Radiotherapy of Parasellar Tumours

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Keywords

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Abstract

Parasellar tumours represent a wide group of intracranial lesions, both benign and malignant. They may arise from several structures located within the parasellar area or they may infiltrate or metastasize this region. The treatment of the tumours located in these areas is challenging because of their complex anatomical location and their heterogenous histology. It often requires a multimodal approach, including surgery, radiation therapy (RT), and medical therapy. Due to the proximity of critical structures and the risks of side effects related to the procedure, a successful surgical resection is often not achievable. Thus, RT plays a crucial role in the treatment of several parasellar tumours. Conventional fractionated RT and modern radiation techniques, like stereotactic radiosurgery and proton beam RT, have become a standard management option, in particular for cases with residual or recurrent tumours after surgery and for those cases where surgery is contraindicated. This review examines the role of RT in parasellar tumours analysing several techniques, outcomes and side effects.

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Introduction

The parasellar region is a complex anatomical area situated laterally and to either side of the sella turcica; it contains relevant neurovascular structures [1]. For most authors, this region includes all areas around the sella, encompassing the cavernous sinuses, located lateral to the sella turcica, the sphenoid sinus, and the suprasellar cistern structures [2]. The cavernous sinus is the most important structure of the parasellar region; it contains cranial nerves III (oculomotor), IV (trochlear), V1 (ophthalmic division of the trigeminal nerve), V2 (maxillary division of the trigeminal nerve) and VI (abducens). It also includes the cavernous segment of the internal carotid artery. The suprasellar cistern contains the optic chiasm and nerves, the anterior third ventricle, the hypothalamus, the pituitary infundibulum and the infundibular and suprachiasmatic recesses of the third ventricle [2].

Several tumours of different histological nature may arise in the parasellar region or may infiltrate or metastasize it. Pituitary adenomas are the most common parasellar tumours as they tend to extend into the parasellar areas. Other benign tumours affecting the parasellar region include craniopharyngiomas, schwannomas, meningiomas, epidermoid tumours, dermoid tumours, hamarto-

mas, lipomas and Rathke's cyst. Parasellar tumours with different levels of aggressiveness include chordomas, chondrosarcomas, hemangiopericytomas, optic or hypothalamic gliomas, whereas malignant lesions are typically represented by germ cell tumours, primary lymphomas and brain metastases [1, 3].

The treatment of parasellar tumours is challenging because of their complex anatomical location and their heterogeneous histology. It commonly requires a multimodal approach, including surgery, radiation therapy and medical therapy. Surgical treatment is often the first step as it allows for pathologic analysis and complete or partial tumour removal. Due to the proximity of critical structures, like blood vessels, optic pathways and cranial nerves, a successful surgical procedure may often not be achievable due to the high risks related to the procedure itself [4]. Radiation therapy has been usually employed as an adjuvant treatment in patients with residual or recurrent tumours following surgery or as primary therapy for those where surgery is contraindicated [1, 4, 5].

In this paper, we provide an overview of different radiation techniques for parasellar tumours. For convenience, due to the wide published papers about radiotherapy (RT) for pituitary adenomas, we have focused our review on non-adenomatous tumours. Both well-established and newer indications, results and radiation treatment associated morbidity are discussed.

Methods and Materials

A literature search was conducted in MEDLINE PubMed that evaluated patient with benign and malignant parasellar tumours. The MEDLINE and EMBASE databases were searched using a combination of the following keywords: "parasellar" and "radiation therapy" or "radiosurgery" or "fractionated stereotactic RT (FSRT)" or "protons." Further research was performed by adding the definitions of different parasellar tumours ("craniopharyngioma," "chordoma/chondrosarcoma," "schwannoma," "dermoid and epidermoid tumours," "hamartomas," "lipomas," "Rathke's cyst" "hemangiopericytomas," "optic or hypothalamic gliomas," "germ cell tumours," "primary lymphomas," and "brain metastases"). The search focused on randomized, prospective and retrospective trials. Articles were excluded from the review in the following cases: non-English abstract, not available through PubMed, case studies involving <10 patients (except for rare tumours) or duplicated publications. The results of the literature research were used and included if appropriate.

Radiation Techniques

Conventional radiation therapy (CRT) has been traditionally used for residual or recurrent parasellar tumours. It has been reported effective in reducing the rate of local recurrence in many

parasellar tumours at a total dose of 45–60 Gray (Gy) using 3–4 coplanar beams delivered in 25–33 fractions (1.6–2.0 Gy/day, 5 days a week for 5–7 weeks); however, its role has been a matter of debate because of the risk of potential long-term toxicity which includes hypopituitarism, radiation-induced optic neuropathy, impairment of neurocognitive function and cranial nerves deficits. In the last decades, radiation techniques have evolved from CRT to 3 dimensional (3-D) conformal and stereotactic techniques, either stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT), with technical improvements seen in all aspects of radiation treatment, including better immobilization, enhanced imaging, and improvements in planning and dose delivery, resulting in a more precise dose delivery and reduction of normal brain structures irradiated to high radiation doses, such as the optic pathway and the brainstem [6].

SRS, which refers to the delivery of large doses of radiation to small targets, is frequently employed in patients with residual or recurrent parasellar tumours and, more recently, as primary treatment in selected cases when surgery is contraindicated. SRS is usually given in single fraction or, less frequently, in a reduced number of fractions (from 2 to a maximum of 5); in the latter case, it is called hypofractionated SRT or multisession SRS. The techniques mainly used include gamma knife (GK) or a modified linear accelerator (LINAC)-based radiosurgical system.

The GK system consists of an array of 192 or 201 sources of cobalt-60 that align with an inner collimator to direct the resulting photon beams. All the beams converge at a single point called the isocenter. The dose is typically prescribed at 50% to obtain the maximum dose at the centre of each pinpointed target and minimal dose at target edge. Historically, GK has been characterised by the application of a stereotactic head frame using 4 pins that attach to the skull. The GK Icon, the most recent model, incorporates an onboard cone beam computed tomography scanner and an infra-red intrafraction motion management system. These 2 additions allow a thermoplastic mask to be used for immobilisation without the need for an invasive frame [7].

LINAC modified system uses multiple fixed fields or arcs shaped using a multileaf collimator with a leaf width ranged from 2.5 to 5 mm for shaping the radiation beam to the shape of tumour and optimal dose distribution can be achieved by modulating leaf movements during irradiation. Immobilisation is usually achieved with the use of more precise mask systems, with a reported repositioning accuracy of 1–2 mm [8]. Combinations of treatment table, gantry rotations, and collimator rotations are employed to direct the photon beams to the intracranial target from several directions. As in GK system, the intersecting arcs produce a high target dose with minimal radiation delivered to the surrounding brain tissue [9]. Further technical advances include the use of orthogonal X-rays (ExacTrac®) and cone beam CT. These are in-room imaging systems that are able to improve patient's repositioning accuracy in the treatment room with sub-millimetric accuracy [10–12].

CyberKnife is a relatively new technological device that combines a mobile LINAC mounted on a robotic arm with an image-guided robotic system [13]. Patients are fixed in a thermoplastic mask, and the treatment can be delivered as single fraction or multi-fraction SRS using a variable number of overlapping beams (up to 200), and positioning errors are corrected by a sophisticated digital X-ray images system achieving similar level of targeting precision as frame-based SRS [14].

Table 1. Summary of normal tissue constrains following standard fractionation (2 Gy/fraction) and radiosurgery

Organ	Type of radiation	Dose constrains (toxicity rate)	Type of toxicity	References
Brain	Standard fractionation Single-fraction SRS 3-fraction SRS	Dmax <60 Gy to whole organ (<3%) 12 Gy to <5–10 mL (<20%) 18 Gy (6 Gy/fx) to <26 mL (3%)	Symptomatic necrosis	Emami et al. [16], 1991; Bentzen et al. [17], 2010; Minniti et al. [24], 2016
Brainstem	Standard fractionation Single-fraction SRS 3-fraction SRS 5-fraction SRS	Dmax <54 Gy to whole structure (<5%) Dmax <12.5 Gy (<5%) Dmax 18 Gy (6 Gy/fx) to <1 mL (<3%) Dmax 26 Gy (5.2 Gy/fx) to <1 mL (<3%)	Permanent cranial deficit or necrosis	Emami et al. [16], 1991; Bentzen et al. [17], 2010; Mayo et al. [18], 2010
Optic nerve/chiasm	Standard fractionation Single-fraction SRS 3-fraction SRS 5-fraction SRS	Dmax <55 Gy to whole structure (<3%) Dmax <10 Gy (<1%) Dmax 20 Gy (<1%) Dmax 25 Gy (<1%)	Optic neuropathy	Emami et al. [16], 1991; Bentzen et al. [17], 2010; Mayo et al. [18], 2010; Leavitt et al. [19], 2013; Milano et al. [20], 2018
Pituitary gland	Standard fractionation Single-fraction SRS	Dmax ≤45–50.4 Gy (20–40% at 5 years) Dmax <15 Gy (10–40% at 5 years)	Hypopituitarism	Leenstra et al. [23], 2010; Marek et al. [21], 2011
Carotid artery	Single-fraction SRS	Dmax <20–23 Gy (<1%)	Occlusion	Abeloos et al. [22], 2007

Gy, gray; SRS, stereotactic radiosurgery; Dmax, maximal dose; Gy, Gray; fx, fraction.

Despite several differences in treatment-related parameters among GK, Cyberknife and LINAC, there are no comparative studies demonstrating the clinical superiority of a technique over the others in terms of local control and radiation-induced toxicity for patients with brain tumours. The superiority in terms of dose delivery and distribution for each of these techniques remains a matter of debate.

Particle radiation has been also applied successfully in the treatment of parasellar tumours. Dosimetric characteristics of protons include high dose conformality, better sparing of normal tissue, lower integral dose and no exit dose beyond the target [15]. Data on the efficacy of protons in paediatric cancers, ocular melanomas, chordomas and chondrosarcomas are available, with the treatment typically given as conventional fractionation using doses up to 76–78 Gy. Although promising results have been and continue to be reported for many other types of cancers, the small number of patients treated and the limited follow-up time do not allow for definitive conclusions regarding the superiority of protons over photons.

Neuroanatomical Considerations and Risk of Radiation-Induced Toxicity

Cranial nerves, cavernous sinus and the pituitary gland are among the most important structures at risk of radiation-induced toxicity during radiation treatment for parasellar tumours. The risk following irradiation is influenced by different factors, including the total dose, dose per fraction, number of fractions and the volume of normal tissue irradiated at high doses. A summary of dose data and clinical risk estimates for skull base structures, based on a combination of clinical observations and reviews, is reported in Table 1 [16–24]. After SRS, a risk of radiation-induced optic neuropathy up to 2% has been reported for doses to the optic pathway <8–10 Gy [20]; however, the risk remains low for maximum doses of 10–12 Gy to small portions of the optic pathway. A similar low risk has been reported for

maximum doses of 20 Gy in 3 fractions and 25 Gy in 5 fractions [20].

This means that the decision of whether to use SRS or FSRT for parasellar tumours is mainly based on the volume of the target lesion and its proximity to sensitive brain structures, for example, optic pathway; fractionated irradiation is usually preferred over SRS for patients with tumours large than 3 cm in size and or involving the optic pathways [25]. The other nerves enclosed in the parasellar region, like oculomotor nerves and trigeminal nerve, tolerate higher doses. Tishler et al. [26] investigated the tolerance of cranial nerves of the cavernous sinus in 29 patients treated by LINAC and 33 patients by GK. Twelve new neuropathies (19.3%) occurred. They concluded that doses up to 40 Gy were relatively safe for nerves in the parasellar region. Although the maximum tolerable dose to the cavernous sinus nerves is unknown, an incidence of radiation-induced toxicity <4% has been observed for doses up to 18–20 Gy to the cavernous sinus [4].

Delayed onset of one or more hormonal pituitary deficits is the main side effects of radiation therapy of parasellar tumours, particularly those involving the sella. Several studies have evaluated the relationship between radiation doses to the normal pituitary gland and distal infundibulum and the development of hypopituitarism. If possible, mean radiation doses to the pituitary gland and stalk should be kept under 15 and 7–10 Gy, respectively, since higher doses have been associated with an incidence of hypopituitarism over 30% at 5 years [6, 27]. Although multisession SRS seems to represent an effective and safe treatment option for relatively large tumours in close proximity to optic apparatus that are not suitable for single-fraction SRS, larger series with longer follow-up times need to confirm the efficacy and safety of fractionated schedules over other radiation techniques [28]. In the respect of the limited follow-up, other complications, such as brain necrosis, second tumours, cerebrovascular disease, and neurocognitive decline, have been rarely reported after stereotactic radiation [22, 29].

Table 2. Summary of selected published studies on RT for parasellar meningiomas

Authors	Patients, <i>n</i>	Technique, %	Volume, mL	Dose, Gy	FU, months	Local tumour control, %	Late toxicity, %
Goldsmith et al. [33], 1994	117	CRT	NA	54	40	89 at 5 and 77 at 10 years	3.6
Nutting et al. [34], 1999	82	CRT	NA	55–60*	41	92 at 5 and 83 at 10 years	14
Vendrey et al. [35], 1999	156	CRT	NA	50	40	79 at 5 years	11.5
Nicolato et al. [45], 2002	122	GK	8.1	14.8	48.9	96.5 at 5 years	1
Lee et al. [46], 2002	159	GK	6.5	13	35	93 at 5 and 93 at 10 years	6.7
Mendenhall et al. [36], 2003	101	CRT	NA	54	64	95 at 5, 92 at 10–15 years	8
Henzel et al. [41], 2006	84	FSRT	11.1	56	30	100 at last FU	NA
Hasegawa et al. [47], 2007	115	GK	14	13	62	94 at 5 and 92 at 10 years	12
Tanzler et al. [38], 2010	144	FSRT	NA	52.7	87	97 at 5 and 95 at 10 years	7
Skeie et al. [48], 2010	100	GK	11.1	13	32	90.4 at 5 and 10 years	6
Spiegelmann et al. [56], 2010	117	LINAC	7	13.5	67	98 at 5 years	4
Williams et al. [49], 2011	138	GK	7.5	13.7	84	95 at 5 and 71 at 10 years	10
Minniti et al. [39], 2011	52	FSRT	35.4	50	42	93 at 5 years	5.5
Slater et al. [43], 2012	68	PBT	27.6	57	74	96 at 5 years	9
Santacroce et al. [50], 2012	3,768	GK	4.8	14	63	95.2 at 5 and 88.6 at 10 years	6.6
Solda et al. [42], 2013	222	FSRT	12	50–55*	43	100 at 5 and 10 years	4.5
Combs et al. [37], 2013	507	FSRT/IMRT	NA	57.6	107	91 at 10 years	1.8
Fokas et al. [40], 2014	253	FSRT	14.4	55.8	50	92.9 at 5 and 87.5 at 10 years	3
Starke et al. [52], 2014	254	GK	NA	13	71	93 at 5 and 84 at 10 years	6.4
Sheean et al. [51], 2014	763	GK	4.1	13	66.7	95 at 5 and 82 at 10 years	9.6
Marchetti et al. [57], 2015	143	CK	11	14–25*	44	93 at 5 years	5.1
Cohen-Inbar et al. [53], 2018	189	GK	5.6	14	71	98.1 at 4 and 84.8 at 10 years	9.8
Park et al. [54], 2018	200	GK	7.5	13	101	93 at 5 and 85 at 10 years	9
Akyoldas et al. [55], 2019	61	GK	3.2	12	75	100% at last FU	0

* Range.

RT, radiotherapy; CRT, conventional radiation therapy; FSRT, fractionated stereotactic radiation therapy; GK, gamma knife radiosurgery; CK, cyberknife radiosurgery; PBT, proton beam radiotherapy; NA, not assessed; FU, follow-up; Gy, Gray.

Results of Radiation Treatments in Parasellar Tumours

Meningiomas

Parasellar meningiomas, usually with benign histopathology (WHO Grade I tumours), may arise from arachnoidal cells of anterior clinoid, tuberculum sellae, diaphragma sellae or inner wing of the sphenoid. Surgical excision is the treatment of choice for accessible parasellar meningiomas; however, complete resection is often not feasible due to the complex anatomy and significant high risks of neurovascular damage. Beyond surgery, radiation therapy, either FSRT or SRS, is frequently used to increase local control after incomplete resection of a large and symptomatic benign meningioma arising at unfavourable locations. In addition, SRS or FSRT have become a primary treatment, alternative to surgical resection, for asymptomatic or mildly symptomatic parasellar meningiomas, like cavernous sinus meningiomas [30–32].

Using postoperative CRT with a dose of 50–55 Gy in 30–33 fractions, local tumour control rates are ranged from 79 to 95% at 5 years [33–36]. Recent series report on the use of new radiation techniques for meningiomas (Table 2). In a series of 507 patients with a skull base meningioma who received FSRT ($n = 376$) or IMRT ($n = 131$), Combs et al. [37] have observed comparable local control rates of 91% at 10 years for patients with a benign meningioma; similar tumour control rates have been observed in other published series (Table 2) [38–42]. Hypopituitarism is reported in 5–15% of patients. Radiation injury to the optic apparatus, presenting as decreased visual acuity or visual field defects, is reported in 0–3% of irradiated patients. Other cranial deficits are reported in <2% of patients [37].

The reported tumour control after proton beam RT is ranged from 90 to 96% at 5 years, similar to that observed with fractionated photon techniques (Table 2) [43, 44].

Table 3. Summary of selected published studies on RT for craniopharyngiomas

Authors	Patients, <i>n</i>	Technique, %	Volume, mL	Dose, Gy	FU, months	Local tumour control, %	Late toxicity, %
Regine et al. [71], 1993	58	CRT	NA	56–62*	17 years	82 at 10 years	NA
Rajan et al. [74], 1993	173	CRT	NA	50	12 years	83 at 10 years	50
Hetelekidis et al. [72], 1993	37	CRT	NA	54	49	86 at 10 years	60
Habrand et al. [69], 1999	37	CRT	NA	50	NA	78 and 56.5 at 5 and 10 years	40
Chung et al. [84], 2000	31	GK	8.9	12.2	36	87 at last FU	3.6
Yu et al. [85], 2000	38	GK	13.5	8–18*	15	89.5 at last FU	2.2
Stripp et al. [66], 2004	76	CRT	NA	55	7.6 years	84 at 10 years	20
Moon et al. [70], 2005	50	CRT	12	54	12.8 years	96 and 91 at 5 and 10 years	15
Pemberton et al. [77], 2005	87	CRT	NA	43	8 years	77 and 66 at 10 and 20 years	15
Combs et al. [75], 2007	40	FSRT	13.3	52	98	100 at 10 years	5
Minniti et al. [78], 2007	39	FSRT	10.2	50	40	92 at 5 years	2.5
Hasegawa et al. [86], 2010	97	GK	3.3	11.4	68	69 at last FU	5
Niranjan et al. [87], 2010	46	GK	1.0	13.0	62	68.6 at last FU	4.3
Xu et al. [88], 2011	37	GK	1.6	14.5	50	68 at last FU	NA
Iwata et al. [89], 2011	40	CK	2	13–25*	40	85 at 3 years	2.5
Kobayashi et al. [90], 2012	100	GK	3.5	11.5	65	79.6 at last FU	0
Saleem et al. [91], 2013	35	GK	12	11.5	22	88.5 at last FU	2.8
Lee et al. [92], 2014	137	GK	5.5	12	46	70.9 at last FU	10.2
Bishop et al. [80], 2014	21	PBT	NA	50.4	2.7 years	91 at last FU	77
Jimenez et al. [82], 2014	56	PBT	NA	52.2	2.6 years	96 at last FU	4
Harrabi et al. [79], 2014	55	FSRT	31.2	52.2	128	95.3 at 5 years	3.6
Losa et al. [93], 2018	50	GK	2.1	14.3	75	86 at last FU	2

* Range.

RT, radiotherapy; CRT, conventional radiation therapy; FSRT, fractionated stereotactic radiation therapy; GK, gamma knife radiosurgery; CK, cyberknife radiosurgery; PBT, proton beam radiotherapy; NA, not assessed; FU, follow-up; Gy, Gray.

The reported actuarial control rates after SRS is in the range of 90–95% at 5 years and 80–90% at 10 and 15 years using a median margin dose to the tumour of 13–15 Gy, with a variable improvement of neurological functions in up to 60% of patients [45–56]. The rate of significant complications at doses of 13–15 Gy is <10%, being represented by either transient or permanent complications [45, 51]. A few studies have reported the use of multisession SRS (2–5 daily fractions) for relatively large meningioma close to the anterior optic pathway. Using doses of 21–25 Gy delivered in 3–5 fractions, a few series report a local control of 93–95% at 5 years, and this has been associated with low cranial nerves toxicity [57].

Parasellar atypical meningiomas are rare. Postoperative RT is recommended for residual tumours after incomplete surgery. Using doses of 55–60 Gy in 30–33 fractions, several studies report a variable median 5-year progression-free survival rates from 40 to 80% and median overall survival rates of 50–100% after RT [58–60]. In contrast, the efficacy of postoperative RT versus observa-

tion for completely resected atypical meningiomas remains an unresolved question, and conflicting results have been published. The recently closed study ROAM/EORTC 1,308 trial [61], including 190 patients randomized to receive early adjuvant-fractionated RT or active surveillance, will help answer the important clinical question of the efficacy of RT versus observation following surgical resection of atypical meningiomas.

Craniopharyngioma

Craniopharyngiomas are included among parasellar tumours. Surgery represents the main treatment. Gross total tumour removal is, in fact, associated with the best long-term overall and recurrence-free survival [62, 63]. Adjuvant irradiation is frequently employed after subtotal resection or tumour recurrence, providing better long-term tumour control rates at 10 years than surgery alone [64–67]. Stripp et al. [66] compared 57 patients treated only with subtotal resection to the 18 cases treated with subtotal resection followed by RT, finding a 10-year tu-

Table 4. Summary of selected published studies on RT for chordomas

Authors	Patients, <i>n</i>	Type of RT	Median dose, Gy	FU, months	Tumour control, %
Forsyth et al. [97], 1993	39	CRT	50	99	39 at 5 years
Watkins et al. [98], 1993	38	CRT	50–60*	84	34 at 5 years
Catton et al. [99], 1996	20	CRT	50	62	23 at 5 years
Debus et al. [102], 1997	37	FSRT	66.6	27	50 at 5 years
Munzenrider et al. [109], 1999	169	PhT/PBT	66–83*	41	73 at 5 years and 54 at 10 years
Terahara et al. [110], 1999	115	PhT/PBT	68.9	41	59 at 5 years and 44 at 10 years
Crockard et al. [107], 1999	26	GK*	15	51	NA
Hug et al. [111], 2000	33	PBT	71.9	33	76 at last FU
Krishnan et al. [106], 2005	25	GK*	15	56	32 at 5 years
Hasegawa et al. [104], 2007	30	GK*	14	59	72 at 5 years
Liu et al. [103], 2008	31	GK	12.7	28	21 at 5 years
Ares et al. [112], 2009	42	PBT	73.5	38	81 at 5 years
Kano et al. [105], 2011	71	GK	15	60	66 at 5 years
Deraniyagala et al. [113], 2014	33	PBT	77.4–79.4*	21	86 at 2 years
Sahgal et al. [100], 2015	24	IMRT	76	36	65.3 at 5 years
Choy et al. [101], 2016	57	SRS/FSRT	SRS 17.8 FSRT 63.4	57.8	SRS 20 at 5 years FSRT 40.6 at 5 years

* Range.

RT, radiotherapy; CRT, conventional radiation therapy; FSRT, fractionated stereotactic radiation therapy; GK, gamma knife radiosurgery; PBT, proton beam radiotherapy; PhT, photon beam radiotherapy; NA, not assessed; FU, follow-up; Gy, Gray.

mour control rate of 42% after surgery alone and 84% after subtotal resection and radiation. In the National Cancer Database, Rao et al. [68] confirmed that among 697 patients treated between 2004 and 2012, incomplete surgery followed by RT was associated with improved survival compared to incomplete surgery alone. It is still debated whether radiation should be employed immediately after surgery or at regrowth of the tumour. Some paediatric series indicate that irradiation given immediately after surgery is preferable to radiation therapy at recurrence in terms of reduced morbidity and tumour control [69–71]. Different doses between 50 and 60 Gy have been used for fractionated radiation by different authors in both adult and children with craniopharyngiomas [67]. New pituitary deficits or a worsening of a partial hypopituitarism represents the most commonly reported late complication of CRT, occurring in 20–60% of irradiated patients after 5–10 years [66, 67, 69, 72–74]. The reported incidence of radiation-induced optic neuropathy resulting in visual deficit is 2–8% [67, 70, 75–79]. In general, studies reporting on FSRT for craniopharyngiomas have observed low toxicity rates, suggesting that new irradiation techniques could further reduce the toxicity of CRT.

A few case series about proton therapy in craniopharyngioma are available in the medical literature [80, 82]. Although local control is comparable with the results of series of FSRT, protons may represent a better treatment in paediatric patients, possibly limiting potential radiation-induced long-term neurocognitive decline, hypopituitarism and risk of radiation-induced tumours [67, 83].

Several studies have reported the safety and efficacy of SRS in patients with residual or recurrent craniopharyngiomas after surgery (Table 3) [84–93]. In a study of 98 patients treated with SRS, Kobayashi et al. [90] reported a 5- and 10-year survival rates of 94.1 and 91% with respective progression-free survival rates of 60.8 and 53.8% at a median follow-up of 65 months. Losa et al. [93] reported the results of single fraction and multitreatment GK for craniopharyngioma. With a mean marginal dose ranging from 12 to 14 Gy, 5- and 10-year recurrence-free survival rates were 90.3 and 78.4%, respectively. Late toxicity after SRS includes hypopituitarism and visual deficits, whereas other complications are rare [93]. The development of new hypopituitarism is reported between 0 and 38% at 5 years [93, 94]. Vi-

Table 5. Summary of selected published studies on RT for rare parasellar tumours

Authors	Type of tumours, <i>n</i>	Patients, <i>n</i>	Technique, %	Volume, mL	Dose, Gy	FU, months	Local control, %	Late toxicity, %
Kano et al. [122], 2009	Trigeminal Schwannoma	33	GK	4.2	15	72	87.9 at last FU	9
Hagesawa et al. [128], 2013	Trigeminal Schwannoma	53	GK	6.0	14	98	90 at 5 and 82 at 10 years	22
Vasquez et al. [123], 2016	Epidermoid tumor	3	GK	4.4	12	37.6	100 at 3 years	33.3
West et al. [124], 2019	Rathke's cyst	5	CK	0.34	12.5	34.2	100 at 3 years	0
Regis et al. [129], 2017	Hamartoma	48	GK	3.7	17	71	NA	NA
Cohen-Inbar et al. [125], 2017	Hemangiopericytoma	16*	GK	4.9	15	59	82.1 at 4 years and 53.7 at 10 years	6.7**
Combs et al. [127], 2005	Optic/hypothalamic glioma	15	FSRT	28.3	52.2	97	72% at 5 years	20
El-Shehaby et al. [126], 2016	Optic/hypothalamic glioma	22	GK	3.1	11.5	43	83 at 3 years	5.7

* Parasellar; ** RTOG II-III.

RT, radiotherapy; GK, gamma knife radiosurgery; CK, cyberknife radiosurgery; FSRT, fractionated stereotactic radiotherapy; Gy, gray; FU, follow-up.

sual deficits are observed in up to 20% of patients, although most series report lower complication rates [87, 88, 95].

A few studies have investigated the outcomes of multisession SRS in craniopharyngioma [89, 93]. In a series of 43 patients treated with single-fraction (14 Gy) or multisession (16–25 Gy in 2–5 fractions) SRS, Iwata et al. [89] reported a 3-year tumour control rate of 85% at a median follow-up of 40 months. One patient developed hypopituitarism while no cases of visual deterioration were reported. Although promising, the superiority of multifraction SRS in terms of tumour control and long-term toxicity over single-fraction SRS remains to be proven [89, 93].

Chordoma and Chondrosarcoma

Chordomas of the parasellar region are rare bone tumours originating from remnants of the notochord with locally aggressive behaviour and high recurrence rates. Postoperative radiation therapy is usually recommended to reduce the risk of local recurrence, even after total resection. Chordomas require high cumulative fractionated radiation doses up to 70–75 Gy, although with increased risks for adjacent neurological structures, for example, spinal cord, brainstem, and optic pathways. Using CRT at median doses of up to 60 Gy, a few studies report a local control at 5 years in the range of 17–41% [96–99]. New radiation techniques, including both IMRT and FSRT, which allow higher doses of radiation to the tumour while sparing more surrounding normal tissue, have been associated with better outcome (Table 4) [100, 101]. Using IMRT with a median dose of 76 Gy given in 2 Gy per fraction in 24 patients, Sahgal et al. [100] reported a 5-year survival and local control rates of 85.6 and 65.3%, respec-

tively, at a median follow-up of 36 months. In another series of 37 patients with skull base chordomas irradiated with FSRT using a median dose of 66.6 Gy, Debus et al. [102] observed 5-year overall survival and local control rates of 82 and 50%, respectively, at a median follow-up of 27 months. SRS may be valuable for the treatment of small residual or recurrent tumour with a reported local control rates of 21–72% at 5 years [103–107]. Complications are reported from 0 to 33%, mainly represented by cranial nerve deficits and brain necrosis; however, serious radiation-related complications are rarely reported. In a multicentre study of the North American GK Consortium including 71 patients with small sized chordomas of the skull base treated with GK using a marginal dose of 15 Gy, Kano et al. [105] have reported 5-year actuarial overall survival and local control rates of 80 and 66%, respectively. At present, surgery followed by proton beam RT has becoming the standard treatment for skull base chordomas. Several studies have reported the safety and efficacy using doses ranging between 63 and 83 Cobalt Gray Equivalent at fractionation of 1.8–2.0 Cobalt Gray Equivalent for either adults or children with residual or recurrent chordomas of any size [108–113]. In a large study of 169 patients treated with proton beam RT at Massachusetts General Hospital, 5- and 10-year local control rates were 73 and 54%, and respective overall survival rates were 80 and 54%, at a median follow-up of 41 months [109]; similar results have been reported in several retrospective studies [112, 113]. Late complications have been reported in up to 45% of patients, including visual deterioration [109, 112, 114], pituitary deficits [109, 115, 116], hearing loss [117], and radiation necrosis at the temporal lobe [102, 117, 118]. Overall, data from literature support the use of proton beam RT as an effective and safe treat-

ment option for chordomas, although its superiority over photon irradiation in terms of efficacy and toxicity remains matter of debate.

Chondrosarcomas are relatively slow-growing and locally invasive tumours. They are rarely completely resected, similarly to chordomas. Several studies reported higher recurrence rates in patients treated with surgical resection alone than patients who had surgery followed by radiation [119, 120].

Studies using proton radiation reported overall survival and local tumour control rates at 5 years above 90%. Combs et al. [121], in fact, have reported a 5-year progression-free survival of 100% in a series of patients who underwent fractionated proton therapy with doses ranging from 66 to 76 Gy without cranial nerve deficits. A similar local control has been observed after postoperative SRS using doses of 15 Gy in patients with small residual tumours [105].

Rare Parasellar Tumours

Rare tumours that appear in the parasellar region may include either benign tumours, for example, schwannomas, epidermoids, dermoids, hamartomas, lipomas, Rathke's cyst, or locally aggressive tumours, for example, hemangiopericytomas, optic/hypothalamic gliomas, or malignant lesions, for example, germ cell tumours, primary lymphomas, and brain metastases [1]. Infiltrative aggressive tumours are typically treated with fractionated RT up to doses of 50–60 Gy, whereas SRS is usually employed for small-to-moderate benign lesions or in the setting of recurrent tumours. A summary of recent selected studies of fractionated RT and SRS for these rare parasellar tumours is shown in Table 5 [122–129].

References

- 1 Kaltsas GA, Evanson J, Chrisoulidou A, Grossman AB. The diagnosis and management of parasellar tumours of the pituitary. *Endocr Relat Cancer*. 2008 Dec;15(4):885–903.
- 2 Johnston JL. Parasellar syndromes. *Curr Neurol Neurosci Rep*. 2002 Sep;2(5):423–31.
- 3 Smith JK. Parasellar tumors: suprasellar and cavernous sinuses. *Top Magn Reson Imaging*. 2005 Jul;16(4):307–15.
- 4 Amichetti M, Amelio D, Minniti G. Radiosurgery with photons or protons for benign and malignant tumours of the skull base: a review. *Radiat Oncol*. 2012 Dec;7(1):210.
- 5 Brada M, Cruickshank G. Radiosurgery for brain tumours. *BMJ*. 1999 Feb;318(7181):411–2.
- 6 Minniti G, Clarke E, Scaringi C, Enrici RM. Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas. *Rep Pract Oncol Radiother*. 2016 Jul-Aug;21(4):370–8.
- 7 Vulpe H, Save AV, Xu Y, Elliston CD, Garrett MD, Wu CC, et al. Frameless Stereotactic Radiosurgery on the Gamma Knife Icon: Early Experience From 100 Patients. *Neurosurgery*. 2019 Aug;nyz227.
- 8 Minniti G, Scaringi C, Clarke E, Valeriani M, Osti M, Enrici RM. Frameless linac-based stereotactic radiosurgery (SRS) for brain metastases: analysis of patient repositioning using a mask fixation system and clinical outcomes. *Radiat Oncol*. 2011 Nov;6(1):158.
- 9 Friedman WA. Linear accelerator radiosurgery. *Clin Neurosurg*. 1992;38:445–71.
- 10 Gevaert T, Verellen D, Tournel K, Linthout N, Bral S, Engels B, et al. Setup accuracy of the Novalis ExacTrac 6DOF system for frameless radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012 Apr;82(5):1627–35.
- 11 Mancosu P, Fogliata A, Stravato A, Tomatis S, Cozzi L, Scorsetti M. Accuracy evaluation of the optical surface monitoring system on EDGE linear accelerator in a phantom study. *Med Dosim*. 2016;41(2):173–9.
- 12 Wurm RE, Erbel S, Schwenkert I, Gum F, Agaoglu D, Schild R, et al. Novalis frameless image-guided noninvasive radiosurgery: initial experience. *Neurosurgery*. 2008 May;62(5 Suppl):A11–7.

Conclusion

RT is an effective treatment for incomplete resected parasellar tumours or for those located at inaccessible surgical sites. Both fractionated RT and SRS are associated with a similar local control, and the choice of technique is mainly based on the volume and site of the tumour. In general, fractionated RT is preferred over SRS for large aggressive infiltrative tumours. In the respect of recommended normal tissue dose constraints, the reported radiation toxicity is acceptable. Because of their dosimetric advantages in terms of conformality and reduction of integral radiation dose to normal brain tissue, protons are typically recommended in patients with large aggressive parasellar tumours which require higher doses, such as chordomas and chondrosarcomas. A better understanding of molecular mechanisms underlying tumour progression of different parasellar tumours will help predict which patients will benefit from adjuvant RT.

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- 13 Kuo JS, Yu C, Petrovich Z, Apuzzo ML. The CyberKnife stereotactic radiosurgery system: description, installation, and an initial evaluation of use and functionality. *Neurosurgery*. 2008 Feb;62 Suppl 2:785–9.
- 14 Murphy MJ, Chang SD, Gibbs IC, Le QT, Hai J, Kim D, et al. Patterns of patient movement during frameless image-guided radiosurgery. *Int J Radiat Oncol Biol Phys*. 2003 Apr;55(5):1400–8.
- 15 DeLaney TF; Burr Proton Therapy Center. Clinical proton radiation therapy research at the Francis H. *Technol Cancer Res Treat*. 2007 Aug;6(4 Suppl):61–6.
- 16 Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, et al. Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys*. 1991 May;21(1):109–22.
- 17 Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys*. 2010 Mar;76(3 Suppl):S3–9.
- 18 Mayo C, Yorke E, Merchant TE. Radiation associated brainstem injury. *Int J Radiat Oncol Biol Phys*. 2010 Mar;76(3 Suppl):S36–41.
- 19 Leavitt JA, Stafford SL, Link MJ, Pollock BE. Long-term evaluation of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2013 Nov;87(3):524–7.
- 20 Milano MT, Grimm J, Soltys SG, Yorke E, Moiseenko V, Tomé WA, et al. Single- and Multi-Fraction Stereotactic Radiosurgery Dose Tolerances of the Optic Pathways. *Int J Radiat Oncol Biol Phys*. 2018 Jan; S0360-3016(18)30125-1.
- 21 Marek J, Jezková J, Hána V, Krsek M, Bandúrová L, Pecan L, et al. Is it possible to avoid hypopituitarism after irradiation of pituitary adenomas by the Leksell gamma knife? *Eur J Endocrinol*. 2011 Feb;164(2):169–78.
- 22 Abeloos L, Levivier M, Devriendt D, Massager N. Internal carotid occlusion following gamma knife radiosurgery for cavernous sinus meningioma. *Stereotact Funct Neurosurg*. 2007;85(6):303–6.
- 23 Leenstra JL, Tanaka S, Kline RW, Brown PD, Link MJ, Nippoldt TB, et al. Factors associated with endocrine deficits after stereotactic radiosurgery of pituitary adenomas. *Neurosurgery*. 2010 Jul;67(1):27–32.
- 24 Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumors. *Radiat Oncol*. 2016 Oct;11(1):135.
- 25 McTyre E, Helis CA, Farris M, Wilkins L, Sloan D, Hinson WH, et al. Emerging Indications for Fractionated Gamma Knife Radiosurgery. *Neurosurgery*. 2017 Feb;80(2):210–6.
- 26 Tishler RB, Loeffler JS, Lunsford LD, Duma C, Alexander E 3rd, Kooy HM, et al. Tolerance of cranial nerves of the cavernous sinus to radiosurgery. *Int J Radiat Oncol Biol Phys*. 1993 Sep;27(2):215–21.
- 27 Cordeiro D, Xu Z, Mehta GU, Ding D, Vance ML, Kano H, et al. Hypopituitarism after Gamma Knife radiosurgery for pituitary adenomas: a multicenter, international study. *J Neurosurg*. 2018, Epub ahead of print.
- 28 Albano L, Losa M, Nadin F, Barzaghi LR, Parisi V, Del Vecchio A, et al. Safety and efficacy of multisession gamma knife radiosurgery for residual or recurrent pituitary adenomas. *Endocrine*. 2019 Jun;64(3):639–47.
- 29 Parhar PK, Duckworth T, Shah P, DeWyn-gaert JK, Narayana A, Formenti SC, et al. Decreasing temporal lobe dose with five-field intensity-modulated radiotherapy for treatment of pituitary macroadenomas. *Int J Radiat Oncol Biol Phys*. 2010 Oct;78(2):379–84.
- 30 Lee CC, Trifiletti DM, Sahgal A, DeSalles A, Fariselli L, Hayashi M, et al. Stereotactic Radiosurgery for Benign (World Health Organization Grade I) Cavernous Sinus Meningiomas-International Stereotactic Radiosurgery Society (ISRS) Practice Guideline: A Systematic Review. *Neurosurgery*. 2018 Dec;83(6):1128–42.
- 31 Stafford SL, Pollock BE, Foote RL, Link MJ, Gorman DA, Schomberg PJ, et al. Meningioma radiosurgery: tumor control, outcomes, and complications among 190 consecutive patients. *Neurosurgery*. 2001 Nov;49(5):1029–37.
- 32 Starke RM, Williams BJ, Hiles C, Nguyen JH, Elsharkawy MY, Sheehan JP. Gamma knife surgery for skull base meningiomas. *J Neurosurg*. 2012 Mar;116(3):588–97.
- 33 Goldsmith BJ, Wara WM, Wilson CB, Larson DA. Postoperative irradiation for subtotally resected meningiomas. A retrospective analysis of 140 patients treated from 1967 to 1990. *J Neurosurg*. 1994 Feb;80(2):195–201.
- 34 Nutting C, Brada M, Brazil L, Sibtain A, Saran F, Westbury C, et al. Radiotherapy in the treatment of benign meningioma of the skull base. *J Neurosurg*. 1999 May;90(5):823–7.
- 35 Vendrely V, Maire JP, Darrouzet V, Bonichon N, San Galli F, Celerier D, et al. [Fractionated radiotherapy of intracranial meningiomas: 15 years' experience at the Bordeaux University Hospital Center]. *Cancer Radiother*. 1999 Jul-Aug;3(4):311–7.
- 36 Mendenhall WM, Morris CG, Amdur RJ, Foote KD, Friedman WA. Radiotherapy alone or after subtotal resection for benign skull base meningiomas. *Cancer*. 2003 Oct; 98(7):1473–82.
- 37 Combs SE, Adeberg S, Dittmar JO, Welzel T, Rieken S, Habermehl D, et al. Skull base meningiomas: long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). *Radiation Oncol*. 2013 Feb;106(2):186–91.
- 38 Tanzler E, Morris CG, Kirwan JM, Amdur RJ, Mendenhall WM. Outcomes of WHO Grade I meningiomas receiving definitive or postoperative radiotherapy. *Int J Radiat Oncol Biol Phys*. 2011 Feb;79(2):508–13.
- 39 Minniti G, Clarke E, Cavallo L, Osti MF, Esposito V, Cantore G, et al. Fractionated stereotactic conformal radiotherapy for large benign skull base meningiomas. *Radiat Oncol*. 2011 Apr;6(1):36.
- 40 Fokas E, Henzel M, Surber G, Hamm K, Engenhardt-Cabillic R. Stereotactic radiation therapy for benign meningioma: long-term outcome in 318 patients. *Int J Radiat Oncol Biol Phys*. 2014 Jul;89(3):569–75.
- 41 Henzel M, Gross MW, Hamm K, Surber G, Kleinert G, Failing T, et al. Significant tumor volume reduction of meningiomas after stereotactic radiotherapy: results of a prospective multicenter study. *Neurosurgery*. 2006 Dec;59(6):1188–94.
- 42 Soldà F, Wharram B, De Ieso PB, Bonner J, Ashley S, Brada M. Long-term efficacy of fractionated radiotherapy for benign meningiomas. *Radiation Oncol*. 2013 Nov;109(2):330–4.
- 43 Slater JD, Loredò LN, Chung A, Bush DA, Patyal B, Johnson WD, et al. Fractionated proton radiotherapy for benign cavernous sinus meningiomas. *Int J Radiat Oncol Biol Phys*. 2012 Aug;83(5):e633–7.
- 44 Halasz LM, Bussièrè MR, Dennis ER, Niemierko A, Chapman PH, Loeffler JS, et al. Proton stereotactic radiosurgery for the treatment of benign meningiomas. *Int J Radiat Oncol Biol Phys*. 2011 Dec;81(5):1428–35.
- 45 Nicolato A, Foroni R, Alessandrini F, Maluta S, Bricolo A, Gerosa M. The role of Gamma Knife radiosurgery in the management of cavernous sinus meningiomas. *Int J Radiat Oncol Biol Phys*. 2002 Jul;53(4):992–1000.
- 46 Lee JY, Niranjan A, McInerney J, Kondziolka D, Flickinger JC, Lunsford LD. Stereotactic radiosurgery providing long-term tumor control of cavernous sinus meningiomas. *J Neurosurg*. 2002 Jul;97(1):65–72.
- 47 Hasegawa T, Kida Y, Yoshimoto M, Koike J, Iizuka H, Ishii D. Long-term outcomes of Gamma Knife surgery for cavernous sinus meningioma. *J Neurosurg*. 2007 Oct;107(4):745–51.
- 48 Skeie BS, Enger PO, Skeie GO, Thorsen F, Pedersen PH. Gamma knife surgery of meningiomas involving the cavernous sinus: long-term follow-up of 100 patients. *Neurosurgery*. 2010 Apr;66(4):661–8.
- 49 Williams BJ, Yen CP, Starke RM, Basina B, Nguyen J, Rainey J, et al. Gamma Knife surgery for parasellar meningiomas: long-term results including complications, predictive factors, and progression-free survival. *J Neurosurg*. 2011 Jun;114(6):1571–7.
- 50 Santacrose A, Walier M, Régis J, Liščák R, Motti E, Lindquist C, et al. Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. *Neurosurgery*. 2012 Jan;70(1):32–9.
- 51 Sheehan JP, Starke RM, Kano H, Kaufmann AM, Mathieu D, Zeiler FA, et al. Gamma Knife radiosurgery for sellar and parasellar meningiomas: a multicenter study. *J Neurosurg*. 2014 Jun;120(6):1268–77.

- 52 Starke R, Kano H, Ding D, Nakaji P, Barnett GH, Mathieu D, et al. Stereotactic radiosurgery of petroclival meningiomas: a multicenter study. *J Neurooncol*. 2014 Aug;119(1):169–76.
- 53 Cohen-Inbar O, Tata A, Moosa S, Lee CC, Sheehan JP. Stereotactic radiosurgery in the treatment of parasellar meningiomas: long-term volumetric evaluation. *J Neurosurg*. 2018 Feb;128(2):362–72.
- 54 Park KJ, Kano H, Iyer A, Liu X, Tonetti DA, Lehocky C, et al. Gamma Knife stereotactic radiosurgery for cavernous sinus meningioma: long-term follow-up in 200 patients. *J Neurosurg*. 2018, Epub ahead of print.
- 55 Akyoldas G, Hergunsel OB, Yilmaz M, Senoz M, Peker S. Gamma Knife Radiosurgery for Anterior Clinoid Process Meningiomas: A Series of 61 Consecutive Patients. *World Neurosurg*. 2020 Jan;133:e529–34.
- 56 Spiegelmann R, Cohen ZR, Nissim O, Alezra D, Pfeffer R. Cavernous sinus meningiomas: a large LINAC radiosurgery series. *J Neurooncol*. 2010 Jun;98(2):195–202.
- 57 Marchetti M, Bianchi S, Pinzi V, Tramacere I, Fumagalli ML, Milanese IM, et al. Multisession Radiosurgery for Sellar and Parasellar Benign Meningiomas: Long-term Tumor Growth Control and Visual Outcome. *Neurosurgery*. 2016 May;78(5):638–46.
- 58 Goyal LK, Suh JH, Mohan DS, Prayson RA, Lee J, Barnett GH. Local control and overall survival in atypical meningioma: a retrospective study. *Int J Radiat Oncol Biol Phys*. 2000 Jan;46(1):57–61.
- 59 Pasquier D, Bijmolt S, Veninga T, Rezvoy N, Villa S, Krengli M, et al.; Rare Cancer Network. Atypical and malignant meningioma: outcome and prognostic factors in 119 irradiated patients. A multicenter, retrospective study of the Rare Cancer Network. *Int J Radiat Oncol Biol Phys*. 2008 Aug;71(5):1388–93.
- 60 Mair R, Morris K, Scott I, Carroll TA. Radiotherapy for atypical meningiomas. *J Neurosurg*. 2011 Oct;115(4):811–9.
- 61 Jenkinson MD, Javadpour M, Haylock BJ, Young B, Gillard H, Vinten J, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. *Trials*. 2015 Nov;16(1):519.
- 62 Karavitaki N, Cudlip S, Adams CB, Wass JA. Craniopharyngiomas. *Endocr Rev*. 2006 Jun;27(4):371–97.
- 63 Mortini P, Gagliardi F, Boari N, Losa M. Surgical strategies and modern therapeutic options in the treatment of craniopharyngiomas. *Crit Rev Oncol Hematol*. 2013 Dec;88(3):514–29.
- 64 Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: experience with 168 patients. *J Neurosurg*. 1999 Feb;90(2):237–50.
- 65 Lin LL, El Naqa I, Leonard JR, Park TS, Hollander AS, Michalski JM, et al. Long-term outcome in children treated for craniopharyngioma with and without radiotherapy. *J Neurosurg Pediatr*. 2008 Feb;1(2):126–30.
- 66 Stripp DC, Maity A, Janss AJ, Belasco JB, Tochner ZA, Goldwein JW, et al. Surgery with or without radiation therapy in the management of craniopharyngiomas in children and young adults. *Int J Radiat Oncol Biol Phys*. 2004 Mar;58(3):714–20.
- 67 Minniti G, Esposito V, Amichetti M, Enrici RM. The role of fractionated radiotherapy and radiosurgery in the management of patients with craniopharyngioma. *Neurosurg Rev*. 2009 Apr;32(2):125–32.
- 68 Rao YJ, Hassanzadeh C, Fischer-Valuck B, Chicoine MR, Kim AH, Perkins SM, et al. Patterns of care and treatment outcomes of patients with Craniopharyngioma in the national cancer database. *J Neurooncol*. 2017 Mar;132(1):109–17.
- 69 Habrand JL, Ganry O, Couanet D, Rouxel V, Levy-Piedbois C, Pierre-Kahn A, et al. The role of radiation therapy in the management of craniopharyngioma: a 25-year experience and review of the literature. *Int J Radiat Oncol Biol Phys*. 1999 May;44(2):255–63.
- 70 Moon SH, Kim IH, Park SW, Kim I, Hong S, Park CI, et al. Early adjuvant radiotherapy toward long-term survival and better quality of life for craniopharyngiomas—a study in single institute. *Childs Nerv Syst*. 2005 Aug;21(8-9):799–807.
- 71 Regine WF, Mohiuddin M, Kramer S. Long-term results of pediatric and adult craniopharyngiomas treated with combined surgery and radiation. *Radiother Oncol*. 1993 Apr;27(1):13–21.
- 72 Hetelekidis S, Barnes PD, Tao ML, Fischer EG, Schneider L, Scott RM, et al. 20-year experience in childhood craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 1993 Sep;27(2):189–95.
- 73 Karavitaki N, Brufani C, Warner JT, Adams CB, Richards P, Ansorge O, et al. Craniopharyngiomas in children and adults: systematic analysis of 121 cases with long-term follow-up. *Clin Endocrinol (Oxf)*. 2005 Apr;62(4):397–409.
- 74 Rajan B, Ashley S, Gorman C, Jose CC, Horwich A, Bloom HJ, et al. Craniopharyngioma—a long-term results following limited surgery and radiotherapy. *Radiother Oncol*. 1993 Jan;26(1):1–10.
- 75 Combs SE, Thilmann C, Huber PE, Hoess A, Debus J, Schulz-Ertner D. Achievement of long-term local control in patients with craniopharyngiomas using high precision stereotactic radiotherapy. *Cancer*. 2007 Jun;109(11):2308–14.
- 76 Flickinger JC, Lunsford LD, Singer J, Cano ER, Deutsch M. Megavoltage external beam irradiation of craniopharyngiomas: analysis of tumor control and morbidity. *Int J Radiat Oncol Biol Phys*. 1990 Jul;19(1):117–22.
- 77 Pemberton LS, Dougal M, Magee B, Gattamaneni HR. Experience of external beam radiotherapy given adjuvantly or at relapse following surgery for craniopharyngioma. *Radiother Oncol*. 2005 Oct;77(1):99–104.
- 78 Minniti G, Saran F, Traish D, Soomal R, Sardell S, Gonsalves A, et al. Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. *Radiother Oncol*. 2007 Jan;82(1):90–5.
- 79 Harrabi SB, Adeberg S, Welzel T, Rieken S, Habermehl D, Debus J, et al. Long term results after fractionated stereotactic radiotherapy (FSRT) in patients with craniopharyngioma: maximal tumor control with minimal side effects. *Radiat Oncol*. 2014 Sep;9(1):203.
- 80 Bishop AJ, Greenfield B, Mahajan A, Paulino AC, Okcu MF, Allen PK, et al. Proton beam therapy versus conformal photon radiation therapy for childhood craniopharyngioma: multi-institutional analysis of outcomes, cyst dynamics, and toxicity. *Int J Radiat Oncol Biol Phys*. 2014 Oct;90(2):354–61.
- 81 Luu QT, Loreda LN, Archambeau JO, Yonemoto LT, Slater JM, Slater JD. Fractionated proton radiation treatment for pediatric craniopharyngioma: preliminary report. *Cancer J*. 2006 Mar-Apr;12(2):155–9.
- 82 Jimenez RB, Chin JY, Tseng YD, Adams J, Yock TI, Ebb D, et al. Proton Radiation Therapy for Pediatric Craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 2014;90(1):S725.
- 83 Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer*. 2008 Jul;51(1):110–7.
- 84 Chung WY, Pan DH, Shiao CY, Guo WY, Wang LW. Gamma knife radiosurgery for craniopharyngiomas. *J Neurosurg*. 2000 Dec;93 Suppl 3:47–56.
- 85 Yu X, Liu Z, Li S. Combined treatment with stereotactic intracavitary irradiation and gamma knife surgery for craniopharyngiomas. *Stereotact Funct Neurosurg*. 2000;75(2-3):117–22.
- 86 Hasegawa T, Kobayashi T, Kida Y. Tolerance of the optic apparatus in single-fraction irradiation using stereotactic radiosurgery: evaluation in 100 patients with craniopharyngioma. *Neurosurgery*. 2010 Apr;66(4):688–94.
- 87 Niranjana A, Kano H, Mathieu D, Kondziolka D, Flickinger JC, Lunsford LD. Radiosurgery for craniopharyngioma. *Int J Radiat Oncol Biol Phys*. 2010 Sep;78(1):64–71.
- 88 Xu Z, Yen CP, Schlesinger D, Sheehan J. Outcomes of Gamma Knife surgery for craniopharyngiomas. *J Neurooncol*. 2011 Aug;104(1):305–13.
- 89 Iwata H, Tatewaki K, Inoue M, Yokota N, Baba Y, Nomura R, et al. Single and hypofractionated stereotactic radiotherapy with CyberKnife for craniopharyngioma. *J Neurooncol*. 2012 Feb;106(3):571–7.
- 90 Kobayashi T, Mori Y, Tsugawa T, Hashizume C, Takahashi H. Prognostic factors for tumor recurrence after gamma knife radiosurgery of partially resected and recurrent craniopharyngiomas. *Nagoya J Med Sci*. 2012 Feb;74(1-2):141–7.

- 91 Saleem MA, Hashim AS, Rashid A, Ali M. Role of gamma knife radiosurgery in multimodality management of craniopharyngioma. *Acta Neurochir Suppl.* 2013;116:55–60.
- 92 Lee CC, Yang HC, Chen CJ, Hung YC, Wu HM, Shiau CY, et al. Gamma Knife surgery for craniopharyngioma: report on a 20-year experience. *J Neurosurg.* 2014 Dec;121 Suppl:167–78.
- 93 Losa M, Pieri V, Bailo M, Gagliardi F, Barzagli LR, Gioia L, et al. Single fraction and multisession Gamma Knife radiosurgery for craniopharyngioma. *Pituitary.* 2018 Oct;21(5):499–506.
- 94 Ulfarsson E, Lindquist C, Roberts M, Råhn T, Lindquist M, Thorén M, et al. Gamma knife radiosurgery for craniopharyngiomas: long-term results in the first Swedish patients. *J Neurosurg.* 2002 Dec;97(5 Suppl):613–22.
- 95 Yomo S, Hayashi M, Chernov M, Tamura N, Izawa M, Okada Y, et al. Stereotactic radiosurgery of residual or recurrent craniopharyngioma: new treatment concept using Leksell gamma knife model C with automatic positioning system. *Stereotact Funct Neurosurg.* 2009;87(6):360–7.
- 96 Romero J, Cardenes H, la Torre A, Valcarcel F, Magallon R, Regueiro C, et al. Chordoma: results of radiation therapy in eighteen patients. *Radiother Oncol.* 1993 Oct;29(1):27–32.
- 97 Forsyth PA, Cascino TL, Shaw EG, Scheithauer BW, O'Fallon JR, Dozier JC, et al. Intracranial chordomas: a clinicopathological and prognostic study of 51 cases. *J Neurosurg.* 1993 May;78(5):741–7.
- 98 Watkins L, Khudados ES, Kaleoglu M, Revesz T, Sacares P, Crockard HA. Skull base chordomas: a review of 38 patients, 1958–88. *Br J Neurosurg.* 1993;7(3):241–8.
- 99 Catton C, O'Sullivan B, Bell R, Laperriere N, Cummings B, Fornasier V, et al. Chordoma: long-term follow-up after radical photon irradiation. *Radiother Oncol.* 1996 Oct;41(1):67–72.
- 100 Sahgal A, Chan MW, Atenafu EG, Masson-Cote L, Bahl G, Yu E, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: preliminary outcomes. *Neuro-oncol.* 2015 Jun;17(6):889–94.
- 101 Choy W, Terterov S, Ung N, Kaprelian T, Trang A, DeSalles A, et al. Adjuvant Stereotactic Radiosurgery and Radiation Therapy for the Treatment of Intracranial Chordomas. *J Neurol Surg B Skull Base.* 2016 Feb;77(1):38–46.
- 102 Debus J, Hug EB, Liebsch NJ, O'Farrel D, Finkelstein D, Efid J, et al. Brainstem tolerance to conformal radiotherapy of skull base tumors. *Int J Radiat Oncol Biol Phys.* 1997 Dec;39(5):967–75.
- 103 Liu AL, Wang ZC, Sun SB, Wang MH, Luo B, Liu P. Gamma knife radiosurgery for residual skull base chordomas. *Neurol Res.* 2008 Jul;30(6):557–61.
- 104 Hasegawa T, Ishii D, Kida Y, Yoshimoto M, Koike J, Iizuka H. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg.* 2007 Oct;107(4):752–7.
- 105 Kano H, Iqbal FO, Sheehan J, Mathieu D, Seymour ZA, Niranjana A, et al. Stereotactic radiosurgery for chordoma: a report from the North American Gamma Knife Consortium. *Neurosurgery.* 2011 Feb;68(2):379–89.
- 106 Krishnan S, Foote RL, Brown PD, Pollock BE, Link MJ, Garces YI. Radiosurgery for cranial base chordomas and chondrosarcomas. *Neurosurgery.* 2005 Apr;56(4):777–84.
- 107 Crockard A, Macaulay E, Plowman PN. Stereotactic radiosurgery. VI. Posterior displacement of the brainstem facilitates safer high dose radiosurgery for clival chordoma. *Br J Neurosurg.* 1999 Feb;13(1):65–70.
- 108 Fuji H, Nakasu Y, Ishida Y, Horiguchi S, Mitsuya K, Kashiwagi H, et al. Feasibility of proton beam therapy for chordoma and chondrosarcoma of the skull base. *Skull Base.* 2011 May;21(3):201–6.
- 109 Munzenrider JE, Liebsch NJ. Proton therapy for tumors of the skull base. *Strahlenther Onkol.* 1999 Jun;175(Suppl 2):57–63.
- 110 Terahara A, Niemierko A, Goitein M, Finkelstein D, Hug E, Liebsch N, et al. Analysis of the relationship between tumor dose inhomogeneity and local control in patients with skull base chordoma. *Int J Radiat Oncol Biol Phys.* 1999 Sep;45(2):351–8.
- 111 Hug EB, Slater JD. Proton radiation therapy for chordomas and chondrosarcomas of the skull base. *Neurosurg Clin N Am.* 2000 Oct;11(4):627–38.
- 112 Ares C, Hug EB, Lomax AJ, Bolsi A, Timmermann B, Rutz HP, et al. Effectiveness and safety of spot scanning proton radiation therapy for chordomas and chondrosarcomas of the skull base: first long-term report. *Int J Radiat Oncol Biol Phys.* 2009 Nov;75(4):1111–8.
- 113 Deraniyagala RL, Yeung D, Mendenhall WM, Li Z, Morris CG, Mendenhall NP, et al. Proton therapy for skull base chordomas: an outcome study from the university of Florida proton therapy institute. *J Neurol Surg B Skull Base.* 2014 Feb;75(1):53–7.
- 114 Austin-Seymour M, Munzenrider J, Goitein M, Verhey L, Urie M, Gentry R, et al. Fractionated proton radiation therapy of chordoma and low-grade chondrosarcoma of the base of the skull. *J Neurosurg.* 1989 Jan;70(1):13–7.
- 115 Weber DC, Rutz HP, Pedroni ES, Bolsi A, Timmermann B, Verwey J, et al. Results of spot-scanning proton radiation therapy for chordoma and chondrosarcoma of the skull base: the Paul Scherrer Institut experience. *Int J Radiat Oncol Biol Phys.* 2005 Oct;63(2):401–9.
- 116 Pai HH, Thornton A, Katznelson L, Finkelstein DM, Adams JA, Fullerton BC, et al. Hypothalamic/pituitary function following high-dose conformal radiotherapy to the base of skull: demonstration of a dose-effect relationship using dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys.* 2001 Mar;49(4):1079–92.
- 117 Santoni R, Liebsch N, Finkelstein DM, Hug E, Hanssens P, Goitein M, et al. Temporal lobe (TL) damage following surgery and high-dose photon and proton irradiation in 96 patients affected by chordomas and chondrosarcomas of the base of the skull. *Int J Radiat Oncol Biol Phys.* 1998 Apr;41(1):59–68.
- 118 Colli BO, Al-Mefty O. Chordomas of the skull base: follow-up review and prognostic factors. *Neurosurg Focus.* 2001 Mar;10(3):E1.
- 119 Kano H, Niranjana A, Lunsford LD. Radiosurgery for Chordoma and Chondrosarcoma. *Prog Neurol Surg.* 2019;34:207–14.
- 120 Bloch OG, Jian BJ, Yang I, Han SJ, Aranda D, Ahn BJ, et al. A systematic review of intracranial chondrosarcoma and survival. *J Clin Neurosci.* 2009 Dec;16(12):1547–51.
- 121 Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. *Semin Radiat Oncol.* 2013 Apr;23(2):120–6.
- 122 Kano H, Niranjana A, Kondziolka D, Flickinger JC, Dade Lunsford L. Stereotactic radiosurgery for trigeminal schwannoma: tumor control and functional preservation Clinical article. *J Neurosurg.* 2009 Mar;110(3):553–8.
- 123 Vasquez JA, Fonnegra JR, Diez JC, Fonnegra A. Treatment of epidermoid tumors with gamma knife radiosurgery: case series. *Surg Neurol Int.* 2016 Feb;7(5 Suppl 4):S116–20.
- 124 West JL, Soike MH, Renfrow JJ, Chan MD, Laxton AW, Tatter SB. Successful application of stereotactic radiosurgery for multiply recurrent Rathke's cleft cysts. *J Neurosurg.* 2019, Epub ahead of print.
- 125 Cohen-Inbar O, Lee CC, Mousavi SH, Kano H, Mathieu D, Meola A, et al. Stereotactic radiosurgery for intracranial hemangiopericytomas: a multicenter study. *J Neurosurg.* 2017 Mar;126(3):744–54.
- 126 El-Shehaby AM, Reda WA, Abdel Karim KM, Emad Eldin RM, Nabeel AM. Single-session Gamma Knife radiosurgery for optic pathway/hypothalamic gliomas. *J Neurosurg.* 2016 Dec;125 Suppl 1:50–7.
- 127 Combs SE, Schulz-Ertner D, Moschos D, Thilmann C, Huber PE, Debus J. Fractionated stereotactic radiotherapy of optic pathway gliomas: tolerance and long-term outcome. *Int J Radiat Oncol Biol Phys.* 2005 Jul;62(3):814–9.
- 128 Hasegawa T, Kato T, Iizuka H, Kida Y. Long-term results for trigeminal schwannomas treated with gamma knife surgery. *Int J Radiat Oncol Biol Phys.* 2013 Dec;87(5):1115–21.
- 129 Régis J, Lagmari M, Carron R, Hayashi M, McGonigal A, Daquin G, et al. Safety and efficacy of Gamma Knife radiosurgery in hypothalamic hamartomas with severe epilepsies: A prospective trial in 48 patients and review of the literature. *Epilepsia.* 2017 Jun;58 Suppl 2:60–71.