuroradiologist, radio-oncologist, neuro-oncologist, neurologist and medical physicist. Finally, in the face of the growing demand for and increasingly frequent publication of guidelines on the topic, we decided that it would be useful to provide the interested reader with a summary of the main guidelines on the treatment of CNS MNs available in the literature.

The ultimate aim of the editors was to provide a monograph that could offer a comprehensive and up-to-date overview of SRS treatment of CNS MN, including its indications and contraindications, and its advantages and limitations, in order to enhance and disseminate the available evidence on a disease that is often complex and challenging to manage. We hope that we have succeeded in this regard.

We would like to dedicate this book to Prof. Federico Colombo and Prof. Massimo Gerosa, considered—together with Prof. Enrico Motti, member of the team who edited this volume—among the "fathers" of Italian neuroradiosurgery. We also extend our heartfelt thanks to all of the authors herein for their commitment, dedication and the clarity of their precious contributions.

Verona, Italy — Michele Longhi
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Introduction

1

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Abbreviations

CNS	Central nervous system
CT	Computed tomography
Gy	Gray
LGK	Leksell Gamma Knife
LTC	Local tumour control
MN	Intracranial meningiomas
MRI	Magnetic resonance imaging
PI	Prescription isodose
SBMN	MN of the skull base
STRS	Stereotaxic radiosurgery
WHO	World Health Organization

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The average annual incidence of intracranial meningiomas (MNs) is 5–6 new cases per 100,000 people/year [1–8], with age-related risk increasing dramatically from the paediatric population to a peak during the sixth and seventh decade of life [9, 10]. In adults (ages 24–84), MNs occur in 2.4 per 100,000 people/year [11]. The female-to-male ratio varies from roughly 2:1 to 3:1 [6, 12–14], and this imbalance is presumably related to cytoactivation mediated by an as yet not fully known oestrogen/progesterone receptor interaction [6, 10, 15].

MNs originate from arachnoid cap, or "meningothelial" cells, and represent the most frequently reported neuro-oncological challenge, accounting for 12–30% of all primary intracranial tumours [1–3, 5–7, 16]. In general, the growth index of such tumours has been estimated at between 2 and 24 mm/year, although the calcified forms of MN very rarely tend to expand over time [17].

Microsurgery is still the primary treatment option for MNs. However, the actuarial rates of local tumour control (LTC) for World Health Organization (WHO) grade I MN at 10 and 15 years after complete microsurgical resection (Simpson Grade I/III) vary between 61–80% and 40–76%, respectively, and after incomplete removal (Simpson grade IV/V) between 0–48% and 9–32%, respectively. After 20 years, the overall LCT drops to 43% after full removal and to 32% after partial resection [18–20]. If we con-

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sider critical anatomical locations such as the skull base (SBMN), the incidence of permanent postoperative cranial nerve deficits is estimated at around 56%, and the reported mortality rates as high as 9% (median 3.6%), even despite the huge advances in neurosurgical technology and equipment [21]. For all these reasons, in recent decades stereotaxic radiosurgery (SRS) has become an attractive alternative to microsurgery in selected cases.

The first case of intracranial MN treated with SRS was reported by E.O. Backlund in 1971 [22]. Subsequently, the widespread diffusion of modern imaging technologies (high-definition computed tomography, CT, and magnetic resonance imaging, MRI) and their combination with SRS systems has greatly facilitated the worldwide application of SRS treatments for numerous intracranial pathologies, including MNs. Indeed, since the early 1990s, the role of SRS within the spectrum of treatment options for intracranial MNs has also been increasingly emphasized as an alternative primary treatment to microsurgery, especially in the elderly and in tumours located in critical locations. The significant impact this has had on surgical morbidity, mortality and postoperative recurrence, and therefore the quality of life of patients and caregivers, has triggered a dramatic shift in the therapeutic paradigm.

The change in approach and therapeutic strategy in cases of MN of the skull base is a classic example of this phenomenon. Currently, most of these tumours are treated directly with SRS, limiting surgical approaches to the role of reducing the size of larger MNs. As for location, SBMNs, especially in the cavernous sinus and posterior cranial fossa, are deemed the most suitable for non-invasive radiosurgical treatment.

As of December 2018, 182,900 [23] patients worldwide had undergone SRS for MN via Gamma Knife (GK) alone, to which we can add thousands of other cases treated using different devices (LINAC, Cyberknife, Proton therapy). The increasing number of patients undergoing SRS for MN can be explained by several factors. First and foremost, the advantageous features of the radiosurgical procedure itself provide for a simple, easy and rapid execution of the treatment plan, modelled with multiple isocentres and a non-invasive approach that requires, in most cases, only a few hours of hospitalization. Indeed, the recommended prescription, or peripheral, dose, adopted by SRS centres varies between 10 Gy and 16 Gy, depending on the volume and location of the target, to 50–80% of the prescription isodose, depending on the technology used for radiosurgical treatment. In particular, in GK radiosurgery the body is exposed to up to 100 times less radiation than with other devices. Furthermore, the irradiation is isocentric and the parts of the device do not move once the patient, helmet and emitter are locked in place, and therefore there is no need for test films and no loss of focusing accuracy caused by mechanical tolerance of moving parts in the emitter or patient support. The mechanical focusing mechanism is also highly accurate, and the radiation coincidence extremely high (0.3 mm). Moreover, there is a high dose gradient between the target centre and the periphery, and treatment plans can therefore be highly conformational and very precise.

Second, the biological characteristics intrinsic to most MNs make them particularly treatable via SRS. Many MNs are slow-growing—for WHO grade I MNs, the reported growth rate is about 0.8 mm/year [24]. This means that, from a radiobiological standpoint, MN belongs to a group of tumours with low α/β ratio [5], and for these types of tumour a dose of between 10 and 16 Gy is considered to provide effective long-term LTC. In addition, this dose range is extremely well tolerated by the surrounding healthy brain tissue, and is associated with a very low risk of permanent neurological complications arising from radiotoxicity. A slow-growing tumour (with a low α/β ratio) also enables surgeons to take advantage of an adequate time window for the desired cytotoxic effects and vascular obliteration to be induced by irradiation.

Third, the neuroradiological features typical of MNs make them ideal targets for SRS; they are usually based in the dura, with an extra-axial position and a clear demarcation between tumour and normal brain tissue. This makes it possible to obtain accurate localization using stereo-MRI. In addition, MNs usually display homogeneous

capture of the contrast medium, clear and well-defined margins, and excellent delimitation of the dural "tail" of the lesion. The selected MRI sequences that permit accurate localization of the MN with a view to SRS treatment, all contrast enhanced, usually include: T1 axial, T1 fat-saturation (to obtain clear demarcation of the volume, morphology and boundaries of the MN) and constructive interference in steady state (CISS) sequences (for clear definition of cranial nerves and other critical brain structures to be preserved during the course of treatment).

Finally, excellent results in terms of effectiveness and safety have been reported in such cases throughout the years. In fact, the data reported are extremely interesting; actuarial survival rates with 5-year LTC are between 86.2% and 97.9% [18, 25–37], and stable or improved neurological conditions are achieved in the vast majority of cases [38]. SRS is associated with very low rates of morbidity, with severe neurological deterioration being extremely rare, and an absence of secondary mortality [39–41], especially when following the usual recommended indications, particularly those pertaining to tumour volume (less than 15–20 cc) and histological grade (WHO MN grade I and small MN WHO grade II residual/recurrent tumours).

Recently, indications for SRS treatment of intracranial MNs have been expanded. Over the past decade, a growing number of larger MNs and MNs close to critical brain structures—such as the anterior optic pathways or brainstem—have been treated via SRS. This is thanks to the introduction of innovative irradiation techniques and SRS modes such as "volume staging" (treatment of portions of the lesion at different times) and fractionation (3–5 consecutive fractions) [42–47].

Just as the number of intracranial MN patients treated by means of SRS has grown exponentially over the past 2 decades, similarly, the number of scientific publications relating to this issue has also markedly increased. As of August 2018, the total number of publications on this topic was more than 1000 scientific papers. The publication and dissemination of evidence-based guidelines for the diagnosis and treatment of intracranial MNs in recent years has led to major changes in their management. Furthermore, a new WHO classification of CNS tumours, including MNs, has been drawn up following their assessment of long-term outcomes and the effects of radiosurgery to these usually slow-growing tumours in large numbers of patients with a minimum observation period of at least 10 years.

In this volume, we present a panoramic view of the different aspects related to radiosurgical treatment of CNS MNs. The outcomes of radiosurgery to MNs located at the various intracranial and spinal sites are presented and discussed. Particular attention is also paid to the prognosis of patients given radiosurgical treatment for atypical and anaplastic forms of MN (WHO grades II and III) and to the new fractionated methods of radiosurgery. Finally, several chapters are devoted to the physical and medical aspects of radiosurgical treatment for CNS MNs, the features and peculiarities of imaging for radiosurgery, the management of neurological problems that can arise before or after radiosurgical treatment of MNs, and the drug treatments adjuvant to SRS used in forms of MN with aggressive histological characteristics.

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2 Physics and Radiation Dosage Issues in Neuroradiosurgical Treatment of Meningiomas

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2.1 Materials and Methods: Evidence Collection

Literature references were identified through searches on PubMed (https://www.ncbi.nlm.nih.gov/pubmed) using specific keywords and combinations thereof. In addition, guidelines published by national and international scientific associations were collected when available. The final list of references was drawn up on the basis of the articles' originality and relevance to the scope of this review.

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2.2 Introduction

Neuroradiosurgery is a method by which intracranial targets can be treated via ionizing radiation. Radiosurgical treatment involves the delivery of the required dose in either a single session or, in the case of so-called multisession radiosurgery, a small number of fractions (up to 5). The basic requirements of a radiosurgical treatment are high target coverage (ablative treatment) and steepest dose gradient possible in order to minimize exposure of the healthy surrounding tissues. To this end, it is necessary for the equipment to provide high mechanical, geometric and dosimetric accuracy and a submillimetric accuracy of patient positioning. Indeed, when administering a limited number of fractions, the impact of all potential systematic and random uncertainties tends to be more significant than with conventional treatment.

High spatial accuracy in patient positioning can be achieved by means of various different immobilization systems. Current technologies rely on either the application of a stereotactic frame or the use of a thermoplastic mask with a position-correction system featuring submillimetric spatial accuracy. The properties of radiosurgical devices (described below) make them useful not only in cancer, but also for functional applications in conditions such as trigeminal neuralgia, Parkinson's disease, and arteriovenous malformations (AVMs). Schematically, there are

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Fig. 2.1 Main radiosurgery system equipment; from top left: (1) linac, (2) CyberKnife, (3) TomoTherapy, (4) Gamma Knife. Courtesy of Accuray and Elekta

frame-based radiosurgical techniques, in which the positioning and localization of the patient are essentially based on a stereotactic system of external coordinates, and *frameless* types, in which positioning is based on medical imaging. A frame-based technique only makes sense if the patient is rigidly connected to the source of radiation; otherwise, accurate patient positioning must necessarily involve the implementation of an image-guided system.

Once radiological images are acquired, stereotactic treatment involves the transfer of these images to dedicated planning software to devise a treatment plan and dose delivery schedule, both of which must be verified via appropriate multimodal phantoms and specific dosimeters suitable to the complexities of the technique. In general, the conformation of the dose distribution in radiosurgical treatments is obtained via small, non-coplanar, non-isocentric fields and is almost always highly inhomogeneous. For this reason, the prescription dose is generally limited to the minimum isodose that can completely cover the target volume. The current guidelines on dosimetry and planning make reference to specific technical documents, namely the International Commission on Radiation Units and Measurements (ICRU) Report 91 [1], which covers volume definition and prescription/assessment in treatment planning, and the International Atomic Energy Agency (IAEA) TRS-483 [2], which discusses external dosimetry of small static fields.

2.3 Equipment and Technology

There are several options available in terms of the equipment used for performing radiosurgical treatment. The main devices are:

1. Linear accelerator (linac, different manufacturers)
2. CyberKnife (Accuray, USA)

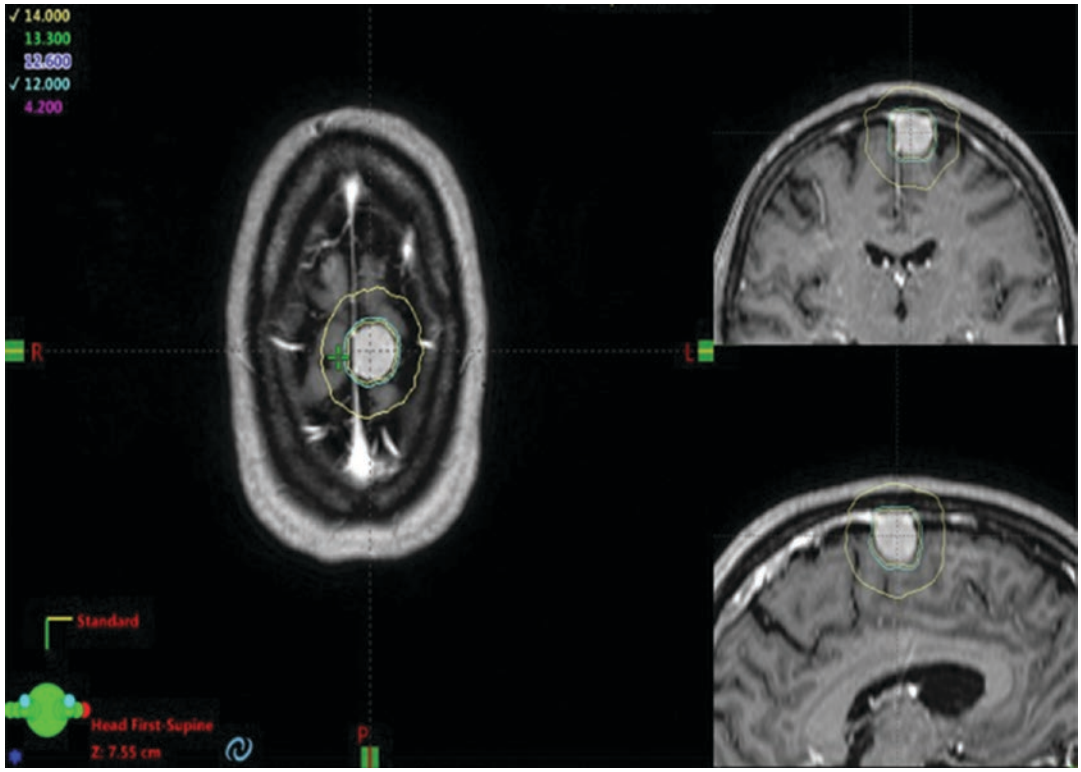
3. TomoTherapy (Accuray, USA)
4. Gamma Knife (Elekta AB, Sweden)

The Gamma Knife is dedicated exclusively to the treatment of intracranial lesions, while the first three **devices** can also be used in other body districts. All of the aforementioned equipment types employ high-energy photon beams and, with the exception of the Gamma Knife Perfexion, feature an integrated imaging system for controlling patient position. In fact, the substantial difference between the various systems is essentially related to the type of technique/system that is used to locate the patient. The Gamma Unit, for example, is the only frame-based device in which positioning is achieved by means of a stereotactic **frame**, rigidly **fixed** to the patient's head. In the case of both linac and tomotherapy, on the other hand, position verification is achieved, generally before the start of the treatment, via a 2D or volumetric imaging system. Lastly, CyberKnife is the only device equipped with a tracking system that can locate the patient and verify the correct positioning not only before treatment but also during the procedure.

These systems are described in detail below, and descriptions are accompanied by the equipment-specific treatment plan for meningioma, prepared on images of the same representative patient, featuring the isodoses corresponding to 14 Gy (yellow line), and 12 and 3 Gy (green line).

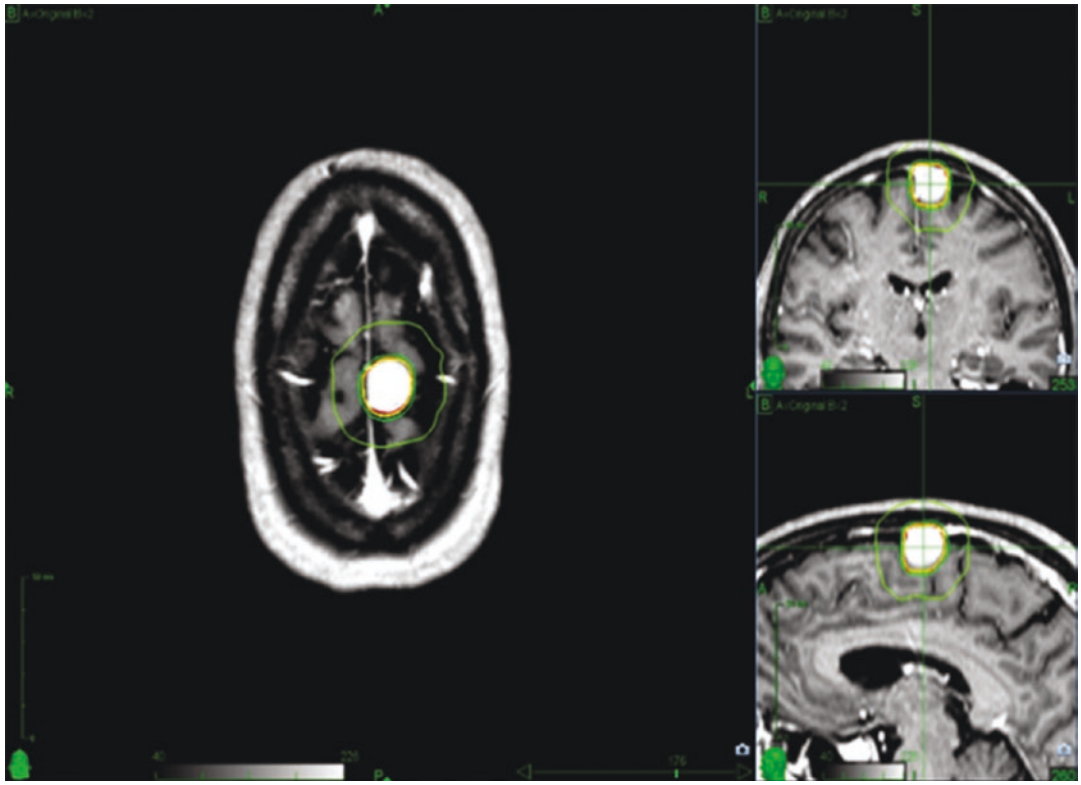
2.3.1 Linear Accelerator

A linear accelerator (linac) is used for external beam radiotherapy, and was not specifically designed for intracranial stereotactic radiosurgery. The linac equipment consists of a couch for the patient, a gantry, and a multi-leaf collimator (MLC), used to deliver the high-energy photon beams (typically 6–18 MV, megavolts) generated by the device. The couch, gantry, and collimator revolve around three axes, the intersection of which defines the isocentre of the equipment. The couch can both slide and rotate, allowing treatment via non-coplanar beams. The radiant unit is integrated by devices to verify and correct the positioning of the patient being treated, namely isocentric planar (portal imaging) or volumetric (cone-beam CT) imaging systems and external optical tracking systems (infrared). In radiosurgical applications, 6-MV photon beams are used, and the linac is generally equipped with special devices to achieve the highest level of ballistic accuracy required for treatment. These devices may already be integrated into some commercial linac equipment, expressly developed for stereotactic treatments, or can be added to non-dedicated linacs; they consist of (a) micro-MLC collimator or conical collimator capable of conforming small radiant beams (from a few mm to a few tens of mm) with sharper dose gradients than MLC devices for general use and (b) repositionable patient couch with six degrees of freedom for correcting the patient's positioning based on image capture. In recent years, the technological development of linacs for radiotherapy has enabled the use of photon beams without a homogenizing filter (flattening filter free, FFF), the main advantages of which are steeper dose gradient as compared to that of a beam with a flattening filter; reduction of radiation spread by the collimator, which in the case of single-session radiosurgical treatment could significantly affect the integral dose received by the patient; and increase in dose rate (up to four times), resulting in a reduction in the duration of treatment. Indeed, the session duration could affect the ballistic accuracy of the treatment, particularly if the immobilization system used is a thermoplastic mask, as some studies have suggested an association between longer duration of treatment and greater intrafraction movement by the patient. A reduction in the integral dose, on the other hand, is related to a decrease in the risk of secondary stochastic effects of radiotherapy.



2.3.2 CyberKnife

CyberKnife (CK) is a radiosurgery system that delivers multiple non-coplanar treatment beams with high precision under the continuous guidance of X-ray imaging. The CK unit consists of a compact 6-megavolt linac mounted on a robotic arm, a repositionable treatment couch, two X-ray tubes with their detectors, and a computerized targeting system.



The CK linac has a very compact design, and is equipped with 12 fixed secondary collimators with circular field sizes ranging from 0.5 cm to 6 cm in diameter. Also available, optionally, is the Iris™ Variable Aperture Collimator, which replicates the 12 fixed collimator sizes with characteristics virtually identical. The latest version of the machine is also equipped with a mini–multi-leaf collimator, consisting of 2.5 mm wide leaves capable of generating a maximum field size of 10 cm × 11.5 cm. The introduction of multi-leaf technology enables CK to treat larger, irregularly shaped tumours.

The robotic arm supporting the linac can move with six degrees of freedom, thereby enabling the administration of hundreds of beams of highly focused radiation from multiple directions with high geometric flexibility and a positioning repeatability of better than 0.12 mm. These beams meet at the target volume location, where they maximize dose delivery while minimizing the exposure of the surrounding healthy tissue. This system does not require the use of rigid head-mounted frames, as it monitors and compensates for changes in the patient's position that occur during treatment. In fact, at the beginning of and during each session, the operating system aligns the radiation beams on the basis of digitally reconstructed radiographic images (DRRs), automatically generated from the 3D model of the patient, and live images captured by the X-ray imaging system located in the treatment room. This enables the position of the patient and the target volume to be monitored in real time; the resulting information is transferred to the robotic arm so that it can compensate for changes in the target's position during treatment by adjusting the radiation beam ballistics, rather than moving the patient [3]. For intracranial applications such as meningioma treatment, the image co-registration algorithm uses high-contrast information pertaining to the bone within the field of view (6D skull tracking). The ability to track target movement using image guidance results in a

high degree of intra-treatment dose conformity and delivery accuracy, and is also useful in multi-fraction radiosurgery, expanding the range of clinical indications of CK, not only to tumours but also to other pathologies such as trigeminal neuralgia, Parkinson's disease, and arteriovenous malformations (AVMs). Another advantage of image guidance is that it enables the treatment of both intracranial and extracranial targets, larger lesions, and targets localized in the cerebral eloquent cortex.

The treatment planning system (TPS) software relies on multimodal imaging (CT, MR, PET, 3D rotational angiography) to outline target volumes, organs at risk, and other structures of clinical relevance. Treatment beam ballistics are then automatically determined by the TPS software via an iterative inverse planning system based on a sequence of optimization steps that enable maximization of the therapeutic dose to the tumour volume while at the same time sparing the surrounding healthy tissue.

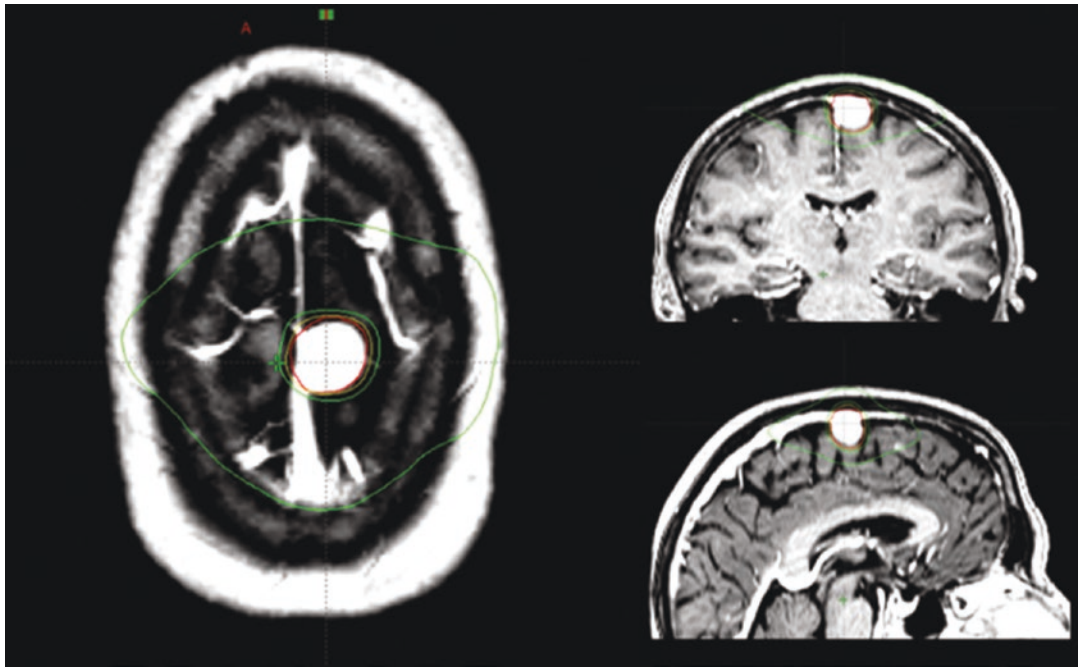
2.3.3 Tomotherapy

Helical tomotherapy (HT), although not specifically designed for stereotactic treatments, has been proven to be capable of providing a degree of precision and accuracy similar to that of dedicated systems [4, 5]. Hi-ART II is a machine able to deliver modulated beams in a helical way, thanks to the gantry rotation synchronous to the longitudinal couch movement, equipped by a fully integrated image-guided system capable of acquiring megavoltage CTs (MVCTs) of the patient before the start of the treatment.

The source of radiation, a 6-MV photon linac, is fitted on a circular gantry similar to a CT scanner, with an isocentre positioning accuracy of 0.2 mm. The gantry rotates in sync with the continuous longitudinal movement of the couch, thereby creating a modulated intense spiral beam that is collimated via a system of primary collimators—capable of generating a maximum field size of 40 cm (x) × 5 cm (y)—and an associated binary multi-leaf collimator (MLC) consisting of 60 leaves, each with a cross section of 6.25 mm. Three field widths are generally used in clinical practice, specifically 10, 25, and 50 mm.

In addition to the choice of field width, the treatment plan can be optimized through the selection of two other parameters, namely the modulation factor—which determines the range of intensity values available for the leaves—and the pitch—which defines the fraction of the field that is treated in a single rotation, based on the movement of the couch; these two parameters directly affect the conformation of the dose distribution, and, inversely, the treatment time. To reduce penumbra and minimize the longitudinal dose drop, the system can be equipped with dynamic primary jaws (dynamic jaws). Specifically for HT, the image-guided system is fully integrated, with the same radiation source used for treatment as that used for MVCT acquiring with a low energy (3.5 MV); comparison between the CT images on which the treatment plan is based and the MVCT images enables assessment of the correct positioning and anatomy of the patient.

Not being designed for radiosurgical treatments, there are some factors that should be borne in mind when HT is used for these specific radiation treatments:

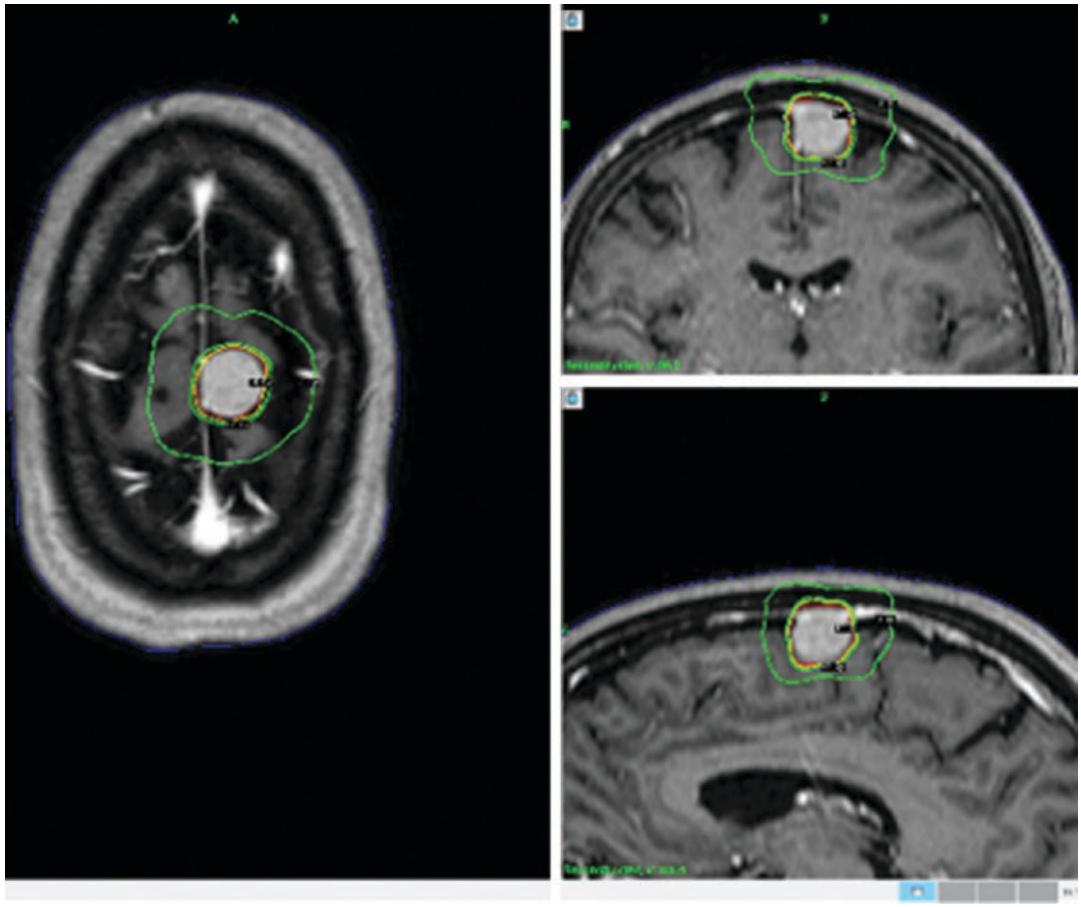


- The delivery is non-isocentric, and therefore potentially more efficient for multiple or irregularly shaped targets than conventional linac, which would require the use of multiple isocentres; on the other hand, HT irradiation can only be performed via coplanar beams, and therefore the dose gradient is potentially lower compared with the one generated with non-coplanar beams.
- For radiosurgical treatments, the smallest field of 10 mm is to be preferred, but this being the smallest size available, when applied to very small lesions (<1 cc) it could provide worse results than dedicated equipment with smaller fields.
- The HT-specific optimization algorithm tends to create highly homogeneous dose distributions typical of conventional fractional treatments; to generate non-uniform distributions, generally required for radiosurgery, specific tricks should be adopted during optimization.
- The integrated imaging system only enables the patient's position to be verified before treatment; in order to handle the long treatment times typical of HT and the frameless approach, intra-fraction imaging should be considered to assess the correct positioning of the patient. This would entail delivery of the prescribed dose in multiple stages, interspersed with further verification of the patient's position. In any case, given the high dose/fraction typical of a radiosurgical treatment, and given the maximum limit of the gantry rotation period of 60 s, in some cases it may be mechanically impossible to deliver the total dose in a single stage.

2.3.4 Gamma Knife

The Leksell Gamma Knife (GK) is a unit designed for intracranial stereotactic radiosurgery only. Its operating principle is simple but effective; specifically, 192 gamma beams originating from an equal number of ^{60}Co sources are focused on a single point, referred to as the unit centre point (UCP). The total energy in the UCP is the sum of the energies of the individual beams, and each source thereby contributes 1/192° to the total dose, enabling irradiation of

healthy structures to be minimized and the dose received by the target to be maximized. The target irradiation accuracy is less than 0.3 mm, and is guaranteed for the life of the machine. Unlike other equipment, in which the beam moves around the lesion to be treated, with the GK it is the target that is moved around the UCP by means of the patient positioning system (PPS). The GK PPS is a motorized system that moves the patient couch, and therefore the lesion to be treated, to the desired position with submillimetric accuracy, according to stereotactic coordinates defined during treatment planning. The precision of the PPS (repeatability of positioning <0.05 mm) is complemented by the use of a stereotactic frame (Leksell Coordinate Frame G), which is rigidly attached to the patient's skull so as to prevent any movement during the treatment. In the traditional version of the equipment, a system for controlling the patient's position was, therefore, unnecessary, but in the latest version of the machine (ICON) a custom thermoplastic mask and headrest set is used instead of the frame; the positioning accuracy therefore needs to be ensured by means of an integrated CBCT scanner to determine the stereotactic coordinates, and an infrared system for continuous monitoring of patient movements; a stereoscopic camera tracks the movements of a reflective marker placed on the patient's nose with respect to two fixed reference markers in the headrest [6]. If the patient moves during the irradiation, exceeding the tolerance level set by the clinicians, the treatment is automatically discontinued and the coordinates realigned through the acquisition of a control low-dose CBCT. The treatment delivered via GK can therefore be either frame based or frameless, with comparable levels of accuracy, according to several literature reports [7–10]. That being said, the frameless option appears to be particularly convenient for multisession treatments, which could previously only be performed by keeping the frame mounted on the patient for several days, with consequent patient discomfort. Another advantage of frameless treatment is that image capture, and therefore treatment planning, does not need to be performed at the same time as the treatment itself, whereas frame-based systems rely on planning based on MRI/CT images taken with the frame in place. Frameless systems therefore make it possible to plan especially complex cases in advance, without causing undue patient discomfort. Furthermore, a stereotactic frame may cause imaging artifacts, which should not be an issue with frameless systems.



However, while the frameless approach has broadened the range of indications for multisession treatment, initial researchers have recommended that cases for treatment (single- and multisession) via a thermoplastic mask be carefully selected. Indeed, for tolerability reasons, the duration of treatment should be kept below 30–40 min per session. Moreover, the patient must maintain their own position, and therefore cannot be sedated. In addition, in some cases, particularly when obesity is an issue, the patient's chest and abdomen can interfere with the stereoscopic camera's field of view, inactivating the infrared tracking system [11].

2.4 Planning Stereotactic Radiosurgery

Every patient undergoing radiosurgery requires a specific treatment plan. This is devised using dedicated software, and involves the following: acquisition of CT and/or MRI scans of the patient's brain, with or without the intended immobilization system (helmet or mask); potentially co-registration/merging of multimodal images; detection and "outlining" of the target volume to be treated and relevant organs at risk on these images; and software simulation of the radiation beam "geometry". Several different software systems are available based on different

calculation algorithms, and in some cases are specific to the particular radiotherapy device (GK, CK, or HT).

2.4.1 Defining Volumes

In 2017, the International Commission on Radiation Units and Measurements (ICRU) pointed out that it is essential to define certain volumes specific to both target and organs at risk in both the planning phase and the reporting and registration phase of radiosurgical treatment. According to ICRU 91 [1], the following should be defined and considered:

- Gross tumour volume (GTV): lesion identifiable on radiological images. Generally speaking, almost all radiosurgical treatments are based on a GTV, except for surgical treatment of a cavity.
- Clinical tumour volume (CTV): this is the volume of tissue that contains both the GTV and the subclinically diseased tissue; it takes into account microscopic tumour infiltration. Historically, the distinction between GTV and CTV has rarely been made in the clinical practice of radiosurgery, as dosing the penumbra region was thought to be sufficient to treat microscopic tumour infiltration. However, the ICRU 91 has suggested the need for clearer definition of the CTV so that the dose it receives can be more precisely prescribed and reported.
- Planning target volume (PTV): this is a geometric concept that takes into account all possible uncertainties so that the prescription dose is being provided to the entire CTV with an acceptable probability.
- Organs at risk (OAR): these are organs that, if irradiated, could be affected by significant complications, and therefore must be taken into account in planning optimization.
- Planning organ volume at risk (PVR): as with the CTV, a margin should be taken into account for possible uncertainties and changes in the position of the body during treatment.
- Remaining volume at risk (RVR): this is defined as the difference between the body volume and the CTV and OAR volumes that have been defined on each image slice.

Although the concepts of GTV, CTV, and PTV described in the various ICRU reports have never been strictly adhered to in radiosurgery, lately [12] they seem to have been re-evaluated, both because we have gone from single-session to fractional treatments [3–5] and because the implementation of radiosurgical techniques involves the use of a series of non-dedicated devices in which the head is not rigidly connected to the source of radiation. Indeed, accurate assessment of the margins of both the tumour and organs at risk allows, during planning optimization, a better balance between target coverage and "safe dose" (below the tolerance limit) to the organs at risk.

2.4.2 Prescription and Treatment Plan Assessment

Historically, the evaluation of a radiosurgical treatment plan has always been somewhat qualitative, i.e. based on the use of a "coverage" isodose, represented by a kind of minimum dose to the target. As in conventional radiotherapy treatments, however, dose distribution assessment should be quantified by the use of dose volume histograms (DVH), which provide information necessary for the evaluation and reporting of a treatment plan. According to ICRU 91, radiosurgery planning assessment and reporting should include the following:

- The **median dose** absorbed by the PTV (D50%); the median dose to the CTV and GTV can also be evaluated and reported if the GTV and CTV have also been defined.
- **Dnear-max**: This indicates the dose close to the maximum. For a PTV of 2 cm^3 or more, Dnear-max coincides with the dose corresponding to 2% of the PTV (D2%), while for smaller PTVs (<2 cm^3), the Dnear-max is the

dose corresponding to an absolute volume of 0.035 cm^3.

- **Dnear-min**: This indicates the dose close to the minimum dose. For a PTV of 2 cm^3 or more, Dnear-min coincides with the dose corresponding to 98% of the PTV (D98%), whereas for smaller PTVs (<2 cm^3), Dnear-min is the dose corresponding to the volume of PTV subtracted of 0.035 cm^3.

As mentioned above, the PTV is a geometric concept that is generally defined taking into account potential uncertainties and inaccuracies in the entire radiotherapy procedure, and the treatment plan is generally planned so that the PTV receives a dose at its surface generally lower than that at its central volume; this means that the dose actually delivered to the CTV is closer to the desired dose distribution. For this reason, DVHs for PTVs tend to exaggerate the lack of homogeneity in the CTV, while DVHs for CTVs, together with the median dose, should be more consistent. This would suggest that in radiosurgical treatments the same parameters indicated for PTV should also be indicated for CTV/GTV.

Regarding organs at risk, the parameters to be evaluated and reported differ depending on whether they are parallel or serial structures. For parallel structures, the average dose or tissue volume (defined as a percentage or absolute value) that receives a dose considered clinically related to a complication should be evaluated and reported. For the serial organs, the dose close to the maximum dose should be evaluated, i.e. the dose corresponding to a volume of 2% if the volume of the considered structure has a volume greater than 2 cm^3, or the dose corresponding to 0.035 cm^3 if the volume of the structure is less than 2 cm^3.

Dose limits clinically useful for the optimization and evaluation of radiosurgery treatment plans (up to five fractions) can be found in the Task Group Report 101 by the American Association of Physicists in Medicine (AAPM) [13] or International Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) guidelines [14].

In addition to these parameters, treatment plan assessment could be based on the following indices:

- **Dose homogeneity (HI)**: an index that is related to the uniformity of the dose distribution. Different indices and definitions of dose distribution homogeneity have been proposed in the literature. In radiosurgery the homogeneity of the dose distribution is generally low. In fact, the dose is generally prescribed at an isodose of between 50% and 80% in order to obtain high doses within the target volume.
- **Dose compliance (CI)**: an index that quantifies the degree to which the high-dose region conforms to the target PTV. The most widely used index is the Paddick conformity index (PCI) ($PCI = VT_{PIV}^2/(VT \times PIV)$), where VT indicates the volume of the target, VT_{PIV} the volume of the target within the volume of the prescription isodose, and PIV the volume of the prescription isodose. An optimal value should be $CI > 0.85$.
- **Gradient index** (GI): an index that indicates the degree of the dose distribution gradient. It is generally defined as GI = PIVhalf/PIV, i.e. the ratio between the volume inside the isodose equal to 50% of the prescription isodose and the volume inside the prescription isodose. An ideal value might be $GI < 3$.

While optimizing and evaluating a treatment plan, special attention should also be paid to the total treatment time. Indeed, a significant increase in treatment time could, on the one hand, reduce the patient positioning accuracy, especially when using non-invasive or non-tracking techniques, and on the other reduce the effectiveness of the treatment itself, taking into account the tumour cell ability to repair the radio-induced damage.

2.5 Radiobiology

Radiosensitivity is defined as the ability of cells to be damaged or inactivated by ionizing radiation. To compare the radiosensitivity of different organs

and/or tissues, we can use parameters derived from mathematical models or cell survival curves for standard dose radiation (2 Gy), although in reality the classic reference models were created and validated for radiotherapy, and their application in the field of radiosurgery remains very controversial [15–17]. Despite disagreement between the different authors, the linear quadratic model (LQ) and the concepts of BED (biologically effective dose) and EQD2 (equivalent dose in 2 Gy fractions) are also widely used in radiosurgery, where there is a great need for predictive models for both tumours and healthy tissues. Several studies claim that the LQ model overestimates the rate of cell death under the hypofractionation regime, while other authors believe that the LQ model has demonstrated good predictivity of radio-induced damage up to doses of 18 Gy dispensed in a single fraction. Above 10 Gy seems to be becoming progressively less accepted but on the basis of data derived from animal experiments, it is still acceptable [18, 19].

The greatest limitation, not only of the LQ model but also of all the mathematical and radiobiological models available to date, remains the α/β ratio, which is usually borrowed from radiotherapy but which is suspected to be markedly different in radiosurgery. The choice of the α/β parameter is decisive in the calculation of all radiobiological indices, and also in the use of the LQ model; the differences in terms of maximum permissible dose and/or prescription dose per fraction vary greatly, depending on the value of the α/β adopted. The fact that there have been no clinical issues in cases where the LQ model has been used in radiosurgery, despite the great uncertainty related to the α/β value, probably means that it overestimates the risk of damage to healthy organs while underestimating the equivalent dose delivered to tumours. In the specific case of meningiomas, an α/β value of $\approx$3.3 seems to be the one that best responds to the equivalence of the data pertaining to patients treated via conventional radiotherapy and hypofractionated radiosurgery, allowing the same BED value to be obtained.

2.5.1 Hypoxia and Reoxygenation

It has now been well established that the reoxygenation of irradiated cells increases their radiosensitivity, and that the oxygenation status of a tumour is one of the most important factors in determining its response to radiotherapy treatments. However, this can only occur in conventional fractionation. That being said, a large number of studies [20] have reported experimental data showing that after high-dose hypofractionated radiation (typical of stereotactic radiosurgery, SRS, and stereotactic body radiotherapy, SBRT) there is significant vascular damage, which plays a very important role in the indirect death of cancer cells. For high doses delivered over a short time, cell death due to vascular damage seems to be significantly amplified by the immune response to hypoxia.

2.5.2 Dose Rate

For the brief bursts of radiation typical of conventional fractionation, survival curves are linear and quadratic. When the dose rate decreases and the treatment time increases, the function gradually loses the quadratic component, resulting in the damage repair model being incomplete.

Regardless of the model used when preparing treatment plans, it is necessary to bear in mind that **increasing treatment time means decreasing effectiveness**. Although all the lesion to be irradiated may be within the same curve, the BED of isocentres with longer planned treatment times can be far greater than that due to other isocentres, with the known cellular consequences. The importance of this issue has grown over the years, with the advances in technology that now allow the rapid use of a large number of isocentres to better conform the radiation field around the lesion to be treated.

When calculating the total treatment time, it is also necessary to include the “dead” time due to travel between isocentres, not just the actual

radiation time. Typically, **the average time for tumour repair of damage can vary from 28 to 120 min**, and for this reason some radiobiologists believe that for treatment times greater than this interval, the dose should be increased in a percentual manner. This concept is well expressed by the **modified linear quadratic model** [21]:

$$-\ln S = N\left(\alpha D + G\beta D^2\right) - \frac{0.693T}{T_{\text{pot}}}$$

where T is the total treatment time; T_{pot} is the potential time for duplication; and G is a function that depends on the dose rate, radiation time, and rate of repair of sublethal damage. If G is very small, S tends to infinity, while if G grows considerably, S tends towards zero. This model is also very simple, although not immediate, to use to compare the effectiveness of different treatment plans.

2.5.3 Uneven Dose Distribution

Another peculiarity of the radiosurgical treatment is the **lack of uniformity in dose distribution within the target**. This feature is not always considered a negative, but rather can be used to create "hot spots" where a higher dose is required (such as the point of origin of meningioma). This makes it possible to plan the treatment in a way that is certainly more effective than simply using dose constraints. Several authors have addressed the issue of the unevenness of dose distribution. As early as 1997, Niemierko [22] introduced the concept of equivalent uniform dose (EUD), which is defined as the dose that, if it were homogenously delivered to a tumour, would allow survival of the same number of clonogens as the non-uniform dose distribution considered. The assumption is that radiation treatment of a tumour via a homogeneous or non-homogeneous dose distribution is biologically equivalent, as long as the two radiations have the same EUD, or the fraction of surviving clonogens is the same. The concept of EUD can also be applied to healthy tissues, as it is heavily dependent on the type of tissue irradiated. McGary et al. [23] found a not insignificant dependence of EUD on the parameters of the linear quadratic model, especially when the dose differences within the distribution are large.

2.5.4 Irradiated Volume-Associated Complications

The risk of complications increases as the irradiated volume increases. Also the toxicity grows rapidly if the volume of healthy tissue receiving a dose greater than 12 Gy in single fraction or equivalent (if multi-fraction) exceeds 5–10 cm^3. This limit needs to be further reduced if eloquent areas are exposed. There is no accepted modelling solution to this problem, and QUANTEC BRAIN suggests to create a database in which to register the V(12) and the irradiated areas that could be used to assess the toxicity to the patients.

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3 Imaging Approaches for Radiosurgical Treatment of Meningiomas

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Magnetic resonance imaging (MRI) has now become the reference standard for targeting lesions in radiosurgery; T2- and post-contrast T1-weighted sequences provide the best contrast between soft tissues, and the best definition of critical targets and structures. Moreover, planning directly on MRI prevents systematic errors that may occur during CT-MRI registration, and eliminates the radiation exposure linked to CT scans [1, 2]. However, this latter advantage should be weighed against the potential disadvantages arising from not using CT, which include possible spatial distortion due to non-linear gradient encoding and lack of uniformity of the magnetic field induced by the presence of the patient in the scanner. Furthermore, local distortions, such as airborne interfaces, are also common in MRI, and can cause geometric errors of 1–2 mm at short distances from the interface (<1 cm) [3]. In addition, the lack of information on electron density, which is used to calculate the distribution of the attenuation coefficient and verify patient positioning during treatment in robotic stereotactic radiosurgery systems (CyberKnife) [4], can be a problem without adequate correction.

In order to combine the benefits of MRI and CT, it has historically been necessary to record all these images in the treatment planning system. In certain cases, it is possible to perform Gamma Knife treatments with an Extend frame device, where MRI is used at the first treatment session to identify the target and generate the contour of the head. In subsequent sessions the initial MRI is co-registered with CT, which is also used to assess tissue heterogeneity through a convolution algorithm.

Nonetheless, it should always be taken into account that, despite the technological advances and provision of co-registration algorithms for increasingly precise MRI and CT scans, in this type of approach there is always the possibility of errors in achieving the perfect anatomical match between the two types of scan [1]. Although the accuracy of the co-registration algorithms available for the various systems is constantly improving, it is still variable, and verification by those who are to carry out the procedure is still necessary, and therefore operator dependent.

Advanced magnetic resonance imaging techniques such as spectroscopy, diffusion, diffusion tensor, perfusion, and functional magnetic resonance imaging can provide physiological

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information to add to the anatomical and structural information gleaned from conventional MRI. However, these techniques and how to interpret their readings are still the subject of much investigation. Non-radiological imaging techniques include PET-CT and PET-MRI [5], which can be useful in selected cases to distinguish between lesion residue or recurrence and post-operative scarring components (such as 111 indium-octreotide in post-surgical meningioma residue or meningiomas difficult to delineate from other anatomical structures with similar contrast uptake).

3.1 Lesions in Specific Locations

In the case of radiosurgical treatment of meningiomas that cannot be radically resected, such as those located adjacent to critical vascular or nerve structures in certain strategic locations (cavernous sinus, petroclival fissure, optic nerve sheath), it is vital to choose the appropriate examination technique [6]. One of the situations that deserve the most attention is the examination of meningiomas originating in or near the cranial base; in such locations, the lesion often tends to infiltrate the bone, making it difficult to detect the bone–tumour interface due to the spontaneous hyperintensity of such structures in T1 sequences. The treatment target is delineated in T1 after intravenous administration of contrast medium, but even so the tumour takes up the contrast non-uniformly, and is therefore barely distinguishable from the cancellous bone. In addition, cranial base meningiomas located between the intra- and extracranial spaces, especially at the infratemporal fossa, are difficult to distinguish from the fat that abounds there. In all these cases, therefore, it is extremely useful to capture contrast-enhanced fat-suppressed T1-weighted images, which significantly increase the visibility of the actual extent of the target mass (Fig. 3.1).

Another location where the delimitation of tumour margins is often problematic is the retro- and intraorbital area. Meningiomas in such locations must be carefully distinguished from the optic nerve in order to avoid overexposure of such a highly radiation-sensitive structure. Intraorbital meningiomas or those invading the optic foramen should therefore be carefully studied by means of multiplanar and fat-suppressed imaging in order to enable accurate identification of the interface between tumour and nerve structure (Fig. 3.2). In the retro-orbital area, a complex problem is the delineation of lesions implanted on the anterior and posterior clinoid processes and/or the walls of the cavernous sinus. Here, in addition to the fat in the cancellous bone, it is necessary to distinguish the patent blood vessels. Although multiplanar volumetric scans can provide iso-voxel details of the anatomy, they have the disadvantage of representing important vessels, such as the carotid syphons, as strongly hyperintense after contrast. In such cases, the exact ratios with respect to the tumour tissue must be well identified on post-contrast two-dimensional spin-echo sequences, in which the vessels appear hypointense even after contrast (Fig. 3.3).

As regards meningiomas involving the walls of cavernous sinus in various ways [7], several authors have stressed the importance of capturing heavily T2-weighted images (constructive interference in steady state, CISS; fast imaging employing steady-state acquisition-cycled, FIESTA-C; fast spin echo: FSSE; balanced fast field echo, BFFE) after contrast [8]. Indeed, this allows differentiation between the hyperintense tumour from adjacent or wrapped nerve structures, which also appear hypointense and are therefore otherwise difficult to distinguish from the target. Moreover, heavily T2-weighted sequences better evidence the interface with other organs at risk, such as the cranial nerves and brainstem.

3.2 Anaplastic and Atypical Meningiomas

The role of radiosurgical methods is also particularly important in grade II and III meningiomas, in which recurrence is very frequent [9, 10]. When

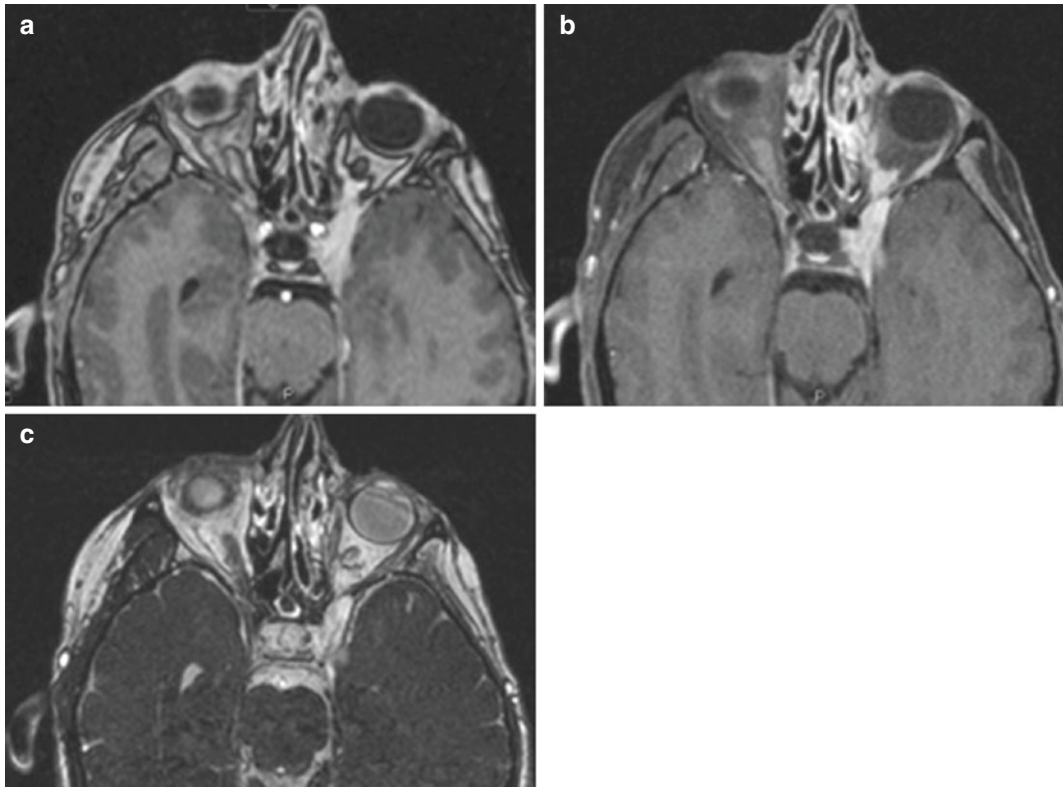

Fig. 3.1 Retro- and intraorbital meningioma invading the cavernous sinus: (**a**) volumetric post-contrast magnetization-prepared rapid gradient echo; (**b**) thin-slice fat-saturated post-contrast T1-weighted spin echo; (**c**) post-contrast constructive interference in steady state (CISS)

The fat-saturated image (**b**) better delineates the real extension of the meningioma within the cavernous sinus and intraorbital space. CISS image (**c**) shows the presence of a tiny linear hypointense nerve within the cavernous sinus

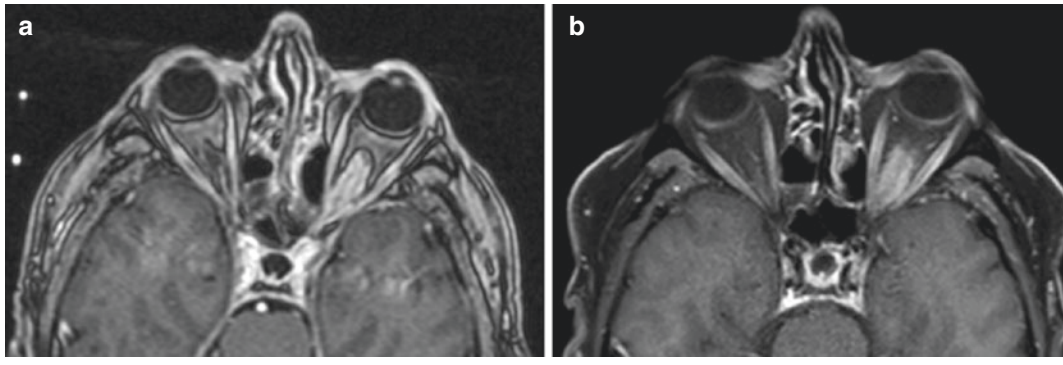

Fig. 3.2 Intraorbital meningioma surrounding the optic nerve: (**a**) volumetric post-contrast magnetization-prepared rapid gradient echo; (**b**) thin-slice fat-saturated post-contrast T1-weighted spin echo

The fat-saturated image (**b**) better delineates the presence of the hypointense optic nerve within the enhanced optic-nerve sheath meningioma

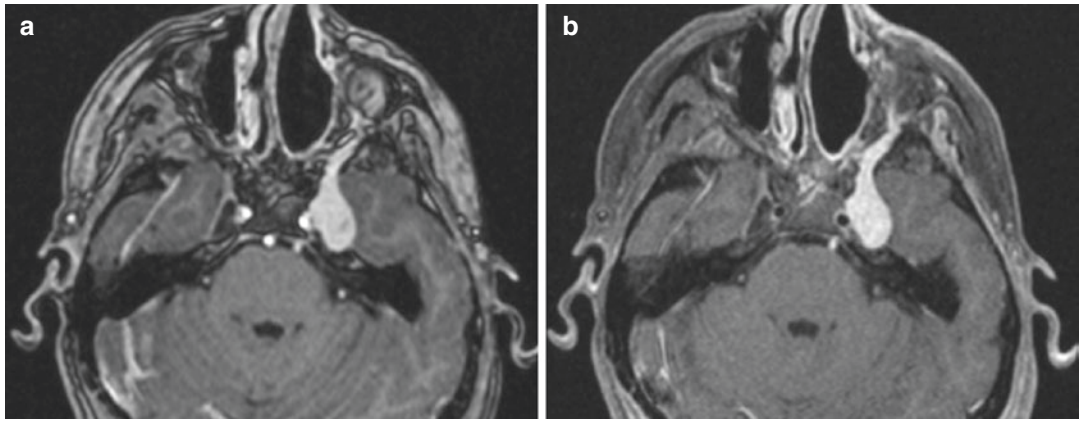

Fig. 3.3 Cavernous sinus paraclival meningioma invading the orbital apex: (**a**) volumetric post-contrast magnetization-prepared rapid gradient echo; (**b**) thin-slice fat-saturated post-contrast T1-weighted spin echo The fat-saturated image (**b**) helps delineate the retro-orbital component of the meningioma, differentiating it from the hypointense medially located carotid syphon

this type of lesion is post-operatively diagnosed, close follow-up will be required using images to detect any recurrence (which is more frequent at the margins of the surgical wound) early on, when the small size of the recurring tumour makes it easily treatable via radiosurgery. In this context, numerous attempts have been made over the years to identify conventional or advanced imaging markers that would allow accurate identification of this type of tumour before treatment. Early identification of this type of feature would also allow for the removal of tumours with a high probability of recurrence when they are still small enough to be generally considered of low neurosurgical interest, especially if asymptomatic. Advanced MRI techniques such as spectroscopy, perfusion, and diffusion have been explored in this regard. The ultimate aim is to achieve a more accurate characterization of meningiomas, but thus far no significant correlation between imaging findings and subsequent pathological diagnosis has been identified (OK).

In fact, the most reliable information for the detection of atypical or anaplastic meningiomas (GII and GIII) has for many years been provided by conventional MRI; the characteristics of meningiomas most commonly associated with malignant composition [11, 12] can be summarized as follows:

1. Located in the cerebral convexity (vs. cranial base location)
2. Extensive oedema around the lesion
3. Absence of interface between tumour and adjacent nerve tissue, especially in T1-weighted images without contrast

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4 Medical Management of Meningiomas

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Meningiomas account for 25–30% of intracranial cancers, with an estimated incidence of 5 per 1000 people in English-speaking countries [1]. They mainly affect adult subjects with an average age of 60–70 years, and are more prevalent in females (male/female ratio 1:2). Meningiomas are extra-axial tumours, originating from the arachnoid cells of the meninges, and in 80% of cases have a supratentorial site, in particular the parasellar region, at the cerebellar tentorium or cerebral falx. They typically present as a single lesion, but multiple tumours are seen in some cases, such as in patients with neurofibromatosis type 2 [2]. Based on their histological appearance, they are classified into three grades (Word Health Organization, WHO, 2016), of which the most common is Grade I [3].

The diagnosis of meningioma is made on magnetic resonance imaging (MRI) scans of the brain; these tumours effectively take up contrast medium, and in most cases present as round-looking lesions, in close contact with the dura mater. Computed tomography (CT) can be used to identify calcifications and any associated bleeding.

Meningiomas are mainly detected when performing brain imaging for other purposes, and 90% of patients who have them are asymptomatic. However, the clinical manifestations that may arise depend on the location and size of the meningioma and also on the rate of growth of the lesion [4]. The main symptoms and/or associated signs are headache, seizures (14–50%), and sensory and/or motor deficits [5].

The treatment of meningiomas needs to take into account several factors, namely the size and location of the tumour, the histological grade, and the risk of aggressiveness and growth, as well as the patient's age and comorbidities. In most cases a "wait-and-see" approach is indicated, i.e. periodic radiological check-ups, since such tumours are often discovered by accident, patients are often asymptomatic, and most cases are low-grade, slow-growing tumours. A conservative approach is also recommended if the meningioma is located in the eloquent cortex, provided that it is not causing a mass effect, and if radiological findings are indicative of a benign form [5].

That being said, the histological WHO grade of meningioma needs to be considered, as most Grade I meningiomas are slow growing, while Grade II and III meningiomas are associated with a worse prognosis; according to the literature,

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10-year survival rate for Grade II meningioma has been estimated at 53–79%, while for Grade III it is 14–34% [6].

The ideal treatment is neurosurgical resection, associated or not with radiotherapy. Nevertheless, clinical trials concerning the medical treatment of meningiomas are not easy to carry out, as Grade I histological forms are relatively indolent, while the course of Grade II and III forms is extremely variable, so determining outcome measures is often complicated. Furthermore, a common radiological criterion for defining tumour growth has not yet been identified, as some researchers identify it by measuring the maximum diameter, while others instead the maximum area [6].

4.1 Chemotherapy

In patients who are not eligible for neurosurgery and/or radiotherapy, or in cases in which such procedures are not entirely successful (for example, if total resection has not been possible, or if the tumour grows back after removal), chemotherapy should be considered. However, according to the literature, chemotherapy agents appear to have poor efficacy in meningioma, without drastically improving the patient's survival [7]. Clinical animal trials have also highlighted an important limitation of chemotherapy, specifically that there is as yet no preclinical animal model that reproduces the heterogeneity of meningiomas, one of the major causes of the lack of or poor response to such treatments.

That being said, one study showed that hydroxyurea, a ribonucleotide reductase inhibitor, at a dose of 20 mg/kg/day was able to prevent the recurrence of fully resected malignant meningioma for 24 months in one patient [8]. However, several Phase II studies conducted with this chemotherapeutic agent showed response rates of less than 5%, with only 50% of patients achieving a stable disease and median progression-free survival of between 44 and 176 weeks [7].

Combinations of hydroxyurea with irinotecan and hydroxyurea with verapamil have also been studied, but in both cases survival was not prolonged in treated patients. In cases of anaplastic meningioma, studies have shown that 3–6 cycles of cyclophosphamide in combination with doxorubicin and vincristine enable radiological outcomes to be maintained, with a median progression time of 4.6 years and a global survival rate of 5.3 years.

Temozolomide, on the other hand, appears to be poorly effective, probably due to the fact that the activity of the enzyme O^6-methylguanine DNA methyltransferase (MGMT) remains intact in meningiomas. Similarly, no benefit was found with irinotecan in clinical trials, despite promising results in vitro [9].

4.2 Growth Factor Receptor Inhibitor Treatment

Studies have shown that in meningiomas, at the cellular level, there is dysregulation of signal pathways involving various receptors, including that of epidermal growth factor (EGF-R), platelet-derived growth factor (PDGF-R), and vascular endothelial growth factor receptors (VEGF-R). In fact, the EGF-R receptor is present in 60% of meningiomas, and its activation appears to lead to increased tumour growth. Studies on EGF-R inhibitors (gefitinib and erlotinib) have shown that they may be efficacious in maintaining the tumour stable [10].

Similarly, studies have shown that bevacizumab, a monoclonal antibody directed against VEGF-R, is effective in maintaining tumour stability in cases unresponsive to other treatments [11]. Indeed, vascular endothelial growth factor (VEGF) is a powerful activator of angiogenesis in many cancers, and in meningioma the levels of its expression are related to the histological grade. VEGF is also known to be associated with certain phenotypic characteristics of meningioma, including peritumoral oedema and necrosis.

Atypical meningiomas with malignant appearance, on the other hand, have been found to highly express platelet-derived growth factor receptors (PDGF-R), but an effective response with inhibitors of this receptor system, such as imatinib, has not been verified.

4.3 Hormone Therapy

Meningiomas seem to have a correlation with the hormonal system, which would explain why they are more frequent in females of childbearing age, as well as the fact that they exhibit greater growth during pregnancy and a reduced incidence after the menopause [6]. Interestingly, a greater incidence of meningioma has also been reported in patients with breast cancer [12].

Literature data shows that about 10% of meningiomas have receptors for oestrogen, and that the progesterone receptor is the most prevalent. Indeed, the less common malignant forms of meningioma are predominantly associated with greater expression of the oestrogen receptor, while the progestogen receptor is more prevalent in low-grade forms [7]. As meningiomas of different histological grades are likely to have different levels of hormone receptor expression, clinical trials can be difficult to perform. However, studies have shown that mifepristone, an anti-progestogenic, is effective in some cases, while tamoxifen, an anti-estrogenic, has proven to be ineffective [13–15].

Meningiomas also express somatostatin receptors, and research has been conducted showing that the use of somatostatin analogues such as octreotide can lead to beneficial disease stabilization in some cases [7].

4.4 Target Therapy

With genetic analysis, mutations in several different genes have been identified in meningiomas, among others *AKT1, SMO, KLF4, TRAF7*, *PIK3CA*, *SUFU, BAP1, SMARCB1/E,* and *POL2RA*, in addition to the well-known *NF2* [6]. Mutations in AKT1 and PI3KCA have been identified in 9% and 7% of meningiomas, respectively, mostly Grade I tumours. The role of AKT1 inhibition in the treatment of recurrent or progressive meningioma is currently the subject of clinical trials.

4.5 Immunotherapy

Meningiomas, especially high-grade meningiomas, are associated with marked activation of the immune system, especially monocytes and cytotoxic T cells, and seem to be modulated by this system. Studies support the effectiveness of immunotherapy, and interferon (IFN-alpha) has been shown to achieve a good response in terms of disease stabilization or mild regression [6].

4.6 Combined Drug Therapy

Intra-tumour genomic heterogeneity often makes subpopulations of cancer cells immune to targeted therapies, resulting in disease progression due to the replication of treatment-resistant cells. However, combined therapies can overcome this problem by targeting multiple pathways at the same time. Examples may be the association of hydroxyurea with imatinib, or hydroxyurea associated with verapamil [6].

4.7 Anti-oedemogenic Treatment

As with other brain cancers, when oedema is present, anti-oedemogenic therapy with mannitol and/or dexamethasone is indicated.

4.8 Treatment of Meningioma-Related Seizures

In the event of seizures secondary to meningioma or after neurosurgical intervention, antiepileptic treatment is indicated to reduce the risk of seizure recurrence as much as possible. In fact, epileptic seizures, whether focal or secondarily generalized, are a frequent complication of meningiomas. They may arise as both a symptom of meningioma onset (in 20–50% of cases) and, in the peri- and/or post-operative phase, an

unwanted outcome of neurosurgical resection of the lesion. The type of seizure varies according to the location and size of the meningioma, and the risk of onset is more frequent in slow-growing forms. The dynamics of the epileptogenic mechanism that arises in such cases is unclear [16]. However, it has been hypothesized that "distortion" of the peritumoral cortex may occur by way of a multifactorial mechanism characterized by the release of amino acids, neuronal acid–base imbalance, and neurotransmitter-level alterations (particularly glutamate).

There is also the possibility of seizures after intervention to remove large tumours, even in cases in which seizures were previously absent (according to some studies in 2.6% of early-stage cases, i.e. within a week of neurosurgical intervention—the so-called early seizures—and in 7% of cases later than this procedure—the so-called late seizures). Early seizures are considered acute symptomatic seizures and, unlike late seizures, do not appear to be associated with recurrence, so long-term therapy is not indicated. An aetiopathogenic hypothesis of post-surgical seizures consists of possible cortical irritation due to the intervention, and the onset of complications related to the procedure, namely haematoma, infection, hydrocephalus, and perifocal oedema [5].

Some specific characteristics of the meningioma may influence the onset of seizures. Specifically, tumour location at the parietal convexity, a lack of bone implant, and a conspicuous wound size are related to an increased risk of the onset of post-resection epilepsy [17]. Some studies therefore support the introduction of prophylactic post-intervention antiepileptic therapy to reduce the risk of seizures. However, more recent research has shown that the risk of seizures in post-operated patients given prophylactic antiepileptics does not differ from the risk in those who have not. Hence, antiepileptic therapy, with its potential associated side effects, appears to be superfluous [5].

There are a large number of antiepileptics on the market, more than 20, which have different mechanisms of action: some act on sodium channels (e.g. carbamazepine, lamotrigine, lacosamide), while others modulate the activity of SV2A synaptic vesicles (such as levetiracetam and brivaracetam), and others have a mixed mechanism of action (like valoneic acid, which inhibits the sodium channel, enhances GABA-inhibitor activity, and acts on glutamate receptors). The choice of antiepileptic will therefore vary from case to case; any comorbidities and concomitant drugs that the patient is already taking should be considered with a view to preventing drug interactions and enhancing their side effects. Note that latest generation antiepileptics (such as levetiracetam, lacosamide, perampanel, and others) have a lower risk of side effects and drug interactions.

If a patient's seizures are poorly controlled, a switch to other antiepileptics or the combination of multiple antiepileptics should be considered. Moreover, neurosurgical intervention often results in a cure from seizures. It is important to consider whether and when to discontinue antiepileptic therapy in a patient with meningioma in follow-up or post-operatively. The option to suspend treatment should be evaluated on a case-to-case basis, bearing in mind seizure recurrence, size of the neurosurgical scar, and electroencephalogram results.

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5 Systemic Treatments for Grade II and III Meningiomas (WHO)

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Abbreviations

6mPFS	6-Month progression-free survival
CTCAE	Common Terminology Criteria for Adverse Events (CTCAE)
FAK	Focal adhesion kinase
mTOR	Mammalian target of rapamycin
mTORC1	mTOR complex 1
NF2	Neurofibromatosis type 2
OS	Overall survival
PDGF-R	Platelet-derived growth factor receptor
PR	Partial response
SMO/PTCH1	Smoothened protein/protein patched homolog 1
VEGF-R	Vascular endothelial growth factor receptor
WHO	World Health Organization

Meningiomas represent the most frequent primary intracranial tumour, and are classified according to the World Health Organization (WHO) criteria as Grade I, II (atypical meningiomas) or III (anaplastic meningiomas), depending on their histological characteristics, aggressiveness and invasiveness [1]. The standard treatment for newly diagnosed meningiomas consists of surgery—with as broad and safe approach as possible—followed or not by radiotherapy (depending on the tumour grade and the extent of surgical resection). With regard to the possibility of effective treatment in meningioma relapse after neurosurgery or in radiotherapy-refractory tumours, there is little evidence in the literature to support a systemic therapeutic approach, as few cases have been studied thus far and data is prospective and weak. However, increased knowledge of the molecular and genetic aspects of meningioma pathology has led to trials of new systemic therapy strategies; these have a high potential for gaining greater control of this type of pathology and ensuring better outcomes for this patient population.

At present, systemic treatment is recommended only in cases of meningioma recurrence, when further surgical or radiotherapy approaches are not possible. The systemic drug most studied to date is hydroxyurea; some retrospective studies have shown disease stability or modest response to hydroxyurea treatment in patients with unresectable meningioma recurrence [2–4]. Nonetheless, two more recent retrospective clinical case series [5, 6] revealed no radiological response to hydroxyurea in patients with relapsed Grade I, II and III meningiomas. As for

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the possibility of adding systemic treatment as an adjuvant therapy after surgery, a small prospective study [7] on 14 patients treated with post-surgical radiotherapy and a chemotherapy regimen based on cyclophosphamide, doxorubicin and vincristine demonstrated a partial response in three patients and radiological disease stability in 11 patients; the median overall survival (OS) was 5.3 years.

As progesterone receptors are highly expressed in meningiomas, some hormonal agents have been studied as possible systemic therapies in these patients. In particular, a Phase II trial showed that tamoxifen provoked a partial response in 3 patients and disease stability in 6 out of 19 cases of unresectable and refractory meningioma [8]. In a larger, randomized, Phase III study (SWOG S9005) [9], however, another anti-progestogen, mifepristone, yielded no significant difference in terms of overall survival as compared to placebo alone.

Another type of therapeutic approach that has been studied is somatostatin analogues; in a small trial, a somatostatin analogue yielded a partial response in 5 patients and disease stability in 5 out of 16 patients with recurrent meningioma who showed overexpression of somatostatin receptors [10]. In contrast, a Phase II prospective trial using octreotide as a somatostatin analogue found no radiological response, the best outcome being disease stability in 33% of nine patients [11]. Similarly, another Phase II trial, this time using pasireotide (an analogue with high affinity for the somatostatin receptor), showed no radiological benefit, nor improvement in 6-month progression-free survival (6mPFS) in patients with WHO Grade I, II or III meningioma [12]. Nonetheless, a Phase II trial combining octreotide and everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is currently underway (NCT02333565).

The possibility of using targeted therapies in this patient population has also been investigated, but so far only rather modest results have been documented. In particular, the high level of expression of pro-angiogenic factors in meningioma has led researchers to focus on drugs that inhibit angiogenesis. In this regard, the efficacy of sunitinib, a small-molecule tyrosine kinase inhibitor of vascular endothelial growth factor receptor (VEGF-R) and platelet-derived growth factor receptor (PDGF-R), has been assessed in patients with WHO Grade II and III meningioma; in that Phase II trial, the 6mPFS rate was reported as 42%, and the OS 24.6 months [13]. However, about 60% of the patients suffered grade 3–4 toxicity, according to the Common Terminology Criteria for Adverse Events (CTCAE). Vatalanib, another anti-angiogenic tyrosine kinase inhibitor directed against VEGF-R, has also been tested in a Phase II trial, this one involving only patients with WHO Grade II and Grade III meningioma, in whom 6mPFSs of 64.3% and 37.5%, respectively, were recorded [14].

In another retrospective study, the anti-angiogenic drug bevacizumab (a monoclonal antibody directed against VEGF) was investigated, and it demonstrated a 6mPFS of 43.8% in high-grade meningiomas and 86% in WHO Grades I, II and III [15, 16]. However, in another Phase II trial of bevacizumab, tested in 40 patients, the best response was a partial response (PR), and only in 5% of atypical meningiomas; disease stability was shown in 100%, 85% and 82% of WHO Grade I, II and III meningiomas, respectively [17].

Other drugs have been tested in combination with bevacizumab. For instance, a Phase II trial assessed a combination of bevacizumab with everolimus, obtaining disease stability in 15 of the 17 patients enrolled with 69% 6mPFS and an OS of 23.8 months as the best response [18]. In a similar vein, better understanding of the molecular and genetic aspects of meningioma pathology has led to several other trials, most of which are still underway, designed to study target molecules that have the potential to allow greater individualization of treatment. For example, a Phase II trial is underway with vismodegib, a Hedgehog signal transduction pathway inhibitor used in the treatment of basal cell carcinoma, combined with focal adhesion kinase (FAK) inhibitor (GSK2256098SMO) in patients with malignant meningioma characterized by SMO/PTCH1 mutations; however, this trial is still in the recruitment phase, and no results are avail-

able at this time (NCT02523014). Another Phase II trial is experimenting with using vistusertib (an mTORC1/2 inhibitor) in patients with relapsed meningioma and the presence versus the absence of the NF2 mutation (NCT03071874). Other innovative drugs are being tested, including trabectedin—a new anticancer drug that is currently the subject of a Phase II trial on patients with high-grade meningioma. Although no results have been reported as yet, trabectedin has shown remarkable in vitro activity in high-grade meningioma cell lines [19]. In addition, the growing international interest in immunotherapy with immune checkpoint inhibitors for oncological purposes, and the exceptional results obtained with this therapeutic approach in various other types of cancers, has given impetus to the study of these drugs in patients with meningioma; trials testing the effectiveness of nivolumab (NCT02648997) and pembrolizumab (NCT03016091) in meningioma patients are currently underway.

Although meningioma is the most common brain cancer, it has only been over the last few years that a clearer molecular and genetic profile of the disease that can help select the most appropriate and effective systemic therapy has emerged. Hence, further prospective studies are urgently required to clarify the potential role of systemic therapy in relapsed meningioma and those refractory to locoregional treatments, which still remains a challenge for modern oncology.

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6 Gamma Knife Radiosurgery for Posterior Cranial Fossa Meningioma

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Abbreviations

BED	Biologically effective dose
CPA	Cerebellopontine angle
CT	Computed tomography
FM	Foramen magnum
GK	Gamma Knife
LINAC	Linear accelerator
MRI	Magnetic resonance imaging
PCFM	Posterior cranial fossa meningioma
PFS	Progression-free survival
SRS	Stereotactic radiosurgery
WHO	World Health Organization

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6.1 Introduction

Meningiomas of the posterior cranial fossa (PCFM) make up between 7% and 12% of all intracranial meningiomas [2].

They remain a formidable challenge for the neurosurgeon due to the complex anatomical location, and in view of the often substantial size reached by these tumours before they are diagnosed. Surgical exeresis is the recommended treatment for patients with PCFM, and has greatly improved thanks to advances in microsurgical, endoscopic, anaesthesiological and intraoperative monitoring techniques [3–16].

However, PCFM surgery is burdened by high rates of complications and non-negligible mortality rates, as it often requires prolonged dissection and manipulation of the cranial nerves, brainstem and vascular structures, as well as a not insignificant percentage of incomplete resection [10, 17–25]. Therefore, although "open" surgery remains the first-line treatment option in symptomatic lesions or in the event of intracranial hypertension, stereotactic radiosurgery (SRS) is becom-

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ing seen as an appealing tool in neurosurgery armamentarium as both a first-line treatment for small lesions and a complementary treatment for tumour residues or post-surgical relapse, which can also occur after resection of Simpson grade I meningioma [17, 26–28].

For over 30 years now, SRS has been performed using the Gamma Knife (GK, Elekta AB, Sweden) [29–33], with LINAC-based equipment [34–41] and proton therapy and adrotherapy [42] being later additions to the SRS.

Some studies have reported comparable outcomes in terms of tumour control and recurrence-free survival in patients treated via SRS for WHO grade I meningioma with respect to those surgically treated for Simpson grade I meningioma [43, 44]. SRS also appears to provide better morbidity outcomes than surgery in tumours of up to 3 cm in certain locations (cavernous sinus meningioma and PCFM) [24].

Furthermore, the revision of the WHO criteria used for classification of meningiomas starting from 2000, which determined the increase of number of meningiomas classified as grade II and a parallel reduction in those classified as grade I, has led to a radical review of the concept of gross total resection of meningiomas at all costs at the expense of neurological function; nowadays, also for the evolution in SRS technology, it should not be justified as an overly "heroic" tumour resection [19].

This concept is so important in such a vital area as the cranial base that a part of the neurosurgical community promotes a treatment strategy involving subtotal resection followed by SRS (the so-called Simpson grade 4 gamma [45]), potentially performed even soon after surgery, without waiting for the residue to grow.

6.2 Overview of Posterior Fossa Meningiomas Gamma Knife Treatment

Here we examine the relevance of GK in affecting the paradigm of radical exeresis in the treatment of WHO grade I PCFMs, discussing some aspects of the use of SRS-GK in this type of tumour. We begin with an analysis of the data from the most important case series reported in the literature, studies that reported exclusively on PCFMs treated by means of SRS-GK (see Table 6.1). These were all monocentric series, with the exception of one multicentric study [46–50]. Like the majority of similar research on meningiomas, these studies analyse both surgically treated cases, for the most part WHO grade I PCFMs, as demonstrated by histological analysis, and untreated cases, with clinical and neuroradiological characteristics suggestive of WHO grade I PCFM. Nevertheless, the findings under consideration are not easily comparable.

6.2.1 Outcomes

The oldest study [46] we examined was by Nicolato et al. (from 2001), and represents the first relevant case study on this group of tumours treated with SRS-GK. It reports on 57 cases with 62 PCFMs, of which 49 were in the petroclival region. In 43.5% of those cases, tumours were residual or recurrences (seven of these were WHO grades II or III), and median follow-up was 29 months (6–64). Fifty-three patients were alive and in stable neurological condition at the end of follow-up; two deaths were due to tumour progression, and two unrelated to the underlying disease. Neuroradiological assessment documented meningioma size reduction in 34/62 cases (55%), stability in 25/62 (40%) and progression in only 3/62 (5% and 2 were WHO grades II and III). The side effects observed were transient, and due to post-SRS oedema (6.5%). Tumour grade (WHO I) was found the only factor to significantly affect the efficacy of radiosurgery for tumour growth control.

In a later study (2010), by Flannery et al. [47], SRS-GK was used as a primary or adjuvant (in 40% of cases) treatment of 168 petroclival meningiomas over a period of 21 years. Median follow-up was 72 months, and tumour control (reduction or stability) was achieved in 90% of cases, while 16 patients (10%) required further treatment (8 patients repeated SRS-GK, 4 underwent surgical exeresis and 4 fractionated radio-

Table 6.1 Summary of major case series of posterior cranial fossa meningioma treated with SRS-GK

Author (year)	Cases	Prior surgery (%)	WHO grade	TV (cc)	MD	Mean follow-up (months)	Tumour control	Comp. (%)	Perm. morb.
Nicolato (2001) [46]	57	43.5	I[a]	5.9	15.2	29	95	7	0
Flannery (2010) [47]	168	40	I	6.1	13	72	90	8	15
Starke (2011) [48]	152	51	I	5.7	13.4	84	87	9	9
Sheehan (2015) [49]	675	43.3	I	6.5	13.6	60	91	7.7	7.7
Patibandla (2018) [50]	120	35	I	4	15	79	89	7.5	5.8

Legenda: TV mean tumour volume, *MD* median marginal dose, *Comp.* complication rate (side effects, transitory and permanent), *Perm. Morb.* permanent morbidity
[a]7/27 was grade II/III

therapy). The 5- and 10-year progression-free survival (PFS) rates—equivalent to tumour growth control—were 91% and 86%, respectively. Post-radiosurgery complications included hydrocephalus, which was treated with ventriculoperitoneal shunt in seven patients (4%), and permanent neurological morbidity, which at 15% was the highest reported among the studies considered here and correlated to tumour volume of >8 cm^3, and therefore the authors concluded that SRS-GK is indicated in patients with symptomatic petroclival meningiomas that are under this volume.

In the case series [48] of the University of Virginia (published in 2011), 152 patients with PCFMs were analysed, of which 77 (51%) were previously surgically treated, with the pre- and post-SRS factors predictive of poor outcome (i.e. the tumour progression and therefore the failure of SRS-GK): age greater than 65 years plus reduced dose at the tumour margin (<12 Gy) and onset of shunt-dependent hydrocephalus were identified, respectively. Besides, Starke et al. reported the petroclival site as being predictive of an increased risk of neurological deficit onset or worsening, which occurred in 9% of the cases.

In the multicentric study [49] conducted by the North American Gamma Knife Consortium (2015), which also included data from the previous work, a total of 675 patients were treated with SRS-GK for PCFMs over a period spanning more than two decades in a multi-institutional experience. A prior surgical exeresis had been performed in 43.3% of the cases under examination. With an average follow-up of 60 months, clinical stability or improvement was achieved in 92.3% of patients, and tumour growth control rates were 95%, 92% and 81% at 3, 5 and 10 years after radiosurgery, respectively. Factors predictive of unfavourable outcome (tumour progression after SRS-GK and/or new or worsening neurological function) included a previous history of conventional radiotherapy and increasing tumour volume. After SRS-GK, subsequent treatments for hydrocephalus or tumour progression, namely ventriculoperitoneal shunt, "open" surgery and LINAC radiotherapy, were performed in 1.6%, 3.6% and 1.5% of cases, respectively. This study reported that SRS-GK affords a high rate of tumour control and neurological preservation for patients with PCFMs.

Finally, the most recent study [50] we analysed (published in 2018) included patients with post-surgical residual tumour or recurrence (35% of cases) and reported 89% tumour control at a median follow-up of almost 80 months. Out of 120 patients, 13 developed tumour progression, 9 in the irradiation field and 4 outside of it; 2 of these 13 patients underwent surgery, and other 2 were treated with repeat SRS-GK. In that series, tumour control was correlated with a higher median dose than in other studies (≥16 Gy), without an increase in complications due to radiotoxicity (7.5%) or post-SRS morbidity (5.8%). Patibandla et al. concluded that lesion volumetric response at short-term follow-up of 3 years is predictive of long-term disease control at 5 and 10 years.

6.2.2 GK Treatment Planning and Response Assessment

The main goal of SRS is disease control, to stop tumour growth over time, while maintaining the function of brain tissue and cranial nerves adjacent to the tumour. The use of SRS-GK for intracranial meningiomas is now widely described in literature [51–54], with the largest study to date being conducted by the European Gamma Knife Society [55]. This study included 4565 patients treated via SRS-GK, using an average marginal dose of 14 Gy. The authors found that SRS-GK determines 5- and 10-year PFS rates of 95.2% and 88.6%, respectively. In addition, this study found that radiological control of the tumour was better in patients who had not undergone previous surgery, in a statistically significant manner ($p < 0.001$).

Nowadays, the widespread use of magnetic resonance imaging (MRI) of the brain means that there has been an increase in the detection, often incidental, of small and well-demarcated brain tumours that would otherwise remain occult, being asymptomatic. These lesions, particularly if located in the cranial base, are eligible for SRS,

since, as already mentioned, "open" surgery in this region is associated with a greater risk of nerve and vascular damage [10, 17–25].

According to the literature, tumour growth is seen in only 11–37% of patients with asymptomatic meningiomas over a follow-up over 5 years [56]. However, the natural history of meningiomas rarely coincides with tumour regression, so such quiescence rates may be comparable to the tumour stability rates observed after SRS-GK, which can, and not uncommonly, lead to tumour regression [57].

A recent survey by UK Neurosurgery revealed that SRS was generally the preferred approach for incidental growing of meningiomas in the cranial base [58]. In the case of SRS-GK for PCFM, it is essential to make an early diagnosis by contrast-enhanced CT and MRI (sequences should allow 3D reconstruction of the tumour, e.g. fast-field echo (FFE) or multiplanar reconstruction (MPR) T1-weighted scans and constructive interference steady state (CISS) or driven equilibrium (DRIVE) T2-weighted scans, preferably with 1 mm slices). At radiological diagnosis it is also crucial to determine the site of origin, i.e. the site of dural attachment, which is often not easy to determine when the tumour has reached a relevant size.

As regards the site of origin, it should be briefly remembered that at present there is no single way of classifying meningiomas of this anatomical region. However, several and varied classification systems have been proposed, from the first by Cushing to that by Castellano and Ruggiero [59], who have classified PCFMs according to their site of attachment discovered intraoperatively (cerebellar convexity, tentorium, posterior surface of the petrous ridge, clivus, foramen magnum), up to the recent one by Yaşargil who has proposed an additional classification (clivus, divided into petroclival and sphenopetroclival, foramen magnum and cerebellopontine angle).

Neuroradiological imaging is also fundamental for SRS-GK treatment planning [60]. As PCFMs are located in a region featuring various critical structures (e.g. cranial nerves, brainstem, small and large vessels, venous sinuses and cochlea), careful radiosurgical planning is essential. MRI images, acquired after positioning of Leksell stereotactic frame, enable correct definition of the target and determination of an isodose at the tumour margin by maximizing dose to the target while minimizing the dose to the surrounding structures, referring to the radiosurgery indices [61]. Thanks to the ability of SRS-GK to apply multiple isocentres, it is possible to adjust the shape of the isodose to that of the tumour ("tailored" SRS), which is often irregular, while maintaining a steep fall of dose outside the target. As far as future developments are concerned, it would be desirable to enhance radiosurgical planning by making use of diffusion tensor imaging (DTI) and tractography, co-registered with stereotactic MRI, to define the position of the corticospinal pathway, and thereby minimize potential damage to it given its proximity to the site of such tumours.

Another key aspect of imaging is the assessment of tumour response to radiosurgery. Given the anatomy of the region, PCFMs take on particularly irregular forms, so linear measurements based on their largest diameter fail to provide a correct assessment of the size of the tumour either before or after treatment. Therefore a volumetric measurement would be recommended [60, 62], similar to that obtained by segmenting the lesion during SRS-GK treatment planning, but at present this is still difficult to implement in the daily practice of neuroradiological sites. On a related note, it is interesting that the volumetric rather than linear growth rate has recently been raised as a factor that could potentially correlate with the predicting of histological grade and clinical outcome [63].

6.2.3 Radiobiology, Side Effects and Complications

In order to assess the effects of SRS-GK, long-term follow-up is essential, so much so that the importance of such was mentioned in all studies analysed here, having a substantial follow-up and spanning the heterogeneous group of PCFMs. From a radiobiological perspective, the size of

the tumour is the first aspect to consider in terms of indication for SRS-GK. In the case series considered, the average target volume was between 4 and 6.5 cm^3. Indeed, it is known that larger tumour volumes are associated with worse SRS-GK outcomes, both in general and in the particular case of meningiomas of the cranial base. Some authors [64, 65] examined the results of SRS-GK in larger meningiomas of the cranial base: in tumour volumes greater than 8 cm^3 (which corresponds to a diameter of about 2.5 cm), 5- and 10-year PFS rates were, respectively, reported as 88.6 and 77.2%.

Another important aspect from the radiobiological point of view is the median dose administered at the tumour margin. Meningiomas are classically considered "late-responding" tissues, and, due to its physical and technical features, SRS-GK appears to be capable of administering to this type of tumour a higher biologically effective dose (BED) than conventional fractionated radiotherapy or LINAC SRS (e.g. the reference marginal isodose is usually around 50% with SRS-GK as compared to 80% with LINAC).

In general, for PCFMs, doses <12 Gy are associated with a failure to control the growth of the meningioma, while doses >16 Gy are associated with an increased risk of post-radiosurgical oedema without improving tumour control. This confirms the evidence in the literature [51, 66–68], where it is noted that marginal doses between 12 and 15 Gy provide the best balance between valid tumour control and acceptable radiotoxicity; in the studies in Table 6.1, the median marginal dose was between 13 and 15.2 (the latter in the study which included several WHO grade II and III meningiomas). In those studies, factors that influenced dose selection included tumour volume, proximity of the disease to the brainstem and to other critical neurovascular structures, a history of previous fractionated radiotherapy and presence of a pre-existing neurological deficit. Notably, the data concerning tumour growth control and PFS reported in those studies are comparable to the best outcomes reported for surgical case series.

The most common side effect of SRS-GK for PCFMs is oedema; as described for other locations [69, 70], it is usually late onset (6–36 months after SRS-GK) and transient. It is detectable on MRI performed at follow-up but is not always symptomatic. The incidence reported in the literature is lower than that of meningiomas of the cerebral convexity [71].

Due to the position of PCFMs, SRS-GK could cause damage to the cranial nerves and/or brainstem, which are therefore identified as organs at risk during radiosurgical planning. A special case is meningioma of the foramen magnum extending towards the medullary tract, in which the risk of complications related to spinal involvement must be taken into account.

The somatomotor nerves (e.g. oculomotor nerves) are known to have a dose tolerance over 20 Gy, and can even show functional recovery after SRS-GK, as noted in other sites of the cranial base [72]; for the trigeminal nerve, on the other hand, the dose tolerance limit is considered to be 19 Gy, whereas the seventh and eighth cranial nerves should not be subjected to a dose higher than 12 Gy in the treatment of meningioma [67, 68, 73].

Irrespective of the above, studies that combined the results of all meningiomas of the cranial base showed new or progressive cranial neuropathy in 1.5–8.6% of patients [74, 75]. The risk of cranial neuropathy seems to be associated with the target volume, and cranial neuropathy after SRS-GK for large intracranial meningiomas (>10 cm^3) has been reported as 8% at all sites [64]. Flannery's case series [46] showed a new-onset cranial neuropathy or worsening of a pre-existing deficit after SRS in almost 15% of patients with tumours greater than 8 cm^3.

Since PCFMs can be directly adjacent to or compress the brainstem, exposure of the brain to radiation is often unavoidable with SRS-GK. The ideal radiosurgical target is a tumour located at least a few millimetres away from the surface of the brainstem. That being said, the brainstem seems to be able to tolerate a maximum dose of 15 Gy, albeit with increased risk of collateral damage to the auditory and facial nerves [29].

The American Society for Radiation Oncology (ASTRO) conducted an analysis, called the QUANTEC (Quantitative Analyses of Normal

Tissue Effects in the Clinic), of the maximum radiation doses tolerated by normal tissues. Based on the data pertaining to previous radiotherapy and radiosurgery papers on injuries adjacent to the brainstem, they concluded that exposing the brainstem to doses less than or equal to 12.5 Gy was associated with a complication rate of less than 5% [76, 77]. However, no case of obvious brainstem toxicity was recorded in the examined multicentric study [49] of 675 cases of PCFM.

Vascular injury too is a potential complication of SRS-GK, particularly at the base of the skull, but cases of serious injury to a cerebrovascular structure caused by radiosurgery for a meningioma of the cranial base are quite rare. Ventricular obstruction and consequent hydrocephalus are less rare, due to swelling of the tumour after SRS-GK, especially if the tumour volume exceeds 8 cm^3 [46]. In fact, 2.1% of the 675 patients treated for PCFMs in the multicentric study showed hydrocephalus upon follow-up MRI, and 1.6% required surgery.

It is precisely to minimize the side effects of treating large tumour volumes, close to the brainstem, that a multisession SRS-GK has been proposed, also taking into account the fact that patients with tumours larger than 14 cm^3 have a worse long-term PFS after SRS-GK [65]. In the so-called volume-staged SRS-GK, the tumour is virtually divided into two different volumes, each treated with the same dose at a few months' interval between the two sessions [78]. Fractionated SRS-GK, on the other hand, involves treating the entire tumour volume in 2–5 daily consecutive fractions, and can be performed with Leksell frame left head-mounted continuously from the first to the last fraction, or with the help of the Extend (Elekta SA, Stockholm) palatal bite immobilization system, or finally with a mask in the latest generation of Gamma Knife equipment, the Icon (Elekta SA, Stockholm) model.

In a recent systematic review it appears that fractionated treatments are associated with better tumour control rate and fewer side effects as compared to single-session treatments [79].

At last, radiation-induced cancers, much-feared risk especially in patients with benign lesions, are rarely reported in the literature, probably due, in the SRS-GK for PCFMs, to the steep dose gradient and the use of marginal doses below 16 Gy. However, the malignant transformation after SRS-GK could be the result of the natural course of the disease rather than the radiosurgery. It is also possible that some malignant cases are ascribable to erroneous attribution of the histological grade during diagnosis, especially in light of the latest review of the WHO classification of meningiomas mentioned above [19, 67].

In order to monitor both the tumour response (not being able to exclude recurrence even after a considerable period of time) and the potential side effects, the management of benign meningiomas in general, and PCFMs in particular, should include MRI surveillance at 6 and 12 months after SRS-GK, then annually for the first 5 years and then every 2–3 years for the rest of the patient's life [75, 80].

Figures 6.1a, b and 6.2a, b, for example, allow us to compare the tumour response to radiosurgical treatment over time on MRIs, at the treatment time and at the follow-up, of two patients treated at the Niguarda Hospital Gamma Knife Centre in Milan, Italy.

6.3 Conclusions

PCFMs remain a formidable challenge for the neurosurgeon, as the risks of injury to the neurovascular structures adjacent to the brainstem are high. Surgical removal is the first choice for PCFMs, but residual or recurrent cancer is not uncommon despite advances in microsurgical and anaesthesiological technology, including intraoperative neurophysiological monitoring.

Since many of these tumours are discovered incidentally, observation is an important option, particularly in elderly patients or those with an asymptomatic tumour, stable for volume. In carefully selected patients, however, SRS-GK can be used to treat PCFMs with a high local control rate and a low incidence of side effects (Table 6.2).

"Primary" indication: Asymptomatic growing tumours, smaller than 2.5 cm in diameter

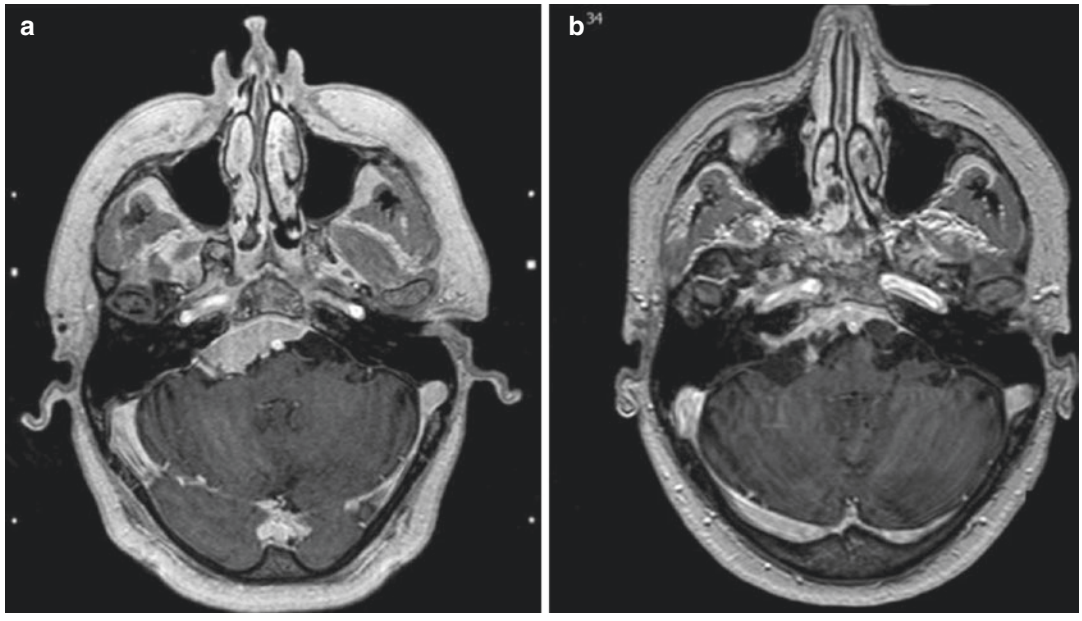

Fig. 6.1 Petroclival meningioma (WHO I), previously operated with subtotal excision and then treated with single-fraction GK SRS. (**a**) Axial CE (contrast enhanced) T1-weighted MRI for radiosurgical treatment planning of residual tumour. (**b**) Axial CE T1-weighted follow-up MRI obtained 18 months after GK SRS showing a regression of tumour

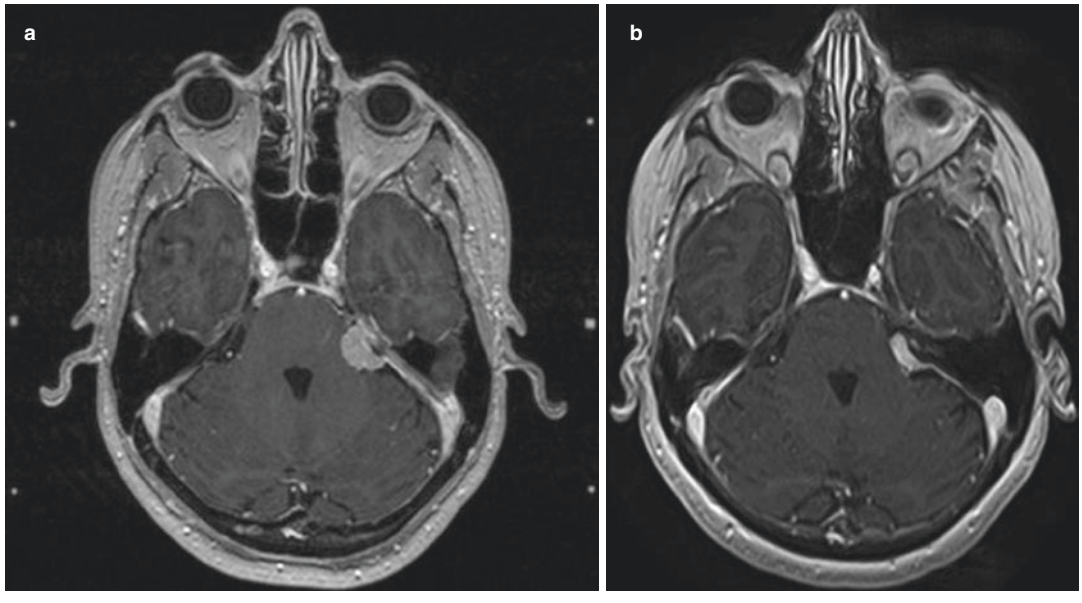

Fig. 6.2 Meningioma of the posterior surface of the petrous bone, treated with primary GK SRS. (**a**) Axial CE T1-weighted MRI for radiosurgical treatment planning of meningioma. (**b**) Axial CE T1-weighted follow-up MRI obtained 80 months after GK SRS, demonstrating long-term local control of the disease and its size reduction

Table 6.2 Summary of SRS-GK indications in posterior cranial fossa meningiomas

Primary	Secondary
Small, growing untreated tumour with radiological evidence of WHO I meningioma and no mass effect	Residual tumour after surgery
Elderly or patient with contraindications for surgery (volume-staged or fractionated SRS-GK to be considered for large lesions)	Tumour recurrence, after surgery, SRS or radiotherapy

(maximum volume around 8 cm^3), and elderly patients or those with major comorbidities are suitable for treatment with SRS-GK, as a first-line treatment. In younger patients, especially those with tumours in sites where total removal may be easy, "open" surgery has to be preferred, as it allows histological confirmation of the tumour and its grade, as well as long-lasting disease control.

"Secondary" indication: In residual after subtotal resection (planned or not) or in tumour recurrence, SRS-GK may be used as a second-line treatment. In such cases it can be performed even a few months after surgery, without waiting for residue growth.

To better understand the benefits of SRS-GK in the treatment of WHO grade I meningiomas, future case-control observational studies on treated matched to conservatively treated cases will be required.

The SRS-GK offers the likelihood to control tumour growth and spare neurological functions. It should therefore be considered as part of a new patient-oriented perspective in which the neurosurgeon's goal is to achieve, in the light of an acceptable compromise between tumour exeresis and function preservation, an individual better quality of life rather than a radical tumour removal.

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Conflict of Interest: The authors declare that they know of no conflict of interest concerning the materials or methods used in this study, or the findings reported in this chapter.

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Stereotactic Radiosurgery for Cavernous Sinus Meningiomas

7

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Abbreviations

AVM	Arteriovenous malformation
CISS	Constructive interference in steady state
CS	Cavernous sinus
CSMN	Cavernous sinus meningioma
CT	Computed tomography
GTV	Gross target volume
Gy	Gray
ID	Integral dose
LGKRS	Leksell Gamma Knife radiosurgery
Linac	Linear accelerator
LTC	Local tumour control
MD	Maximum dose
MN	Meningioma
MRI	Magnetic resonance imaging
MT	Malignant transformation
NHS	National Health Service
PD	Prescription dose
PI	Prescription isodose
RIT	Radiation-induced tumorigenesis
RT	Radiotherapy
SRS	Stereotactic radiosurgery
WHO	World Health Organization

7.1 Introduction

Cavernous sinus meningiomas (CSMNs) occur in 0.5/100,000 people in the general population, and account for more than 90% of cavernous sinus tumours [1, 2]. From an epidemiological

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perspective, CSMNs are more common in females and in middle to advanced age [2]. In most cases, CSMNs are histologically Grade I on the WHO classification or show imaging features compatible with benign forms [1, 3].

Surgical treatment is the primary therapeutic choice for intracranial meningiomas. However, CSMNs constitute a great surgical challenge due to their close anatomical relationships with particularly delicate and vital vascular, endocrine and nerve structures (cavernous segment of the inner carotid artery, upper and lower petrous sinuses, basilar plexus, cavernous sinus, anterior visual pathways, pituitary stalk, ocular nerves, first and second branches of the trigeminal nerve and brainstem) [4]. As a result, and despite considerable advances in neurosurgical technology and intraoperative neurophysiological monitoring methods, the surgical approach is burdened by a high risk of serious and long-lasting side effects, especially in attempts at radical resection. In fact, the literature reports high rates of permanent neurological complications (17.9–74.0%) and a post-operative mortality rate of up to 9.5% associated with such interventions [5–7].

Stereotactic radiosurgery (SRS), on the other hand, is minimally invasive and associated with excellent efficacy (high local tumour control, LTC) and safety, a very low risk of permanent neurological side effects and no secondary mortality. These features have facilitated the rapid diffusion of this therapeutic approach in selected cases of CSMNs (maximum diameter of less than 3 cm or volume less than 15–20 cm^3 and which do not significantly compromise the anterior visual pathways) around the world, both as an alternative to surgery (primary treatment, especially when the morphological and volumetric features of a meningioma preclude the surgical approach) and as part of a combined surgical treatment (adjuvant removal of residual tumour following resection, or as a salvage treatment for progressing or recurring tumours) [8, 9].

Worldwide, over 10,000 CSMNs have thus far been treated via SRS and reported in the literature—a total of about 150 published articles. Reported outcomes are excellent, with regard to both LTC (85–100% at 5 years and 75–98% at 10 years) and risk of permanent side effects (an incidence of between 0% and 19%); radiosurgical treatment is associated with a 0.0% mortality rate (Table 7.1). That being said, few studies have evaluated the effectiveness and safety of SRS for CSMNs in the long term, i.e. after an observation period of longer than 10 years. Hence, in this chapter, we present the results of our retrospective study on 200 CSMN patients treated via Leksell Gamma Knife radiosurgery (LGKRS) and subjected to neuroradiological and clinical follow-up for at least 10 years. In addition, we share data from our uni- and multivariate statistical analysis, performed to assess the prognostic role of several independent variables, namely age, sex, gross tumour volume (GTV), prescription dose (PD), stereo-CT vs. stereo-MRI, location limited to the cavernous sinus vs. local spread, primary vs. adjuvant/salvage LGKRS and WHO Grade I vs. II classification, in the post-SRS LTC (end point). Finally, we compare our data with those collected from a wide range of literature reports on the subject.

Table 7.1 Total actuarial LTC across the entire series of 200 patients at 5, 10 and 15 years

5-year LTC	10-year LTC	15-year LTC
94%	91%	89%

7.2 Materials and Methods

Between February 1993 and December 2007, 200 CSMN patients underwent SRS **with** Leksell Gamma Knife (LGKRS) at our department. All selected patients were followed up for at least 10 years. At the time of admission, signed consent was obtained from all patients included in the study, as the general policy at our LGKRS centre (Verona University Hospital) is to acquire consent from all patients before their medical records and radiological images are used for research purposes. The sample comprised 51 males and 149 females, of average age 53.7 years (range 25–83 years). CSMNs were classified by site as either limited to the cavernous sinus (limited) or spread to nearby structures of the cranial base (spread). There were 97/200 WHO Grade I

CSMNs, 91/200 with neuroradiological characteristics compatible with a benign form and 12/200 Grade II CSMNs. LGKRS was used as a primary treatment in 91/200 patients (45.5%), as an adjuvant in 77/200 cases (38.5%) and as salvage therapy in 32/200 patients (16.0%).

On the day of radiosurgical treatment, the MRI-compatible Leksell model G stereotactic **frame** (Elekta Instruments) was **positioned** to the patient's head. Then, stereo-CT was performed in 69 patients and stereo-MRI in 131. Currently, our stereo-MRI protocol for CSMNs includes the following algorithms and specific sequences, all with contrast: T1 sequences for saturated fats, constructive interference in steady-state (CISS) sequences and 1 mm isovoxel Q1 volumetric sequences. SRS procedures were carried out using an LGK C 201 unit with Co^{60} source until June 2008, and LGK Perfexion (both from Elekta Instruments) thereafter. Three-dimensional treatment planning was developed using commercially available programmes, namely Kula (Elekta Instruments) from February 1993 to February 1998 and Leksell Gamma Plan (versions 4.12, 5.34 and 8.3, Elekta Instruments) after February 1998. The neurosurgeon, radio-oncologist and medical physicist jointly created an extremely conformational treatment plan using multiple collimators, selecting the dose most appropriate for the individual case. The treatment plan was carried out with the aim of achieving full and highly conformational coverage of the tumour, sparing and preserving the surrounding healthy structures (cranial nerves, pituitary stalk, etc.). The average parameters and their treatment plan ranges were as follows: GTV 9.88 cc (1.4–42.6), PD 14.2 Gy (10–22.5), PI 48.3% (48.3% 30–60), MD 29.8 Gy (16.9–66.7), ID 169.7 mJ (26–713) and number of shots 13.8 (3–35). The DP and MD of the SRS treatment were selected and administered in accordance with the known radio-tolerance levels for the optic nerve, optic chiasm and pituitary stalk.

The first scheduled **follow-up** was at 6 months after SRS, then annually for 2 years and then every 2–3 years. Patient status was monitored at these time points using MRI, field-of-vision analysis, Hess–Lancaster screen and full pituitary hormone profiling.

Actuarial LTC rate curves were plotted using the Kaplan–Meier method [10], and log-rank univariate analysis was used to assess factors potentially related to LTC. Statistical significance was calculated using Fisher's exact test. Next, to assess statistical significance more accurately, regression analyses were performed using a logistic model. Uni- and multivariate statistical analyses were performed to assess which of the following independent variables could potentially affect the LTC (end point): age, gender, GTV, PD, stereo-CT vs. stereo-MRI, limited vs. spread site, primary vs. adjuvant/salvage LGKRS and WHO Grade I vs. II. Based on the internationally accepted criteria, p values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using Stata software, version 13.1 (Stata Corp.). Since this is a retrospective, single-centre study, the possibility of bias in patient selection cannot be ruled out.

7.3 Results

The median observation period was 165.9 months (137.0–256.0). **Clinical neurological outcome was classified as stable** (52/200) or improved (121/200) in 173 patients (86.5%), regardless of the extent of tumour reduction. The median clinical performance index, based on Karnofsky classification, rose from 80.5% in the period prior to LGKRS to 85.7% at the last clinical-neurological check-up after radiosurgical treatment ($p = 0.041$). Among the 27/200 patients with neurological deterioration, 22 had worsened due to tumour progression. In five cases (2.5%) there was a slight permanent fifth and/or sixth cranial nerve deficit secondary to the LGKRS treatment. During the observation period, there were ten deaths, one being a patient with pre-LGKRS WHO Grade II MN which exhibited dramatic late progression leading to death; a further two patients diagnosed with WHO Grade I MN had uncontrollable local progression after LGKRS leading to their deaths; and in the remaining seven cases, the cause of death was not related to meningioma. None of the cases in our clinical series resulted in radiosurgery-related mortality,

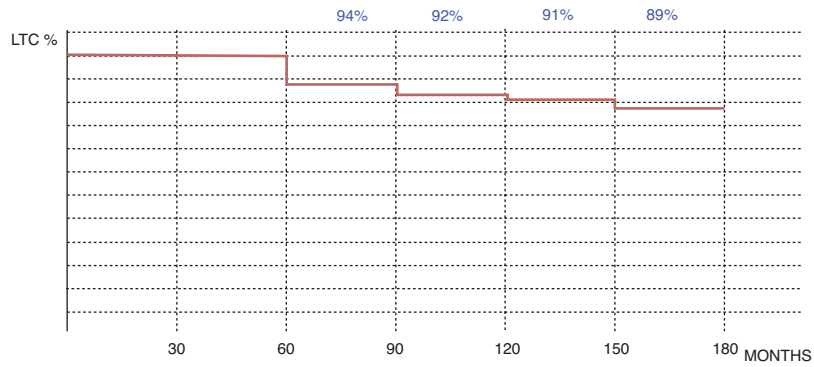

Fig. 7.1 Comprehensive actuarial LTC on our entire series of 200 patients with CSMNs treated via LGKRS and monitored for at least 10 years

and in the 10 years after SRS, there were no cases of radiation-induced cancer or proven malignant transformation. Overall, 171/200 patients (85.5%) had actuarial LTC rates of 94%, 91% and 89% at 5, 10 and 15 years, respectively (Fig. 7.1 and Table 7.1). A comparison between Grade I CSMNs (97/200), or those with neuroradiological characteristics compatible with benign meningioma (91/200), and WHO Grade II (12/200) revealed actuarial LTCs of 94.9%, 94.9% and 89.3% at 10, 15 and 20 years, respectively, for Grade I CSMNs, and 76.2%, 76.2% and 0.0% at the corresponding time points for Grade II CSMNs (Fig. 7.2 and Table 7.2). Among the 27/200 CSMNs that displayed progression after LGKRS, 11/97 (11%) had originally been diagnosed as WHO Grade I, 9/91 (10%) had CSMNs with neuroradiological characteristics compatible with benign forms and 7/12 (58%) were originally WHO Grade II. According to uni- and multivariate statistical analyses, the only independent variables that significantly influenced the LTC were primary vs. adjuvant/salvage treatment ($p = 0.037$) and histology (WHO Grade I vs. Grade II) ($p = 0.019$). In other words, our results indicate that patients treated **with** LGKRS without having previously undergone neurosurgical intervention and those suffering from a CSMN of WHO Grade I or with neuroradiological characteristics compatible with benign forms have a more favourable prognosis for survival without local progression.

7.4 Discussion

7.4.1 Epidemiology, Anatomy and Clinical Data

As mentioned in Sect. 7.1, CSMNs occur in 0.5/100,000 people in the general population, and account for more than 90% of tumours of the cavernous sinus [1, 2]. They are more common in the middle decades of life, but also occur frequently in old age. The ratio of female to male patients is 2:1 [2]. CSMNs have distinctive features related to their location, owing to their close anatomical relationships with particularly delicate but vital vascular, endocrine and nerve structures, including the cavernous segment of the inner carotid artery, upper and lower petrous sinuses, basilar plexus, cavernous sinus, anterior visual pathways, pituitary stalk, ocular nerves, first and second branches of the trigeminal nerve and brainstem [4]. Indeed, they tend to cause clinical symptoms secondary to compression or invasion of neighbouring neurovascular structures, often diplopia, ophthalmoplegia and/or eyelid ptosis. Compression of the anterior visual pathways or infiltration of the optic tract can cause visual impairment, resulting in complete loss of visual acuity, as well as a complete or partial trigeminal syndrome secondary to the compression of the fifth cranial nerve. More rarely, hormonal deficits due to impaired pituitary function are also seen. Patients with CSMNs involving the sphenoid

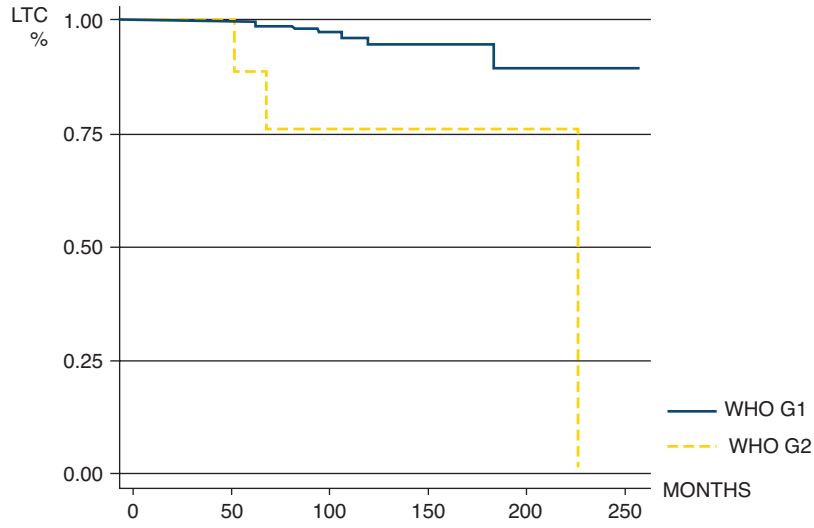

Fig. 7.2 Comparison of actuarial LTC rates following LGKRS treatment in WHO Grade I CSMNs or those with neuroradiological characteristics compatible with a benign form versus Grade II CSMNs over an observation period of at least 10 years

Table 7.2 Comparison of actuarial LTC rates at 10, 15 and 20 years for WHO Grade I CSMNs or those with neuroradiological characteristics compatible with a benign form versus Grade II CSMNs

WHO grade	10-year LTC	15-year LTC	20-year LTC
Grade I	94.9%	94.9%	89.3%
Grade II	76.2%	76.2%	–

wing and infiltrating the cavernous sinus may suffer seizures or corticospinal motor deficits. Finally, CSMNs are frequently associated with headache [2].

7.4.2 Imaging

The neuroradiological characteristics compatible with meningioma are extra-axial localization, homogeneous intake of contrast medium, base in the dura mater, clear demarcation from the normal surrounding brain tissue, slow and gradual tumour growth at repeat neuroradiological exams, exclusion of systemic metastasis and, in some cases, tumour calcification [3, 9]. These morphological features lend themselves to accurate localization using stereo-MRI. In addition, with their generally homogeneous capture of the contrast medium, clear and well-defined margins and excellent delimitation of the dural tail of the lesion, meningiomas—in particular CSMNs—are ideal targets for treatment via SRS. MRI sequences employed to obtain accurate CSMN localization for the purposes of SRS, all using contrast medium, generally include T1 sequences for saturated fats (to provide clear demarcation of the volume, morphology and boundaries of the MN); CISS sequences (for clear definition of the cranial nerves and other critical brain structures to be preserved during SRS); and axial T1 sequences; these imaging protocols provide excellent definition of the tumour margins within the cavernous sinus and orbit.

7.4.3 Surgical Treatment

Surgery is usually the primary treatment option proposed for intracranial meningioma. However, although technically possible in the case of CSMNs, surgical resection may involve a very laborious and complex operating procedure. In addition, due to above reasons it is also associated with a very high risk of permanent neurological side effects, and a non-negligible probability of post- and perioperative mortality, without ensuring the possibility of complete tumour removal. In fact, several literature reports, even those on recent and numerous CSMN case series, cite rates of permanent neurological damage ranging from 17.9% to 74.0%, and a post-

operative mortality rate of between 0.0% and 9.5% [5, 7]. Moreover, the probability of recurrence after partial or subtotal surgical resection of CSMN remains significant (13% at 3 years and 38% at 5 years) [2].

7.4.4 SRS and Its Advantages

SRS, on the other hand, has numerous advantages over surgical treatment for CSMN. First and foremost, it is associated with excellent outcomes in terms of efficacy and safety. Actuarial survival rates with 5-year LTC are reported as being between 85.7% and 100%, associated with stable or improved neurological conditions in the vast majority of cases; SRS limits the progression of the disease in most patients, with very low risks of retreatment. In addition, SRS has very low morbidity and secondary mortality, with severe neurological deterioration being extremely rare. Indeed, via SRS it is possible to obtain extremely accurate tumour localization using stereo-MRI images, since CSMNs usually display homogeneous capture of the contrast medium, clear and well-defined margins and excellent delimitation of their dural tail. Additional advantageous features of the radiosurgical procedure include simple, easy and rapidly implemented treatment plan, modelled with multiple isocentres, and a non-invasive intervention that requires, in most cases, only a few hours of hospitalization.

Hence, hospitalization costs are also low as compared to surgery. According to the UK National Health Service (NHS) clinical commissioning policy for stereotactic radiosurgery/radiotherapy for meningioma (D05/P/e) published by the NHS England SRS reference group in September 2013 [11], there is evidence—from a comparative study of the costs of microsurgery vs. SRS—that the total expenditure on microsurgery is more than double that of SRS. Indeed, SRS requires significantly shorter hospitalization than microsurgery, and has a less harmful impact on the quality of life. Furthermore, secondary mortality is avoided, and there is a lower incidence of treatment-related complications, making the savings for the NHS in England considerable. In fact, SRS is usually carried out in day surgery under local anaesthesia, whereas microsurgical resection necessarily requires general anaesthesia, and usually entails operating from 2 to 10 h or more, depending on the complexity and volume of the meningioma to be removed. In addition, patients undergoing microsurgery require a minimum stay of 12–24 h in an intensive care environment. Hospital stays are usually between 4 and 10 days, but can extend to several weeks or months if post-operative complications occur (such as cerebrospinal fluid leak, severe motor deficits), which could put a strain on neurological rehabilitation resources. In conclusion, compared to microsurgery SRS offers shorter hospitalization, less harmful impact on quality of life, no post-operative mortality, lower incidence of treatment-related complications and much lower costs.

7.4.5 Comparison of Different Cases

Thus far, there have been reports on several thousand patients treated via SRS for CSMNs published in the literature (Tables 7.3 and 7.4). These clinical series, with an average or median observation period of less than or equal to 62 months, indicate that the actuarial LTC rates range between 85.7% and 100% at 5 years and between 75.8% and 98% at 10 years (Table 7.3). Moreover, a clear relationship between the volume of the CSMNs treated and the post-SRS prognosis emerges. Specifically, when the average or median treatment volume remains below 10 mL, the LTC at 5 and 10 years generally remains above 90%. From a clinical perspective, the possibility of neurological improvement, especially at the expense of cranial nerve deficits, in patients already symptomatic before SRS treatment is very significant. In fact, the improvement frequency reported in the literature varies between 20% and 69.3% (Table 7.3). Conversely, the risk of permanent side effects secondary to SRS treatment is always very low (0.0–19.2%). Once again, a relationship seems to exist, this time directly proportional, between the treated tumour

Table 7.3 Summary of outcomes in CSMN series treated via SRS with a mean/median observation period of less than 62 months

Author. publication year, technology	N° Patients	N° Sess.	Volume Mn/ Md (mL)	PD Mn/Md (Gy)	Obs. P. Mn/ Md (Months)	5-year LTC (%)	10-year LTC (%)	Neur. Improv. (%)	Perm. Comp. Post-SRS (%)[a]	Prognostic factors
Hazar (2017), GK [12]	166	Single	10.0 Mn	13.0 Mn	32.4 Mn	90.1	75.8	40.4	10.8	• Adj./Salv. SRS ± RT pre-SRS[c] • Greater volume[b]
Hafez (2015), GK [2]	62	Single	5.7 Mn	14.4 Mn	36.0 Mn	95.0	—	41.7	8.0	—
Kano (2013), GK [5]	273	Single	8.0–7.7 Md	13.0 Mn	62.0 Md	94.0	86.0	28.4 • 37.0 Pri. • 14.0 Adj.	11.0	• Adj./Salv. SRS[c]
Zeiler (2012), GK [13]	26	Single	7.9 Me	13.5 Mn	36.1 Mn	92.3	overall	24.0	19.2	—
Hayashi (2012), GK [14]	19	Single	—	12.0 Mn	55.0 Mn	100.0	overall	—	0.0	—
Kimball (2009), linac [15]	47	Single	5.9 Md	12.86 Md	50.0 Md	100.0	98.0	65.0	3.5	• Number of pre-SRS CN deficit[c]
Franzin (2007), GK [16]	123	Single	7.99 Mn	13.8 Mn	36.0 Md	90.5	—	31.1	2.4	—
Hasegawa T 2007, GK [17]	115	Single	14.0 Mn	13.0 Mn	62.0 Md	94.0	92.0	43.0	4.0	—
Pamir (2005), GK [18]	26 Pr 12 Ad	Single	—	—	4.3 years Mn 5.2 years Mn	94.4	—	• 40.0 Pri. • 52.4 Adj.	0.0 Pri. 0.0 Adj.	—
Pollock (2005), GK [19]	49	Single	10.2 Mn	15.9 Mn	58.0 Mn	80.0	at 7 years	26.0	14.3	—
Maruyama (2004), GK [20]	40	Single	5.4 Mn	16.0 Md	47.0 Md	94.1	—	20.0	12.5	—
Iwai (2003), GK [21]	43	Single (2 sessions in 3/43 patients	14.7 Mn	11.0 Mn	49.4 Mn	92.0	—	28.6	0.0	—
Spiegelmann (2002), linac [22]	42	Single	8.2 Md 8.4 Mn	14.0 Mn	36.0 Md 38.0 Me	97.5	at 7 years	27.8	16.7	—
Nicolato (2002), GK [23]	122	Single	8.3 Mn	14.6 Mn	48.9 Md	96.5	—	69.3	1.0	—

(continued)

Table 7.3 (continued)

Author. publication year, technology	N° Patients	N° Sess.	Volume Mn/ Md (mL)	PD Mn/Md (Gy)	Obs. P. Mn/ Md (Months)	5-year LTC (%)	10-year LTC (%)	Neur. Improv. (%)	Perm. Comp. Post-SRS (%)[a]	Prognostic factors
Lee (2002), GK [24]	159	Single	6.5 Md	13.0 Md	39.0 Mn	93.1 WHO GI • 96.9 Pri. • 90.4 Adj. WHO GI • 25.0 WHO GII/III	93.1 WHO GI	29.0	6.7	—
De Salles (2001), linac [25]	33	Single (fractionated RT in 2/33 patients)	Range: 1.6–36.0	range: 12.0–22.0	30.0 Mn	76.0	overall	30.0	7.5	• Larger CSMN (Grade IV-V)[a,b]
Shin (2001), GK [26]	40	Single ± fractionated RT	4.3 Md	18.0 Md	42.0 Md	86.4 at 3 years	82.3	—	2.5	• WHO GII/III, suboptimal dose coverage, larger tumour [b]
Roche (2000), GK [27]	80	Single	4.7 Md 5.8 Mn	28.0 Mn	30.5 Md	92.8	—	44.1	3.75	—
Liscak (1999), GK [28]	53	Single	7.8 Md	12.0 Mn	19.0 Md	100.0	overall	35.8	0.0	—
Sibtain (1999), linac [29]	28	Single	—	—	12–83	100.0	overall	—	—	—
Chang (1998), linac [30]	24	Single	6.83 Mn	17.7 Mn	45.6 Mn	100.0 at 2 years	—	42.0	4.2	—
Pendl (1998), GK [31]	41	Single	15.4 Mn	13.2 Mn	39.0 Mn	100.0	overall	54.2	0.0	—
Kurita (1997), GK [32]	18	Single	23.4 Mn (diameter)	17.0 Mn	34.8 Mn	85.7	—	5.6	5.6	—
Duma (1993), GK [33]	34	Single	5.17 Md	16.0 Md	26.0 Md	100.0	overall	24.0	5.9	—

N°. number, *Sess.* sessions, *Mn/Md (mL)* mean/median (millilitres), *PD* prescription dose, *Gy* Gray, *Obs. P.* observation period, *LTC* local tumour control, *Neur. Imp.* neurological improvement, *Perm. Comp.* permanent complications, *MT* malignant transformation, *GK* Gamma Knife, *Pri.* primary SRS, *Adj.* adjuvant SRS; *Salv.* salvage SRS, *CN* cranial nerve, *linac* linear accelerator, *RT* radiotherapy

[a]Mortality secondary to SRS for CSMN reported in no case series

[b]Correlated with a lower probability of LTC

[c]Correlated with a lower probability of neurological improvement after SRS

Table 7.4 Summary of outcomes in CSMN series treated via SRS with a mean/median observation period greater than 62 months

Author, publication year, technology	N° Patients	N° Sess.	Volume Mn/Md (mL)	PD Mn/Md (Gy)	Obs. P. Mn/Md (Months)	10-year LTC (%)	15-year LTC (%)	20-year LTC (%)	Neur. Improv. (%)	Perm. Comp. Post-SRS (%)[a]	Tumorigenesis/ malignant transformation	Prognostic factors
Park (2018), GK [9]	200	Single	7.5 Md	13.0 Md	101.0 Md	84.0	75.0 • 85.0 Pri. • 74.0 Adj. • 57.0 Salv.	—	26.0	9.0 • 7.5% CN • 1.5% Hypop.	• No tumorigenesis • No MT	• Salv. SRS[b] • Volume >10 mL[c] • New CN deficit after surgery[d]
Correa (2014), linac [1]	32	Single	6.0 Md	14.0 Md	73.0 Md	95.7	90.3	—	41.6	0.0	• No tumorigenesis	—
Nicolato (2013), GK [34]	170	Single	9.4 Mn	14.6 Mn	160.9 Md	92.0	89.0	—	56.5	2.3	—	• Adj./Salv. SRS[b] • WHO GII[b]
Pollock (2013), GK [35]	115	Single	9.3 Md	16.0 Md	89.0 Md	93.0	—	—	31.0	12.0	• No tumorigenesis • No MT	• Volume >9.3 mL[c]
Santacroce (2012), GK [36]	1.272 CSMN/5.300 MN	Single	4.8 Md Whole series	14.0 Md Whole series	70.9 Mn Whole series	88.5 Whole series	—	—	53.5 Whole series	10.7 CSMN + sellar region+ middle CF	• No tumorigenesis • 8/2.324 (0.34%) from WHO GI to GII/III post-SRS	• Male[b] • Adj./Salv. SRS[b] pre-SRS[b] growth • Multiple MN[b] • Convex MN[b]
Dos Santos (2011), linac [37]	88	Single	• 3.7 Mn primary SRS • 5.9 Mn Adjuv./ Salv. SRS	14.0 Mn	86.8 Mn	82.5	—	—	51.1	12.5	—	—

(continued)

Table 7.4 (continued)

Author, publication year, technology	N° Patients	N° Sess.	Volume Mn/Md (mL)	PD Mn/ Md (Gy)	Obs. P. Mn/Md (Months)	10-year LTC (%)	15-year LTC (%)	20-year LTC (%)	Neur. Improv. (%)	Perm. Comp. Post-SRS (%)[a]	Tumorigenesis/ malignant transformation	Prognostic factors
Skeie (2010), GK [38]	100	Single	7.39 Mn	12.4 Mn	82.0 Md	91.6	—	—	21.0	6.0	—	• Suboptimal dose coverage[b] • WHO GII[b] • PD <12.5 Gy[b]
Spiegelmann (2010), linac [39]	102	Single	7.2 Md	13.5 Md	68.0 Mn	—	—	—	32.0	7.8	—	• Adj./Salv. SRS[d]
Metellus (2005), GK [40]	36	Single	5.2 Mn 5.9 Md	14.0 Mn 15.0 Md	63.6 Md	94.4	—	—	58.3	0.0	—	—
Current series, GK	200	Single	9.88 Mn	14.2 Mn	165.9 Md	94.9 WHO GI	94.9 WHO GI	89.3 WHO GI	60.5	2.5	• No tumorigenesis • No MT	• Adj./Salv. SRS[b] • WHO GII[b]

N° number, *Sess.* sessions, *Mn/Md (mL)* mean/median (millilitres), *PD* prescription dose, *Gy* Gray, *Obs. P.* observation period, *LTC* local tumour control, *Neur. Imp.* neurological improvement, *Perm. Comp.* permanent complications, *MT* malignant transformation, *GK* Gamma Knife, *Pri.* primary SRS, *Adj.* adjuvant SRS, *Salv.* salvage SRS, *CN* cranial nerve, *Hypoppop.* hypopituitarism, *CF* cranial fossa, *linac* linear accelerator

[a]Mortality secondary to SRS for CSMN reported in no case series

[b]Correlated with a lower probability of LTC

[c]Correlated with an increased risk of permanent CN deficit

[d]Correlated with a lower probability of neurological improvement after SRS

volume and the onset of complications. In fact, iatrogenic worsening due to radiation is usually reported as being less than 10% in clinical series with average or median treated volumes of less than 10 mL.

Patient series with a medium-term observation period of 62 months have also led to the identification of several prognostic factors related to LTC and neurological improvement (Table 7.3). In particular, the increased extent and volume of CSMNs, suboptimal coverage of tumour volume by the treatment dose and more aggressive histological grade (WHO Grade II/III) all appear to correlate with a lower probability of LTC. On the other hand, SRS treatments on CSMNs that have never previously been operated on (primary treatments) and the number and entity of modest cranial nerve deficits appear to be associated with a greater likelihood of neurological improvement after SRS (Table 7.3).

However, since CSMNs are usually benign and therefore affect patients with a prolonged life expectancy, it is fair to ask whether the effects of SRS, in terms of efficacy and safety, on this type of cranial base tumour are maintained in the long term. In order to clarify this issue, the outcomes in selected larger case series (exceeding 30 patients) and an average or median observation period of more than 62 months (Table 7.4) were compared. These studies also confirm the stability of the effects of radiosurgery for CSMN over time, with 15-year LTC rates ranging from 75% to 94.9%. In particular, in our study on 200 CSMNs treated via LGK and with a median observation period of 165.9 months, the LTC at 20 years in the 188 CSMNs with baseline WHO Grade I or neuroradiological features compatible with a benign form was extremely high (89.3%). From a clinical perspective, these patient series with long-term follow-up also demonstrate that SRS is associated with an improvement in the neurological status, especially with regard to cranial nerve deficit (from 21% to 60.5%) (Table 7.4). Similarly, the risk of permanent neurological complications secondary to SRS—especially those involving the cranial nerves—remains particularly low, with sequelae occurring in between 0.0% and 12.5% of cases.

Finally, studies with long observation periods and numerous cases (at least 100 patients) have also identified some prognostic factors related to LTC and neurological status. Specifically, SRS is associated with a greater success rate when applied as a primary treatment for WHO Grade I sporadic (i.e. single) meningiomas, particularly in females. Furthermore, success rates are higher when the treatment plan involves full tumour coverage and a radiant dose to the surface of ≥13 Gy. In contrast, adjuvant or salvage SRS for MN volumes >10 mL seems to be a factor associated with the onset of new cranial nerve deficits and worse neurological prognosis for CSMN patients (Table 7.4).

7.4.6 Long-Term Complications

7.4.6.1 Stroke Risk

Another pertinent topic is the long-term risk of stroke after radiosurgical treatment of CSMNs. While the risk of stroke after proton or photon RT for partially resected MN has been examined over long-term observation periods, the frequency of stroke after single-session SRS had never been previously studied in patients with MN. However, a recent randomized study by Massachusetts General Hospital on 44 patients with relapsed or progressed WHO Grade I MN who had previously undergone incomplete surgical resection and were subsequently treated using fractional proton-photon therapy at a minimum total dose of 55.8 Gy revealed that, at a median follow-up of 17.1 years, the risk of stroke onset was 20.5%, with an average interval between RT term and stroke diagnosis of 5.6 years [41]. This stroke risk is up to ten times higher than the 2–6% calculated and expected for the general population aged 40–79 years, according to recent statistics published by the American Heart Association [42]. However, more recently, prompted by this data, McClelland et al. [43] carried out a detailed study of PubMed looking for articles related to the treatment of SRS on MNs. On the basis of precise inclusion criteria—(a) median/average clinical follow-up of at least 6 years (interval chosen to ensure that these studies had exceeded

the 5–6-year period between RT and stroke onset established by the Sanford et al. study); (b) minimum 30 patients; (c) written in English; (d) single-session SRS exclusively for meningioma; (e) inclusion of post-SRS morbidity analysis; and (f) patient pool not reported in multiple published studies—they selected 14 studies with long-term follow-up, comprising a total of 1431 patients followed up for a median/average interval of 75–144 months. Overall, stroke following SRS treatment was reported in 24 patients, i.e. 1.7%. This long-term stroke rate after single-session photon SRS for benign MN is more than 12 times lower than that reported in the above fractional proton-photon therapy clinical series, and was comparable to that expected for the general population. Most of these patients underwent surgical resection prior to SRS, and the authors concluded that to avoid the high risk of stroke associated with fractional proton-photon therapy, patients with benign MN should instead undergo SRS, which seems not to raise the stroke risk as compared to the general population.

7.4.6.2 Tumorigenesis and Malignant Transformation

There are two possible carcinogenic effects associated with SRS treatments: radiation-induced tumorigenesis (RIT) and malignant transformation (MT). Nonetheless, the real risk of RIT or MT after single-session SRS to intracranial targets remains undefined, despite more than 1,000,000 patients having already undergone this type of treatment to date. That being said, it does appear to be particularly low and is certainly significantly lower than that associated with fractional RT. The term "radiation-induced tumorigenesis", however, seems inappropriate because it implies that there is definitive molecular evidence that radiation is the causal factor. This information has never been reported, and the term "radiation-associated" may therefore be a more appropriate definition [44, 45]. At present, however, the definition of SRS-associated tumorigenesis is still based on the indirect criteria developed by Cahan et al. [46] in 1948; specifically, secondary cancer must develop within the field of previous irradiation; it should not be present before RT; there must be some period of latency between the treatment and tumour onset (usually 5 years); the secondary cancer must be histologically distinct from the original pathology; and there must be no genetic predisposition for the onset of a secondary tumour or cancer progression.

With regard to the risk of SRS-associated tumorigenesis, according to the literature data the incidence of SRS-associated cancers is between 0.0 and 3.0 per 200,000 patients per year [47], or, to cite a more recent estimate, between 0.04% and 2.6% at 15 years [48, 49]. In this regard, Rowe et al. [50] conducted a retrospective cohort study comparing the incidence of new central nervous system malignancies in their SRS-treated patients with the UK national incidence. Based on 4877 patients treated via SRS and more than 30,000 patients followed up for a median 5.2 years, the authors reported one new astrocytoma in the SRS group in the entire follow-up period, as compared to an expected incidence of 2.5 cases. In 2014, Patel and Chiang, on the other hand, reviewed the published literature on this topic and identified 19 cases of RIT and 17 cases of MT following SRS out of approximately 80,000 selected patients [48]. Based on this estimate of 80,000 patients treated via SRS for benign brain pathology with an observation period of at least 15 years, it was estimated that the combined risk of SRS-associated tumorigenesis and MT onset was 0.04% at 15 years.

Similarly, Rahman et al. compared the number of cancer cases observed in a group of patients after linac SRS with the number of cancer cases one would expect in a group of age- and sex-matched patients, as extracted from the Surveillance, Epidemiology and End Results (SEER) database [51]. Out of a total of 627 patients with more than 5 years of follow-up—comprising 202 MNs, 223 intracranial schwannomas, 165 arteriovenous malformations (AVM) and 37 other cancers—the cancer rate observed in patients with MN was 3.96%, as compared to the expected rate of 10% (binomial confidence interval of 95%, CI = 1.85–7.94). The authors concluded that after long periods of observation of a large population of patients treated for intra-

cranial MN, there was no increased risk of cancer associated with linac SRS with respect to the general population. More recently, Kondziolka and Lunsford observed no cases of SRS-associated tumorigenesis in more than 13,000 SRS patients treated at the University of Pittsburgh between 1987 and 2013 [52]. Finally, Pollock et al. [53] carried out a retrospective review of 1142 patients treated via single-fraction intracranial radiosurgery at the Mayo Clinic College of Medicine between 1990 and 2009. Their sample comprised 233 AVM, 316 MN, 358 vestibular schwannomas, 188 pituitary adenomas and 47 jugular glomus tumours, divided into two patient populations, similar in gender, age, number of previous surgical resections, prescribed ID and number of doses, on the basis of whether they were excluded or included in the study. Specifically, patients were excluded if they refused permission for research, had a genetic predisposition for cancer or had been subjected to RT either previously or concurrently with the intracranial radiosurgery. Any case of RIT or MT was recorded, irrespective of the duration of the observation period, although the median neuroradiological follow-up of the 1142 patients was 9.0 years (range 5–24.9). The authors identified no cases of RIT in the 11,264 patients throughout the observation period. Therefore, according to the authors' conclusions, the risk of developing a RIT after SRS remained 0.0% at 5, 10 and 15 years.

In summary, the lessons learned so far on the risk of SRS-associated RIT lead to the following final considerations and recommendations: (1) RIT can occur both within the full-dose region and in peripheral regions exposed to very low doses; (2) the risk of RIT is substantially lower with SRS than in patients treated with radiation to larger volumes and/or with fractionated treatment regimes; (3) the latency period after SRS is similar to that observed with fractionated RT, with a range of 6–20 years, and malignant tumours have a shorter latency period than benign radiation-induced forms; (4) a long-term observation period should be mandatory for all SRS patients to detect benign brain injuries; and (5) current standard guidance regarding SRS should not be changed, due to the extremely low risk of associated RIT.

As regards MT, this is defined as occurring when a purported or histologically proven benign tumour shows progression after SRS, and histopathological examination at surgery or re-intervention reveals a higher tumour grade or a real malignant cancer [53]. It is particularly unfeasible to assess the relative risk of MT in SRS for intracranial MNs without a non-irradiated control group of patients, since MN MT has also been observed in patients who have never been previously given RT [54, 55]. Nonetheless, Patel and Chiang [48] reported that the risk of MT following SRS was 0.04% at 15 years in a series of 80,000 patients treated for benign intracranial MN. Kondziolka et al. [56], on the other hand, published a retrospective study of 290 patients consecutively treated via LGKRS for intracranial MN (97% Grade I WHO or with imaging characteristics typical of benign MN) between 1987 and 1997, and with a median clinical observation period of 56 months after SRS. In the 6 patients who underwent surgical resection after MN progression following SRS, documented by imaging, no MT was identified. The same team [9] reported on 200 patients with WHO Grade I CSMNs consecutively treated via LGKRS and with an average neuroradiological follow-up time of 101 months. In this long-term observational study, no patient developed radiation-related secondary cancers. Finally, Pollock et al. [53] evaluated MT in a sample of 1142 patients who underwent single-session SRS and had a neuroradiological follow-up of at least 5 years. Of the 316 patients with MN, they observed MT in 7 (2.2%) over a median observation period of 4.9 years (range 2.8–13.8). They reported 5-, 10- and 15-year actuarial risks of MT of 0.5%, 0.8% and 2.4%, respectively. All seven affected patients had previously undergone surgical resection of the MN prior to SRS, and WHO Grade I was confirmed histologically in all cases. After re-intervention, however, MNs were found to be WHO Grade II in four cases and Grade III in three. Statistical analysis led the authors to conclude that patients with intracranial MN and previous surgical resection were at increased risk

of MT. Nevertheless, a 2.2% rate of MT is extremely low as, if we consider the histopathological classification criteria and patterns reported for 2000, 2007 and 2016, the incidence of Grade II tumours has drastically increased in frequency from 3–4% to 20–35% in MNs recently subjected to primary resection and diagnosis [57–59]. In addition, several clinical series have shown that up to 2% of all benign MNs spontaneously turn into higher grade histological forms (II or III), while up to 28.5% of all previously irradiated surgical recurrences of benign MN turn out to be atypical or anaplastic at histological examination [60].

Overall, these studies show that the incidence of SRS-associated tumorigenesis is certainly extremely low, and that the potential risk of secondary cancer associated with SRS should be weighed against the potential benefits of the procedure. In particular, the oncogenic risk linked to SRS is generally considered to be significantly lower than that observed after fractional RT, due to the steeper dose gradients, minimal irradiated volumes of healthy cerebral parenchyma and significantly lower total doses overall associated with the former [61, 62]. In addition, there is growing evidence that the genesis of new cancers is more likely after combined treatment methods (radiotherapy and chemotherapy)—now an increasingly common therapeutic approach in clinical practice [44, 45]. Finally, it should always be borne in mind that alternative treatments, if available, are also not devoid of risk, and sometimes there are no other therapeutic options available in place of SRS. In summary, it is possible to conclude that the risk of RIT or MT after SRS is very low, and should not therefore be used as a justification for choosing alternative therapeutic approaches (surgical resection, observation) to SRS in properly selected patients suffering from intracranial MNs.

7.5 Conclusions

Our experience and the data collected from our careful literature review on the subject lead us to the following conclusions:

- SRS is a safe, effective and reliable treatment option for symptomatic patients with CSMNs (volume <15–20 cc and not adhering to the anterior visual pathways), both as a first choice and as part of an approach combined with surgery (adjuvant or salvage treatment); in most cases SRS provides excellent LTC (volume reduction or halting tumour growth) and an improvement in or stabilization of neurological deficits, with a minimal risk of permanent neurological side effects, as confirmed by data after prolonged periods of observation (over 10 years).
- Several prognostic factors related to LTC and neurological outcomes of SRS have been identified; greater success rates on CSMNs of volume >10 mL are associated with primary radiosurgical treatment, female sex, sporadic (i.e. single) WHO Grade I, inclusion of the entire volume of meningioma in the treatment plan and a radiation dose ≥13 Gy to the surface of the meningioma, whereas adjuvant or salvage SRS treatments following neurosurgery may be associated with the onset of new cranial nerve deficits and worse neurological prognosis.
- Finally, numerous cases followed up over long periods of time reveal that SRS does not expose CSMN patients to an increased risk of either malignant transformation or an increase in the incidence of new cancers, as compared to the general population.

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8 Hypofractionated Radiosurgery for Perioptic Meningiomas: Current Practice, Principles, and Treatment Quandary

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Abbreviations

AANS	American Association of Neurological Surgeons
AOP	Anterior optic pathways
CNS	Congress of Neurological Surgeons
FSRT	Fractionated stereotactic radiotherapy
GKRS	Gamma Knife radiosurgery
LINAC	Linear accelerator
RION	Radiation-induced optic neuropathy
SRS	Stereotactic radiosurgery

8.1 Introduction

Perioptic meningiomas are defined as those in contact or adjacent (within a 2 or 3 mm distance) to the anterior optic pathways (AOP, optic nerves, and chiasm) [1–11]. The treatment of these tumors is comprised of microsurgical resection and ablative radiation therapies. The aim of microsurgical resection, which is usually proposed as the first-line treatment, is to immediately decompress the AOP, so as to restore visual function or prevent its decline. However, the complete surgical removal of these tumors is not always feasible due to the risk of damaging the AOP during surgical manipulation and due to the tumor's infiltrative growth and invasion of the skull base dura and cavernous sinus [12, 13]. Radiation ablative therapies, which include conventionally fractionated stereotactic radiation therapy (FSRT) and stereotactic radiosurgery (SRS), are commonly used as salvage or adjuvant treatments for recurrent or residual meningiomas after surgical resection, respectively. Finally, they can be used as up-front treatments for small tumors or for patients who are not good surgical candidates due to advanced age and/or serious medical comorbidities. The main concern with SRS delivered in the usual single fraction is that a single large dose of radiation may damage the adjacent AOP and pituitary gland and stalk, which are exquisitely radiation sensitive [14, 15]. Therefore, in the last two decades, a handful of studies have investigated the effects of fractionating the radiosurgical dose in up to five larger fractions to control the growth of perioptic meningiomas while mitigating the risk of damaging the AOP [1, 2, 4–11, 16]. The rationale of this

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approach, namely hypofractionated radiosurgery, is to allow interfractional normal tissue repair of sublethal damage while delivering a biologically effective dose capable of controlling the tumor growth [17]. Those studies have demonstrated that hypofractionated SRS is effective in controlling the growth of perioptic meningiomas with little visual toxicity, though the follow-up assessment periods and number of patients are limited (Table 8.1) [1, 2, 4–11, 18]. More recently, advancements in neuroimaging and radiosurgical platforms have rekindled an interest in delivering single-session SRS for the management of perioptic meningiomas [19, 20]. As a matter of fact, some authors have demonstrated in their studies that single-session SRS for perioptic meningiomas is safe to the AOP as well as effective in controlling tumors' growth, comparably with hypofractionated SRS or conventionally fractionated radiotherapy [15, 19–21]. However, the safe radiation dose to be delivered in a single session to perioptic meningiomas and the AOP is yet to be established. The aim of the following sections is to review the literature about stereotactic hypofractionated radiosurgery for the treatment of perioptic meningiomas. These are compared with the outcomes of alternative therapies including conventionally fractionated radiation therapy and single-session radiosurgery. Finally, the radiation tolerance of the optic pathways to the different radiation delivery regimens is discussed.

8.2 Results of Hypofractionated Radiosurgery for Perioptic Meningiomas

According to a consensus of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS), "SRS typically is performed in a single session, using a rigidly attached stereotactic guiding device, other immobilization technology and/or a stereotactic image-guidance system, but can be performed in a limited number of sessions, up to a maximum of five" [22].

SRS delivered in a number of large fractions between two and five is referred to as hypofractionated SRS. Since the last two decades, hypofractionated stereotactic radiosurgery has been introduced to treat some large neoplasms or intracranial tumors abutting critical and radiosensible structures, due to the perceived risks with single-session radiosurgery. In the case of perioptic tumors, the radiation gradient falloff typical of commonly used radiosurgery delivery platforms, including the Gamma Knife, was thought to be not steep enough to effectively control tumor's growth while at the same time not injuring the AOP with a single-session treatment [7]. Contrastingly, hypofractionated SRS which integrates the benefits of focused high-dose radiation and conformity typically associated with SRS platforms with the radiobiological advantages of fractionation was considered safer to the AOP [23]. As such, a handful of studies have investigated the effectiveness of hypofractionated SRS for the treatment of perioptic tumors (Table 8.1) [1, 3–9, 11, 16, 24–26]. Initially, the Stanford's group reported preliminary positive results in the treatment of perioptic tumors with hypofractionated SRS using the CyberKnife (Accuray, Inc., Sunnyvale, CA). No patients developed RION in that study; however the follow-up assessment time was short [8]. In the most recent clinical report of that group, Adler et al. reported on 49 patients treated with multisession CyberKnife-mediated SRS and observed that radiation-induced optic neuropathy (RION) developed in a single patient after a mean follow-up period of 46 months. Notably, that patient's tumor had received multiple radiation treatments before SRS. For all patients, the reported tumor control rate was 94% at final evaluations [1]. Following the Stanford's experience, other groups confirmed the safety and efficacy of hypofractionated SRS for the management of meningiomas and a range of slow-growing benign tumors adjacent to the visual pathways, including pituitary adenoma and craniopharyngioma [3–7, 9–11, 16]. In those studies, various radiosurgical devices were used to deliver hypofractionated/multisession SRS. The CyberKnife was the most popular [1, 5–7, 9–11, 16, 24], whereas Gamma Knife radiosurgery (GKRS) was used in a limited number of studies [3, 4]. Kim and colleagues

Table 8.1 Studies investigating the effects of hypofractionated or multisession stereotactic radiosurgery for the treatment of perioptic tumors

Author/year	SRS platform	Head fixation system	Number of patients	Numebr of fractions	Fraction dose, Gy	Cumulative prescribed dose, Gy	Tumor control at the last follow-up, %	Pituitary function defict, number of patients (%)	Patients developing RION, number of patients (%)	Lenght of follow-up, months.
Metha (2002)[a]	CK	Moulded face mask	13	2–5	NS	17.85–25	100	0	0	median 18
Pham (2004)[a]	CK	Moulded face mask	34	2–5	NS	15–30	94.2	NS	1(2.9)[b]	Mean 29
Adler (2006)[a]	CK	Moulded face mask	49	2–5	5–7.5	15–30	94	NS	1(2.9)[b]	mean 46
Kim (2008)[a]	GK	Pin-based frame	22	3–4	NS	15–20	96	0	0	Mean 29
Jee (2014)[a]	GK	Pin-based frame	38	3–4	4–5	20	94.6	6	1	Median 38.2
Nguyen (2014)[a]	GK	Extend relocatable system	15	3–5	NS	15–25	100	NS	0	Mean 17.7; Median 13.8
Devriendt (2015)[a]	GK	Extend relocatable system	12	4–5	5–6	24–25	100	NS	0	Mean 19.3
Conti (2015)[a]	CK	Moulded face mask	64	2–15	2.6–9	18–40	100	0	0	mean 32±23
Marchetti (2016)	CK	Moulded face mask	143	3–5	NS	14–25	90 at 5 years	NS	5.1	Mean 44; Median 32
McTyre (2017)[a]	GK	Extend relocatable system	19	4	NS	20	100	NS	100	Median 7.6
Puataweepong (2018)[a]	CK	Moulded face mask	100	3–5	NS	20–35	97.5	0	0	Median 37.5
Marchetti (2019)	CK	Moulded face mask	167	5	5	25	95.2	NS	3.7	Mean 56; Median 51
Personal series (unpublished data), (2020)	GK	Pin-based frame	167	3	5–7.5	15–24	90.4	3(1.8)	2.4	Mean 51.8; median 43.6

[a]This study included patients with nerve optic-nerve sheath meningiomas or pituitary adenomas

[b]This patient was previously treated with a course of conventionally fractionated radiotherapy and three separate sessions of radiosurgery

treated 22 patients with perioptic benign tumors using GKRS with a tumor control rate of 96% and no visual compromise at a mean follow-up of 29 months [4]. That series was extended to include 38 patients and found comparable results after a mean period of 38.2 months following radiosurgery. A single patient developed RION at the last clinical assessment [3]. Finally, in an attempt to reduce the discomfort associated with prolonged stereotactic frame application, some authors investigated the use of a relocatable stereotactic frame compatible with the Gamma Knife Perfexion system (Extend system, Elekta AB instruments, Stockholm, Sweden). Nguyen reported on 15 patients with perioptic tumors (including 12 meningiomas) who were treated with hypofractionated GKRS using the relocatable Extend system and found that tumor's growth was controlled in all patients, with no case of visual deterioration after a median follow-up of 13.8 months following radiosurgery. Similar results were achieved in the study of Devriendt et al. All the 11 patients with perioptic meningiomas who were included in that study did not develop RION or had tumor progression following five-session GKRS using the relocatable Extend system (mean follow-up time of 19 months) [2, 7, 9, 16].

Overall, hypofractionated SRS delivered with frameless or frame-based devices was demonstrated to be safe in terms of visual function preservation and effective in controlling perioptic meningiomas' growth. In most series, visual function deterioration was caused by tumor progression rather than radiation damage. Most recently, the Italian Gamma Knife Research Study Group (IGKRS) has collected clinical and radiosurgical data of 167 patients treated with three-session hypofractionated GKRS for meningiomas in contact with the AOP (unpublished data). After a mean follow-up period of 51.8 months, longer than in most published studies, four patients developed RION, thus confirming the safety of three-session radiosurgery. The investigators observed that tumor control rate was lower in those patients treated with hypofractionated GKRS as a salvage or adjuvant treatment than in those treated with up-front GKRS. Since radiosurgery is an image-guided surgery, an unsuccessful prior resection can make defining the radiosurgical target as well as delineating the critical structures more difficult [19]. Therefore, some parts of recurrent or residual tumors might have received a lower non-ablative dose. This finding is concordant with some previous reports [27–29].

8.3 Radiation Tolerance of the Optic Apparatus During Radiosurgery

Visual impairment from RION is uncommon but disabling. It usually presents with painless rapid visual loss. Vascular injury has been suggested as a significant contributor to RION, although other factors may play a role in its development. The interval between radiation therapy and development of visual symptoms is generally ≤3 years (mode, 1–1.5; median, 2.5) [21]. To mitigate the risk of RION when targeting a perioptic meningioma with stereotactic radiation therapies, the knowledge of the radiation dose-response characteristics of the AOP is essential. At the present time, the safe radiation dose for such delicate nerve structures delivered with single or fractionated SRS treatments is controversial [30]. The seminal study investigating the AOP's tolerance to single-session SRS was published by Tishler and colleagues in 1993 [31]. In that retrospective study, 17 patients with perioptic meningiomas were treated with a radiation dose to the AOP exceeding 8 Gy using either a linear accelerator or a GKRS. The authors found that radiation-induced optic nerve injury occurred in four of these patients after a median period of 19 months following SRS. Contrastingly, none of the 35 patients who were treated with a dose below 8 Gy developed RION. According to their results, Duma and colleagues found no visual complications when the dose of the radiation delivered to the AOP was below 9 Gy [32]. Based on those initial investigations, the safe dose to the AOP during single-session radiosurgery was kept below 8 Gy by many radiosurgeons. However,

those initial studies were conducted early in the overall radiosurgical experience and had major limitations in the determination of the dose delivered to the AOP. First, the majority of patients included underwent computed tomography (CT) as the imaging modality used for dose planning. CT is limited in clearly identifying some intracranial structures, especially those near the skull base, such as the AOP. Assigning an exact dose to the AOP may have therefore either overestimated or underestimated the actual dose delivered. With modern treatment delivery platforms, the AOP is identified and contoured on high-resolution MRI exams that allow for more accurate volumes' definition and dose estimates. Second, in the initial studies the maximum dose received by the AOP was based on computer-generated isodose curves being laid over the actual images, which is a fairly inaccurate method for estimating the dose delivered to a single structure, especially when using a treatment delivery technology with a rapid dose gradient falloff such as the Gamma Knife. Data analyzed to derive the 8 Gy threshold were thus relatively imprecise compared with those analyzed with more current and precise dose planning software that provide point dose statistics and dose-volume histograms for any chosen structures [33]. As a result, in 1998, Leber and colleagues investigated the neuro-ophthalmological outcomes of SRS using the Gamma Knife in 66 eyes of 45 patients treated with single-session SRS for benign skull base tumors involving the cavernous sinus. After a mean follow-up period of 40 months, the actuarial risk of developing RION was zero for patients receiving a maximum dose below 10 Gy, 26.7% for patients receiving 10–15 Gy, and 77.8% for those receiving more than 15 Gy. The authors concluded that the visual pathways appear to tolerate doses up to 10 Gy with acceptable risk [30]. Subsequently, similar studies examined the radiation tolerance of the optic pathways and suggested that the 8 Gy threshold is likely a conservative estimate for the single-fraction tolerance of the optic apparatus, and concluded that up to 10 Gy can be justified on a theoretical basis [34, 35]. That is, Morita et al. at the Mayo Clinic reviewed their experience with radiosurgery for skull base meningiomas, and observed that in 35 patients that were treated with a dose superior to 8 Gy to the optic apparatus (the median dose to the optic apparatus was 10 Gy, range 1–16 Gy), none developed RION after a median period of 35 months following SRS [35]. Stafford and colleagues later extended this series to include 215 patients and observed that the risk of developing a clinically significant RION was 1.9% (4 patients) for patients receiving 12 Gy or less to the AOP after a median period of 31 months following SRS. Three out of the four patients who developed RION in that study had been previously treated with radiotherapy, which, in accord with previous studies [30, 36], is a known risk factor for RION. Thereafter, several other studies analyzed the dose-volume tolerance of the AOP to single-fraction SRS delivered with contemporary radiation delivery techniques. Overall, those investigations confirmed that patients with parasellar benign lesions who have not had prior irradiation can receive doses up to 12 Gy to the AOP with a low risk of RION (see Fig. 8.1) [25]. For example, Hasegawa et al. [37] reported on 100 patients with craniopharyngiomas treated with single-fraction SRS using GKRS. Of the three patients who developed RION, one had undergone external body radiotherapy prior to SRS, whereas the other two patients received a maximum radiation dose to the AOP of 15 Gy and 18 Gy, respectively. They concluded that radiation doses up to 14 Gy to small portions of the AOP are safe with a low risk of RION. Leavitt et al. [20] reviewed 222 patients who underwent GKRS for perioptic tumors and who had not undergone previous irradiation. One patient who received a maximum radiation dose of 12.8 Gy to the AOP developed unilateral blindness 18 months after GKRS, and the overall risk of RION in patients receiving a dose greater than 8 Gy to the AOP was 1%. In 2014, Pollock et al. [25] reported on their series of patients with parasellar tumors treated with single-session GKRS and without prior irradiation. Overall, no patient developed RION after a median follow-up of 32 months.

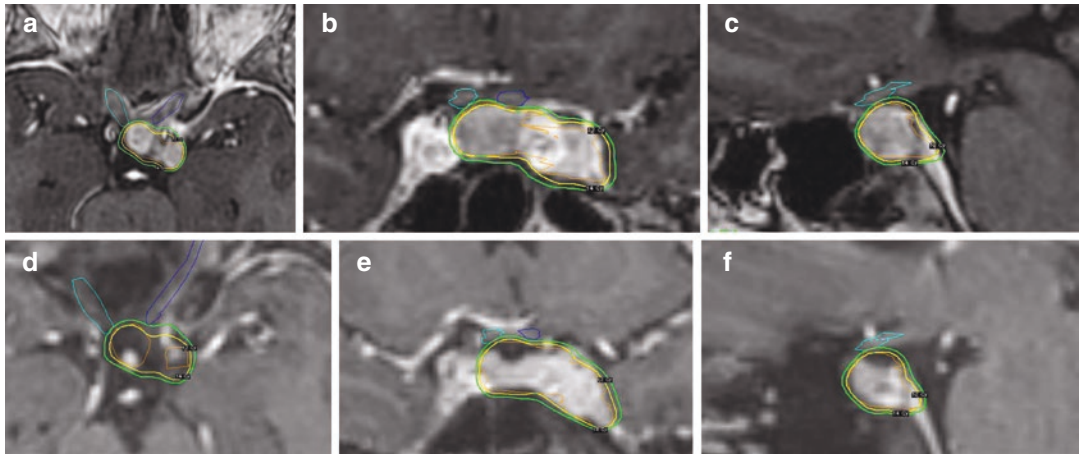

Fig. 8.1 Axial (**a**), coronal (**b**), and sagittal (**c**) post-contrast T1-weighted magnetic resonance images showing a perioptic meningioma treated with Gamma Knife radiosurgery. At the 2-year imaging follow-up assessment, the tumor's volume significantly decreased, as showed in the postoperative axial (**d**), coronal (**e**), and sagittal (**f**) scans

Taken as a whole, all these studies suggest that a dose below 12 Gy can safely be delivered in a single fraction to the AOP with little risk of causing RION [21].

The primary factors associated with the development of RION after single-fraction SRS include previous radiation treatment to the perioptic area and maximum radiation dose to the optic apparatus. A recent literature review suggested a crude approximately tenfold increased risk of RION in patients previously treated with radiation therapy to the perioptic area [38]. The other factors that are assumed to contribute to radiation-related vision loss include comorbid conditions (i.e., vasculopathies, hypertension, diabetes), tumor volume, extent of optic apparatus involvement and high-irradiated volume of the AOP, prior surgery, and optic pathway compression [25, 39]. Whereas abundant data about the radiation tolerance of the optic apparatus using single-session SRS have been published, minimal data exists relatively to patients receiving hypofractionated schedules [21], although it is recognized that hypofractionation may reduce the risk of normal tissue toxicity [18]. Therefore, appropriate dose constraints to the AOP for hypofractionated radiosurgery remain poorly defined [18]. Timmermann et al. proposed the unvalidated maximum AOP dose constraints of 19.5 Gy in three fractions and 25 Gy in five fractions [18, 40]. Subsequently, the detailed analysis of Hiniker and coworkers regarding the tolerance of the visual pathway to radiosurgery estimated that delivering to the AOP a cumulative maximum radiation dose up to 24 Gy in three fractions and 30 Gy in five fractions is associated with a limited risk of RION (1.9% in both cases). Therefore, the previously unvalidated estimates of Timmerman et al. may underestimate the tolerance of the AOP, particularly in patients without prior radiation [18].

8.4 Alternatives to Hypofractionated Radiosurgery for Perioptic Meningiomas

Given the results of the abovementioned recent studies, single-session SRS can be considered as a valid treatment option for perioptic meningiomas, alternative to hypofractionation radiosurgery (see Fig. 8.2). However, prospective studies investigating the radiation tolerance of the AOP with single-session SRS and comparing the outcomes of that treatment delivery modality with hypofractionated SRS are lacking in the literature. Ultimately, a definitive dose-volume relationship cannot be established as of yet. The devices that have been used to deliver single-session SRS for the man-

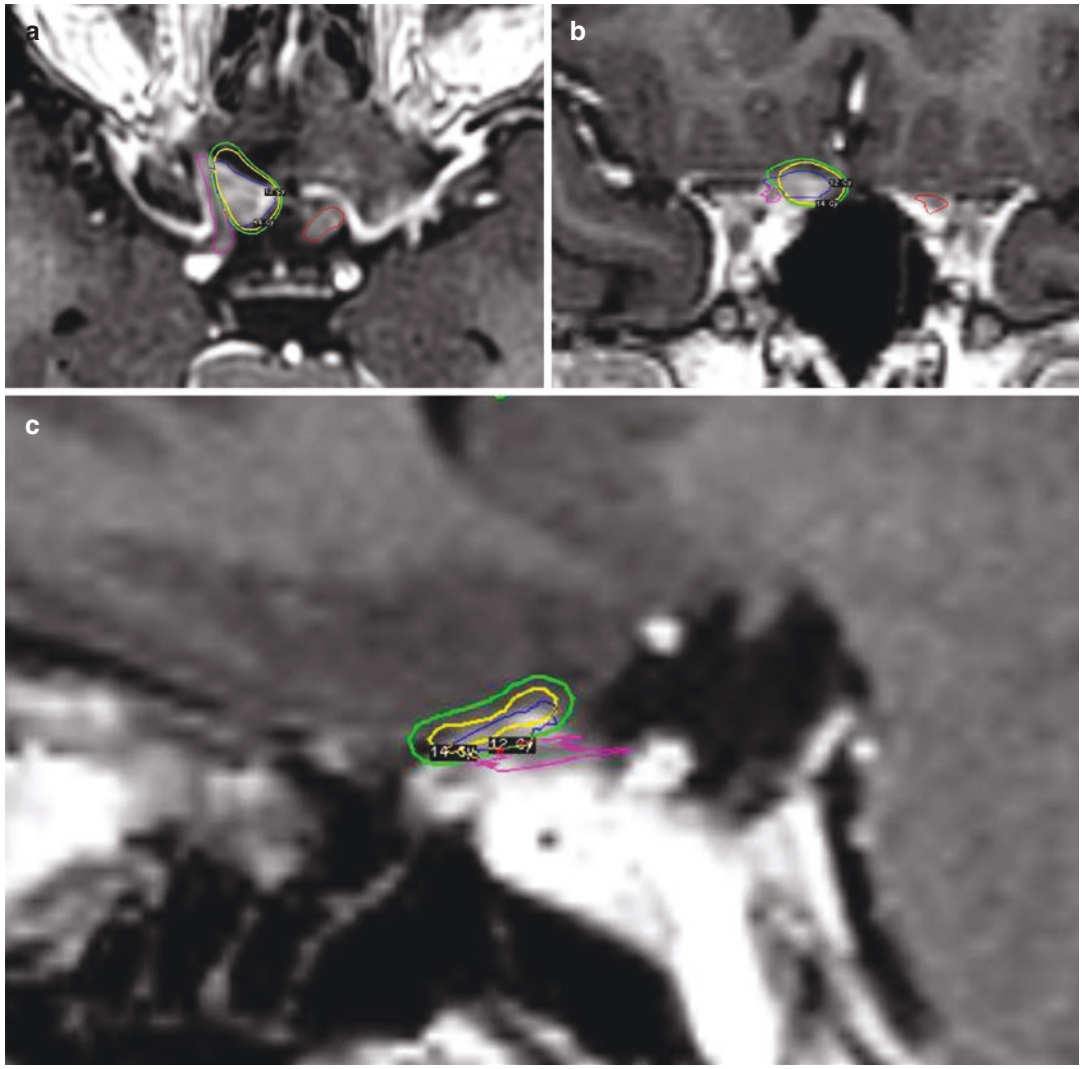

Fig. 8.2 Axial (**a**), coronal (**b**), and sagittal (**c**) post-contrast magnetic resonance images showing the radiosurgical plan for the single-session radiosurgical treatment of a meningioma adjacent to the anterior optic pathways. The treatment is planned so that the 12 Gy isodose line is contacting with the optic apparatus. At the same time, the meningioma is completely covered by the 14 Gy isodose line

agement of perioptic meningiomas have included the Gamma Knife [18, 20] and linear accelerators (LINACs) [41, 42], which both achieved high rates of tumor growth control with little risk of RION. That is, Spiegelmann and colleagues reported on a series of 117 patients treated with frame-based LINAC radiosurgery for meningiomas involving the cavernous sinus. 10 Gy was their maximal exposure limit dose to the AOP. With that limit respected, after a mean follow-up period of 67 months, visual function deteriorated in one case, although the authors did not specify if such visual decline was due to tumor progression or RION. Also, when the authors considered the whole cohort of patients with lesions in the perisellar area that had been treated with single-session LINAC radiosurgery at their institution, they found out that the incidence of optic neuropathy was below 1% (2 cases in 234 patients at risk). These authors conclude therefore

that LINAC SRS in a single fraction can be delivered safely and effectively to control the growth of benign tumors adjacent to the AOP. Such low risk of RION may be related to the frame-based head fixation, which eliminates head positioning inaccuracies inherent to frameless fixation devices (e.g., molded face masks) [31]. FSRT is also an established treatment option for perioptic meningiomas. This irradiation technique combines the accuracy of stereotactic positioning and targeting with the radiobiological advantage of fractionation and leads to a reduction in the volume of normal brain irradiated at high doses in comparison to conventional external beam radiotherapy [43]. The frequency and severity of radiation-induced complications using these techniques [44], including induced carcinogenesis, neurocognitive decline, delayed pituitary failure, and cranial neuropathies, are extremely low, due to the improvement in radiotherapy techniques and the advent of modern devices with mini–multileaf collimators [45, 46]. Several studies investigating FSRT for skull base meningiomas have reported good outcomes both in terms of tumor growth control and visual function preservation, with a low 0–6% incidence of visual loss for meningiomas around the anterior visual pathways [46–54]. However, despite these positive results, the outcomes of one of the largest studies investigating FSRT for perioptic meningiomas that was conducted by Astradsson et al. compared unfavorably with earlier series, as 10% of patients with perioptic meningiomas developed RION [55]. In line with these data, Stiebel-Kalish et al. found an overall 12% incidence of worsening visual function in their reported series of patients [56]. Although studies are controversial about visual function preservation, FSRT results as an especially valuable technique for large meningiomas in close proximity to the visual pathways, or those severely distorting or encasing the AOP for which single-session or hypofractionated SRS may not be suitable due to excessive radiation-induced toxicity [55]. As a matter of fact, in their landmark study comparing the outcomes of single-session SRS and FSRT in the treatment of cavernous sinus meningiomas, Metellus and colleagues pointed out that FSRT and SRS are aimed at two different types of tumors. Single-session SRS is reserved for small tumors, or residual and recurrent meningiomas after microsurgical resection, which do not severely compress or encase the AOP. Contrastingly, FSRT is deemed to be reserved for inoperable patients with voluminous, extensive tumors showing close relationship with the optic apparatus and skull base dural spreading [44]. A main difference between the two techniques is that the larger dose per session that characterizes radiosurgery results in a higher biological equivalent dose and subsequently correlates with greater tumor shrinkage on follow-up imaging, although tumor control rates are overlapping [1, 44, 57]. Ultimately, both SRS and FSRT are effective treatment options for benign skull base meningiomas and the choice of stereotactic technique should be based on the characteristics of the tumors [43]. In most centers single- or hypofractionated SRS is usually reserved for tumors less than 3 cm of maximum diameter not encasing or compressing the AOP, whereas FSRT is employed for larger meningiomas.

8.5 Conclusions

According to the present literature, hypofractionated SRS seems to be an effective technique for the control of perioptic meningiomas' growth with little risk of causing RION. Notably, different radiosurgical platforms employing a frameless or frame-based head fixation system can be used, with little difference in terms of outcomes and safety. Alternative radiotherapy modalities are available and effective. These include single-session SRS and FSRT. Single-session SRS, owing to recent studies, which have defined the radiation tolerance of the AOP during single-session SRS, can be safely used for perioptic tumors. FSRT is mostly reserved to the treatment of large tumors or those which cannot be treated with single-session or hypofractionated SRS, due to an increased risk of normal tissue toxicity. Ultimately, the decision whether to use one technique over the other should be made in a case-by-case basis and should take into account various factors such as the volume of the target tumor, the

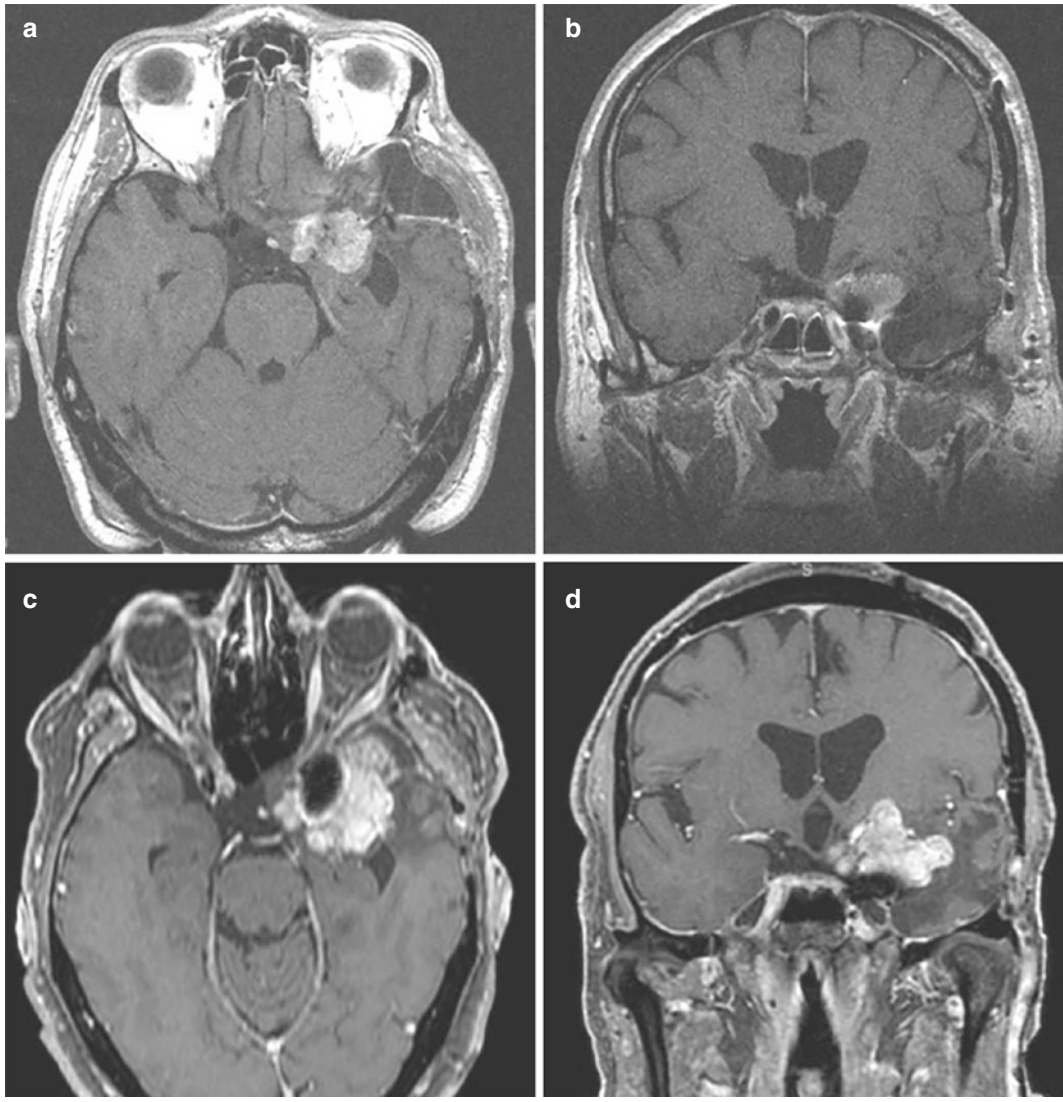

Fig. 8.3 Axial (**a**) and coronal (**b**) post-contrast magnetic resonance images showing a perioptic meningioma treated with three-session hypofractionated Gamma Knife radiosurgery. At the 7-year follow-up radiologic assessment, the tumor recurred (**c**, **d**)

treating center's experience with each technique, and patient's preference to undergo a single- or multiple-session treatment schedule. Available literature regarding the long-term efficacy and safety of hypofractionated radiosurgery for perioptic meningiomas is scarce. Further studies including large group of patients who have been followed up for long periods are needed to detect the actual recurrence rate with various fractionation protocols (Fig. 8.3).

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9 Single- Versus Multiple-Fraction Stereotactic Radiotherapy

Alfredo Conti and Giuseppe Minniti

9.1 Introduction

Skull base meningiomas are common primary brain tumours. According to the WHO classification, most meningiomas are benign lesions, whereas a minority are classified as atypical (Grade II) or malignant (Grade III). Surgical resection is the treatment of choice, resulting in tumour growth control rates of about 75–90% at 10 years [1–3], and represents the definitive treatment for the majority of patients, especially those with benign tumours at favourable locations. However, there are a group of complex tumours, including those closely adjacent to the optic apparatus and encasing neurovascular structures, in which surgical resection entails a higher risk of complications. Conventional external beam radiation therapy (RT) has traditionally been used to improve local tumour control after incomplete resection of a benign meningioma arising at an unfavourable location, or after macroscopic surgical resection of atypical and malignant meningiomas. The reported control and survival rates following incomplete surgical resection and conventional RT are similar to those observed after complete resection, and better than those achieved with incomplete resection alone [4–7].

Over the past three decades, advances in radiological imaging and computer sciences, and their application in radiotherapy planning and delivery techniques, have led to more accurate and focused treatment, rendering many commonly held views of the "old" RT obsolete. The application of conventional RT to skull base meningiomas has evolved with the development of conformal and stereotactic techniques, which allow a steeper dose gradient between the target and the surrounding healthy tissue, thereby reducing the risk of long-term toxicity with respect to conventional RT. Currently available advanced radiation techniques include fractionated stereotactic radiotherapy (FSRT), intensity-modulated radiotherapy (IMRT), and stereotactic radiosurgery (SRS); these all allow a steeper dose gradient, resulting in more favourable dose distribution to the target than conventional RT.

In particular, SRS has progressively emerged as an accepted treatment option for both incompletely resected and intact skull base meningiomas, e.g. cavernous sinus meningiomas. According to the American College of Radiology (ACR) and American Society for Radiation Oncology (ASTRO) Practice Guidelines for the Performance of Stereotactic Radiosurgery, SRS

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is defined as "radiation therapy delivered via stereotactic guidance with an approximately 1 mm targeting accuracy to intracranial targets in 1–5 fractions" [8]. Several terms have been used interchangeably for SRS delivered in 2–5 fractions, including "fractionated SRS", "multi-fraction SRS", "multi-dose SRS", "multisession SRS", "hypofractionated SRS", and "hypofractionated stereotactic radiotherapy". SRT, on the other hand, refers to the treatment delivered in more than five fractions with the same level of accuracy.

Although SRS is virtually non-invasive, the treatment of tumours growing in the skull base region may carry a risk of radiation-induced toxicity ranging up to 15% [9]. Hence, the presence of structures that are highly sensitive to radiation, such as the brainstem and optic nerves and chiasm, represents the main concern in the use of SRS for skull base tumours, even though adverse effects induced by radiation appear to be less frequent in skull base meningiomas as compared to convexity or parasagittal tumours. Here we provide an overview of the efficacy and toxicity of modern radiation techniques for those tumours, with special regard to the emerging role of fractionated SRS.

9.1.1 Advanced Fractionated Radiation Techniques

For patients with brain tumours, fractionated techniques have evolved from conventional RT to more sophisticated conformal and stereotactic techniques, including FSRT, IMRT, and volumetric arc therapy (VMAT). To deliver 3D conformal RT, IMRT combines two advanced concepts: inverse treatment planning with optimization by computer and computer-controlled intensity modulation of the beams during dose delivery. VMAT entails IMRT delivery while the gantry is moving, using dynamic leaf motion, thereby allowing a reduction in treatment time. IMRT and VMAT result in better conformation of radiation to complex targets with concave regions, and a reduction in radiation doses to surrounding sensitive structures, such as the optic pathway and the brainstem, as compared to conventional RT. Indeed, the main advance exploited by stereotactic radiation techniques is improved immobilization using a precision mask system, with relocation accuracy in the region of 1–2 mm [10]. Treatment delivery is also improved by the use of a multileaf collimator (MLC) with smaller leaves (mini- or micro-MLC), which projects multiple (usually 4–8) fixed, shaped beams.

A summary of selected published series on FSRT and IMRT for skull base meningiomas is shown in Table 9.1. Using FSRT with doses of 50–58 Gy in 30–33 daily fractions, several large series, including patients with large complex-shaped meningioma, have reported local control rates of 90–100%, and overall survival times of up to 100% at 10 years [11]. Toxicity is reported in up to 12% of patients, and includes the development of radiation-induced optic neuropathy (RION), cranial nerve deficits, and hypopituitarism. Similar clinical outcomes have been observed in the few series reporting on IMRT, with low toxicity and a reported local control rate of 93–97% at a median follow-up of 19–36 months [12–14]. In a series of 506 patients with a skull base meningioma who received FSRT (n = 376) or IMRT (n = 131), Combs et al. [15] observed 10-year local control rates of 91% for benign meningiomas and 53% for high-risk meningiomas, with no significant differences between groups at a median follow-up of 107 months. The treatment was well tolerated. Quality of life was unchanged in 47.7% and improved in 37.5% of patients. In summary, published results support the efficacy and safety of both FSRT and IMRT for the treatment of skull base meningiomas of any size and/or involving neurovascular structures of the sellar and parasellar regions.

9.1.2 Stereotactic Radiosurgery (SRS)

SRS, which typically refers to the use of single-fraction SRS, has been extensively employed in the treatment of benign skull base meningiomas as an alternative treatment for lesions not amenable to surgical removal. The majority of published series report on the use of Gamma Knife

Table 9.1 Summary of selected published studies on fractionated radiotherapy of intracranial meningiomas

Authors	Patients (N)	Technique	Volume (mL)	Dose (Gy)	Follow-up (months)	Local control (%)	Late toxicity (%)
Goldsmith et al. (1994) [3]	117	CRT	NA	54	40	89 at 5 and 77 at 10 years	3.6
Maire et al. (1995) [65]	91	CRT	NA	52	40	94	6.5
Nutting et al. (1999) [66]	82	CRT	NA	55–60	41	92 at 5 and 83 at 10 years	14
Vendrely et al. (1999) [67]	156	CRT	NA	50	40	79 at 5 years	11.5
Mendenhall et al. (200 3) [68]	101	CRT	NA	54	64	92 at 10 and 15 years	8
Henzel et al. (2006) [48]	84	FSRT	11.1	56	30	100	NA
Tanzler et al. (2010) [69]	144	FSRT	NA	52.7	87	97 at 5 and 95 at 10 years	7
Minniti et al. (2011) [50]	52	FSRT	35.4	50	42	93 at 5 years	5.5
Slater et al. (2012) [70]	68	Proton beam	27.6	57	74	99 at 5 years	9
Weber et al. (2012) [71]	29	Proton beam	21.5	56	62	100 at 5 years	15.5
Solda et al. (2013) [72]	222	FSRT	12	50/55	43	100 at 5 and 10 years	4.5
Combs et al. (2013) [15]	507	FSRT/ IMRT	NA	57.6	107	91 at 10 years	1.8
Fokas et al. (2014) [73]	253	FSRT	14.4	55.8	50	93 at 5 and 87.5 at 10 years	3

CRT conventional radiation therapy, *FSRT* fractionated stereotactic radiation therapy, *IMRT* intensity-modulated radiation therapy, *NA* not assessed

(GK) SRS, in which patients are typically immobilized in a fixed frame, and radiation dose is prescribed to the 50% isodose, and delivered in a single session using multiple isocentre plans to optimize conformality and rapid dose fall-off.

SRS technology has recently evolved with the development of frameless SRS, in which patients are usually immobilized in a high-precision mask fixation system, and the treatment can now be delivered as either single-fraction SRS or multi-fraction SRS (2–5 fractions). Commonly used frameless SRS techniques include the image-guided robotic radiosurgery system CyberKnife (CK) and a modified linear accelerator (linac), e.g. Novalis, TrueBeam Stx. [16–19]. The CyberKnife (Accuray, Sunnyvale, CA) combines a mobile linear accelerator mounted on a robotic arm with an image-guided robotic system [17]. A variable number of 80–200 overlapping beams are delivered to the target, with the number and direction of beams being chosen and dose distribution analysed by a sophisticated computer optimization programme through an inverse planning process. With linac-based SRS, the dose is delivered throughout multiple fixed fields or arcs shaped with a micro-multileaf collimator (2.5–3.0 mm leaf), and conformity is improved by the use of IMRT and VMAT techniques. Further enhancements to frameless CK and linac-based SRS techniques include improved accuracy of patient repositioning via the use of either orthogonal X-rays or cone-beam computed tomography (CBCT) in-room imaging systems that are able to correct positioning errors by translating and rotating the treatment table in six directions with an accuracy of <0.5–1 mm [20, 21]. A few studies have shown a comparably high degree of dose conformity for irregularly shaped brain tumours planned with either GK, CK, or linac-based SRS [19, 22]. Indeed, despite several technical differences amongst GK, CK, and linac-based SRS, reported outcomes in terms of clinical

Table 9.2 Summary of selected published studies on stereotactic radiosurgery (SRS) of intracranial meningiomas

Authors	Patients (N)	SRS technique	Volume (mL)	Dose (Gy)	Follow-up (months)	Local control rates (%)	Late toxicity (%)
Kreil et al. (2005) [74]	200	GK	6.5	12	95	98 at 5 and 97 at 10 years	4.5
Kollova et al. (2007) [11]	368	GK	4.4	12.5	60	98 at 5 years	15.9
Feigl et al. (2007) [75]	214	GK	6.5	13.6	24	86.3 at 4 years	6.7
Kondziolka et al. (2008) [11]	972	GK	7.4	14	48	87 at 10 and 15 years	7.7
Colombo et al. (2009) [11]	199	CK	7.5	16–25[a]	30	96	3.5
Skeie et al. (2010) [76]	100	GK	11.1	13	32	90.4 at 5 and 10 years	6
Halasz et al. (2011) [77]	50	Proton beam	27.4	13	36	94 at 3 years	5.9
Pollock et al. (2012) [34]	251	GK	7.7	15.8	62.9	99.4 at 10 years	11 at 5 years
Santacroce et al. (2012) [29]	3768	GK	4.8	14	63	95 at 5 and 88 at 10 years	6.6
Starke et al. (2014) [78]	254	GK	NA	13	71	93 at 5 and 84 at 10 years	6.4
Ding et al. (2014) [79]	177	GK	3.6	13	47	93 at 5 and 77 at 10 years	9
Sheehan et al. (2014) [11]	763	GK	4.1	13	66.7	95 at 5 and 82 at 10 years	9.6
Marchetti et al. (2016) [11]	143	CK	11	21–25[b]	44	93 at 5 years	5.1

GK Gamma Knife, *CK* CyberKnife
[a]16–25 Gy delivered in 2–5 fractions in 150 patients
[b]21–25 Gy delivered in 3–5 fractions

stabilization, tumour growth control, and toxicity do not support the superiority of one technique over another; all display equivalent 5-year tumour control rates of about 90–95%, with comparably low rates of treatment-related complications [23] (Table 9.2).

9.1.3 Outcomes of Single-Fraction SRS

A summary of selected series of SRS for benign skull base meningiomas is shown in Table 9.2. In a large single-centre series of 972 patients, most with skull base meningiomas, who underwent GK SRS using a median marginal dose of 13 Gy at the University of Pittsburgh, Kondziolka et al. [24] reported tumour control rates of 93% at 5 years and 87% at 10 and 15 years. Tumour volumes decreased in 34%, remained stable in 60%, and increased in 6% of patients. With regard to the clinical scenario, there were no differences between the 384 patients who were treated with post-operative SRS and the 488 patients who received upfront SRS. In another large retrospective multicentric study, of 4565 consecutive patients harbouring 5300 benign meningiomas who received GK SRS, 5-year and 10-year progression-free survival (PFS) rates were 95.2% and 88.6%, respectively, at a median follow-up of 63 months. Tumour volumes decreased in 58%, remained unchanged in 34.5%, and increased in 7.5% of lesions, giving a control rate of 92.5%. In a meta-analysis of 2734 patients with brain meningiomas receiving GK or linac SRS, Pannullo et al. [25] found an equivalent tumour control of 89% in both, with similar outcomes in upfront versus post-operative SRS. In the few studies on CK SRS, the reported tumour control of 90–95% at 5 years is consistent with that observed following GK and linac-based SRS (Table 9.2).

SRS dose for skull base meningiomas is highly dependent upon the technique applied, the prescribed isodose, the proximity of organs at risk (OARs), and the size and configuration of the tumour. In most of the published studies, doses administered range between 12 and 18 Gy, with a progressive dose reduction over recent years. Using doses of 12–14 Gy, the rates of tumour control at 5 years remain in the same range as for higher doses, specifically 90–95% [26–28]. The rate of tumour shrinkage reported for the different studies varies, ranging from 16% to 69%, and tends to increase in patients with longer follow-up.

With regard to the factors predicting local tumour control, the majority of studies show no significant differences between patients who received SRS as an upfront treatment and those who received SRS after incompletely resected or recurrent meningiomas [24, 25, 29]. Neither patient age, sex, or neurological status nor the site of the meningioma significantly affected outcomes in most published series. However, larger meningiomas have been reported to be associated with worse long-term local control [24, 30]. For instance, DiBiase et al. [30] reported significantly higher 5-year tumour control in patients with tumour volumes of <10 mL than in those with larger tumours (92% vs. 68%, $p = 0.038$).

An important goal of SRS treatment is improving or maintaining neurological function. Variable improvements in neurological functions, including vision and ocular motility recovery, have been shown in 10–60% of patients. Furthermore, the rate of significant complications (transient or permanent) at doses of 13–14 Gy (as currently used in the majority of centres) is less than 8%, although a few series report a higher rate of long-term toxicity. Kondziolka et al. [24], for example, reported permanent neurological deficits in 9% of 972 patients at 10 and 15 years after GK SRS for intracranial meningioma. The morbidity rate for cavernous sinus meningiomas was 6.3%, and included optic neuropathy, sixth nerve palsy, and trigeminal neuropathy. In the series treated by Nicolato et al. [31] late complications occurred in 4.5% of patients, being transient in 80% of them, and similar complication rates have been reported in other large published series (Table 9.2). Further complications, such as epilepsy, internal carotid occlusion, and hypopituitarism, have rarely been reported (fewer than 1–2% of cases).

As regards radiation-induced toxicity, a clear dose–volume relationship has been reported for side effects [32–34], e.g. cranial nerve deficits and risk of radionecrosis, after SRS (Table 9.3). Specifically, for patients receiving SRS, the risk of clinically significant RION is 1–2% following doses below 8–10 Gy to the optic chiasm, while this percentage may significantly increase at higher doses [35–38]. Cranial neuropathies and brain necrosis are rarely reported when doses of less than 16 Gy are administered [39, 40]. The risk of developing a new tumour after SRS appears to be significantly less than the risk seen following fractionated RT [41]. However longer follow-ups are needed for definitive conclusions on this issue to be drawn. Factors related to a higher risk of delayed onset of hypopituitarism include maximum doses of 15 Gy delivered to the pituitary gland, and 7–10 Gy to the pituitary stalk [42–44]. Overall, the reported long-term toxicity of SRS at doses of 13–15 Gy is relatively low when radiation doses to organs at risk around the tumour are within the accepted maximum tolerance doses for normal brain structures (Table 9.3). Based on these data, limitations can be seen for complex masses adjacent to organs at risk, and with increasing size, while fractionated treatments are associated with a comparable dose profile, irrespective of tumour volume or diameter [28, 45–50].

9.1.4 Outcomes of Fractionated SRS

More recently, fractionated SRS (2–5 fractions by definition) has emerged as an effective treatment option for brain tumours. It aims to maintain the precision and accuracy of treatment delivery while exploiting the potential radiobiological advantage of fractionation in terms of tumour control and reduced toxicity [51–53]. Hence, it may represent an alternative treatment

Table 9.3 Summary of normal tissue constraints for conventional fractionation (2 Gy/fr) and stereotactic radiosurgery (SRS)

Organ	Type of radiation	Estimated toxicity rate and dose tolerance limits	Type of toxicity	References
Brain parenchyma	Conventional fractionation Single-fraction SRS Fractionated SRS	<3% for Dmax <60 Gy to whole brain <10% for Dmax 12 Gy to <10 mL brain volume <5% for Dmax 18 Gy/3fx to <26 mL brain volume	Symptomatic necrosis	[61, 64, 76, 103, 104]
Brainstem	Standard fractionation Single-fraction SRS Fractionated SRS	<5% for Dmax <54 Gy to whole organ <5% for Dmax <12.5 Gy to whole organ <3% for Dmax of 18 Gy/3fx or 26 Gy/5fx to <1 mL	Permanent cranial deficit or necrosis	[61, 103, 105]
Optic nerve/ chiasm	Standard fractionation Single-fraction SRS Fractionated SRS	<3% for Dmax <55 Gy to whole organ <3% for Dmax <8 Gy and <10% for Dmax 8–12 Gy <3% for Dmax of 19.5 Gy/3fx and 25 Gy/5fx	Optic neuropathy	[61, 103, 105–107]
Cochlea	Standard fractionation Single-fraction SRS Fractionated SRS	<15% for mean doses ≤45 Gy to whole organ <25% for Dmax ≤14 Gy <3% for Dmax of 20/3fx and 27.5 Gy/5fx	Hearing loss	[61, 103, 105]
Pituitary gland	Standard fractionation Single-fraction SRS	20–40% at 5 years for Dmax ≤45 Gy to whole gland 10–30% at 5 years for Dmax <15 Gy	Hypopituitarism	[70, 108, 109]
Medulla oblongata	Standard fractionation Single-fraction SRS Fractionated SRS	1% for Dmax 54 Gy, 10% for Dmax of 61 Gy 1% for Dmax 13 Gy 1% for Dmax 22.5 Gy/3fx and 30 Gy/5fx	Myelopathy	[61, 63, 103, 105]

D_{max} maximum dose

option to single-fraction SRS for large skull base meningiomas located in close proximity to critical anatomical structures such as the optic apparatus or the brainstem. Techniques commonly used to deliver fractionated SRS are the CK and modified linac. Recently, the latest version of GK (Icon) has enabled the use of a mask system for frameless SRS.

In a series of 199 benign intracranial meningiomas, including 157 skull base tumours, Colombo et al. [23] reported a 5-year control rate of 93.5%. Tumours larger than 8 mL and/or located close to critical structures were treated with fractionated SRS, typically 21 Gy in three fractions or 25 Gy in five fractions. The tumour volume decreased in 36 patients, remained unchanged in 148 patients, and increased in 7 patients. Clinical symptoms improved in 30 patients. Tumour control in 63 patients with tumour volume up to 65 mL treated via fractionated SRS was similar to that obtained in patients with smaller meningiomas receiving single-fraction SRS. Neurological deterioration, mainly represented by visual deficits, was observed in 4% of patients. In a series of 60 patients with skull base meningioma treated at the University of Pittsburgh via CK with a median dose of 17.5 Gy (range 6–27 Gy) delivered in 2–5 fractions (mainly 3 fractions), Bria et al. [54] observed 96% local control at a median follow-up of 16.1 months. A subjective improvement in the existing tumour-related symptoms occurred in 60% of patients, with grade 3 toxicity observed in one patient. In another large retrospective study of 143 patients, treated for perioptic meningioma using CK SRS at a dose of 15–25 Gy delivered in 3–5 fractions at Besta Hospital in Milan, Marchetti et al. [55] reported local control rates of 100%, 93%, and 90% after 3, 5, and 8 years, respectively. As regards neurological outcome, vision improved in 42% and worsened in 3.7% of patients. Similar clinical outcomes and low toxicity have been reported by other authors [56–60].

The late neurological toxicity of fractionated SRS at doses of 21–25 Gy in 3–5 fractions is reportedly low, with an apparent incidence of RION and other cranial nerve deficits affecting visual motility in fewer than 2–3% of patients [23, 54, 56, 58]. In a large retrospective cooperative study of 167 patients with large skull base meningioma in close proximity to the anterior optic pathways who received fractionated 25 Gy SRS in five fractions, at Besta Hospital in Milan and University of Messina, Italy, Marchetti et al. [58] reported visual deterioration in 3.7% of patients, all with pretreatment visual deficits, at a median follow-up time of 51 months. In another series of 46 patients with perioptic meningioma or pituitary adenoma within 2 mm from the optic apparatus who received 18–25 Gy CK SRS delivered in 2–5 sessions, Adler et al. [56] reported no visual impairments at a median follow-up of 49 months. Similar low toxicities have been reported in other series [23, 54]. Although these outcomes are reassuring in terms of the safety of hypofractionated schedules for skull base meningiomas, data on central nervous system (CNS) and organs at risk (OARs) tolerance doses to fractionated SRS, e.g. cranial nerve deficits, hypopituitarism, and impaired neurocognitive function rates, are relatively limited. For three-fraction and five-fraction SRS, a summary of dose–volume data and clinical risk estimates for OARs is presented in Table 9.3.

9.2 Comparison of Radiotherapy Techniques

Several published retrospective studies have suggested that SRT, given as either hypofractionation or conventional fractionation, may offer a better balance of efficacy and toxicity as compared with single-fraction SRS in patients with large brain tumours and/or tumours located in close proximity to critical brain structures [61–63]. For example, a recent systematic review has compared the safety and long-term efficacy of SRS and SRT in patients with intracranial meningiomas [63], based on an analysis of 12 retrospective studies on a total of 1736 patients who received SRS, fractionated SRS, or FSRT. The median tumour sizes at the time of treatment with SRS, fractionated SRS, or FSRT were 2.84 cm^3, 5.45 cm^3, and 12.75 cm^3, respectively. At a median follow-up of 36 months, SRS was associated with significantly worse radiographic tumour control and higher risk of neurological toxicity than SRT. However, between-group differences in progression-free survival (PFS) at 4–10 years were not statistically significant. In addition, a large retrospective Italian multicentre study compared the clinical outcomes in 341 patients with skull base meningiomas receiving FSRT, 59.4 Gy in 33 fractions, or fractionated CK SRS, 25 Gy, in 5 fractions [62]. At a median follow-up of 36 months, local control rates were 96.8% and 80.3% at 3 and 10 years, respectively, in patients treated via fractionated SRS, and 99% and 79.1% in those receiving FSRT. Grade 3 or higher toxicity rates were 0.5% and 2.1%, respectively. Moreover, in a German retrospective multicentric study of 927 patients treated using SRS or fractionated RT (FSRT or IMRT), at a median follow-up time of 79 months, Combs et al. (2018) [61] reported local control rates of 92% and 86% at 5 and years, respectively. There was no difference between fractionated RT and SRS groups in this regard. In patients receiving fractionated RT, local control rates were similar at doses of 54 Gy and 57.6 Gy. Side effects were below 5% in both groups, without any severe treatment-related complications.

Although data indicate that fractionated SRS may offer optimal balance between efficacy and respect for dose–volume constraints in relatively large skull base meningiomas, published results need to be interpreted with caution. Prospective data need to evaluate the dose–volume constraints for all sensitive sellar and parasellar structures, including the optic chiasm and cavernous sinus cranial nerves, as well as the brainstem, pituitary gland, and stalk, to limit potential long-term toxicity in SRS treatments. Moreover, prospective controlled trials need to evaluate the efficacy and toxicity of fractionated SRS over other radiation techniques.

9.3 Conclusions

The use of radiation to treat benign skull base meningiomas provides satisfactory results, with local control rates that rival those observed following complete surgical resection. Local control at 5 and 10 years after SRS or FSRT is reportedly greater than 80–90%, with comparable results amongst commonly used techniques such as GK, CK, and linac-based SRS. Typical doses are 13–15 Gy for single-fraction SRS, 21–25 Gy in 3 or 5 fractions, and 50–58 Gy in 30–33 daily fractions. When respecting these dose–volume constraints, the observed long-term toxicity, including the development of RION and other cranial nerve deficits, is low. As per the European Association of Neuro-Oncology (EANO) guidelines [64], single-fraction SRS is the recommended treatment for small meningiomas, while fractionated SRS and conventional fractionated RT should be preferred for larger lesions. In clinical practice, this means that fractionated SRS, usually three or five fractions, may represent a safer treatment option than single-fraction SRS for benign skull base meningiomas larger than 2.5–3 cm, or those in close proximity to the optic chiasm, when single doses to the optic apparatus exceed 8–10 Gy. For patients with very large lesions involving the optic apparatus, FSRT with 54–56 Gy in 30–33 daily fractions would be the recommended treatment option.

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10 Atypical and Anaplastic Meningiomas: Is There a Role for Stereotactic Radiosurgery?

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Meningiomas are the most common benign brain tumours (12–30% of primary brain tumours), with an annual incidence in the adult population of 2.4 cases/100,000, and a greater predominance in the female sex (female/male ratio 2:1–3:1). In contrast, they are much rarer in children and adolescents, with an incidence of 0.04–1.19/100,000 [1]. That being said, many small meningiomas remain undiscovered throughout life, and it therefore seems likely that their prevalence is actually higher; in fact, incidental findings in autopsy studies seem to indicate that it may be present in 1.4–3% of the population [2]. Typically, meningiomas are slow-growing, benign tumours adhering to the dura mater that originate from neoplastic arachnoid cells. Meningiomas may occur sporadically, or be associated with genetic diseases. Sporadic meningiomas may arise at multiple sites in 10% of cases [3]. In familial forms, on the other hand, the probability of developing multiple meningiomas is higher, and such neoplasms may be synchronous with other tumours of the central nervous system or other organs or systems, such as neurofibromatosis 2 (NF2) [4], or other pathologies with hereditary non-NF2 meningiomas, such as Li-Fraumeni, Turcot, Von Hippel-Lindau and MEN 1 [5].

The WHO classification (last edition 2016) divides meningiomas into three grades based on their degree of malignancy (WHO Grades I, II and III) [6]. These grades are in turn divided into different histological subtypes as a function of the tumour's histological, anatomical and pathological characteristics. *Grade I* meningiomas are the most frequent, and are histologically characterized by fewer than 4 mitoses (per 10 high-power fields (HPF)). *Grade II* meningiomas are characterized by at least one of the following features: (1) moderate mitotic index (4–19 mitoses per 10 HPF); (2) brain invasion; and (3) at least three of the following: necrosis, prominent nucleoli, high cellularity, small cells and/or altered cell architecture. Finally, *Grade III* are the most aggressive, malignant and rare variant of meningiomas (fewer than 3% of new meningioma diagnoses); they have 20 or more mitoses per 10 HPF, and are characterized predominantly by rhabdoid or papillary morphology. In WHO III meningiomas, occasional metastatic spread outside the

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central nervous system has been reported. In these cases, the organs most affected by metastases are the lung, pleura, skeleton and liver, among others [8]. The biological behaviour and nature of meningiomas are further defined by the discovery of molecular alterations associated with a less favourable course, which, together with WHO grading, enables patients at high risk of progression or recurrence to be identified.

Note that previous WHO classifications (2000 and 2007) also allowed for brain invasion in Grade I [7]. However, the tendency of these brain-invading meningiomas to relapse with a frequency quite similar to that of meningiomas considered atypical at the time had already been described [7], leading to the inclusion of brain invasion as a unique inclusion criterion for Grade II. The new WHO classification therefore revealed that in the past the real number of Grade II meningiomas was underestimated (20–35% of current cases versus 3–4% when using the previous classification system), and consequently that the cases documented before 2016 are inevitably limited by such bias. Finally, Grade III represents the most aggressive, malignant and rare variant of meningiomas (less than 3% of new meningioma diagnoses); they present 20 or more mitoses per 10 HPF and are characterized by predominant rhabdoid or papillary morphology. Occasional metastatic dissemination outside the central nervous system is reported in WHO Grade III meningiomas. In these cases, the organs most affected by metastatic dissemination are lung, pleura, skeleton, liver or other organs [8]. The biological behaviour and nature of meningiomas are further defined by the discovery of molecular alterations associated with less favourable courses, which, together with grading, allows the identification of patients at high risk of progression or relapse.

10.1 Who Grade I Meningiomas

Asymptomatic and small meningiomas grow very slowly or do not grow at all. In these cases, treatment is often deferred in favour of neuroradiological monitoring (using MRI) to document the rate of any growth, which is generally unpredictable [9, 10]. If treatment is indicated, surgery is often the only treatment necessary, but this option is not always without complications or sequelae, which may sometimes not be sufficiently taken into consideration [11]. It is important to take into account the tumour size and proximity to critical organs; these elements can suggest that timely radiosurgical treatment may be warranted [12].

The treatment of meningiomas that demonstrate the evidence of growth or symptoms (epileptic seizures, neurological deficits, behavioural alterations) will depend on the features of both the patient (life expectancy, general conditions, comorbidity, neurological state) and the tumour itself (volume, location, relationship with vascular and nerve structures, which may have been wrapped by the tumour). In symptomatic patients, when the tumour's size and location (convexity, falx, tentorium) permit its almost complete removal with reduced surgical morbidity (less than 2%), surgery is curative, and disease control at 15 years of age exceeds 95%. Surgery can be supported by images (neuronavigation, intraoperative CT or MRI, intraoperative fluorescein angiography), or neurophysiological monitoring.

In most cases, Grade I meningiomas can be treated effectively by surgery, but some grow very close to critical structures, such as blood vessels, nerves or brainstem (skull base meningiomas), enveloping them, so they cannot be treated using surgery alone, as resection must be partial or subtotal to preserve the functional integrity of the patient. One of the possible alternatives to surgical treatment of meningiomas is radiotherapy, which includes single stereotactic radiosurgery (SRS), hypo-fractionated radiosurgery (fSRS), fractionated stereotactic radiotherapy (FSRT) and fractionated conventional radiotherapy (EBRT) [13].

The first radiosurgical treatment was reported by Backlund in 1971, and published by Leksell in 1983 [14]. Later, the development of imaging technology, and the simultaneous diffusion of radiosurgery techniques, furthered widespread application of this practice. Since the early 1990s, the role of radiosurgery in the treatment of meningiomas has become increasingly established, also

as a primary treatment alternative, especially in the elderly and for tumours in critical areas. A comparison with the mortality, morbidity and post-operative recurrence in surgical cases, and the higher quality of life in patients treated with radiosurgery, has significantly changed the therapeutic criteria in these pathologies. A classic example is the treatment of skull base meningiomas, especially of the cavernous sinus and posterior fossa, for which there is greater indication to radiosurgery, although surgery may be used for tumour mass reduction purposes.

To date, hundreds of thousands of meningiomas have been treated by radiosurgery [15]. The number of treatments performed with Gamma Knife is known, but thousands of other cases are treated using other techniques (linac, CyberKnife, proton therapy). Gamma Knife in particular is characterized by extreme mechanical precision, lack of movement of components, lower exposure of the rest of the body to radiation and a high dose gradient. The biological characteristics of slow-growing meningiomas imply a response to radiotherapy treatments likely analogous to that of tissues with a low value of the α/β ratio in the linear quadratic model [16]. This provides a favourable balance between therapeutic effect and toxicity to the surrounding tissues, even with extreme hypo-fractionation schemes or in a single dose. The results in terms of treatment effectiveness and morbidity are excellent: local tumour control (LTC) and progression-free survival are around 86.2–97.9%, according to a study by Pollock et al., in which Gamma Knife is proposed as a first-line therapy for medium–small meningiomas [17]. Indeed, the recent introduction of volume-staging techniques and hypofractionation has broadened its indication to the treatment of meningiomas, including voluminous lesions, close to critical structures.

10.2 WHO Grade II Meningiomas

These are rarer and more aggressive variants than Grade I meningiomas, and have a tendency towards local recidivism. As mentioned above, most of the cases related to WHO Grade II meningiomas were reported prior to 2016, and were therefore diagnosed according to the previous classification system. Unfortunately, there are no clear radiological criteria for distinguishing a WHO Grade I meningioma from a WHO Grade II. Grade II, or atypical meningiomas are often initially indistinguishable from Grade I, but should be treated, whenever possible, by radical surgery (Simpson I). Subsequently, Grade II meningiomas have a greater tendency to recurrence (20% at 5 years), and this percentage is inversely proportional to the extent of resection—at 5 years the disease remains progression free in 59–90% after radical surgery (Simpson I, II or III), but drops to 30–70% after subtotal resection (STR) [18, 19]. All literature data seem to lead to the conclusion that as much of the tumour as possible should be removed (Simpson I, II or III) (although not at the expense of patient morbidity) in order to achieve the best possible control over tumour recurrence and the final outcome for the patient [20] (class III and IV evidence). Nonetheless, unlike in Grade I, there is no evidence that Simpson I resection leads to a better outcome than Simpson Grade II or III [21].

In the case of incomplete resection (STR) of Grade II meningiomas, an adjuvant radiotherapy treatment (stereotactic radiosurgery if the tumour volume is limited or fractionated radiotherapy on the tumour residue) should be considered. Published in 2017, a systematic analysis of 619 patients suffering from atypical meningioma residues reports an average tumour recurrence and 5-year survival rates of 53.5% and 74.9%, respectively, in the group of patients treated with radiosurgery, as compared to 89.8% and 89.8% in untreated patients [22]. While the role of adjuvant radiotherapy appears to receive unanimous confirmation for subtotal resection of Grade II, in cases of complete removal (gross total resection, GTR) its utility is still being studied in trials (RTOG 0539, EORTC22042) [23]. In 2018, the first results of the randomized prospective trial RTOG 0539, started in 2015 with the aim of evaluating the 3-year PFS of patients after GTR and adjuvant RT of Grade II meningiomas, were published. The case studies of the 52 patients revealed that the use of adjuvant RT (54 Gy in 30 frac-

tions) led to a 3-year PFS of 93.8% (as compared to 70% following surgery alone) with an overall survival (OS) rate of 96%, and a minimal occurrence of adverse events [24]. However, other recent retrospective studies have demonstrated no increase in the 5-year survival of patients given GTR and adjuvant RT (81.5% GTR without RT vs. 86.9% GTR + RT; $p = 0.339$) [25]; other studies seem to report an increase in PFS, but no significant differences in OS in patients given adjuvant RT [26].

As with microsurgery, stereotactic radiosurgery (SRS) control of Grade II meningiomas is much less certain. Studies of SRS on Grade II meningiomas mainly involve cases of STR or tumour relapses. Some studies, though mostly retrospective, on limited case series and prior to the new WHO 2016 classification system, report 3-year disease control of 70% and OS of 83.4% [27]. In the published cases it emerges that the peripheral dose, target volume and timing of treatment after surgery are key elements that influence disease control. Kano et al., for example, reported 29.4% 5-year PFS in meningiomas treated with less than 20 Gy, as compared to 68% in those treated with 20 Gy [28]. Other studies did not find this difference, however, reporting a 5-year LCT of 68%, regardless of the dose used (13–36 Gy) [29]. Treatment time also affects outcome; Choi showed increased LTC when SRS was performed within 6 months of surgery, as compared to SRS performed later or only at the time of evidence of progression [30].

Very few prospective studies on the effectiveness of Gamma Knife treatment (GKSRS) on WHO Grade II meningiomas have been conducted since 2016. One of the main case series, published in February 2017, was that of the US Rafaat group; in 97 patients with a histological diagnosis of WHO Grade II meningioma undergoing GKSRS, the 3-year LTC was found to be 68.9%, and at 5 years it was 55.7%. The respective OS was 88.6% and 81.1% at these time points, and the percentage of adverse events was less than 2% [31].

Fractionated SRS treatments have also been used in Grade II meningiomas, often for large volumes or locations close to critical organs. Similar to Grade I cases, this reduces the risk of oedema and side effects, and provides good disease control (88% at 40 months). [32] At present, however, publications on fractionated SRS in atypical meningiomas are scarce, and existing results require further confirmation via future studies.

10.3 WHO Grade III Meningiomas

Grade III (anaplastic) meningiomas tend to relapse quickly even after surgery, and can also metastasize to other sites in the central nervous system or other parts of the body. The utility of adjuvant radiotherapy in Grade III meningiomas is undoubted, and represents a solid recommendation, with both GTR and STR. The effect is beneficial to both OS and local control of relapse [18], and is directly related to the dose administered [33] (class III evidence). Unlike in Grades I and II, the indication for conventional, normally fractionated RT as an adjuvant treatment is well established in Grade III meningiomas. SRS alone is not, however, associated with a very low PFS at 15 months, roughly 17% [34].

In our centre we usually propose a protocol that provides for GKSRS to treat residual/recurrent Grade II meningiomas of suitable size and without mass effect or related symptomatology. In the case of anaplastic meningiomas, we administer a radiosurgery boost in cases of evident disease, and fractionated treatment on the surgical bed. Naturally, treatment choices are also guided by the general conditions of the patient, overall volume to be irradiated and findings from an in-depth interview aimed at highlighting any complications of treatments, even in the long term.

10.3.1 Clinical Case

For exemplative purposes, we here present a case dealt with at our centre (the Fondazione Poliambulanza di Brescia). The patient in question was a 52-year-old man who first underwent surgery to remove an atypical meningioma

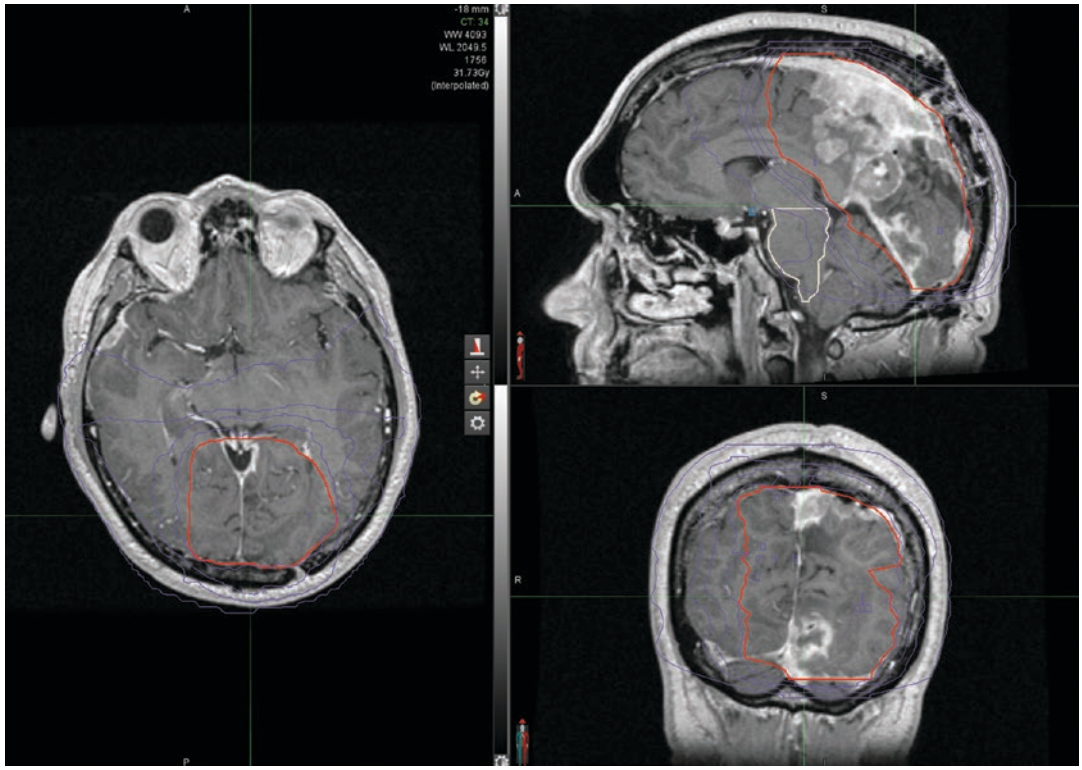

Fig. 10.1 External beam radiation therapy (30.6 Gy in 17 fractions) for a large recurrent anaplastic meningioma. Red: clinical target volume; purple: 30/25/20/10 Gy isodose lines

from the falx in 2010. In January and February 2011, September 2014 and February 2016 he received radiosurgical treatments with Gamma Knife due to recurrence of the disease. In July 2017, his tumour relapsed and he opted for surgical treatment. He was therefore subjected to surgery to remove a mass affecting the posterior third of the left occipital portion of the falx; histology revealed WHO Grade III anaplastic meningioma, i.e. malignant. Indeed, from this point on the disease began to progress quickly and aggressively, as can be seen from the subsequent treatment regimen, briefly outlined below:

- In September 2017, Gamma Knife Icon treatment in frame mode on tentorially based meningioma (16 Gy at 50%)
- From 2nd to 6th October 2017, frameless Gamma Knife Icon (27.5 Gy, 50% isodose) to the posterior third of the falx (post-surgical recurrence after 15 months)
- On 4th October 2017, single-session frameless Gamma Knife Icon (16 Gy, 50% isodose) for an additional meningiomatous nodule at the right temporal site
- From 6th to 9th February 2018, frameless Gamma Knife Icon (20 Gy in 4 sessions, 50% isodose) on tumour progression at the anterior, lower, posterior and lateral ends, towards the convexity of the meningioma of the posterior third of the falx treated in October 2017
- In March 2018, external beam radiation therapy (EBRT) to mass (30.6 Gy in 17 fractions, with intentionally wide margin), including four areas of progression (left posterior parietal and three sites on the falx); volumetric modulated arc technique (VMAT) with 6 MV photons (Fig. 10.1)
- In August 2018, surgical resection of left subgaleal parasagittal meningioma nodule (anaplastic) in light of the rapid growth observed over the course of the previous few months

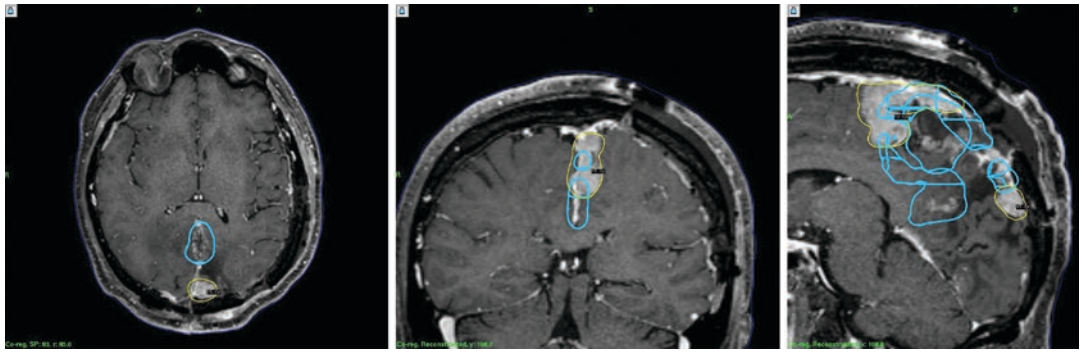

Fig. 10.2 Gamma Knife plan with isodoses of different treatments. Yellow: current treatment; light blue: previous treatments

In October 2018, MRI revealed a new recurrence of the disease in the parietal site, in this case involving also contralateral side, and new growth of the subgaleal nodule. Surgery plus Gamma Knife was scheduled, and on 26th October 2018 the patient underwent surgical exeresis of parieto-temporal convexity meningioma and removal of the subcutaneous nodule. Then, on 30th October 2018 the patient underwent frameless Gamma Knife Icon treatment on two additional meningioma nodules on the falx (15 Gy, 50% isodose) (Fig. 10.2). He was then hospitalized at the rehabilitation department of our hospital for functional recovery (right hemiparesis).

After discharge the patient was sent to our Oncology Centre for assessment, and experimental therapy with hydroxycarbamide was prescribed. However, in February 2019, due to urinary retention occurring after an accidental fall, the patient presented to our Emergency Room; among the various tests administered, total-body CT scans were performed, which revealed new-onset ileal and mediastinal adenopathy. It was therefore decided to hospitalize the patient for further testing. Upon bronchoscopy, there were endoscopic signs of right interlobar adenopathy. Transbronchial lymph node aspiration revealed the presence of atypical cells compatible with the meningioma. Given the extent of the disease, no further treatment was prescribed, and death occurred after a few days.

10.4 Conclusions

Grade II and III meningiomas, the incidence of which is also increasing following the revision of the WHO classification, represent a complex pathology that requires a multidisciplinary therapeutic approach, in which stereotactic radiosurgery has a significant role. However, only randomized prospective studies will make it possible to establish the exact therapeutic pathway.

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CyberKnife Treatment of Atypical Meningiomas (GII)

11

Zeno Perini, Leopoldo S. Casentini, and Umberto Fornezza

11.1 Introduction

11.1.1 Stereotactic Radiosurgery and the CyberKnife

Stereotactic radiosurgery (SRS) involves the concentration of a high dose of radiation from an external source onto a target inside the skull or spine of known location, size and shape. Since the radiation is focussed on the diseased tissue via a kind of "crossfire", exposure to nearby healthy tissues is minimized, and this type of radiosurgery can be classified as minimally invasive surgery [1, 2].

CyberKnife is a radiosurgical device consisting of a CT image guidance system—which enables precise location of the target—and a robotic apparatus—capable of moving around the patient—fitted with a linear accelerator that emits X radiation to be directed onto the target. Precise targeting is achieved via an image comparison system. Specifically, the shape and location of the lesion are reconstructed in 3D based on the processing of CT images, MRI and/or angiography. The treatment plan can thereby be individualized to the target lesion, and the relevant information stored in the radiosurgical system computer. In the room where the CyberKnife system is located, the bunker, two radiological devices (the "eyes" of the machine) control the position of the target by comparing it from time to time with the location, shape and size information previously entered into the system [1–3].

The bony structures of the skull or skeleton close to the lesion to be treated provide the radiological reference points that allow the accuracy of the procedure to be controlled in real time. The position of the target with respect to these reference points is then maintained by detecting and correcting any movements away from the initial location due to involuntary movements [1, 3].

The main advantages in using CyberKnife are the following:

1. The stereotactic "frame", i.e. the system of fixing the head to the treatment couch. With CyberKnife, this takes place atraumatically, with the use of thermoplastic mask individualized to the patient's skull in the pretreatment phase.
2. The possibility of performing hypofractionated treatments and, consequently, the possibility of treating lesions of large dimensions initially considered not suitable for radiosurgical treatment.

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3. The possibility to adapt CyberKnife treatments for spine and spinal cord (metastases, spinal neurinomas, spinal arteriovenous malformations, etc.) and other body districts (lung, pancreas, lymph nodes, etc.) [1–3].

The main disadvantages of CyberKnife are linked to the CT image guidance system—the gold standard for the brain is MRI with contrast. That being said, recent improvements/updates in both exam techniques (latest generation HD CT and 3 T MRI) and image fusion software have allowed us to improve image superimposition and consequently treatment planning; possible margins of error are now submillimetric [1, 3].

11.1.2 Meningiomas

Meningiomas are the most common benign intracranial (and spinal) tumours in the general population. They have an incidence of about 7/100,000 inhabitants [4, 5], with a higher prevalence within the female population. They originate from arachnoid cells, in particular the cells of the arachnoid villi—structures responsible for the resorption of cerebrospinal fluid that are mostly found at the level of the upper sagittal sinus, cavernous sinus, tuberculum sellae, cribriform plate, foramen magnum and torcular Herophili. Surgery is the treatment of choice for most such tumours, when symptomatic, and often proves to be as decisive as it is radical. In fact, these tumours are generally globose, slow growing, well encapsulated and attached to the hard tissues, able to compress the underlying cerebral parenchyma but not to invade it. Hence, such tumours are generally "isolated", making them more readily removed via surgery.

Nonetheless, some lesions are located in areas of the skull that are difficult to access surgically (areas such as the cavernous sinus, the petrous temporal bone or the clivus), as this would expose the patient to a high risk of morbidity and mortality. Moreover, individuals suffering from this type of pathology are often elderly and therefore subject to a higher degree of anaesthesia- and surgery-related risk.

According to the 2007 WHO classification, there are three main grades:

1. **Benign meningioma (Grade I):** a non-malignant tumour that, if radically removed, generally heals completely, with only sporadic recurrence; this type of tumour can be divided into many small histopathological subgroups (meningothelial, psammomatous, angioblastic, cystic, transitional and fibrous).
2. **Atypical meningioma (Grade II):** a tumour without clear and complete malignant features (1–2 mitoses per field and a mitotic index of more than 3%) or remote metastatic capability, but potentially appearing in multiple locations within the skull and associated with a high risk of relapse. Surgery is the treatment of choice, and it is still the subject of debate whether radiosurgery or radiotherapy should be recommended as salvage or adjuvant therapy.
3. **Anaplastic meningioma (Grade III):** also called papillary or sarcomatous meningioma; this type of tumour invades the cortex and is characterized by a high mitotic index; it may rapidly relapse despite radical macroscopic resection. Its frequent mitosis and papillary structure are prognostic indices of malignancy. Metastases beyond the central nervous system are rare but possible, and the most frequently affected organs are the lungs, lymph nodes, liver and heart [5, 6].

Currently, radiosurgery is considered as the first-line option only in meningioma cases in which surgery contraindicates due, for example, to age and/or significant comorbidities (e.g. severe heart disease), or when the patient refuses surgery [5]. It is, however, helpful post-surgery, for example to target residual tumour. Currently, in this type of application radiosurgery, with either X-rays or gamma rays, is considered a more than satisfactory means of achieving tumour control (especially in Grade I meningiomas), with no significant differences between methodologies [5, 6].

However, there is a considerable gap between the excellent results that can be obtained in the

Table 11.1 Number of meningioma patients treated using CyberKnife at Vicenza CyberKnife Centre from 30 January 2003 to 31 December 2018

Histological grading:	Grade I	Grade II	Grade III
No. of patients treated:	784	102	4

treatment of Grade I meningiomas (with tumour control greater than 90–92% at 5 years after radiosurgical treatment) [4, 6], and rather less encouraging outcomes achieved via the irradiation of Grade II, or atypical, meningiomas. Even worse are those achieved in Grade III tumours, which, in our personal experience (CyberKnife Centre, Vicenza), are very limited (Table 11.1).

In this chapter a simple retrospective observational study of our experience of treating atypical meningiomas is reported, with particular focus on tumour control windows.

11.2 Materials and Methods

A total of 890 patients were treated for intracranial meningioma from January 2003 to December 2018 via CyberKnife® (Accuray Inc., Sunnyvale, CA); 102 had Grade II meningioma and 4 had Grade III. Of the 102 Grade II patients included in the study (45 females and 57 males), 74 had previously undergone surgery (on average 77 months before radiosurgery), 25 surgery and radiotherapy and 3 radiotherapy alone. Thirty-nine (38%) had more than one tumour; specifically, 14 (14%) had two and 25 (1/4 of the cohort) in multiple locations. A total of 182 lesions were treated. However, due to objective difficulties concerning follow-up, 102 injuries considered in the first instance were examined.

The patient age at the time of treatment was between 25 and 82 years (average 60.3) and the tumours were mainly located at frontal and anterior skull base sites; of these 34 lesions, 21 were purely frontal, and 13 at ethmoid, sphenoid, anterior clinoid or frontal parasagittal sites. There were also 30 temporal lobe (16) and mid cranial fossa (11) tumours, for example at the cavernous sinus or petrous bone; 30 parietal tumours, 11 of which at parasagittal sites (middle or posterior site of the sinus); and very few tumours at occipital (4) or posterior cranial fossa (4) sites, including the clivus, cerebellar pontine angle and torcular Herophili.

Over the following months, 13 tumours had to be retreated: two patients underwent two retreatments and one patient three retreatments, the former 24 months after the first radiosurgery and the latter after 180 months.

Neurological examination of patients mainly showed paresis of individual limbs or hemiparesis (24/102), epilepsy (7/102) and visual deficit (4/102) with amaurosis; the rest had fifth and seventh cranial nerve deficit and ocular movement deficit, and one had total deafness. Of the 24 patients with paresis/hemiparesis, this had appeared post-intervention in 11 of them, while epilepsy could be considered iatrogenic in only 2 cases.

The treated tumour volumes ranged from 70 to 45,103 mm^3 (average 4459 mm^3), and the maximum treatment doses delivered ranged from 15 to 28 Gy (average 22.71 Gy); isodoses were between 10.5 and 21 Gy (average 17.63 Gy). In particular, a maximum dose of 25 Gy was delivered in 42 patients (40%), while a maximum of 22.5 Gy was used on 22 patients, and a maximum of less than 20 Gy was delivered to 14 patients (Fig. 11.1). The isodose distribution was as follows: 20 Gy in 33 patients, 18 Gy in 25 and 18 Gy or less in 27.

As far as fractionation is concerned, most patients, 72/102, received several fractions, while 30 underwent a single treatment session (Fig. 11.2). No fraction exceeded 35–40 min.

The follow-up programme we implemented consisted of a first outpatient check-up with contrast brain MRI about 3–4 months after treatment, and two later check-ups after roughly 4-month intervals from each other. If the radiosurgical course was deemed regular (stable tumour size and clinical conditions), subsequent check-ups were carried out at roughly 6-month intervals up to 36 months, or a little more, from radiosurgical treatment. From then on, check-up intervals were further prolonged (roughly every 9 months), being scheduled annually from 60 months after treatment. The follow-up to this study was 3461 months in total, with an average of 34 months; 51 patients (50%) had follow-ups of 24 months or more, while 18 of them did not show up for the scheduled check-ups.

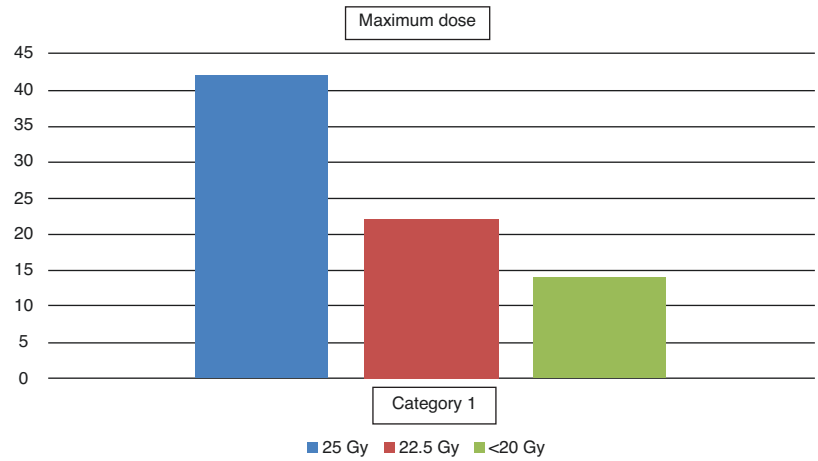

Fig. 11.1 Maximum dose distributed. Most patients (70%) were not given less than 22.5 Gy

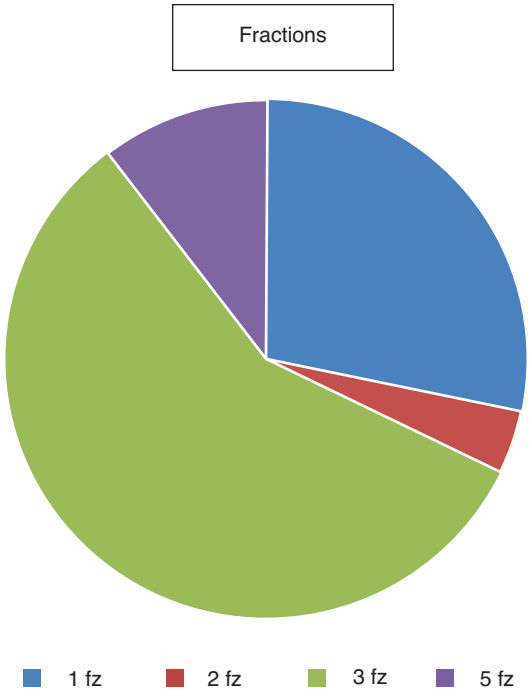

Fig. 11.2 Treatment fractionation summary. Note that most patients had fractionated treatment and none underwent four fractions. *Fz* fraction(s)

11.3 Results

Out of 102 patients, 36 experienced disease progression after CyberKnife®—the former only 3 months after treatment and the latter at 203 months; 17 underwent further surgery, 3 underwent radiotherapy or radiosurgery and 1 had both. Tumour stability was observed in 45 patients, while slight regression was seen in 3. Eighteen patients were lost to follow-up (see above).

Table 11.2 Outcomes in all patients and those with a follow-up of 24 months or more

Results	Stable tumour	Tumour progression	Tumour regression
Total patients	45	36	3
Patients with follow-up of >24 months	26	23	2

With regard to the patients who showed disease progression, this was evidenced on average about 43 months after radiosurgical treatment. Of the 51 patients with a follow-up of 24 months or more, 23 (45%) showed disease progression, while tumour size remained stable in 26 (51%) and regressed slightly in 2 (4%) (Table 11.2).

As regards the maximum doses, 42/102 patients were given 25 Gy, of which 27 had a follow-up of 24 months or more (Fig. 11.3); 11 of these 27 patients (41%) showed tumour progression, while 14/27 (52%) stable tumour; 2 showed a slight regression. Outcomes were fairly similar for the 22 patients who received a maximum dose of 22.5 Gy, of which 10 had a follow-up of 24 months or more (Fig. 11.4); 5/10 (50%) displayed disease progression while the other 5 showed stabilization; no cases of regression were noted.

From a clinical perspective, in three patients there was a slight worsening of a pretreatment epileptic syndrome, which required a simple

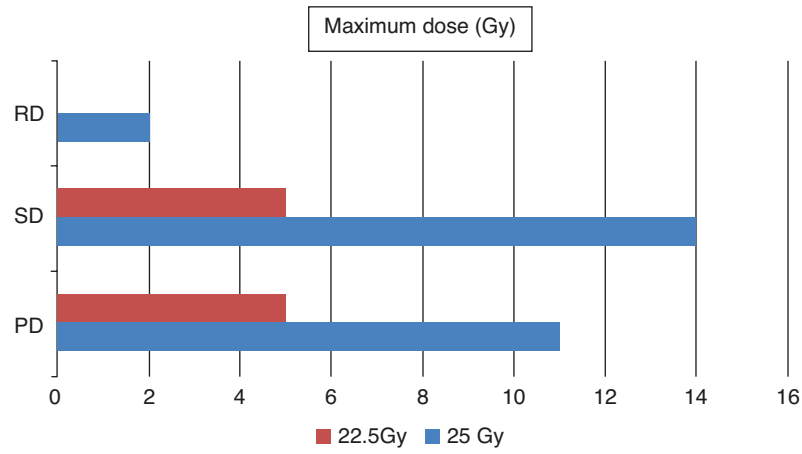

Fig. 11.3 Disease stabilization by maximum dose across the entire sample and those with follow-up >24 months

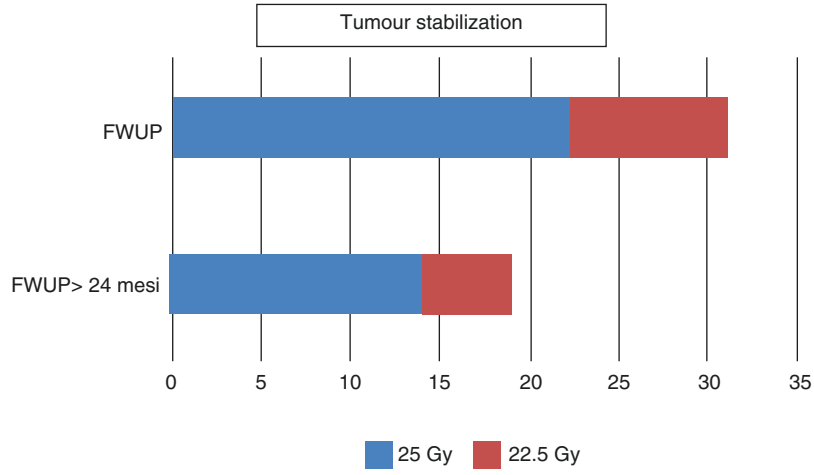

Fig. 11.4 Outcomes by maximum dose in patients with follow-up of 24 months or more. The only two cases of regression observed were in the 25 Gy group. *RD* disease regression, *SD* stable disease, *PD* disease progression

adaptation of the anticonvulsant therapy already being administered. There were no cases of radionecrosis observed upon either neuroradiology or clinical exam.

11.4 Discussion

The results of this study are certainly not easy to interpret. It would appear that many of the radiosurgical parameters generally used in current treatment protocols, including the maximum dose and isodose, have little effect on local tumour control. In fact, there was little difference in outcomes between patients who received a maximum dose of 25 Gys and those who were given 22.5 Gy, for example (Fig. 11.3); likewise, outcomes were similar at isodoses of 18 and 20 Gy.

The importance of dose selection is, however, stated both in a recent article by Valery et al. (2016) and a previous one by Sethi et al. (2015); both studies involved Gamma Knife treatment, and both argued that such tumours should be treated with a minimum dose of not less than 12 Gy (Valery et al.) for there to be a desirable tumour control, even though no statistically significant relationship ($p = 0.09$) was found between dose and tumour control [7]. Sethi et al. also stated that for Grade II and III meningiomas, the dose should be between 16 and 20 Gy, nearby critical structures permitting [8].

The only difference between treatment protocol outcomes we observed in patients with a fol-

low-up of 24 months or more was more frequent disease progression with dose hypofractionation than with single-session treatment. In fact, out of 50 patients with follow-up of >24 months, there were nine cases of disease progression when a single dose was administered, whereas this number doubled in patients given multiple fractions (18/50). When comparing these figures, however, it is important to take into account the difference in tumour volume; specifically, hypofractionation enables treatment of volumes that for obvious radiobiological reasons cannot be addressed in a single treatment session.

That being said, when considering the issue from the perspective of tumour volumes, these were very similar in tumour stabilization and progression groups both across our entire sample (4300 vs. 4200 mm^3), and when only patients with follow-up of over 24 months were considered (3552 vs. 3763 mm^3). This would seem to suggest that tumour volume does not have a fundamental influence on the course of the disease. However, this contrasts with the conclusions of Kaprealian et al. (2016), who argue, after univariate analysis, that parameters such as large tumour volume, as well as high degree of malignancy and SRS setting, are associated with poor disease control at 5 years [9].

We did find a statistical difference in outcomes when dividing our sample on the basis of prior treatment. Indeed, in the 100 patients who received prior surgery, in some cases with adjuvant radiotherapy (25 cases), 35 showed disease progression while 46 displayed tumour stability. That being said, this difference was reduced when considering only cases with a follow-up of 24 months or more (27/51 stability vs. 24/51 progression). In more detail, of the 25 patients who had undergone prior surgery and adjuvant radiotherapy, 11 had a follow-up of 24 months or more; 6 of these displayed tumour stability and 5 disease progression.

On the alleged importance and usefulness of adjuvant radiosurgery in the treatment of these diseases, two recently published studies are of particular interest. The first, by Lagman et al. (2017), demonstrated how radiosurgery in the adjuvant phase can provide valuable assistance in the 5-year control of such tumours, and suggested that it should be included in the treatment guidelines [10]. The second, published by Kessler et al. (2017), supports this recommendation; after a careful review of the international literature on Grade II and III meningiomas, they determined that there are clinical benefits from using adjuvant chemotherapy agents in patients presenting systemic metastases [11]. However, in contrast to these two papers, Messerer et al. (2016) hypothesized that adjuvant radiosurgery or radiotherapy should only be used in selected cases, and that target therapy aimed at altering the molecular make-up of the lesion may instead be the key to revolutionizing the prognosis of these patients [12].

11.5 Conclusions

While excellent responses have so far been obtained in terms of disease control against Grade I meningiomas, Grades II and III remain challenging and difficult to treat [13]. The results obtained in this field so far raise the reasonable question of whether it is not the nature of the disease itself that determines its course, rather than the current treatment protocols in use [14, 15], and, as Messerer et al. [12] have claimed, the real target to be pursued to treat these diseases may be found at the molecular level [12, 15–18].

That being said, the use of radiosurgery in the adjuvant phase would seem to yield encouraging results in terms of tumour control. In fact, our results show that only a quarter of patients had undergone adjuvant radiosurgery or radiotherapy, but that outcomes in these patients were at least partially encouraging. It therefore seems reasonable to increase efforts to carry out new studies, possibly randomized, on the usefulness and effectiveness of radiosurgery in the adjuvant phase [19, 20]. Some of these studies are already underway (ROAM/EORTC-1308 trial) [20], but others are, and will be, necessary in the years to come in order to hopefully obtain a better prognosis for these patients.

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12 SRS and Microsurgery: Antagonistic or Complementary in the Treatment of Meningiomas?

A Single Team Experience

Enrico D. F. Motti, Enrico Giugni, Laura Ventrella, and Federico Rampa

Abbreviations

GK	Gamma Knife
MS	Neuro-microsurgery
pca	Pontocerebellar angle
RT	Conventional radiotherapy
SRS	Stereotactic radiosurgery
W&S	Wait-and-see

12.1 Surgical Removal vs. Gamma Knife in Meningiomas

Following the advances in treatment and imaging over the last quarter of a century, the choice between surgical removal and SRS for the treatment of meningiomas is still "the subject of countless seminars, webinars, book chapters, and informal discussions" as highlighted by Sughrue et al. [1] in their analysis of the daily decision-making by neurosurgeons who practice in meningiomas.

In their paper the authors reflect that most neurosurgeons assess each meningioma by looking at its size, location, and symptoms (or immediate lack thereof); the necessity of deliberate remnants; and the planning of observation; they also show how selection of treatment is not the *aut aut* confrontation between microsurgery (MS) and stereotactic radiosurgery (SRS/GK) and highlight this as the failure of "binary thinking."

Most neurosurgeons likely agree with the above authors that a randomized controlled trial may never take place to resolve the issues of meningioma management, although some important questions are being addressed by the ROAM trial [2].

This limitation, while being common to other surgical specialties, is particularly acute in neurosurgery. For some conditions, in addition to a wait-and-see indication, the patient may receive four different intention-to-treat proposals by radically different methods (MS, SRS, intravascular techniques, conventional radiotherapy (RT)) and also the choice between a variety of instrumentations for radiation delivery. Not surprisingly all the relatively novel techniques are still causing uncertainties in the neurosurgical community and puzzle both the informed patient and the referring physician.

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12.2 Aim

While we are aware that no individual center's series may provide universal answers, we present the experience of a single team which has treated meningiomas over the past 27 years by the three neurosurgical techniques of microsurgery, radiosurgery, and stereotaxis. We think that the neurosurgical practitioner who has gained competence in each of these techniques is possibly free of the most common biases that accompany meningioma decisions [3].

It has become obvious to most that the surgical procedures to the cavernous sinus/petrous apex must be universally discouraged given the tumors' regular recurrence and dramatic potential of the procedures themselves for causing permanent neurological damage [4, 5]. It should also be obvious to most that SRS for convexity meningiomas should be discouraged, except for the smallest lesions, as surgical removal of midsize lesions (and above) offers the best outcome in terms of either radical removal or deliberate partial removal followed by SRS.

Our experience in both surgical and radiosurgical treatment of two of the most common presentations of meningiomas is then outlined in this chapter. Atypical/anaplastic meningiomas will be included whenever warranted, but an in-depth analysis of the still problematic treatment of these histological varieties (found in 2% ≈ 5% of meningiomas) is outside the scope of this chapter.

12.3 Materials and Methods

All surgical procedures as well as all radiosurgical procedures were performed by the same team, the latter on a succession of the three modern Gamma Knife models (model B (1993–2001), model 4 (2002–2009), and Perfexion (2009–2020)). For brevity we refer generically to the instrumentations as Gamma Knife® (GK) Elekta AB.

Over the period 1993–2020, we performed 2234 procedures on meningiomas: 259 were microsurgical removals and 1975 were single-fraction radiosurgical sessions in Gamma Knife. All were overwhelmingly female series, slightly less than ¾ of the total.

Apart from the need to quickly decompress neural structures, that mandates neurosurgical removal, once a meningioma is diagnosed in the parasagittal/midline location (regardless of whether it is a tumor at first diagnosis or a tumor recurrence/remnant) the principles behind the choice of treatment were as follows:

Favoring radiosurgery:

- *Previous surgical removal/s (followed or not by complications)*
- *Multiple localizations*
- *Coexisting medical conditions*
- *Refusal of surgery (if surgery preferable, not if mandatory)*
- *Very small size in young female patients*

Favoring surgical removal:

- *Larger size (early foundational experience with middle-sized tumors had demonstrated a worrying frequency of satellite edema formation complicating the GK aftermath)*
- *Imaging suggesting atypical histology, satellite edema*

Favoring conservative observational treatment:

- *Very small size in male/elderly patients*

12.3.1 Falcine/Parasagittal Meningiomas

457 procedures in 379 patients (265F (70%) and 114 M (30%))

12.3.2 Symptoms

The most common symptoms that led to diagnosis were typical for the motor location: seizures and palsies (also papilledema and diplopia

and fuzziness—possibly in relation with raised venous pressure), but nonetheless the time between complaints and recognition of the lesion averaged about 1 year. Part of the delay has been the protocol of preliminary prescription of CT without contrast that not only fails to identify a midsize lesion adhering to the vertex bone, but also compounds the problem with the faulty reassurance of a report "negative for head lesions" that dissuades from further investigations.

12.3.3 GK Procedures

414 procedures in 339 patients, of whom:

- 113 patients had GK as their up-front treatment
- 226 patients had been operated before GK (among them a subgroup of 60 patients underwent **157** operations), 19 also had previous conventional radiotherapy sessions

12.3.4 Results of GK

After their first GK:

- 12 resorbed and could not be recognized in the imaging
- 105 reduced (46F-59M)
- 59 remained stable in size (44F-15M)
- 48 enlarged (25F-22M) [3 underwent RT] [9 (4F-5M) underwent surgery]
- 82 went on to have one or more GK sessions (65 had one further GK session on a new related target that while belonging in the same location had not been treated in the previous radiosurgery and 16 had a repeat GK session on the same target) and all are stable/reduced
- 39 were lost to follow-up
- 14 deceased (3F-11M) [10 atypical histology/1 WHO I with Ki67 5%/2 myocardial stroke]
- 258 (86% of patients available at follow-up) reached the goal of treatment

12.3.5 Microsurgery Procedures

37 operations in 36 patients who had surgery as up-front treatment for their falcine-parasagittal meningiomas [7 of them (all multiple meningiomas) had the surgery as part of a program in which other meningiomas underwent SRS, 1 was operated twice on the same atypical meningioma, and 1 had 2 falcine meningiomas (radioinduced) and an occluded section of the SSS removed in the same session].

12.3.6 Stereotaxic Procedures

Two patients (both with previous multiple surgical operations and radiosurgery) had a catheter implanted providing cisternal drainage for slowly enlarging cystic formations.

12.3.7 Results of Surgery

- 15 absent on imaging (radically removed and low grade)
- 3 residues are visible and stable (GK eventually planned)
- 8 kept growing (atypical) and underwent either GK or repeat surgery and 1 underwent RT with GK boost
- 7 lost to follow-up
- 3 deceased (within 1, 2, and 7 years after initial surgery as salvage attempt in recurring high-grade meningiomas)

12.3.8 Olfactory Groove Meningiomas

70 procedures in 65 patients (49F (75%) and 16 M (25%))

12.3.9 Symptoms

While symptoms that led to diagnosis were rare in the olfactory/taste sphere (9 patients) and only 12 included behavioral changes (including 3

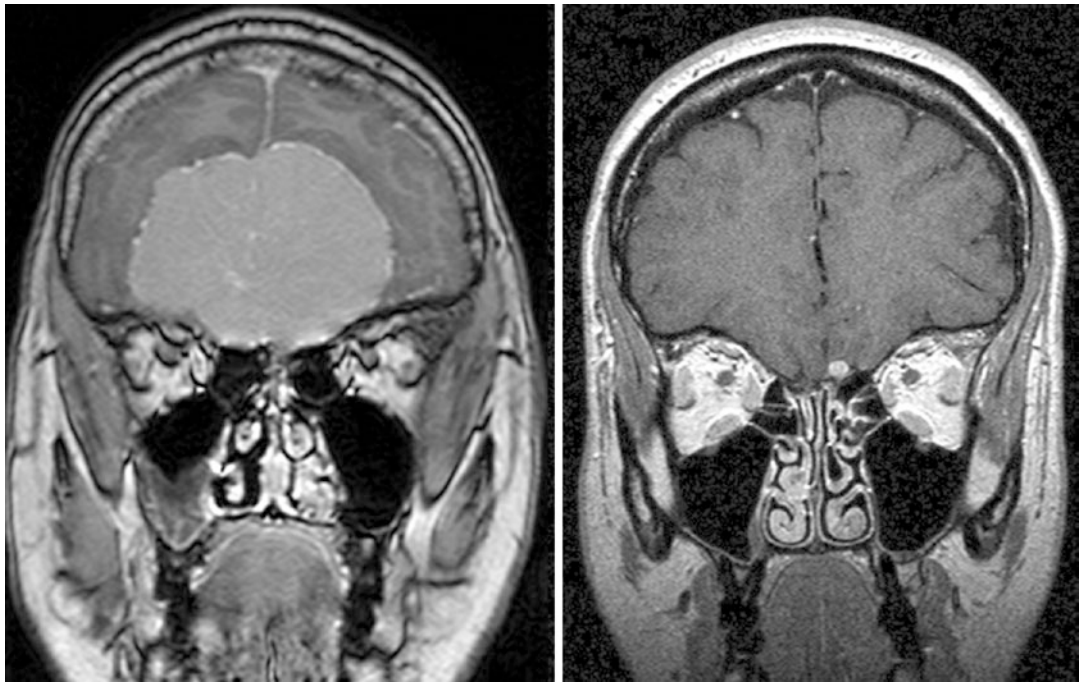

Fig. 12.1 Originally labeled minuscule and incidental at the age of 22 years, this meningothelial meningioma (WHO I, Ki67 = 2%) was reimaged only after florid *Witzelsucht* was apparent (52 years old)

Witzelsucht cases) the most common long-standing symptom (20 cases, ≈1/3) was re-conducible to trigeminal irritation (mostly frontal localized headache and 3 cases of orbital/facial pain).

Two cases had seizures, both initially unrecognized. Other cases suffered from non-localizing and possibly unrelated symptoms (e.g., acoustic/vestibular). 25 cases were asymptomatic and were discovered in imaging prescribed for other medical conditions (some related: multiple meningiomas that included two NF2; some unrelated: traumas, paracusia).

Diagnosis in symptomatic cases was reached:

- Within 6 months (in 4 cases)
- Within 1 year (in 3 cases)
- Between 2 and 5 years (in 9 cases)
- Between 6 and >10 years (in 9 cases)
- After 39 years (in 1 case*: localized frontal pain, anosmia, behavioral changes*)

After recognition of an olfactory meningioma treatment followed:

- Within 6 months (in 28 cases)
- Within 1 year (in 8 cases)
- Between 2 and 5 years (in 24 cases)
- Between 6 and >10 years (in 9 cases)
- After 29 years (in 1 case: *a meningioma originally labeled minuscule and incidental at the age of 22 years was re-examined only after florid Witzelsucht was apparent; see* Fig. 12.1)

12.3.10 GK Procedures

55 procedures in 51 patients (37F, 14 M) who underwent GK for at least one lesion tagged "olfactory," 4 arising "asynchronous."

Less than half (23) had GK as their only treatment up front.

About one-third (18) had at least one previous meningioma surgery (which may have led to dissemination), and 10 had one or more asynchronous radiosurgical treatments for new meningiomatous growths; 2 of these were marginal recurrences of the primary GK treatment.

Overall, about one-fourth (12) had multiple meningiomas and had the olfactory localization treated either as the first one or as a *de novo* meningioma recognized after many years in the course of follow-up following either surgery or radiosurgery.

It is notable that 15 patients had long-standing symptoms (mostly frontal headache) likely due to trigeminal irritation in the first division (meningeal), while only 8 had symptoms in the olfactory/taste sphere and only 5 had behavioral changes (*Witzelsucht* in two large-volume cases).

The volume of target tissue at treatment ranged below 4 cm^3 (0.1–3.9 cm^3) in 43 patients, between 4 and 9 cm^3 in 7 residues/disseminated after surgery, and exceeded the 3 cm max diameter (>10 cm^3) in 5 outliers, all recurring after surgery and invasive of the surrounding anatomical spaces.

12.3.11 Results of GK

- Five patients were treated for recurring high-grade/anaplastic meningiomas which had single/multiple GKs as salvage treatment in the attempt to slow evident regrowth: they had either previous RT or subsequent RT and all were either lost to follow-up or confirmed deceased.
- Six did not have a meaningful follow-up having been treated less than 1 year ago.

All the remaining 40 patients with apparent (33) or confirmed (7) WHO I histology showed control of the growth of the target tumors:

- 37 patients (92.5%) with Ki67 < 3% and a follow-up ranging from >3 years to 15 years all have shown either reduction (30) or no growth (7) of their target/targets. Among these, one previously operated patient (4 years after GK) shows a new separate small growth and will undergo a new GK. Only one patient showed complete resorption of the target tissue.
- Three patients (7.5%) with WHO I meningiomas, but Ki67 ≥ 3%, also currently show reduction, but all at follow-up <3 years.

Headache (present in 11 patients) resolved in 4 patients and persisted in 7 patients (in 1 patient up to 5 years after GK).

After the very first patients who presented with edema changes following GK, our assignment to GK only of candidates with smaller sized olfactory meningiomas mostly prevented this undesired effect (which was noted minimal and asymptomatic in five cases). A single patient lamented side effects following GK for two frontal meningiomas (one falcine, one olfactory). We do not have a complete follow-up in this patient, but about 3 years later the patient was described as "well," with reduced target lesions.[1]

12.3.12 Microsurgical Procedures (15)

15 procedures in 14 patients (two-stage operation in one large bilateral meningioma) who underwent up-front surgery (12F, 2 M) either by the interhemispheric approach (6) or by the subfrontal approach (9), in two of the latter homolateral frontal convexity exploration was also necessary due to asymmetric growth/multiple lesions.

No patient underwent surgery after GK for a meningioma in the olfactory/planum location.

12.3.13 Results After Surgical Removal

All 14 patients were followed up for more than 2 years and up to 15 years.

[1]The patient, in whom the presenting symptom had been seizures, repeatedly refused surgery for the 4.2 cm^3 olfactory microcystic tumor and for the small falx one (2.1 cm^3). About 6 months following GK the patient developed edema and renewed seizures: in addition to the negative prognostic factors, precisely in the period in which the "inflammatory" changes most commonly arise due to SRS, the patient entered a weight-control regimen that included a gastric balloon—a technique explicitly contraindicated whenever a history of epileptic seizures is present.

Headache and trigeminal symptoms resolved in all four of the affected patients.

- Ten were cured by surgical removal as their only treatment (71.5%).
- Four patients (28.5%) went on to be treated by GK:
  - One for a deliberate remnant 2 years after surgery.
  - One had Ki67 ≈ 3% and the recurrence was treated 16 months after surgery.
  - One had an early marginal recurrence (WHO I and Ki67 3–4%).
  - One was a minuscule slow-growing recurrence noted 3 years after surgery and treated by GK 12 years after surgery, after which Ki67 was not obtained.

12.3.14 Wait-and-See

We evaluated another 48 olfactory meningioma patients who for a range of reasons did not proceed to treatment in our service. Most of them, with no previous treatment, refused the surgical removal proposed and were immediately lost to follow-up. However, no patient out of 22 who entered a monitoring program in which significant growth was demonstrated proceeded to the proposed treatment.

12.4 Conclusion

Our data confirm that:

- Minimally invasive therapy by GK is remarkably effective in controlling the growth of benign meningiomas with less recurrences compared to surgery and causing less collateral undesired effects (DeMonte et al. [6], Mathiesen [7], Casali et al. [8]). These effects are mostly temporary and only present in the larger tumors that impinge in F parenchyma.
- Dural irritative symptoms rarely regress after GK and may even exacerbate in the course of the first year after radiosurgery.
- Microsurgery, with its unavoidable typical modifications and risks common to any invasive surgical/anesthesiology procedure, if carefully offered only to those patients who are considered likely to develop undesirable side effects from radiosurgery, is also very efficient in eliminating the tumor. Even though it has a higher incidence of remnant/recurrences, it offers the added advantage of delivering the patient from the trigeminal manifestations of dural irritation, provided that the meningeal site of implant is excised alongside the tumor.
- The presence of headache/trigeminal irritation, size, general medical risks, and objective necessity of a histological grading should then guide our recommendation to the patient even when he/she favors one approach over the other.
- Atypical meningiomas or WHO I meningiomas with a MIB-Ki67 index ≥3% recur more easily after either surgery or GK [9].
- In this meningioma series two cases are not listed (both males, one convexity with erosion of the bone and the other in the falx) which were revealed as cavernous hemangiomas after histological examination [10].

12.5 Discussion

It is not unusual that the neurosurgical patient will receive completely different advice for a cerebral tumor or a cerebral vascular ailment from different hospitals even geographically very close.

This state of affairs hardly changed since the introduction of multidisciplinary meetings in many institutions designed to guarantee the patient a “shared” evaluation vs. the direct prevailing opinion of the “owner” of the “neurosurgical” case. The committee at one extreme either provides the cover of a collegial decision (often anonymous) to proceed with the local preferred treatment or achieves the opposite outcome of paralysis in the refuge of a wait-and-see reprieve. The multidisciplinary offered routinely in all

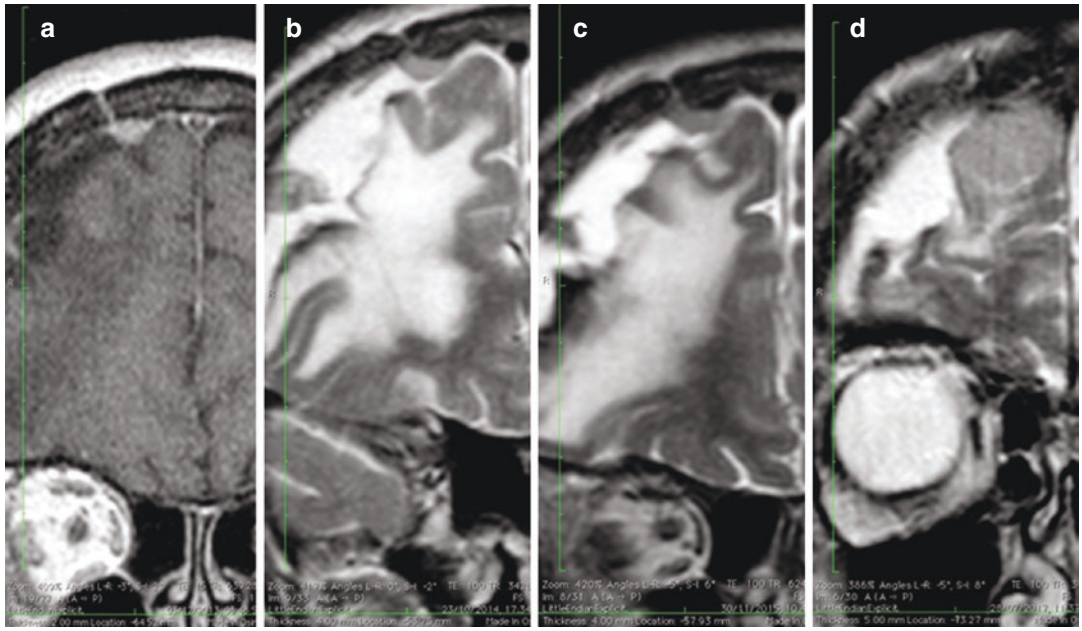

Fig. 12.2 S.G. 74-year-old F, operated in 2011 for a large meningothelial meningioma WHO I, MIB-1Ki67 < 1%. Follow-up imaging in (**a**) December 2013, (**b**) October 2014, and (**c**) November 2015 was always reported to be substantially unchanged and the recurring meningioma was finally recognized after a further 2-year follow-up gap at the age of 80 in (**d**) July 2017. Referred to SRS, she was then reoperated at the age of 81

reports on the subject of competing therapeutical modalities to be employed alone or in association raises interest just because it is so pervasive in print [11] and in conference rooms.

SRS is wrongly perceived as treading on improper turf both by some neurosurgeons and by some radiotherapists, if by different motivations. The interrupted Aruba study [12] was designed since inception for the stated aim to impede *any* treatment in brain arteriovenous malformations (by neurosurgery, SRS, intravascular intervention) before they bleed[2] and has become a dramatic case in point that is the object of very many antagonistic reports [13]. Turf antagonism between open surgery and intravascular treatment has flared also in a more recent cardiological controversy on competing coronary treatments [14]. However, many other topical decisions, based on professional biases, are occurring almost daily far from the medical journals and the specialist conferences, which are no less controversial: witness the reflex diagnosis of myasthenia followed by administration of anticholinesterase drugs whenever blepharoptosis and/or diplopia is encountered. The telltale diplopia with trigeminal discomfort also rushed to surgical realignment of the eyes before imaging targeted to the skull base (not just plain CT) is obtained and evaluated. Witness generic headache labeled migraine without aura if seen by professionals averse to modern imaging, even in the presence of "incidental" lesions located at the meninges. Extreme instances of these therapeutical "rerouting" may include repeated surgery of the Achilles tendon to correct a foot palsy, again avoiding the inconvenience of brain imaging of a meningioma impinging on motor cortex. The wait-and-see program for visible "benign" tumors or their remnants is rendered useless by the exceedingly commonplace radiological report of "*substantially unchanged*" (Fig. 12.2) compared to the immediately precedent study instead of the oldest one always avoiding the reliability of volumetric assessment [15]. I have no explanation why no patient entering our wait-and-see "arm" never reentered for treatment: there may be many reasons for this, but it is also

[2]Mohr J.P., Zürich, July 2005, personal communication.

possible that the patients who initially select a conservative treatment are precisely those that do so out of a distaste for *any* intervention. Small benign meningiomas have the best results. Unfortunately however, due to enduring misconceptions of the indications for SRS, meningiomas are often still referred when their recurrences in older patients are too large and confirmed atypical to warrant meaningful treatment beyond palliative radiotherapy.

There are patients who say: "Doctor, you are never going to open my head, it's Gamma Knife or nothing." Confronted with the choice, we would certainly *feel* the same in their position. The feeling of being comfortable with "tumor control" rather than "tumor removal" overcomes professional bias, as explored in a survey where neurosurgeons had to decide themselves for their own acoustic neuroma [16]. However, we should not discount the occasional person who dislikes "treating"/"letting in place" the lesion and requires that it be removed. Even setting aside the emotions that we share with most of our fellow human beings and examining the rational avoidance of craniotomy and its attendant risks, the choice between surgery and radiosurgery is much less binary and more nuanced once we delve deeper into clinical reality.

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13 Combined Microsurgical and Radiosurgical Treatment in Intracranial Meningiomas

Lina Raffaella Barzaghi, Veronica Parisi, Alfio Spina, and Pietro Mortini

13.1 Treatment of Intracranial Meningiomas: Indications and Different Management Strategies

Intracranial meningiomas require treatment when they are symptomatic (mass effect or seizures), while asymptomatic meningiomas usually are treated in the event of radiological progression, especially if close to critical structures: vessel, nerves, or eloquent parenchymal areas in the central nervous system [1]. There are three main options for first-line meningioma therapy: (a) surgical removal, (b) stereotactic radiosurgery, and (c) combined microsurgery and radiosurgery (in selected cases). Radiotherapy is generally used for adjuvant purposes, especially when histology founds atypical or anaplastic meningiomas. Furthermore, it may be an alternative to radiosurgery in large tumours [1–3].

The treatment strategy adopted in individual patient depends on many factors, including the age and general conditions, as well as the location and size of the tumour, the risk of neurological lesions related to the meningioma or treatment, and the preference expressed by the patient. Microsurgery is the gold standard, especially for radically resectable meningiomas at low risk of morbidity and mortality. The extent of resection, as described by Simpson in 1957, is still the discriminating factor for disease-free survival, the residual tumour volume being linked to the risk of regrowth (10-year recurrence rate for Grade I, complete tumour resection including dural attachment and abnormal bone, 9%; for Grade II, complete tumour resection with coagulation of dural attachment, 19%; for Grade III, complete tumour removal without resection of dural attachment and abnormal bone, 29%; for Grade IV, subtotal tumour resection, 44%) [4–6].

In turn, the probability of achieving a Simpson Grade 1 resection (including the dural implant) is closely related to the location of the tumour. Specifically, it is achieved in more than 95% of convexity tumours and in less than 33% of those affecting the skull base or contiguous with the dural venous sinus [7, 8]. It is known that some meningiomas, such as those of the olfactory groove, sphenoidal ridge, or posterior cranial fossa, have particularly high rates of recurrence after gross total resection (GTR) [7]. However, a recent study about the natural history of untreated meningiomas identified several negative prognostic factors for disease progression (age <60, >25 mm in size at diagnosis, and absence of calcifications) but the anatomical location was not

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among them. Although recent evidences seem to demonstrate some location-related specificity in the expression of certain genetic mutations [9, 10], it would appear that the tumour site actually affects the radicality of surgery rather than the biology of the tumour itself.

In addition to complete resection with removal or coagulation of the dural attachment, the histological grade is another prognostic factor for local growth control after GTR. In brief, the World Health Organization (WHO) classifies slow-growing meningiomas as Grade I, atypical meningiomas as Grade II, and anaplastic meningiomas as Grade III [11]. Grade I is the most common (95%), while only a minority of meningiomas are atypical or malignant [12]. Irrespective of WHO Grade, overall survival rates of 5 and 10 years after surgery are 82% and 64%, respectively, but these rates are lower in Grade II and/or III tumours (65% and 51%) [13, 14].

Radiosurgery, initially introduced for the treatment of tumour relapse, has gradually taken on an increasingly important role in the management of meningiomas, and is currently also indicated as first-line treatment in selected cases (small tumours, especially in critical areas). Currently, there is copious evidence supporting the effectiveness of Gamma Knife treatment for intracranial meningiomas; 10 years' growth control, both after first-line and adjuvant radiosurgery, ranges from 93.2% to 99.4% (Table 13.1) [8, 15–25]. In Grade I tumours, it ensures 5 and 10 years' progression-free survival rates similar to those achieved after total resection (Simpson Grade I) and significantly improves local control after subtotal resection [8, 16, 19, 26].

13.2 Combined Microsurgical and Radiosurgical Treatment

Despite considerable technological progress in neurosurgery, GTR is still associated with high morbidity and mortality in some locations or when neurovascular encasement is present. In fact, it has been shown that partial resection provides with lower morbidity than radical surgical approach; the last one is often achieved via demolition access routes or by requiring vascular reconstruction techniques (bypass) in skull base meningiomas, due to the close contiguity with the cranial nerves and vessels, and in meningiomas that invade the dural sinuses. In addition to this evidence, the high local control of growth obtained by radiosurgery has modified the approach to neurosurgical management of meningiomas in so-called critical locations (skull base, parasagittal sites, falx, or tentorium). In these complex situations, partial exeresis of tumours followed by radiosurgery for the residue is currently considered a valid therapeutic strategy and has become an increasingly widespread practice [27–30].

This combined approach must integrate the limitations and benefits of both surgery and radiosurgery. It should, therefore, be planned by a multidisciplinary team whose job is to attempt to optimize treatment outcomes, bearing in mind the tumour's location, volume, and distance from critical organs while predicting the likely residue in function of the subsequent radiosurgical treatment. The main purpose of surgery is the maximal safe resection, reducing the tumour volume and avoiding damage to nearby blood vessels and nerves. While leaving residual tumour offers an advantage in terms of surgical morbidity, it is important to ensure as much distance as possible between the residue and critical structures in order to reduce the risks of radiation toxicity induced by the second-stage radiosurgical treatment. The latter objective is often difficult to achieve, and must be carefully taken into account during surgical planning and execution.

Another key factor of the combined microsurgery-radiosurgery approach is the timing. Since meningioma residue tends to grow over time and may become difficult to distinguish from critical structures for radiosurgical purposes, radiosurgery should be carried out as soon as the residue is identifiable on magnetic resonance imaging (MRI), without waiting for evidence of its radiological progression. The wait-and-see option and radiosurgery after progression evidence may make radiosurgery suboptimal due to incomplete coverage of the tumour

Table 13.1 Gamma Knife treatment outcomes in major series of intracranial meningioma

Author, year	No.	Site	Prior surgery (%)	Median dose (Gy)	5-Year/10-year LTC	Clinical improvement (%)	Tumour regression (%)	Complications (%)	Mean tumour volume (cm^3)	Mean FU (months)
Stafford (2001) [15]	190	All	8.2	16	93/ -	8	56	13	8.2	47
Flickinger (2003) [16]	219	All	5	14	93.2/–	.	.	8.8	5	29
Pollock (2003) [8]	62	All	7.4	17.7	95/–	13	–	10	7.4	64
DiBiase (2004) [17]	137	All	4.5	14	86.2/–	–	28	8.3	4.5	54
Feigl (2007) [18]	211	All	58.3	13.6	86.3% 4 yrs	43	74.5	24.8	6.46	24
Kollová (2007) [19]	331	All	6.3	12.5	98/–	62	70	10	6.3	68
Kondziolka (2008) [20]	972	All	7.4	14	97/87	11	42	8	7.4	48
Bledsoe (2010) [21]	116	All	17.5	15.1	99/92	–	–	23	17.5	70
Zada (2010) [22]	116	All	3.4	16	99/84	–	26	8	3.4	75
Santacroce (2012) [23]	4565	All	4.8	14	95.2/88.6	53.5	58	6.6	4.8	63
Pollock (2012) [24]	251	All	7.7	15.8	99.4/99.4	–	72.1	11.5	7.7	62.9
Fokas (2014) [25]	318	All	44.7	–	92.9/87.5	–	–	–	–	50

LCT local tumour control, *FU* follow-up

volume or use of a dose lower than effective. Moreover, the natural history of untreated meningiomas in series with less than 2-year mean follow-up shows a volumetric increase occurring in more than 60% of patients; this value may increase to 100% with longer follow-up [9, 31]. The annual volumetric increase reported in the literature ranges from 0.01 to 10 cm^3, with a recent analysis reporting an annual average growth of 2.3 cm^3, equal to about 20% of the initial volume [32].

Given this, when planning radiosurgery, it is also necessary to consider whether it will interfere with post-operative functional recovery. In some cases, it may be better to postpone radiosurgery until the neurological conditions have been stabilized.

To define the patient's decision-making process, a final consideration is that long-term clinical and radiological follow-up will still be necessary to identify early recurrences both within and outside the treated field, even after a combined approach.

13.2.1 Key Points for Radiosurgery

When planning radiosurgical treatment, the prescribed dose and/or fractionation schedule may vary depending on anatomical relationships, tumour volume, and histological grade. In particular, the recommended dose intervals for Grade I, II, and III meningiomas are 12–16, 16–20, and 18–24 Gy, respectively [33, 34]. Although in the literature it has emerged that adjuvant radiotherapy improves the prognosis of patients with atypical or anaplastic meningiomas subjected to gross total resection (GTR), the optimal strategy after subtotal resection (STR) has yet to be defined [35, 36]. In fact, both radiosurgery on the residue and fractionated radiotherapy (fRT) throughout the surgical bed have been described for atypical meningiomas [37–39]. Hence, while a minimum dose of 12 Gy can be recommended for the combined microsurgery-radiosurgery treatment of voluminous Grade I meningiomas at critical sites, atypical meningiomas require careful assessment on a case-by-case basis, taking into consideration focal RT as a potential alternative.

As for the fractionation schedule, single fraction is generally used in radiosurgery, but the multisession technique (over 3–5 consecutive days) has recently been introduced to treat some type of tumours, such as very large skull base meningiomas or those involving the optic pathways [40, 41]. Indeed, although mixed cranial nerves or nerves passing through the cavernous sinus can tolerate radiation relatively well, pure sensory fibres like the optic and cochlear nerves show greater susceptibility to radiation damage [42]. For this reason one of the aims of surgery is to create distance between the tumour and the optic pathways, although this may not always be possible. A significant reduction in the dose to the optic pathways can be obtained via modern radiosurgical planning software, which allows maximum conformation and optimization of the treatment plan. Another strategy that should be considered is fractionating the radiosurgery treatment across 3–5 sessions [41, 43]. The natural tissue complication probability (NTCP) recently calculated for optical pathways is 0.4% for 10 Gy in a single dose, 1.1% for 21 Gy in three fractions, and 1.1% for 25 Gy in five fractions [44].

Finally, with regard to tumour size, it is well known that the amount of volume treated by radiosurgery—both in terms of absolute value and percentage of tumour volume (percentage coverage)—is a prognostic factor for growth control and complication rates, radionecrosis, and oedema mostly [45, 46]. This is why the main role of surgery is to significantly reduce tumour volume. The 5-year progression-free survival (PFS) in meningiomas smaller than 10 cm^3 (equivalent diameter of 2.7 cm) is 91.9%, but it decreases to 68% for larger ones [17]. Furthermore, a better local control and fewer complications have been described after radiosurgical treatment for meningiomas of <3.2 cm^3, whereas for volumes >9.6 cm^3, the complication rate increases from 4.8% to 22.6% [24].

Single-session treatment with dose >14 Gy and tumour volume greater than 4.9 cm^3 were predictive factors for symptomatic oedema after Gamma Knife [47–50]. A volume <14 cm^3 was

recommended as the threshold for single-session Gamma Knife treatment in a study of voluminous skull base meningiomas [40]. In larger tumours treated with radiosurgery, similar growth control rates were obtained with single versus 3–5 sessions, but fewer side effects and lower incidence of symptomatic oedema were associated with the latter [40]. In fact, a recent paper stated that fractionated Gamma Knife can be considered as a good alternative to single-session Gamma Knife in tumours >10 cm^3, with good tumour control and low complication rates [51].

13.2.2 Clinical Case of Combined Microsurgery and Radiosurgery for Meningioma with Vascular Encasement

Figure 13.1 shows the case of a combined microsurgery-radiosurgery approach to a meningioma wrapping the vertebral artery. The patient was a 62-year-old woman who had brain MRI with contrast following the onset of cervicobrachial syndrome. A voluminous meningioma of the right median/paramedian cervical junction (volume = 12.78 cm^3), exerting a significant mass effect and dislocating the brainstem, was found. The right vertebral artery was close and partially incorporated by a stub of the meningioma (Fig. 13.1a). The lesion underwent surgical resection via a far lateral approach, preserving the condyle. Post-operative objective neurological examination showed deficit of the right seventh cranial nerve. Histopathological examination led to a diagnosis of WHO Grade I meningioma (meningothelial), and contrast brain MRI confirmed subtotal resection, with a little tumour residue at the extra–intracranial tract of the vertebral artery. Single-fraction Gamma Knife treatment was scheduled for 27 months after surgery to allow functional recovery of the patient (Fig. 13.1b). A dose of 15 Gy was delivered to the 50% peripheral isodose on a target volume of 1.76 cm^3. At the last follow-up, 96 months after surgery, brain MRI scan with contrast (Fig. 13.1c) showed a slight volumetric reduction of the residue (volume = 988.5 mm^3), and the patient displayed complete recovery from the postoperative deficit.

13.3 Skull Base Meningiomas

Skull base meningiomas account for about 35–50% of all intracranial meningiomas [52]. Traditionally, surgery has been considered the treatment of choice, although complete resection is not always possible and it is further associated with high morbidity and mortality rates, which may even reach up to 85.7% and 20%, respectively [29]. In fact, surgery is very challenging in these cases because of the poor access to the skull base itself and the contiguity with critical vascular and nervous structures. The most frequently reported complications are cranial nerve deficits (new onset and/or worsening of known deficits), with an incidence ranging from 20% to 44% for temporary dysfunction and from 16% to 56% for permanent deficits [30]. Despite the increasingly invasive approaches aimed at removing the osteodural attachment, as in the case of olfactory groove meningiomas, recurrency cannot be completely eliminated. This may be due to the biology of the meningioma itself, which, although histologically benign, is often locally invasive, especially at the skull base [7, 53]. Unfortunately, it is hard to get an idea of the effective recurrence rate, as published series rely on inhomogeneous data in terms of radicality definition and methods used for evaluating it, as well as variations in the duration of follow-up periods. That being said, in clinical trials with at least 10 years of follow-up, local recurrence/progression is reported in 10–33% of skull base meningiomas after GTR (Simpson Grade I or II) and in 55–75% of cases after STR [5, 54–63].

Radiosurgery with Gamma Knife has proven to be effective as both first-line treatment and adjuvant therapy, after STR. In this regard, Starke and collaborators published on a series of patients who underwent Gamma Knife for skull base meningioma with a median follow-up of 78 months. They reported tumour growth control in 86% of patients, with no significant differences

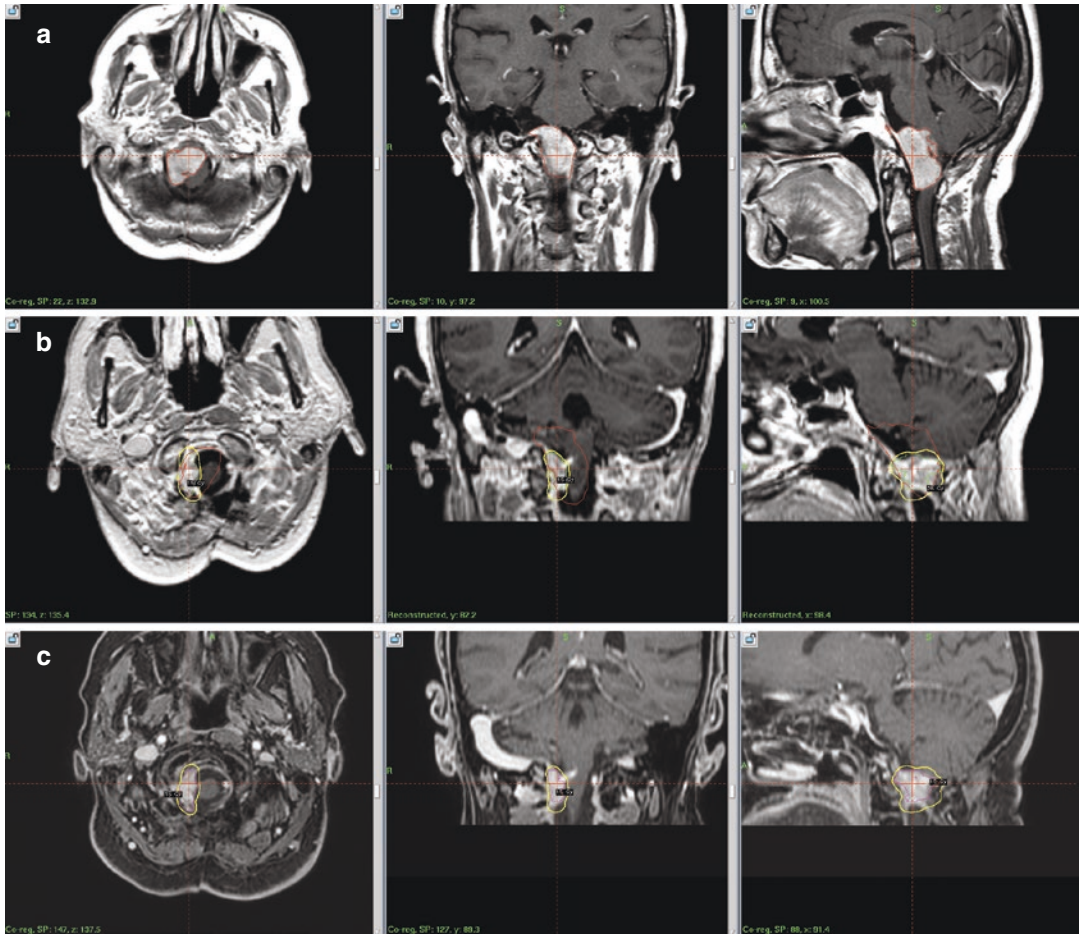

Fig. 13.1 Clinical case: meningioma of the craniocervical junction with right paramedian extension treated using a combined microsurgical and radiosurgical approach. Axial T1-weighted MRI with contrast: before surgery (**a**), during Gamma Knife treatment (**b**), and at the last follow-up, 96 months after surgery (**c**). The initial meningioma volume and 50% isodose line (**b** and **c**) are traced. The marked reduction in tumour volume and decompression of the brainstem achieved by surgery are appreciable; the residue is seen adhering to the vertebral artery at foramen, where it crosses the dura mater

between the group of patients who underwent first-line radiosurgery and those who received Gamma Knife for adjuvant purposes. The progression-free survival rate observed was 99% at 3 years, 96% at 5 years, and 79% at 10 years [63], similar to results reported for other series, as shown in Table 13.2 [52, 55–63].

Given these results, it appears that the best therapeutic strategy for complex skull base meningiomas is combined microsurgical-radiosurgical management, particularly in petroclival and cavernous sinus meningiomas (see below).

13.3.1 Cavernous Sinus Meningiomas

Meningiomas of the cavernous sinus represent a heterogeneous group consisting essentially of three distinct anatomical locations: (1) tumours that originate and are confined within the cavernous sinus; (2) tumours that extend outside the same with limited infiltration of its side wall; and (3) tumours with extensions outside the sinus and involvement of the surrounding structures. Then there are also tumours from adjacent areas that can secondarily invade the cavernous sinus.

Table 13.2 Outcomes in major radiosurgery series of meningiomas according to the site

Author, year	No.	Site	Prior surgery(%)	Median dose (Gy)	5-Year/10-year LTC	Clinical improvement (%)	Tumour regression (%)	Complications (%)	Mean tumour volume (cm^3)	Mean FU (months)
Morita (1999) [55]	88	SBM	55	16	95/–	17	68	–	10	35
Aichholzer (2000) [52]	46	SBM	67	16	96/–	33	52	9	–	48
Eustacchio (2002) [56]	121	SBM	6.8	13	99/–	44.6	60	5	6.8	72
Kreil (2005) [57]	200	SBM	6.5	12	98.5/97	41.5	56.5	2.5	6.5	94
Zachenhofer (2006) [58]	33	SBM	69.4	17	94	44	36	12	–	103
Davidson (2007) [59]	36	SBM	4.1	16	100/94.7	44	14	2.8	4.1	81
Han (2008) [60]	63	SBM	6.3	12.7	90.2/–	45	44	17	6.3	77
Hayashi (2011) [61]	66	SBM	6.6	12	99/–	–	82	1	6.6	46
Iwai (2008) [62]	125	SBM	8.1	12	93/83	13	46	7.2	8.1	86
Starke (2012) [63]	255	SBM	5	14	96/79	–	49	5.1	5	78
Duma (1993) [64]	34	CS	82	16	100/–	24	56	5.8	5.2	26
Roche (2000) [65]	80	CS	5.8	14	92.8/–	27	31	4	5.8	30.5
Shin (2001) [66]	40	CS	4.3	28	91.3/91.3	–	37.5	2.5	4.3	42
Nicolato (2002) [67]	11	CS	8.1	14.8	96/–	66	61	4.5	8.1	48.2
Lee (2002) [68]	159	CS	6.8	13	93.1/93.1	29	34	5	6.8	35
Iwai (2003) [69]	42	CS	12.4	11	92/–	29	59.5	4.7	12.4	42
Maruyama (2004) [70]	40	CS	32.5	16	94.1/–	20	70	25	5.4	47
Pollock (2005) [71]	49	CS	10.2	15.9	100/—	26	59	14	10.2	58
Hasegawa (2007) [72]	115	CS	13.8	13	94/92	46	–	12	13.8	62
Skeie (2010) [73]	100	CS	7.4	12.4	94/91.6	21	22	6	7.4	82
Subach (1998) [74]	62	Petroclival	63	15	86.7/–	21	23	8	–	37
Roche (2003) [75]	32	Petroclival	–	13	100/–	58	12.5	9.3	–	56
Flannery (2010) [76]	168	Petroclival	7.7	13	95/—	26	49	14	7.7	72
Kondziolka (2009) [77]	125	Convexity	7.6	12	86/–	–	26	9.6	7.6	31
Hasegawa (2011) [78]	112	Parasagittal, falx, convexity	59	16	87/71	–	41	7	7.9	72

CS cavernous sinus, *LCT* local tumour control, *SBM* skull base meningioma

The total removal of these meningiomas requires opening of the cavernous sinus and tumour dissection from the cranial nerves and internal carotid artery, in the absence of an arachnoid plane [79]. Hence intracavernous surgery is associated with high morbidity and mortality, with a risk of new onset of oculomotor nerve deficit ranging from 19% to 86% [80–84]. Moreover, data from the literature reveal that an aggressive surgical strategy does not eliminate the risk of recurrence, which is estimated at no less than 10%. These cases are probably due to infiltration of the walls of the cavernous sinus, nerves, connective tissue, internal carotid artery itself, or bone, despite the benign nature of these tumours [80, 85]. Similarly, tumour progression within the orbit can contribute to the risk of recurrence [79–85].

Currently, Gamma Knife radiosurgery is indicated as the first-line treatment option in small cavernous sinus meningiomas, while for larger tumours a combined approach is recommended, with an initial surgical step to reduce the tumour volume followed by radiosurgical treatment within the next 6–12 months [28, 64–73, 86]. The literature shows that volumetric reduction or tumour control can be achieved in about 90% of cases, with cranial nerve deficit rates of about 6%, much lower than those described after surgery [64–73, 86]. It should be noted that the recovery of cranial nerve deficit appears better in patients for whom radiosurgical treatment is used as a first-line approach rather than as an adjuvant therapy, probably because surgery can permanently damage nerve structures and cause difficulties in the correct definition of the radiosurgical target [67, 68]. Given the effectiveness of radiosurgical techniques, the wait-and-see strategy should be considered with caution in such cases, because tumour growth often involves the orbit or optic pathways, making later treatment with Gamma Knife more hard and risky.

13.3.2 Petroclival Meningiomas

Petroclival meningiomas extend between the petrous apex and the upper two-thirds of the clivus. Observation of these untreated meningiomas over a 5-year follow-up revealed growth in 76% of cases, resulting in functional deterioration in 63% of cases [87]. They are very complex tumours in terms of their anatomical relationships, by which they are distinguished into sphenopetroclival, tentorial, and petroclival, often also extending into the cavernous sinus. Initially considered inoperable, with the evolution of skull base access techniques with bone demolition, these tumours were then treated aggressively through surgery [29]. However, very often total surgical removal is impossible due to the extent of the tumour, its adherence to the brainstem, or invasion of the vertebral system. GTR is also associated with high morbidity rates (up to 46%, even in a series published after 2000) [29]. In a comparison between invasive and standard approaches, the number of complications was greater in patients operated on via transpetrous/transcochlear access (85%) than in patients operated on via the retrosigmoid or fronto-orbitozygomatic routes (43%), despite similar GTR rates (53–43%) [88]. For this reason, large petroclival meningiomas may be referred to the combined microsurgical and radiosurgical approach, which yields outcomes similar in terms of tumour growth control, but with less associated morbidity [52, 59, 74–76, 89, 90]. The data reported in Table 13.2 show that subtotal resection followed by adjuvant radiosurgery has a 5-year progression-free survival rate of 86.7–100%, depending on the series, while clinical improvement with low morbidity rates (8–14%) is reported in 21–56% of cases [74–76]. Gamma Knife treatment can be indicated as the first-line treatment for small petroclival tumours.

13.3.2.1 Clinical Case of Combined Microsurgical and Radiosurgical Approach in Petroclival Meningioma

Figure 13.2 depicts the case of a 38-year-old woman who, following the onset of right paraesthesia in the second trigeminal branch, with associated hypaesthesia of the homolateral hemisoma, had a brain MRI with contrast medium. This revealed a left petroclival meningioma extending through the apex of the petrous and exerting a mass effect on the brainstem (volume = 13.22 cm^3), as shown in Fig. 13.2a. The

patient underwent partial surgical removal via a retrosigmoid approach, and histopathological examination confirmed the diagnosis of meningioma WHO Grade I (meningothelial infiltrating the dura mater). Post-operative neurological exam highlighted a new-onset peripheral House-Brackmann (HB) grade IV deficit of the seventh cranial nerve and a sixth cranial nerve impairment associated with hypaesthesia of the right hemisoma. An MRI performed 6 months later with Gamma Knife planning purpose confirmed the presence of tumour residue in the Meckel cavity. The patient was radiologically monitored and the residual tumour, then, treated with stereotactic radiosurgery 18 months later (after neurological stabilization achievement) (Fig. 13.2b). The treatment was performed using Gamma Knife Perfexion (Elekta Instruments, AB, Sweden); a dose of 15 Gy with the 50% peripheral isodose was administered to a target volume of 1.67 cm^3 and 99% of coverage. Brain MRI performed 33 months after treatment and 52 months after surgery (Fig. 13.2c) documented reduced tumour volume (0.980 cm^3); facial nerve paralysis (HB II) stabilized after a gradual improvement in the first year.

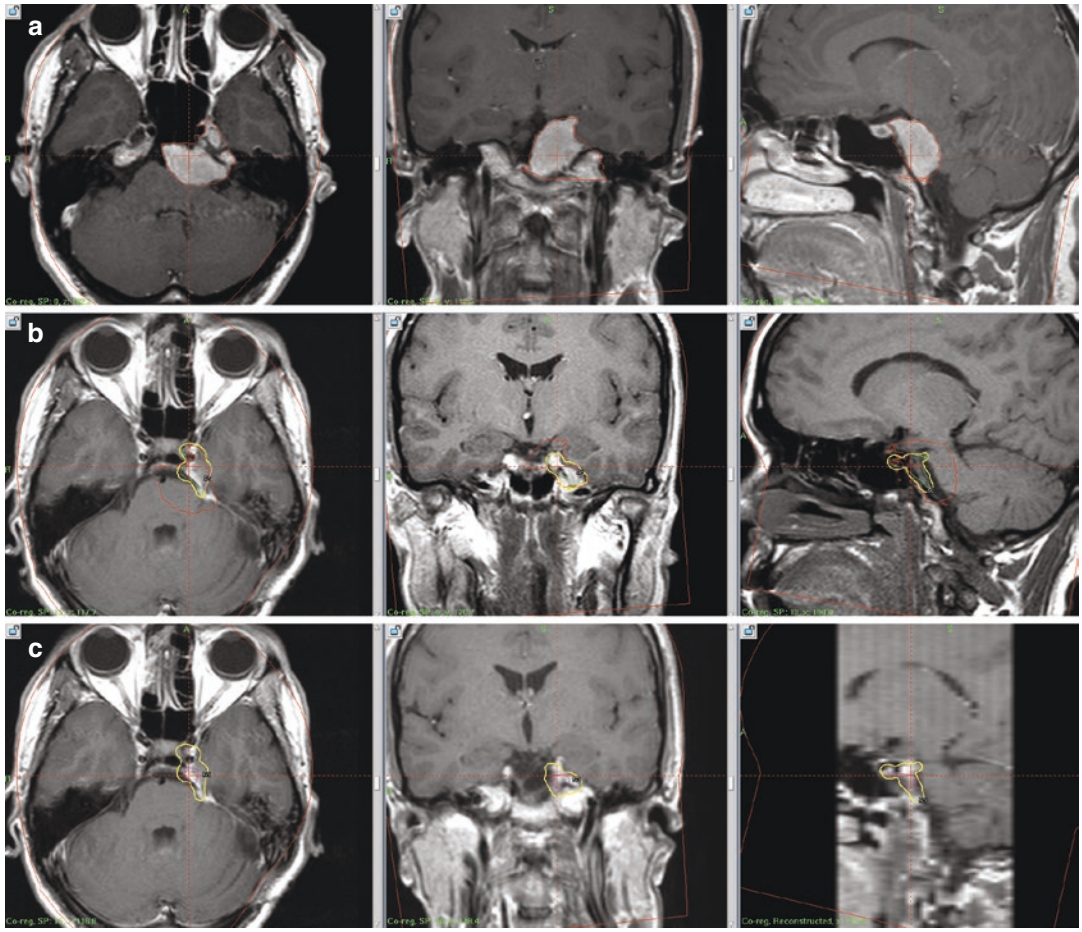

Fig. 13.2 Clinical case: left petroclival meningioma treated via combined microsurgery and radiosurgery. Axial T1-weighted MRI with contrast: before surgery (**a**), during Gamma Knife treatment (**b**), and at the last follow-up, 52 months after surgery (**c**). The initial meningioma volume and 50% isodose line (**b** and **c**) are traced. After surgery the volume of the meningioma is greatly reduced and the compression of the brainstem has disappeared, while residue remains in the Meckel cave

13.4 Meningiomas Extending into Dural Venous Sinuses

Meningiomas in close anatomical relationship with the main venous sinuses make up about 30–35% of intracranial meningiomas. They are distinguished into parasagittal, falcotentorial, and torcular, and are classified according to their location and degree of venous sinus invasion: type I, attachment to outer surface of the sinus wall; type II, fragment inside the lateral recess; type III, invasion of the ipsilateral wall; type IV, invasion of the lateral wall and roof; type V, complete sinus occlusion with one wall free; and type VI, complete sinus occlusion without one wall free [91]. In cases of infiltration and/or occlusion of a dural sinus, long and technically demanding procedures become necessary to achieve radical resection, namely sinus opening, meningioma resection, and reconstruction of the venous wall or ligature of the affected venous sinus with or without bypass [92–96]. This type of surgery is burdened by significant morbidity, since not only venous sinuses but also large cortical drainage veins are often affected. The acute modification of the venous circulation, such as in the case of intra-extracranial compensation of collateral circuits, also carries a high risk of haemorrhage potentially throughout the cerebral hemisphere [96–98].

In parasagittal meningiomas, superior sagittal sinus (SSS) invasion can hinder surgical radicality in about 25% of cases; in addition, the rate of recurrence ranges from 8 to 13% even after radical removal achieved via the aforementioned techniques of venous opening and reconstruction [92–97].

In 2014, Mathiesen and collaborators published on a series of 100 parasagittal meningiomas with dural sinus infiltration treated via subtotal resection followed by Gamma Knife (the so-called Simpson Grade IV/gamma). They reported local tumour control rates that were similar to what would have been achieved via Simpson Grades I and II surgical resection, but with significantly reduced morbidity than that otherwise associated with surgical opening, tumour removal, and reconstructing of the SSS infiltrated by the meningioma [98]. These data have prompted many neurosurgeons to adopt a less aggressive surgical strategy, namely the combined microsurgery-radiosurgery approach [77, 96–100]. That being said, it should be emphasized that optimal control of the tumour residue is not achieved when adjuvant radiosurgery is carried out after progression of the residual meningioma. Hence, if possible, it is much effective to schedule radiosurgical treatment within 6 months of surgery [97]. Adopting Gamma Knife radiosurgery, optimal results have been reported for parasagittal meningiomas with a diameter of up to 3 cm or volume up to 7.5 cm^3 [99].

13.4.1 Clinical Case: Combined Microsurgical and Radiosurgical Approach in Parasagittal Meningioma

Figure 13.3 shows the clinical case of a 40-year-old man with right hemisoma hypaesthesia, short- and long-term memory problems, and blurred vision. She had a brain MRI with contrast which revealed a voluminous left parasagittal meningioma occluding the posterior third of the superior sagittal sinus (volume = 45.23 cm^3; Fig. 13.3a). The patient underwent surgical removal (>90%), leaving only small residue at the superior sagittal sinus. Upon histological examination, the lesion was found to be an atypical meningioma (WHO Grade II). Single-fraction stereotactic Gamma Knife radiosurgery was used on the residual tumour (volume = 3.05 cm^3) invading the superior sagittal sinus 6 months after surgery (Fig. 13.3b). A prescribed dose of 14.5 Gy was administered to the 50% peripheral isodose with 100% coverage. Twelve months after the surgery, the tumour volume was significantly reduced, at 1.39 cm^3 (Fig. 13.3c), and the patient displayed no more neurological deficits and complete recovery from the hemiparesis.

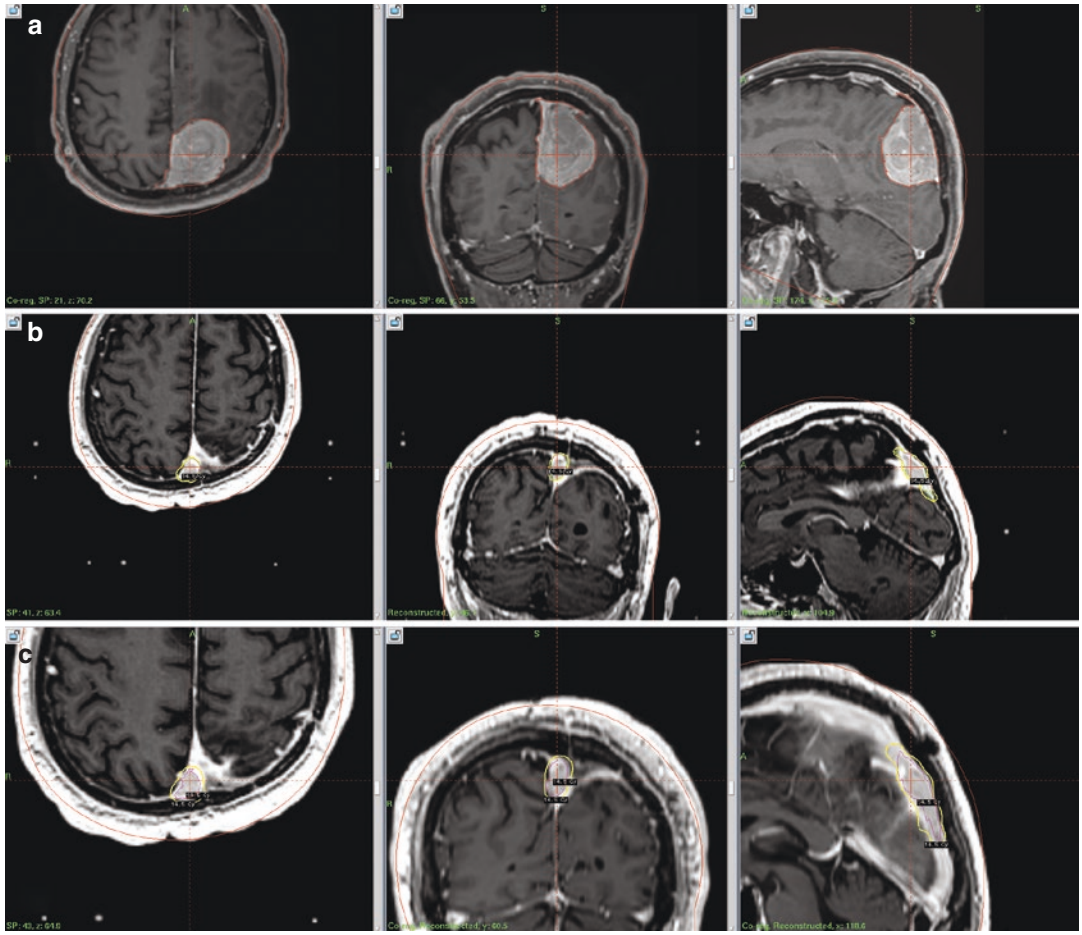

Fig. 13.3 Clinical case: left parasagittal meningioma invading the superior sagittal sinus treated via combined microsurgery and radiosurgery. Axial T1-weighted MRI with contrast: before surgery (**a**), during Gamma Knife treatment (**b**), and at the last follow-up, 12 months after surgery (**c**). The surgery left residue at the superior sagittal sinus, which was treated 6 months later using Gamma Knife

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SRS in Incidental Meningioma: Whether to Treat and When

14

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14.1 Definition

With the term "incidental brain meningiomas" we refer to intracranial neoplasms with radiological features typical of meningiomas identified incidentally during imaging tests performed for other reasons, often also neurological but unrelated to the meningioma itself [1–3]. The literature reports very low percentages for the incidence of incidental meningiomas, specifically only 18 cases (0.9%) in a sample of 2000 brain MRI scans [4]. In a case study involving MRI imaging of 3672 people aged 65 and over enrolled in a population study on cardiovascular and cerebrovascular diseases (Cardiovascular Health Study), Yue (1997) reports an even lower percentage (0.52%), having found 19 cases of meningioma, of which 8 were larger than 2.5 cm; of these, 4 were subsequently operated on for non-specific neurological symptoms and 1 case was found to be an anaplastic meningioma [5].

However, thanks to the increased use and applications of brain imaging, incidental asymptomatic meningiomas are rapidly becoming a medical problem for neurosurgeons and neuro-oncologists, accounting for 30% of primary intracranial tumours diagnosed [2], and patients are becoming so-called victims of modern imaging technology (VOMIT) [6–8]. As regards the growth rate of such lesions, the literature reports a range from 24% to 76%, suggesting that clinicians must take action sooner or later [6, 9, 10]. However, to date there is no consensus on how best to manage this group of meningiomas.

14.1.1 Natural History

Understanding the natural history of incidental meningiomas is fundamental for their management, and to be able to maintain the advantage of early diagnosis. As mentioned, the literature reports that about 37% of tumours of this type grow, whereas 63% will not display size differences over a period of about 90 months. In those that do, the average growth rate is about 4 mm year [11], but growth rates are variable (Table 14.1), with reports ranging from 22.2%, with an enlargement of the average diameter of about 0.24 cm/year [12], to annual volumetric growth rates varying between 0.03 and 2.62 cm^3/year (average 0.796 cm^3/year) [6]. The doubling time of such tumours is reported to be from 1.27 to 143.5 years (average 21.6 years). One report was of an increase in diameter of 0.4 cm per year

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Table 14.1 Synopsis of studies on meningioma growth rates

Authors, 19	Cases	Evaluation criterion	Growth, cases (%)	Average follow-up, years (range)	Tumour growth rate per year
Olivero, Lister, & Elwood (1995) [12]	45	Maximum diameter	10 [22.2%]	2.7 [0.5–15]	0.24 cm
Nakamura, Roser, Michel, Jacobs, & Samii (2003) [9]	47	Volume	Not reported	3.6 [0.5–8.8]	0.796 cm^3 [0.03–2.62]
Hashiba, Hashimoto, Izumoto, Suzuki, Kagawa, & Maruno, (2009) [15]	70	Volume	44 [62.9]	3.3 [1.0–10.3]	15–25%
Oya, Kim, Sade, & Lee, (2011) [28]	273	Diameter	120 [44%]	3.8	Not reported
Liu, Li, & Wang (2015) [13]	82	Diameter	38 [46.3%]	10.5 months [3–18 months]	0.4 cm
Jadid, Feychting, Höijer, Hylin, Kihlström, & Mathiesen (2015) [1]	65	Diameter	[35.4%]: – ≤2 cm—36.4% – >2 cm—33.3%	74 months	Not reported

Note that the reference parameter most often used in these studies for the definition of growth is the maximum diameter of the tumour

in about 46.3% of the meningiomas observed over 10.5 months (range 3–18 months) [13], with an average annual growth of about 3.6% of the volume [14].

There appears to be a relationship between the size of the tumour at diagnosis and the growth rate [1]. Specifically, meningiomas with a diameter of less than or equal to 2 cm at diagnosis are reported as having a 36.4% risk of growth, while meningiomas with a diameter greater than 2 cm have a 33.3% probability of increasing in size over the following 74 months [11]. An attempt has also been made to evaluate the volumetric growth patterns [15] of meningiomas, but this failed to locate any specific patterns. In fact, both exponential and linear patterns that cannot be associated with any existing model have been recognized.

Only in rare cases have meningiomas subjected to radiological follow-up become symptomatic in the observation period [11, 16]. That being said, most incidental meningiomas evolve radiologically and/or clinically to the extent that they require treatment within 5 years of diagnosis [2], but it is not yet clear when and how to intervene to prevent neurological problems. The size of the tumour at the time of diagnosis is the main risk factor for the development of new symptoms during radiological follow-up. Meningiomas smaller than 2.5 cm in diameter tend to remain asymptomatic in a follow-up period of 5 years [10, 17, 18]. A 2019 review by Islim found that lesions with a diameter of more than 3 cm have higher growth rates and increased risk of clinical progression [1, 19].

There are factors predictive of growth in meningiomas. The rate of growth of incidental meningiomas tends to be lower in older patients (over 70 years of age) [10, 18]. Furthermore, the more calcifications there are in a meningioma, the lower the risk of progression. It has also been observed that meningiomas, even those without calcifications, that have a high average Hounsfield unit on CT have a lower rate of growth [20, 21], and this may therefore be a good quantitative indicator of the rate and growth pattern of meningiomas.

It is important to point out, however, that the probability of growth of an asymptomatic meningioma over time will vary according to the WHO grade to which it belongs. At 5 years, WHO Grade II and III meningiomas have a 5–10 times greater risk of progression than the WHO Grade I [3, 20, 21]. Studies have suggested that atypical meningiomas grow exponentially, while benign meningiomas show exponential, linear, or no growth. In order to maintain the diagnostic advantage, it is important to identify and intercept small percentage of meningiomas with an aggressive growth pattern [WHO Grades II and

III]. This represents a significant challenge, and it is essential to find consensus regarding the timing of the follow-up in order to maintain radiological control of the lesions themselves. A further challenge in the management of incidental meningiomas is their differential diagnosis. They need to be distinguished from hemangiopericytomas, which are aggressive and associated with a high risk of recurrence and metastasis, and dural metastases, which are found in 8–9% of patients with advanced systemic cancer at autopsy [22].

14.2 Management

It is very difficult to review the current management strategies for incidental meningiomas. Recently (2019), Islim et al. published one in which, of the 4750 studies on meningiomas collected, only 20 had sufficient data for them to use, i.e. only 2130 cases of incidental meningioma [2]. The most common reason for the imaging that led to their discovery was a non-injury-related neurological disorder (14%), headache (13%), audiovestibular symptoms (11%) and head trauma (10%). Most patients who progressed clinically or radiologically did so within 5 years of diagnosis [2]. In a wide-ranging review in 2006, Yano reiterated the lack of indication for treatment of these meningiomas [11], as intervention can lead to unnecessary risks in terms of mortality and morbidity. In the future, it would be useful to collate the data collected so far in order to develop a risk calculator and identify better management strategies [2].

The choice of the type of treatment depends on the characteristics of the meningioma itself [23], although precise scientific data regarding management are lacking. Surgery, radiosurgery, fractionated radiotherapy and active monitoring are all potential options in incidental meningiomas [6]. Complete resection, including the dural base and underlying bone, is typically the first-line treatment for symptomatic intracranial meningiomas or those that are expected to become so. In all cases where this is not possible, radiosurgery is considered [24]. Radiosurgery is associated with low mortality and morbidity, and according to the literature data [24] can be offered as a first-line treatment in asymptomatic meningiomas in selected cases, such as small lesions that are not easily surgically accessible, but are in locations associated with a risk of major neurological disorder. Radiosurgery may also be the preferred option in young subjects, or should a patient refuse surgery.

Conservative management of intracranial meningiomas in general has been analysed in many studies [2, 6, 9, 20, 25, 26], and according to Vernoij, many incidental meningiomas, about 50%, can be managed by clinical follow-up and brain MRI performed annually, after an initial observation interval of 6 months [4]. Many retrospective series [2, 4] and reviews [10, 18] appear to support guidelines for conservative management (evidence level III, recommendation level C) [23]. Hence, a recent consensus has led to the production of guidelines that suggest that active monitoring is the most appropriate management strategy in the first instance. Nonetheless, the frequency and duration of follow-up have not been specified, which has led to the implementation of a variety of different monitoring strategies, which have different economic implications and are of uncertain benefit to the patient [10, 18]. Furthermore, to date no evidence (class I or II) statistically strong enough to support conservative management (or in fact any other form of management) of incidental meningiomas has been reported.

As a rule, at the time of diagnosis of an incidental meningioma, the following are evaluated: tumour size and location, and the patient's symptoms and clinical conditions. The lack of symptoms that define this category of meningiomas means that prompt intervention at the time of diagnosis is not always necessary. Nevertheless, it is important to understand the right time to intervene. Medium to large meningiomas in easily accessible areas should be considered as potential candidates for surgery, with or without preoperative radiological monitoring. Small asymptomatic meningiomas should be scheduled for radiological follow-up.

There are no precise guidelines for these follow-up intervals, and the data in the literature is

not unequivocal. Nonetheless, it seems sensible to suggest signs of potential evolution, including significant oedema, intralesional alterations or locations at critical, poorly accessible sites, be monitored with contrast brain MRI at 3 months; on the other hand, tumours with indirect indicators of stability, i.e. small–medium-size tumour at a non-critical/easily accessible site, lack of surrounding oedema and/or with large intralesional calcifications, can be reassessed on contrast brain MRI at 6 months and about 1 year after the initial finding [6].

Volumetric comparison with image fusion is recommended for follow-up, a method now common to both modern planning systems (GammaPlan) and neuronavigators that are now part of the ordinary neurosurgery department instrumentation. Following the first check-up (after 4–6 months) annual MRI exams are recommended for the first 5 years, to be brought forward in the event of the appearance of symptoms (there is no class I and II evidence for observation guidelines in meningiomas, but there are various level III studies supporting this practice) [4, 10, 18, 23] (evidence class III). Signs of growth are also an indication to treatment, even of small meningiomas, if symptoms attributable to the lesion appear. To detect growth, follow-up images should be compared with those taken previously by volume rather than by axial diameters, to determine whether there have been any neuroradiological changes indicative of more aggressive behaviour. This recommendation is especially important in younger patients (where there is a longer follow-up period and where a higher growth rate has been demonstrated) (evidence class III) [2, 4, 10, 17, 27]. As already mentioned, however, other variables need to be considered when deciding on the best course of treatment, specifically the:

1. General conditions of the patient
2. Patient's age
3. Tumour proximity to vital neurovascular structures (e.g. optic nerve, arteries or venous sinus)
4. Patient's expressed demand for treatment

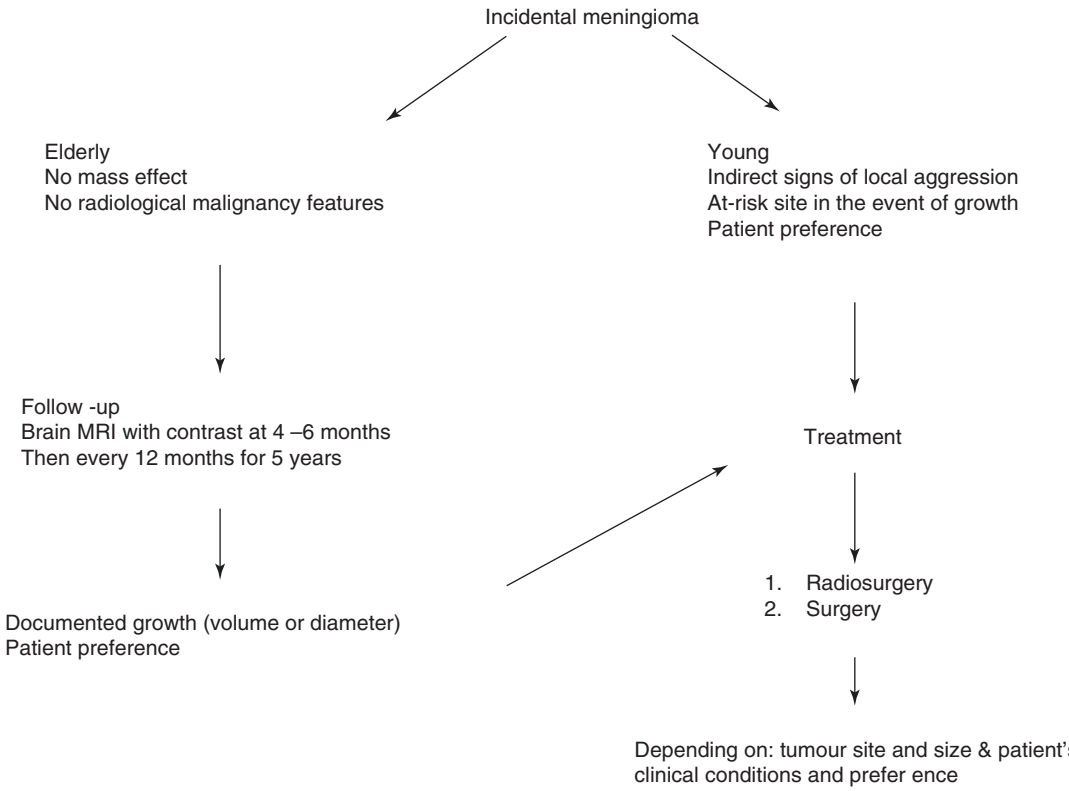
Radiosurgery should be an option in patients with small meningiomas, especially if young, who require treatment for the above reasons [4, 23], it being safe and associated with a low rate of complications [24].

14.3 Conclusions

For incidental meningiomas (i.e. asymptomatic and discovered incidentally) in the elderly, with no symptoms or major mass effect, and no neuroradiological characteristics of malignancy (distinct margins, and no hyperostosis, osteolysis, oedema, digitation or brain invasion), they should be scheduled for clinical and neuroradiological follow-up (brain MRI with contrast) at 4–6 months, and then at 1 year; subsequently, if stable, brain MRI with contrast should be performed every 12 months for 5 years, and then, if stable, every 2 years. In a younger subject with indirect signs of local aggression or marked oedema, even if asymptomatic, in any location, especially if it is surgically inaccessible or located near at-risk organs that might be affected by its growth, the possibility of radiosurgery should be assessed and discussed with the patient.

Meningiomas with documented (preferably volumetrically) growth, symptoms (even minor) or neuroradiological characteristics compatible with aggression must be treated, always taking into account patient preference. Radiosurgery finds the same indications for incidental meningiomas that become symptomatic described in the literature for other meningiomas.

Flow chart.



Proposed decision flow chart protocol.

We have taken into consideration the factors reported in the literature trying to obtain a useful tool for everyday activity.

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15 Side Effects of SRS Treatment of Low-Grade Meningioma: Types, Frequency and Management

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15.1 Introduction

Over the past 25 years, stereotactic radiosurgery has gained a well-defined and growing role in the treatment of intracranial meningiomas. It is used as a first-line therapy in cases of contraindication to or refusal of surgery, in elderly patients or those in poor health, and on tumours at sites that are difficult to reach; it can also be useful as a second-line treatment for surgical residues or tumour recurrence [1–15]. Though it was initially reserved for small-volume tumours (maximum diameter 3 cm or less) at a sufficient distance from critical structures such as the optic chiasm, optic nerves or brainstem, the range of applications of radiosurgery has now expanded. In fact, thanks to the use of hypofractionation techniques (up to five fractions), today radiosurgery can also be used to treat larger tumours and those in contact with organs at risk.

In meningioma therapy, radiosurgery has contributed to the spread of a new conceptual approach. When microsurgery for radical resection presents excessively high risks for the patient in terms of mortality and morbidity, radiosurgery, either alone or in combination with microsurgery, is now considered the best approach to controlling the progression of the disease while preserving neurological functions. The most common radiosurgery devices, Gamma Knife, CyberKnife and linac, allow comparable dose distributions, in terms of target coverage and normal tissue savings, potentially resulting in similar clinical outcomes in both the short and long terms. To date, however, there have been no major comparative studies or randomized controlled trials comparing these techniques, which are used differently depending on the centre; different forms of head fixation, doses, isodoses, imaging techniques and approaches to critical regional anatomy have all been reported, and

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determine a certain variability in terms of outcome and complications [16, 17].

That being said, long-term follow-up studies of patients with radiosurgically treated low-grade meningiomas reveal progression-free survival rates of 98%, 95% and 85% after 3, 5 and 10 years, respectively [18]. Results are even better in meningiomas of the skull base, where the progression-free survival rate after radiosurgery appears to reach 99.5% at 1 year, 98% at 3 years, 95% at 5 years and 90% at 10 years, with a 19% improvement in cranial nerve deficits when present before treatment [19].

Like any form of therapy, however, radiosurgery for low-grade meningioma can also be burdened with undesirable side effects, information on which—in terms of incidence, aetiology, mode of onset, evolution and treatment—would undoubtedly be helpful for the purposes of screening candidates for treatment, as well as assessing radiosurgical risks and predicting post-radiosurgery outcomes.

15.2 Aims

The aim of this review was to analyse the side effects of radiosurgery for meningiomas, with particular regard to the type, incidence, aetiology, mode of onset and predictability features, in order to aid the specialist in selecting candidates for treatment and also providing information on the management of complications, should these occur.

15.3 Materials and Methods

Literature references were identified through PubMed (https://www.ncbi.nlm.nih.gov/pubmed) searches using specific and sensitive keywords, as well as keyword combinations. In particular, the articles published from 1998 to 2020 relevant for the acquisition of data on the effects of toxicity after SRS for meningioma were analysed. The final list of references was made on the basis of their relevance to the scope of this review.

15.4 Discussion

Meningiomas are ideal targets for radiosurgery; they have well-defined and distinct margins under high-field MRI, and, being encapsuled, do not infiltrate surrounding brain tissue. In addition, their blood supply comes exclusively, or predominantly, from their base in the dura, which can be readily included in the treatment volume. This contributes to devascularization of the meningioma, resulting in ischemic tumour necrosis, which is one of the mechanisms through which the treatment exerts its effect.

However, the radiosurgery of meningiomas can be burdened with side effects, including cerebral oedema, radionecrosis, vascular lesions, cranial nerve damage and malignant transformation. The main side effects are summarized in Table 15.1.

The main symptoms related to side effects are summarized in Table 15.2.

15.4.1 Pathophysiology of Cerebral Oedema

In meningiomas, peritumoral oedema is vasogenic, not cytotoxic. Vasogenic oedema is caused by increased intratumoral capillary permeability with overflow of serum proteins and liquid into the extracellular spaces [20–22]. The increased vascular permeability of tumours may be due to

Table 15.1 Radiosurgery of meningiomas - main side effects

– Oedema
– Radionecrosis
– Vascular lesions
– Cranial nerve damage
– Malignant transformation

Table 15.2 Main symptoms related to side effects

– Signs of intracranial hypertension, with headache, nausea, vomiting, ataxia and/or convulsions
– Focal neurological signs and symptoms depending on the function of the damaged structure or cerebral anatomical area
– Skull nerve deficiency

irradiated meningiomas having high levels of expression of angiogenesis and hypoxia markers, vascular endothelial growth factor (VEGF-A) and hypoxia-inducible factor 1 (Hif-1).

Indeed, the VEGF pathway can participate in the formation of cerebral oedema by inducing the capillaries to become permeable, or 'leaky', resulting in the secretion of VEGF-A and plasma into the peritumoral brain tissue [23].

15.4.2 Pathophysiology of Radionecrosis

In cases of radiotreated meningiomas associated with radionecrosis and operated on as a result of uncontrollable worsening of perilesional oedema, histological examination showed intratumor radionecrotic areas, inflammatory infiltrations and vasal hyalinization [24]. The precise mechanism behind radionecrosis of the brain remains to be clarified. However, there are two theories, one based on radiation damage to blood vessels and endothelial cells, and the other involving radiation damage to glial cells. It is likely that both theories are correct to some extent.

According to the vascular hypothesis, radiation causes hyalinization of the blood vessel walls, leading to their thickening and occlusion [25]. Indeed, damage to small- and medium-sized blood vessels can cause ischemic phenomena leading to tissue demyelination and necrosis [26, 27]. Furthermore, animal studies have shown that vascular abnormalities develop before parenchymal damage [28].

According to the glial theory, on the other hand, radionecrosis results from direct damage to glial cells, in particular oligodendroglial cells [27, 29]. This is based on the fact that oligodendrocytes are very sensitive to radiation, which causes their demyelination and radio-induced apoptosis [30, 31]. Therefore, the changes in the white matter and reduction in the parenchymal volume often seen as a result of radiation may be attributable to damage to oligodendrocytes, while neurons are believed to be insensitive to radiation [32].

The host's immune response, inflammatory cytokines and fibrinolytic system disturbances also contribute to the onset of radionecrosis [29, 33].

Based on the interval between radiant treatment and the appearance of side effects, these can be distinguished into acute, subacute and late.

15.4.3 Acute Side Effects

These arise 12–48 h after treatment [34, 35]. They are attributed to the response of neoplastic tissue and peritumoral brain tissue to radiation. Their pathophysiology is not yet fully understood. However, a clear dose-volume relationship has been demonstrated, with a risk to the brain, intracranial vascular structures and cranial nerves that increases with increasing target volume [36, 37]. Oedemogenic mechanisms and radionecrotic phenomena are commonly blamed [38, 39], in particular:

- Intratumoral necrotic tissue and disintegration phenomena, which, by increasing tumour volume and intracapsular pressure, can affect intra- and local extratumoral venous pressure, leading to oedemogenic stasis.
- Direct radionecrotic effects on peritumoral cerebral parenchyma, with associated cerebral oedema.
- Pretreatment anatomical conditions related to the integrity or otherwise of the arachnoid mater and the extension of the meningioma–brain interface: In fact, rupture of this layer can lead to the onset of peritumoral cerebral oedema even before treatment, deteriorating thereafter.
- Direct oedemogenic effects of radiation by alterating the permeability of the blood–brain barrier.

These oedemogenic and radionecrotic phenomena can occur in the short or long term. When symptomatic, they may cause headache, nausea, vomiting, ataxia, epilepsy and other neurological signs and symptoms, depending on the function of the brain area affected.

Morphologically, oedema in the peritumoral area is clearly evident as hypodense on CT and hyperintense on T2-weighted and FLAIR MRI sequences.

As is the case with conventional radiotherapy, acute reactions may occur in association with the onset of transient oedema, occurring 12–48 h after treatment. This may be symptomatic or asymptomatic, but is generally completely reversible and unlikely to cause long-term issues. Routine administration of steroids for the immediate post-intervention period can prevent or mitigate clinical signs [24, 40, 41].

15.4.4 Subacute Side Effects

Subacute reactions occur 3–10 months later, and can either prove to be completely or partially reversible or progress to permanent sequelae. In subacute sequelae of radiosurgical treatment of meningiomas, as is the case in other slow-growing encapsulated extra-axial benign tumours, such as neurinomas, peritumoral oedema may be associated with tumour swelling. This phenomenon, which is not reported in the literature on conventional fractional radiotherapy, is linked to an intratumoral effect of radiosurgery. It is frequently followed, months later, by tumour shrinkage and progressive reduction of the surrounding oedema. It can therefore be considered a favourable prognostic sign, of which the clinician must be fully aware [40, 41].

15.4.5 Late Side Effects

Late reactions, associated with clinical neurological signs and persistent densitometric alterations on MRI scans after 2 years, indicate peritumoral brain damage. This may manifest as coagulation necrosis without mass effect or hypointense colliquative necrosis with mass effect and peritumoral oedema. Radionecrosis is associated with and often results in significant cerebral oedema, and in fewer than 1% of cases the appearance of cystic formations is also detected. When the overall mass effect becomes severe and no longer controllable by anti-oedema therapy, surgical decompression must be considered (Fig. 15.1) [40, 41].

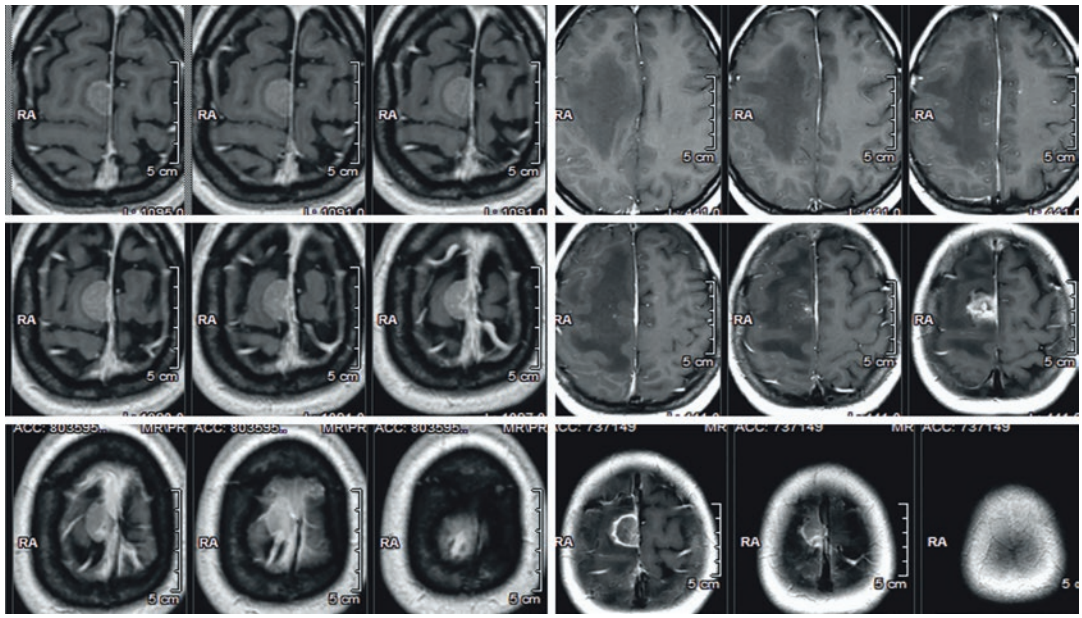

Fig. 15.1 Meningioma of the parasinusal falx treated via Gamma Knife with 13 Gy and 50% isodose (left). Symptomatic oedemogenic reaction associated with tumour volume reduction 12 months after treatment (right)

It has long been known [42–44] that oedemic and radionecrotic effects occur three times more frequently [37] in meningiomas of the cerebral convexity, falx and parasagittal sites, close to the superior sagittal sinus, than in those of the skull base. In some studies, paraspinal parasagittal sites were predictive of a greater likelihood of symptomatic oedema onset [45, 46] than the other two locations, but this has not been confirmed in other studies [24, 40, 41, 47].

One likely explanation for the different incidence of complications between skull base and convexity meningiomas lies in their different growth patterns. While skull base meningiomas usually expand laterally along the cisterns, convexity, falx and parasagittal meningiomas develop deep in the cerebral cortex [48]. In addition, while meningiomas of the skull base are typically and predominantly extra-arachnoid, those of convexity and, in particular, parasagittal are often intra-arachnoid. The lack of the mechanical and biochemical barrier function exercised by the arachnoid membrane against mediators released by the tumour may explain the greater susceptibility to oedema onset [49]. Indeed, meningiomas that have previously undergone surgery are associated with a lower risk of oedema, regardless of their location, due to changes in the interface with the parenchyma.

Peritumoral oedema occurs independently of the invasion and subsequent irradiation of peritumoral veins, including the major sinuses [50]. Furthermore, post-radiosurgical oedema has no link to tumour control [41]. Unfortunately, dose staging, or hypofractionation, does not provide sufficient reassurance in terms of oedema prevention [49].

Post-radiosurgical oedema is treated via cortisone therapy, and may resolve over a period ranging from 2 to 6 months [22, 40, 43], 12 to 16 months [3, 48, 51] or even 2 to 4 years [20, 38, 52]. Nevertheless, symptomatic oedema persists in 1–20% of cases, and determines the need for surgery to remove the meningioma [46, 47, 53, 54]. In such cases, peritumoral oedema decreases almost immediately after meningioma resection. This suggests that the factors responsible for oedema onset lie in the irradiated meningioma, and are not in fact related to a direct effect of radiotherapy on the peritumoral brain and vascular system, as occurs in arteriovenous malformations [49].

15.4.5.1 Cranial Nerve Deficits

Toxicity to cranial nerves mainly arises from skull base meningioma treatment, and generally affects fewer than 5–10% of cases. It is influenced by a number of variables, which include the type of nerve, its irradiated volume, the maximum dose received, pre-existing neurological deficits and/or previous surgeries [19, 55, 56].

Optic neuropathy can arise following the treatment of meningiomas close to the optic nerves, chiasm and pathways. In previous studies it has been shown that radiation-induced optical neuropathy occurs in about 30% of patients given a dose of more than 10 Gy and up to 15 Gy, while with doses above 15 Gy it occurs in about 80% of cases [57]. Single-dose treatments of less than 8 Gy do not cause visual complications. Single-dose treatments of 10 Gy or with a maximum point dose of 12 Gy, and hypofractionated treatments that exceed 20 Gy in three fractions and 25 Gy in five fractions, are associated with a 1% risk of radio-induced optical neuropathy [58].

Other cranial nerves tolerate a higher dose [11]. These may be involved when treating petroclival meningiomas, and those of the cavernous sinus or cerebellopontine angle. Neuropathy can develop in up to 10% of patients given single-dose treatments with an average peripheral dose of 13 Gy and isodose of 50% on an average volume of 8.1 cm^3, with a 3.5% likelihood of onset at 1 year, 5.5% at 2 years and 7% at 5 years [19].

15.4.5.2 Malignant Transformation

In patients treated with stereotactic radiosurgery, the estimated risk of secondary intracranial malignancy within the volume delimited by a peripheral isodose of 2 Gy is low, as is the risk of malignant transformation of Grade I benign meningioma; at long-term follow-up it remains similar to the general population's risk of getting primary cancer of the central nervous system (CNS). In fact, a multicentre retrospective cohort study of cases treated in Europe and the United

States reported that the total incidence of malignant transformation was about 6.80 per 100,000 patient-years after an average follow-up of 8.1 years, while it was 2.26 per 100,000 patient-years for intracranial malignancy associated with radiosurgery. The cumulative 10-year incidence was 0.045% [59]. According to estimates by the Central Brain Tumor Registry of the United States (CBTRUS) and the International Agency for Research on Cancer (IARC), this figure is similar to the risk of the general population of the United States and some European countries developing a malignant CNS tumour. In a further 15-year follow-up study, the incidence of malignant transformation was 2.2% (occurring in 7 out of 316 meningioma patients) [60].

After surgery, the incidence of histological progression of unirradiated Grade 1 meningiomas to a higher malignancy grade ranges from 0.54%, i.e. 5 cases out of 923 primary meningeal tumours operated on over a period of 17 years [61], to 6.28%, i.e. 11 recurrent meningiomas out of 175 operated on, over an average period of 112 months. All of these cases showed histopathological progression to a higher grade, associated with an aggressive clinical course; in particular 6 tumours showed malignant transformation and 5 were classed as atypical [62]. Although prospective cohort studies with longer follow-up are needed to support this data, the available evidence suggests that stereotactic radiosurgery is safe in the long term.

15.5 Conclusions

Stereotactic radiosurgery provides good growth control in low-grade meningiomas. Like any treatment, however, there may be side effects. Knowledge of side effects is therefore of major importance for the assessment of radiosurgical risk, and enables a more rational evaluation of treatment indication. In particular, in order to make a correct pretreatment selection of patients and put in place the appropriate therapeutic measures should they occur, the type, incidence, aetiology, mode of onset and predictability features of these side effects must be taken into consideration.

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Spinal Meningioma Radiosurgery

16

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16.1 Introduction

Tumours of the spine and spinal cord are rare; as a whole they account for about 15% of neoplasms involving the central nervous system. In particular, meningiomas account for 25–46% of primary spinal tumours. They are intradural, extramedullary and generally benign [1]. Spinal meningiomas originate from the hairy cells of the arachnoid, at sites where the nerve roots emerge, or, alternatively, from the fibroblasts contained within the dura or pia mater. The origin of these tumours affects the site of their development within the spinal canal, the former giving rise to lateral lesions and the latter to ventral or dorsal lesions.

They may appear at any age, although their peak incidence is between the fifth and seventh decades of life. Women are the most affected (75–85%). In 80% of cases the dorsal tract of the spinal column is involved, followed, in order of frequency, by the upper cervical spine and the foramen magnum. In the latter case, lower cranial nerve involvement is not uncommon. The lower cervical, lumbar and sacral spines are relatively infrequent sites [2–6].

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Spinal meningiomas are usually single lesions, but in 1–2% of cases they can occur at multiple sites [7]. In most cases they are completely intradural, but in 10% of cases they can have intra-extradural development or be completely extradural [3]. Their base is often larger than might be expected. Intralesional calcifications are possible. Differently from the intracranial counterpart, bone involvement is extremely rare, due especially to the well-defined epidural space of the spine.

16.2 Presentation and Diagnosis

Meningiomas are characterized by slow growth. At the time of diagnosis, patients often complain of symptoms that can date back as far as 1–2 years. These symptoms are typically due to compression of adjacent nervous structures, and vary depending on the location of the tumour development. They often manifest as a common back pain, complex myelopathy or sensory-motor radiculopathy [8–10].

The diagnosis is typically based on MRI, in which meningiomas appear typically isointense on T1- and hyperintense on T2-weighted images, with a moderate, homogenous post-contrast enhancement.

The presence of the typical “dural tail” sign helps distinguish them from schwannomas and neurofibromas, compared to which, in any case,

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they tend less often to be developed through the intervertebral foramina [8, 11, 12]. That being said, the only sure diagnosis is through histopathological examination.

16.3 Treatment Strategies

Possible strategies for treating meningioma include surgery and radiotherapy. Microsurgery, the safety and efficacy of which are well documented, is still the treatment of choice for these tumours [11, 13–17]. However, not all patients are good surgical candidates because of their age or comorbidities, or due to the recurrent nature of the tumour or the presence of multiple tumours. Furthermore, surgery is burdened by a not always negligible morbidity rate [9, 15, 18–21], and since it is often not possible to achieve complete resection, alone it is not always able to guarantee satisfactory local tumour control.

Conformational 3D radiotherapy is generally not considered to have sufficient precision to treat benign lesions in close proximity with the spinal cord.

Radiosurgery, which allows the dose to at-risk organs to be limited, therefore appears to be an extremely appealing option. On the other hand, the current literature evidence strongly supports the efficacy and safety of radiosurgery in the treatment of intracranial counterpart of meningiomas [22–24]. Moreover, while the first radiosurgery systems were exclusively frame based, and therefore unsuitable for the treatment of extracranial tumours, the development of frameless systems based on image guidance has made it possible to extend the technique to spinal lesions. As a fact, radiosurgery for benign spinal tumours including meningiomas is gaining ground gradually [25–30] and today it represents an alternative to treat such lesions. A typical spinal meningioma with its relative radiosurgical plan is depicted in Fig. 16.1.

16.3.1 The Problem of Spinal Cord Tolerance

Given its potential, radiosurgery for the treatment of malignant tumours of the spinal cord has become an appealing field of research and development [31–37]. However, the spinal cord has a low tolerance for radiation, and the risk of radiation-induced myelopathy represents the main limitation to the use of the doses necessary to obtain optimal control of tumours [38–44]. The favourable prognosis and long life expectancy of patients suffering from spinal meningioma make the issue of radiation-induced myelopathy more problematic than ever because of the long time they have to develop it. According to some authors it may even arise as late as 24 months after treatment [25, 45–47]. This, probably, underlies the delay in the development of radiosurgery for the treatment of benign spinal cord tumours.

However, relatively recent data have at least partially mitigated these concerns. Kirkpatrick et al. [40], for example, as part of the QUANTEC project, estimated a radiosurgical risk of myelopathy of <1% for a maximum dose to the spinal cord of less than 13 Gy when administered in a single fraction, and less than 20 Gy when administered in three fractions. Nonetheless, the same authors conclude that the current data are insufficient to calculate an actual dose/volume relationship related to the development of myelopathy for either single- or multiple-session radiosurgical treatments.

Gibbs et al. in 2009 [45] reported only 6 cases of myelotoxicity in over 1000 patients undergoing spinal radiosurgery (benign and malignant lesions). Of particular interest is the fact that only three of these patients received a considerably higher than average dose to the spinal cord.

The authors concluded their analysis by pointing out the low incidence of complications for radiosurgical treatment of spinal lesions (<0.6%). Based on neuropathological observations, the authors hypothesized that myelopathy is medi-

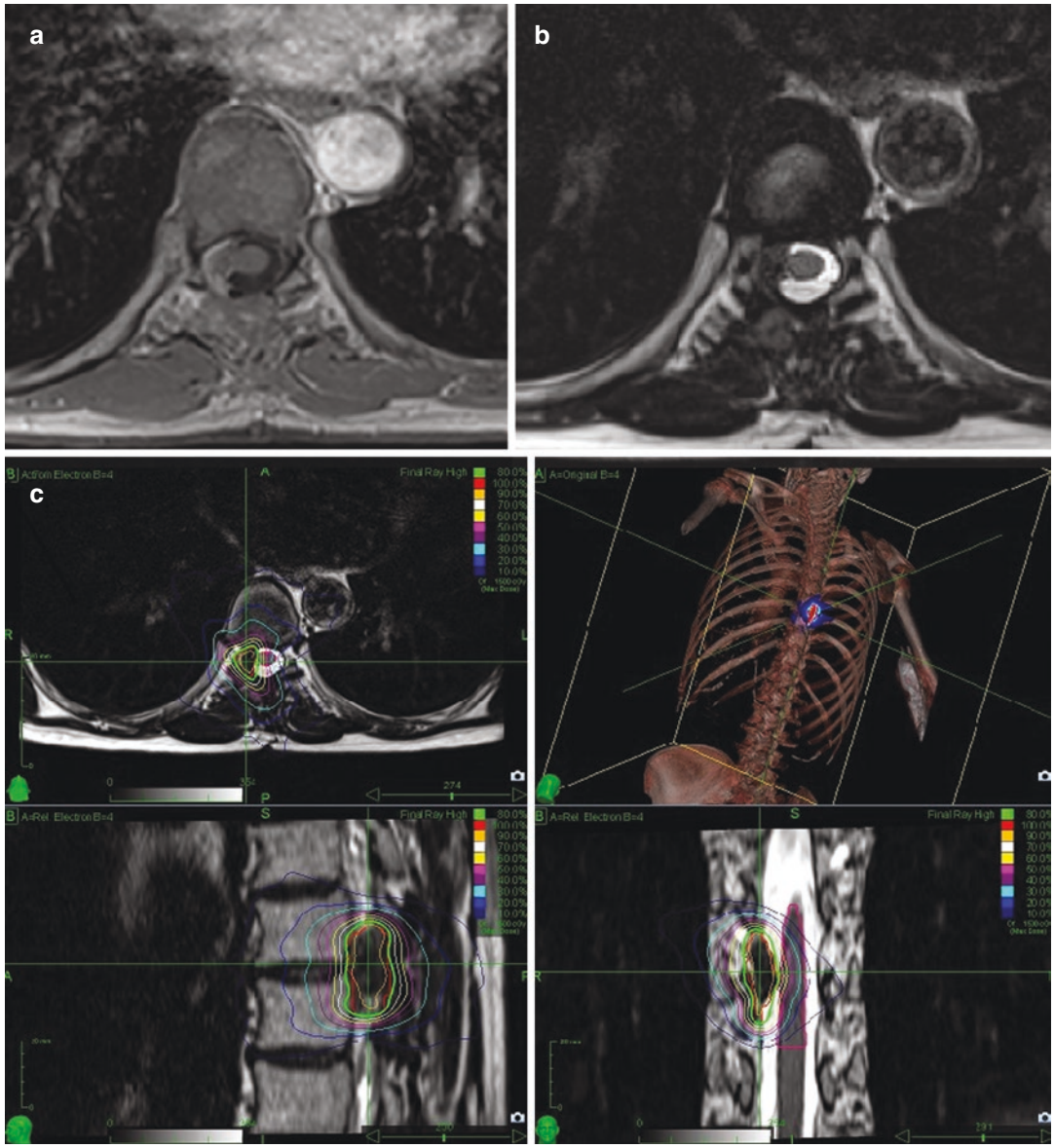

Fig. 16.1 A T8–T9 right-side meningioma is depicted: (**a**) an axial T1-weighted contrast-enhanced image; (**b**) axial T2; (**c**) 3D treatment plan, meningioma is contoured and the main reference isodoses are presented

ated by damage to the white matter and, at the same time, local vascularization. Demyelination, necrosis, increased vascularization, telangiectasia, hyaline degeneration, vasculitis aspects, fibrin exudation, thrombosis and oedema appear to be common. The authors suggested that limiting the volume of irradiated spinal cord may help to reduce the risks of exposure, but pointed out that a precise dose/volume relationship for myelotoxicity is yet to be defined.

Finally, a recent review of patients undergoing spine re-irradiation indicated a cut-off value of BED below which there would be no myelopathy. In this study, in fact, none of the patients treated with cumulative BED_2 of less than 102 Gy (BED_3 85 Gy) developed signs or symptoms related to spinal cord-related toxicity. It is also important to note that the authors documented the absence of toxicity when the interval between treatments was longer than 2 years [48]. Although

still preliminary, the data as a whole seem to support the safety of radiosurgical treatments of the spine.

16.4 Clinical Experiences

Waiting for better defined data on spinal cord tolerance, the efficacy and safety of radiosurgery for the treatment of spinal meningiomas seem to be confirmed by the first clinical experiences.

In 2008, Gerstzen et al. reported about 73 benign spinal tumours treated by single-session radiosurgery, including 13 meningiomas [25]. The average volume of treated meningioma in this case was 4.9 cc (0.8–16 cc), with a mean prescribed dose of 21.25 Gy (17.5–25 Gy). After an average follow-up of 37 months (8–71 months), the authors reported no cases of radiological progression. In one patient, a transient Brown-Sequard syndrome was observed.

In 2011, the Stanford University team published their data on both single- and multiple-session radiosurgical treatment of 103 benign intradural extramedullary spinal lesions, including 32 meningiomas [28]. The average volume of the treated meningioma was 3.03 cc (0.14–11.5 cc), and the average dose administered was 20.6 Gy (16–30 Gy) in 1–5 fractions. After an average observation period of 33 months (range 6–87 months; median 29 months), none of the meningioma treated increased in size (47% were stable and 53% shrank). Neurologically, 91% of those patients displayed stability or improvement. One patient suffering from a relatively small, recurrent (previously debulked), C7-T2 meningioma developed a transient myelitis 9 months after the radiosurgery.

In 2012, Gerszten et al. in a similar experience, but using different radiosurgical technology, reported similar results [26].

Our group have previously reported [27] the results of radiosurgical treatment for 21 benign intradural extramedullary spinal lesions, 13 of which were meningiomas. After an average observation period of 43 months (32–73 months), none of the lesions showed volumetric progression, and neurological conditions were always preserved or improved.

The main outcomes of reported clinical experiences of the treatment of spinal meningiomas are shown in Table 16.1.

Table 16.1 The table shows the results from major published studies with the main treatment parameters

Authors	Meningioma # (included tumours)	Mean FU (months)	Mean volume cc (range)	Device	Mean prescription dose (Gy)	Fractions #	Local control (%)	Toxicity
Gerszten et al. (2008) [25]	13 (73)	37	4.9 (0.8–16)	CK	21.25 (17.5–25)	1	100	1 patient
Sachdev et al. (2011) [28]	32 (103)	33	3.03 (0.14–11.5)	CK	20.6 (16–30)	1–5	100	1 patient (transitory Brown-Sequard syndrome)
Gerszten et al. (2012) [26]	8 (40)	26 (median)	13.7 (0.37–94.5)	Synergy	sRS14 (11–17) mRS 18–21	1 (or 3)	100	0
Marchetti et al. (2013) [27]	13 (21)	43	5.2 (0.5–17.7)	CK	sRS 11.6 (10–12) mRS 22.7 (18.5–25)	1–6	100 (25% PR)	0

sRS single-session radiosurgery, *mRS* multisession radiosurgery, *CK* CyberKnife, *PR* partial response, *FU* follow-up

16.5 Conclusions

Waiting for more definitive results from larger series with a longer follow-up period, the review of the current literature supports the effectiveness and the safety of radiosurgical treatment of spinal meningiomas. Particularly, radiosurgery is confirmed as an effective alternative to treat spinal meningioma, at least for patients who are not suitable for an open surgery as well as for post-surgical remnants or recurrent tumours.

To improve the knowledge regarding the radiation tolerance of the spinal cord and enhance neuroradiological techniques for a better definition of the target volume, further studies are mandatory.

Conflict of Interest The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this chapter.

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17 Guidelines and Evidence-Based Recommendations for the Radiosurgical Treatment of CNS Meningiomas

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Abbreviations

CISS	Constructive interference in steady state
CNS	Central nervous system
CT	Computed tomography
EANO	European Association of Neuro-Oncology
GI	WHO Grade I MN
GII	WHO Grade II MN
GIII	WHO Grade III MN
GLs	Guidelines
GTR	Gross total resection
Gy	Gray
ISRS	International Stereotactic Radiosurgery Society
LGK-RS	Leksell Gamma Knife radiosurgery
LINAC	Linear accelerator
LTC	Local tumour control
MDT	Multidisciplinary team
MNs	Meningiomas
MRI	Magnetic resonance imaging
NHS	National Health System
PD	Prescription dose
PFS	Progression-free survival
PMCC	Princess Margaret Cancer Centre
RT	Radiotherapy
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
STR	Subtotal resection
WHO	World Health Organization

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17.1 Introduction

This chapter covers the use of stereotactic radiosurgery (SRS) for meningiomas (MNs), providing the criteria for identifying the patients for whom this treatment is indicated. MNs are the most common primary intracranial tumours, accounting for 13–35% of intracranial tumours in adults. They are much rarer in children and adolescents, totalling 1.4% of all benign intracranial tumours [1]. The annual incidence of MN is 5–6

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cases per 100,000, and tends to increase with age, particularly from the third to the sixth decades; it is more predominant in women (female/male ratio: 2:1–3:1) [2, 3]. The risk of developing an MN over a lifetime appears to be 1%, and the incidence of the disease is increasing as the average age of the population rises [2, 4].

Although sporadic MN may be multifocal in 10% of cases [4–8], MNs are generally single and slow growing. Retrospective studies have reported estimated annual growth rates of between 0.02 and 0.8 cm per year (**Class III evidence**) [7, 9, 10], and 4-year radiological follow-up studies seem to indicate a linear growth pattern (**Class III evidence**) [11] and a 77% probability of growth. Over 4 years of follow-up, MNs of the cerebral convexity have shown a tendency to grow more readily, with 75% of convexity MNs growing by at least 15% in the volume with respect to only 34% in skull base MNs **(Class III evidence)** [12].

Most MNs are WHO Grade 1 (GI). However, according to the most recent studies, based on the new 2016 WHO classification criteria, the frequency of atypical or malignant variants (GII and GIII) may reach 20–30%, i.e. around a quarter of intracranial MNs [4, 12–18]. 25–50% of MNs involve the skull base [4, 6, 9, 16, 19]. Unlike convexity MNs, which are often asymptomatic until they reach a large size or cause epileptic manifestations, skull base MNs can invade neurovascular structures, resulting in symptoms related to cranial nerve deficit (diplopia, visual impairment, facial paraesthesia, hearing loss) (**Class III evidence**) [20, 21].

Treatment for MN is provided with the aim of stabilizing or improving such symptoms. Since the early 1990s, the role of SRS in the treatment of MNs has become increasingly established, including as a first-line option, especially in the elderly and for MNs in critical areas. The favourable mortality, morbidity and post-operative recurrence rates in comparison to surgery, and the better quality of life in patients treated with SRS, have significantly changed the therapeutic criteria for these pathologies. A classic example is the treatment of skull base MNs, especially those of the cavernous sinus and posterior fossa, for which radiosurgical treatment is preferred, with surgery having the role of reducing tumour mass.

To date, hundreds of thousands of MNs have been treated via SRS [22]. The numbers of treatments performed using Leksell Gamma Knife SRS (LGK-SRS) are known, but thousands of other cases are treated using other SRS techniques (LINAC, CyberKnife, proton therapy). These methods have become widespread thanks to several factors, including the ease with which treatment plans can be defined, the fact that it is generally performed in a single session and the precision of the dose conformation, with one or more isocentres, via immobilization of the head via a rigid, frame-based helmet or thermoplastic mask. LGK-SRS in particular is characterized by extreme mechanical precision, lack of movement of components, lower exposure of the rest of the body to radiation and a high dose gradient. In addition, the biological characteristics of slow-growing MNs (low α/β ratio) provide ample time for the cytotoxic effect and vascular obliteration, enabling an effective and lasting control of tumour growth to be established without toxicity to the surrounding tissues. Targets can be very effectively located on T1-weighted MRI scans with contrast, and constructive interference in steady-state (CISS) sequences can be used to highlight cranial nerves and other critical structures, meaning that treatment plans can be drawn up with extreme accuracy. The results, in terms of treatment efficacy and morbidity, are excellent, with local tumour control (LTC) and progression-free survival (PFS) rates of around 86.2–97.9% [23].

The recent introduction of volume staging and hypofractionation techniques has broadened the indications of SRS to include larger MNs close to critical structures. In recent years, the development and dissemination of different radiotherapy approaches as an alternative to or in combination with traditional neurosurgery for the treatment of MNs have prompted many authors and several international centres to publish guidelines (GLs) on the diagnosis and treatment of MN. In addition, since the new WHO classification of CNS tumours, including MNs, has been issued, long-

follow-up case studies (a minimum observation period of 10 years is now mandatory) assessing the effectiveness of treatments have been providing data that has revolutionized previous approaches. Many studies have confirmed the effectiveness of SRS in MNs, especially those arising on the skull base. In a series exceeding 100 patients treated with marginal doses of 12–15 Gy, PFS exceeds 90% at 5 years [24–26], and morbidity rates are 5–10%. These outcomes are much better than those obtained from microneurosurgery, especially in the treatment of complex MNs of the skull base.

As with microsurgery, control of GII and GIII MNs is much lower; however PFS is 50% at 2 years for the former and 17% at 15 months for the latter [25]. It is therefore timely to include a chapter dedicated to a systematic review of the main GLs published on the issue in this book dedicated to the management and treatment of CNS MNs. The aim of this chapter is to present an overview of the evidence and provide an up-to-date reference on the radiosurgical treatment of intracranial MNs.

17.2 Available Guidelines

PubMed (https://www.ncbi.nlm.nih.gov/pubmed) was screened for relevant references using specific and sensitive keywords and keyword combinations. When available, we also collected existing guidelines from other national and international scientific societies. The final list of references was made on the basis of the articles' originality and relevance to the scope of this review.

The recommendations are based on four classes of scientific evidence, specifically:

- *Class I evidence*: from randomized prospective trials with high statistical power, in full compliance with the criteria for randomization, outcome assessment, exclusion and dropout, and balancing features
- *Class II evidence*: from prospective cohort studies not possessing all the features required of Class 1
- *Class III evidence*: from all other types of clinical trial on representative populations, including those with historical controls
- *Class IV evidence*: from unsealed studies, case reports and expert opinions

Based on these types of evidence, the European Association of Neuro-Oncology (EANO) guidelines [27], in line with those issued by the International Stereotactic Radiosurgery Society (ISRS) and the NHS England Clinical Commissioning Policy: Stereotactic Radiosurgery/Radiotherapy for Meningioma and the clinical practice guidelines CNS-005, version 2, on intracranial meningiomas by the Alberta Health Service [28–30], indicate three levels of recommendations:

A. Indication of efficacy from one or more sources of Class I evidence (randomized prospective trials), or two robust Class II studies (prospective or cohort studies or control cases)
B. Indication of probable efficacy from one or more Class II studies of lower statistical power, or robust Class III studies (retrospective studies)
C. Indication of possible efficacy from two or more Class III studies

Below level C, in the absence of higher levels of evidence, recommendations of "good clinical practice" on the basis of indications of radiosurgical technology experts are made. Indeed, although MN is the most common brain tumour, scientific prospective controlled trials are unfortunately rare, and the treatment of these tumours is often dictated by the experience of the centre, based on retrospective scientific studies of patient series that are not always perfectly homogeneous. This limits the strength of the available recommendations and their applicability on a large scale. In fact, in this field, there is no scientific evidence above Class III. Therefore, treatment recommendation levels are currently only B, C and "good clinical practice".

That being said, the various papers published over the last 6 years do contain some interesting

suggestions that deserve to be mentioned, and since 2012, several guidelines and reviews of the evidence regarding the management of intracranial MNs have been published. In this chapter we report the aspects that are best covered in the literature and appear particularly relevant to the treatment of intracranial MNs.

In June 2012, the Alberta Health Services published the Clinical Practice Guideline CNS-005 version 2 on intracranial MNs [30]. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial CNS Tumour Team and a "Knowledge Management Specialist" from the Guideline Utilization Resource Unit. This document states that small MNs with benign, asymptomatic radiological characteristics can be monitored without therapy via periodic computed tomography (CT) or MRI scans. There is no Class I or II evidence to support this directive, but this approach has been validated in many reviews and retrospective series (**Class III evidence, level C recommendation**). Microsurgery is deemed the correct approach for patients who are not candidates for periodic control alone. Five cardinal recommendations are made on this point, indicated below in brackets. Specifically, surgery is recommended if the injury causes symptoms or shows a tendency to grow over the course of monitoring (*Recommendation 1*). The goal is gross total resection (GTR), which offers the best chances of recovery, especially for GI MNs. There are, however, cases in which MNs cannot be radically removed due to their proximity to critical vascular or neural structures, such as cavernous sinus and petroclival MNs, and those involving the posterior tract of the superior sagittal sinus and the optic nerve sheath. In such cases, for GI MNs that cannot be wholly removed, or for symptomatic relapses, radiotherapy is recommended for primary, adjuvant or salvage purposes (*Recommendation 2*). Radiological diagnosis is considered sufficient for these cases. With regard to Grade II or III MNs, given the frequency of post-operative relapse, microsurgery followed by RT (*Recommendation 3*), or SRS (*Recommendation 4*), if feasible, is recommended, in this event with higher marginal doses. Although there is only limited data available on the use of systemic agents in the treatment of MNs, the Alberta team suggests that systemic treatment may be considered on a clinical trial basis in cases of unresectable tumours or those in which all other therapies have failed to prevent recurrence (*Recommendation 5*).

NHS England's Clinical Commissioning Policy on SRS/stereotactic radiotherapy (SRT) for MN (NHS England D05/P/e), published in September 2013 [29], suggests that the three treatment options (surgery; SRS, SRT or multifractionated RT without or with stereotactic localization, and periodic monitoring alone) be decided upon by a multidisciplinary team. The fundamental role of the multidisciplinary neuro-oncological team for patient selection, the choice of treatment mode (surgery, radiotherapy or conservative), is emphasized.

Microsurgery is recommended in all cases with minimal or absent risk. This solution allows histological diagnosis and cytoreduction, and in some cases radical removal. For MNs located in unfavourable locations or in cases in which surgery would be burdened with the risk of severe neurological damage (skull base, posterior fossa, parasagittal, parafalcine or intraventricular MNs), SRS is recommended as the primary treatment, in line with the data collected over the past 20 years (Class III evidence, level B recommendation). Indeed, the available data show excellent disease control over time [24–26] and a lower impact on the quality of life with only brief hospitalization.

These recommendations, in particular those concerning cavernous sinus MNs, are shared by the ISRS guidelines, drawn up following a systematic review of publications on the subject [28]; their authors also recommend SRS for the treatment of mildly symptomatic cavernous sinus MNs (Class III evidence, level B recommendation). In the treatment of MNs, there is not currently sufficient clinical evidence to support SRS in no more than five fractions. RT in more than five fractions, on the other hand, plays a role in the treatment of bulky MNs of the cranial base (Class III evidence, level C recommendation).

In the above analyses, considerations are also made on the costs of SRS procedures and hospi-

tal stays, which are much lower than for microsurgery, and the expense of post-operative instrumental controls, which are equivalent for both techniques.

There is little data on the natural history of untreated MNs; radiological progression and onset of new deficits are indicated in percentages from 25% to 75% [31–33]. In the particular case of small MNs that are asymptomatic and calcified, especially in the elderly, progression is slow [34], and a wait-and-scan strategy is indicated. However, in cases in which waiting could complicate any intervention due to tumour growth, there is a consensus that action must be taken, as it is impossible to predict whether and how quickly progression will occur. Due to the risk of compression on adjacent structures resulting in permanent neurological deficits, the NHS England Clinical Reference for SRS recommends that a team of radiosurgeons, neuro-oncologists and neuroradiologists establish case selection and design and plan treatment, noting that SRS/SRT are options for primary, adjuvant or salvage therapy.

As for surgery, its radicality is classified according to the following Simpson grades:

- Grade 1: Complete tumour resection, including dural attachment and affected bone
- Grade 2: Complete tumour resection and coagulation of the implant base
- Grade 3: Complete tumour resection, leaving dural attachment and affected bone intact
- Grade 4: Partial resection
- Grade 5: Biopsy

The first three Simpson grades are considered gross total resection (**GTR**), while grade 4 is termed subtotal resection (**STR**).

According to Sun et al. [35], who conducted a review of the literature on the treatment of MNs based on the WHO 2007 criteria, GTR (Simpson grades 1–3) provides better long-term control than the STR (Simpson grade 4) in GI MNs (Class III evidence, level B recommendation). However, they also introduce the term "maximum safe resection" as the most appropriate strategy for GTR in critical locations, irrespective of the MN grade (Class III evidence, level B recommendation).

After GTR of GII MNs, they recommend active surveillance, reserving radiation treatment only for cases of relapse, due to the risk of radiation necrosis (4.2–10.2%), while they deem adjuvant RT/SRS suitable for STR of GII (Class III evidence, level C recommendation). In cases of GIII MNs subjected to STR, on the other hand, SRS can be used after RT failure if the size of the residue allows.

Based on their research, the authors also suggest the following evidence-based medicine (EBM) recommendations for WHO GII and GIII MNs:

A. EBM Level 3, Grade 1C recommendations:
   1. Maximal safe resection of GII and III MNs
   2. Active surveillance after GTR of GII MNs
   3. Adjuvant RT after STR of GII MNs
   4. Adjuvant RT after resection of GIII MNs
B. EBM Level 3, Grade 2C recommendations:
   1. Selective RT for GII MNs, based on the absence of histopathological necrosis
   2. Adjuvant SRS for small residual GII MNs after STR

Following their assessment of the scientific literature, the EANO MN Task Force also proposed a framework of the evidence-based recommendations [27] for the best possible diagnosis and treatment of MNs, which are very similar to those expressed in recent studies. They state that asymptomatic patients, especially if elderly, can be managed by observation alone. No Class I or II evidence exists to support a guideline for observational management of MNs, but many retrospective series and several reviews validate this approach (Class III evidence, level C recommendation).

In symptomatic patients who do require resection, GI MNs do not need additional RT or SRS if GTR is achieved. Instead, patients with GI MNs who cannot undergo surgery can be treated via fractionated RT or SRS (Class III evidence, level B recommendation). If only STR is possible in GI MNs (if the patient is elderly and/or the resi-

due not surgically accessible), SRS should be administered, or RT if the tumour volume precludes SRS.

GII MNs need only periodic monitoring after GTR, without any adjuvant RT. After STR, on the other hand, or in cases of GII progression or relapse, adjuvant or salvage RT or SRS (depending on residue size) should be considered (Class III evidence, level C recommendation). For GIII MNs, the most radical surgery possible is recommended, followed in all cases by fractional RT. As with microsurgery, the control of GII and GIII MNs is much lower, with PFS rates of 50% at 2 years and 17% at 15 months, respectively, having been reported [25].

Regarding the observation period, recommendations available are based more on expert consensus opinion than on scientific evidence ("good clinical practice" recommendation). This dictates that follow-up of GI MNs should be performed annually, and then every 2 years after 5 years; GII MNs should be followed up every 6 months, and then annually after 5 years; GIII MNs should be followed up indefinitely, every 3–6 months.

The GLs for the neurosurgical management of intracranial MNs proposed by the Neuro-oncology section of the Italian Society of Neurosurgery Study Group [36] also rely on the same criteria to indicate the strength of their recommendations. They point out that therapeutic decisions should be dictated by factors related to the patient (age, comorbidity, performance, informed choice), disease (tumour location, size, rapid growth, calcifications, signs of brain invasion) and limitations of the various treatment options (resection potential, operating risks, possibility of control with radiotherapy, risks related to it). They reiterate that drug therapy may play an important role in the future, but data is still scarce.

In 2018, the Princess Margaret Cancer Centre (PMCC) published its Clinical Practice Guidelines [37] for each WHO grade of MN. In WHO GI MNs, complete surgical resection is the treatment of choice for most non-skull base tumours, although it is difficult to achieve Simpson grade I resection in vertex parasagittal tumour locations due to the tumour's attachment to the superior sagittal sinus. In newly diagnosed symptomatic MNs that cannot be treated surgically (e.g. of the cavernous sinus, optic nerve or other skull base locations), RT is usually recommended as a first-line therapy. Upfront RT or delayed RT are also options for MNs subjected to partial resection, and therefore with residual tumour. For recurrent MNs, upfront RT is usually recommended.

In WHO GII MNs, GTR is recommended whenever possible; where GTR has been achieved, observation and RT for recurrence are (usually) recommended, as the 10-year relapse rate is approximately 50%. With STR or recurrent tumours, RT is (usually) recommended. In WHO GIII MNs, on the other hand, GTR is recommended whenever possible, and RT is recommended in all cases, regardless of the degree of resection achieved. With reference to SRS, the PMCC recommends that the maximal tumour diameter should not exceed 3 cm, and that SRS is suitable for skull base MNs at initial presentation, as well as residual/recurrent GI MNs and recurrent GII/III MNs after prior fractionated RT. Advised SRS prescribed doses (PDs) range between 12 and 14 Gy, based on the location and aggressiveness of the tumour.

More recently, the International Stereotactic Radiosurgery Society (ISRS) has published evidence-based practice guidelines for SRS in benign intracranial non-cavernous sinus MNs [38], based on a review of literature from three electronic databases (PubMed, EMBASE and the Cochrane Central Register). Out of the 2844 systematically reviewed articles in English specific to SRS for benign intracranial MN published from January 1964 to April 2018, 27 studies met the criteria for inclusion in their analysis, and all but one were retrospective. The results of the review showed that PDs typically ranging between 12 and 15 Gy, delivered in a single fraction, were associated with 10-year PFS rates ranging from 55% to 97%, and generally low toxicity, with post-SRS neurological deterioration rates ranging from 0% to 13.3% (median 7.4%). The authors concluded that the current literature supporting SRS for benign intracranial MNs lacks Class I and II evidence,

but the large number of Class III studies make it clear that SRS can be recommended as an effective, evidence-based treatment option (Class II recommendation) for GI MNs.

17.3 Summary of Findings

There is no Class I or II evidence to support simple observation of GI MNs, but many retrospective or review studies suggest that this is a reasonable strategy [39, 40]. MRI follow-up should be performed 6 months after discovery, and then annually thereafter. When treatment is required, often only surgery is necessary. However, surgery is not without complications or sequelae, which may sometimes not be sufficiently considered [41]. When justifying observation as a strategy, it is important to consider the tumour size and proximity to at-risk organs, which may point to the need for timely SRS [42, 43] (*good practice level recommendation, expert opinion*).

Surgery is the first choice if growth requires urgent action (*Class II evidence, B level recommendation*). After diagnosis, histological confirmation is not mandatory, but in cases where it is not possible to exclude the diagnosis of metastases, intervention may be necessary (*good practice level recommendation*). Removal must include the involved dura (GTR, Simpson I), to be confirmed by post-operative MRI (48 h or at the latest 3 months after surgery).

In elderly patients, if removal is incomplete or GTR is problematic, SRS can be used if the lesion is of treatable size. Many retrospective studies report tumour control rates of between 86% and 100% for SRS [24–26], while LTC is reported in 75–92% of cases with standard or hypofractionated fractional radiotherapy (*Class III evidence, B level recommendation*) [44]. In terms of outcome, surgery combined with SRS is similar to GTR, but allows "safe" surgical removal (*Class IV evidence, level C recommendation*) [18]. Follow-up is recommended annually for 5 years, and then every 2 years.

As regards WHO GII MNs, they are often not radiologically distinguishable from GI, except for signs of brain invasion. For GII and GIII MNs, Simpson grade I surgery is the treatment of choice (*Class III evidence, level B recommendation*), followed by 6-monthly MRI exams. If only STR is possible, fractional RT is recommended (*Class III evidence, level C recommendation*), although adjuvant RT is supported by retrospective rather than prospective data.

That being said, the ROAM/EORTC-1308 multicentre prospective randomized controlled trial (primary end point progression-free survival of anaplastic MN patients treated with RT vs. simple observation after GTR), which started in 2015, has now recruited 47 adult patients undergoing GTR for intracranial GII MN [45]. It is hoped to recruit 190 eligible patients, and the aims are to evaluate whether early adjuvant RT reduces the risk of tumour recurrence, and whether the potential side effects are justified, as compared to active MRI monitoring and administering RT at recurrence. ROAM/EORTC-1308 is the first of its kind, and should help determine whether early adjuvant RT reduces the risk of tumour recurrence following complete surgical resection of atypical MNs. Currently, in cases of recurrence following surgery plus RT, SRS in one or more fractions is the recommended course of action.

17.4 Conclusions

In summary, evidence-based GLs on SRS for the treatment of CNS MNs published in recent years are in agreement on several points (Fig. 17.1). First of all, there is overall agreement about the effectiveness and safety of SRS in selected cases. Briefly, for elderly patients (older than 65 years), or for tumours not safely accessible by surgery, or after incomplete surgical resection, SRS can be carried out on small tumours. It is indicated as a primary or adjuvant/salvage treatment for WHO GI MNs, particularly for those in anatomically unfavourable locations where microsurgery is deemed to have an unacceptably high risk of neurological deficit, or when MNs cannot be completely removed due to their relationship to vital neural or vascular structures. These locations

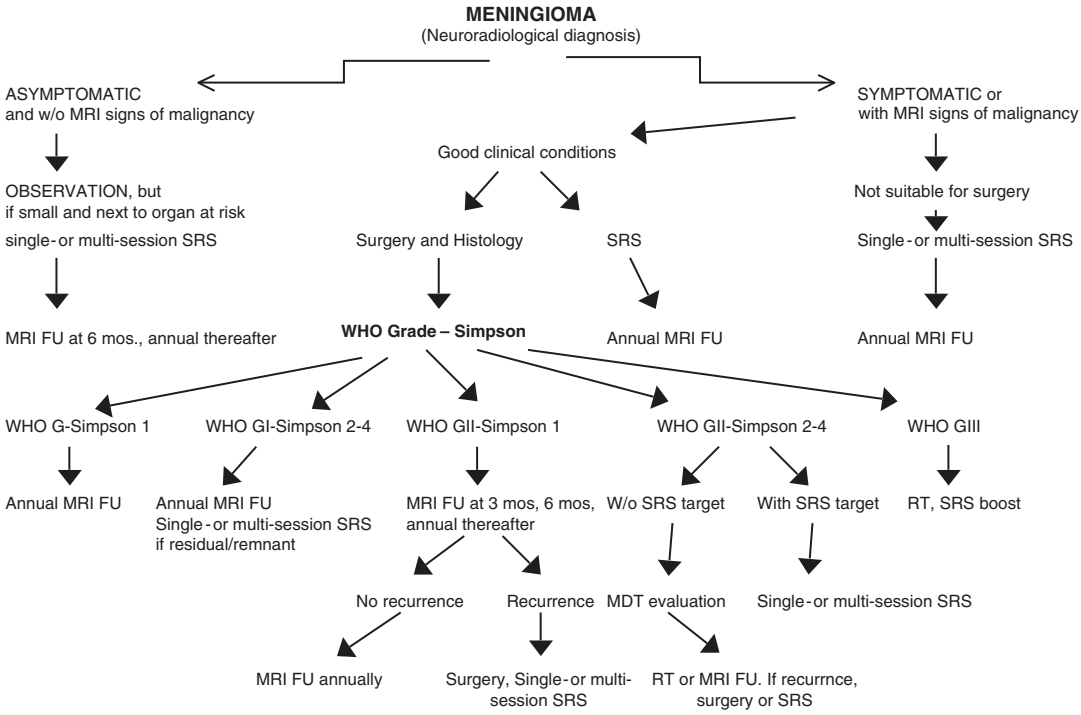

Fig. 17.1 Flow chart summary of the main GLs and evidence-based recommendations for SRS treatment of intracranial meningiomas

include, but are not limited to, the skull base and the posterior fossa (particularly, cavernous sinus and petroclival locations), the posterior aspect of the superior sagittal sinus, and parasagittal, parafalcine, intraventricular and optic nerve sheath sites. With respect to microsurgery, SRS has the advantages of shorter hospitalization, a less detrimental impact on quality of life, avoidance of procedural mortality and a lower incidence of treatment-related complications, as well as far lower overall costs.

In WHO GII MNs, SRS is most often used for patients who are not candidates for surgery and have small- to medium-sized MNs that are surgically inaccessible (first-line treatment), or have residual or recurrent tumours following surgery (adjuvant/salvage treatment). Outcomes of SRS are similar to those of fractionated RT for small tumours or tumour remnants. Finally, SRS is deemed to be indicated in recurrent WHO GIII MNs that have undergone prior fractionated RT.

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