Neuro-Oncology Practice

11(4), 369–382, 2024 | https://doi.org/10.1093/nop/npae040 | Advance Access date 29 April 2024

Controversies in neuro-oncology: Focal proton versus photon radiation therapy for adult brain tumors

Danielle B. P. Eekers, Catharina M. L. Zegers, Kamran A. Ahmed, Dante Amelio, Tejpal Gupta, Semi Ben Harrabi, Tomas Kazda, Daniele Scartoni, Clemens Seidel, Helen A. Shih, and Giuseppe Minniti

All author affiliations are listed at the end of the article

Correspondent Author: Giuseppe Minniti, MD, PhD, Department of Radiological Science, Oncology and Anatomical Pathology, Sapienza University, Policlinico Umberto I Hospital, Rome, Italy (giuseppe.minniti@uniroma1.it).

Abstract

Radiation therapy (RT) plays a fundamental role in the treatment of malignant and benign brain tumors. Current state-of-the-art photon- and proton-based RT combines more conformal dose distribution of target volumes and accurate dose delivery while limiting the adverse radiation effects. PubMed was systematically searched from from 2000 to October 2023 to identify studies reporting outcomes related to treatment of central nervous system (CNS)/skull base tumors with PT in adults. Several studies have demonstrated that proton therapy (PT) provides a reduced dose to healthy brain parenchyma compared with photon-based (xRT) radiation techniques. However, whether dosimetric advantages translate into superior clinical outcomes for different adult brain tumors remains an open question. This review aims at critically reviewing the recent studies on PT in adult patients with brain tumors, including glioma, meningiomas, and chordomas, to explore its potential benefits compared with xRT.

Keywords:

brain tumors | chordomas | gliomas | meningiomas | proton beam | radiotherapy | radiosurgery

Radiation therapy (RT) is an essential and effective part of the management of adult brain tumors. There is a desire within the RT community to further reduce side effects and at the same time maintain or even improve local control of treated tumors. Radiation dose and fractionation schedules depend on the type, volume, and location of the tumor. Over the past decades, several significant technical developments in photon RT (xRT), such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and stereotactic radiotherapy (SRT) have permitted the delivery of more conformal radiation doses to the target while reducing the dose to the surrounding normal tissue compared to conventional three-dimensional (3D) conformal RT (3D-CRT) techniques. In addition, the integration of new technology, eg, 6°C of freedom (6DoF) couch, multileaf-collimator (MLC), new immobilization devices, and continuous imaging monitoring in the treatment room during xRT, so-called image-guided RT (image-guided radiation therapy), has led to an increase in the precision and accuracy of radiation delivery.[1,2]

Proton therapy (PT) has emerged as an alternative radiation treatment modality that directs charged particles instead of photons at the tumor. The main advantage of PT is the deposition of little energy before the end of the proton range where the highest energy deposition is within the target volume (Bragg peak) and minimal residual radiation beyond the target.[3,4] Thanks to these physical characteristics, PT may offer superior dose distribution. In particular, the dose to the surrounding organs at risk (OARs) can significantly be reduced while maintaining the same equivalent dose to the target.[5,6] Advances in proton technology and decreasing equipment costs have led to the expansion of proton beam facilities and increased use of this modality. Currently, there are around 9.000 linear accelerators (LINACs) compared to over 120 PT centers in operation worldwide (https://ptcog.site). Although the number of patients receiving PT for a brain tumor is

increasing, the major obstacles regarding its use in clinical practice are less availability, lack of randomized studies comparing PT with xRT, and the current greater cost of PT treatment.

In the absence of randomized trials, the potential clinical superiority of PT over xRT in patients with brain tumors remains a matter of debate. The main question is if substantial improvements in the dose distribution observed with protons may provide a clinical benefit for patients with either malignant or benign brain tumors. This review summarizes the literature regarding the role of focal PT in adult patients with brain tumors, discusses its potential advantages compared to xRT for different types of primary brain tumors, and identifies areas of research that need further investigation, eg, reduction of long-term side effects using PT and dose escalation for resistant tumors.

Material and Methods

We conducted a search in PubMed to identify studies reporting outcomes related to treatment of central nervous system (CNS)/skull base tumors with PT in adults (≥18 years). The following combinations of keywords were searched, but not limited to: "radiation therapy," "PT," "brain tumors," "chordoma," "chondrosarcoma," "glioma," "meningioma," "schwannoma," "pituitary adenoma," and "craniopharyngioma." Search was limited to papers published in English language from 2000 to October 2023. Clinical trials, original research, review articles, and case series with at least 10 patients were included, and reference lists were carefully explored for relevant papers that would have been missed by electronic search. D.A. and D.S. conducted the database review and selection of studies containing relevant data on clinical outcomes following PT. Finally, 57 papers were discussed qualitatively, and the discussion was supplemented by expert commentary from the authors.

Advances in Photon and Proton RT

Photon radiation techniques have evolved from 3D-CRT to IMRT and stereotactic techniques, including either stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT).[2,7] Compared to 3D-CRT, IMRT improves dose conformity to the target while minimizing radiation exposure to OARs. A further evolution of IMRT technique is represented by volumetric arc therapy (VMAT), where the radiation dose is continuously delivered as the gantry of the LINAC rotates around the patient through single or multiple arcs. For stereotactic techniques, the radiation dose is delivered as single-fraction SRS (commonly 13–22 Gy fractions) or fractionated SRT, using either hypofractionated (3–12 Gy fractions) or conventionally fractionated (1.8–2.0 Gy fractions) schedules. A submillimetric accuracy of patient repositioning can be achieved using a frame-based or a frameless mask-based immobilization system.[8–10] Accurate monitoring of patient positioning in the treatment room is achieved using advanced image-guided radiation therapy technologies, such as orthogonal x-rays (ExacTrac®Xray 6°C of freedom (DoF) system) and cone beam computed tomography,[8,11,12] and surface-guided radiation therapy.[13,14] In clinical practice, IMRT and VMAT are recommended in patients with large, irregularly shaped, and/or invasive brain tumors, whereas focal techniques such as SRS and SRT are typically used for smaller tumors.

Protons present the remarkable characteristics of having a finite range in tissue, lower integral dose with marginal exit dose, and maximal dose deposition just at the end of range, conveniently in the intended target (ie, Bragg peak). Protons can be delivered with passive scattering by using a range shifter wheel and patient-specific apertures and compensators. However, with modern techniques, proton dose dosimetry optimization can be achieved such as pencil beam scanning using a focused proton beam of variable energy and intensity which is magnetically scanning across the treated volume. Using intensity-modulated PT (IPMT) the intensities of beamlets are modified throughout the target volume (active scanning) achieving the desired dose distributions around complex critical structures, allowing improved conformality and sparing of these structures without compromising target coverage.[15,16] An example of an IMPT treatment plan and a photon volumetric-modulated arc therapy (VMAT) for a skull base meningioma is shown in Figure 1.

Daily image-guidance is necessary to ensure that the patient position for daily treatment matches anatomically with the initial planning CT set-up and facilitates adaptation of planning or delivery parameters to match geometric deformation or tissue changes that can occur during a typical course of fractionated radiotherapy.[17,18] Image-guidance for proton beam delivery is of high importance, since density changes influence the dose distribution to a much larger extent than in xRT. The advent of cone-beam CT (cone-beam computed tomography) technology facilitating three-dimensional (3D) volumetric in-room imaging has been a game-changer for image-guidance on modern PT systems.[17,18]

In addition to planar or volumetric imaging, visual image-guidance can also be used for delivery verification through external markers (reflective spheres) placed at relevant locations on the patient's skin that can be tracked prior to and during treatment delivery (gating) or 3D-mapping of the patient's surface generated through a computer that can be localized with surface imaging systems.[13,14,19]

Gliomas

In adults with glioma, existing evidence regarding the superiority of PT over xRT in terms of efficacy and toxicity is, in the absence of large prospective randomized trials, controversial. Most studies reporting on PT focus on lower grade gliomas (WHO 2 and 3),[20–28] whereas only a few studies include patients with glioblastoma (GBM)[29–31] or those receiving reirradiation for recurrent tumors[32–36]; however, no reliable assessment of grading could be made because of the lack of molecular markers (eg, diffuse isocitrate dehydrogenase, IDH1) information in most older studies. Selected series describing the efficacy and toxicity of PT in patients with low-grade and high-grade gliomas are shown in Table 1 (20, 23,25,26,28–31,33–36).

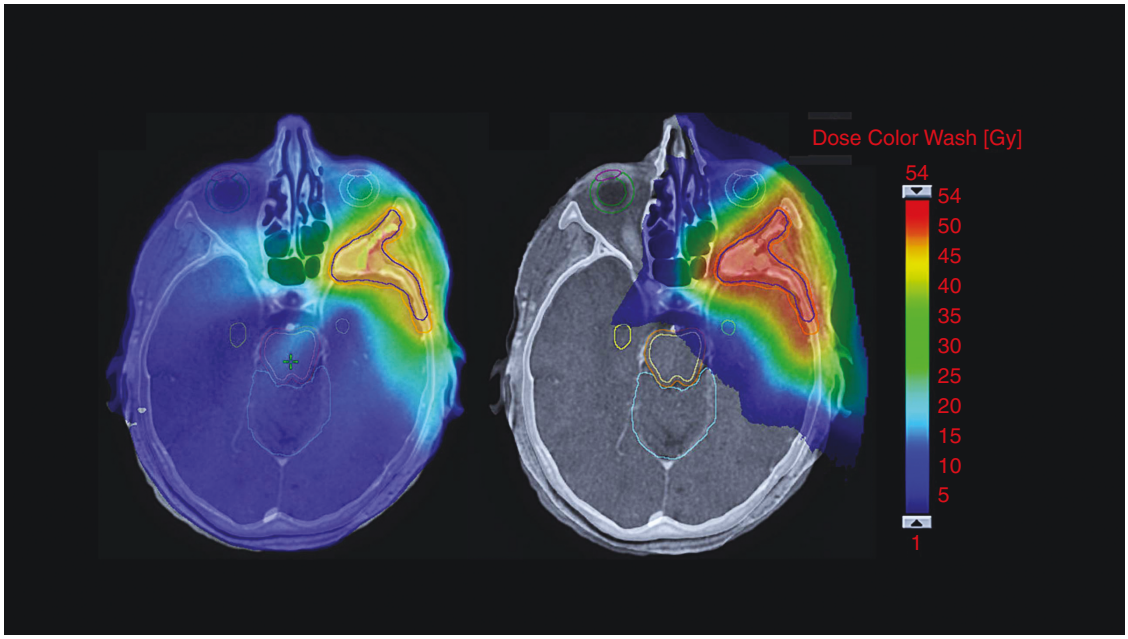

Figure 1. Example of radiation treatment plan for a post-operative patient with a base of right skull meningioma. The gross tumor volume (GTV) is presented in dark blue and the clinical target volume CTV in red. The following organs at risk (OARs) have been contoured according to Eekers et al. (): hippocampi (yellow), brainstem,_interior (yellow), brainstem,_surface (orange), retina (light green), cornea (purple), cerebellum_(cyan). Dose distribution in Gy ranging from low dose depicted in blue to high dose in red are given for xRT volumetric-modulated arc therapy (A) and proton therapy IMPT (B) (robust) treatment plans in the axial view.

Grade 2 and 3 Gliomas

The current standard treatment of most adults with adult-type IDH mutant (IDH_{mt}) grade 2 and 3 astrocytoma and oligodendroglioma requiring post-surgical treatment involves xRT followed by chemotherapy (CT) Procarbazine, Lomustine and Vincristine (PCV) or Temozolomide chemotherapy (TMZ).[37] Data from controlled prospective studies have demonstrated the superiority of combined treatment over RT alone for either grade 2 and 3 gliomas.[38–46] In the phase III NRG Oncology/RTOG 9802 trial in which 251 patients with low-grade glioma were randomized between xRT (54 Gy/30 fractions) versus xRT plus PCV, Buckner et al.[43] observed 10-year overall survival rates of 40% and 60% after xRT and xRT + PCV, respectively. The survival benefit was observed in patients with either IDH_{mt} astrocytoma or oligodendroglioma but not in those with IDH-wild-type (IDH_{wt}) tumors.[45] Improved overall survival after combined radiotherapy (59.4 Gy in 1.8 years fractions) and PCV or temozolomide over radiotherapy alone has been demonstrated for either grade 3 astrocytomas or oligodendrogliomas in 3 phase 3 RTOG and EORTC randomized trials.[41,42,46]

Concerning PT, both prospective[20,22,26,27] and retrospective[21,23–25,28] published studies have evaluated the use of PT in patients with grades 2 and 3 gliomas. While the older publications had relatively small sample sizes,[20,23,29] the most recent publications provide results for more than 100 patients.[25,27,28] Most treatments were given with a median of 54 Gy relative biological effectiveness (RBE), while WHO 3 gliomas were treated with a higher median dose of 60 Gy_{RBE}.

The reported 5-year overall survival for grade 2 and 3 gliomas varied from 23% to 87%, with more recent publications observing a better 5-year overall survival of around 85% in grade 2 tumors and 67% in grade 3 tumors. Unfortunately, combinations of proton treatment with chemotherapy are not precisely stated in most of the studies. Comparative analysis of the existing data of photons and protons appears somewhat inadequate due to the significant heterogeneity of applied treatment regimens and included molecular tumor subtypes. Then, the increased efficacy of PT remains to be proven. Currently, multiple research groups are investigating the proton-Immunotherapy combination in the treatment of lung, head, neck, and brain tumors. Further evaluation is warranted to validate preclinical findings in a clinical context.[47] Controlled trials, including the German GlioProPh trial (NCT05190172) and the US NRG BN005 trial on IMPT versus IMRT (NCT03180502) should provide an adequate comparison to address answer the question of the superiority of proton vs. photon treatment in low-grade gliomas.

With regards to toxicity, proton treatment shows potential regarding reducing the dose to the surrounding tissue. Dosimetric studies comparing PT and conventional xRT show better sparing of relevant CNS structures with protons[3,5,48]; however, clinical validation of this assumption on a large scale is still lacking. In the clinical series reported in Table 1 severe toxicity ≥ grade 3 as defined by the common terminology criteria for adverse events was rare. In 6 studies including 503 patients with grade 2 or 3 glioma who received PT, the reported acute toxicity ≥ grade 3 was < 1%.[20,23,25,26,28,29] Most studies do not report results

Table 1. Selected Published Series of Proton Beam Therapy for Newly Diagnosed and Recurrent Gliomas

Reference	Institution	Period	Patients (*n*) (WHO grade)	Median dose (GyRBE)	Technique	Median follow-up (months)	PFS (months)	OS (months)	RN
Fitzek et al. 2001[20]	MGH	1993–1996	20 (G2-3)	G2, 68.2 G3,79.7	PS + PH	NR	NR	G2,71% at 5 y G3,23% at 5 y	35% any grade
Mizumoto et al. 2010[29]	Tsukuba PTC	2001–2008	20 (G4)	50.4/73.5/ 96.6*	PS	24.6	NR	71.1% at 1 y 45.3% at 2 y	No G3
Badivan et al.2017	PSI	1997–2014	28 (G1-2)	54	AS	30.7	56% at 3 y	83.4% at 3 y	4% G3
Kamran et al. 2019[25]	MGH	2005–2015	141 (G1-3)	54	PS	46.7	60% at 5 y	84% at 5 y	NR
Tabrizi et al.2019 *[26]	MGH	2006–2010	20 (G2)	54	PS	78	39% at 6 y	79% at 6 y	9% G3
Kong et al. 2020[30]	Shanghai PTC	2015–2018	50 (G3-4)	(60) + boost^	AS	14.3	59.8% at 18 months	72.8% at 18 months	22% G1-2, No G3
Brown et al. 2021[31]	MDACC	2016–2019	67 (G4)	60	29 AS/PS 39 pIMRT°	48.7	G4 6.6 (pRT) G4 8.9 (IMRT)	G4,21.2 (IMRT) G4 24.5 (pRT)	No G3 in both groups
Eichkorn et al. 2022 *	HIT	2010–2020	194 (G2-3)	G2, 54 G3, 60	AS	61	G2, 60% at 5 y G3, 30% at 5 y	G2, 85% at 5 y G3, 67% at 5 y	4% G3 RICE
Galle et al. 2015[33]	Indianapolis PTC	2005–2012	20 (G2-4)	54-59.4**	PS	NR	NR	G3, 10.2 G4, 8.2	10% G1-2, No G3
Saeed et al. 2020[34]	PCG	2012–2018	45 (G4)	46.2**	AS/PS	10.7	13.9	14.2	11% G3
Scartoni et al. 2020[36]	Trento PTC	2015–2018	33 (G4)	36**	AS	NR	5.9, 45% at 6 months	8.7, 33% at 1 y	9% G1-2, No G3;
Gulidov et al. 2021[35]	Obninsk PTC	2016–2019	44 (G2-4)	55** (EQD2)	AS	NR	30.5% at 1 y 10.2% at 2 y	49.6% at 1 y 35.1% at 2 y	6.8% any grade

WHO, world health organization; RBE, relative biological effectiveness; MGH, Massachusetts General Hospital; PS, passive scattering; AS, active scattering; PH, photon radiotherapy; y, years; OS, overall survival; RN, radiation necrosis; NR, not reported; PSI, Paul Sherrer Institute; MDACC, MD Anderson Cancer Center; *, 50.4 to the planning target volume (PTV), 73.5 to PTV2, 96.6 to PTV3; HIT, Heidelberg Ion-Beam Therapy Center; PFS, progression-free survival; G, grade; RICE, radiation-induced contrast, enhancements; PTC, Proton therapy center; ^ carbon-ion radiotherapy boost (26 patients); pIMRT, photon intensity-modulated radiotherapy; EQD2, radiation dose converted to the equivalent dose in 2-Gy fraction; PCG, Proton Collaborative Group; **, Recurrent gliomas.

on quality of life (QoL) and neurocognitive outcomes. Regarding the risk of late radiation-induced toxicity, any grade radionecrosis was observed in up to 35% of patients, with ≥ grade 3 radionecrosis ranging from 0% to 9% (Table 1). Related to radiation necrosis and of particular interest is the phenomenon of radiation-induced contrast enhancement (RICE) on MRI, which is observed in 17%–29% of patients following PT.[27,28] In the series of Eichkorn et al.,[28] RICE was associated with grade 3 common terminology criteria for adverse events toxicity in 4% of 194 patients, with no ≥ grade 3 toxicity observed. In the study from Harrabi et al.,[27] symptomatic RICE occurred in 1% of the cases, and a similar low incidence of ≥ grade 3 toxicity was seen in other large studies.[49] However, it needs to be stated that detection of RICE symptoms requires a standardized follow-up including neuropsychologic testing that has not been performed in the mentioned series. Potential long-term detrimental effects of RICE, eg, on neurocognition, need to be examined in future research. Neurocognitive effects after PT were studied by Sherman at al. in 20 adult patients with low-grade glioma up to 5 years after treatment. Patients remained stable in cognitive function, and authors hypothesize that PT may contribute to the preservation of cognitive functioning.[50]

It can be concluded that lower rates of symptomatic toxicity following PT for lower-grade gliomas have been observed in recent publications, assuming that technological improvements over the last 20 years have increased the quality of treatments. However, controlled comparative studies for prospective monitoring of short- and long-term toxicity and neurocognitive and QoL outcomes are urgently needed. The high prevalence of contrast-enhancing lesions on MRI after treatment should be carefully evaluated and closely monitored.

Glioblastoma

With standard chemoradiation for primary GBM involving xRT and concomitant and adjuvant temozolomide, reported median time and 1-year rate OS are around 22 months and 70%, respectively, in patients with

methylated O^6-Methylguanine-DNA methyltransferase (MGMT) promoter, and 12.7 months and 50%, respectively, in patients with unmethylated MGMT promoter.[51] The use of PT in patients with newly diagnosed GBM has been described in a few prospective and retrospective studies.[29–31] In a recent randomized prospective phase II trial comparing PT and xRT in 90 patients with newly diagnosed GBM, Brown et al.[31] failed to show the superiority of PT regarding its primary endpoint of neurocognitive failure and survival. With a median follow-up of 48.7 months, there was no difference in progression-free survival in 67 evaluable patients (HR, 0.74; 95% CI: 0.44–1.23; $P = .24$) or overall survival (HR, 0.86; 95% CI: 0.49–1.50; $P = .60$). Furthermore, there was no significant difference in time to cognitive failure between treatment arms (HR, 0.88; 95% CI: 0.45–1.75; $P = .74$). PT was associated with a lower rate of fatigue (24% vs 58%, $P = .05$), but otherwise, there were no significant differences in patient-reported outcomes at 6 months. In a small prospective phase I/II trial of 20 patients with supratentorial GBM, Mitzumoto et al.[29] investigated the efficacy and safety of hypofractionated PT (28 × 1,8 Gy) with concomitant boost (14 × 1,65 Gy_{RBE}). The median OS time and 1-year survival rate were 21.6 months and 71%, respectively, suggesting that dose escalation with PT might have potential to improve survival. Acute hematologic toxicity was observed in half of the patients, which was mainly attributed to the treatment with nimustine. No grade ≥ 3 radiation-induced acute toxicity occurred, with late radiation necrosis and leukoencephalopathy that was reported in only one (5%) patient. In another series of 50 patients with GBM or anaplastic glioma treated with either PT (30 × 2 Gy_{RBE}) or PT plus carbon-ion boost, Kong et al.[30] observed 1-year overall survival rates of 87.8% for the whole population and 77.4% for patients with GBM. Radiation necrosis occurred in 22% of patients, with no ≥ 3 toxicity observed. Mohan et al.[52] specifically investigated the differences in radiation-induced > grade 3 lymphopenia in patients with GBM. The strongest predictors were sex, baseline absolute lymphocyte count and whole brain V20. Due to the reduced brain volumes receiving a low/intermediate dose, PT consequently reduced the chance of grade 3 lymphopenia. In the absence of high-quality evidence, it remains controversial if there is any superiority of PT over xRT in terms of efficacy and toxicity.[35] Currently, a phase 3 trial (GRIPS trial) conducted in Germany is evaluating cumulative toxicity and survivals in patients with newly diagnosed glioblastoma treated with either modern photon radiation techniques (standard arm) or proton beams (experimental arm).[53]

Reirradiation

There is limited literature available on the use of PT for reirradiation in patients with adult diffuse gliomas.[31–34,36] Using doses of 36 to 54 $Gy_{RBE,}$ the median progression-free survival after PT reirradiation reported in 4 studies including 142 patients was between 5.3 to 9.3 months; median overall survival time and 1-year survival rates ranged from 8.2 to 14.1 months and from 33% to 58%, respectively (Table 1). The reported median survival time following single-fraction SRS, hypofractionated SRT, and conventional fractionation seen in published studies is similar. Reirradiation was well tolerated, with acute treatment-related toxicity that was generally mild and no grade 3 acute toxicities. Grade 3 radionecrosis has been observed in 6.8% to 11% of patients, being similar to those observed following photon reirradiation using the same radiation doses.[54] No grade 4 or 5 toxicity has been reported in all studies. Scartoni et al.[36] have assessed the QoL in 33 patients treated with PT for a recurrent GBM. Proton reirradiation was able to preserve the health-related quality of life (HRQoL) in the majority of patients until disease progression, with all pre-selected domains being stable or improved, eg, global health, social functioning, and motor dysfunction.

Meningiomas

Grade 1 Meningiomas

xRT given as SRS or SRT is frequently used to improve local control after incomplete resection of a large and symptomatic grade 1 meningioma arising at unfavorable locations or small asymptomatic meningiomas patients not in need of invasive surgery.[55] Following a dose of 50–57.6 Gy given in 30–33 fractions, local tumor control rates reported in recent large retrospective series range from 90% to 100% at 5 years.[56] In a series of 507 patients with a skull base meningioma who received conventionally fractionated SRT ($n = 376$) or IMRT ($n = 131$), Combs et al.[57] have observed equivalent local control rates of 91% at 10 years for patients with a benign meningioma and similar tumor control rates have been observed in other large published series.[58–60] Depending on tumor location, long-term toxicity includes hypopituitarism in 5%–15% of patients and decreased visual acuity or visual field defects in 0%–3% of irradiated patients; other adverse radiation effects such as cranial deficits or neurocognitive impairment are rarely reported; however, no results of neurocognitive formal testing have been reported in published studies. Using single-fraction SRS doses of 13–15 Gy, reported tumor control rates are in the range of 90%–95% at 5 years and 80%–90% at 10 and 15 years, with a variable improvement of neurological functions seen in up to 60% of patients.[58,61–63] The rate of adverse effects is < 8% in most published series, including radiation-induced optic neuropathy and transient or permanent damage of cranial nerves located in the cavernous sinus (III, IV, and VI cranial nerves). Fractionated SRS (2–5 daily fractions) has been employed as an alternative to single-fraction SRS for relatively large meningiomas in close proximity 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 was associated with no ≥ 3 cranial nerves toxicity.[64,65]

Several studies published in the years 2001 to 2022 evaluated the efficacy of PT in patients with grade 1 meningiomas.[66–80] Selected series of PT are shown in Table 2.[68–71,73,74,76–81] Following conventionally fractionated doses of 50.4 to 61 Gy_{RBE}, 5-year local control rates of 71%

Table 2. Selected Published Series of Proton Beam Therapy for Grade 1–3 Meningiomas

Reference	Institution	Period	Patients (tumor type)	Median dose (GyRBE)	Technique	Median follow-up (months)	Local control	Overall survival	Toxicity ≥ G3
Noel et al. 2005	CPO	1994–2000	G1, 51	60.6*	PS	21	98% at 4 y	100% at 4 y	4%
Slater et al. 2012[69]	Loma Linda	1991–2012	G1,72	59	PS	74	99% at 5 y	99% at 5 y	4%
Murray et al. 2012	PSI	1997–2015	G1, 61 G2, 35	54 62	AS	56.9	95.7% at 5 y 68.5% at 5 y	92.1% at 5 y 80.7% at 5 y	10.9 %
El Shafie et al. 2018[71]	Heidelberg	2010–2014	G1, 60	54	AS	51	96.6% at 5 y	96.2% at 5 y	Acute (1.8%), Late (3.8%)
Champeaux-Depond et al. 2021[73]	SNDS	2008–2017	G1, 171 G2, 13 G3, 9	54 54	PS	52	G1, 71.5% at 5 y, G2, 55.6% at 5 y, G3, 35.6% at 5 y	G1, 93% at 5 y, G2, 77.4% at 5 y, G3, 44.4% at 5 y	NR
Holtzman et al. 2023[74]	Florida	2007–2019	G1, 59	50.4	PS	76	94% at 5 y,	87% at 5 y	3%
Halasz et al. 2011[75]	MGH	1996–2001	G1, 50	13 (sf-SRS)	PS	32	94% at 3 y,	100% at 3 y	G2, 5.9%, G3, 0%
Vlachogiannis et al. 2017[80]	Uppsala	1994–2007	G1, 170	14-46/3-8 fractions	PS	84	85% at 10 y	98.3% at 10 y	Any grade, 9.4%, G3, 1%
Hug et al. 2021	PSI Florida	1973–1995	G2-3, 56	62.5	PS	59	G2, 38% at 5 y G3, 52% at 5 y	G2, 89% at 5 y G3, 51% at 5 y	9%
Boskos et al. 2021	CPO	1999–2006	G2-3, 24	68*	PS	45.5	46.7% at 5 y	53.2% at 5 y	NR
McDonald et al. 2021	Indianapolis	2005–2013	G2, 35	63	PS	39	71.1% at 5 y	100% at 5 y	4.5%

CPO, Orsay Proton therapy Center; PSI, Paul Scherrer Institute; CNAO, Centro Nazionale di Adroterapia Oncologica; CH, chordoma; CS, Chondrosarcoma; *combined PT/PH regimens; ^dose adaptative protocol; **NCDB, National Cancer Database; NR, not reported; y, years; h-PIT, hypopituitarism; DSS, disease-specific survival.

to 99% have been reported in 8 retrospective series that include 634 patients (Table 2).[68–71,73–75,79,80] In a study of 51 patients with grade 1 meningioma treated at Paul Scherrer Institute, clinical improvements were noted in 68.8% of patients with eye-related symptoms and 67% of patients with other symptoms within 24.0 months after treatment. Radiation-induced toxicity, including visual adverse events and brain necrosis, has been observed in less than 5% of patients. In another series of 44 patients with grade 1 meningioma randomized to receive 55.8 or 63.0 Gy_{RBE} at the Massachusetts General Hospital from 1991 to 2000, 3 patients had local recurrence in the 55.8 Gy(RBE) arm and 2 in the 63 Gy_{RBE} arm, resulting in tumor control rates at 15 years of 85% and 95%, respectively. A total of 26 patients (59%) experienced a grade 2 or higher late toxicity, including 9 patients (20%) who had a cerebrovascular accident.

A similar 5-year local control of 88%–94% has been reported following either hypofractionated stereotactic PT or proton SRS.[75,80] In a series of 170 WHO grade I meningioma patients treated with hypofractionated (3–4 Gy_{RBE} per fraction) PT, Vlachogiannis et al.[81] observed progression-free survival rates of 93% and 85% at 5 and 10 years, respectively. Radiation-induced adverse events were seen in 9.4% of patients. The most common toxicity was hypopituitarism, while radiation necrosis was observed in 2.9% of patients. Overall, both xRT and PT offer excellent local control in grade 1 meningiomas and this is associated with acceptable toxicity. In the absence of randomized trials, the superiority of one technique over another remains unproven. In this regard, the COG-PROTON-01 trail randomizing PT versus xRT in 160 patients with cavernous sinus meningioma has been planned in France (NCT05895344).

Grades 2 and 3 Meningiomas

RT is an important component of the therapeutic armamentarium for the treatment of patients with atypical (grade 2) meningiomas. Results of postoperative RT for grade 2 meningiomas after gross total resection have been reported in 2 prospective phase II trials recently published by the RTOG and the EORTC.[81–83] Using a dose of 60 Gy given in 30 fractions, the estimated 3-year PFS for 60 patients evaluated in the EORTC trial was 88.7%, with a late toxicity of grade 3 or more observed in about 14% of patients. A similar PFS of 93.8% was observed in the RTOG trial using doses of 54 Gy given in 30 fractions, with adverse events that were limited to grades 1 and 2 only.

Vagnoni et al.[84] have conducted a recent review on the efficacy and toxicity of adjuvant RT in patients with either grade 2 or 3 meningiomas. For grade 2 meningiomas, the reported 5-year PFS and OS rates were around 82% and 79%, respectively, using doses of 54–60 Gy given in 1.8–2 Gy per fraction. For patients with grade 3 meningiomas, the reported 3-year PFS and OS rates ranged from 30% to 60%, and from 35% to 70%, respectively, using median doses of 60 Gy given in 2 Gy fractions.[82–88]

Currently, no studies have prospectively compared xRT and PT in patients with grades 2 and 3 meningiomas. Table 2 shows selected retrospective studies published between 2000 and 2021 reporting the outcome of PT in 171 patients with atypical and malignant meningiomas.[70,73,74,77,78] The 5-year local control and overall survival rates range from 38% to 71% and 53% to 100%, respectively for grade 2 tumors and from 35.6% to 52% and from 44.4% to 51%, respectively, for grade 3 tumors. A similar mean local control rates of 59.6% at 5 years has been observed by Coggins et al.[89] in a systematic review including 6 studies with 82 patients with grades 2 and 3 meningiomas who received PT. Acute and late ≥ 3 toxicities occurred in less than 10% of patients. A prescribed dose of more than 60 Gy has been associated with better clinical outcomes.

Because of the retrospective nature of studies and the small number of patients reported in published studies, no conclusions can be drawn regarding the respective efficacy of PT and xRT in the setting of grades 2 and 3 meningiomas. Randomized controlled studies with larger sample sizes comparing photons and proton RT are necessary to prove the superiority of a technique over another in terms of efficacy and safety.

Cranial Base Chordomas and Chondrosarcomas

Chordomas and chondrosarcomas are often grouped together because of their similar appearance on imaging, similar appearance on histopathological examination and similar biological behavior.[90,91] However, the tumors are significantly different in origin and response to treatment. Chordomas are rare, locally aggressive slowly growing bone tumors that are developed from the notochord remnant in clivus of sphenoid bone and are diagnosed typically in adults between the ages of 40 and 70 years, commonly presenting by headache and diplopia. The typical localization is within the midline axial skeleton with about one-third of cases arising in the clivus, other common localizations are sacrococcygeal or mobile spine (not discussed here). Chondrosarcomas are also rare malignant tumors but arise within cartilaginous structures (chondrocytes surrounded by cartilage matrix), typically arising in more lateralized locations, and account for approximately five percent of all skull base tumors. Their distinction in diagnosis from chordomas is crucial due to their better prognosis.

The therapeutic approach to chordoma and chondrosarcoma has traditionally been surgery, followed by RT unless a truly complete resection has been performed with a low probability of residual microscopic disease.[92,93] Maximal safe surgical resection is essential to verify the disease, reduce tumor burden, and optimize results with adjuvant RT. Unfortunately, due to the localization of the lesion in the proximity of critical neurovascular structures around the skull base, radical resection of these tumors is only possible in a subset of patients, typically those with smaller tumors. Recurrence occurs in more than half of chordomas and in a slightly smaller number of chondrosarcomas. Thus, postoperative RT is indicated in most patients with these diseases with the possibility of postoperative surveillance only in selected cases of low-grade well-differentiated chondrosarcomas after comprehensive resection.[92,93]

Even though no randomized trials comparing different radiation techniques are available, PT has been historically recommended for virtually all patients with chordomas and chondrosarcomas because the high radiation doses needed for local control historically could not be safely given with photon therapy. For these tumors, the administration of the recommended doses varies from 60 to 76 Gy for chondrosarcomas and from 70 to 80 Gy for chordomas, while often compromising target coverage to respect dose-volume constraints for surrounding normal structures, eg, of the brainstem and cranial nerves, was difficult to obtain with conventional xRT.

A few systematic reviews focusing on the efficacy and safety of PT in patients with chordoma and chondrosarcoma[94–97] showed a 5-year local control rates of around 65% to 85% for chordomas and 90% to 94% for chondrosarcoma, respectively. We have identified eight studies published between 2005 and 2023 including more than 100 patients with chordomas or chondrosarcomas (Table 3).[98–103] With a median dose ranging from 63 to 78.4 Gy_{RBE}, the reported 5-year local control rates range from 61% to 75% and from 93% to 96%, respectively, for chondromas and chondrosarcomas; respective 5-year OS rates range from 78% to 91% and 95%, respectively. Grade 3 or higher adverse radiation effects are reported in about 10% of patients; however, hypopituitarism may occur in up to 37% of patients in three studies (Table 3). Regarding different PT techniques, clinical outcomes are similar for patients treated with pencil beam PT compared with those receiving passive scattering PT. Doses > 68–70 Gy in 2 Gy fractions are typically recommended, being slightly higher for chordomas (up to 73.8 Gy).

The role of xRT, either SRT or SRS, in patients with chordomas or chondrosarcomas has been investigated in previous published systematic reviews.[56,94,104,105] In contrast with old studies reporting local control rates in the range of 17%–41% at 5 years following conventional RT,[106–109] new radiation techniques offer improved clinical outcomes[110–115]; however, the reported 5-year local control rates remain lower than those observed after PT. Using IMRT with a median dose of 76 Gy for chondroma and 70 Gy for chondrosarcoma given in 2 Gy fractions, Sahgal et al.[110] reported 5-year survival rates of 85.6% and 84.1%, respectively, in 24 patients at a median follow-up of 36 months. The 5-year cumulative incidences of local failure were 34.7% and 11.9% for the chordoma and chondrosarcoma cohorts, respectively.

Debus et al.[111] observed 5-year overall survival and local control rates of 82 and 50%, respectively in 37 patients

Table 3. Selected Published Series of Proton Beam Therapy for Chordomas and Chondrosarcomas

Reference	Institution	Period	Patients (Tumor type)	Median dose (GyRBE)	Technique	Median follow-up (months)	Local control	Overall survival	Toxicity ≥ G3
Noel et al. 2005	CPO	1993–2002	100 (CH)	67 (PH + PT)	PS	31	86.3% at 2 y, 53.8% at 4 y	94.3% at 2 y, 80.5% at 5 y	Acute, 100%; late, 42% any grade
Weber et al. 2016[99]	PSI	1998–2012	222 (CH/CS)	72.5	AS	50	CH, 70.9 at 7 y; CS, 93.6% 7 y	CH, 72.9% at 7 y; CS, 94.1% at 7 y	8.1% late
Feuvret el al. 2016[100]	CPO	1996–2013	159 (CS)	70.2	PS/PH + PT	77	96.4% at 5 y, 93.5% at 10 y	94.9% at 5 y, 87% at 10 y	6.9% late
Fung et al. 2018	CPO	2006–2012	106 (CH)	73.8/72/ 70.2/68^	AS/PS/ PH + PT	61	88.6% at 2 y, 75.1% at 5 y	99% at 2 y, 88.3% at 5 y	7% at 5 y; h-PIT 16%
Weber et al. 2018[82]	PSI + CPO	1996–2015	251 (CS)	70.2	AS/PS	87.3	NR	93.6% at 7 y	15.1% late, h-PIT 37%
Holtzman et al. 2021[101]	Jackson-ville, Florida	2007–2019	112 (CH)	73.8	AS/PS/ PH + PT	52	74% at 5 y	78% at 5 y	5% RN; h-PIT 17%
Nunna et al. 2022[102]	NCDB**	2004–2016	159 (CH)	NR.	NR.	NR.	NR	85.4% at 5 y	NR
Mattke et al. 2023[103]	HIT	2006–2019	111 (CI) 32(PT)	66/20 (CI) 74 (PT)	PS	49.3	65% at 5 y, 61% at 5 y	83% at 2 y, 91% at 5 y	G1-3, 29.8% G1-3, 31%

CPO, Orsay Protontherapy Center; PSI, Paul Scherrer Institute; CNAO, Centro Nazionale di Adroterapia Oncologica; CH, chordoma; CS, Chondrosarcoma;*different PT/PH regimens; ^dose adaptative protocol; **NCDB, National Cancer Database; NR, not reported; y, years; h-PIT, hypopituitarism.

with skull base chordomas receiving postoperative conventionally fractionated SRT with a median dose of 66.6 Gy. For patients receiving single-fraction SRS, local control rates of 21%–72% at 5 years have been observed in patients with small residual or recurrent chordomas and chondrosarcomas.[112–115] In a multicentre study of 71 patients with small-sized chordomas of the skull base treated with GK SRS using a marginal dose of 15 Gy, Kano et al.[112] showed 5-year actuarial overall survival and local control rates of 80% and 66%, respectively. In another large retrospective multicentric study of 93 patients with intracranial chordoma receiving GK SRS with a median dose of 17 Gy, Pikis et al.[113] reported 5- and 10-year tumor progression-free survival rates of 54.7% and 34.7%, respectively, with 5- and 10-year overall survival rates of 83% and 70%, respectively. Complications associated with SRS are reported in 10% to 33% of patients, mainly represented by cranial nerve deficits and brain necrosis; however, grade 3 or more toxicities are reported in less than 10%.

In summary, RT remains an effective treatment for chordomas and chondrosarcomas, with doses around 70 Gy or higher usually recommended to achieve better local control. New stereotactic techniques have significantly improved the conformality and precision of radiation treatments and their potential efficacy have been suggested in a few studies; however, the reported 5-year survival is higher with PT than xRT for either chordomas or chondrosarcomas and there is still a consensus that proton beam therapy represents a more effective and safe approach in such patients, especially for larger tumors. Currently, no prospective controlled randomized clinical trials are comparing proton- versus photon-based therapy, while two ongoing prospective phase III clinical trials are evaluating proton versus carbon-ion radiotherapy in patients with either chordoma (NCT01182779, Heidelberg) or chondrosarcoma (NCT01182753, Heidelberg).

Other Skull Base Tumors

Pituitary adenomas are benign brain tumors that comprise 10%–20% of all CNS neoplasms. For patients with either secreting or nonfunctioning pituitary adenomas, multiple treatment options exist including systemic treatments, surgery, and RT. Both SRS and fractionated SRT are frequently employed in patients with postoperative residual or progressive nonfunctioning tumors or in those with secreting tumors resistant or intolerant to systemic therapy.[116,117] Using either SRS with doses of 13–16 Gy for nonfunctioning pituitary adenomas and 16–24 Gy for secreting adenomas or conventionally fractionated SRT with doses of 45–54.0 Gy, the reported tumor control in large retrospective series ranges from 85% to 95% at 5–10 years, with normalization of hormone hypersecretion in more than 50% of patients. Hypopituitarism represents the most common late complication of radiation treatments, whereas other late effect radiation complications, including radiation-induced optic neuropathy and cranial nerves deficits, occur in < 5% of cases.

Data on PT for pituitary adenomas using either conventional fractionation, 50.4 - 54 Gy_{RBE} in 1.8 Gy fractions, or

pSRS with a median dose of 20 Gy_{RBE}, indicates an excellent 5-year local control rate of more than 90%.[118–122] For secreting pituitary adenomas, hormone hypersecretion normalization rates range from 38% to 85.7% with a median time to biochemical remission of 18 to 62 months, similar to those observed for xRT.[119–122] The most common reported toxicity is the development of hypopituitarism, with an incidence of one or multiple pituitary hormone deficits between 30% and 62%. The high risk of hypopituitarism is because of the inclusion of the normal gland in the target volume and/or dose fall-off, as well the irradiation of the pituitary stalk.[123] Radiation-induced optic neuropathy and other cranial deficits are observed in < 5%. No radiation-induced secondary tumors were reported.

Vestibular schwannomas are benign, slow-growing tumors originating from the Schwann cells of the 8th cranial nerve. Treatment decisions include observation, microsurgery, and SRS/SRT. The choice of xRT technique and number of fractions depends on the dimension and position of the tumor. SRT is usually preferred over SRS for large lesions > 3 cm in close proximity to the brainstem.[124] Efficacy and toxicity of PT for vestibular schwannomas have been evaluated in 9 studies published between 2002 and 2022.[125–132] Following either conventionally fractionated RT, 50.4 to 59.4 Gy_{RBE} in 1.8 Gy fractions, or hypofractionated RT, 23 Gy_{RBE} in 3 fractions, or SRS, 12 Gy_{RBE} in single fraction, the 5-year local tumor control rate ranges from 93% to100%. The reported overall rate of facial nerve and hearing preservation ranges from 89.6% to 97.7% and from 29.4 to 51.8 at 5 years. The 5-year local control rate and nerve function preservation are similar following conventionally fractionated RT, hypofractionated RT, and single-fraction SRS; in addition, the outcome does not change significantly between passive scattering and scanning techniques. Regarding xRT, published systematic reviews indicate similar efficacy and hearing/facial nerve preservation following either SRS or SRT.[133–136] Across evaluated studies, the pooled rates of tumor control, hearing, facial nerve, and trigeminal nerve preservation were around 95%, 37%, 97%, and 98%, respectively.

For patients with a craniopharyngioma, RT is frequently employed after subtotal resection or at tumor recurrence, providing better long-term tumor control rates at 10 years than surgery alone with a local control of 80–90 at 10 years.[137–140] The reported incidence of radiation-induced optic neuropathy resulting in visual deficit is 2%–8%.[141–144] The proximity of craniopharyngioma to the optic pathways provides a major limitation to the use of SRS; however, in very selected series of relatively small residual tumors not involving the optic apparatus, the reported 10-year local control rate ranges from 53% to 78% using 11–15 Gy in single-fraction or 25 Gy in 5 fractions[145–151] A few studies of PT for craniopharyngioma are available in the medical literature, mainly pediatric series.[152–154] Although the reported local control around 90% at 5 years is comparable with the results of series of xRT, PT may represent a better treatment in pediatric patients, possibly limiting potential radiation-induced long-term neurocognitive decline, hypopituitarism and risk of radiation-induced tumors. In a small series of 14 adult patients with craniopharyngioma receiving a mean dose of 54 Gy_{RBE} in 1.8 Gy_{RBE} fractions, Rutenberg et al.[155] observed 3-year local control and overall survival rates of 100% with no grade 3 or greater acute or late radiotherapy-related side effects. To date no experience with proton SRS has been reported.

Current clinical results indicate a similar control for adult patients with benign skull base tumors using either xRT or xPT. Currently, available data coming from relatively small retrospective series does not allow any definitive conclusion about the superiority of proton-based over photon-based techniques. The main reason to use PT for these benign tumors is to minimize normal tissue toxicity rather than increase local control. Because the difference between techniques may be quite small, this means that large numbers of patients with 10–20 years of follow-up would be necessary to show any clinically significant advantage of PT over xRT for such tumors.

Cost-Effectiveness Considerations

A formal cost-effectiveness assessment is a key consideration for medical decision-making. PT is expensive, since large investments are required for building accelerators, beam transport systems, and gantries. It is therefore important to evaluate whether the medical benefits of PT are such as to justify the higher costs.

Several studies have provided economic evaluation of PT in different types of cancers.[156–160] PBT offers promising cost-effectiveness for some tumors, such as well-selected breast cancers, locoregionally advanced NSCLC, and high-risk head/neck cancers, while it seems not cost-effective for prostate cancer or early-stage NSCLC. In a recent systematic review, Verna et al.[160] found that PT was the most cost-effective option for several pediatric brain tumors. The investigators posited that their finding was the result of a drastic reduction in the development of chronic toxicity attributable to radiation exposure that typically occurs after traditional xRT. In contrast, the major problem with evaluating PT for adult brain tumors is the limited number of clinical studies. This means that cost-effectiveness is more based on the assumptions of the reduced treatment expenses for late radiation-induced toxicities following PT rather than evidence from randomized clinical trials.

In 2017, the Canadian Agency for Drugs and Technologies in Health published a health technology assessment, including a systematic review of 215 publications on PT for the treatment of cancer in children and adults.[161] In children with brain tumors, PT resulted in fewer adverse events, but similar overall survival and progression-free survival compared to those treated with xRT. In contrast, adverse events, overall survival, and progression-free survival are similar in adults with brain tumors. Then, the economic evidence suggests that PT may be cost-effective in pediatric populations with medulloblastoma; however, studies were based on limited clinical evidence. In other indications, the cost-effectiveness of PT is unclear.

In summary, based on findings in the literature, PT is likely cost-effective compared with xRT in children with brain tumors, eg, medulloblastoma and craniopharyngioma, but cost-effectiveness remains unclear in adults with focal

brain tumors. Future studies should identify the appropriate PT-eligible risk groups for whom investing in a PT facility may be cost-effective compared to xRT. In this regard, the benefits of PT would increase in patients at higher risk of adverse reactions.

Conclusion and Recommendations

Irradiating brain tumors with photons using state-of-the-art irradiation techniques provides excellent conformality, nevertheless, the volume receiving a low radiation dose can be reduced with the aid of protons. The outcome of large, randomized trials comparing photon versus proton radiation in brain tumor patients are on the way but not yet available at this moment. Since protons are less available worldwide and the cost to date is higher than photons, it is critical to determine which patients are most likely to benefit from this treatment. The evidence presented in this review shows a reduction, but also different side effects with PT eg, the RICE, with comparable local control and overall survival rates. Whether this potential reduction in side effects is currently clinically relevant cannot be objectified at this time because data on neurological/neurocognitive outcome and QoL after treatment are missing on a large scale. A longer follow-up period of some recently started and promising studies is needed to learn more about the impact on QoL and cognitive evaluation. The radiation oncologists within the European proton therapy network promote strongly close collaboration, uniformity and extensive OARs delineation, nomenclature, follow-up, and data collection in order to fasten the process of the promising development of normal tissue complication probability models in the near future. Increasing the availability of validated normal tissue complication probability neuro models will enable us to select the right patient for the most optimal radiation technique.

It is recommended to perform a plan comparison between xRT and PT and consider the dose to various OARs and target coverage, as is the golden standard in several European countries, before deciding which technique is best, not limiting the decision to pathology only.

Funding

No funding supported the research.

Conflict of interest statement

HS receives honoraria from UpToDate (section editor, writer), MedLink Neurology (writer). GM has received honoraria for speaker activity and travel support from Brainlab and Accuray.

Affiliations

Department of Radiation Oncology (Maastro), Maastricht University Medical Center, GROW-School for Oncology and Reproduction, Maastricht, The Netherlands (D.B.P.E., C.M.L.Z.); Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida, USA(K.A.A.); Departments of Oncologic Sciences, University of South Florida Morsani College of Medicine, Tampa, Florida, USA (K.A.A.); Trento Proton Therapy Center, Azienda Provinciale per i Servizi Sanitari (APSS), Trento, Italy (D.A., D.S.); Department of Radiation Oncology, ACTREC/TMH, Tata Memorial Centre, Homi Bhabha National Institute (HBNI), Mumbai, India (T.G.); Department of Radiation Oncology, Heidelberg Ion Beam Therapy Center (HIT), University Hospital Heidelberg, Heidelberg, Germany (S.B.H.); Department of Radiation Oncology, Faculty of Medicine, Masaryk University and Masaryk Memorial Cancer Institute, Brno, Czech Republic (T.K.); Department of Radiation Oncology, University of Leipzig Medical Center, Leipzig, Germany (C.S.); Comprehensive Cancer Center Central Germany, Leipzig, Germany (C.S.); Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA (H.A.S.); Department of Radiological Sciences, Oncology and Anatomical Pathology, Sapienza University of Rome, Policlinico Umberto I, Rome, Italy(G.M.); IRCCS Neuromed, Pozzilli IS, Italy (G.M.)

References

1. Sahgal A, Ma L, Chang E, et al. Advances in technology for intracranial stereotactic radiosurgery. *Technol Cancer Res Treat*. 2009;8(4):271–280.
2. Scaringi C, Agolli L, Minniti G. Technical advances in radiation therapy for brain tumors. *Anticancer Res*. 2018;38(11):6041–6045.
3. Eekers DBP, Roelofs E, Cubillos-Mesías M, et al. Intensity-modulated proton therapy decreases dose to organs at risk in low-grade glioma patients: Results of a multicentric in silico ROCOCO trial. *Acta Oncol*. 2019;58(1):57–65.
4. Lesueur P, Calugaru V, Nauraye C, et al. Proton therapy for treatment of intracranial benign tumors in adults: A systematic review. *Cancer Treat Rev*. 2019;72(1):56–64.
5. Harrabi SB, Bougatf N, Mohr A, et al. Dosimetric advantages of proton therapy over conventional radiotherapy with photons in young patients and adults with low-grade glioma. *Strahlenther Onkol*. 2016;192(11):759–769.
6. Eekers DB, In 't Ven L, Roelofs E, et al; "European Particle Therapy Network" of ESTRO. The EPTN consensus-based atlas for CT- and MR-based contouring in neuro-oncology. *Radiother Oncol*. 2018;128(1):37–43.
7. Garibaldi C, Jereczek-Fossa BA, Marvaso G, et al. Recent advances in radiation oncology. *Ecancermedicalscience*. 2017;11:785.
8. Gevaert T, Verellen D, Tournel K, et al. Setup accuracy of the Novalis ExacTrac 6DOF system for frameless radiosurgery. *Int J Radiat Oncol Biol Phys*. 2012;82(5):1627–1635.
9. Carminucci A, Nie K, Weiner J, Hargreaves E, Danish SF. Assessment of motion error for frame-based and noninvasive mask-based fixation using the Leksell Gamma Knife Icon radiosurgery system. *J Neurosurg*. 2018;129(suppl 1):133–139.

10. Kienzler JC, Tenn S, Chivukula S, et al. Linear accelerator-based radiosurgery for trigeminal neuralgia: Comparative outcomes of frame-based and mask-based techniques. *J Neurosurg.* 2021;137(1):1–10.
11. Ma J, Chang Z, Wang Z, et al. ExacTrac X-ray 6 degree-of-freedom image-guidance for intracranial non-invasive stereotactic radiotherapy: Comparison with kilo-voltage cone-beam CT. *Radiother Oncol.* 2009;93(3):602–608.
12. Ramakrishna N, Rosca F, Friesen S, et al. A clinical comparison of patient setup and intra-fraction motion using frame-based radiosurgery versus a frameless image-guided radiosurgery system for intracranial lesions. *Radiother Oncol.* 2010;95(1):109–115.
13. Al-Hallaq HA, Cerviño L, Gutierrez AN, et al. AAPM task group report 302: Surface-guided radiotherapy. *Med Phys.* 2022;49(4):e82–e112.
14. Bryant JM, Doniparthi A, Weygand J, et al. Treatment of central nervous system tumors on combination MR-Linear accelerators: Review of current practice and future directions. *Cancers (Basel).* 2023;15(21):5200.
15. Paganetti H, Niemierko A, Ancukiewicz M, et al. Relative biological effectiveness (RBE) values for proton beam therapy. *Int J Radiat Oncol Biol Phys.* 2002;53(2):407–421.
16. Kahan J, Martinez C, Tsien C. Critical appraisal of proton therapy for patients with Central Nervous System (CNS) Malignancies. *Curr Treat Options Oncol.* 2023;24(8):988–1003.
17. Landry G, Hua CH. Current state and future applications of radiological image guidance for particle therapy. *Med Phys.* 2018;45(11):e1086–e1095.
18. Lane SA, Slater JM, Yang GY. Image-guided proton therapy: A comprehensive review. *Cancers (Basel).* 2023;15(9):2555.
19. Hoisak JDP, Pawlicki T. The role of optical surface imaging systems in radiation therapy. *Semin Radiat Oncol.* 2018;28(3):185–193.
20. Fitzek MM, Thornton AF, Harsh G, et al. Dose-escalation with proton/photon irradiation for Daumas-Duport lower-grade glioma: Results of an institutional phase I/II trial. *Int J Radiat Oncol Biol Phys.* 2001;51(1):131–137.
21. Hauswald H, Rieken S, Ecker S, et al. First experiences in treatment of low-grade glioma grade I and II with proton therapy. *Radiat Oncol.* 2012;7:189.
22. Shih HA, Sherman JC, Nachtigall LB, et al. Proton therapy for low-grade gliomas: Results from a prospective trial. *Cancer.* 2015;121(10):1712–1719.
23. Badiyan SN, Ulmer S, Ahlhelm FJ, et al. Clinical and radiologic outcomes in adults and children treated with pencil-beam scanning proton therapy for low-grade glioma. *Int J Part Ther.* 2017;3(4):450–460.
24. Bronk JK, Guha-Thakurta N, Allen PK, et al. Analysis of pseudoprogression after proton or photon therapy of 99 patients with low grade and anaplastic glioma. *Clin Transl Radiat Oncol.* 2018;9:30–34.
25. Kamran SC, Dworkin M, Niemierko A, et al. Patterns of failure among patients with low-grade glioma treated with proton radiation therapy. *Pract Radiat Oncol.* 2019;9(4):e356–e361.
26. Tabrizi S, Yeap BY, Sherman JC, et al. Long-term outcomes and late adverse effects of a prospective study on proton radiotherapy for patients with low-grade glioma. *Radiother Oncol.* 2019;137:95–101.
27. Harrabi SB, von Nettelbladt B, Gudden C, et al. Radiation induced contrast enhancement after proton beam therapy in patients with low grade glioma - How safe are protons? *Radiother Oncol.* 2022;167:211–218.
28. Eichkorn T, Lischalk JW, Hörner-Rieber J, et al. Analysis of safety and efficacy of proton radiotherapy for IDH-mutated glioma WHO grade 2 and 3. *J Neurooncol.*2023;162(3):489–501.
29. Mizumoto M, Tsuboi K, Igaki H, et al. Phase I/II trial of hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme. *Int J Radiat Oncol Biol Phys.* 2010;77(1):98–105.
30. Kong L, Wu J, Gao J, et al. Particle radiation therapy in the management of malignant glioma: Early experience at the Shanghai Proton and Heavy Ion Center. *Cancer.* 2020;126(12):2802–2810.
31. Brown PD, Chung C, Liu DD, et al. A prospective phase II randomized trial of proton radiotherapy vs intensity-modulated radiotherapy for patients with newly diagnosed glioblastoma. *Neuro Oncol.* 2021;23(8):1337–1347.
32. Mizumoto M, Okumura T, Ishikawa E, et al. Reirradiation for recurrent malignant brain tumor with radiotherapy or proton beam therapy. Technical considerations based on experience at a single institution. *Strahlenther Onkol.* 2013;189(8):656–663.
33. Galle JO, McDonald MW, Simoneaux V, Buchsbaum JC. Reirradiation with proton therapy for recurrent gliomas. *Int J Part Ther.* 2015;2(1):11–18.
34. Saeed AM, Khairnar R, Sharma AM, et al. Clinical outcomes in patients with recurrent glioblastoma treated with proton beam therapy reirradiation: Analysis of the multi-institutional proton collaborative group registry. *Adv Radiat Oncol.* 2020;5(5):978–983.
35. Gulidov I, Gordon K, Semenov A, et al. Proton re-irradiation of unresectable recurrent brain gliomas: Clinical outcomes and toxicity. *J BUON.* 2021;26(3):970–976.
36. Scartoni D, Amelio D, Palumbo P, Giacomelli I, Amichetti M. Proton therapy re-irradiation preserves health-related quality of life in large recurrent glioblastoma. *J Cancer Res Clin Oncol.* 2020;146(6):1615–1622.
37. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. *Nat Rev Clin Oncol.* 2021;18(3):170–186.
38. Cairncross G, Berkey B, Shaw E, et al; Intergroup Radiation Therapy Oncology Group Trial 9402. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup radiation therapy oncology group trial 9402. *J Clin Oncol.* 2006;24(18):2707–2714.
39. van den Bent MJ, Carpentier AF, Brandes AA, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: A randomized European Organisation for Research and Treatment of Cancer phase III trial. *J Clin Oncol.* 2006;24(18):2715–2722.
40. Shaw EG, Wang M, Coons SW, et al. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine chemotherapy for supratentorial adult low-grade glioma: Initial results of RTOG 9802. *J Clin Oncol.* 2012;30(25):3065–3070.
41. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: Long-term results of RTOG 9402. *J Clin Oncol.* 2013;31(3):337–343.
42. van den Bent MJ, Brandes AA, Taphoorn MJB, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: Long-term follow-up of EORTC brain tumor group study 26951. *J Clin Oncol.* 2013;31(3):344–350.
43. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med.* 2016;374(14):1344–1355.
44. van den Bent MJ, Baumert B, Erridge SC, et al. Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: A phase 3, randomised, open-label intergroup study. *Lancet.* 2017;390(10103):1645–1653.
45. Bell EH, Zhang P, Shaw EG, et al. Comprehensive genomic analysis in NRG oncology/RTOG 9802: A Phase III trial of radiation versus radiation plus procarbazine, lomustine (CCNU), and vincristine in high-risk low-grade glioma. *J Clin Oncol.* 2020;38(29):3407–3417.
46. van den Bent MJ, Tesileanu CMS, Wick W, et al. Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): Second interim analysis of a randomised, open-label, phase 3 study. *Lancet Oncol.* 2021;22(6):813–823.

47. Gaikwad U, Bajpai J, Jalali R. Combinatorial approach of immuno-proton therapy in cancer: Rationale and potential impact. *Asia Pac J Clin Oncol.* 2024;20(2):188–197.
48. Adeberg S, Harrabi SB, Bougatf N, et al. Intensity-modulated proton therapy, volumetric-modulated arc therapy, and 3D conformal radiotherapy in anaplastic astrocytoma and glioblastoma: A dosimetric comparison. *Strahlenther Onkol.* 2016;192(11):770–779.
49. Dworkin M, Mehan W, Niemierko A, et al. Increase of pseudoprogression and other treatment related effects in low-grade glioma patients treated with proton radiation and temozolomide. *J Neurooncol.* 2019;142(1):69–77.
50. Sherman JC, Colvin MK, Mancuso SM, et al. Neurocognitive effects of proton radiation therapy in adults with low-grade glioma. *J Neurooncol.* 2016;126(1):157–164.
51. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997–1003.
52. Mohan R, Liu AY, Brown PD, et al. Proton therapy reduces the likelihood of high-grade radiation-induced lymphopenia in glioblastoma patients: Phase II randomized study of protons vs photons. *Neuro Oncol.* 2021;23(2):284–294.
53. König L, Jäkel C, von Knebel Doeberitz N, et al. Glioblastoma radiotherapy using Intensity modulated Radiotherapy (IMRT) or proton Radiotherapy-GRIPS Trial (Glioblastoma Radiotherapy via IMRT or Proton BeamS): A study protocol for a multicenter, prospective, open-label, randomized, two-arm, phase III study. *Radiat Oncol.* 2021;16(1):240.
54. De Pietro R, Zaccaro L, Marampon F, et al. The evolving role of reirradiation in the management of recurrent brain tumors. *J Neurooncol.* 2023;164(2):271–286.
55. Goldbrunner R, Stavrinou P, Jenkinson MD, et al. EANO guideline on the diagnosis and management of meningiomas. *Neuro Oncol.* 2021;23(11):1821–1834.
56. Albano L, Losa M, Flickinger J, Mortini P, Minniti G. Radiotherapy of parasellar tumours. *Neuroendocrinology.* 2020;110(9-10):848–858.
57. Combs SE, Adeberg S, Dittmar JO, 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). *Radiother Oncol.* 2013;106(2):186–191.
58. Soldà F, Wharram B, De Ieso PB, et al. Long-term efficacy of fractionated radiotherapy for benign meningiomas. *Radiother Oncol.* 2013;109(2):330–334.
59. Henzel M, Gross MW, Hamm K, et al. Significant tumor volume reduction of meningiomas after stereotactic radiotherapy: Results of a prospective multicenter study. *Neurosurgery.* 2006;59(6):1188–94; discussion 1194.
60. Fokas E, Henzel M, Surber G, Hamm K, Engenhart-Cabillic R. Stereotactic radiation therapy for benign meningioma: Long-term outcome in 318 patients. *Int J Radiat Oncol Biol Phys.* 2014;89(3):569–575.
61. Spiegelmann R, Cohen ZR, Nissim O, Alezra D, Pfeffer R. Cavernous sinus meningiomas: A large LINAC radiosurgery series. *J Neurooncol.* 2010;98(2):195–202.
62. Santacroce A, Walier M, Régis J, et al. Long-term tumor control of benign intracranial meningiomas after radiosurgery in a series of 4565 patients. *Neurosurgery.* 2012;70(1):32–9; discussion 39.
63. Sheehan JP, Starke RM, Kano H, et al. Gamma Knife radiosurgery for sellar and parasellar meningiomas: A multicenter study. *J Neurosurg.* 2014;120(6):1268–1277.
64. Marchetti M, Bianchi S, Pinzi V, et al. Multisession radiosurgery for sellar and parasellar benign meningiomas: Long-term tumor growth control and visual outcome. *Neurosurgery.* 2016;78(5):638–646.
65. Pinzi V, Marchetti M, Viola A, et al. Hypofractionated radiosurgery for large or in critical-site intracranial meningioma: Results of a phase 2 prospective study. *Int J Radiat Oncol Biol Phys.* 2023;115(1):153–163.
66. Wenkel E, Thornton AF, Finkelstein D, et al. Benign meningioma: Partially resected, biopsied, and recurrent intracranial tumors treated with combined proton and photon radiotherapy. *Int J Radiat Oncol Biol Phys.* 2000;48(5):1363–1370.
67. Vernimmen FJ, Harris JK, Wilson JA, et al. Stereotactic proton beam therapy of skull base meningiomas. *Int J Radiat Oncol Biol Phys.* 2001;49(1):99–105.
68. Noël G, Bollet MA, Calugaru V, et al. Functional outcome of patients with benign meningioma treated by 3D conformal irradiation with a combination of photons and protons. *Int J Radiat Oncol Biol Phys.* 2005;62(5):1412–1422.
69. Slater JD, Loredo LN, Chung A, et al. Fractionated proton radiotherapy for benign cavernous sinus meningiomas. *Int J Radiat Oncol Biol Phys.* 2012;83(5):e633–e637.
70. Murray FR, Snider JW, Bolsi A, et al. Long-term clinical outcomes of pencil beam scanning proton therapy for benign and non-benign intracranial meningiomas. *Int J Radiat Oncol Biol Phys.* 2017;99(5):1190–1198.
71. El Shafie RA, Czech M, Kessel KA, et al. Clinical outcome after particle therapy for meningiomas of the skull base: Toxicity and local control in patients treated with active rasterscanning. *Radiat Oncol.* 2018;13(1):54.
72. Sato H, Mizumoto M, Okumura T, et al. Long-term outcomes of patients with unresectable benign meningioma treated with proton beam therapy. *J Radiat Res.* 2021;62(3):427–437.
73. Champeaux-Depond C, Weller J. Outcome after proton therapy for progression or recurrence of surgically treated meningioma. *Brain Tumor Res Treat.* 2021;9(2):46–57.
74. Holtzman AL, Glassman GE, Dagan R, et al. Long-term outcomes of fractionated proton beam therapy for benign or radiographic intracranial meningioma. *J Neurooncol.* 2023;161(3):481–489.
75. Halasz LM, Bussière MR, Dennis ER, et al. Proton stereotactic radiosurgery for the treatment of benign meningiomas. *Int J Radiat Oncol Biol Phys.* 2011;81(5):1428–1435.
76. Hug EB, Devries A, Thornton AF, et al. Management of atypical and malignant meningiomas: Role of high-dose, 3D-conformal radiation therapy. *J Neurooncol.* 2000;48(2):151–160.
77. Boskos C, Feuvret L, Noel G, et al. Combined proton and photon conformal radiotherapy for intracranial atypical and malignant meningioma. *Int J Radiat Oncol Biol Phys.* 2009;75(2):399–406.
78. McDonald MW, Plankenhorn DA, McMullen KP, et al. Proton therapy for atypical meningiomas. *J Neurooncol.* 2015;123(1):123–128.
79. Sanford NN, Yeap BY, Larvie M, et al. Prospective, randomized study of radiation dose escalation with combined proton-photon therapy for benign meningiomas. *Int J Radiat Oncol Biol Phys.* 2017;99(4):787–796.
80. Vlachogiannis P, Gudjonsson O, Montelius A, et al. Hypofractionated high-energy proton-beam irradiation is an alternative treatment for WHO grade I meningiomas. *Acta Neurochir (Wien).* 2017;159(12):2391–2400.
81. Rogers CL, Won M, Vogelbaum MA, et al. High-risk meningioma: initial outcomes from NRG Oncology/RTOG 0539. *Int J Radiat Oncol Biol Phys.* 2020;106(4):790–799.
82. Weber DC, Ares C, Villa S, et al. Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: A phase-II parallel non-randomized and observation study (EORTC 22042-26042). *Radiother Oncol.* 2018;128(2):260–265.
83. Rogers L, Zhang P, Vogelbaum MA, et al. Intermediate-risk meningioma: Initial outcomes from NRG Oncology RTOG 0539. *J Neurosurg.* 2018;129(1):35–47.
84. Vagnoni L, Aburas S, Giraffa M, et al. Radiation therapy for atypical and anaplastic meningiomas: An overview of current results and controversial issues. *Neurosurg Rev.* 2022;45(5):3019–3033.
85. Champeaux C, Jecko V, Houston D, et al. Malignant meningioma: An international multicentre retrospective study. *Neurosurgery.* 2019;85(3):E461–E469.

86. Rosenberg LA, Prayson RA, Lee J, et al. Long-term experience with World Health Organization grade III (malignant) meningiomas at a single institution. *Int J Radiat Oncol Biol Phys.* 2009;74(2):427–432.
87. Sumner WA, Amini A, Hankinson TC, et al. Survival benefit of post-operative radiation in papillary meningioma: Analysis of the National Cancer Data Base. *Rep Pract Oncol Radiother.* 2017;22(6):495–501.
88. Sughrue ME, Sanai N, Shangari G, et al. Outcome and survival following primary and repeat surgery for World Health Organization Grade III meningiomas. *J Neurosurg.* 2010;113(2):202–209.
89. Coggins WS, Pham NK, Nguyen AV, et al. A systematic review of ion radiotherapy in maintaining local control regarding atypical and anaplastic meningiomas. *World Neurosurg.* 2019;132:282–291.
90. Almefty K, Pravdenkova S, Colli BO, Al-Mefty O, Gokden M. Chordoma and chondrosarcoma: Similar, but quite different, skull base tumors. *Cancer.* 2007;110(11):2457–2467.
91. Kremenevski N, Schlaffer SM, Coras R, et al. Skull base chordomas and chondrosarcomas. *Neuroendocrinology.* 2020;110(9-10):836–847.
92. Biermann JS, Chow W, Reed DR, et al. NCCN guidelines insights: Bone cancer, Version 2.2017. *J Natl Compr Canc Netw.* 2017;15(2):155–167.
93. Stacchiotti S, Sommer J; Chordoma Global Consensus Group. Building a global consensus approach to chordoma: A position paper from the medical and patient community. *Lancet Oncol.* 2015;16(2):e71–e83.
94. Amichetti M, Cianchetti M, Amelio D, Enrici RM, Minniti G. Proton therapy in chordoma of the base of the skull: a systematic review. *Neurosurg Rev.* 2009;32(4):403–416.
95. Mercado CE, Holtzman AL, Rotondo R, Rutenberg MS, Mendenhall WM. Proton therapy for skull base tumors: A review of clinical outcomes for chordomas and chondrosarcomas. *Head Neck.* 2019;41(2):536–541.
96. Nie M, Chen L, Zhang J, Qiu X. Pure proton therapy for skull base chordomas and chondrosarcomas: A systematic review of clinical experience. *Front Oncol.* 2022;12(11):1016857.
97. Pahwa B, Medani K, Lu VM, Elarjani T. Proton beam therapy for skull base chordomas: A systematic review of tumor control rates and survival rates. *Neurosurg Rev.* 2022;45(6):3551–3563.
98. Noël G, Feuvret L, Calugaru V, et al. Chordomas of the base of the skull and upper cervical spine. One hundred patients irradiated by a 3D conformal technique combining photon and proton beams. *Acta Oncol.* 2005;44(7):700–708.
99. Weber DC, Malyapa R, Albertini F, et al. Long term outcomes of patients with skull-base low-grade chondrosarcoma and chordoma patients treated with pencil beam scanning proton therapy. *Radiother Oncol.* 2016;120(1):169–174.
100. Feuvret L, Bracci S, Calugaru V, et al. Efficacy and safety of adjuvant proton therapy combined with surgery for chondrosarcoma of the skull base: A retrospective, population-based study. *Int J Radiat Oncol Biol Phys.* 2016;95(1):312–321.
101. Holtzman AL, Rotondo RL, Rutenberg MS, et al. Clinical outcomes following dose-escalated proton therapy for skull-base chordoma. *Int J Part Ther.* 2021;8(1):179–188.
102. Nunna R, Patel S, Karuparti S, et al. Chordoma of the skull base: A national cancer database analysis of current practice patterns and outcomes. *World Neurosurg.* 2022;168:e260–e268.
103. Mattke M, Ohlinger M, Bougatf N, et al. Proton and carbon ion beam treatment with active raster scanning method in 147 patients with skull base chordoma at the Heidelberg Ion Beam Therapy Center-a single-center experience. *Strahlenther Onkol.* 2023;199(2):160–168.
104. El Sayed I, Trifiletti DM, Lehrer EJ, Showalter TN, Dutta SW. Protons versus photons for the treatment of chordoma. *Cochrane Database Syst Rev.* 2021;7(7):CD013224.
105. Bin-Alamer O, Mallela AN, Palmisciano P, et al. Adjuvant stereotactic radiosurgery with or without postoperative fractionated radiation therapy in adults with skull base chordomas: A systematic review. *Neurosurg Focus.* 2022;53(5):E5.
106. Romero J, Cardenes H, la Torre A, et al. Chordoma: Results of radiation therapy in eighteen patients. *Radiother Oncol.* 1993;29(1):27–32.
107. Forsyth PA, Cascino TL, Shaw EG, et al. Intracranial chordomas: A clinicopathological and prognostic study of 51 cases. *J Neurosurg.* 1993;78(5):741–747.
108. Watkins L, Khudados ES, Kaleoglu M, et al. Skull base chordomas: A review of 38 patients, 1958-88. *Br J Neurosurg.* 1993;7(3):241–248.
109. Catton C, O'Sullivan B, Bell R, et al. Chordoma: long-term follow-up after radical photon irradiation. *Radiother Oncol.* 1996;41(1):67–72.
110. Sahgal A, Chan MW, Atenafu EG, et al. Image-guided, intensity-modulated radiation therapy (IG-IMRT) for skull base chordoma and chondrosarcoma: Preliminary outcomes. *Neuro Oncol.* 2015;17(6):889–894.
111. Debus J, Schulz-Ertner D, Schad L, et al. Stereotactic fractionated radiotherapy for chordomas and chondrosarcomas of the skull base. *Int J Radiat Oncol Biol Phys.* 2000;47(3):591–596.
112. Kano H, Iqbal FO, Sheehan J, et al. Stereotactic radiosurgery for chordoma: A report from the North American Gamma Knife Consortium. *Neurosurgery.* 2011;68(2):379–389.
113. Pikis S, Mantziaris G, Peker S, et al. Stereotactic radiosurgery for intracranial chordomas: An international multiinstitutional study. *J Neurosurg.* 2022;137(4):977–984.
114. Hasegawa T, Ishii D, Kida Y, et al. Gamma Knife surgery for skull base chordomas and chondrosarcomas. *J Neurosurg.* 2007;107(4):752–757.
115. Krishnan S, Foote RL, Brown PD, et al. Radiosurgery for cranial base chordomas and chondrosarcomas. *Neurosurgery.* 2005;56(4):777–84; discussion 777.
116. Minniti G, Clarke E, Scaringi C, Enrici RM. Stereotactic radiotherapy and radiosurgery for non-functioning and secreting pituitary adenomas. *Rep Pract Oncol Radiother.* 2016;21(4):370–378.
117. Minniti G, Osti MF, Niyazi M. Target delineation and optimal radiosurgical dose for pituitary tumors. *Radiat Oncol.* 2016;11(1):135.
118. 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;7:210.
119. Ronson BB, Schulte RW, Han KP, et al. Fractionated proton beam irradiation of pituitary adenomas. *Int J Radiat Oncol Biol Phys.* 2006;64(2):425–434.
120. Petit JH, Biller BMK, Coen JJ, et al. Proton stereotactic radiosurgery in management of persistent acromegaly. *Endocr Pract.* 2007;13(7):726–734.
121. Petit JH, Biller BMK, Yock TI, et al. Proton stereotactic radiotherapy for persistent adrenocorticotropin-producing adenomas. *J Clin Endocrinol Metab.* 2008;93(2):393–399.
122. Wattson DA, Tanguturi SK, Spiegel DY, et al. Outcomes of proton therapy for patients with functional pituitary adenomas. *Int J Radiat Oncol Biol Phys.* 2014;90(3):532–539.
123. Combs SE, Baumert BG, Bendszus M, et al. ESTRO ACROP guideline for target volume delineation of skull base tumors. *Radiother Oncol.* 2021;156:80–94.
124. Goldbrunner R, Weller M, Regis J, et al. EANO guideline on the diagnosis and treatment of vestibular schwannoma. *Neuro Oncol.* 2020;22(1):31–45.
125. Bush DA, McAllister CJ, Loredo LN, et al. Fractionated proton beam radiotherapy for acoustic neuroma. *Neurosurgery.* 2002;50(2):270–3; discussion 273.
126. Harsh GR, Thornton AF, Chapman PH, et al. Proton beam stereotactic radiosurgery of vestibular schwannomas. *Int J Radiat Oncol Biol Phys.* 2002;54(1):35–44.

127. Weber DC, Chan AW, Bussiere MR, et al. Proton beam radiosurgery for vestibular schwannoma: Tumor control and cranial nerve toxicity. *Neurosurgery.* 2003;53(3):577–86; discussion 586.
128. Barnes CJ, Bush DA, Grove RI, Loredo LN, Slater JD. Fractionated proton beam therapy for acoustic neuromas: Tumor control and hearing preservation. *Int J Part Ther.* 2018;4(4):28–36.
129. Vernimmen FJAI, Mohamed Z, Slabbert JP, Wilson J. Long-term results of stereotactic proton beam radiotherapy for acoustic neuromas. *Radiother Oncol.* 2009;90(2):208–212.
130. Zhu S, Rotondo R, Mendenhall WM, et al. Long-term outcomes of fractionated stereotactic proton therapy for vestibular schwannoma: A case series. *Int J Part Ther.* 2018;4(4):37–46.
131. Koetsier KS, Hensen EF, Niemierko A, et al. Outcome and toxicity of proton therapy for vestibular schwannoma: A cohort study. *Otol Neurotol.* 2021;42(10):1560–1571.
132. Saraf A, Pike LRG, Franck KH, et al. Fractionated proton radiation therapy and hearing preservation for vestibular schwannoma: Preliminary analysis of a prospective phase 2 clinical trial. *Neurosurgery.* 2022;90(5):506–514.
133. Tuleasca C, Kotecha R, Sahgal A, et al. Single-fraction radiosurgery outcomes for large vestibular schwannomas in the upfront or post-surgical setting: A systematic review and International Stereotactic Radiosurgery Society (ISRS) Practice Guidelines. *J Neurooncol.* 2023;165(1):1–20.
134. Balossier A, Tuleasca C, Delsanti C, et al. Long-term hearing outcome after radiosurgery for vestibular schwannoma: A systematic review and meta-analysis. *Neurosurgery.* 2023;92(6):1130–1141.
135. Nguyen T, Duong C, Sheppard JP, et al. Hypo-fractionated stereotactic radiotherapy of five fractions with linear accelerator for vestibular schwannomas: A systematic review and meta-analysis. *Clin Neurol Neurosurg.* 2018;166:116–123.
136. Persson O, Bartek J, Shalom NB, et al. Stereotactic radiosurgery vs. fractionated radiotherapy for tumor control in vestibular schwannoma patients: A systematic review. *Acta Neurochir (Wien).* 2017;159(6):1013–1021.
137. Fahlbusch R, Honegger J, Paulus W, Huk W, Buchfelder M. Surgical treatment of craniopharyngiomas: Experience with 168 patients. *J Neurosurg.* 1999;90(2):237–250.
138. Stripp DCH, Maity A, Janss AJ, 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;58(3):714–720.
139. 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;32(2):125–32; discussion 132.
140. Rao YJ, Hassanzadeh C, Fischer-Valuck B, et al. Patterns of care and treatment outcomes of patients with Craniopharyngioma in the national cancer database. *J Neurooncol.* 2017;132(1):109–117.
141. 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;77(1):99–104.
142. Minniti G, Saran F, Traish D, et al. Fractionated stereotactic conformal radiotherapy following conservative surgery in the control of craniopharyngiomas. *Radiother Oncol.* 2007;82(1):90–95.
143. Combs SE, Thilmann C, Huber PE, et al. Achievement of long-term local control in patients with craniopharyngiomas using high precision stereotactic radiotherapy. *Cancer.* 2007;109(11):2308–2314.
144. Harrabi SB, Adeberg S, Welzel T, et al. Long term results after fractionated stereotactic radiotherapy (FSRT) in patients with craniopharyngioma: Maximal tumor control with minimal side effects. *Radiat Oncol.* 2014;9:203.
145. 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;66(4):688–94; discussion 694.
146. Niranjan A, Kano H, Mathieu D, et al. Radiosurgery for craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2010;78(1):64–71.
147. Xu Z, Yen CP, Schlesinger D, Sheehan J. Outcomes of Gamma Knife surgery for craniopharyngiomas. *J Neurooncol.* 2011;104(1):305–313.
148. Iwata H, Tatewaki K, Inoue M, et al. Single and hypofractionated stereotactic radiotherapy with CyberKnife for craniopharyngioma. *J Neurooncol.* 2012;106(3):571–577.
149. Saleem MA, Hashim ASM, Rashid A, Ali M. Role of gamma knife radiosurgery in multimodality management of craniopharyngioma. *Acta Neurochir Suppl.* 2013;116:55–60.
150. Lee CC, Yang HC, Chen CJ, et al. Gamma Knife surgery for craniopharyngioma: Report on a 20-year experience. *J Neurosurg.* 2014;121(suppl):167–178.
151. Losa M, Pieri V, Bailo M, et al. Single fraction and multisession Gamma Knife radiosurgery for craniopharyngioma. *Pituitary.* 2018;21(5):499–506.
152. Beltran C, Roca M, Merchant TE. On the benefits and risks of proton therapy in pediatric craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2012;82(2):e281–e287.
153. Bishop AJ, Greenfield B, Mahajan A, 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;90(2):354–361.
154. Jimenez RB, Ahmed S, Johnson A, et al. Proton radiation therapy for pediatric craniopharyngioma. *Int J Radiat Oncol Biol Phys.* 2021;110(5):1480–1487.
155. Rutenberg MS, Rotondo RL, Rao D, et al. Clinical outcomes following proton therapy for adult craniopharyngioma: A single-institution cohort study. *J Neurooncol.* 2020;147(2):387–395.
156. Li CC, Lin YC, Liang JA, et al. Health economic evaluation of proton therapy for lung cancer: Asystematic review. *Int J Environ Res Public Health.* 2023;20(6):4727.
157. Aldenhoven L, Ramaekers B, Degens J, et al. Cost-effectiveness of proton radiotherapy versus photon radiotherapy for non-small cell lung cancer patients: Exploring the model-based approach. *Radiother Oncol.* 2023;183:109417.
158. Ontario Health (Quality). Proton beam therapy for cancer in children and adults: A health technology assessment. *Ont Health Technol Assess Ser.* 2021;21(1):1–142.
159. Jones DA, Smith J, Mei XW, et al. A systematic review of health economic evaluations of proton beam therapy for adult cancer: Appraising methodology and quality. *Clin Transl Radiat Oncol.* 2020;20:19–26.
160. Verma V, Mishra MV, Mehta MP. A systematic review of the cost and cost-effectiveness studies of proton radiotherapy. *Cancer.* 2016;122(10):1483–1501.
161. Kim J, Wells C, Khangura S, et al. *Proton Beam Therapy for the Treatment of Cancer in Children and Adults: A Health Technology Assessment [Internet].* Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2017. http://www.ncbi.nlm.nih.gov/books/NBK531691/