Chapter

Stereotactic Radiotherapy for Benign Skull Base Tumors

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Abstract

Benign skull base tumors include meningiomas, pituitary adenomas, craniopharyngiomas, and vestibular schwannomas. As an adjuvant therapy to surgery or when surgical treatment carries too high a risk of complications, a highly precise focused radiation, known as stereotactic radiosurgery or fractionated stereotactic radiation therapy, can be delivered to the tumor. The aim of this chapter is to systematically discuss benefits of the therapy, i.e., tumor control as well as complications and risk factors of the therapy relating to vision, hearing, hormone secreting regions, and cerebral vasculature. Meningiomas, pituitary adenomas, craniopharyngiomas, and vestibular schwannomas constitute the majority of primary skull base tumors amenable to stereotactic radiation therapy or radiosurgery and will be described in this chapter.

Keywords: skull base tumors, stereotactic radiosurgery, fractionated stereotactic radiotherapy, tumor control, vision, hearing, hormonal, stroke

1. Introduction

Stereotactic radiosurgery (SRS) is defined as a single application of a high dose of radiation to a stereotactically precisely defined target [1, 2]. Stereotactic radiosurgery of the brain using the Gamma Knife or a Linear accelerator (LINAC) is a well-established and very effective therapy for brain metastases, arteriovenous malformations, and benign skull base tumors [1, 2]. The treatment utilizes differences in the biological sensitivity and repair capability of normal and pathologic tissue [3]. Stereotactic principles are used for calculating the radiation field. The patient wears a stereotactic head frame and undergoes a computed tomography (CT), which is subsequently fused with a preexisting magnetic resonance (MRI) scan, or an MRI is performed in the stereotactic head frame, the disadvantage being that there are often distortions of the magnetic field [4]. However, most lesions are better demonstrated on MRI scans. The aim of dose planning is to deliver a maximal dose to the tumor, while minimizing radiation dose to healthy brain structures. This is accomplished with conforming the radiation to the target and applying steep dose gradients [1, 2].

LINAC-based radiosurgery and radiation therapy devices accelerate electrons, and the electron beam is aimed at a heavy metal alloy target [1]. The resulting interactions between the electrons and the target produce photons, which can be collimated and focused on a patient. Multiple radiation beams are applied, each of which has its own entrance and exit points, while all are directed at the same target where they cross each other [1]. In LINAC radiosurgery and fractionated radiation

therapy, both the gantry and the treatment table rotate around the isocenter of the lesion for accurate delivery of the multiple beams [1]. The single radiosurgery radiation dose prescribed in LINAC-based radiosurgery for benign skull base tumors is commonly 10–17.5 Gy [1, 4, 5, 6]. Notably, in case of lesions adjacent to radiosensitive structures, fractionation is the preferred method of delivery, in which case different dose regimes apply [1, 7, 8]. In contrast to the Gamma Knife, LINAC offers the option of dose fractionation. Fractionated stereotactic radiation therapy (FSRT) utilizes the principles of conventional fractionation while taking advantage of stereotactic dosimetric techniques to conform the radiation to the tumor target. It is particularly suitable for treating skull base tumors, close to eloquent structures, such as the pituitary gland and optic nerves. A commonly used prescription dose for benign skull base tumors is a total of 54 Gy given with 1.8–2.0 Gy per fraction.

Radiosurgery with the Gamma Knife uses 201 separate cobalt sources, all aimed at a high dose at precisely one fixed target, with one or more isocenters employed, depending on the size and shape of the tumor [1, 2, 3]. A commonly used dose for benign skull base tumors is 12 Gy–16 Gy [3, 9].

Cyberknife is used in some centers and is a frameless robotic radiosurgery system, which is typically delivered in multiple session. It is a relatively safe and effective treatment for skull base tumors [10].

More recently, proton beam therapy has been introduced and is gaining progressively widespread use. It relies on protons produced end emitted by a synchrotron or cyclotron. The protons travel to a specific depth in the body depending on their energy and when striking the tumor rapidly emit their energy. It is well suited and used for various benign skull base tumors. Proton beam therapy is an effective treatment modality, with favorable long-term tumor control rates [11, 12].

The differences between Gamma Knife, LINAC and Cyberknife are summarized in **Table 1**.

	Gamma knife	**LINAC**	**Cyberknife**
Use	Developed exclusively for brain surgery	Not developed exclusively for brain surgery	Developed primarily for brain surgery but can be used for other regions
Accuracy	Millimeter accuracy	Millimeter accuracy	Submillimeter accuracy
Irradiation source	Gamma rays from Cobalt-60 source	6-MV X-rays	Compact linac with 6 MeV photons
Beam arrangements	201 fixed concentric non-opposed beams	Non-coplanar arcs • Dynamic arc rotation • Conical rotation - Static beam arrangements	Robotic arm with 6 degrees of freedom of movement; nonisocentric, where beams can be directed from any desired angle
Head fixation	A lightweight stereotactic frame is affixed to the head for rigid stabilization	Thermoplastic face mask, less rigid	Does not need head fixation, thus more flexible
Number of treatment sessions	Single treatment session	Single or multiple (i.e., 30) treatment sessions	Single or multiple (hypofractionated) up to five treatment sessions

Table 1.
Differences between gamma knife, LINAC, and cyberknife.

2. Stereotactic radiosurgery and fractionated stereotactic radiation therapy of benign skull base tumors

Meningiomas, pituitary adenomas, craniopharyngiomas, and vestibular schwannomas constitute the vast majority of primary skull base tumors suitable for stereotactic radiation therapy or radiosurgery.

2.1 Meningiomas

Meningiomas are the most common primary intracranial tumors, the prevalence being approximately 100 per 100,000 [13, 14]. They are slow-growing tumors, most often benign and dural-based. Meningiomas are classified according to the World Health Organization (WHO) classification of grade, where grade I is benign, grade II atypical, and grade III anaplastic [13, 15–17]. Approximately 95% of intracranial meningiomas are benign and approximately 5% are atypical or anaplastic [13, 15]. Atypical and anaplastic meningiomas have an increased recurrence and mortality risk [15, 16]. In addition to WHO grade, prognosis and recurrence risk depend on the radicality of resection [13, 18]. Anterior skull base meningiomas are defined as arising anterior to the chiasmatic sulcus, which separates the middle and the anterior cranial fossa. Anterior skull base meningiomas include olfactory groove, tuberculum sellae, sphenoid wing, cavernous sinus, and optic nerve sheath meningiomas [19, 20]. Medial skull base meningiomas include clival and petroclival meningiomas [21]. Olfactory groove meningiomas arise from the cribriform plate in the midline and often compress or distort the olfactory and optic nerves and optic chiasm (**Figure 1**). Tuberculum sellae meningiomas are usually located in the suprasellar and subchiasmal region in the midline and often compress the optic nerves and internal carotid arteries (**Figure 2**). Sphenoid wing meningiomas arise from the sphenoid wing and often involve the optic nerves, the cavernous sinus, or carotid arteries, and cause neurological damage by direct compression of adjacent cranial nerves (**Figure 3**). Cavernous sinus meningiomas may either originate within the cavernous sinus and spread outside of it or originate outside the cavernous sinus and invade it. Cavernous sinus meningiomas often present with symptoms related to compression of structures within the cavernous sinus, resulting in ophthalmoplegia or facial pain or numbness or ischemic stroke due to compression of the carotid artery and with tumor extending beyond the cavernous sinus, can also affect the optic nerves and chiasm or the pituitary gland (**Figure 4**). Total resection is often not possible, and resection is also associated with risks to the carotid artery, or damage to the cranial nerves of the cavernous sinus [22]. Optic nerve sheath meningiomas are rare, accounting for 1–2% of intracranial meningiomas, and due to their localization, management is often conservative. Finally, clival and petroclival meningiomas arise from the clivus and typically compress the brain stem, and they often involve the cavernous sinus and are surgically particularly challenging (**Figure 5**) [21].

With incompletely resected or recurrent skull base meningiomas, stereotactic radiation therapy or radiosurgery is recommended [13, 23]. Also, the extent of surgical tumor removal is dependent on tumor's localization adjacent to critical structures. Surgical treatment of cavernous sinus meningiomas, in particular, is associated with a high risk of cranial nerve injury, especially ophthalmoplegia, and therefore a high proportion of cavernous sinus meningiomas are treated by stereotactic radiation or radiosurgery and in some institutions is the first-line treatment. Generally, stereotactic radiosurgery or fractionated radiation therapy is frequently used as primary therapy in surgically high-risk tumors, resulting in good local control [4, 10, 13, 23, 24].

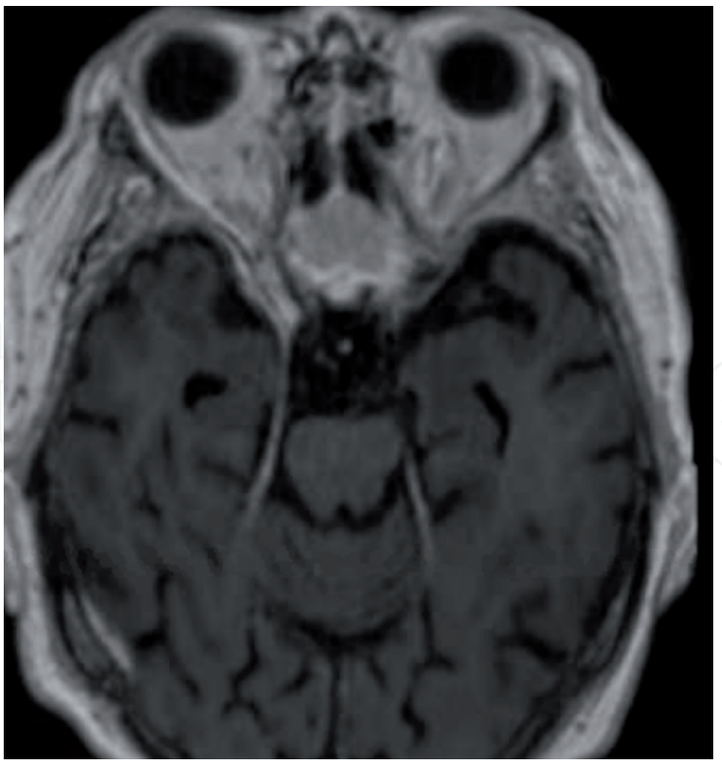

Figure 1.
MRI scan with gadolinium (Gd) of an olfactory groove meningioma.

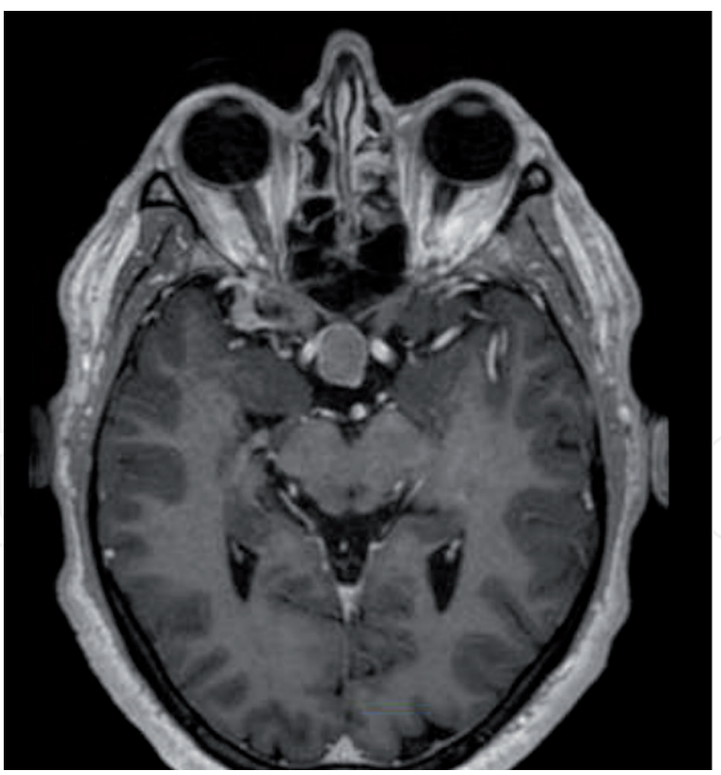

Figure 2.
MRI scan with Gd of a tuberculum sellae meningioma.

2.2 Pituitary adenomas

Pituitary adenomas are one of the most common intracranial tumors and are associated with a high rate of morbidity and mortality [25]. The prevalence of pituitary adenomas is approximately 100 per 100.000 [26–28]. Radical tumor

resection is indicated, with a transsphenoidal approach [29]. Adenomas that secrete hormones are called functioning adenomas, and adenomas that do not secrete hormones are called nonfunctioning adenomas [28]. Nonfunctioning

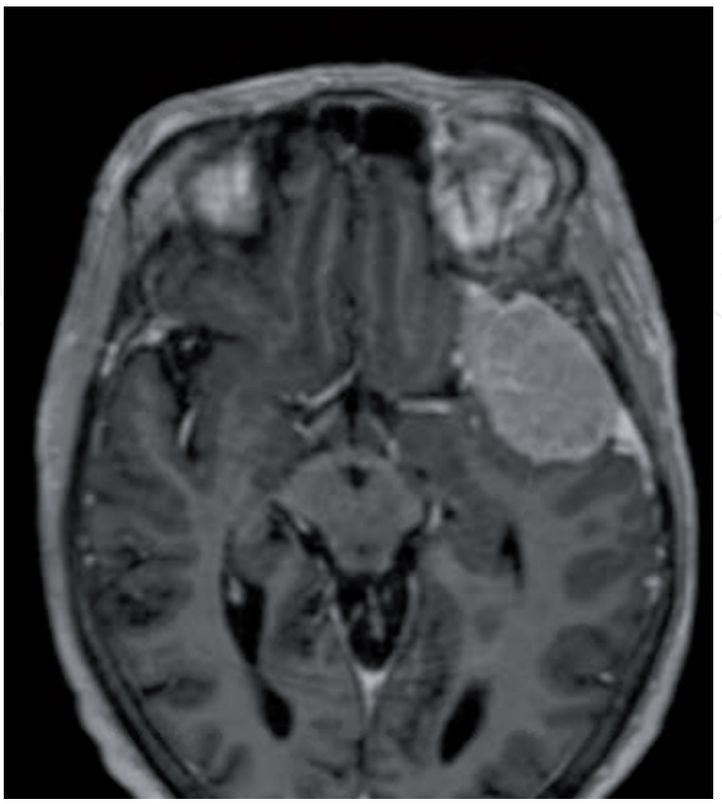

Figure 3.
MRI scan with Gd of a large left-sided sphenoid wing meningioma.

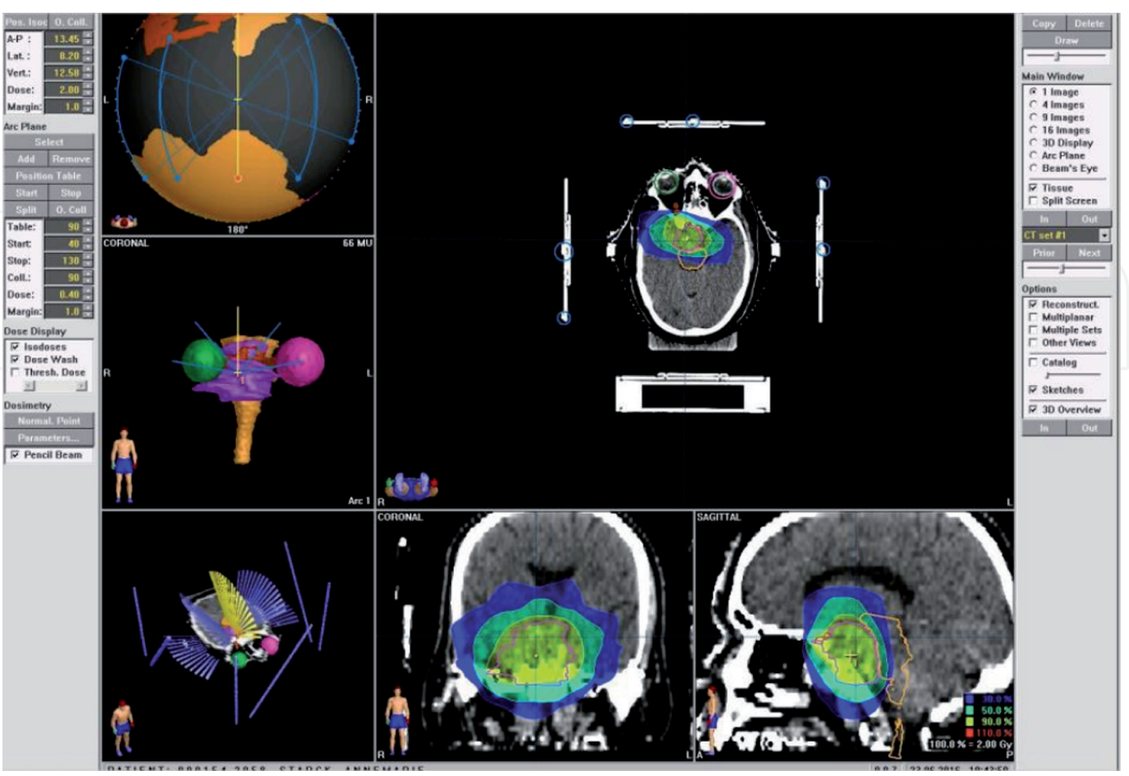

Figure 4.
Stereotactic radiation therapy dose plan in BrainLab/iPlan, of a right cavernous sinus meningioma, with isodose lines, demonstrating collateral irradiation of the optic chiasm, pituitary gland, and vascular structures of the cavernous sinus and circle of Willis.

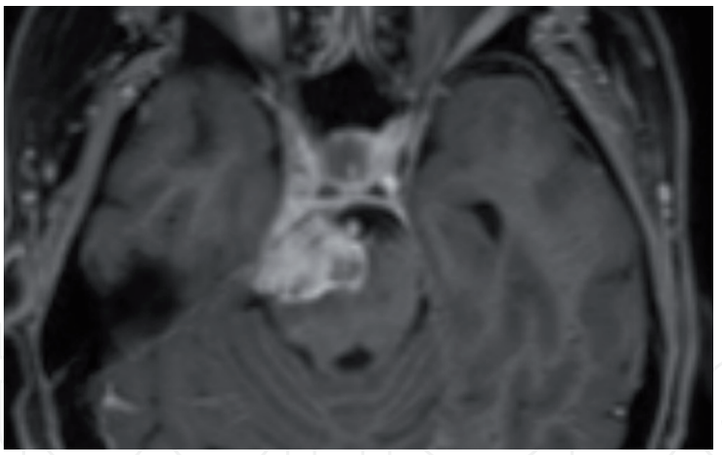

Figure 5.
MRI scan with Gd of a right petroclival meningioma.

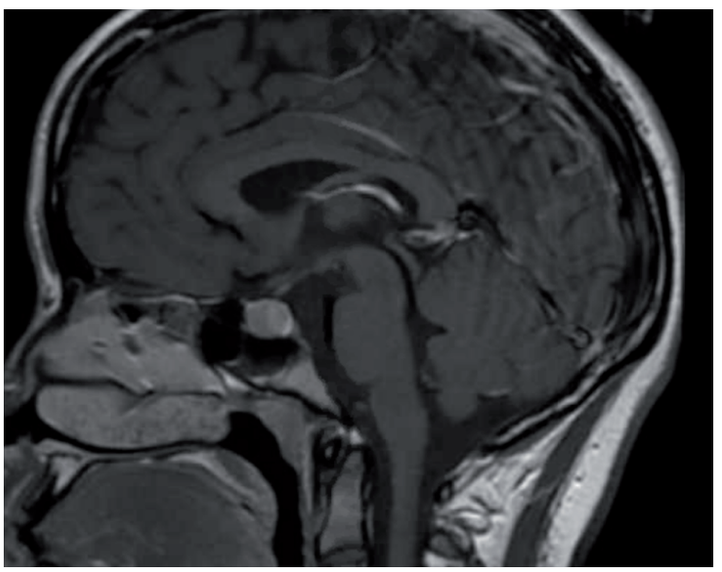

Figure 6.
MRI sagittal T1 with Gd of a pituitary microadenoma.

and prolactin-secreting adenomas are the most common types of pituitary adenomas, followed by growth hormone secreting and corticotroph adenomas, thyrotropin, and gonadotropin secretin) g adenomas [26, 28, 29]. Macroadenomas, which are defined as tumors with a diameter > 10 mm, are more common than microadenomas, which are <10 mm in diameter [28, 29]. The first-line treatment of prolactinomas is medical, with a dopamine agonist (**Figure 6**) [28].

Nonfunctioning pituitary adenomas are often large at presentation and are usually diagnosed due to their mass effect, visual loss, and hypopituitarism [27, 28]. Occasionally, they may constitute an asymptomatic incidental finding. They may also cause hyperprolactinemia due to pressure on the pituitary stalk. The main indication for surgery is reversal of visual loss, and in many cases, it may reverse hypopituitarism [29]. When surgical treatment does not provide sufficient disease control or has serious side effects, such as visual loss, then stereotactic radiosurgery or fractionated stereotactic radiation therapy is indicated, and in some instances, this may then be the sole treatment of the tumor (**Figure 7**). Also, stereotactic irradiation may be effective when surgery has failed to restore biochemical control in hormone-secreting adenomas [7].

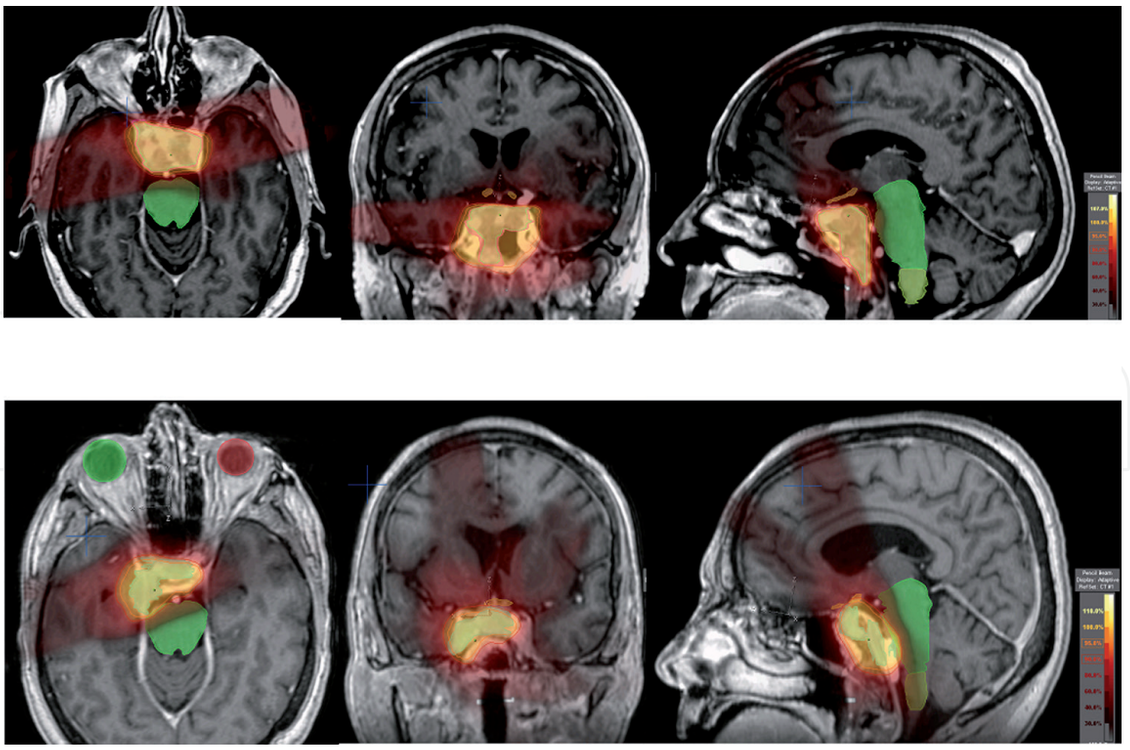

Figure 7.
FSRT dose plan of a large pituitary macroadenoma.

2.3 Craniopharyngiomas

Craniopharyngiomas are usually benign epithelial tumors originating from remnants of the Rathke's pouch, localized in the sellar or suprasellar region [30]. They are rare, with an incidence of 0.5–2 per 100,000 a year [31, 32]. They often present during childhood or adolescence and persist into adulthood [32]. They are cystic or solid or mixed cystic and solid and frequently contain calcifications (**Figure 8**) [31]. Presenting symptoms include visual field defects, pituitary hormone deficiency, and diabetes insipidus [30–32]. Craniopharyngiomas can be very challenging in terms of surgical management and can cause significant morbidity, despite their benign nature [33]. There are two distinct histological types of craniopharyngiomas. The adamantinomatous type is predominant in children, is more cystic and calcified and large, and often adherent to the brain. The less common papillary type almost exclusively presents in adults, is less infiltrative, and may be more amenable to surgery [34]. However, papillary craniopharyngiomas are well suited for stereotactic radiosurgery or fractionated stereotactic radiation therapy, as they are more radiosensitive and rarely recur after irradiation. Due to the high recurrence rate after subtotal resection, adjuvant irradiation is often warranted, with stereotactic radiosurgery or fractionated stereotactic radiation therapy [30, 35]. The main indication for stereotactic radiation therapy or stereotactic radiosurgery for craniopharyngiomas is thus when surgical control is not possible, or in case of tumor recurrence where the risks of surgery outweigh the benefits [36, 37].

2.4 Vestibular schwannomas

Vestibular schwannomas are slow-growing and benign tumors originating from the Schwann cell sheath of the cochleovestibular nerve (**Figure 9**) [38, 39]. The incidence is 1–2 in 100.000 a year [38, 39]. As the vestibular schwannomas grow, they affect hearing and balance, with unilateral hearing loss, tinnitus, and balance

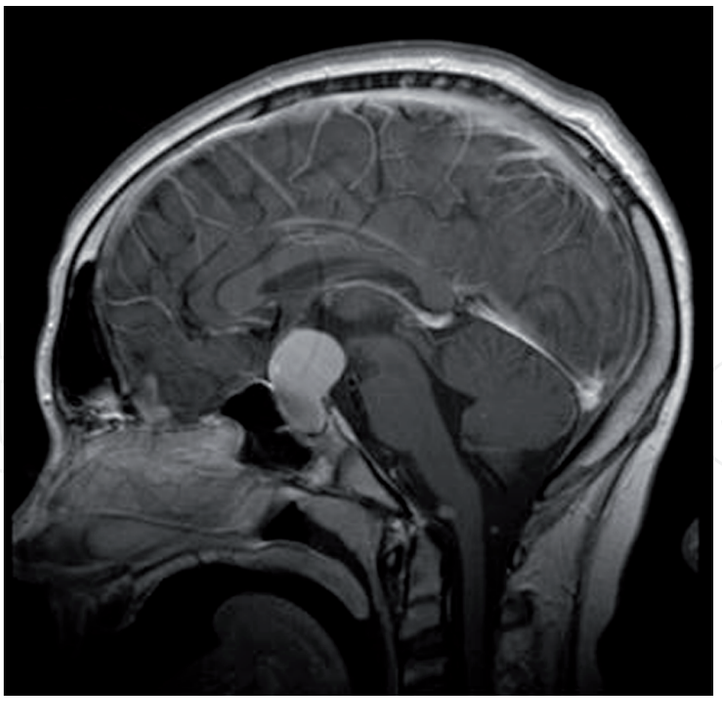

Figure 8.
MRI scan sagittal with Gd demonstrating a mainly solid craniopharyngioma in a 16-year-old adolescent.

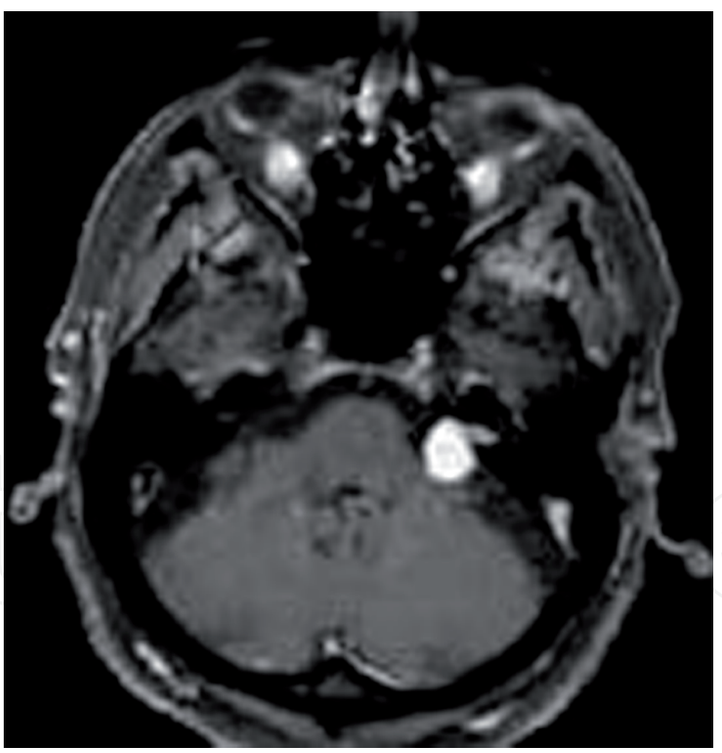

Figure 9.
MRI scan with Gd demonstrating a small left-sided vestibular schwannoma.

disturbances [39, 40]. With increasing tumor growth, the facial nerve can also be affected. Bilateral vestibular schwannomas with bilateral hearing loss are usually associated with neurofibromatosis type 2. Surgery is the standard treatment of vestibular schwannomas, including microsurgery and hearing preservation surgery [38]. More recently, stereotactic radiosurgery and radiation therapy have been introduced for the treatment of vestibular schwannomas with the aim of tumor control and hearing preservation, and controlled studies have found the results to

be superior to microsurgery for small tumors less than 3 cm [38, 39, 40]. Sometimes a conservative wait and scan approach is appropriate, reserving treatment in case of tumor growth or neurological deterioration.

3. Tumor control and biochemical control

For skull base meningiomas, nonfunctioning pituitary adenomas, craniopharyngiomas, and vestibular schwannomas, the major goal of treatment is tumor control. Tumor control is defined as stable or reduced size of tumor after treatment. Long-term tumor control after fractionated stereotactic radiation therapy of benign anterior skull base tumors is well established from several large series and in several cases is superior to surgery, with long-term tumor control rates reported in the range of 88–100% for skull base meningiomas [4, 24, 41–46], 92–99% for pituitary adenomas [47–53], 75–100% for craniopharyngiomas [34, 37, 54, 55], and 85–100% for vestibular schwannomas [38, 40]. Long-term tumor control rates after stereotactic radiosurgery with LINAC or Gamma Knife have been reported to be similar [2, 4, 6, 8, 9, 36, 38, 56]. For hormone-secreting pituitary adenomas, an equally important goal of treatment is biochemical control [56]. For nonfunctioning pituitary adenomas, biochemical control rates of 50% of hormone-producing adenomas have been reported [7].

Tumor control can be evaluated on a contrast-enhanced MRI scan compared with the MRI scan before the radiation therapy. Pre- and post-therapy MRI and CT scans of the treatment plans are fused, with the gross tumor volume as reference [57]. Tumor volume is then calculated using 3D volumetric assessment with treatment planning software, i.e., from Electa, BrainLab, or Varian Eclipse. Tumor control is defined as stable size or regression of the tumor. A change in tumor volume by ≥25% can be considered a change in size, and a change in tumor volume < 25% can be considered stable size [34].

Serial neuroimaging follow-up until at least 10 years after treatment is generally recommended.

3.1 Visual complications

During the irradiation of tumors, with close anatomical relation to the optic chiasm and nerves, a certain degree of collateral irradiation of these intact but sensitive structures occurs [58, 59]. In therapy protocols, the optic nerves, chiasm, and tracts are usually outlined and defined as organs at risk (OAR) [57]. Radiation-induced optic neuropathy (RION) is defined as painless rapid visual loss and is attributed to radiation necrosis of the anterior optic pathways [60]. It often has a delayed onset and can result in either visual acuity or visual field loss. The risk of radiation-induced optic neuropathy is dependent on both the total cumulated radiation dose and the fraction dose [60]. The risk is markedly increased at cumulated optic chiasm radiation doses of ≥60 Gy in the case of fractionated stereotactic radiation therapy and at a single dose of >12 Gy in the case of radiosurgery [60]. The risk is greater with increasing age, preexisting compression of the optic nerves/chiasm, and previous radiation therapy. Percentages of 3–7 and 7–20% of RION in the dose ranges 55–60 and above 60 Gy, respectively, have been reported, as presented in the review by the QUANTEC initiative [60].

Fractionated stereotactic radiation therapy combines the advantage of a high accuracy of stereotactic technique and the biological advantage of fractionation [1, 48]. For stereotactic radiosurgery (SRS) of tumors in the vicinity of the optic structures, there is a dose-limiting factor, meaning that the minimal effective tumor

dose may be equal to or greater than the dose tolerated by the optic structures. For example, the treatment of tumors of the cavernous sinus, with single-dose SRS, has been shown not to affect the optic pathways at a single dose of <10, whereas the incidence of optic neuropathy has been shown to be 27% after a single dose of 10 Gy–15 Gy and 78% after a single dose of >15 Gy [58]. Other SRS studies of perioptic tumors have reported variable results [4–6, 61–64].

3.2 Hypopituitarism

The pituitary gland is particularly sensitive to radiation, and hypopituitarism is the most common side effect after radiation therapy [65]. When high-dose radiation is applied directly to the pituitary gland for the treatment of pituitary adenomas, frequently it results in pituitary deficiency of one or more hormonal axes, and this correlates well with radiation dose to the pituitary gland [65, 66]. Furthermore, radiation damage of the hypothalamus can result in hypopituitarism [50]. Treatment requiring hypopituitarism of one or more hormonal axes has been reported in around 8% of these patients [7].

3.3 Cerebral infarction

Occlusion of the carotid artery or its branches leading to cerebral infarction or ischemic stroke is a potentially serious and life-threatening complication after stereotactic radiation therapy involving the extra- or intracavernous portion of the carotid artery or the Circle of Willis [67]. Although considered to be relatively rare, radiation-induced cerebral infarction has been reported after single fraction stereotactic radiosurgery or radiation therapy of meningiomas, pituitary adenomas, craniopharyngiomas, and vestibular schwannomas, with an occurrence of 1–7% [24, 46, 68, 69, 70]. However, the risk of cerebral infarction may not be increased when compared with the incidence in the general population. Predisposing risk factors identified for ischemic events are smoking, hypertension, and hyperlipidemia, as well as increased age [70]. Cerebral infarction is by definition a clinical diagnosis; therefore, subclinical infarctions only detectable by neuroimaging may occur [70].

3.4 Hearing loss

Both stereotactic radiosurgery and fractionated stereotactic radiation therapy have been shown to accelerate the naturally occurring hearing loss in patients in around 50% of treated patients with vestibular schwannoma, and the degree of hearing loss is correlated to the radiation dose to the cochlea [38, 40].

3.5 Malignancies

The occurrence of intracranial malignancies after conventional radiation therapy is well known but is not well established following stereotactic radiation therapy and radiosurgery, but since this is often a late event, existing studies may not have had long enough follow-up. It would be feasible to conduct such a study, but with very long-term (10–20 years) follow-up.

4. Conclusions

Benign anterior skull base tumors include meningiomas, pituitary adenomas, craniopharyngiomas, and vestibular schwannomas. As an adjuvant therapy to

surgery or when surgical treatment carries too high a risk of complications, a highly precise focused radiation, known as fractionated stereotactic radiation therapy (FSRT) or stereotactic radiosurgery (SRS) can be delivered to the tumor. Treatment modalities include Gamma Knife for SRS, LINAC for FSRT/SRS, Cyberknife for SRS or hypo fractionated FSRT, and more recently, proton beam therapy. FSRT in particular combines the high accuracy of stereotactic radiosurgery and the benefit of fractionation. Existing studies include systematic analysis of complications and risk factors FSRT/SRS of tumors with localizations relating to vision, hormone-secreting regions, cerebral vasculature, and hearing. Paying attention to risk reduction is extremely important to prevent complications. Existing studies provide evidence of good long-term tumor control for benign tumors of the skull base. Upweighting the risks against surgical complications and uncontrolled tumor growth, stereotactic radiotherapy and radiosurgery appear to be relatively safe as a treatment of patients with benign anterior skull base tumors. However, improved dose planning techniques may be able to reduce the incidence of side effects further. Further studies with very long-time follow-up including the potential for malignancy are needed.

Conflict of interest

The author declares no conflict of interest.

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