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Review

Review of photon and proton radiotherapy for skull base tumours

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ABSTRACT

An extremely large variety of benign and malignant tumours occur at skull base; these tumour lesions are in the proximity to structures deputed to relevant physiologic functions, limiting extensive surgical approaches to this body district. Most recent progresses of surgery and radiotherapy have allowed to improve local control with acceptable rates of side effects. Various photon radiotherapy techniques are employed, including 3-dimensional conformal radiotherapy, intensity modulated radiotherapy (IMRT), stereotactic radiotherapy (SRT) and brachytherapy that is manly limited to the treatment of primary or recurrent nasopharyngeal carcinoma. Proton beam radiotherapy is also extensively used thanks to its physical characteristics. Our review, focusing in particular on meningioma, chordoma, and chondrosarcoma, suggests that proton therapy plays a major role in the treatment of malignant tumours whereas photon therapy still plays a relevant role in the treatment of benign tumour lesions.

1. Background

The base of skull is a structure at the interface between the intracranial content and the rest of the body where a number of neoplasms can arise from tissues of various origin including meningeal sheets, bone, cartilage, soft tissues, muscles, lymphatic tissue, mucosal epithelium, nerves and nerve sheets and embryonic remnants. This explains the extremely large variety of benign and malignant tumours occurring at this anatomic site. A peculiar aspect of the skull base lesions is the proximity to structures deputed to relevant physiologic functions, like the temporal lobes, brainstem, cranial nerves, major vessels, pituitary gland, and inner and middle ears, limiting extensive surgical approaches aimed to achieve a really radical oncologic result, otherwise possible in other body districts. For these reasons, only the most recent progresses of surgery and radiotherapy have allowed to improve the results in terms of local control with acceptable rates of side effects and complications.[1] In order to obtain acceptable

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Table 1 – Dose constraints for the principal organs at risk.

OAR	Photon conventional fractionation (1.8–2 Gy)	Photon single fraction	Protons conventional fractionation	Source
Brainstem	Entire organ < 54 Gy, D_{max} < 64 Gy	D_{max} < 15 Gy D_{1cc} < 10 Gy	D_{max} Centre ≤ 53 Gy (RBE) Surface ≤ 64 Gy (RBE)	Mayo 2010[2], Timmerman 2008[7], Munzenrider 1999[9]
Optic pathways	Entire organ < 55 Gy	D_{max} < 10 Gy $D_{0.2cc}$ < 8 Gy	D_{max} ≤56–60 Gy (RBE)	Mayo 2010[3], Timmerman 2008[7], Noel 2005[10], Munzenrider 1999[9]
Cochlea	Entire organ < 45 Gy	D_{max} < 12–14 Gy	D_{max} ≤55 Gy (RBE)	Bhandare 2010[4], Timmerman 2008[7], Noel 2005[10]
Temporal lobe	Not well established: constraints in the range from V_{45} < 15 cc to V_{40} < 55 have been suggested	(Brain) V_{12} < 5–10 cc	D_{max} ≤63 Gy (RBE)	Zhou 2014[5], Su 2013[6], Lawrence 2010[8], Wenkel 2000[11]

rates of local control, malignant tumours in the skull base must be irradiated to a dose that exceeds the constraints of the above listed organs at risk (OARs). In case of a benign disease, doses employed can be lower and comparable to the tolerance of OARs but the long prognosis raises the issues of long-term side effects. A complete review of skull base dose constraints is beyond the scope of the present work; however, Table 1 summarizes dose constraints to the most significant OARs commonly used in clinical practice for photons and protons, considering both conventional fractionation and short course treatments for photons.[2–11]

2. Aim

The purpose of this paper is to review the techniques and the main results of photon and proton radiotherapy for the treatment of skull base tumours. To highlight strengths and disadvantages of different techniques, we have selected meningioma and chordoma/chondrosarcoma as examples of benign and malignant diseases in this region.

3. Materials and methods

A literature search was performed in Pubmed using the following keywords (meningioma or chordoma or chondrosarcoma or skull-base or nasopharyngeal carcinoma and radiotherapy or radiation or radiosurgery or SRT or brachytherapy or proton therapy). In principle, papers published since 2000 were selected, listed and analysed for relevance based on their abstract. Case reports were excluded, whereas review papers were analysed.

4. Results

4.1. *Photon radiotherapy*

4.1.1. *Intensity modulated radiation therapy (IMRT)*

Intensity modulated radiotherapy (IMRT) represents an advanced modality of 3-dimensional conformal radiotherapy (3D-CRT) and it is employed for the treatment of many different tumours, in particular in the case of irregular target shapes and closeness to critical structures.[12] The advantage of using IMRT for skull base tumours is evident because of the proximity of various sensitive anatomic structures, such as the brainstem, optic nerves and chiasm and brain tissue.[13]

IMRT involves a treatment delivery employing hundreds or thousands of small beams, created by a multi leaf collimator (MLC), each with intensity generated using an inverse treatment planning system. Inverse planning involves a process that uses computer optimization techniques aimed to modulate intensities across the target volume and normal tissues, starting from a specified dose distribution[14] and reaching the desiderate outcome.[15] As a result, a high dose conformation is reached and delivered to irregularly shaped targets, while the dose to surrounding non-target structures is minimized.[12]

IMRT can be delivered in different ways: (a) IMRT with static field segments (step and shoot), where the field is divided into different segments and radiation is delivered after the leaves movement to create the next segment; (b) with dynamic delivery (sliding windows), in which the leaves move across the field during treatment and the time-dependent position of each leaf determines the intensity; and (c) with rotational technique using volumetric modulated arc therapy (VMAT) or tomotherapy; in VMAT, the MLC has the leaf pattern changing continuously as the gantry rotates, allowing the simultaneous variation in dose rate, and in tomotherapy, the gantry continuously rotates while the patient couch is translated in the rotation plane.[16]

A pre-requisite of such a sophisticated technology is the importance of precise targeting and delivering of daily RT because of the steep gradients between high and low-dose regions. The advent of image guided RT (IGRT) allowed a target position correction, performing imaging prior to each radiation fraction.[17]

4.1.2. *Stereotactic radiotherapy*

Stereotactic radiotherapy (SRT) dates back to the early '50s with the pioneering experience of Leksell in Sweden.[18] Originally, it was defined as the delivery of high RT dose with multiple entrance portals, a steep dose gradient, optimal sparing of surrounding tissues and a precise patient immobilization. Immobilization was achieved with invasive fixation of the patient anatomy to an external rigid stereotactic frame, which made fractionated treatment impractical. Treatment

schedule were either of a single (stereotactic radiosurgery SRS) or of a limited (between 3 and 5) number of fractions (stereotactic radiotherapy SRT). More recently, the advances in image guidance have been employed to reposition the patient with sub-millimetric accuracy without rigid fixation and deliver SRT without invasive procedures. This so-called frameless stereotactic radiotherapy enabled delivery of fractionated treatment schedules.[19] In modern clinical practice, SRT can be delivered either with multiple cobalt sources: gamma knife (GK) (Elekta Instruments AB, Stockholm, Sweden) or with linear accelerators (LINACs). There are commercially available dedicated machines, such as CyberKnife (CK) (Accuray, Sunnyvale, CA, USA) that is a small LINAC mounted on a 6 degree of freedom robotic arm, but also general purpose accelerators can be used. In SRT, multiple beams are focused on the target volume from different angles in an isocentric way. Typically, no inverse planning is performed and, therefore, a non-uniform dose is achieved with a gradient between the centre and the periphery of the tumour. Dose prescription is not done according to ICRU reports but according to isodose prescription and concave dose distributions cannot be achieved.[20]

Cyberknife, even though usually listed as a SRT modality, can be considered to be at the border between IMRT and SRT as it uses inverse planning, and, thanks to its ability to perform non-isocentric treatments, can deliver concave or even donut shaped dose distributions.[21]

4.1.3. *Clinical results with photon external beam radiotherapy (EBRT)*

Several clinical series are available on the use of EBRT in patients with skull base tumours. For the present review, we focused on meningioma, chordoma, and chondrosarcoma. Meningioma is typically treated with doses comparable to OARs tolerance, whereas chordoma and chondrosarcoma need substantially higher doses.

For meningioma, 102 papers were selected and 37 articles reporting data of more than 20 patients were specifically analysed.

Dosimetric and clinical data of more than 5000 patients treated with stereotactic radiotherapy with long term follow-up are reported in Table 2.[13,22–57] Local control for benign meningioma is typically in the range of 80–90% with minimal toxicity. Atypical and malignant meningioma have a significantly worse outcome and may be candidate to alternative or experimental approaches. Radiotherapy has been used as alternative to surgery or in post-operative setting or as a salvage treatment. Technique and fractionation are chosen according to the availability and clinical judgement but an underlying pattern is evident with fractionated treatment typically used for lesions that are larger and or close to OARs and IMRT used for lesion of complex shape.

A recent clinical series with a 10 years follow-up time analysed 507 patients with skull base meningioma treated by IMRT (131 patients) or fractionated stereotactic RT (376 patients).[38] Local control for the whole cohort was 94% at 5 years and 88% at 10 years. The treatment technique did not affect progression-free survival. This is the first study, with such a long follow-up, that analysed the impact of treatment on the quality of life and showed that it was unchanged in 47.7% of the patients, and improved in 37.5%. Late toxicity with such a long follow-up was observed in only 3% of patients. This large clinical series confirmed the improvement of volume conformity and normal tissue protection with highly conformal RT techniques, and reported, in 87% of patients' self-reported outcome, unimpaired or improved quality of life.

For chordoma and chondrosarcoma, 18 papers were selected and 7 articles reporting data of more than 10 patients were specifically analysed. Results are summarized in Table 3.[58–68] For these diseases, particle therapy has been historically employed, results in terms of local control and progression free survival with photons RT are acceptable for chondrosarcoma but were on average rather disappointing for chordomas with only one series reporting 5-year local control in excess of 80% and other series reporting local control or progression free survival from 15% to 66%. It is difficult to draw any conclusions from these scarce and heterogeneous data; nevertheless, outcome appears not to be equivalent to that of particles and these findings may suggest that even modern advanced photons cannot achieve adequate target coverage in the skull base for prescription doses in excess of 70 Gy.

4.1.4. *Brachytherapy*

Although most tumours in the skull base are treated with external beam radiotherapy (EBRT) exclusively, in some cases a boost with intracavitary or interstitial implants can be used. The niche for brachytherapy in the skull base is basically limited to nasopharyngeal carcinoma.[69,70]

Generally, only patients affected by primary or recurrent superficial nasopharyngeal tumours with thickness not exceeding 10 mm and not involving the bone or the infratemporal space, are ideal candidates for brachytherapy.

Brachytherapy is mostly indicated as a boost after EBRT, offering a confined dose escalation especially for superficially large tumours (local control is in general considered highly related to the total dose), even if some authors have reported no advantage when an additional irradiation with brachytherapy was combined to EBRT.[71,72]

Brachytherapy can be used as the sole salvage treatment, in particular in the case of re-irradiation for local residual occurring within 6 months, or well circumscribed/non-bulky recurrent disease diagnosed after achievement of complete remission with radical radiotherapy.[73–76] Very selected nasopharyngeal recurrence from other skull base tumours may also be candidate to brachytherapy reirradiation.[77]

Compared to conventional EBRT, the main advantages of temporary or permanent brachytherapy, bringing the radiation sources directly near and/or into the tumour include a higher localized dose around the target volume and a shorter overall treatment time. The rapid fall-off of doses around sources allows relative sparing of critical normal tissues. The main disadvantage is a potential not-treatment of foci of cancer in areas outside the treated volume encompassed by the isodose surface corresponding to the minimal target dose. Even with brachytherapy, the anatomical challenges of this site remain relevant and a more sophisticated technique is beneficial: Ren et al. demonstrated on a large population of patients treated with brachytherapy boost after EBRT that 3D-HDR was more effective than 2D-HDR techniques, with a statistically significant improvement in local control.[78]

Table 2 – Results of the main series of meningioma treated with photon radiation therapy.

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Aicholzer et al.[22]	2000	46	Gamma knife	9–25 Gy margin dose in single fraction	48	LC 96%	Minimal toxicity: 1 case (2%) of transient paresis, 1 case (2%) of hypopituitarism	No difference in outcome in post operative vs. radical treatment
Zachenhofer et al.[23]	2006	36	Gamma knife	9–25 Gy margin dose in single fraction	103	LC 94%	1 abducens nerve palsy, 1 focal seizure, 1 hypopituitarims (8% developed toxicity)	Subset of Aicholzer's series with longer follow-up, confirms same findings
Metellus et al.[24]	2005	74	3D-CRT (38 patients) Gamma knife (36 patients)	50–55 Gy (1.6–2 Gy/fr) for 3D-CRT; 6–25 Gy in single fraction prescription 30–70% isodose	91 (median) for 3D-CRT (extrapolated from graph); 80 (median) for GK (extrapolated from graph)	LC 97.4% for 3D-CRT; LC 94.4% for GK	No significant toxicity in 3D-CRT group, 1 transient stroke in GK group	Pts treated with GK had smaller tumours, there was no apparent difference in outcome between the two modalities
Kreil et al.[25]	2005	200	Gamma knife	7–25 Gy in single fraction prescription 20–80% isodose	95 (median)	Actuarial 5y LC 98.5% 10y LC 97.2%	1 pt (0.5%) with worsening cranial nerve symptoms	SRS may replace surgery in selected cases
Han et al.[26]	2008	63	Gamma knife	7–20 Gy margin dose in single fraction	77	LC 94%	2 pts (2%) had recurrent seizures, 10 pts (16%) had worsening of cranial nerves symptoms	SRT can be an alternative to surgery, toxicity is acceptable but not negligible
Igaki et al.[27]	2009	98	Gamma knife	14–18 Gy in single fraction prescription 40–50% isodose	53 (median)	Actuarial 5y LC 87% 10y LC 79%	4 pts (4%) with worsening of cranial nerve symptoms	Tumour volume smaller than 4 cc and complete target coverage were associated with better LC
Nakaya et al.[28]	2010	44	Gamma knife	13 Gy margin dose in single fraction	60 (median)	LC 100%	1 pt (worsening of neurological deficit)	SRT can be an alternative to surgery. All tumours caused brainstem compression
Pollock et al.[29]	2012	251	Gamma knife	Mean margin dose 15.8 ± 2 Gy	62.9	98.8%	Toxicity in 23 patients (9.2%): cranial nerves deficit 15 pts, headache 5 pts, hemiparesis 5 pts, seizure 4 pts, cyst formation 1 pts, stroke 1 pts	Long follow up is needed, local recurrence were observed after more than 10 years
Chuang et al.[30]	2004	43	LINAC SRT	7–25 Gy in single fraction prescription 80% isodose	74.5 (median)	Actuarial 7y LC 89.7%	2 pts (4.7%) with toxicity (actuarial 7y LC 89.7%)	No difference in outcome in post operative vs. radical treatment
Selch et al.[31]	2004	45	LINAC SRT	42.5–54 Gy (2 Gy/fr), 90% isodose	36 (median)	98%	1 cerebrovascular event	All tumours were in the cavernous sinus

Table 2 (*Continued*)

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Correa et al.[32]	2014	89	LINAC SRS (single fraction), or fSRT	fSRT: 45–50 Gy in (1.8–2 Gy/fr); SRS 13–15 Gy at 80–90% isodose	73 (median)	Actuarial 5y, 10y and 15y DFS: 98.8%, 92.3%, 92.3%	No sever toxicity, only transient events	All tumours were in the cavernous sinus, larger lesion and lesion close to optic pathways were treated with SRT. There was no difference in outcome between SRS and SRT
Kaul et al.[33]	2014	136	LINAC fSRT	32.4–63 Gy (1.8–2 Gy/fr)	44.9 (median)	Actuarial 5y PFS: 93.8%, 10y PFS 91.5%	37.5% of the patients showed grade I or II late fatigue or headache	Fractionated SRT is used for tumours close to OAR, there may be a relevant selection bias when comparing with SRS
Soldà et al.[34]	2013	145	LINAC fSRT	50–55 Gy (1.5–1.66 Gy/fr)	43 (median)	Actuarial 5y LC 93% 10y LC 86%	8 pts (3.5%) worsening vision, 1 pt (0.5%) trigeminal neuralgia, 2 pts (1%) cognitive impairment, 2 pts (1%) cerebrovascular accidents	Selection bias may hinder retrospective series comparison with different techniques
Tanzler et al.[35]	2011	103	3D-CRTor IMRT or fSRT	50.4–55.8 Gy (1.86 Gy/fr)	88 (median)	Actuarial 5y LC 96% 10y LC 95%	10 pts (7%) had significant toxicity: - 2 pts developed brain necrosis and 1 pt died of it, - 2 pts developed bilateral optic neuropathy and blindness, - 1 pt developed unilateral retinopathy an impaired vision - 1 pt developed cataract, - 1 pt developed hydrocephalus and necessitated a shunt, - 1 pt developed osteomyielitis of ear canal and required surgical debridement, - 1 pt died of steroid therapy complications	All tumours where WHO grade I. There was no difference in outcome between post operative and definitive RT. Fractionated SRT is a treatment option for patients not candidate to radical surgery or SRS
Litré et al.[36]	2009	100	LINAC fSRT	45 Gy (1.8 Gy/fr)	33	Actuarial 7y LC 94%	Toxicity in 23 patients(9.2%): cranial nerves deficit 15 pts, headache 5 pts, hemiparesis 5 pts, seizure 4 pts, cyst formation 1 pt, stroke 1 pt	All tumours where in the cavernous sinus, fractionated SRT is the first option for meningioma in the cavernous sinus

Table 2 (*Continued*)

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Hamm et al.[37]	2008	224	LINAC fSRT/SRS	fSRT: 60 Gy (1.8–2 Gy/fr); SRS single fraction of 4–5 Gy	36 (median)	Actuarial 5YPFS 96.9%	Late grade III toxicity 2.7%	Radiotherapy may be an alternative to surgery, for large tumours or tumours close to critical structures fractionated RT may be beneficial
Combs et al.[38]	2013	507	IMRT/fSRT with LINAC or tomotherapy	25–68 Gy (1.6–5 Gy/fr)	107 (median)	Actuarial 5y LC 95% 10y LC 88%	QOL was decreased due to disease or therapy only in 8 patients (3%). S	Atypical and anaplastic histologies had significantly worse outcome (10YLC 53%). Small lesions may be treated with SRS, lesion close to critical organ may benefit from fSRT, complex shape lesion may benefit from IMRT. The choice between wait and see, surgery or RT should be made in a multidisciplinary setting
Milker-Zabel et al.[13]	2007	94	IMRT	50.4–62 Gy (1.8 Gy/fr)	53 (median)	93.6%	4.3% of the pts had worsening of neurological symptoms	IMRT can be useful in complex shaped tumours
Minniti et al.[39]	2011	52	LINAC fSRT	50 Gy (1.66 Gy/fr)	42 (median)	Actuarial 5y LC 93%	10 pts (19%) developed hypopituitarism, 1 pt had neurocognitive impairment and 1 pt had increase in seizure frequency	fSRT is an acceptable technique
Colombo et al.[40]	2009	199	Cyberknife	11–25 Gy in 3–5 fr at 70–90% isodose	30	96.5%	Worsening cranial nerve deficit in 0.5% of the pts	Cyberknife allowed treatment of pts not candidate to SRS
Choi et al.[41]	2010	25	Cyberknife	16–30 Gy in 1–4 fr to 62–91% isodose	28 (median)	Actuarial 3y LC 74%	1 pt with brain necrosis, 1 pt with hydrocephalus	All pts were WHO grade II, post op irradiation may be beneficial in these subset, SRT may be an alternative to surgery
Oermann et al.[42]	2013	38	Cyberknife	25– 35 Gy in 5 fraction	20 (median)	100%	Only transient toxicity	Fractionation may be beneficial for large lesions
Starke et al.[43]	2012	225	Gamma knife	8–30 Gy in single fraction at 28–80% isodose	78 (median)	LC at last FU 86%; actuarial 5y LC 96% 10y LC 79%	25 pts (10%) had worsening of neurological symptoms	SRS is useful for tumours in critical sites
Pourel et al.[44]	2001	28 skull base pts out of 45 meningioma	3D-CRT	50–70 Gy (1.8–2 Gy/fr)	30 (median)	Actuarial 5yPFS 75%; 8y PFS 67%, results reported for the whole series (45 pts)	1 case of hemiparesis, trigeminal neuralgia, and decline of cognitive function,	Series include exclusive RT, post op RT and salvage RT

Table 2 (*Continued*)

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Jalali et al.[45]	2002	41	LINAC fSRT	50–55 Gy in 30–33 fractions	21 (median)	100%	2 cases of hypopituarism, 2 cases of worsening neurocognitive impairment, 1 case of worsening visual field deficit	fSRT is alternative to surgery for tumours difficult to resect
Torres et al.[46]	2003	128	LINAC SRT or SRS	SRS 12–22.85 Gy peripheral dose, SRST 23.8–54 Gy in 5–30 fractions	32.5	94.8% (SRS 92% SRT 97.2%)	5 pts had worsening of pre-existing symptoms	Difference between SRS and SRT are likely due to bias in length of follow up and imaging quality, results were much worse (tumour control at last FU 38.1% in atypical tumours)
Henzel et al.[47]	2006	84	LINAC fSRT	50.4–60 Gy (1.8–2 Gy/fr)	30 (median)	100%	Not reported	Only WHO grade I, volume shrinkage depends on initial tumour volume and age, young (<56 years) patient with small tumours showed more tumour regression
Brell et al.[48]	2006	30	LINAC fSRT	50–56 Gy (2 Gy/fr)	50 (median)	Actuarial 4YLPFS 93%	1 pt with neuropsychological deficit and seizure, 1 pts with short term memory loss and dysphasia	All tumours in cavernous sinus
Kondziolka et al.[49]	2008	563 skull base pts out of 972 reported meningiomas	Gamma knife	14 Gy mean peripheral dose	48 (median)	WHO I 93% WHO II 50% WHO III 17% (both skull base and non skull base data)	15-Year actuarial complication rates 9.1%: hydrocephalus 0.4%, cranial nerve deficit 3.4%, headaches 2.2%, seizures 2.4%, motor deficit 1.4%, sensory deficit 0.3% (non skull base pts included)	SRS can be used for recurrent meningioma or as first line treatment
Kollová et al.[50]	2007	368	Gamma knife	6.5–24 Gy margin dose in single fraction at isodose 40–90%	60 (median)	Actuarial 5y LC 97.9%	Permanent morbidity in 5.7% of the patients	Marginal dose of less than 12–16 Gy is associated with worse local control
Hasegawa et al.[51]	2007	115	Gamma knife	7.5–17 Gy margin dose	62 (median)	Actuarial 5y LC 94%; 10y LC 92%	11 pts (12%) had worsening of pre-existing symptoms or developed new symptoms	SRS is alternative to surgery in cavernous sinus meningioma

Table 2 (*Continued*)

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Malik et al.[52]	2005	277	Gamma knife	10–30 Gy to the tumour margins	44	WHOI actuarial 5y LC 87%, 8y LC 75%; WHO II actuarial 5y LC 49%; WHO III actuarial 5y LC 0%, gross LC 28%	1 case of worsening VII cranial nerve deficit, 3 cases of transient trigeminal pain, 3 cases of diplopia 2 cases of weakness (tumour close to motor cortex)	Tumour grade was the strongest predictor of local control
Nicolato et al.[53]	2002	122	Gamma knife	11–22.5 Gy in single fraction at 30–65% isodose	48.9 (median)	Actuarial 5y PFS 96.5%	1 case of intracranial hypertension and worsening cranial nerve deficit	All tumours were in the cavernous sinus; SRS may be considered the first-choice treatment modality cavernous sinus meningioma
Roche et al.[54]	2000	92	Gamma knife	6–25 Gy at isodose of 30%-70%	30.5 (median)	Actuarial 5y-PFS 92.8%	1 case of worsening trigeminal neuralgia, 1 case of complex partial seizures and 1 case of transient carotid occlusion	Gamma knife can be alternative to surgery for meningioma of the cavernous sinus
Villavicencio et al.[55]	2001	56	LINAC SRS	9–18.5 Gy margin dose in single fraction	26 (median)	95%	5 pts (9%) had permanent late toxicity: 1 difficulty in gait, 2 visual field deficit, 2 cerebral oedema	SRS is indicated both in adjuvant setting and as first line for poor surgical candidates
Friedman et al.[56]	2005	210	LINAC SRS	10–20 Gy in single fraction at 70–80% isodose	24 (minimum)	Actuarial 5y LC WHO I 96%, WHO II 77% WHO III 19%	5 pts (2.3%) permanent toxicity, all in WHO III tumours	LINAC SRS is an optimal treatment for WHO I meningiomas
Stafford et al.[57]	2001	147 skull base cases out of 190 meningiomas	Gamma knife	12–36 Gy in single fraction at 50% isodose	47 (median)	Actuarial 5y LC WHOI 93%, WHO II 68% WHO III 0%	24 pts (13%) had permanent late toxicity: 15 cranial nerve deficit, 5 symptomatic MR detectable parenchyma change, 2 carotid stenosis, 2 cystic lesion	SRS can be used in the treatment of meningioma; grade II and III tumours have worse outcome

LC = local control (LC as freedom form tumour progression at last FU); FU = follow up; pt/pts = patient/patients; GK = gamma knife; SRT = stereotactic radiotherapy; fSRT = fractionated SRS; SRS = radiosurgery; fr = fraction; PFS = progression free survival; OAR = organ at risk; DFS = disease free survival.

Table 3 – Results of the main series of chordoma and chondrosarcoma treated with photon radiation therapy.

Author	Year of Publication	N. pts	Technique	Dose and fractionation	Mean follow up (months)	Outcome	Toxicity	Comments and authors conclusion
Chang et al.[58]	2001	10	Cyberknife or LINAC SRT	18–24 Gy at 70–80% isodose in 1–3 fractions	48	1 pt with tumour reduction, 7 pt with radiological stability, 2 pts with tumour growth	No improvement of pre-existing symptoms, no radiation induced toxicity	Small patient number, outcome is not reported with actuarial calculation. The authors claim that outcome is as good if not superior to particle series
Debus et al.[59]	2000	45 (37 chordomas, 8 chondrosarcomas)	LINAC FSRT	66.6 Gy for chordoma, 64.9 Gy for chondrosarcoma (1.8 Gy/fr)	27 chordoma, 19 chon-drosarcoma	Actuarial 5y LC: chordoma 50%, chondrosarcoma 100%	1 case of ischaemic lesion in the pons with hemiparesis	Particle therapy is recommended for chordoma
Hauptman et al.[60]	2012	15 (13 chordomas, 2 chondrosarcomas)	LINAC SRT or LINAC SRS	SRS: 13.2–17.9 Gy in single fraction. SRT: 53–84 Gy (2 Gy/fr)	44	LC at last follow up 66% (extrapolated)	1 pts with dysphagia, dysarthria, bilateral facial numbness and unilateral blindness, 1 pt with pituitary deficit requiring replacement therapy	Particle therapy may have better result but is scarcely available
Jiang et al.[61]	2012	20 (12 in the skull base)	Cyber knife	18–50 Gy in 1–5 fractions	34 (median)	LC at last FU 55%, actuarial 5y OS 52.5% (whole series including non skull base cases)	No reported toxicity	8 pts had recurrence after previous RT with protons (7 pts) or photons (1pt). Particle therapy may give better outcome but is scarcely available
Kano et al.[62]	2011	71 (51 pts first diagnosis, 20 pts recurrence after RT)	Gamma knife	Marginal dose of 9–16 Gy in recurrent pts marginal dose of 10–25 Gy in naive pt	60 (median)	Treated tumour actuarial 5y LC 66.4% (recurrent pts 62%; naive pts 69%); 5y LC including marginal failures is not reported but may be extrapolated from graph at about 60%	4 pts developed neuropathy (abducens and facial) 2 pts with pituitary dysfunction	Dose > 15 Gy and tumour volume < 7 cc correlate with better outcome. SRS may be adequate for smaller tumour, the author recommend RCT of SRS vs. particle therapy
Koga et al.[63]	2010	14 (10 chordomas, 4 chondrosarcomas)	Gamma knife	Marginal dose 10–20 Gy	65	Actuarial 5y PFS 43% (100% for chondrosarcoma, 15% for chordoma)	Only transient toxicity reported	Marginal dose of more than 16 Gy is needed for local control. 4 patients had recurrent chordoma after RT

Table 3 (*Continued*)

Author	Year of Publication	N. pts	Technique	Dose and fractionation	Mean follow up (months)	Outcome	Toxicity	Comments and authors conclusion
Krishnan et al.[64]	2005	29 (25 chordomas, 4 chondrosarcomas)	Gamma knife + -EBRT	SRS: marginal dose 10–20 Gy; EBRT 45–54 Gy	Not reported	Actuarial 5y LC 51% (100% for chondrosarcoma, 32% for chordoma)	10 pts (34%) had complication: diplopia 3, ocular neuromyotonia 1, hearing loss 1, dysarthria 1, dysphagia 1, brain necrosis 5 and anterior pituitary dysfunction 3	SRS and EBRT are effective in treating chondrosarcoma, particle therapy may give better results for chordoma but has limited availability
Potluri et al.[65]	2011	19	EBRT or FSRT or IMRT	65–70 Gy in fractions of 1.8–2 Gy	53 (median)	Actuarial 5y LC 83%	Not reported	Smaller tumour volume (<30 cc) correlated with better outcome (LC 100%). Highly sophisticated photons RT may be used alternatively to particle therapy for small residual tumours
Zorlu et al.[66]	2000	18	EBRT	53–60 Gy with conventional fractionation	43	Actuarial 5y PFS 23%	Not reported	Extended resection and high dose RT is needed in the treatment of chordoma
Bugoci et al.[67]	2013	12	fSRT	48.6–68.4 Gy (1.8 Gy/fr)	42 (median)	Actuarial 5y – PFS 37.5%	Non-relevant	fSRT may be alternative to particle therapy
Sahgal et al.[68]	2014	42 (24 chordomas, 18 chondrosarcomas)	Image guided IMRT	Chordoma 76 Gy; chondrosarcoma 70 Gy (2 Gy/fr)	Chordoma 36; chondrosar-coma 67	Actuarial 5y LC 88% for chondrosarcoma, 65% for chordoma	8 pts had late toxicity including 1 pts with radiation induced cancer	Favourable survival, local control and adverse event rates following high dose Image guide-IMRT

LC = local control (LC as freedom form tumour progression at last FU); FU = follow up; pt/pts = patient/patients; GK = gamma knife; SRT = stereotactic radiotherapy; fSRT = fractionated SRS; SRS = radiosurgery; fr = fraction; PFS = progression free survival; OAR = organ at risk; DFS = disease free survival; IMRT = intensity modulated radiotherapy.

When brachytherapy is used as a boost, the total treatment duration should be condensed to reduce tumour cell repopulation, with a rest period of 1–2 weeks, depending on the degree of mucositis; the HDR technique is preferred and the recommended schedule is 2–6 fractions, 2–5 Gy per fraction (rarely higher), according to the total dose of EBRT (generally 60–70 Gy).

In exclusive HDR BT, the prescribed dose is 20–40 Gy, 2–5 Gy per fraction, whereas in LDR/PDR BT, a dose rate of 0.4–0.6 Gy/h is usually selected to administrate about 60 Gy.[79,80]

Brachytherapy is well tolerated with minimal morbidity: severe long-term toxicity such as necrosis of the surrounding and affiliated tissues of the nasopharynx is reported in about 7% of patients. Headache and foul odour are the representative signs: necrosis is life threatening when the internal carotid artery is eroded.[81] Higher incidence is observed in re-irradiated patients, with up to 10% of nasopharyngeal necrosis and endocrine dysfunction.[76]

For brachytherapy as a boost for nasopharyngeal carcinoma, 57 papers were selected and 12 articles reporting data of more than 20 patients were specifically analysed. Clinical results are summarized in Table 4.[71,72,78,82–90] As can be observed, the outcome of patients treated with brachytherapy appears superior to that of patients treated with EBRT alone without increased toxicity. Of course, the difference may be due to a selection bias as T3 and T4 patients are not candidate to brachytherapy. The interest in this modality has recently decreased as results of IMRT or SRT boost may be equivalent to those of brachytherapy.

4.2. *Proton radiotherapy*

Protons have physical characteristics that differ from those of photons. Protons permit better sparing of critical organs due to their particular ballistic, dose deposition being mainly limited to the so called Bragg-peak which can be spread-out. Thus, the integral dose is low and the treatment is extremely conformal to the target volume. Upon these concepts, protons have been used for radiation treatment of skull base tumours over the last decades.

Most of the studies report on the use of passive scattering technique and only few recent ones on the use of active delivery systems that allow an even better sparing of healthy tissue nearby the target. A few articles describe also the use of a mixed proton/photon beam (Table 5[9–11,91–102]). From the methodological point of view, the large majority of the studies are retrospective and may include different tumour types: chordoma, chondrosarcoma, and meningioma of grade I–III. We excluded from our analysis series containing paediatric patients and re-irradiation for relapse after photon radiotherapy.

Historical data are described in two papers from 1999 about skull base chordoma and chondrosarcoma with a relevant number of patients that describe the experience of two institutions pioneering proton radiotherapy in USA: the Massachusetts General Hospital (MGH) in Boston and Loma Linda University Medical Center (LLUMC) in Loma Linda. The first large clinical series of 519 cases of skull chordoma and chondrosarcoma were reported from MGH in Boston. Patients were treated to a total dose ranging from 66 to 83 Gy (relative biological effectiveness – RBE) obtained by multiplying physical dose by the RBE value (usually 1.1 for protons). Local relapse free survival rates of 73% and 80% at 5 years were observed for chordoma and chondrosarcoma, respectively, with relatively low toxicity findings.[9] The series treated at LLUMC reviewed the results of 58 patients treated with proton therapy to a total dose of 65–79 Gy (RBE) after surgical resection. Local control and overall survival at 5 years were obtained in 59% and 79%, respectively, for chordoma and 75% and 100% for chondrosarcoma.[91] The review on chordoma and chondrosarcoma includes the results of proton radiotherapy delivered after one or more surgical resections (Table 5[9–11,91–102]). All series were treated to very high doses of up to 83 Gy (RBE). The results in terms of local control and survival at 5 years appear more favourable for chondrosarcoma, ranging, respectively, from 75% to 94% and from 91% to 100%, rather than for chordoma, ranging, respectively, from 46% to 81% and from 67% to 81%. Most of the results reported in the series treated with proton radiotherapy appear more favourable than those reported after EBRT. Unfavourable prognostic factors emerging from these series are large target volume, brainstem compression,[91,92] minimal dose to GTV, and the percentage of tumour volume included in the 95% isodose.[10] In terms of toxicity, literature data describe severe late side effects in a relatively small percentage of patients and include brain and brainstem injuries often related to tissue necrosis, vision and hearing loss, and endocrinopathy related to pituitary dysfunction.

In the meningioma literature series, the authors report on the results of patients affected either by benign or atypical and malignant meningioma. The dose level is quite similar to that used in the series treated by photon radiotherapy and the rationale of using protons resides in a potentially better sparing of the critical structures close to the target region. Several series include either skull base or convexity lesions and patients with both primary and recurrent tumours after surgery. Local control at 5 years was obtained in 85–100% of benign skull base meningioma cases and in 47–71% of atypical/malignant meningioma cases. The occurrence of long-term side effects is quite low and similar to that of EBRT, but patient selection was often unfavourable due to inclusion of many inoperable cases extending towards critical structures such as brainstem, temporal lobes, pituitary gland, and optic nerves.

5. Discussion

Skull base remains an extremely challenging tumour site. Generally, IMRT can achieve more uniform dose distribution and avoid hot spots, is ideally suited for complex-shaped targets whereas SRT can achieve a highest dose gradient, and is ideally suited for targets of a simple shape. On the other hand, radiosurgery would be more rationally used in round or oval lesions that do not abut critical structures. These general concepts are supported by in silico treatment plans that compared fractionated SRT with IMRT, and confirmed IMRT superiority in avoiding hot spots within the CTV and in obtaining a more uniform dose distribution.[103,104] Also clinical data suggest that IMRT may be advantageous for tumour diameter

Table 4 – Results of the main series of nasopharyngeal carcinoma treated with brachytherapy.

Author	Year of publication	N. pts and characteristics	Stage	EBRT dose	BRT dose	CT	FU (months)	LC rate	Toxicity
Teo et al.[82]	2000	(A) BRT boost: 162 (A1) 101 with local persistence (A2) 62 after complete remission (B) EBRT alone: 346	(A) Stage I-IIa: 54.6% Stage IIb-IV: 45.4% (B) Stage I-IIa: 34.7% Stage IIb-IV: 65.3%	60–71.2 Gy	(A1) 24 Gy/3 fr/15 days (A2) 18 Gy/ 3 fr/15 days	(A) 6.1% (B) 16.5%	(A) 88 (B) 79.1	(A1) 94.9% at 5y (A2) 94.5% at 5y (B) 89.7% at 5y	Chronic ulceration or necrosis: (A) 6.13% (B) 0.29%
Ozyar et al[72]	2002	(A) BRT boost: 106 (B) EBRT alone: 38	(A) Stage II-II: 37.7% Stage III-IV: 62.3% (B) Stage I-II: 15.8% Stage III-IV: 84.2%	(A) 58.8–71 Gy (B) 58.8–74 Gy	HDR 12 Gy/3 fr	(A) 55.9% (B) 71.1%	(A) 31 (12–71) (B) 43 (12–80)	(A) 86% at 3y (B) 94% at 3y	Nasal synechy 2.8% Neural complication: (A) 0.9% (B) 10%
Lee et al.[83]	2002	(A) 43 pts with primary tumours (B) 12 pts with recurrence tumours	Stage II-II: 31 pts Stage III-IV: 24 pts	(A) 50–72 Gy (B) 30–42 Gy	LDR 10–54 Gy (29 pts) HDR 5–7 Gy, 1–2 fr (24 pts) PDR (2 pts)	(A) 40% (B) 8%	(A) 36 (B) 50	(A) 89% at 5y (B) 64% at 5y	Acute mucositis G2: 70.9% Late xerostomia G2: 58.2% Osteoradionecrosis of the clivus: 2%
Levendag et al.[84]	2002	91 pts with primary tumours treated with EBRT + BRT	Stage I-IIb: 36 pts Stage III-IV: 55 pts	60–70 Gy	12–18 Gy in 4–6 fr bid	23%	48	Stage I-IIb: 96–100% Stage III-IV: 65–86%	Synechiae of the nasal mucosa Dry-mouth syndrome
Lu et al.[85]	2004	33 (T1: 22 pts, T2: 11 pts)	Stage II-II: 17 pts Stage III-IV: 16 pts	66–70 Gy	10 Gy/2 fr 1 week apart	In stage III-IV (16 pts)	29 (17–38)	93.6% at 2y	18% G4 acute toxicity 1% G4 toxicity
Yau et al.[86]	2004	(A) BRT boost: 24 (B) SRT boost: 21	T2-T4 persistent disease after EBRT	EBRT 66 Gy (2 Gy/fr)	HDR 10–24 Gy twice-weekly fr	30%	33	(A) 71% at 3y (B) 82% at 3y	Late toxicity ≥G3 (A) 28% (B) 27%
Ng et al[87]	2005	38 pts treated with BRT boost	T1-T2: 87% T3-T4: 13% N0: 63%	54.4–64 Gy	6–15 Gy/2–5 fr	71%	47 (2–84)	96% at 5y	Choanal stricture 2.6% No necrosis

Table 4 (*Continued*)

Author	Year of publication	N. pts and characteristics	Stage	EBRT dose	BRT dose	CT	FU (months)	LC rate	Toxicity
Teo et al.[88]	2006	(A) BRT boost: 146 (B) EBRT/SRT boost: 1426		66 Gy	(A) BRT: 10–21 Gy (5–8 fr) (B) 15 Gy (5 Gy/fr)	24.3%	52	80–85% at 5 y	No significant differences in time to-death from RT complications between pts who had a boost and those who did not
Ren et al[89]	2010	(A) BRT boost: 40 (B) EBRT alone: 101	Non mestatastic T2b	(A) 60 Gy (B) 66–70 Gy	12–20 Gy	NA	NA	(A) 97% at 5y (B) 80.2% at 5y	Xerostomia (A) 20% (B) 28.7% Middle ulceration/necrosis (A) 17.5% (B) 18.8%
Levendag et al.[90]	2013	(A) Vienna: 126 (B) Rotterdam: 72 (C) Amsterdam: 76	(A) T1,2N + 61; T3,4N0 + 65 (B) T1,2N + 34; T3,4N0 + 38 (C) T1,2N + 40 T3,4N0 + 36	(A) Vienna EBRT 76 Gy + BT boost + neadj & concomit CHT (B) Rotterdam EBRT 76 Gy + BT boost + neadj CHT (C) Amsterdam EBRT 76 Gy + concomit CHT (no boost)	11 Gy	All	NA	T1,2N + EBRT + BT 100% vs EBRT alone 90% T3,4N0 + EBRT + BT 89% vs EBRT alone 89%	NA
Ren et al.[78]	2014	(A) 2D-BRT boost: 101 (B) 3D-BRT boost: 118	T1-2a intracavitary T2b interstitial	56–62 Gy	Mean 12 Gy (8–20 Gy) 2.5–5 Gy/fr	(A) 26.7% (B) 28%	57.8 (33.9–117)	(A) 93.1% at 5y (B) 100% at 5y	G2 ulceration/necrosis: 3%
Rosenblatt et al.[71]	2014	(A) Induction CT and RT + CT: 139 (B) Induction CT and CT + RT + BRT: 135	(A) T3-4 N2-3: 24.5% (B) T3-4 N2-3: 26.7%	70 Gy	LDR: 11 Gy HDR: 9 Gy/3 fr	Neoadjuvant and concomitant	29 (2–67)	(A) 59.7% at 3y (B) 54.4% at 3y	G3-G4: (A) 21.6% (B) 24.4%

LC = local control (LC as freedom form tumour progression at last FU); FU = follow up; pt/pts = patient/patients; BRT = brachytherapy; CT = chemotherapy; EBRT = external beam radiotherapy; NA = not available.

Table 5 – Results of the main series of chordoma, chondrosarcoma and meningioma treated with proton radiation therapy.

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Munzenrider et al.[9]	1999	519/621 290 chordoma, 229 CS	Passive scattering	66–83 CGE Protons 4 fxs/week (1.92 CGE) Photons 1 fx/week (1.8 Gy)	41	5y LRFS 73% chordoma 80% CS 5y OS 80% chordoma 91% CS	Moderate to severe: - 3 death due to brainstem injury - 8 temporal lobe injury - 12 optic neuropathy Other toxicities reported: - hearing loss (2/3 of pts receiving ≥62.7 CGE to the cochlea), - endocrinopathy.	Postoperative high dose radiation therapy for skull base chordoma and low grade CS represent the best management with acceptable treatment related morbidity.
Hug et al.[91]	1999	58 33 chordoma, 25 CS	Passive scattering	65–79 GyE	33	5y LC and OS 59% and 79% (chordoma) and 75% and 100% (CS)	Late toxicity ≥ grade 3 (4/58; 7%) LENT SOMA: - 2 hearing impairment - 1 temporal lobe injury - 1 focal seizure	High dose proton RT offers excellent chances of lasting tumour control and survival with acceptable risks.
Igaki et al.[92]	2004	13 chordoma	Passive scattering	72 Gy (RBE)	69.3	5y LC rate 46% 5y OS rate 66.7% 5y DFS rate 42% LC higher for small tumours (<30 ml): 75% vs. 50% at 3y and 60% vs. 0% at 5y	Late ≥ grade 3: - 2 brain necrosis - 1 oral mucosa ulceration	PBR is effective for pts with skull base chordoma, especially for those with small tumours.
Noel et al.[10]	2005	88/100 chordoma	Passive scattering	RT median dose 67 CGE	31	2-y LC 86% 4-y LC 54% 2-y OS 94% 5-y OS 81% Independent prognostic factors of LC: - minimum dose to the tumour - tumour volume included n the 95% isodose	42 late toxicity: - 8 optic neuropathy - 11 neuropsychological disorder - 21 decreased hearing -16 pituitary dysfunction	The quality of PBR, reflected by homogeneity of the dose into the tumour volume is a major factor of LC.
Ares et al.[93]	2009	64 41 chordoma, 22 CS	Active spot scanning	Median total dose 73.5 Gy (RBE) for chordoma 68.4 Gy (RBE) for CS	38	5y LC - 81% chordoma - 94% CS 5y DFS - 81% chordoma - 100% CS 5y OS - 62% chordoma - 91% CS	94% 5-y freedom from high-grade toxicity Late toxicity ≥ grade 3 (CTCAE v. 3.0): - 2 optic neuropathy - 2 symptomatic temporal lobe damage	Spot scanning PBR is safe and offers high tumour control rates of skull base chordoma and CS, similar to passive scattering based PBR series.

Table 5 (*Continued*)

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
						Factors associated with low LC: - Brainstem compression - GTV > 25 ml		
Deraniyagala et al.[94]	2014	33 chordoma	Passive scattering	77.4–79.4 CGE	21	2y LC 86% 2y OS 92%	Unilateral grade 2 hearing loss toxicity in 18% of pts. No grade ≥2 optic or brainstem toxicities (RTOG/EORTC)	PBR is an effective treatment modality for skull base chordoma. Toxicity profile is acceptable.
Grosshans et al.[95]	2014	15 10 chordoma, 5 CS	Active spot scanning	Mean dose: 69.8 Gy (RBE) for chordoma 68.4 Gy (RBE) for CS	27	1 local recurrence 1 distant mts All pts alive at time of analysis	At 23 months 1 neurotoxicity grade 2 (numbness of the right lower lip) No other subacute or late toxicity recorded.	In comparison to passive scattering, spot scanning PBR improved high dose conformality. Treatments well tolerated.
Wenkel et al.[11]	2000	46 benign meningioma	Passive scattering	59 CGE	53	5y OS 93% 10y OS 77% Recurrence free rate 5y 100% and 10y 88%	1 pts died from brainstem necrosis 22 months after RT; Late toxicity ≥3: - ophthalmologic 4 pts - neurologic 4 pts - otologic 2 pts.	Combined proton and photon RT is an effective treatment for benign recurrent or postoperative residual intracranial meningioma.
Vernimmen et al.[96]	2001	23 meningioma	Passive scattering Stereotactic - SRT 5 pts - HSRT18pts	20.3 CGE (mean) for HSRT 57.9 CGE (mean) for SRT	31	HSRT: 88% radiological control SRT: 100% radiological control.	Late side effects HSRT: -1 ipsilateral hearing partial loss -1 temporal lobe epilepsy SRT: -1 short-term memory disturbance	Stereotactic PBR is effective and safe in controlling large and complex-shape skull base meningiomas.
Noel et al.[97]	2005	45/51 benign meningioma	Passive scattering	60.6 CGE	25.4	4y LC 98% 4y OS 100%	Late toxicity ≥ G3 (LENT SOMA): -1 hypophysis insufficiency -1 hearing loss required a hearing aid	Fractionated combined proton-photon irradiation is efficacy in the treatment of meningiomas, especially on cranial nerve palsies, without severe toxicity.
Boskos et al.[98]	2009	7/24 atypical and malignant meningioma	Passive scattering	64.24 (median) CGE for atypical 68 (median) CGE for malignant meningioma	48	5y OS 53.2% 5y LC 46.7% Mean local relapse free interval: 27.2 months	1 pt developed radiation necrosis 16 months after treatment	Postoperative combination of proton-photon PBR for atypical and malignant meningiomas is a well-tolerated treatment producing long-term tumour stabilization

Table 5 (*Continued*)

Author	Year of publication	N. pts	Technique	Dose and fractionation	Mean FU (months)	Outcome	Toxicity	Comments and authors conclusion
Halasz et al.[99]	2011	38/50 benign meningioma	Passive scattering SRS	13 CGE prescribed to 90% isodose line	32	3y actuarial tumour control rate 94% 5 radiological progression (median time to progression 48 months) 3/5 in field progression.	3/50 (5.9%) late toxicity: - 2 seizure - 1 panhypopituitarism	Proton SRS is effective for small benign meningiomas, with a potentially lower rate of long-term treatment related morbidity. Longer follow-up is needed to assess durability of LC and late effects
Slater et al.[100]	2012	72 cavernous sinus meningioma	Passive scattering	59 Gy (RBE) grade 2 57 Gy (RBE) grade 1 or no histological verification	74	5y actuarial LC rate 96% (99% in grade 1 or absent histological finding and 50% for those with atypical histology)	Toxicity: - 3 optic neuropathy - 2 post-treatment oedema (1 required surgical debulking) - 3 panhypopituitarism.	Fractionated PBR for grade 1 cavernous sinus meningiomas achieves excellent control rates with minimal toxicity regardless of surgical intervention or use of histologic diagnosis.
Weber et al.[101]	2012	32/39 meningioma	Active spot scanning	52.2–56 Gy (RBE), 1.8–2 Gy/fx	62	5y actuarial LC 84.8% OS 81.8% Adverse prognostic factors: WHO grade and tumour volume	Late side effects $\geq$ 3 (CTCAE v 3.0): - 3 brain necrosis/oedema interfering with daily living - 2 optic neuropathy (5y Grade $\geq$ 3 late toxicity free survival 84.5%)	PBR is a safe and effective treatment for pts with untreated, recurrent or incompletely resected intracranial meningiomas.
McDonald et al.[102]	2015	6/22 atypical meningioma	Active scanning	63 Gy (RBE)	39	5y LC 71.1% (5y LC 87.5% following dose > 60 Gy vs. 50% for $\leq$60 Gy) 5/22 developed in local tumour progression; all were in field. (median time to progression 20 months)	1 Grade 3 temporal lobe radiation necrosis.	Fractionated PBR is associated with favourable control rates for grade 2 meningiomas. Prospective studies are needed to define the optimal RT dose.

CS = chondrosarcoma; CGE = Cobalt Gray equivalent; fx = fraction; LRFS = local recurrence free survival; LC = local control; DFS = disease free survival; OS = overall survival; pt/pts = patient/patients; tox = toxicity; PBR = proton beam radiotherapy; RT = radiotherapy; SRS = stereotactic radiosurgery; SRT = stereotactic radiotherapy; HSRT = hypofractionated stereotactic radiotherapy; RBE = Relative Biological Effectiveness.

greater than 3.5 cm or with irregular margins, and less than 3–5 mm distance from the optic nerves or chiasm, and abutting the brainstem.[14,105] The ability of IMRT to achieve excellent dose distribution for the most complex targets allows moderate dose escalation to the tumour while respecting dose constraints.[106–108] Proton radiotherapy results in an even better capability to cover the target while sparing surrounding critical structures, especially in the case of tumours with challenging "L" and "C" shapes, compared to photon IMRT and SRT. Any radiation technique needs to be combined with an optimal surgical resection aiming at tumour debulking to reduce as much of the tumour volume as possible and at achieving the best geometrical configuration to facilitate the adequate target coverage.[109]

For benign tumour, several results of highly advanced photon techniques are satisfactory in terms of both outcome and toxicity. On the other hand, for malignant diseases in the base of skull, proton radiotherapy and, in selected cases, ion therapy can be considered the first treatment option and photons should be mainly reserved to patient that do not have access to particle therapy.[109]

The role of brachytherapy is mainly limited to the treatment of primary and recurrent nasopharyngeal carcinoma where it can significantly improve the therapeutic window.[110]

6. Conclusion

Photon radiotherapy plays a main role in the treatment of benign skull base lesions such as benign meningioma, IMRT being more often used for large and irregularly shaped lesions and SRT for small round lesions. For malignant tumours, such as chordoma and chondrosarcoma, proton radiotherapy should be the first option and photon techniques can be used when particle therapy is unavailable. Anyway, radiation therapy for skull base tumours requires a special expertise and a multidisciplinary team for an optimal management.

Conflict of interest

None declared.

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None declared.

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