Skull Base Tumors

38

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Introduction

This chapter will focus on the rarer skull base tumors not discussed in detail in the respective meningioma, pituitary, and schwannoma chapters.

These skull base tumors can be divided into those that are unique to a particular region and those that can occur throughout the skull base. These tumors may derive from the bone, paranasal sinuses, nasopharynx, inner ear, dura, cranial nerves, or brain. They may be primary tumors invading local structures, or metastatic disease. They can also be divided into benign and malignant lesions.

Unfortunately, even benign lesions can become life threatening if critically located, rendering them unresectable or otherwise not amenable to effective local therapy.

Tumors of the skull base pose the greatest challenge to neurosurgeons as they tend to grow around and invade critical structures such as cranial nerves and vessels, hindering complete resections as the risk of neurologic deficits and morbidity is high. Especially here, the advantages of modern, high-precision radiosurgery with its high rate of local control with minimal risk due to optimal sparing of these critical structures become an attractive alternative. Primary radiosurgery can also be an alternative for inoperable patients or a palliative alternative for those with a poor prognosis. For these, symptom relief such as tumor-related facial pain is common. In general however, the goals of radiosurgery are long-term prevention of tumor growth, maintenance of patient function and quality of life, as well as prevention of new neurologic deficits. Very few complications occur after stereotactic radiosurgery, such as perifocal edema, delayed intratumoral hemorrhage, or radionecrosis requiring neurosurgical intervention [1, 2].

In general, single-fraction stereotactic radiosurgery is used for small localized lesions under 3 cm in diameter by using external stereotactic techniques such as Gamma Knife which requires the applications of an invasive stereotactic frame attached to the skull with four pins. The same technique has also been adapted to linac-based systems and charged-particle therapy such as protons. However, in the last decade, noninvasive alternatives have emerged, using noninvasive fixation, most commonly thermoplastic masks or a vacuum-mouthpiece [3–5]. This allows temporal separation of the imaging, planning, and treatment sessions as well as the option of fractionation should this be required. The inherent repositioning inaccuracy and intrafraction motion of noninvasive fixation systems are fully compensated by image guidance and, in many cases even six degrees of freedom treatment couches [6]. As of late, it has become possible to fractionate treatment with the Gamma Knife as well, using the abovementioned vacuum-mouthpiece [5, 7].

Linac-based radiosurgery can be performed with various techniques, such as the traditional arc-based approach with circular collimators [8], static beams [9]. Dynamic Circular Arc (DCA) [10] and intensity-modulated techniques (IMRT/IMSRS) [11]. When circular collimators are used for irregular treatment volumes (Gamma Knife, but also so equipped Linacs), multiple isocenters are usually required. These result in overlapping beams which in turn cause substantial dose inhomogeneity within the treatment volume. This inhomogeneity may damage organs at risk (OAR), in cases where these OARs are located within the treated volume. This can be of special relevance at the base of skull where cranial nerves abound [12]. The introduction of (micro-) multileaf collimation in linac radiosurgery improved conformity and homogeneity [13].

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L.S. Chin and W.F. Regine (eds.), *Principles and Practice of Stereotactic Radiosurgery*,
DOI 10.1007/978-1-4614-8363-2_38,

Table 38.1 Advantages of different radiosurgical techniques; a literature review

First Author (year)	Methods compared	Patients (*N*)	PTV (cm^3)	Results
Bourland et al. (‘94) [9]	Noncoplanar circular arc vs. conformal fixed beam	NA	NA	Smaller high-dose volume and better homogeneity for fixed beam
Hamilton et al. (‘95) [99]	Noncoplanar circular arc vs. conformal fixed beam	1	3.5	Smaller high-dose volume and better homogeneity for fixed beam
Shiu et al. (‘97) [100]	Noncoplanar circular arc vs. conformal fixed beam	2	4.5–9	Smaller high-dose volume and better homogeneity for fixed beam
Kubo et al. (‘97) [101]	Noncoplanar circular arc vs. conformal fixed beam	11	0.4–17.6	Lower doses to normal tissues and shorter planning time for fixed beam
Kramer et al. (‘98) [102]	Noncoplanar circular arc vs. IMSRT	1	NA	Better CI, lower max. Dose, better HI, but larger penumbra in IMSRT
Yu et al. (‘99) [14]	Noncoplanar circular arc vs. IMSRT vs. conformal fixed beam	3	9.6–36.7	IMSRT: better CI, lower dose to normal brain than others
Cardinale et al. (‘98) [103]	Noncoplanar circular arc vs. conformal fixed beam vs. IMSRT	3	11.5	Depending upon shape: IMSRT better conformity and OAR-sparing (irregular) or arcs better (ellipsoid)
Benedict et al. (‘01) [104]	Noncoplanar circular arc vs. conformal fixed beam-IMSRT	4	2.3–3.5	IMSRS: lower dose to OAR, lower volume normal brain receiving >50 % of prescr. Dose
Leavitt et al. (‘01) [105]	DCA vs. IMSRS/IMSRT	3	8.7–55	Lower dose to OAR in IMSRS/IMSRT
Yu et al. (‘02) [10]	3D conformal fixed beam vs. DCA vs. IMSRT	50	Large volumes, no SRS	DCA: best conformity, lower dose to normal tissues than conformal beam but not IMSRT
Perks et al. (‘03) [13]	Gamma Knife vs. Conformal Fixed Beam vs. DCA	8	0.3–10.6	Gamma Knife: best conformity, fixed beam and arc : better homogeneity
Baumert et al. (‘03) [11]	DCA vs. IMSRS	10	15–43	IMSRS: better coverage and lower OAR dose, but higher low-dose regions in the normal brain
Ernst-Stecken et al. (‘05) [106]	DCA vs. IMSRS	6	1.1–10.4	IMSRS: lower volume of normal brain receiving >90 % of PD but higher integral dose. RTOG criteria best met by DCA

NA not available, *CI* conformity index, *HI* homogeneity index, *IMSRT* intensity-modulated stereotactic radiotherapy, *IMSRS* intensity-modulated stereotactic radiosurgery, *OAR* organ at risk, *DCA* dynamic conformal arc

Table 38.1 summarizes the evolution of techniques with their inherent advantages and disadvantages in the form of a literature review; initially, static beams showed superior conformality compared to circular collimator arc treatment [14]. Perks et al. showed that more beams don’t necessarily translate into better normal brain sparing as four to six noncoplanar beams yielded similar results as plans using up to 30 fields [15]. Then followed the next level of conformality in the form of DCA therapy, where the beam is continually MLC-shaped during gantry rotation [16]. Most recently, IMSRS has been shown to offer superior treatment volume (PTV) coverage and lower OAR doses for irregular and concave targets [11].

Dose Limitations at the Skull Base

Radiosurgery in the region of the skull base poses special challenges, as many critical structures converge there, most notably the optic apparatus and cranial nerves. Table 38.2 summarizes the current data from literature, which can assist in determining the feasibility of radiosurgery itself or a given plan. We cannot emphasize enough that these data are to be used with utmost caution as, with exception of the RTOG 90–05 data, they are not the result of dose escalation or randomized trials but stem originate mostly from retrospective clinical outcome data, with not

Table 38.2 Summary of radiosurgical tolerance doses at the base of skull

Organ	# fx	Vol. cm^3	Vol. %	Vol. limit (Gy)	Max. limit (Gy)	
Major vessels	1	0.035–10		31–37	37	
	3	5–10		21–39	45	
	4	1–10		35–43	49	
	5	10		47	53	
Pituitary gland	1	NA				
Brainstem	1	1		10	15	
	3	1		18	23	
	5	1		26	31	
	5	100		20		
Brain	5		100	20		
Chiasm	1				8–15	10 Gy safe → 77 % chance of RON above 15 Gy
	3	0.2		15		
	5	0.2	100	20	25	
Cranial nerves	1				20–30	Fifth cranial nerve 20 Gy max
Cochlea	1				12	
	3				20	
	5				27.5	
Lens	1				2–3	
	2				3–6	
	3				3–7	
	5				3–7	
Retina and lacrimal gland	1				5	
	2				5–10	
	3				5–15	
	5				5–15	
Neurovascular bundle	5		20–50	38		
Optic nerve	1				8–15	
	2				10	
	3	0.2		15	19.5	
	5	0.03–0.5		12.5–25	25–30	
Area postrema					6.2	

Adapted from Grimm J, LaCouture T, Croce R, Yeo I, Zhu Y, Xue J. Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. Journal of Applied Clinical Medical Physics/American College of Medical Physics. 2011; 12(2): 3368; (open source journal)

only limited long-term outcome data but also small patient collectives.

From these data, one can surmise that the most critical structures are the optic pathways. The risk of clinically significant radiation optic neuropathy for patients receiving SRS for skull base tumors is 1–2 % following doses to optic chiasm below 10 Gy and this percentage may significantly increase for higher doses [17, 18]. Leber et al. reviewed 50 patients having SRS for benign skull base tumors in which the optic nerves or chiasm were exposed to 4.5 Gy or more. For patients receiving 10–15 Gy and greater than 15 Gy, the risk of radiation-induced optic neuropathy was 26.7 % and 77.8 %, respectively, however no optic neuropathy was observed when a dose less than 10 Gy was delivered to the optic apparatus [19]. Stafford et al. found that the risk of developing a clinically significant optic neuropathy was 1.1 % for patients receiving a maximum point dose of 12 Gy or less [20] and similar results have been reported by others [21]. Considering an effective dose of 13–16 Gy to achieve local control of a given tumor and a recommended dose of 8 Gy as the maximum for the optic chiasm this means that in clinical practice a distance between tumor margin and optic apparatus should be at least of 2–3 mm to avoid visual deterioration.

The auditory apparatus is second in line with 12–15 Gy SRS tolerance using a single fraction or 18 Gy in three fractions. Then follows the trigeminal nerve and finally the motor cranial nerves [2, 4, 6, 7, 9–12] which have rarely been reported having a deficit using doses under 16 Gy.

Considering these data and published risks of optic neuropathy for conventionally fractionated radiotherapy, α/β[alpha/beta] ratios in the range of 0–1 seem reasonable for estimating radiosurgery dose equivalents for optic and cranial nerves.

Re-irradiation at the Skull Base

This often represents a relatively high-risk treatment, as critical tolerance doses have usually been applied in the first course of treatment. Historically, most radiation oncologists have refused re-irradiation due to concern about the risks of late central nervous system toxicity, especially radionecrosis, which may appear several months to years after treatment. Re-irradiation of brain tumors has recently attracted more interest as our understanding of the tolerance of the brain to radiation evolves, and developments in radiation technology and imaging make highly accurate targeting of biologically relevant tumor volumes possible. Prospective data addressing this approach is however lacking.

Obviously, the applicable doses depend to large extent on time since initial treatment, treatment volume, fractionation used and location as well as individual factors such as histology, location, and imminent danger to the patient, so that individual recommendations are well beyond the scope of this book.

However, it seems reasonable to apply the same rationale to re-irradiation in the base of skull regions as is applicable to the brain itself; own and other published clinical experiences have yet to describe any major untoward effects of such re-irradiation if certain radiobiological principles are followed:

Although available data come mainly from animal spinal models, the pathogenesis of radiation toxicity and recovery potential in the brain is assumed to be similar with a similar, low α/β[alpha/beta] [22]. Animal spinal cord models suggest that significant recovery follows irradiation; conservative estimates being up to 50 % recovery within 1–2 years after initial exposure [23, 24]. An increasing body of evidence is available (mainly for re-irradiation of gliomas) resulting in a solid clinical rationale should re-irradiation be required. But there may also be a case to be made for repeat radiosurgery in the base of skull region, i.e. for acoustic neuromas [25].

In summary, re-irradiation at the skull base remains a complex procedure and should be left to centers with extensive experience herein. With developments in molecular-targeted therapy, further exploration of the role of re-irradiation on its own or in combination with novel agents is needed.

Clinical Entities

Skull base tumors are relatively rare. Approximately 0.1 % of all intracranial tumors are chondrosarcomas and also approximately 0.1 % of all intracranial tumors are chordomas. For benign tumors of the skull base such as glomus tumors, local control rates of 90–100 % have been reported. On the other end of the spectrum, local control rates for chordomas range from 50 to 70 %.

On the following pages, the radiosurgical options for primary malignant and benign skull base tumors will be discussed.

Angiofibroma

Disease Pathophysiology

Juvenile angiofibroma is one of the most common benign nasal tumors affecting males between 9 and 19 years of age accounting for 0.05 % of all head and neck tumors [26]. In the USA it is the most common Head and Neck tumor of adolescence [27]. The tumor originates from the broad area of the posterolateral wall of the nasal cavity in the region of the sphenopalatine foramen [28]. The etiology is still unclear, however recent electron microscope studies suggest it is rather a vascular malformation, possibly associated with incomplete regression of the first brachial artery, than a tumor [29]. They often act in a malignant manner by eroding into the surrounding sinuses developing an aggressive growth pattern. Intracranial extension is noted in 10–20 % of cases. Different staging systems based on tumor extension have been proposed [30].

Typical clinical symptoms are frequent epistaxis, nasal obstructions, and rhinorrhea. Chronic rhinosinusitis, swelling of the cheek, alteration of olfaction are possible; unilateral otitis media may result by eustachian tube blockage. By eroding into the cranial fossa, diplopia may occur as well as symptomatic pressure of the chiasm and optic nerves.

Treatment Options

After CT/MRT and bilateral angiography for staging and determination of blood supply, treatment of choice in patients with primary and recurrent juvenile nasopharyngeal angiofibroma is surgical resection as sole treatment of early-stage tumor when gross total resection can be achieved. Preoperative embolization is recommended by most authors to reduce intraoperative blood loss [31]. In the last decade, endoscopic resections have evolved, providing reduction of complications and intraoperative bleeding and thus an alternative to open surgery for early to intermediate stage angiofibromas [30]. Complications in advanced-stage angiofibromas after surgery include intraoperative blood loss requiring transfusions, neuralgia, hearing loss, and ophthalmoplegia [32]. Surgical contraindications include unresectable intracranial involvement.

After primary resection of extracranial angiofibromas, cure rates of nearly 100 % can be achieved compared with results in patients with intracranial lesions where the cure rates are approximately 70 %.

In case of incomplete resection, or in advanced-stage lesions, a combination of surgery followed by radiotherapy is indicated due to the high recurrence rate in these patients. Advanced-stage disease with cranial base involvement and intracranial extension often allows only subtotal resection of the tumor.

External beam irradiation has been shown to be a useful adjunct to therapy in patients with unresectable recurrent disease. Gamma Knife and linac-based radiosurgery with a dose of 20 Gy to the tumor margin (55 % isodose line) is an effective way to deliver high-dose radiation to incompletely resected angiofibromas [32] as they represent slow-growing and late-responding tissues. Therefore, a radiobiological advantage to radiosurgery may be given. Radiosurgery is regarded as a reasonable strategy in small-volume and localized angiofibromas.

For larger angiofibromas, fractionated conformal radiation therapy with total doses of 36–46 Gy is also effective and may reduce the risk of late effects such as cranial nerve deficits, bone and soft tissue necrosis. Another treatment technique described in the literature is the use of intensity-modulated radiation therapy (IMRT) in three cases [33]. The applied tumor dose varied from 34 to 45 Gy. In all three cases, a reduction of tumor size occurred without significant toxicity. Especially in children, inhibition of facial bone growth and second malignancy are severe possible side effects and must be considered in treatment decisions [34–36].

Esthesioneuroblastoma

Disease Pathophysiology

Esthesioneuroblastomas are rare tumors originating from the olfactory epithelium of the upper nasal cavity [36]. The sex distribution of esthesioneuroblastomas is uniform. The olfactory nerves perforate the groove in the ethmoid bone in the cribriform plate and continue into the subarachnoid spaces. Therefore, a high incidence of intracranial extension results. This highly dedifferentiated tumor occurs in all periods of life with a bimodal peak at the second and sixth decades. The two most common clinical signs of esthesioneuroblastoma constitute unilateral nasal obstruction and epistaxis. Other clinical symptoms include headache, swelling of the cheek, blurred vision, and dental pain. Esthesioneuroblastoma can metastasize to regional lymph nodes, primarily of the neck [37] lung, or bones. According to the WHO classification system, the terms *olfactory neuroblastoma* and *olfactory neurogenic tumors* are used. The Kadish staging classification is shown in Table 38.3.

Table 38.3 Staging of esthesioneuroblastoma according to Kadish et al.

Stage	Characteristic
A	Confined to the nasal cavity
B	Confined to the nasal cavity and one or more paranasal sinuses
C	Extending beyond the nasal cavity or paranasal sinuses, including involvement of the orbit, base of skull or intracranial cavity, cervical lymph nodes or distant metastatic sides

From Kadish S, Goodman M, Wang CC. Olfactory neuroblastoma. A clinical analysis of 17 cases. Cancer. 1976; 37(3): 1571–6; used with permission

Rationale for Treatment and Alternatives

Because of the rarity of esthesioneuroblastoma and its wide variety of clinical behavior, there is no definitive consensus regarding the optimal treatment. For small, low-grade tumors confined to the ethmoids, surgery alone appears to be an adequate method. Patients with locally advanced disease or high-grade tumors should receive aggressive treatment with combined modalities such as surgery, radiation therapy, and chemotherapy [38]. Most authors recommend *en bloc* resection, combined with radiation therapy [39, 40]. Local failure rates of 44 % in low-grade and 60 % in high-grade tumors and metastatic rates of 25 % in low-grade and 47 % in high-grade tumors are described [41]. A significantly lower recurrence rate with overall 5- and 10-year survival rates of 81 and 54.5 % in patients with response to neoadjuvant radiotherapy combined with chemotherapy has been reported [42]. At recurrence, either surgical and/or radiosurgical retreatment can lead to long lasting remissions in 42 % of patients [43, 44]. Thus close follow-up is recommended.

Radiosurgery for Esthesioneuroblastoma

Very few studies report on radiosurgical treatment in the primary situation; the limiting factors are usually the radiosensitivity of cranial nerves as discussed in Table 38.1.

Walch et al. [45] reported on three patients with olfactory neuroblastoma treated with a combination of endoscopic surgery and Gamma Knife. Stereotactic radiosurgery was performed within the first 3 months of surgery. The maximum diameter of the tumors was approximately 24.3 mm and the marginal dose to the tumor varied from 16 to 34 Gy; 1–5 isocenters were used. Radiation-induced side effects were nasal discharge and crusts. One patient developed bilateral frontal chronic sinusitis, and in a second, endoscopic operation was necessary.

An Austrian group described the combined treatment of endoscopic surgery and radiosurgery for olfactory neuroblastoma [46]. Median marginal doses ranged from 15 to 34 Gy at a marginal isodose between 45 and 85 %.

The maximum tumor volume treated with radiosurgery was approximately 20 cm^3. The median follow-up period was 58 months. Observed radiosurgical side effects were mild and transient, such as cephalea and dizziness. No changes in mental status were observed. No new pathology of the optic pathway was described during follow-up.

IMRT is recommended for larger and more complex-shaped Esthesioneuroblastoma [40]. However also here, the required conventionally fractionated doses of 50–60 Gy (postoperatively) or 65–70 Gy required for inoperable cases, the challenge remains similar [47, 48].

Craniopharyngioma

Disease Pathophysiology

Craniopharyngiomas are benign tumors located at the base of the skull next to the pituitary gland. Differentiation between craniopharyngioma and pituitary can therefore sometimes be difficult on CT or magnetic resonance (MR) scans. Approximately 5–10 % of primary brain tumors are craniopharyngiomas. They typically occur in childhood as well as in the sixth to eighth decades [29]. Histopathologically, craniopharyngiomas are benign tumors arising from squamous cell remnants of the Rathke pouch during embryogenesis at the junction of the pituitary stalk and pituitary. Craniopharyngiomas present as a suprasellar lesion, frequently partially calcified and usually including an intrasellar component. These tumors are often composed of solid and cholesterol-rich cystic components. Cystic or solid components of this tumor extension may occur laterally into the middle or into the posterior cranial fossa. Symptoms relate to compression effects of the tumor due to its vicinity to pituitary gland, chiasm, optic nerves, and hypothalamic region. Locally, these tumors can produce signs and symptoms of increased intracranial pressure such as headache, drowsiness, or vomiting at the time of diagnosis and are due to hydrocephalus by obstruction of the foramen Monro by tumor parts within the third ventricle in 55–85 % of the patients [49]. Compression of the pituitary and hypothalamic region can produce antidiuretic hormone and growth hormone deficiency or obesity in children. Diabetes insipidus is present in approximately 10 % of the patients. Visual field defects and decreased vision due to compression of the optic chiasm and optic pathways are the initial symptoms in approximately 40–60 % of these patients [50, 51] (Table 38.4).

Rationale for Treatment and Alternatives

The main treatment modality for craniopharyngiomas is surgery. Microsurgery allows complete tumor removal in 49–100 % of the patients with low morbidity and operative mortality [52–54]. After radical resection, 10-year progression-free survival rates between 60 and 93 % are reported [55, 56]. Treatment modalities include complete resection of the tumor with radiation therapy at the time of recurrence or subtotal resection followed by radiotherapy. The probability of complete tumor resection decreases with increasing tumor volume. Because of the proximity to critical normal structures and the relatively high association of radical surgery with visual loss and impaired hormone function requiring replacement therapy, many authors recommend less radical surgery (partial resection, biopsy, and aspiration of cystic contents) followed by radiation therapy or radiosurgery. With this strategy, local control rates of 70–83 % after 10 years are reported [57, 58] and assumed to be similar to complete surgical resection of the tumor [59]. Treatment-related toxicities after subtotal resection followed by radiotherapy include impairment of hormone function. Impairment of vision is reported for less than 10 % of all patients treated with the combination of subtotal resection and irradiation compared with up to 20 % after complete tumor resection [60]. Other side effects such as radionecrosis, radiation-induced malignancies, vascular morbidity, and cognitive decline occur less frequently [60, 61].

Table 38.4 Review of the literature for radiosurgery of craniopharyngioma

Author	*N*	Median follow-up (range)	Mean peripheral dose (range)	Local control (%)[a]	Morbidity
Chung et al. [64]	31	33 months (5–69)[b]	12.2 Gy (9.5–16)	87.2	Visual field deficit (1 patient)
Mokry [65]	23	23 months (6–57)	10.8 Gy (8–15)	78.2	None
Ulfarsson et al. [67]	21	42 months (6–348)[b]	30 Gy (20–50)[c]	36.4	Visual field deficit (8 patients)
Kobayashi et al. [68]	98	66 months (6–148)	11.5 Gy (NA)	79.5	Visual/endocrine (6 %)
Iwata [62]	44	40 (12–92)	13–25 Gy (1–5 fractions)	85	Hypopituitarism (1 patient)

[a]Crude local control rates
[b]Median values
[c]Given in maximum dose

The major goal of radiotherapy treatment strategies is sparing of critical normal structures. Radiosurgery as well as intracavitary irradiation with stereotactically applied β[beta]-emitting radioisotopes maximize normal tissue sparing. The cystic nature of craniopharyngioma has led to trials of intracystic applications of β[beta]-emitting radioisotopes such as yttrium-90 or phosphorus-32. The use of radiosurgery has been reported in patients with minimal residual or recurrent disease. However, for patients with larger target volumes, tumors immediately abutting the optic apparatus and multiple cystic configured lesions, fractionated stereotactic radiotherapy should be preferred as excellent local control with minimal morbidity can be realized [62, 63].

Treatment Planning and Results for Radiosurgery

The target volume for craniopharyngiomas is narrowly defined to the tumor volume, including solid and cystic components. In cases with cyst aspiration or subtotal resection, it is important to cover the complete cyst wall. This technique can be used for selected patients with smaller tumors (<2 cm) not abutting critical structures such as the chiasm and the brain stem. Median doses to the margin of the tumor range from 9 to 16 Gy. Chung et al. recommend a margin dose of 12 Gy to induce satisfactory tumor response [64]. The main restriction with radiosurgery treatment is the tolerance dose of the neighboring visual pathway. The dose to the optic nerves and the chiasm should be kept below 8 Gy with single-dose techniques to avoid damage to these structures. Stereotactic radiosurgery has been used to treat small residual or recurrent tumors after surgical intervention.

Mokry et al. [65] treated 23 patients with Gamma Knife radiosurgery for craniopharyngioma and found no relevant morbidity. Ten patients had additional therapy with intracystic bleomycin before radiosurgery. Tumor progression was observed in 5 of 23 patients. They conclude that the best results might be obtained in monocystic tumors amenable to stereotactic drainage and intracystic bleomycin treatment. The Cologne group of Kickingrieder et al. summarizes their results on 53 patients with cystic craniopharyngiomas treated with stereotactically applied colloidal β-emitting radioactive sources. They concede few but notable severe side effects (hemiparesis and third nerve palsy) as well as suboptimal progression-free survival (79.4 ± 6.1, 72.4 ± 6.8, and 45.6 ± 8.7 % at 12, 24, and 60 months, respectively) [66].

After an average follow-up of 36 months, Chung et al. reported a tumor control rate of 87 % for 31 patients treated with Gamma Knife radiosurgery and a prescribed dose to the tumor margin from 9.5 to 16 Gy [64]. One patient developed a mildly restricted visual field. None of the patients showed additional endocrinologic impairment or neurologic deterioration related to radiosurgery. In a Swedish study, 21 patients were treated with Gamma Knife radiosurgery. They found a statistically significant difference between tumor progression and applied dose; a higher progression rate was found in patients treated with less than 6 Gy to the margin than in patients treated with a dose higher than 6 Gy. Four of these patients developed pituitary dysfunction [67]. In the literature, parenchymal injuries of the brain or second malignancies caused by radiotherapy are estimated to be less than 1–2 % [68].

Chordomas, Chondromas, and Chondrosarcomas

Disease Pathophysiology

Chondromas are rare benign tumors arising at the base of the skull, especially in the area close to the pituitary gland. It is a very-slow-growing tumor and might be present for a long time before causing any symptoms. Chondromas are composed of cartilage formed by the meninges and is usually attached to the dura mater. Surgical intervention might be the treatment of primary choice because of their usually well-defined margins.

Chordomas are relatively rare, slow-growing, primary bone tumors arising from embryonic remnants of the notochord (chorda dorsalis) at the two extreme ends of the vertebral axis. They are most often diagnosed in the second or third decade of life, more common in males (2:1) and comprise less than 1 % of intracranial tumors [69, 70]. Twenty five to forty percent of chordomas occur in the sphenoccipital or skull base region. The clivus is the most common site. Chordomas are locally more aggressive with a poorer outcome compared with chondrosarcomas.

Chondrosarcomas are malignant tumors composed of cartilage-producing cells encountered in the skull base. Two histologic variants of chordoma have been described. The first is chondroid chordoma, a typical chordoma that also contains areas resembling low-grade hyaline chondrosarcoma. The second variant is dedifferentiated chordoma, which contains areas of typical chordoma mixed with components that resemble high-grade or poorly differentiated spindle cell sarcoma. Chondrosarcomas rarely metastasize, are slow-growing but often invade local structures. Prognostic factors that most influence choice of treatment are location, local tumor extension, and surgical resectability.

Approximately 0.1 % of all intracranial tumors are chondrosarcomas. This locally invasive tumor is a malignant variant of a benign chondroma arising from bone and is composed of cartilage.

Chondrosarcomas are mostly located in the sphenoid bone or clivus. Chondrosarcomas are also more common in

Table 38.5 Radiosurgical literature on chordoma and chondrosarcoma

Author	*N*	Median follow-up (range)	Median peripheral dose in Gy (range)	Local control*(%)	Morbidity	Comments
Krishnan et al. [107]		4.8 years (0.8–11.4)	15 (10–20)			
Chordoma	25			32‡	34 % (all with combined EBRT)	
Chondrosarcoma	4			100		
Feigl et al. [82]		17 months (6–36)†	17 (14–18)†			
Chordoma	3			33	Cranial nerve deficits, headaches, diplopia	
Chondrosarcoma	10			100		
Pamir et al. [89]		23.3 months (NA)†	NA	29	NA	
Chordoma	7					
Chang et al. [108]§		4 years (1–9)†	19.4 (18–24)†			
Chordoma	10			80‡	None	
Hauptman et al. [85]	5	4.5 years	15.5 (to 90 % isodose line)	60	Cranial neuropathy, visual deficits	
Koga et al. [84]	14	65 months (12–167)	15 (10–20)			Local relapse in all cases of Radiosurgery after fractionated xRT, Marginal doses of >16 Gy crucial
Chordoma	10	40.5 (12–167) months	13.7 (10–20)	15	1 transient visual deficit	
Chondrosarcoma	4	20 (45–145) months	15.5 (12–20)	100	1 transient visual deficit	
Martin et al. [109]		7.7 years (2–17)	16.5 (10–25)			
Chordoma	18	88 months		62.9‡	1 transient effect	
Chondrosarcoma	10	88 months		80‡		
Hasegawa et al. [110]		59 months (1–172)	14 (9–20)	80‡	1 worsening of facial numbness	Under 20 mL volume sig. better LC, at least 15 Gy marginal dose required
Chordoma	30			0.72		
Chondrosarcoma	7					

males than in females (1.5:1). They can be classified into three grades (I–III). Lower-grade tumors are less aggressive and act clinically similar to chordomas. Historically, skull base chordoma and chondrosarcoma were often pooled together in reported series due to the rarity of these tumors; however, recently published studies have shown important differences with respect to diagnosis, treatment, and prognosis, strongly suggesting a more aggressive therapy for chordomas than chondrosarcomas [71] (Table 38.5).

Rationale for Treatment and Alternatives

Treatment of choice is total surgical resection, if feasible, followed by radiation therapy. The best results in the treatment of chordomas have been obtained by complete surgical resection followed by high doses of proton irradiation [72]. Complete resection of these tumors at the skull base is challenging and associated with higher rates of morbidity and mortality. Furthermore, it is difficult to treat skull base chordomas and chondrosarcomas with radiotherapy alone because of the large tumor size, the extent of infiltrated tissues, and because of dose limitations imposed by the sensitivity of adjacent critical normal tissues such as the brain stem and cranial nerves [73]. Frequently used fractionated doses are 55–66 Gy. A clear dose-response relationship with improved outcomes after doses exceeding 60 Gy have been shown in chordomas [74]. Similar effects have been shown with radiosurgery with better results after marginal doses >15 Gy [73]. Because of the slow proliferative nature of chordomas, high linear energy transfer may be useful. To yield good results with respect to local tumor control, high-dose radiation therapy with photons combined with proton beam boost [75, 76] or particle therapy alone [77, 78], are reported. Heavily charged particles such as protons or carbon ions may be superior because of their finite range in tissues. This radiation technique offers an excellent chance of cure with acceptable radiation-induced toxicity. However,

IMRT has also shown its effectiveness [79], so that the final verdict may ultimately require long-term results from a randomized trial.

Radiosurgery for Chordomas and Chondrosarcomas

There is a strong argument for radiosurgical treatment of chordomas and chondrosarcomas to reduce the incidence of brain or bone necrosis in smaller circumscribed post-surgical tumor-remnants. In literature, lesions with a diameter of less than 30 mm were treated with 17–20 Gy to the tumor margin [73, 80, 81].

Kondziolka et al. [73] reported on four patients with chordoma and two patients with chondrosarcoma treated with radiosurgery. All tumors were less than 30 mm in diameter and were treated with 20 Gy to the tumor margin. During a mean follow-up of 22 months (range, 8–36 months), no in-field progression was seen. Three patients showed improvement of preexisting neurologic deficits. The other three patients remained in stable neurologic condition. Serial follow-up imaging studies showed tumor volume reduction in two patients, whereas the other four patients showed stable tumor size. One patient showed tumor progression outside the irradiated tumor volume. In the study of Feigl et al., 13 patients with chordoma and chondrosarcoma were treated with Gamma Knife radiosurgery after maximal tumor resection [82]. The mean treated tumor volume was 9.7 cm^3 (range 1.4–20.3 cm^3). The mean treatment dose was 17 Gy and the mean marginal isodose was 52 %. After a mean follow-up of 17 months, only one recurrence of disease was seen at the margin of the radiation field. Pamir et al. reported on 26 skull base chordomas with a mean follow-up period of 48.5 months receiving multimodality treatment with various combinations of conventional surgery, skull base surgical techniques, and Gamma Knife surgery [83]. The mean follow-up after Gamma Knife treatment was 23.3 months. They recommend Gamma Knife radiosurgery immediately after initial surgical intervention if the tumor volume is less than 30 cm^3. This suggested treatment algorithm of Pamir and colleagues is shown in Fig. 38.1.

Interesting results were published by the Tokyo group by Koga et al. [84] on ten chordoma and four chondrosarcoma patients with tumor volumes at radiosurgery ranging from 3.4 to 55.5 cm^3. Four chordoma patients received radiosurgery with lower marginal doses (12 Gy) after 60 Gy fractionated radiotherapy. All four patients recurred locally. One chondrosarcoma patient receiving 12 Gy marginal dose recurred locally. Five-year PFS rates for patients with higher and lower marginal doses were 80 % and 14 % respectively ($p = 0.0005$). The authors conclude that a marginal dose of at least 16 Gy is required for local control.

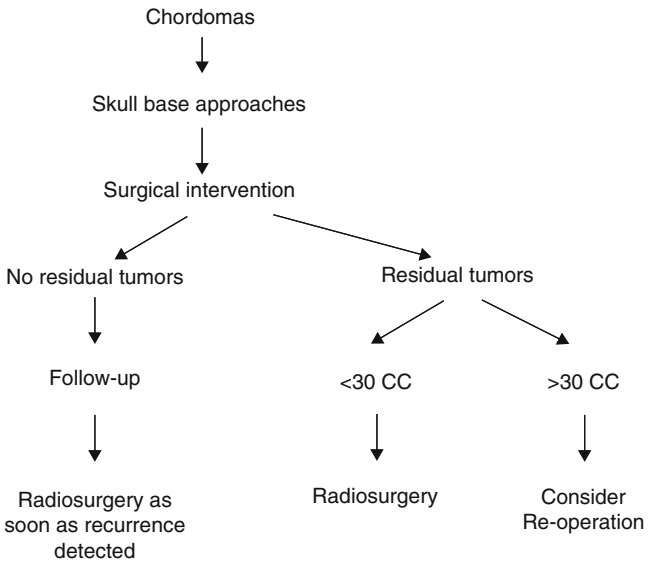

Fig. 38.1 Radiosurgical management algorithm for skull base chordomas according to Pamir et al. [83]. Should re-operation not be possible, high-dose particle beam therapy or IMRT should be recommended

Glomus Jugulare Tumors/Chemodectoma/Paraganglioma

Disease Pathophysiology

Glomus jugulare tumors are rare, radiosensitive tumors of the skull base/neck regions, slow-growing, hypervascular, and histologically benign. They comprise 0.6 % of all tumors and are closely associated with the sympathetic system, arising from the paraganglia of the chemoreceptor system. Thus, *chemodectoma* and *paraganglioma* are frequently used synonyms. Due of their tendency to invade and compress adjacent tissues, local problems can evolve.

Typical clinical symptoms are gradual hearing loss, unilateral pulsatile tinnitus, or imbalance.

Familial as well as multilocal/bilateral occurrence is possible and should be excluded by MRI of the skull base and neck (Fig. 38.2).

These tumors can show metabolic activity on PET/SPECT which may change disease management [85]. Malignant transformation rates are rare (2–5 %) with metastatic spread to lung, liver, and bone [86, 87]. Because of their slow growth, up to 10 years of follow-up is necessary to establish a cure rate for these lesions [88].

Rationale for Treatment and Alternatives

The treatment options for glomus jugulare tumors include surgery, radiosurgery, radiotherapy, and endovascular occlusion of feeding vessels either in combination or alone [89–91].

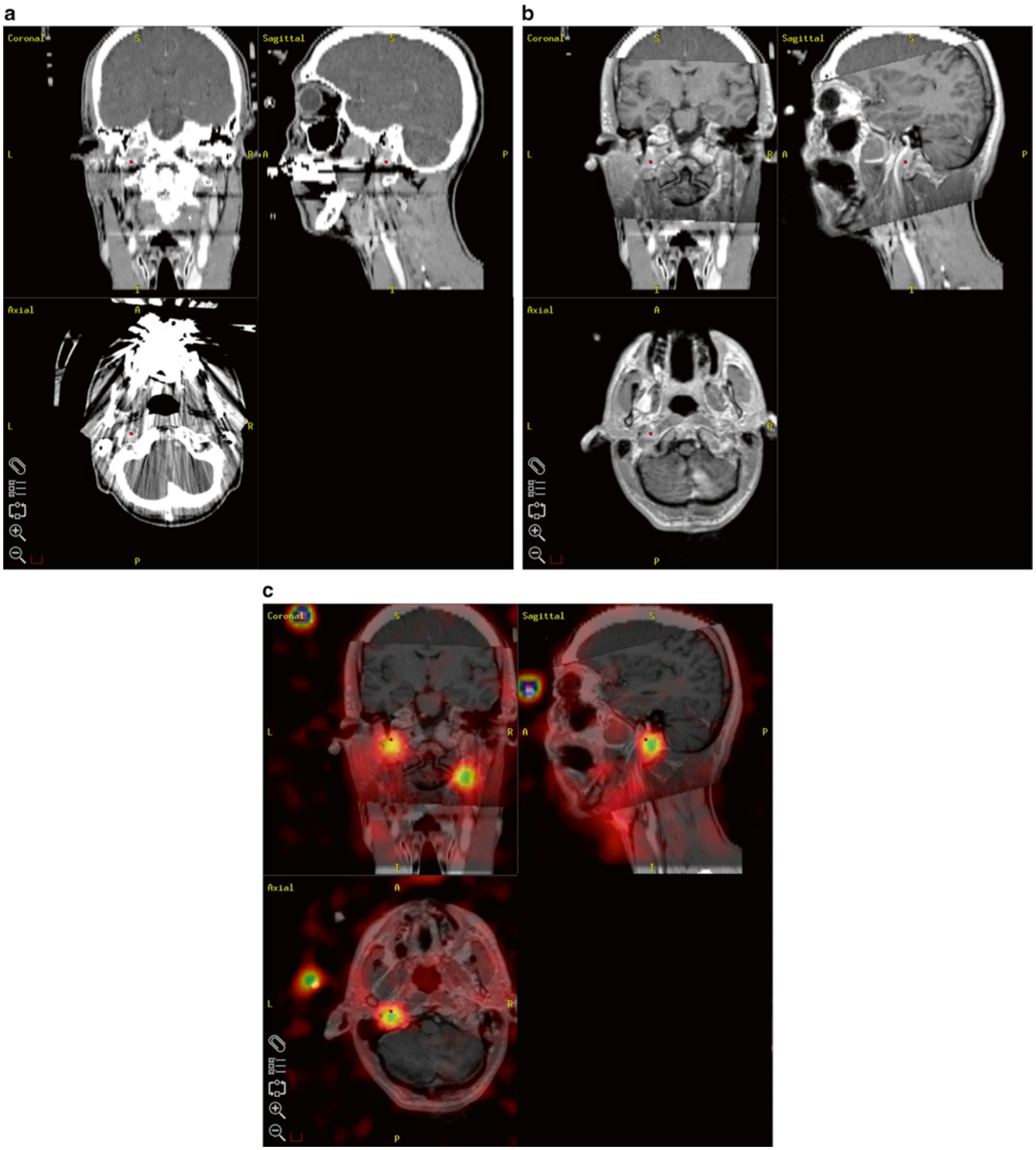

Fig. 38.2 This right sided incidental jugular glomus tumor was detected on ^{99m}Tc-octreotide SPECT imaging (*bottom* in fusion with MRI) after being missed on both CT (*top*) and MRI (*middle*) for a left sided glomus tumor at the level of the carotid bifurcation. Retrospectively, it is quite obvious in MRI

Embolization alone does not prevent further tumor progression [92]. Surgical resection is the only treatment option that can offer immediate and complete tumor elimination. Contraindications to surgical intervention of skull base tumors are based on the patients' comorbidities. Surgical resection of glomus jugulare tumors carries a high complication rate, due to their high vascularity and the involvement of critical vascular and neuronal structures, which included stroke,

cranial nerve injury with 8–40 %, and an overall mortality rate of 5–13 % [93]. Compared with radiosurgery, fractionated stereotactic radiotherapy may reduce the risk of radiation-induced side effects providing additional radiobiologic sparing and should be recommended for larger tumors or those, which cannot be precisely defined by imaging.

Patient Selection for Radiosurgery and Treatment Planning Details

For radiosurgical techniques, the prescribed dose to the tumor margin ranges from 12 to 25 Gy with typical doses greater than 20 Gy for small- to medium-sized tumors but lower doses to larger tumors due to an increased risk of radiation-induced side effects [82, 83, 94]. Median tumor volumes of glomus tumors should be less than 10 cm^3 because of the possible increased risk of radiation-induced cranial nerve deficits due to the radiosensitivity of cranial nerves. On the other hand and in analogy to excellent control rates after only 45–50 Gy in fractionated radiotherapy [95] 12 Gy single fraction or 25 in 5 Gy fractions [96] likely suffice, especially in critical locations.

Review of the Literature

For well-defined and noninfiltrating glomus jugulare tumors, stereotactic radiotherapy should be particularly beneficial. They usually present in a small size due to their proximity to cranial nerves whose dysfunctions often herald the presence of the tumor. The steep dose gradient achievable with radiosurgery minimizes the irradiation dose to surrounding normal tissue. Whereas diagnostic imaging techniques have been much improved within recent years, they cannot reliably separate tumor from adjacent cranial nerve when targeting radiosurgery treatment. Because of the close proximity of glomus tumors to cranial nerves, permanent cranial nerve deficits are possible side effects of radiosurgery. Most published studies reported only transient dizziness or occasional hearing loss (Table 38.6).

Jordan et al. [82] reported on eight patients treated with Gamma Knife radiosurgery between 1990 and 1998. The mean tumor volume of these patients was 9.8 cm^3 (range, 17.3–4.3 cm^3). The mean applied marginal dose was 16.3 Gy (range, 12–20 Gy). None of these patients developed delayed cranial neuropathy or tumor progression during a mean follow-up of 27 months.

Lim et al. [94] reported on ten patients treated with radiosurgery, whereas four patients were treated with primary radiosurgery due to several comorbidities. The other five had prior surgeries for their tumor. Tumor size ranged from 1.2 to 3.6 cm at the largest diameter with an average of 2.4 cm. Six patients were treated with a frame-based linac system and four with the CyberKnife. Prescribed dose to the 80 % isodose ranged from 16 to 25 Gy to the tumor margin. After a median follow-up of 21.5 months, nine patients had no change of tumor size, whereas one patient showed tumor regression. Nine patients had stable neurologic symptoms and only one patient experienced transient ipsilateral tongue weakness and hearing loss (Fig.38.3).

Table 38.6 Side effects of radiosurgery

Author	*N*	Median follow-up (range)	Median peripheral dose (range)	Local control[a]	Morbidity	Comments
Jordan et al. [82]	8	27 months (9.7–102)[b]	16.3 Gy (12–20)[b]	1	Acute vertigo (1 patient)	
Foote et al. [89]	25	37 months (11–118)	15 Gy (12–18)	1	Late vertigo (1 patient)	8 decreased in size
Eustacchio et al. [111]	19	7 years (1.5–10)	14 Gy (12–20)	0.95	None	
Maarouf et al. [83]	12	4 years (0.8–9)	15 Gy (11–20)	1	Moderate facial palsy (1 patient)	8 decreased in size
Liscak et al. [88]	52	24 months (4–70)	16.5 Gy (10–30)	1	Tinnitus (2 patients)	Tumor size decreased in 40 %
Gottfried et al. [112][c]	142	39.4 months[b]		0.98	8.5 % morbidity	
Pollock et al. [113]	42	44 (6–149 months)	14.9[b](	0.98	15 % new deficits (4× hearing loss, 2× vocal cord paralysis, temporary imbalance/vertigo ×1	
Hurmuz et al. [96]	14	39 months (7–60)	25 (18–30) (in 1–5 fractions)	1	None	Tumor regression in 6

[a]Crude local control rates
[b]Mean values
[c]Literature review

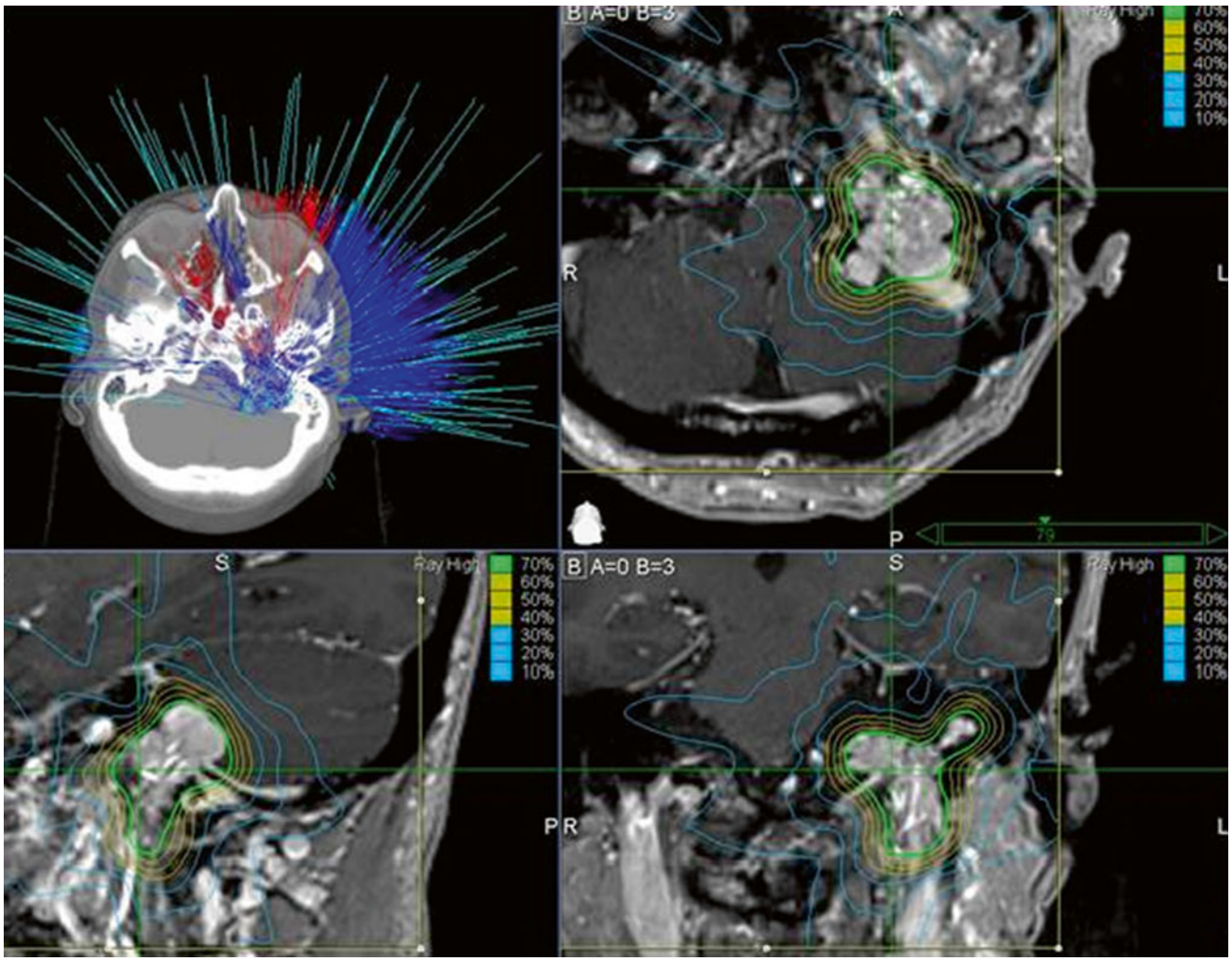

Fig. 38.3 Treatment plan of a patient presenting with hearing deficit, vertigo and vocal cord paresis. MR imaging showed a left sided glomus tumor treated radiosurgically with 17 Gy marginal dose (70 % isodose). After 24 months the tumor has shrunk, no new toxicity (courtesy of Dr. A. Muacevic, CyberKnife Centre Munich)

After an observation period of up to 6.7 years, Saringer and co-workers [90] reported on 13 patients with glomus tumors treated with Gamma Knife radiosurgery. Three of these patients showed tumor size reduction, whereas ten had stable tumor volume. Clinical symptoms remained unchanged in six, and six patients showed an improvement of clinical symptoms. One patient failed the follow-up. Two patients developed transient cranial nerve complications (worsening of preexisting swallowing disorders and temporary facial nerve palsy 1 and 12 months after radiosurgery, respectively).

The Mayo Clinic experiences were published by Foote et al. in 2002 [97]. They described treatment outcome for a total of 25 patients and long-term results for a cohort of 9 patients with a median largest diameter of 3.3 cm. No acute neurologic toxicity was identified in all 25 patients. Only one patient experienced clinically significant vertigo 8.5 months after treatment. They observed no new or progressive neuropathy of cranial nerves V–XII.

Recently, even clearer evidence for radiosurgery's role has been published in the form of a meta-analysis of 869 patients with glomus tumors. Subtotal resection (STR), gross total resection (GTR), STR + postoperative radiosurgery and radiosurgery alone were compared in terms of local control and cranial neuropathy. Local control after radiosurgery was significantly ($p < 0.01$) higher than the other groups. The GTR patient group had higher rates of deficits than those who underwent SRS alone. The authors concluded that higher rates of morbidity are not associated with improved local control rates, compared to radiosurgery [98].

Conclusion

It can be generalized in the base of skull region as well, that when radiosurgery is limited to lesions that are 3 cm or less, dose fall-off is sharp and only a small amount of normal brain tissue receives a high radiation dose. At larger volumes, the radiation fall-off into the surrounding normal tissue is not as steep and the risk of delayed radiation-induced side effects increases. Still, many patients with skull base tumors larger than 30 mm can undergo radiosurgery safely because these tumors are often in contact with the brain for only a portion of their surface, and therefore, radiation fall-off occurs in the bone, the sinuses, or the infratemporal or cervical regions. For larger lesions and those located next to the optic pathway, fractionated radiation therapy should be recommended due to its radiobiological advantages.

However, in order to maximize radiosurgical benefits and minimize its dangers, all highly precise radiation techniques must be preceded by the integration of optimal imaging (see Chap. 2) into the treatment planning process. This is especially challenging and critical in the base of skull region.

Whether chordomas and chondrosarcomas are better treated with particles such as protons and/or ions is awaiting clarification, ideally in the form of randomized studies. Radiosurgery should be the considered treatment of choice for smaller and well-defined glomus tumors due to minimal morbidity compared to surgery as well as shorter treatment times and better normal tissue sparing compared to fractionated radiotherapy.

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