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Proton therapy for treatment of intracranial benign tumors in adults: A systematic review

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ABSTRACT

Introduction: The depth-dose distribution of a proton beam, materialized by the Bragg peak makes it an attractive radiation modality as it reduces exposure of healthy tissues to radiations, compared with photon therapy Prominent indications, based on a long-standing experience are: intraocular melanomas, low-grade skull-base and spinal canal malignancies. However, many others potential indications are under investigations such as the benign morbid conditions that are compatible with an extended life-expectancy: low grade meningiomas, paragangliomas, pituitary adenomas, neurinomas craniopharyngioma or recurrent pleomorphic adenomas.
Materials: Given the radiation-induced risk of secondary cancer and the potential neurocognitive and functional alteration with photonic radiotherapy, we systematically analyzed the existing clinical literature about the use of proton therapy as an irradiation modality for cervical or intracranial benign tumors. The aim of this review was to report clinical outcomes of adult patients with benign intracranial or cervical tumors treated with proton therapy and to discuss about potential advantages of proton therapy over intensity modulated radiotherapy or radiosurgery.
Results: Twenty-four studies were included. There was no randomized studies. Most studies dealt with low grade meningiomas (n = 9). Studies concerning neurinoma (n = 4), pituitary adenoma (n = 5), paraganglioma (n = 5), or craniopharyngioma (n = 1) were fewer. Whatever the indication, long term local control was systematically higher than 90% and equivalent to series with conventional radiotherapy.
Conclusion: Proton-therapy for treatment of adult benign intracranial and cervical tumors is safe. Randomized or prospective cohorts with long term cognitive evaluations are needed to assess the real place of proton-therapy in the treatment of adults benign head and neck tumors.

Introduction

For the past decade, thanks to the growing number of proton therapy centers worldwide, proton therapy, an innovative radiotherapeutic modality for cancer, has confirmed its benefits related with its unique ballistic properties, in multiple challenging clinical situations. The depth-dose distribution of a proton beam, materialized by the Bragg peak makes it an attractive radiation modality as it reduces exposure of healthy tissues to radiations, compared with photon therapy [1]. The Bragg peak allows reduced radiation exposure to healthy tissues located upstream (although somewhat mitigated by spread-out), and complete sparing of those located downstream of the target. Conversely, photon technology has dramatically improved in terms of mastering beams' intensity modulation, intra and extra fractional

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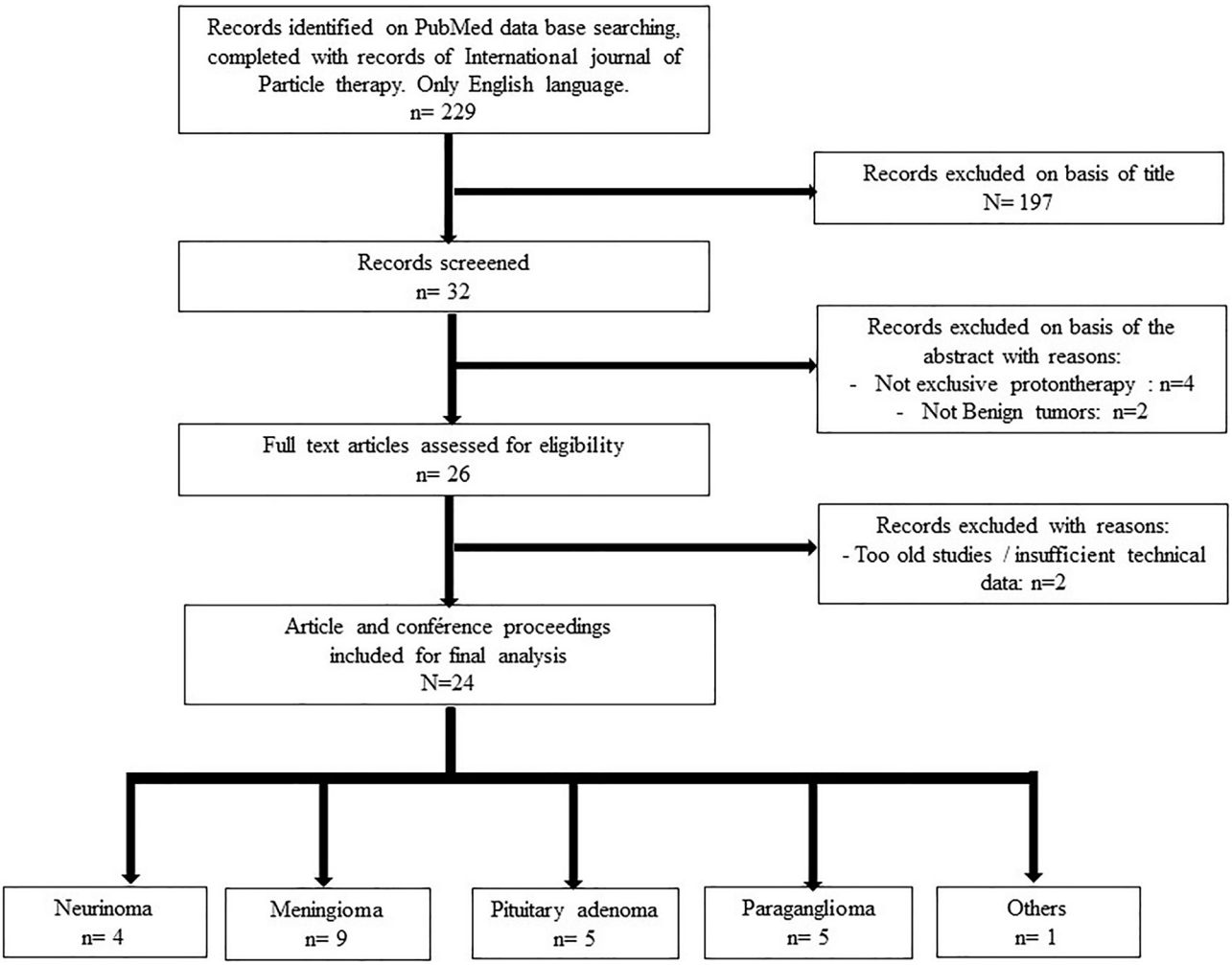

Fig. 1. PRISMA flow chart.

uncertainties, and breathing gating. These approaches combined together in modern radiotherapy suites, make possible a safe and reliable administration of regular or escalated doses per fraction, that can achieve a 1–3 mm accuracy, in stereotactic programs. Technologies such as volumetric arc-therapy, tomotherapy®, cyberknife®… share most of the time, an excellent conformation to, and dose-homogeneity in the target volume. High dose per fraction administered safely has also opened-up the possibility of controlling simultaneously multiple metastatic foci with near curative intent. But there is a "price" to pay for photons: all these approaches share an unprecedented proliferation of uniform or non-uniform convergent beams or "beamlets" (i.e. micro beams) that increases likewise the integral dose to the surrounding normal tissues. Although most spread-out dose is below 20 Gy, such unwanted "bath" is acknowledged to increase risk of carcinogenicity, and even impair organs functions in adults (e.g. lungs, liver, kidney, brain…), and most of them in younger age leading to functional impairment such as neurocognitive disorder for example. Moreover after exposure to brain conventional photonic radiotherapy, late vascular effect have been reported including cerebrovascular accidents, lacunar lesions, vascular occlusive disease including moya-moya syndrome, vascular malformations, and hemorrhage [2]. This "price" is far below, as far as protons, are also catching-up quickly technologically, e.g. rotating gantries, active beams' scanning, 3D intensity modulation…

Since the early 2000s, there has been a spectacular multiplication of proton facilities (and to a lesser extent of light ions facilities) with 66 fully operational centers (end 2017), and almost as much in preparation stage. This has been paralleled by a similar trend for clinical studies (over 300 registered at PTCOG website, in 2017). Very few are randomized, but consensus conferences have come up with recommendations such as those provided by the ASTRO [3]. Prominent indications, based on a long-standing experience and unsurpassed patients' inclusion are: intraocular melanomas, and low grade skull-base and spinal canal malignancies. Solid tumors in children younger than 18 years of age, although limited in experience, fall in this category, due to the intensity of sequelae associated with conventional radiations, along with convincing dosimetric inter-comparisons which plead for an improved quality of life in the adulthood. There are many more potential indications, under investigations such as the benign morbid conditions that are compatible with an extended life-expectancy, and can evidence adverse prognosticators such as genetic risks of a second primary, or young age. A large part of them sits in the head and neck area: low grade meningiomas, paragangliomas, pituitary adenomas, neurinomas, craniopharyngioma and recurrent pleomorphic adenomas. Radiation therapy is either recommended for unresectable, or ill-resectable tumors, or implicating a substantial risk of surgical morbidity/mortality due to the proximity of highly functional organs located close or abutting the tumor (optic chiasm, optic nerves, temporal lobes, brain stem, cranial nerves…). Another group at risk is represented by patients who have failed following an initial radiation course. In these contexts, proton therapy can represent an elegant alternative to advanced photon technologies, although the experience is much more limited compared with advanced photon approaches [4–7].

Given the radiation-induced risk of secondary cancer, vascular damages and the potential neurocognitive and functional alteration with

photonic radiotherapy [8], we systematically analyzed the existing clinical literature about the use of proton therapy as an irradiation modality for cervical and intracranial benign tumors. The aim of this review was to report clinical outcomes of patients with benign head and neck tumors treated with proton therapy.

Material and methods

We conducted a bibliographical investigation according to PRISMA guidelines [9]. We looked for all retrospective or prospective clinical studies related with the use proton therapy in benign tumors in adults such as: low grade meningioma, paraganglioma, neurinoma, pituitary adenoma, benign craniopharyngioma, and pleiomorphic adenoma. We investigated the PubMed database without any limiting dates or interval, based on following keywords: (Proton therapy OR Proton irradiation OR Proton beam) AND (Meningioma OR pituitary adenoma OR neuroma OR craniopharyngioma OR pleomorphic adenoma OR paraganglioma). We also ordered ASTRO and ESTRO congress proceedings and international journal of particle therapy, which were not indexed in Pubmed Database. The literature search was limited to “human” and “English” language. Studies with combined proton and photon therapy were excluded. These schedules were mostly favored by first generation proton therapy facilities with limited time slots access in a basic physics environment. Furthermore, papers including reports of heterogenous particle treatment or heterogenous primaries, from which it was impossible to extract precise data were excluded. The PRISMA flowchart is presented in Fig. 1. Doses were reported in Gy(RBE) considering a relative biological effectiveness of proton equal to 1.1 [10,11].

Results

Twenty-four clinical articles were included. Most studies dealt with low grade meningiomas (n = 9) (Table 1) and 4, 5, 5 and 1 included neurinomas (Table 2) pituitary adenomas (Table 3), paragangliomas (Table 4), and craniopharyngioma respectively. No study was found for pleomorphic adenomas. For nine of the 24 studies recorded, proton irradiation was delivered using active pencil beam scanning (or rasterscanning). The other studies used passive scattering (PS) technical. For each selected article, local progression free survival rate and toxicity outcomes were extracted when possible.

Benign meningioma

Meningiomas are extra-axial, slow-growing tumors that arise from the arachnoid cap cells of the central nervous system. Meningiomas account for ~20% of intracranial tumors, roughly 94% of which are regarded as benign. Total surgical resection of the meningioma and its associated dural base is generally the treatment of choice, since it results in long-term disease-free survival in a majority of patients [12]. However, not all meningiomas can be totally resected without any risk to the patient. Such risks include postoperative neurological deficits, particularly cranial nerve paralyses. Thus, radiotherapy is often needed for patients with postoperative residue, or with recurrent meningioma. For patients with multiple or inoperable meningioma, radiotherapy often remains an adapted solution too. Nine studies reported outcomes of proton therapy for treatment of WHO Grade I meningioma. Indications of proton irradiation included primary treatment, residual tumor following surgery, and recurrent tumor following surgery. Fractionated proton therapy led to five years excellent local control rates ranging from 88% to 100% (Table 1) [13–18]. Fractionated proton therapy usually delivered 54–60 Gy(RBE) in five 1.8–2 Gy daily fractions per week to the tumour volume. Similarly, local control rates higher than 90%, after 5 years were achieved with hypofractionated stereotactic proton therapy [13,19–21]. In case of proton radiosurgery, the dose was prescribed on the 90–95% isoline. Fractionated proton therapy achieved excellent control rates with minimal toxicities. Neurologic

Table 1
Protontherapy for grade I meningioma.

Reference	n Patients	Dose	Technical	Local control (LC or PFS)	Toxicity	Follow up
Murray et al. [16]	61	54 Gy(RBE) [50.4–64 Gy(RBE)]	Fractionated; PBS	5 years LC = 95.7%	5 years grade III Free survival = 89.1%	56.9 months
Vlachogiannis et al. [19]	170	21.9 Gy [14–46 Gy]	Hypofractionated stereotactic, PS	5 years LC = 93%	9.41% of patients developed pituitary insufficiency, radiation necrosis, visual impairment or expansive tumour cyst	84 months
Slater et al. [18]	47	59 Gy(RBE)	Fractionated; PS	5 years LC = 99%	13% of patients developed neurologic symptoms 6% of patient presented pan hypopituitarism	74 months
Weber et al. [14]	23	54 Gy(RBE) [52.2–56 Gy(RBE)]	Fractionated; PBS	5 years LC = 100%	Cumulative 5-year Grade 3 late toxicity-free survival: 84.5%.	62 months
Halasz et al. [20]	50	13 Gy(RBE)[10–15.5Gy(RBE)) in 1 fr	Radiosurgery, PS	3 years LC = 94%	5.9% potential permanent effects	32 months
Vernimmen et al. [13]	23	54 Gy(RBE) in 27 fr to 61.6 Gy(RBE) in 16 fr 20.3Gy(RBE) 3 Fr	Stereotactic fractionated radiotherapy (n = 5), PS Hypofractionated stereotactic radiotherapy (n = 18), PS	5 years LC = 91.3% (88% for HFSRT and 100% for SRS)	1 patient developed short-term memory disturbance 11% late side effects (hearing loss and temporal epilepsy)	40 months
Gudjonsson et al. [21]	19	24 Gy(RBE) [14–24 Gy(RBE)], 4 fr	Hypofractionated stereotactic radiotherapy, PS	3 years LC = 100%	No toxicity. No additional cranial nerve dysfunctions have occurred during follow-up.	36 months
Weber et al. [15]	13	56 Gy(RBE) [52.2–64 Gy(RBE)]	Fractionated; PBS	3 years LC = 100%	Cumulative 3-year toxicity free survival : 76.2%	34,1 months
El Shafie et al. [17]	102	54 Gy(RBE) [50–60 Gy(RBE)] in single doses of 1.8 GyE or 2 GyE	Fractionated; PBS	5 years PFS = 96.6%	2 Patients with grade III radionecrosis. 1 patient with grade III asthenia secondary to hypopituitarism.	58 months

Table 2
Protontherapy for pituitary adenoma.

Reference	n Patients	Dose	Technical	Local control	Toxicity	Follow up
Weber et al. [29]	88	12 Gy(RBE) [10–18 Gy(RBE)]	Proton radiosurgery, PS	5 years local control rate: 93.6% 5-years radiological reduction rate was 94.7%	33.3% retained serviceable hearing ability. 5-year normal facial and trigeminal nerve function preservation rates: 91.1% and 89.4%	38.7 months
Harsh et al. [31]	61	12 Gy(RBE) [9–13 Gy(RBE)]	Proton radiosurgery, PS	2 years local control rate:94% 5 years local control rate: 84%	4.7% and 9.4% of severe/persistent or Mild/transient respectively alteration of V/VII 4.7% severe hydrocephaly or ataxia. 66% of progressive lost hearing for patients with initially serviceable hearing ability. 3.2% appearance of tinnitus	34 months
Bush et al. [28]	30	If useful hearing, 54 Gy(RBE) no hearing 60 Gy(RBE)	Proton Fractionated, PS	Local control rate at last follow up 100%	31% of patients with initially serviceable hearing maintained useful hearing. No transient or permanent treatment-related V or VII nerve dysfunction	34 months (mean)
Vernimmen et al. [30]	51	21.4 Gy(RBE) [14–33 Gy (RBE)], 3 fr	Hypofractionated stereotactic proton therapy, PS	5-years local control rate: 98% 10-years local control rate: 87%	5-years hearing preservation rate of 42% for patients with initially serviceable hearing. 8.3% and 9.5% developed a new V and VII respectively neuropathy	60 months (mean)

Table 3
Protontherapy for schwanomma.

Reference	n patients	Dose	Technical	Local control	Toxicity	follow up
Ronson et al. [48]	47	54 Gy(RBE) [50.4–56 Gy (RBE)]	Fractionated, PS	LC: 100% (29% tumor regression and 24% tumor resolution) at last follow up. 85.7% had normalized or decreased hormone levels at last follow up 5 years hormonal normalization rate: 22.8%	23.3% reported new minor visual deficits. 1 patient with resolutive brain radio necrosis. 20% and 35% of Hypopituitarism in patients with nonsecreting and secreting adenomas	47 months (radiological) 83 months (endocrinological)
Wattson et al. [47]	165	20 Gy(RBE) [15–24 Gy (RBE)] n = 152 (50.4–54 Gy(RBE)) n = 13	Proton radiosurgery or stereotactic proton therapy PS (n = 162) Fractionated proton therapy PS (n = 13)	LC: 98% at last follow up. 5 years hormonal normalization rate: 59%	3-year and 5-year rates of new deficiency of at least 1 axis requiring replacement were 45% and 62%, respectively. 2.4% of temporal seizure.	48 months (radiological) 52 months (endocrinologic)
Petit et al. [46]	22	20 Gy(RBE) [15–24 Gy (RBE)]	Proton Radiosurgery PS	Overall response rate: 95% 5 years hormonal normalization rate: 59%	38% of new pituitary deficits	72 months
Aghi et al. [49]	31	20 Gy(RBE)	Proton Radiosurgery PS	58% cured (morning fasting serum cortisol $< 5\,\mu g/dL$, urine cortisol $< 20\,\mu g/24\,h$)	42% developed proton beam-induced endocrine dysfunction. none developed cranial nerve neuropathies	43 months
Petit et al. [45]	38	20 Gy(RBE) [15–20 Gy (RBE)]	Proton Radiosurgery PS	5 years hormonal normalization rate: 58%	52% of new pituitary deficits	62 months

Table 4
Protontherapy for paraganglioma.

Reference	n Patients	Dose	Technical	Local control	Toxicity	follow up
Ioannides et al. [57]	7	35 Gy(RBE) en 15 fr (n = 5) 54 Gy(RBE) en 30 fr (n = 1) 59.4 Gy(RBE) en 33 fr (n = 1)	Fractionated proton therapy. PBS	100% of local control at last follow up	No late toxicity	52 months
Chowdury et al. [56]	18	50.4 Gy(RBE) [45–70 Gy(RBE)]	unknown	53% of objective radiological response	No late toxicity reported	30.9 months
Giacomelli et al. [59]	6	50 Gy(RBE)	Fractionated proton therapy PBS	At time of analysis 100% of local control	No late toxicity reported	unknown
Kang et al. [55]	41	50.4 Gy(RBE) [45–68 Gy(RBE)]	Fractionated proton therapy. PBS	100% of local control at last follow up 63.4% of patients reported an improvement of their symptoms	No grade III toxicity	54.7 months
Cao et al. [58]	10	50.4 Gy(RBE) (45.0–67.0 Gy)	Fractionated proton therapy. PS	100% of local control at last follow up	NO grade III–IV acute or late toxicity	24.6 months

toxicity was more pronounced in case of cavernous sinus involvement [18] or if meningioma was adjacent to or encased the optic pathway [15]. In Slater's study, in which all patients had cavernous sinus involvement; 8.3% of patients developed neurologic symptoms including optic neuropathy. However for half of them, it was only transient symptoms, and they resolved after symptomatic treatment such as corticoids supplementation. Six per cent of patients had pan hypopituitarism. Two thirds of patients with toxicities had received > 59.4 Gy (RBE), an unusual dose for grade I meningioma. Among the nine studies recorded, no patients with non-skull base tumors suffered from complications related to proton therapy. Even for extensive tumors, such as in Vernimmen' study [13], where 39% of the patients had lesions bigger than 14 cm^3, toxicity was limited. Proton therapy, whatever its mode of administration, lead to similar outcomes than radiosurgery, hypofractionated stereotactic radiotherapy [4,22] or fractionated radiotherapy [23]. Indeed, in case of photonic irradiation long-term local control rates, are also superior to 90%, even for large base-of-skull meningioma or cavernous sinus localization [24,25]. Despite the usual difference in the treated tumor volume, radiosurgery (SRS), hypofractionated stereotactic radiotherapy (hFSRT), and fractionated stereotactic radiotherapy (FSRT) seem to provide equal radiographic and clinical control in patients with meningioma. Moreover, while we were waiting for higher late toxicity rate for hypofractionated schema, considering the higher BED delivered, and the presence of organ at risk inside the clinical target volume, no significant difference were showed [26,27].

In conclusion, high local control was achieved after proton therapy for intracranial meningioma, with acceptable radiation-induced toxicity. Proton-therapy should be probably reserved for complex, high volume meningioma, and obviously secondary radiation induced meningioma.

Neurinoma

Neurinomas, also called schwannomas, are benign tumors that arise from Schwann cells lining the nerves. Neurinomas can develop in cranial nerves and more particularly in the intra-cranial portion of the eighth cranial nerve near the cerebellopontine angle. Traditional treatment has been complete surgical resection. Although surgery provides excellent local tumor control, it is associated with significant risk of injury to the Vth, VIIth, and VIIIth cranial nerves, which can cause permanent dysfunction. Since the nineties, stereotactic radiosurgery (using photon-based irradiation delivered as a single high dose fraction) has been used as a definitive nonsurgical approach. Published reports have demonstrated excellent local tumor control. Four studies reported outcomes and toxicity of proton therapy [28–31] (Table 2). The 5-year local control rate was comprised between 87 and 98%. Three of the four studies recorded, reported outcomes with stereotactic proton therapy, delivering a median dose of 12 Gy(RBE) for radiosurgery and 21.4 Gy(RBE) for three fractions stereotactic proton therapy. Weber radiosurgical series [29] (44) showed a 5-year control rate of 93.6% associated with a radiological shrinking for 94.7% of the patients. Fractionated proton therapy led to similar results. In all studies, about a third of patients with initially serviceable hearing ability, retained serviceable hearing ability after irradiation. Post proton therapy serviceable hearing was a little bit higher in Vernimnen study: about 42% after 5 years and 10 years follow up. Vernimnen [30] presented 10 years Vth and VIIth nerve function preservation rate of 93 and 90.5% respectively. Furthermore, almost a third of patient with preexisting Vth or VIIth nerve alteration, showed an improvement of their symptoms after proton therapy [30]. Overall proton-based radiosurgery or stereotactic fractionated proton therapy achieved a long-term local control similar to photon-based radiosurgical or conventional fractionated series [26,32,33] with a comparable preservation rate of cranial nerve function. It is however expected that fewer second cancers will be observed due to absence of low – intermediate

dose spillage. Proton irradiation could be interesting in case of neurinoma or meningioma associated to genetic type 1 neurofibromatosis (NF1). In fact, irradiation in these patients lead to a fivefold increase of cerebral arteriopathies or MoyaMoya syndrome [34]. Furthermore, individuals with NF1 are at increased risk of developing radiation-induced cancers. Pre-clinical studies clearly demonstrated Nf1 heterozygosity potentiated the mutagenic effects of irradiation [35,36]. Dose sparing to vascular critical structures and surrounded healthy tissues is thus essential for these patients.

Pituitary adenoma

Treatment with medications or trans-sphenoidal surgery are generally the first-line treatments for patients with prolactinoma and other adenoma subtypes respectively [37]. Trans-sphenoidal surgery performed by experienced surgeons results in a cure rate of 60–80% [38–41] depending on tumor histology, size, degree of cavernous sinus or dural invasion, and surgical technique. However, for inoperable patients or patients with persistent disease after one or more surgical procedures, irradiation is a treatment option. It is noteworthy that the first indications of proton therapy (with passive dose delivery) in 1954 were for pituitary adenomas. The first reported series was from Harvard medical school, in 1974, with 531 patients treated by proton radiosurgery. Pituitary adenoma were irradiated with a target dose of 70 Gy in one fraction [42,43]. In 1989, Lüdecke reported the results of a small study (30 patients) designed to compare the effectiveness of two different types of radiation in patients with acromegaly where surgical therapy had failed to normalize growth hormone: conventional radiotherapy (55.8 Gy) and proton radiosurgery with a target dose from 60 to 131 Gy (medium = 91 Gy) [44]. If hormone normalization was quite similar in each group, quite logically, side effects as additional pituitary deficits and oculomotor palsies were more often seen after proton treatment. These results, produced with old techniques and high dose irradiation, which are no longer used, probably explain the increase of side effects in this study. It maybe hindered the development of proton therapy and explain the lack of published data during the 90s. Five studies [45–49] of proton therapy for pituitary adenoma were recorded, in which all kinds of pituitary adenoma were represented (Table 3). Most of the patients underwent prior resection. For 83% of the patients in these studies, proton radiosurgery with passive delivery, was the modality of irradiation. The median prescribed dose was 20 Gy(RBE) (range 15–24 Gy(RBE)] on the 90% isoline. The other 17% were treated with fractionated proton therapy at a dose ranging from 50.4 Gy(RBE) to 56 Gy(RBE). Ronson [48] and Wattson [47] reported high radiological control rates, between 98% and 100% after a 4 years follow up, whatever the proton therapy fractionation. Endocrinological control was probably a more interesting endpoint. Biochemical complete response was defined as at least 3 months of sustained normalized hormone levels, after all medical therapy was withdrawn. In Wattson [47], Aghi [49], and Petit's studies [45,46], complete biochemical normalization rates were about 60%, 5 years after irradiation. Ronson [48] reported a lower biochemical normalization rate of 22.8% at five years but at last follow-up, 85.7% had normalized or decreased hormone levels. Aghi reported a 58% rate of cured Acromegaly was significantly associated with longer time to biochemical complete response. In fact, Wattson reported a median time to complete biochemical response of 62 months [47]. On the opposite, corticotropic adenoma exhibited a shorter median time to complete response, between 14 and 32 months. Concerning morbidity, 20–62% of the patients developed new pituitary deficiency of at least 1 axis requiring pharmacological replacement. After a long term visual follow up, in Ronson [48] series, 7 patients developed minor visual deficits and 2 patients developed major visual deficits that consisted of de novo quadranopsia and bilateral optic nerve atrophy. Both of these patients had Cushing's disease and none of them received a dose superior to 54 Gy(RBE) to the chiasma. The authors hypothesized that the longstanding effects of hypercortisolism predisposed the optic chiasm microvasculature of Cushingoid patients to radiation damage. No cerebro vascular event was reported. Retrospective series evaluating stereotactic radiotherapy also showed excellent outcomes with avoiding optic ways toxicity [50–52].

Considering these data, proton therapy seems to be a safe and efficient treatment of pituitary adenoma and could be considered as an alternative to SRS or HFSRT.

Paraganglioma

Paragangliomas, which are also called chemodectomas or glomus tumors, of the head and neck are vascular neuroendocrine tumors of the autonomic ganglia derived from embryonic neural crest tissues. Paraganglioma is a rare disease with an estimated occurrence of 2–5 patients per million per year [53]. They may arise along the glossopharyngeal or vagal nerves or branches thereof in the temporal bone, jugular foramen, vagal, or carotid body locations. Despite a slow growth rate, paragangliomas can result in significant toxicity because of involvement of cranial nerves. Complete surgical removal is curative but associated with some risk of iatrogenic injury. Radiotherapy leads to excellent local control outcomes with much less toxicity [54]. The largest retrospective series reported 41 patients treated with fractionated proton therapy [55]. At last follow up, 100% of the patients exhibited local control, and 63.4% of them reported improvement of their symptoms. Tumor shrinkage was noted on imaging post-RT in 46.3% of patients at a median of 13 months (0–39) following start of RT. Tumor shrinkage seemed to be greater for proton irradiation in comparison with photon irradiation, and consequently symptoms improvements were more common for proton therapy [56,57]. Among the 5 recorded studies, no late toxicity was reported [55–59]. Outcomes resulting from proton therapy are quite similar with stereotactic radiotherapy data. According to dosimetric comparison the mean dose delivered to non tumoral tissue with proton beam was more than 2 fold lower than with volumetric arc therapy: 3.4 Gy(RBE) vs 8.2 Gy(RBE) [57].

Patients with hereditary paraganglioma-pheochromocytoma syndromes, carriers of SDH complex mutation (SDHA, SDHB, SDHC, SDHD), could particularly benefit from proton therapy. Indeed, these patients often present bilateral tumors, synchronous or metachronous, and will receive multiple irradiation courses. All dispositions should be taken to spare healthy tissues and allow multiple irradiations.

Given that outcomes, proton therapy could be considered as a safe and efficient therapeutic for the treatment of paraganglioma, while avoiding unnecessary irradiation of healthy tissues.

Others histologies

Concerning craniopharyngioma, if the literature is "abundant" concerning protontherapy for children [60–62], there was not any study reporting exclusively adult data. Only one study from Ajithkumar et al., reported a series of 16 craniopharyngioma treated with protontherapy in which 3 patients were adults [63]. After 54 Gy(RBE) delivered and a follow up of 25 months, the 3 patients exhibited a complete radiological response. All of them presented a panhypopituitarism and two of them a diabete insipidus.

There was no clinical published data about proton beam irradiation for pleiomorphic adenoma.

Discussion

Proton therapy has benefited from significant improvements for the past 10 years. If most proton therapy patients are still treated with passive scattering, in the next coming years, the majority of patients will be treated with pencil beam scanning (or spot scanning) allowing treatment optimization superior to what is achievable with photons, with respect to low and intermediate dose spillage. Intensity modulated proton therapy (IMPT, which range energy modulation offers one

additional degree of freedom compared to IMRT) and robust optimization offers unprecedented dose shaping capabilities [64]. Benign tumors could be one of the first indication to benefit from proton therapy dissemination. The principal aim should be, then, to offer excellent local control, while limiting secondary cancer risk, vascular damages and avoiding neurocognitive impairment.

Few authors have already tried to report the secondary cancer risk after irradiation of benign tumors [65]. After analysis of 426 patients irradiated with conformal or 3D radiotherapy for pituitary adenoma, Minniti et al. reported an increased cumulative risk of second brain tumors of 2.4% (95% CI, 1.2–5.0%) 20 years after irradiation [66,67]. The relative risk of second brain tumor compared with the incidence in the normal population was 10.5 (95% CI, 4.3–16.7). For meningioma, based on the analysis of 10 irradiation treatment plans (54 Gy(RBE)), Arvold et al. estimated an excess risk of second tumors of 2.8 for 10,000 patients per year in case of classical radiotherapy [8]. IMRT probably further increases the risk of secondary malignancies even if clinical evidence is limited [68]. Data concerning radiosurgery are rather comforting, but in case of important tumor size or proximity to critical structures the dose sparing of close organs at risks might limit the anti tumoral efficacy. It limits SRS use. According to dosimetric models and long follow up studies, proton therapy for benign brain tumors seems to reduce secondary cancer risk between 38% [69] and 54% [8]. Winkfield et al. compared different irradiation modalities with photon or proton for the treatment of pituitary adenoma and estimated the risk of secondary cancer using the method proposed by Schneider [70]. Approximately 5 additional tumors per 10,000 patients per year are estimated with the use of a two-field proton plan, while 12 additional cases are estimated to be seen with three field proton plans. In comparison, the excess number of second tumors with IMRT and SRT was 20.4 and 25, respectively.

The second fear of the radiotherapist, when irradiating a benign tumor, is the alteration of neurocognitive functions. The association between hippocampal dose and long-term neurocognitive function impairment for benign or low-grade adult brain tumors treated with fractionated stereotactic radiotherapy has been evaluated by Gondi. Considering an hippocampic α/β ratio of 2 Gy, an equivalent dose in 2-Gy fractions greater than 7.3 Gy to 40% of the bilateral hippocampi was associated with long-term memory impairment [71]. A recent controlled randomized trial compared stereotactic conformal radiotherapy with conventional radiotherapy for treating low grade and benign cerebral tumors in children and young adults [72]. The author concluded, that stereotactic radiotherapy compared with conventional irradiation achieves superior neurocognitive and neuroendocrine functional outcomes, over 5 years without compromising survival. Given the stereotactic irradiation dosimetric characteristics, it confirms that sparing irradiation dose delivered to neurocognitive structure is essential to preserve cognitive function.

Finally, according to data from pediatric population, the incidence of vasculopathy after radiation therapy has a considerable correlation with radiation dose. In a retrospective study including 32 pediatric patients, in whom radiation therapy had been given to fields including the circle of Willis and major cerebral arteries, 6 of them developed vasculopathy with MRI Steno-occlusive changes [73]. Moreover the occurrence of cavernoma increased after brain irradiation, especially for children younger than 10 years old at irradiation. In adults, conclusions are less obvious, but cavernomas seem to occur only after radiation dosages higher than 30 Gy [74]. In every case, this aids in proposing protontherapy for young adults patients with brain benign tumors.

It is worth to note, that almost half of studies recorded here used proton radiosurgery or stereotactic hypofractionated proton therapy for treating these benign tumors. However, among proton therapy centers, only a few of them proposed stereotactic proton therapy. Accurate planning and delivery in proton radiosurgery remains challenging due to small target volumes and typically, high doses delivered in a limited number of fractions (typically 1–6). In passively scattered proton therapy, or pencil beam scanning proton therapy, linear energy transfer (LET) of protons increases significantly over the last few millimeters of depth dose distribution the range ultimately leading to an increased relative biological effectiveness (RBE) and a higher effectiveness [10]. In case of small tumors, less than 2–3 cm, the number of Bragg peaks used to build the spread out bragg Peak (SOBP) and cover the tumor is necessarily restricted. Small tumors are then treated with higher LET, all issued from highly weighted Bragg peaks. It could lead to potentially significant differences in RBE-weighted doses, and higher efficacy (or toxicity). LET-based relative biological effectiveness (RBE) dosimetric models should be used to optimize stereotactic proton therapy.

However, with proton therapy, at a low dose per fraction, tumors with low α/β of 2–3 Gy, have higher RBEs than tissue with high α/β ratios but this difference may be reversed at a high dose per fraction, leading to lower RBEs in low α/β tissues such as benign tumors. The RBE depends on the dose. In general, it is higher for lower doses and lower for higher doses because of the shape of the shoulder of the survival curve [16,17]. Consequently, high dose per fraction could erase biological advantage of proton therapy over photonic irradiation [75].

Another critical factor associated with small field proton beam, is the uncertainties of dose calculation method. Effects such as aperture scatter or multiple-Coulomb scattering have a more drastic impact on dose distribution characteristics the smaller the cross section of the beam is. Scattering at the aperture and aperture thickness are typically not taken into account as they are generally modeled as binary 2D objects [76,77]. The impact of these effects is likely most significant when treating with small fields. With decreasing aperture size and increasing beam range in patients, the scattering in small fields results in a decrease in dose along the central axis of the Bragg peak due to lack of lateral equilibrium. It means that for small proton field, the aperture is so small that there is little or no uniform dose region, the transverse profile of the beam becomes entirely penumbra. Depending on the depth of the target, the penumbra can also be significantly widened due to scattering in the patient. Consequently, planning systems need to be able to predict the correct dose distributions and clinical dosimetry has to predict the correct output factor (dose per UM). In clinical practice output factor correction methods based on field size have to be applied and accurate dose algorithms (using Monte Carlo simulation) that can accommodate small proton fields should be developed [76,78].

Despite these difficulties, it is worth mentioning that all of the 10 studies reporting proton radiosurgery or hypofractionated proton therapy were performed using double scattering. Pencil beam scanning was only used in classical fractionated proton therapy.

If, we want to take maximum advantage of proton therapy and more particularly with stereotactic delivery, most efficient and complex TPS have to be built. Concomitantly to intensity modulated proton therapy (IMPT) development, Cao et al. and his team [79] proposed a LET-incorporated optimization for maximizing LET in target volumes and minimizing LET in critical structures and normal tissues. This may have substantial advantages in improving tumor control and reducing normal tissue toxicities.

This is a report of literature dealing with the place of proton therapy in intracranial or cervical benign tumors, in adults. Tumor control and toxicity rates are excellent. However, despite higher cost, clinical benefit of proton therapy over IMRT or photon SRS remains marginal. With the expansion of proton therapy centers worldwide, it is clearly necessary to build large prospective randomized studies with long term follow up and restrictive inclusion criteria (young patients), in order to appraise its potential impact.

Conflict of interest statement

All the authors certify that they have NO affiliations with or involvement in any organization or entity with any financial or other

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