Chapter 17
Radiosurgery for Brain Tumors

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Key Points

- Intracranial stereotactic radiosurgery (SRS) is a treatment technique known for its ability to provide high doses of ionizing radiation highly conformal and extremely precise.
- Radiosurgery is useful for the treatment of benign, malignant, and functional intracranial pathology.
- The SRS exposes a target volume to a single high dose of ionizing radiation that eventually results in a specific radiobiological response.
- Accurate destruction of a defined target containing healthy and/or pathological cells, without significant concomitant or late damage to healthy tissue, is an important consideration.

17.1 Introduction

The field of stereotactic neurosurgery was developed just over 100 years ago. The beginning is marked with publications by Horsley and Clarke in 1906 and 1998, in which they presented the results obtained using a stereotactic device in monkeys for the purpose of studying deep structures of the brain, without damaging the cortex above them. They gave their technique the name "stereotaxis" derived from the Greek word stereo: "three-dimensional" and taxia: "arrangement" [1]. Subsequently, in 1973, it was proposed that the term "stereotactic" replaces "stereotaxis" because the purpose of this procedure was thought as "touching" the desired area [2].

Nearly 40 years later, Spiegel and Wycis, using a Cartesian coordinate system and a safety ring attached to the skull to locate intracranial structures, performed the first stereotactic neurosurgery, which was published in 1947 [3].

Neurosurgical procedures at the time, especially those related to deep-location injuries, resulted in unacceptable morbidity and mortality rates. Taking this situation as a premise, Leksell, in 1951, conceived the concept of stereotactic radiosurgery (SRS), and then, in conjunction with Larsson, they led the construction of the first Gamma Knife unit [4].

In 1983, at a hospital in Buenos Aires, Argentina, Betti and Derechinsky developed the concept of a modified linear accelerator (LINAC) for SRS. Shortly thereafter, in several parts of the world (United States, Germany, Spain, Italy and Canada), they continued to develop innovative ideas for SRS, based on linear accelerators. These modifications and innovations in LINACS allow us today to provide treatment with submillimeter precision [5–12].

Leksell remained active in advancing the state of the art of SRS and was one of the many visionaries who exploited the spatial information provided by volumetric imaging studies such as computerized axial tomography and magnetic resonance imaging, creating the image-guided stereotaxia field [13]. Leksell believed that SRS was best indicated for benign and functional intracranial pathologies and not malignant tumors [14].

SRS was established and accepted as an important neurosurgical technique in the 1980s and 1990s [15, 16]. Its value transcended the original proposals by Leksell, as

it has been shown to be effective in the most common intracranial malignant pathologies of the central nervous system (CNS) and metastatic disease [17–19]. Currently, the scope of this technique extends beyond the limits of cranial disease, as it is possible to treat spinal, lung, liver, bone, and ganglion injuries among others [20–22].

17.2 Definition

Intracranial stereotactic radiosurgery (SRS) is a treatment technique known for its ability to provide high doses of ionizing radiation, highly conformal and extremely precise, aimed at a target, while limiting irradiation to healthy tissue, due to the abrupt drop of dose outside the prescription volume. For this reason, it has become a valuable and effective tool increasingly used by neurosurgeons and radiation oncologists for the treatment of benign, malignant and functional intracranial pathology [23–25].

The American College of Radiology (ACR) and the American Society for Radiation Oncology (ASTRO), in 2006, defined SRS as delivering "a high dose of ionizing radiation with a high degree of precision and spatial accuracy". A collaborative and multidisciplinary effort between neurosurgeons, radiation oncologists and medical physicists was recommended to optimize the quality and operational efficiency of successful radiosurgery [26]. In 2007, the SRS committee formed by the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons defined the role, in detail, of the neurosurgeon in SRS, in conjunction with ASTRO, made distinctions between SRS and fractionated stereotactic radiation therapy (FSRT), determining that "SRS refers to the use of image-guided ionization radiation to eradicate or inactivate a specific target of intracranial or spinal location. It is typically performed in a single session (SF-SRS), 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 (MF-SRS), up to a maximum of five" [14, 26].

In 2017, the International Commission on Radiation Units and Measurements (ICRU) published 91 reports for the prescription, recording and reporting of stereotactic treatments of small photon beams. In this, it defines SRS as single-fraction intracranial treatment, stereotactic radiation therapy (SRT) as intracranial treatment of 2–12 fractions and stereotactic body radiation therapy (SBRT) as extracranial treatment of 2–12 fractions [27].

17.3 Platforms or Equipment for SRS or SBRT

Intra or extracranial radiosurgery using photons is performed using a variety of dedicated or multipurpose radiotherapy units. Initially, stereotactic treatments were performed with convergent kilovoltage x-rays beams; however, current photon treatment is granted with megavoltage beams, both gamma rays from ^{60}Co sources or X-rays generated from a linear accelerator (Fig. 17.1).

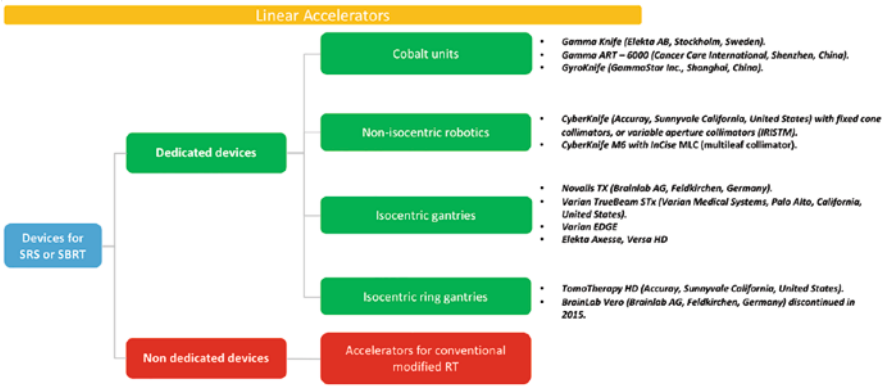

Fig. 17.1 Linear accelerators

17.4 Radiobiology of Radiosurgery

Loss of a cell's reproductive ability, due to the double-chain rupture of DNA, is the primary means by which radiation kills cells; any cell that is unable to reproduce indefinitely is by definition considered "death", despite being able to be metabolically active for some time. The response of tumors to radiation has been widely characterized in terms of factors that influence the ability of radiation to damage DNA, and thereby affect the recovery of tumor cell populations.

In 1975, Whiters, in his article "The four R's of radiotherapy", describes four critical mechanisms that determine the biological response of a tissue to radiation [28], and a decade later in 1989, Steel, McMillan and Peacock, proposed "The 5Rs of radiobiology" [29, 30] (Fig. 17.2).

The effectiveness of conventional radiation therapy is based on an interaction of these principles in which repair and repopulation increase the survival of tumor cells, while reordering, reoxygenation and radiosensitivity increase tumor cell death. Based on the above, it is possible to mention some real and potential radiobiological advantages and disadvantages of SRS with respect to conventional radiation therapy (1.8–2 Grays per fraction) [31] (Fig. 17.3).

The linear quadratic model (LQ) has been used to calculate the effects of ionizing radiation on normal and tumor cells; it calculates iso-effect dose between different therapeutic regimens and describes tumor cell death with these five principles in mind [32]. The radiobiology and application of the linear quadratic model for SRS continues as a subject of research and debate since clinical results have been validated for doses in ranges of 1–5 Gray (Gy) per fraction. In vitro studies, single doses greater than 5 Gy, commonly used in SRS, are considered by some, doses that affect the validity of the LQ model, as it is theorized that these underestimate tumor

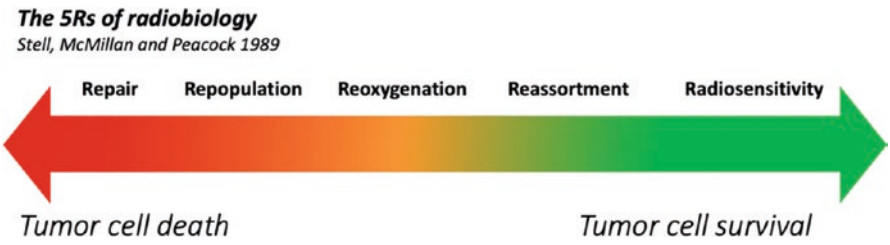

Fig. 17.2 The 5Rs of radiobiology

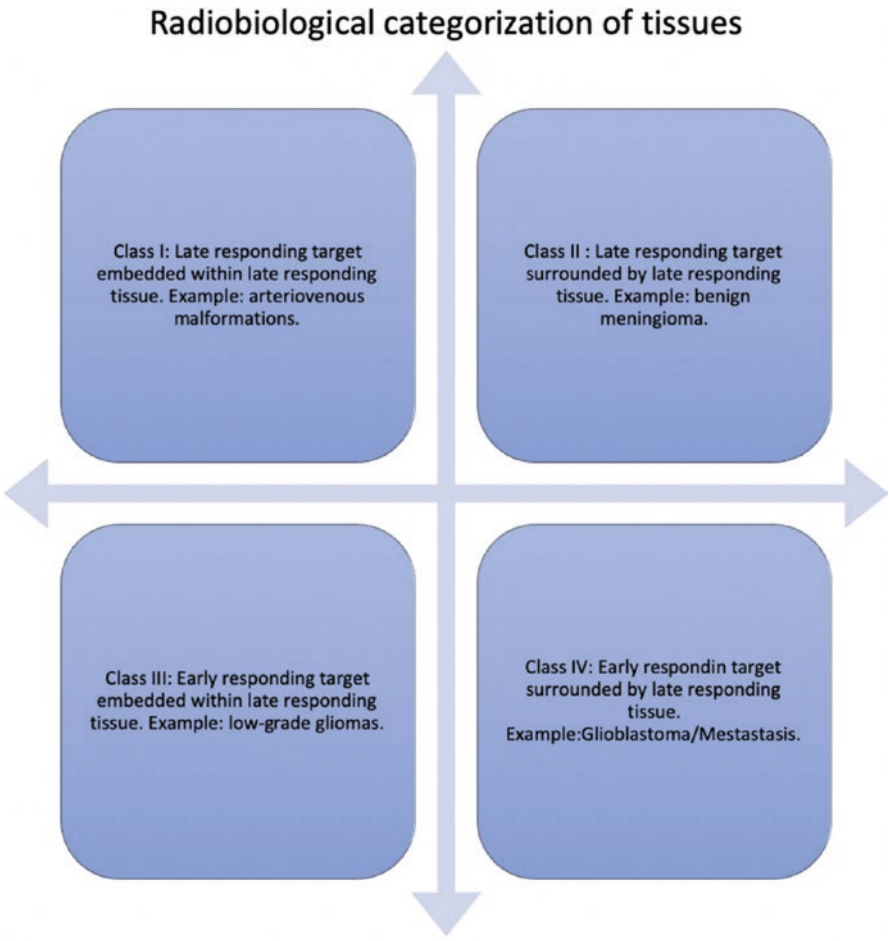

Fig. 17.3 Radiobiological categorization of tissues

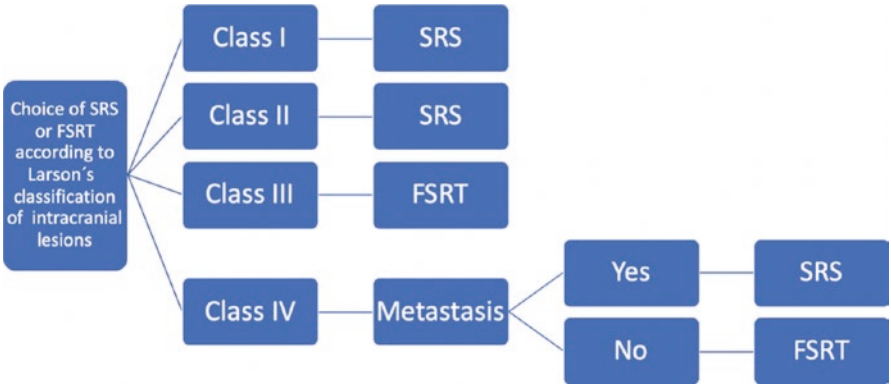

Fig. 17.4 SRS: Larson's classification

control, and does not reflect other mechanisms involved in tumor cell death. However, due to the simplicity of application and experience gained from the databases of its use in different studies; the LQ model remains the most appropriate option to give a biological sense to SRS. It is hypothesized that doses greater than 10 Gy per fraction causes vascular damage, resulting in decreased blood infusion and indirect tumor cell death [33–36].

The alpha beta ratio (α/β ratio) is based on preclinical and clinical information and is ~2 Gy for central nervous tissue, 3 Gy for late responding tissues, and 10 Gy for early responding tissues. The α/β ratio is necessary when the equation of the LQ model is calculated to determine the equivalent dose (EQD2) to a conventional radiation therapy regimen and the biological effective dose (BED) [37]. These ratios can be used to determine the dose for better tumor control while minimizing toxicity to healthy tissue. In general, primary CNS metastases and malignancies have a high α/β ratio; it is estimated to be close to 10 Gy and represent early responding tissues, while benign slow-growth tumors such as pituitary adenomas, arteriovenous malformations and benign meningiomas have low α/β ratios, close to 3 Gy, and represent late responding tissues [37, 38].

Taking into account the classification of the tissues based on α/β ratios, in 1933, Larson proposed a categorization of the potential targets for SRS, which is suggested in (Fig. 17.4).

According to the above, categories I and II are the best targets for SRS, while categories III and IV benefit most from conventional radiation therapy; however, in the specific case of metastasis, SRS has proven to be highly effective in local control of these injuries. Despite the indications of SRS according to the type of tissue, it is essential to consider other variables such as:

- Anatomical location of the target, since not all structures within the CNS have the same tolerance to radiation, and proximity to the visual pathway or brain stem can be a limiting factor to the prescribed dose.
- The volume of the target and the ability of the unit to be able to provide a highly conformal, precise and safe treatment [37, 39].

As a summary, it can be said that the objectives of the SRS are:

1. Expose a target volume to a single high dose of ionizing radiation that eventually results in a specific radiobiological response [40].
2. Accurate destruction of a defined target containing healthy and/or pathological cells, without significant concomitant or late damage to healthy tissue [41].

17.5 Clinical Applications of Intracranial Radiosurgery

SRS for tumor management has been greatly enhanced with the introduction of MRI, which facilitates the acquisition of high-resolution images of brain tissue and precise target volume delineation. Since the 1980s, the number of patients with benign intracranial pathology treated with SRS increased and in the 1990s radiosurgery took an important step in the treatment of intracranial malignant diseases. SRS offers an alternative treatment modality with advantages over surgical intervention or radiation therapy. SRS has typically been used for small lesions, classically less than 3–4 cm in diameter length, considering the indications for its application, the mass effect of the lesion, location, proximity to critical structures and the tumor load of the systemic disease [42]. Larson's categorization of intracranial lesions supports the choice of SRS or FSRT, a decision algorithm based on this classification is suggested in (Fig. 17.4).

17.5.1 Vestibular Schwannoma

The occurrence of a vestibular schwannoma (VS) and its presentation symptoms often have a negative impact on the patient's quality of life [43]. Key management options in this pathology are observation, microsurgery and radiosurgery. Early interventions when tumors are small and hearing functions are preserved, have been shown to increase the chance of obtaining the best results [44].

All patients should have a pretreatment evaluation for hearing function, and a record of symptoms such as tinnitus, vertigo, imbalance, and hearing loss. A detailed neurological examination should be performed to compare with post-treatment evaluations, including facial nerve function, trigeminal sensation, and function of low cranial nerves [44].

Gradation of hearing function is usually done with the Gardner-Robertson classification system (G-R) [45]. House-Brackmann's classification for facial weakness allows for classifying the degree of facial nerve injury post-treatment [46, 47]. Koos's classification is used to categorize VS according to their size [48].

The average growth of an untreated VS is 0.7 ± 1.4 mm/year. 82% of these will grow less than 1 mm/year, 18% 1 mm or more per year, and only 13% will grow more than 2 mm/year. Tumor growth has been reported as the most significant factor in changing

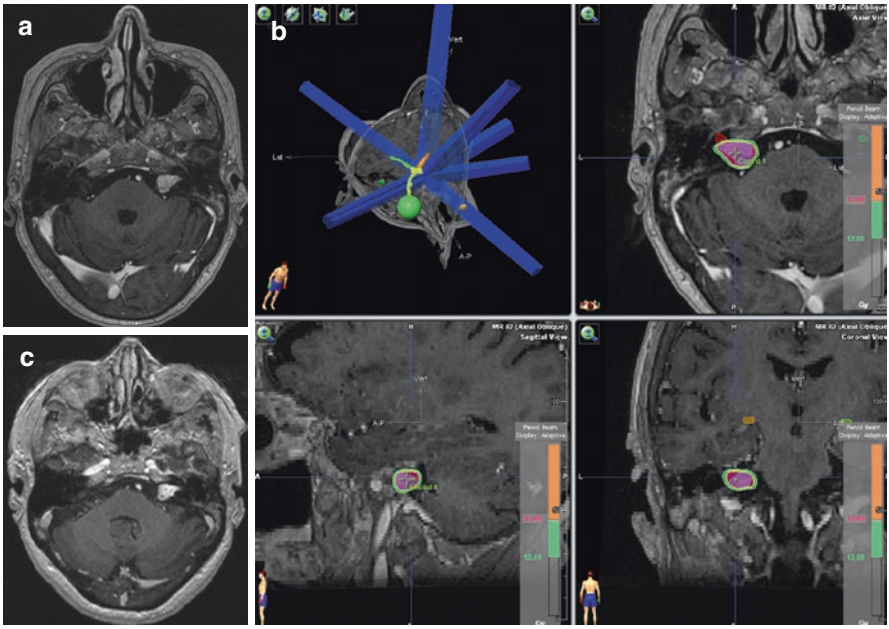

Fig. 17.5 Left vestibular Schwannoma. (**a**) MRI before SRS. (**b**) Treatment plan SRS, Dose prescription 13 Gy periphery. (**c**) MRI 1 year follow up

management from observation to intervention. A voluminous tumor at diagnosis and the presence of tinnitus have been associated with a higher growth rate [49, 50].

Observation could be a restricted option to asymptomatic VS Koos I in elderly patients with comorbidities.

The SRS granted to VS under 15 cc, that do not displace the brain stem and compress the fourth ventricle, achieves progression-free survival (PFS) of 96–97% at 10 years against PFS of 56% at 5 years in tumors greater than 15 cc and PFS at 5 years of 74% in tumors that compress the stem [51]. For every 1 cc in VS volume increase PFS decreases by 1.5% at 5 years [52].

Patients eligible for fractionated or hypofractionated stereotactic radiotherapy (FSRT or SRT) are those with vs Koos grade II-III of small to moderate size less than 30 mm at their maximum diameter [53, 54].

The tumor control of the 5-year vs treated with SRS (Gamma Knife or LINAC), FSRT or SRT is 81–100%. SRS doses of 12–14 Gy achieve 5-year tumor control of 90–99%, with hearing preservation rates of 41–79%, facial nerve preservation rates 95–100%, and trigeminal preservation rates of 79–99% (Fig. 17.5) [53, 55–60].

17.5.2 Craniopharyngioma

The treatment of craniopharyngiomas is a topic of controversy. Total resection is often curative in this technically "benign" neoplasm. It is reported in current series

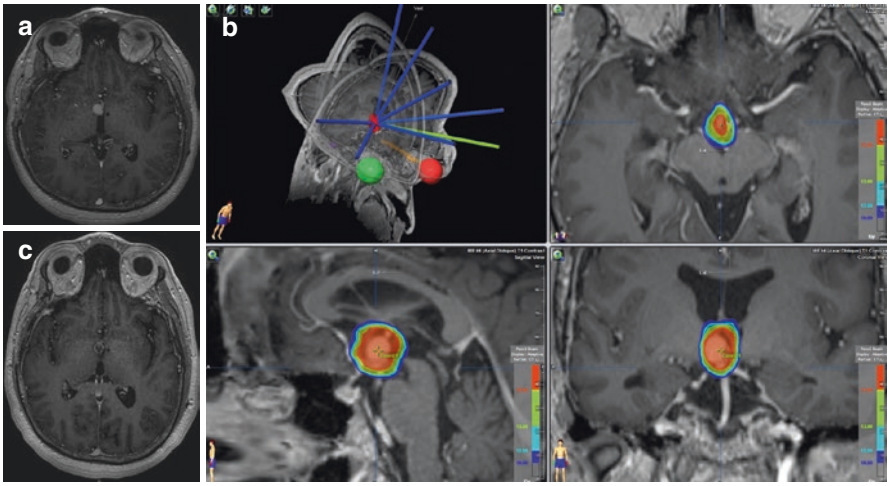

Fig. 17.6 Craniopharyngioma. (**a**) MRI before SRS. (**b**) Treatment plan SRS, Dose prescription 15 Gy periphery. (**c**) MRI 1 year follow up

that total resection is achieved in 50–80% of cases, and postoperative images show residual evidence in 15–50% of "completely resected" cases. The recurrence rate, even when the post-operative image confirms total resection, is 15–30%. In addition to the benefit of total resection to reduce the risk of recurrence, there is the risk of postoperative morbidity that occurs in 10–20% of cases. Extensive resections are associated with diabetes insipidus (90%), hypothalamic obesity (50%), and behavioral disorders (15–20%).

Transsphenoidal tumor resection, compared to a transcranial approach, has been associated with a reduction in the risk of severe perioperative complications. Residual tumors, after partial resection, have been reported to progress in 71–97% of patients, and that repeating surgery for recurrent craniopharyngiomas raises the risk of complications and maintains a low cure rate, increasing the mortality rate (19.5–40.6%) [61–67].

Marginal doses of 11–13 Gy are associated with high tumor control. Currently with resonance imaging-based treatment planning, tumors in contact with the optic chiasm may receive SRS, limiting the dose, at the site of the tumor's contact with the optic chiasm, to 9–10 Gy, while the rest of the optical pathway should not receive more than 8 Gy [68].

Global survival at 5 and 10 years after SRS ranges from 91.5–97.1% to 83.9–86% respectively, and PFS at 5 and 10 years after SRS ranges from 91.6% (for solid tumors), 68% (for solid and cystic tumors) to 43.8–76% respectively [68–70].

SRS morbidity is reported at 4% and tumor regression after SRS is considered to be a prognostic factor of a favorable quality of life. Radiosurgery is most effective for small, solid or pure cystic tumors, and with full radiosurgical coverage (Fig. 17.6) [71–74].

17.5.3 Pituitary Adenomas

Harvey Cushing, in his work "The Pituitary Body and its Disorders", recognized the limits of microsurgery and the usefulness of ionizing radiation as a supplemental measure for the treatment of patients with pituitary adenomas [75, 76]. Currently the use of radiotherapy, in its different modalities, has become a fundamental pillar for the treatment of patients with recurrent or residual pituitary adenoma. Radiosurgery is a treatment that seeks to improve the therapeutic index, because it seeks a greater probability of tumor control; it also seeks the preservation of adjacent neural, vascular and hormonal structures, while limiting the potential complications of healthy tissue [77].

In non-functioning pituitary adenomas, radiotherapy is indicated in cases of postoperative residual or in the context of recurrence. SRS is usually indicated for tumors less than 2.5–3 cm in diameter, and when the distance to the visual pathway allows the dose to optic structures to be limited to less than 8–10 Gy [78]. Local control with prescription doses between 12 and 20 Gy, is around 95–92% in 4 and 5 years respectively, with decreased tumor volume reported between 20 and 60% of cases. Predictive factors of good local control after SRS are: tumor volumes less than 5 cc and with limited suprasellar extension [79–82].

SRS is indicated in patients with growth hormone-secreting pituitary adenomas resistant to medical treatment and/or who fail surgery [78]. With doses between 20 and 25 Gy, local control at 5 years is around 95% and 5-year biochemical remission is 47% [83–93]. In Cushing disease with doses of 20–25 Gy, tumor control of 98% at 5 years is achieved, with biochemical remission of the disease of 54% at 46 months [86, 94–103].

In prolactinomas, SRS is usually reserved for those resistant to medical treatment with dopamine agonists. With doses between 15 and 33 Gy, local control of up to 95% is achieved and biochemical remission rates of 44% at 4 years are achieved [83, 96, 98, 104–109].

According to complications, the incidence of hypopituitarism within 5 years after SRS is up to 24%, with ranges ranging from 10 to 40%, and factors related to a high risk of hypopituitarism development are: previous hormonal deficit, bulky tumors, increased doses of radiation given to the pituitary gland and infundibulum, and a long follow-up. The risk of radiation-induced optic neuropathy is 0–3% when the one-off dose to the optical pathway does not exceed 8–10 Gy. Cranial nerve neuropathy III-VI and radionecrosis have been reported in less than 2%. The risk for developing a second neoplasm with SRS is very low, its global incidence is estimated to be 6.8 cases per 100,000 patients per year (Fig. 17.7) [87, 89, 95, 98, 105, 107, 110–113].

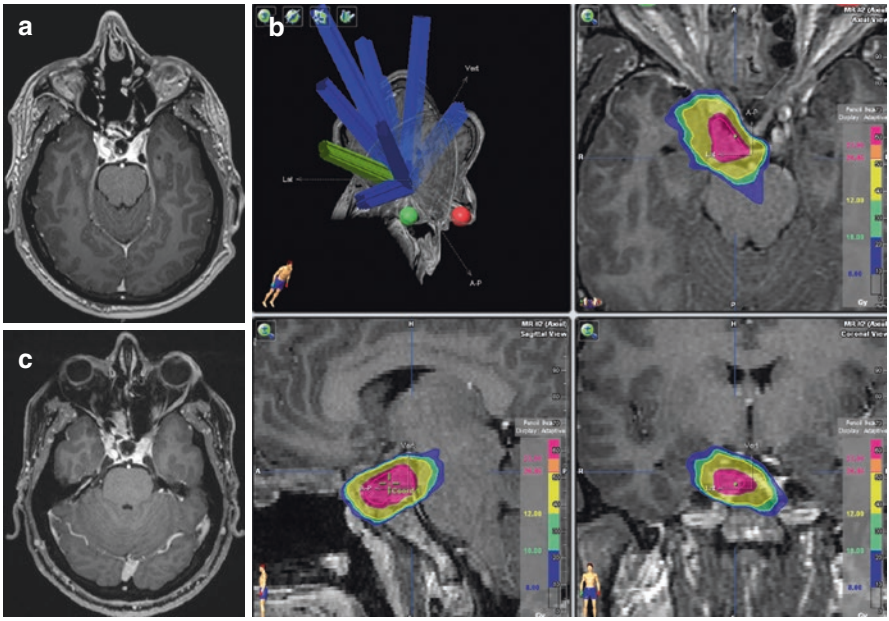

Fig. 17.7 Growth Hormone secreting pituitary adenoma. (**a**) MRI before SRS. (**b**) Treatment plan SRS, Dose prescription 23 Gy periphery. (**c**) MRI 3 years follow up

17.5.4 Meningiomas

Initially used for the management of difficult to resect skull base meningiomas, SRS has emerged as a valuable treatment modality for meningiomas in other locations, as it has demonstrated acceptable tumor control with a low toxicity profile [114].

Meningiomas have multiple characteristics that make them excellent tumors for SRS [115]. First, they have slow growth; second, they are easily identifiable on MRI, making it easier to plan; and third, they rarely invade adjacent healthy tissue, so the likelihood of healthy tissue complications decreases [116].

Tumor control in small, grade I meningiomas at 5, 10 and 15 years has been reported from 97%, 87.2%, and 87.2% respectively [117–119]. Adjuvant SRS increases progression-free survival compared to patients with total macroscopic resection without adjuvant treatment [120]. In patients with grade II and grade III meningiomas, the actuarial tumor control achieved at 10 years with SRS is, as reported, 81% and 60% respectively [121].

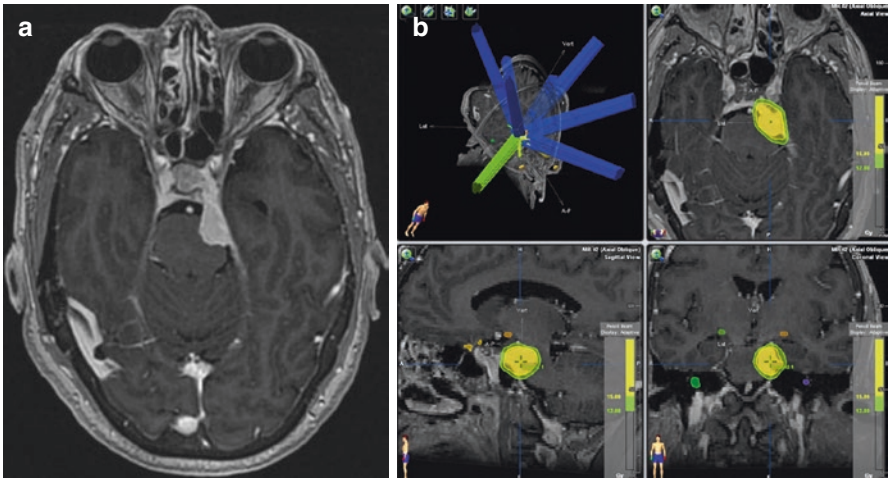

Fig. 17.8 Left cavernous sinus meningioma. (**a**) MRI before SRS. (**b**) Treatment plan SRS, Dose prescription 15 Gy periphery

At the National Institute of Neurology and Neurosurgery in Mexico City, a retrospective study was conducted on patients with grade I meningiomas who underwent SRS from January 2002 to August 2012. 36 patients went to primary SRS and 39 to adjuvant SRS, finding tumor control of 93% at 5 years and progression-free survival of 93%, with low toxicity profiles, acute toxicity was 2.6% and chronic toxicity grade I and II was 26.6%, with edema being the most common chronic toxicity [122].

The recommended doses are 12–14 Gy (according to size) for meningiomas adjacent to the stem, the cavernous sinus, the optic nerve sheath (depending on the state of vision, if the dose is preserved it will be ≤12 Gy and respecting the tolerance of the visual pathway), and meningiomas associated with pre-SRS edema. It is recommended to increase doses in meningiomas grade II and II from 14 to 20 Gy, and in context of recurrence to grant doses ≥20 Gy (Fig. 17.8) [123–125].

17.5.5 Intracranial Metastases

Whole-brain radiotherapy has been the standard modality of radiation treatment for brain metastases. This paradigm has evolved from the last three decades, since Leksell introduced the concept of SRS. The goal of SRS in these injuries is to provide a high dose of radiation sought to improve tumor control and minimize the effects of radiation on healthy nerve tissue, resulting in obtaining better results in cognitive function [126].

Metastases have characteristics that make them ideal targets for SRS. They generally have spheroid shape, located at the cortico-subcortical junction, most have a maximum diameter of less than 4 cm, and perhaps, most importantly, they have no infiltrative nature as opposed to high-grade primary gliomas. These features enable proper and accurate delineation, planning and delivery of treatment. A high and unique dose of radiation seems to have the same effect on all types of tumors, including among radio-resistant tumors such as renal cell carcinoma and melanoma [127–130].

Decision making to administer SRS to a patient depends on multiple factors such as age, functional status, extracranial extension of the disease, and histology of the primary tumor. There are multiple prognostic factors that support decision-making such as recursive partitioning analysis (RPA), score index for radiosurgery (SIR), basic score for brain metastases (BSBM), graded prognostic assessment (GPA), modified RPA, and more recently, the brain metastasis velocity (BMV), the latter specifies for post SRS tracking [131–138].

In patients with metastases greater than 3 cm in diameter, with symptomatic, mass effect, the first treatment option is often considered to be surgical resection; however, many patients are not optimal surgical candidates, either by course, extensive extracranial disease or multiple intracranial metastases. Treatment options in patientes with brain metastasis would be whole-brain radiation therapy with or without SRS, or SRS as the primary modality. SRS can be performed safely in patients with multiple metastases, it has been shown that in terms of global survival, SRS is not inferior to whole brain radiation therapy in patients with 2–4 metastases or even with 5–10 metastases without exceeding 15 cc or even 25 cc of tumor volume. Subsequent studies have shown that patients with more than 10 intracranial metastases are not unfavorable candidates for SRS alone, always taking into account for decision-making, the patient's functional status, primary tumor histology and extracranial disease control. Patients with big size or big volume metastasis would be treated with fractionated SRS or with staged (adaptative) SRS [139–144]. After surgery, failure of the surgical cavity occurs in approximately 60% of cases within 2 years. Local control with SRS to the cavity ranges from 72 and 90% at 1 year [145, 146]. Preoperative SRS has managed to reduce the risk of subdural plantings from 61.5% /12 monts to just 14.3% /12 months, obtaining local controls of 97.8%, 85.6% and 71.8% at 6, 12, and 14 months [147].

Local control with primary SRS depends on several factors: marginal dose, lesion size and possibly primary histology. Doses of at least 20 Gy to the periphery in lesions less than 6 mm and 10 mm in diameter achieve control of 100% and 90% at 12 months and 19 months respectively, with incidence of complications less than 3%. It is recommended to evaluate the treatment response using the criteria of the multidisciplinary international working group on the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) (Fig. 17.9) [139, 143, 144].

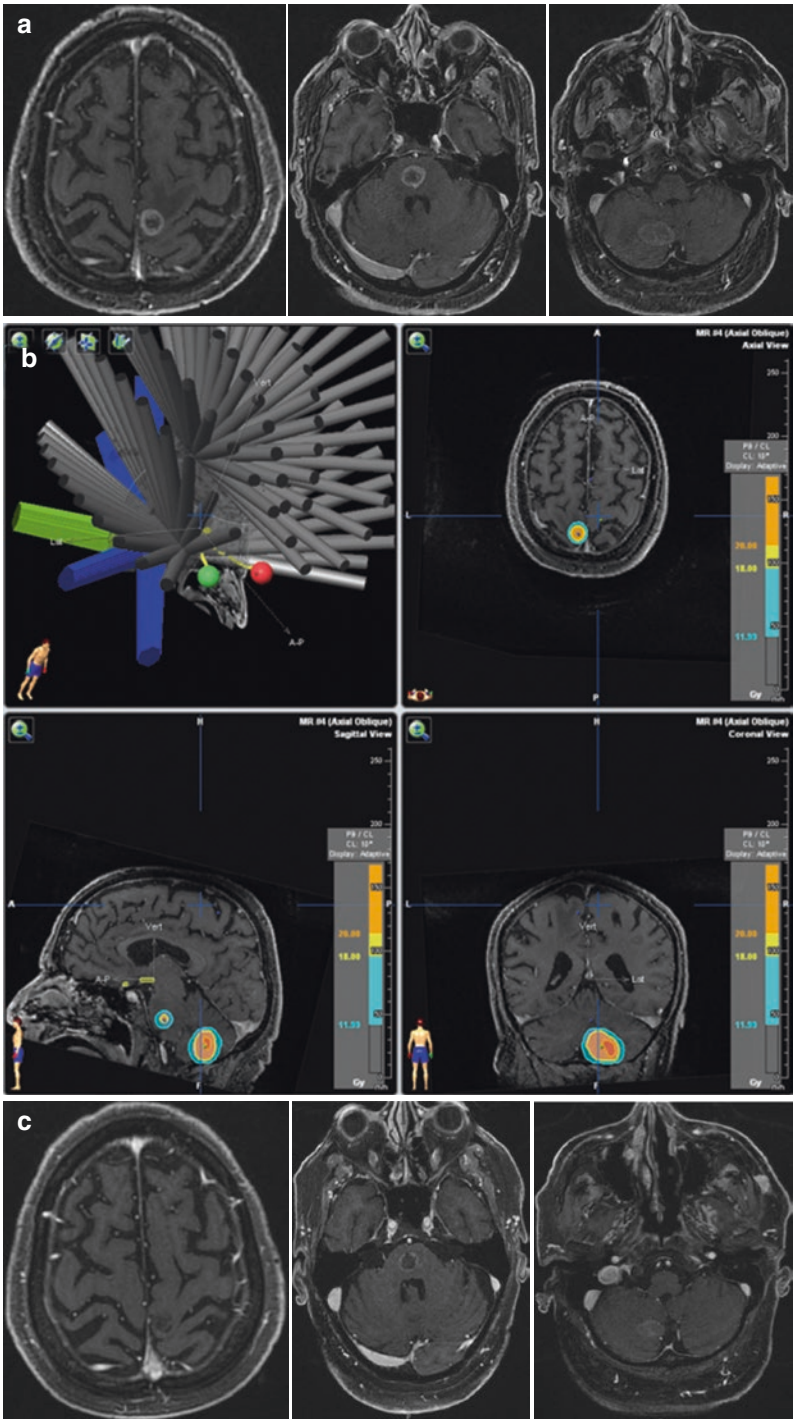

Fig. 17.9 (**a**) Brain metastasis of colon cancer, MRI before SRS. (**b**) Treatment plan with SRS, Dose prescription 20 Gy periphery. (**c**) MRI 2 months follow up

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