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Hadrontherapy and its role in Oncology

REVIEW ARTICLE

RADIATION ONCOLOGY

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Abstract

Hadrontherapy is a promising treatment modality in radiation oncology. Due to the physical characteristics of particle radiation, hadrontherapy has the potential of concentrating dose delivery to the target volume while sparing surrounding tissue. While hadrontherapy has been used in the treatment of several neoplasms, there is still controversy over its role in radiation oncology. In this review, we evaluated the clinical outcomes, radiation-related adverse events and cost-effectiveness of hadrontherapy in a few selected clinical situations: uveal melanoma, pediatric central nervous system tumors, head and neck cancers, skull-base tumors and prostate adenocarcinoma.

Based on current evidence, we conclude that hadrontherapy is a clinically effective, safe and cost-effective treatment option for uveal melanoma, skull-base tumors and pediatric brain tumors. Furthermore, for prostate cancer as well as head and neck cancers, it is at least equivalent to photon beam radiotherapy, though there is not enough evidence about the advantages of hadrontherapy to make it a cost-effective option.

More clinical trials are needed to further clarify the role of hadrontherapy, and several ongoing clinical trials will soon provide new data.

Keywords

Proton Therapy, Heavy Ion Radiotherapy, Uveal melanoma, Central Nervous System Neoplasms, Head and Neck Neoplasms, Skull Base Neoplasms, Prostate Neoplasms

Resumo

A hadroterapia é uma modalidade de tratamento promissora em radio-oncologia. Devido às características físicas da radiação de partículas, a hadroterapia tem o potencial de concentrar a administração da dose no volume alvo, poupando o tecido circundante. Embora a hadroterapia tenha sido utilizada no tratamento de várias neoplasias, o seu papel na radio-oncologia é controverso. Nesta revisão, avaliamos os resultados clínicos, os eventos adversos relacionados com a radiação e a custo-efetividade da hadroterapia em algumas situações clínicas selecionadas: melanoma da úvea, tumores pediátricos do sistema nervoso central, cancro da cabeça e pescoço, tumores da base do crânio e adenocarcinoma da próstata.

Com base nas evidências atuais, concluímos que a hadroterapia é uma opção clinicamente eficaz, segura e custo-efetiva para o melanoma da úvea tumores na base do crânio e tumores cerebrais pediátricos. Além disso, tanto para o cancro de próstata quanto para o cancro de cabeça e pescoço, é, pelo menos, equivalente à radioterapia convencional, embora não haja evidências suficientes sobre as vantagens da hadroterapia para torná-la a opção custo-efetiva.

São necessários mais ensaios clínicos para esclarecer melhor o papel da hadroterapia, e vários ensaios clínicos a decorrer fornecerão em breve novos dados.

Palavras-chave

Terapêutica com protões, Radioterapia com iões pesados, Melanoma da úvea, Tumores do sistema nervoso central, Tumores de cabeça e do pescoço, Tumores da base do crânio, Tumores da próstata

Abbreviations List

Abbreviations used in this text.

ADT – Androgen deprivation therapy.

CFPT – Conventionally fractioned proton therapy.

CMBs – Cerebral microbleeds.

CNS – Central nervous system.

CSI – Craniospinal irradiation.

CSS – Cancer-specific survival.

DFS – Disease-free survival.

EPIC – Expanded Prostate Cancer Index Composite.

GI – Gastrointestinal.

GU – Genitourinary.

HFPT – Hypofractioned proton therapy.

ICER – Incremental cost-effectiveness ratio.

IMPT – Intensity modulated proton therapy.

IMRT – Intensity modulated radiotherapy.

IPSS – International Prostate Symptom Score.

LCR – Local control rate.

LET – Linear energy transfer.

OER – Oxygen enhancement ratio.

OS – Overall survival.

PBT – Protom beam therapy.

PFS – Progression-free survival.

QALY – Quality-adjusted life year.

QOL – Quality of life.

RBE – Relative biological effectiveness.

RION – Radiation-induced optic neuropathy.

SBRT – Stereotactic body radiation therapy.

SCBT – Scanning beam proton therapy.

Introduction

Since its development in the last century, radiotherapy has become an effective and indispensable treatment modality in oncology. Radiotherapy is based on the use of ionizing radiation, delivered either by an external or internal source, corresponding to external beam radiotherapy or brachytherapy, respectively. However, there has been an ever-growing interest in hadrontherapy, also referred to as 'particle therapy', which makes use of hadrons as opposed to photons. The most common particles currently used are protons, carbon-ions and neutrons. However, there is much debate on the role of hadrontherapy in radiation oncology.

Brief History of Hadrontherapy

In 1936, Gordon Locher proposed the therapeutic use of neutrons in the treatment of superficial tumors. Previous research had already shown differences in the effects of neutrons in biological tissue in opposition to X-rays. (1)

In September 1938, merely 6 years after the discovery of the neutron, Robert Stone used fast neutrons, produced by bombarding a beryllium target with accelerated deuterons, for the first time in a clinical setting. (2) During the following year, 24 patients, all with advanced cancer, received a single fraction irradiation. The early results were deemed successful and led to the development of a dedicated larger cyclotron (3). A second series of patients ran until 1943, with 226 patients treated with neutrons, doses fractioned similarly to the common X-ray protocols for that time. However, Stone observed such severe late reactions that neutron therapy was discontinued. (3, 4)

With a better understanding of the biological effects of radiation, interest in neutron therapy resurfaced in the 1950's, especially in hypoxic tumors. Patient treatment began at the Hammersmith hospital, with early results reported deemed positive, though severe late reactions were revealed during follow-up. (3)

Meanwhile, in 1946, Robert Wilson proposed the use of charged particles in medical therapy, taking advantage of their dose distribution to optimize radiation on the tumor. In 1954, researchers at the Lawrence-Berkley Laboratory used protons to ablate the pituitary gland in patients with hormone-sensitive metastatic breast cancer. (5) In 1957, Börje Larsson led the first use of proton therapy in Europe, irradiating a patient with cervical cancer at the Uppsala cyclotron. In 1961, Raymond Kjellberg irradiated the first malignant brain tumor at the Harvard cyclotron. (6)

In the next decades, new cyclotrons were built across the globe. The most notable were the facilities in Harvard Cyclotron Laboratory (1961), Dubna (1964), Moscow (1969), St.

Petersburg (1975), Chiba (1979), Tsukuba (1983) and the Paul Scherrer Institute (1984). All of these locations were physics laboratories instead of dedicated medical facilities. The first center built for medical use was in Loma Linda University Center, California, which treated the first patient in 1990. (3)

In parallel, heavier ions where also being researched, with the underlying assumption that they were more effective in hypoxic tumors than either protons or photons. Treatment with helium-ions started in 1957 and with neon-ions in 1975. (6) The medical use of carbon-ions started in 1994, at the Heavy Ion Medical Accelerator in Chiba, Japan, which is still currently operating. In Europe, the first carbon-ion facility was built in Darmstadt, Germany, in 1997. (7)

As of February 2020, there are 101 particle therapy facilities operating world-wide, with the vast majority located in Japan and the United States, with more than 200 000 patients treated with hadrontherapy. (8)

Cyclotrons

In the early days of hadrontherapy, particles were accelerated to the desired speeds using *cyclotrons*. The cyclotron was developed in 1932 at the University of California, Berkeley, by Ernest Orlando Lawrence and Milton Stanley Livingston. In essence, a cyclotron is a particle accelerator that uses an alternating electric field and a uniform magnetic field to accelerate particles to very high speeds. The principle behind it is straightforward: two semi-circular metal electrodes, referred to as 'dees' (for they have the shape of the letter D), are separated by a thin gap inside a vacuum chamber. The electrodes are placed in a uniform perpendicular magnetic field. Under its influence, a charged particle moves in a circular trajectory (Fig.1). Furthermore, the dees are subject to a rapidly alternating electric potential difference, synchronized so that the polarity of the dees reverses every time the particles cross the gap. (10)

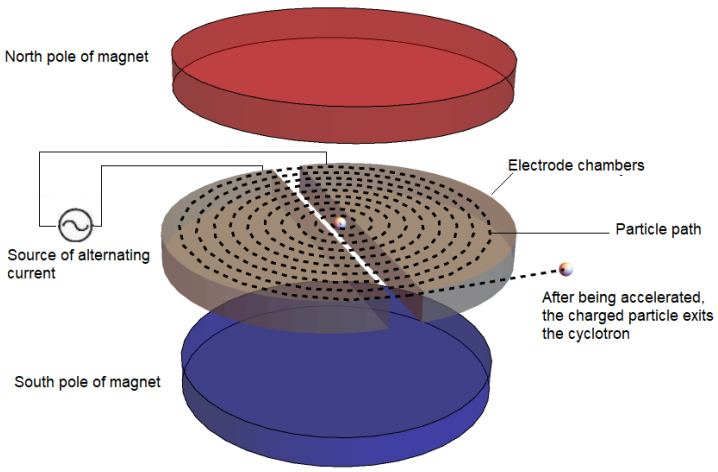

Figure 1 - Schematic diagram of a cyclotron. Adapted from El-Saftawy. (10)

Today, cyclotrons have been largely replaced by synchrotrons, which operate on a different principle. In the synchrotron the magnetic field also varies in time, allowing the particles to travel in a circular trajectory of fixed radius, instead of the spiral path in the cyclotron. The principle behind synchrotrons was developed in 1944 by Vladimir Veksler, but the first synchrotron was constructed by Edwin McMillan in 1945. For carbon-ions, synchrotrons are the only option available. (6, 9)

Physics aspects of hadrontherapy

To understand the differences between hadrontherapy and photon beam radiotherapy, a few basic definitions are needed (7, 11):

- Linear energy transfer (LET) measures the energy transferred by the particle per unit length.
- Relative biological effectiveness (RBE) is the ratio of a dose of a reference radiation (usually ^{60}Co γ-rays or 250 keV X-rays) to dose of a test radiation, given the same biological effects (typically, reducing the survival probability of the cell to 10%). Given this definition, it is clear the RBE depends on several factors, such as the specific cell type, dose distribution and presence of oxygen.
- Oxygen enhancement ratio (OER), is the ratio of the radiation dose needed to obtain the same biological effect with hypoxia *versus* no lack of oxygen.

In photon beam radiotherapy, the dose delivered decreases steadily with increasing tissue penetration depth, therefore leading to a larger dose at superficial tissues and a lesser dose in deeper ones.

With hadrons, the dose distribution is markedly different. As charged particles move through a medium, they interact through Coulomb forces with the electrons and nuclei of the medium. (11) The energy loss is, approximately, inversely proportional to the square of the speed. That is, as the velocity of the particle decreases, the energy loss increases. This means that, after travelling a specific distance, hadrons are slowed down by interactions with matter, stopping abruptly. Hence, we have a low dose proximal to the target, and the dose quickly falls to zero distally to the target. This particular distribution is called Bragg's peak (Fig. 2).

For protons, the majority of energy loss is due to interactions with the electrons, with the interactions with the nuclei accounting for little. Protons have a lower LET than other charged particles, and their RBE is around 1.0-1.1. (12) The RBE is not uniformly distributed, however, being higher near the end of the proton range, a phenomenon which creates uncertainty in treatment planning, and must be taken into consideration.

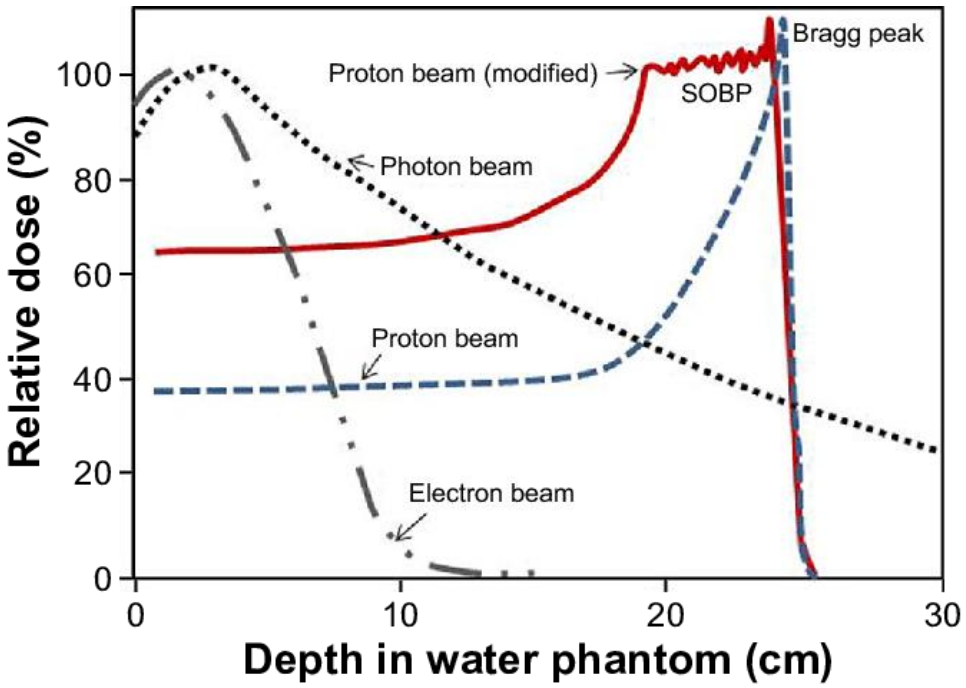

Figure 2 - Dose-depth curve for several types of radiation. For photons and electrons, the dose delivered quickly decays as depth increases. Protons (blue dashed curve), on the other hand, have a low entry dose, and then have a sharp dose delivery at a certain depth, followed by an abrupt drop. This is called the Bragg peak. Combining several proton beams with different energies creates a more uniform dose delivery, creating a "spread out Bragg peak". Figure reproduced from Yamoah (93) with permission. Original publisher: Dove Medical Press.

Heavier ions, such as carbon-ions, having a larger mass than protons, show less bean scattering and have a higher RBE. With heavy ions, peripheral collisions can fragment the ions, creating secondary smaller ions, which usually have a different RBE and a different linear range, causing some damage beyond the Bragg peak. (11) These effects are important and must be taken into account when planning heavy-ion therapy.

In general, hadrontherapy uses high LET radiation. While there are still many unknown factors in the interaction of hadrons wtih human cells, the predominant biological effect is a result of the direct ionization of the atoms in key structures of the target cells (such as nucleic acids or proteins). Photon based radiotherapy, on the other hand, is mainly based on the radiolysis of water, generating free radicals from water and oxygen. Hence, for hadrontherapy the tissue damage is therefore mainly based on nuclear interactions creating single- and double-strand breaks on the target cell's nucleic acids, providing a theoretical advantage in tumors with hypoxic cells, which are traditionally radiation-resistant. (7,11)

Hadrontherapy techniques

With a single proton-beam energy, the Bragg peak is too narrow for practical purposes. By combining several beams with different depths of the Bragg peaks and appropriate weights, we can create a uniform, leveled, “spread-out Bragg peak”, whose extent can vary with the number of peaks used (Fig.3). This allows a uniform dose distribution to the tumor. However, this has the disadvantage of a higher dose delivered before the Bragg peak, that is, the dose delivered for tissues proximal to the tumor is higher. (13)

In order to adequately cover the three-dimensional target volume, there are three types of irradiation techniques for proton therapy, which can also be used for heavier ions.

With passively scattered proton bean therapy, a narrow proton beam is scattered by specialized equipment, such as scatter foils and range shifter wheels. Brass collimators and compensators are used to further refine the shape of the beam, but these devices must be custom-built for each patient. (14, 15)

Uniform scanning uses magnets to spread the proton beam, but it still requires collimators to adjust the shape. (14)

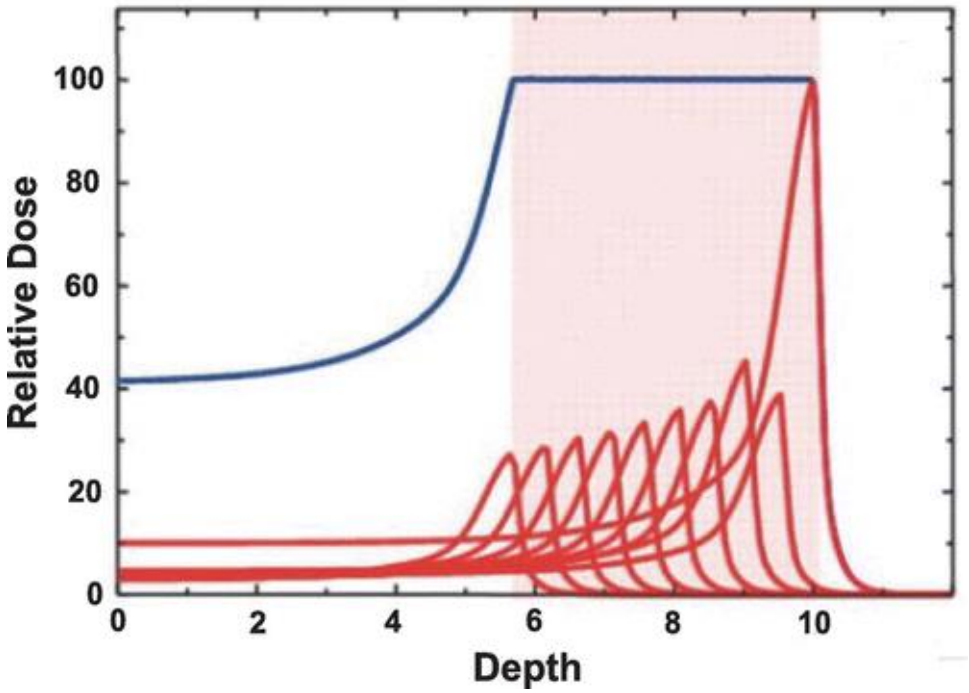

Figure 3 - Superimposed proton beams and Spread-out Bragg peak. Superimposing several proton beams with different energies (in red), and therefore with different depths of the Bragg peak, and appropriate weights, we can create a uniform, leveled, “spread-out Bragg peak” (in blue). This allows a uniform dose distribution to the tumor, but it also delivers a higher entry dose. Reproduced from Battistoni et al. (11)

Intensity modulated proton therapy (IMPT), also known as ‘'pencil beam’ or ‘active scanning’ proton therapy is the most recent technique. Unlike intensity modulated radiotherapy (IMRT), which uses multiple beams and collimators to shape the irradiation field, IMPT uses electromagnets to guide narrow, monoenergetic, proton beams (the so-called ‘pencil beams’). By varying the number of protons and their energy, these beams scan over the tumor at different points with various depths. This technique does not require the use of customized collimators, but its high precision makes it very sensitive to organ movement. (14, 15)

Goal

The goal of this review is to evaluate clinical outcomes, radiation-related adverse events and cost-effectiveness of hadrontherapy in a few selected clinical situations, where some data are already available: uveal melanoma, pediatric central nervous system tumors, head and neck cancers, skull-base tumors and prostate adenocarcinoma. We intend to clarify, based on current evidence, for which clinical indications would hadrontherapy be most advantageous.

Material and Methods

In order to achieve our goal, a search for original articles using the on-line databases PUBMED and EMBASE was conducted, filtering for articles published after 2010 and in English. The search terms used where ‘Proton Therapy’ (MeSH term) or ‘Heavy Ion Radiotherapy’ (MeSH term) combined with ‘Uveal melanoma’ (MeSH term), ‘Central Nervous System Neoplasms’ (MeSH term), ‘Head and Neck Neoplasms’ (MeSH term), ‘Skull Base Neoplasms’ (MeSH term) and ‘Prostate Neoplasms’ (MeSH term).

The articles that were deemed most relevant in evaluating the outcomes of hadrontherapy were selected, either regarding disease control or adverse events, and articles evaluating cost-effectiveness for hadrontherapy. Firstly, articles were screened by title and abstract. Criteria for exclusion include duplicate articles, articles not focusing on humans, articles focusing in dosimetry or physical aspects of hadrontherapy and patient samples with fewer than 10 patients. In the case of central nervous systems neoplasm, only articles with patients under 21 years old were selected. When different studies followed the same patient series, the most recent publication was included. No selection was made regarding study design or radiation delivery technique.

Furthermore, the online database ClincalTrials.gov was accessed, with the same search parameters, in order to identify ongoing, non-recruiting, clinical trials.

Results

Table I resumes the most relevant data of the studies selected for this work.

All articles that report on survival statistics used Kaplan-Meier estimators. Adverse events reported were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. In general, grade 1 corresponds to mild symptoms, grade 2 to moderate symptoms, grade 3 for severe but not life-threatening adverse events, grade 4 for life-threatening events and grade 5 for death. Cost-effective analyses are based on estimations for quality-adjusted life year (QALY), a generic measure of disease burden, and incremental cost-effectiveness ratios (ICER), a measure of increase cost per extra unit of health effect, usually QALYs.

Table II summarizes the aims and study design for the ongoing clinical trials on hadrontherapy.

The results will be reported according to different pathologies.

Uveal Melanoma

Uveal melanoma is the most common primary eye tumor in adults (15), and can affect the choroid, ciliary body or iris. Its primary treatment is radiation, mainly delivered in the form of brachytherapy by plaques, but also by stereotactic techniques or hadrontherapy.

The dosimetric advantages of hadrontherapy make it an interesting therapeutic choice for these tumors, and indeed this has been true since 1975. (17)

Fifteen studies were selected. (18-32) Tens studies focused on clinical outcomes, four had adverse events for the primary outcome, and one was a cost-analysis. In terms of study design, five studies were prospective and seven were retrospective. The total dose received varied between 50 and 85 Gy_{RBE}. The size of the cohorts ranged from 27 to 3088 patients, with a median follow-up ranging from 29 months to 14.6 years for patients who received hadrontherapy.

Clinical Outcomes

A study by Sikuade et al (18) compared 191 patients with uveal melanoma treated with either stereotactic techniques (85 patients, median follow-up of 27 months, median age at treatment 64 years, all patients received a dose of 35 Gy) or proton therapy (106 patients, median follow-up of 29 months, median age at treatment 59 years, all patients received a dose of 53.1 Gy_{RBE}). They showed comparable local recurrence-free rates (98% and 95%, respectively) for the follow-up period. Furthermore, visual acuity was better at last review in the proton therapy branch (54% against 33% with 6/60 or better), with no significant difference found for tumors farther than 0.5 mm from the optic disc. As for adverse events, the rates of radiation

retinopathy, optic neuropathy and neovascular glaucoma were 24%, 28%, 11% in the proton therapy branch against 30%, 13%, 5% in the stereotactic branch, respectively. The rates of enucleation were 2.4% and 3.7%.

A randomized clinical trial by Mishra et al (19) compared 184 patients with uveal melanoma treated with either helium-ion particle therapy or iodine-125 plaque therapy. The particle therapy arm consisted of 86 patients, with a median follow-up 14.6 years and mean age at treatment of 53.4 years. The plaque arm consisted of 98 patients, with a median follow-up 12.3 years and mean age at treatment of 58.4 years. Both arms received a dose of 70 Gy_{RBE} (with a RBE of 1.3 for helium-ions and 1 for iodine-125). They reported a superior 5-year local control rate (LCR) for particle therapy compared to plaque therapy, 100% against 84%. The 12-year LCR were, respectively, 98% and 79%. The 5- and 12-year enucleation rates for the particle and plaque arms, were, respectively, 11% against 22% and 17% against 37%. They reported that hadrontherapy was the most significant predictor of local control and eye preservation.

In terms of long-term survival, a study by Lane et al (20) in a population of 3088 patients treated with proton therapy ascertained that 41.6% of the deceased patients died of uveal melanoma, with mortality rate by melanoma at 15, 20 and 25 years after treatment being 24.6%, 25.8% and 26.4%, respectively. Annual mortality rates decreased after 6 years. This is similar to alternative therapeutic modalities.

In a series by Thariat et al (21), 865 patients with parapapillary uveal melanoma, treated with proton therapy, showed a 5-year relapse free survival rate of 92.7% and visual acuity ≥20/200 in 47.2% of patients at the last follow-up. As for adverse events, they reported neovascular glaucoma, radiation-induced optic neuropathy, maculopathy in 17.9%, 47.5%, and 33.6% of patients, respectively.

A recent study by Seibel et al (22) evaluated long term outcomes in 27 patients with uveal melanoma with posterior extraocular extension, treated with proton therapy. With a median follow-up of 80 months, they found no cases of local recurrences, even when optic nerve invasion was present. In addition, they report 3 cases of enucleation, due to unresponsive neovascular glaucoma.

A study of 886 patients by Caujolle et al (23) reported a 5-year recurrence-free rate of 93.9%. The 5- and 10-year metastasis-free survival rates were 88.3% and 76.4%. As for 5-and 10-year eye retention rates, they were 91.1% and 87.3%, respectively. Visual acuity did not decrease for 34% of the patients. The main adverse events reported were cataracts (31.67%), glaucoma (17%, of which neovascular glaucoma accounts for 11.17%), radiation retinopathy (27.54%), and radiation neuropathy (7.79%).

Choi et al (24) reported on a series of 20 patients treated with gated proton therapy. With a median follow-up of 43 months, the LCR was 95% and disease control rate was 90%. Four patients maintained visual acuity, and reported adverse events were vitreous hemorrhages, cataracts, neovascular glaucoma and posterior synechiae.

In an interesting study by Petrovic et al (25), 43 patients under 21 years of age were matched with 3 adult controls each, in a total of 129 adult control patients. The mean follow-up was 155 months for the juvenile patients and 79 months for the adult controls. Younger patients showed an increased survival rate and lower 10-year-metastatic rates (93% *versus* 65% and 11% *versus* 34%, respectively). However, no significant differences were found in the rates of eye retention (90% at 15 years against 67% at 15 years), or incidences of retinal ischemia (37% *versus* 16%) or neovascular glaucoma (19% in both cases).

Macdonald et al (26) reported on a 147 Scottish patient series of with medium or large size tumors, treated with proton therapy. They reported a 5-year eye retention rate of 71.3%. Reasons for enucleation were mainly suspicion of recurrence (48%) or neovascular glaucoma (42%). The 5-year specific survival rate was 87.7%, a comparable rate with other studies.

As for heavy-ion radiotherapy, a study by Toyama et al (27) followed 116 patients with uveal melanoma that was locally advanced or in an unfavorable location, treated with carbon-ion therapy. The 5-year overall survival (OS), cancer-specific survival (CSS), local control, distant metastasis-free survival, and eye retention rates were 80.4%, 82.2%, 92.8%, 72.1%, and 92.8%, respectively. In an effort to reduce the incidence of neovascular glaucoma, 2-port orthogonal irradiation was used in 51 of the patients, with a significant decrease in the incidence (41.6% and 13.9%).

Adverse events

Apart from previously described side effects, studies with a primary outcome for adverse events were selected.

A study by Lee et al (28) evaluated the acute adverse events of 92 patients who underwent proton therapy. In the follow-up 6 months after treatment, 10 patients (10.9%) experienced corneal toxicity. Reported risk factors were anterior location of the tumor and a larger tumor size. The dose-volume histogram parameters mean corneal dose, V25 and V45, even when adjusted for tumor location, also independently predicted for corneal toxicity when they exceeded cutoff values of 32 Gy_{RBE}, 58% and 32%, respectively.

In a study by Mishra et al (29) they described the incidence of neovascular glaucoma in 704 patients treated with proton therapy, with a median follow-up of 58.3 months. They reported a 12.7% incidence, with an associated 5-year enucleation rate of 4.9%. Moreover, they reported

as risk factors for neovascular glaucoma: larger tumors, higher T stage, greater height and proximity to the disc. In particular, the incidence was highest when both anterior and posterior critical structures received threshold dose levels.

Lanteri et al (30) researched the risk of radiation induced damage to the lacrimal gland, and subsequent dry eye syndrome, in uveal melanomas with a temporal superior location treated with proton therapy. In a series of 1445 patients, with all patients receiving a total dose of 52 Gy_{RBE}, 14.7% developed dry eye syndrome, and 2.0% developed a corneal ulcer. The 5-year dry eye syndrome survival rate of 83.6%. They did not conclude that a temporal superior location of uveal melanoma should be a contraindication of proton therapy, as it is a manageable adverse event.

Seibel et al (31) investigated the cataract incidence in 258 patients, mean age 50 years, treated with proton therapy. With a median follow-up of 72.6 months, they showed a cataract incidence of around 74% within 5 years, with no advantage in comparison in this regard with other forms of radiotherapy. This effect is likely dose-dependent, as higher doses are associated with higher incidence. However, neither the cataracts nor the cataract correcting surgery appeared to affect the long-term visual outcome.

Cost-effectiveness

An American study on the cost-effectiveness of treatment options for uveal melanoma by Moriarty (32) suggested both proton therapy and plaque brachytherapy had a higher cost per quality-adjusted life-year in comparison to primary enucleation. However, the authors note that this result was dependent on sensitive parameters and could change with more evidence of the comparative efficacy between treatments.

Tumors of the Central Nervous System in Pediatric Patients

Central nervous system (CNS) tumors are the most common non-hematological cancers in the pediatric population. While varying with the specific histology, the treatments available for pediatric CNS tumors are a combination of surgery, chemotherapy and radiotherapy. For some of these malignancies, such as medulloblastoma, current protocols dictate the use of an additional craniospinal irradiation (CSI).

It is not surprising that the promise of minimizing radiation dose to the surrounding tissues made hadrontherapy an attractive option for these malignancies.

For all of these studies, two or more different histologies are represented. In all cases, the majority of tumors represented are some of the following: astrocytoma, atypical rhabdoid

teratoid tumor, craniopharyngioma, ependymoma, germinoma, low-grade glioma, medulloblastoma or meningioma.

Twenty-three publications were selected. (33-55) Primary outcomes were clinical outcomes in seven studies, adverse events in fourteen studies, and two were cost-analysis. In terms of study design, seven studies were prospective and fourteen were retrospective. Reported median ages at treatment varied between 2.5 and 11.9 years. The total dose received varied between 50 and 60 Gy_{RBE}. The size of the cohorts ranged from 30 to 644 patients, with a median follow-up ranging from 0.6 years to 5.6 years for patients who received hadrontherapy.

Clinical Outcomes

In a phase II study by DeNunzio et al (33), 5-year outcomes were evaluated for 100 patients. Cancer-free survival was 84% and OS was 94%. Better results were achieved for gliomas and craniopharyngiomas (cancer-free survival of 94% and 100%, respectively) and worse outcomes occurred in ependymomas (cancer free survival of 68%). In addition, they did not report any *de novo* hearing loss, but there were 13 new cases of endocrine deficiency post treatment, correlated with increased dose to the pituitary and hypothalamus. Neurocognitive and quality of life scores were stable, and no radiation induced necrosis was reported.

Pulsifer et al (34) evaluated a cohort of 155 patients. Of them, 60 received CSI (with median dose 24.3 Gy_{RBE}). The remaining patients received only focal proton therapy. Mean IQ scores declined from 105.4 to 102.5, with the effect being predominant only in children younger than six years old. Moreover, patients who received CSI showed significantly worse scores in IQ, processing and working memory. However, adaptive skills were stable in general.

As part of a larger ongoing study, Antonini et al (35) followed a cohort of 39 patients, of which 21 received CSI and 18 focal irradiations. They evaluated the executive functioning, processing speed and attention of the patients, and found that as a whole the cohort did not deviate from population standards. However, patients who underwent CSI showed relatively worse results in processing speed.

Grieco et al (36) evaluated the developmental and behavioral functioning at the beginning of treatment and at follow-up consultations for 35 patients, all under 3 years of age at the time of treatment, with mean age 2.5 years. The treatment consisted of either focal proton therapy or CSI. There was no significant change found in adaptive skills, emotional or behavioral functioning, and executive skills. Significant declines in intelligence and communication skills were observed in patients who underwent CSI, but still within acceptable ranges.

Gross et al (37) followed a cohort of 125 patients with a primary brain tumor. They received either proton therapy (58 patients) or photon therapy (67 patients). A multivariable analysis

showed favorable outcomes in full-scale IQ, processing speed, verbal IQ and general adaptive functioning in the proton therapy cohort relative to the photon therapy cohort. Of note, patients in the photon therapy branch had a higher median follow-up time, 6.7 years *versus* 2.6 years for the proton therapy branch. However, the general trend of the results was maintained even after truncating follow-up time in the photon therapy cohort.

Indelicato et al (38) followed 166 patients and reported a 3-year LCR of 91%, and 3-year overall survival of 96%. Cyst expansion was reported in 13 patients with craniopharyngioma, leading to visual impairment in one case. Reported adverse events include *de novo* seizures (1.8%), symptomatic vasculopathy (1.8%) and symptomatic brain stem necrosis (0.6%).

Kahalley et al (39) worked with a cohort of 150 patients, 60 of which received photon therapy (mean age at treatment 8.1 years, median total dose to tumor 54.0 Gy, mean follow-up 5.4 years) and the remaining 90 received proton therapy (mean age 9.2 years, median total dose to tumor 54.0 Gy_{RBE}, mean follow-up of 2.7 years). They reported a decrease of 1.1 IQ points per year for patients who received photon therapy, but no significant change over time was reported for patients who received proton therapy. Interestingly, if we consider only patients who received CSI, there was no significant IQ difference in both treatment options. Evolution of IQ over time showed no significant differences between both treatment groups, regardless of the use of CSI.

Adverse events

Ondrová et al (40) reported on a 99-patient cohort, who received proton therapy due to CNS tumor or, in 10 patients, another diagnosis that required CNS irradiation. These patients were considered at risk for CNS toxicity because they received more than 50 Gy_{RBE} to CNS structures. With a median follow-up of 24 months, they report an incidence of clinically significant CNS toxicity (adverse events grade 2 or higher) of 5.05%. Furthermore, they report a death due to brainstem and cervical spine necrosis.

Yock et al (41) collected parent-proxy quality of live scores 3 years after treatment for 57 patients treated with proton therapy. They were paired with 63 patients treated with photon therapy for comparison (median age at treatment was 7.7 years, median follow-up was 2.9 years). The assessment tool used was the PedsQL Core Module. The total scores were significantly different for patients treated with proton therapy, patients treated with photon therapy, and the general population. The scores were, respectively, 75.9, 65.4 and 80.9. The cohort treated with proton therapy scored lower than the general population in psychological domains, but not in the physical domains. In addition, the cohort treated with protons scored higher compared to the cohort treated with photons in all domains.

Song et al (42) evaluated the hematological and gastrointestinal adverse events of 30 patients who underwent CSI, with a mean age of 10 years. The mean irradiation dose was 32.1 Gy_{RBE} (range: 23.4-39.6 Gy_{RBE}). They were compared with a control group of 13 patients who received photon CSI (mean age at treatment 11 years, median follow-up of 22 months and mean dose delivered 29.4 Gy, with range 19.8-39.6 Gy). Patients who underwent proton CSI had less severe thrombocytopenia and higher recovery rates of leucocytes and platelets. In the group of patients treated with proton CSI, there were no cases of diarrhea, as opposed to a 23% incidence in the patients who received photon CSI. Dysphagia occurred in 47% of the proton cohort, and in 15% in the photon cohort; however, all cases of dysphagia were grade 1 or 2. Non hematological grade 3 adverse events occurred in two patients in the proton group (anorexia and vomiting), and one patient in the photon group (diarrhea).

Frakuli (43) et al assessed the incidence of early ototoxicity in a cohort of 63 children, mostly with medulloblastoma or atypical rhabdoid teratoid tumor, who received CSI in the posterior fossa using pencil beam proton therapy. The median CSI dose was 24 Gy_{RBE} (range: 18-36 Gy_{RBE}) and median boost dose was 30.6 Gy_{RBE} (10.8-36 Gy_{RBE}). They report a low rate of early ototoxicity at 1-year follow-up, with only six children presenting severe hearing loss, and in four cases it was present before treatment. They found no correlations with age, sex or median dose to the cochlea.

Kralik et al (44) studied a cohort of 100 patients with primary brain tumors, and evaluated the presence of radiation induced cerebral microbleeds (CMBs). The incidence of CMBs was 43% 1 year after treatment, 83% 5 years after treatment, and 81% 6 years or more after treatment. The median time to develop CMBs was 8 months. As risk factors, they report younger age, higher maximum dose, and the percentage and volume of brain exposed to 30 or more Gy_{RBE}. These findings are similar to those with photon-based external beam radiotherapy. Another study including 75 patients found similar results (45), with an incidence of large vessel cerebral vasculopathy of 6.7%, with a median time of development of 1.5 years, and 5.3% patients experienced a stroke. Also, Hall et al (46) reported the incidence of vasculopathy (including asymptomatic blood vessel narrowing) or stroke on a cohort of 644 patients after proton therapy. The 3-year cumulative rate was 6.4% for any vasculopathy, and 2.6% of the patients had permanent neurological complications or required surgical revascularization due to the severity of the vasculopathy. Moreover, 1.2% of the patients experienced a stroke with permanent damage. The main risk factors reported were young age (less than 5 years) and a maximum dose of 54 Gy_{RBE} or higher to the optic chiasm.

Bojaxhiu et al (47) had a cohort of 171 pediatric patients with brain or skull base tumors treated with beam scanning proton therapy. Their goal was evaluating the incidence of radiation necrosis and white matter lesions. 17% patients developed radiation necrosis, and 7% were

symptomatic, with a median time of development of 5 months. Additionally, 11% of the patients developed white matter lesions, and 3% were symptomatic. The 5-year radiation necrosis-free and white matter lesion-free rates were, respectively, 83% and 87%. The indicated risk factors were chemotherapy, ependymomas and hydrocephalus present before treatment. These results were similar to previous studies.

Gentile et al (48) studied a cohort of 216 patients with posterior fossa tumors (medulloblastoma, ependymoma, and atypical teratoid rhabdoid tumor) treated with proton therapy. They state an incidence of brain stem injury of 2.3% in all patients, with a 5-year cumulative incidence of 2.0%. Furthermore, they suggest that brainstem injure is rare when the maximum point dose received in the brainstem is below 55.8 Gy_{RBE} and median volume of the brainstem receiving 55 or more Gy_{RBE} is below 6.0%.

In a similar study, Indelicato et al (49) observed the brainstem toxicity outcomes in a cohort of 313 patients, with brain or skull base tumors, treated with proton therapy and receiving more than 50.4 Gy_{RBE} in the brainstem. They reported a two-year brainstem toxicity cumulative incidence of 3.8%, with 2.1% manifesting grade 3 toxicity or higher. They report as significant risk factors patient younger than 5 years and tumor located in the posterior fossa. These incidence rates are similar to those of photon-beam radiotherapy.

Fukushima et al (50) evaluated the presence of co-morbidities and quality of life on a cohort 60 Japanese patients, diagnosed with primary brain or head and neck tumors. The patients were treated with proton therapy. Of the 32 still surviving patients, 11 had at least one co-morbidity of grade 3 or 4. They assessed quality-of-life scores in 17 patients, and the average score was above the norm for Japanese children and adolescents, regardless of co-morbidity. In addition, quality-of-life scores were correlated with a longer time interval since treatment.

Eaton et al (51) evaluated health related quality-of-life scores, with PedsQL Core and Brain Tumor Modules, in a cohort of 40 children treated with proton therapy at age 3 years or younger. They reported that lower scores were associated with increased dose to the supratentorial brain and the hypothalamus-pituitary axis. Most of the children (90%) attended a regular classroom, with 48% requiring an individualized education program.

In terms of acute adverse events, Suneja et al (52) obtained the records of acute adverse events during treatment for a group of 48 patients. The patients were treated with proton therapy, and 25% underwent CSI. The most common adverse events were low-grade (grade 1 or 2), and included fatigue, alopecia and dermatitis. Insomnia and vomiting were rare. Grade 3 adverse events were rare: 2% of patients experienced grade 3 headache and 4% experienced grade 3 anorexia. Infratentorial locations were associated with more severe headaches, vomiting and nausea, and CSI correlated with more severe anorexia, nausea and alopecia.

Viswanathan et al (53) assessed the incidence of endocrine dysfunction in a cohort of 31 patients. 19 received only proton therapy (mean dose 53.84 Gy_{RBE}) and 12 received a combination of proton and photon radiotherapy (mean dose 57.75 Gy_{RBE}). They reported an incidence of 47% for the group treated only with protons and of 33% in the grouped treated with combined therapy, with no significant difference between them. The group treated only with protons, however, developed the endocrine dysfunction significantly latter than the group treated with combined therapy, 1.17 years *versus* 0.33 years, respectively.

Cost-effectiveness

A Swedish analysis by Lundkvist et al (54) used Markov simulation analysis to compare proton therapy with photon-based external beam radiotherapy for 5-year-old children with medulloblastoma. They found proton therapy led to cost savings of €23 600 and 0.68 additional 0.68 QALY per patient. This was due mainly to the reduced complication-associated costs in proton therapy, in particular due to better results in IQ maintenance and growth hormone levels. (54)

An American cost-effective analysis done by Mailhot et al (55) was based on a population of pediatric medulloblastoma patients who received treatment at age 5 years. Using a Monte Carlo simulation, they found that proton therapy was associated with higher quality-adjusted life years and lower costs in comparison with photon radiotherapy.

Head and Neck Tumors

The treatment of head and neck tumors is based on surgery, chemotherapy and radiotherapy. Due to the complex anatomy and geometry of the head and neck, as well critical structures and organs in close proximity, head and neck cancers are particularly challenging in radiation oncology. Highly advanced conformation techniques are required, in order to maximize dose delivery to the target volume and minimize it elsewhere.

Therefore, the dosimetry advantages of hadrontherapy make it a promising option in the current treatment of head and neck tumors.

There is a wide variety of head and neck tumors. In order to focus on the general topic, articles that discussed oropharyngeal cancer, nasopharyngeal carcinoma and sinonasal cancer were selected.

Seventeen studies were included. (56-58, 60-73) Seven studies focused primarily on clinical outcomes, nine studies in adverse events, and one was a cost-analysis. In terms of study design, seven studies were prospective and fourteen were retrospective. Reported median ages at treatment varied between 15.3 and 64 years. The total dose received varied between

59 and 79.4 Gy_{RBE}. Cohorts varied from 13 to 458 patients, with a median follow-up between 7.7 months to 82 months.

Clinical outcomes

Uezono et al (56) analyzed the outcomes of 17 pediatric patients (median age 15.3 years) with nasopharyngeal carcinoma treated with induction chemotherapy followed by proton therapy. At a median follow-up of 3.0 years, the overall, progression-free survival (PFS) and LCR were 100% each. With the exception of two patients, all patients developed mucositis, which resolved in every case. Serious adverse reported were cataract, esophageal stenosis, and sensorineural hearing loss (one case each) and hormone deficiency (in five cases).

Williams et al (57) reported the clinic outcomes of 21 patients with locally advanced nasopharyngeal carcinoma treated with proton therapy. At median follow-up of 16 months, the LCR, metastasis-free rate and OS were, respectively, 95%, 90% and 90%. Acute adverse events consisted of grade 3 mucositis and dermatitis. As for late adverse events, two patients presented with grade 2 xerostomia, three patients with hearing loss and one patient with dependence of the gastrostomy tube.

Gunn et al (58) reported the early clinical outcomes of 50 patients with oropharyngeal cancer treated with proton therapy. They describe a 2-year progression-free and OS of 88.6% and 94.5%, respectively. The main adverse events were acute mucositis (58%) and late dysphagia (12%). They report no adverse events grade 4 or higher. In a later case-matched analysis, (59), the patients were matched with 100 patients with the same tumor characteristics treated with photons, (mean age 61.1 years, median follow-up of 32 months). Both OS and progression free survival were similar in both groups, but the presence of gastrostomy tube at 3 months and weight loss of grade 3 or the presence of a gastrostomy tube after 1 year of treatment were significantly reduced for the group treated with proton therapy.

Koto et al (60), in a sub-analysis of a large multicenter retrospective study of 4 carbon-ion facilities in Japan, evaluated the outcomes of 458 patients with of locally advanced sinonasal tumors (including 65 tumor recurrences), mostly located in the nasal cavity, maxillary sinus and ethmoid sinus. The 2-year overall local control and survival rates were, respectively, 84.1% and 79.6%. The incidence of late adverse events grade 3 or higher was high, but still acceptable: 17%. The most common complication was visual impairment, including 5% of patients who developed ipsilateral blindness.

Toyomasu et al (61), reported on a series of 59 patients with sinonasal squamous cell carcinoma, treated either with proton or carbon-ion therapy. The dose administered ranged between 65 and 70.2 Gy_{RBE} for proton therapy and between 57.6 and 70.2 Gy_{RBE} for carbon-

ion therapy. The 3- and 5-year LCR were 54.0% and 50.4%, respectively. For the same time periods, progression free survival rates 42.9% and 34.7% and OS rates 56.2% and 41.6%. The incidence of late toxicities grade 3 or higher was 22%, again mostly visual impairment, including 2 cases of bilateral blindness.

Dagan et al (62) reported similar results with a cohort of 84 patients with sinonasal cancer (mostly olfactory neuroblastoma, squamous cell carcinoma or adenoid cystic carcinoma) treated with proton therapy as primary or adjuvant therapy. They report a 3-year local control, disease-free survival (DFS), and OS rates of 83%, 63%, and 68%, respectively. The LCR was 90% when associated with gross total resection. In terms of late adverse events, 24% of patients experienced late adverse events grade 3 or higher, including ipsilateral blindness in 2 patients and 3 deaths. The significant predictors of survival were tumor grade and continuous local control.

Russo et al (63), reported a 5-year local control and OS rate of 80% and 47% for a cohort of 54 patients with sinonasal squamous cell carcinoma stage III or IV. Smokers were correlated with worse local control (5-year control rate of 23%). Nine patients experienced grade 3 or 4 adverse events, mostly related with wounds.

Adverse events

In a recent study, Bagley et al (64) assessed the xerostomia related quality-of-life in 69 patients with oropharyngeal cancer treated with proton therapy. The questionnaires were applied before, during and up to 2 years after treatment. The greatest reported impairment occurred in the 6-week after treatment checkpoint, with 49% showing improvement by the 10th week. Nonetheless, 2 years after treatment the xerostomia related quality of life remained worse when compared with the beginning of treatment. Correlated factors reported were baseline scores and invasion of lymph nodes. A similar study, (65) assessed the dysphagia-related quality-of-life in 66 patients with oropharyngeal cancer treated with proton therapy, with questionnaires applied before, during and up to 2 years after treatment. The worse scores occurred at the end of treatment, with significant improvement by the 10th week after treatment. 14% of patients had persistently depressed scores at 2 years.

Bahig et al (66) evaluated the incidence of adverse events of IMPT in 103 patients with oropharyngeal squamous cell cancer. They report as acute adverse events grade 3 mucositis (46%), grade 3 dermatitis (43%) and grade 3 dysphagia in (15%). No grade 4 or higher adverse events were reported. 26% of patients required a gastrostomy tube during treatment. The 5-year rates of OS, LCR and DFS were, respectively, 80%, 90%, and 77%. Better survival outcomes were associated with stage I disease and patients who never smoked.

A study by Goldsmith et al (67) evaluated swallowing function for 24 patients with nasopharyngeal cancer. Videofluoroscopic swallowing studies were performed at baseline, 3 months and up to 2 years after treatment. The median follow-up period was 2.3 years, and LCR was 100%. There were abnormalities in swallowing thicker consistencies in 10% of patients at baseline, 43% after three months and 38% after 12-24 months. They report penetration-aspiration, nasal regurgitation and pharyngeal residue to be rare, and a superior swallowing function compared with historical data.

Sio et al (68), evaluated the symptom burden (based on patient-reported outcome surveys) of complications for 81 patients with oropharyngeal cancer, with thirty-five patients receiving proton therapy and forty-six patients received photon beam radiotherapy. Baseline symptom burdens were similar for both groups. Subacute (3 months after treatment) and chronic changes in taste and appetite scored were significantly better in patients treated with proton therapy.

McDonald et al (69) compared the acute adverse events of proton therapy and photon-based radiotherapy on 40 patients with nasopharynx and paranasal sinus cancers. Fourteen patients were treated with proton therapy and twenty-six were treated with IMRT. Proton therapy was associated with a lower need for opioid pain relievers and gastrostomy tube dependence 3 months after radiation. Furthermore, they found that the mean doses to the oral cavity, esophagus, larynx and parotid salivary glands to be significantly lower with proton therapy.

Zenda et al (70) conducted a retrospective analysis of 90 patients with tumors of the nasal cavity, paranasal sinuses or skull base to evaluate the incidence of late-term adverse events. They report an incidence of 26% of adverse events grade 3 or higher. The most severe complications reported were encephalomyelitis or optic nerve disorders (7%).

Holliday et al (71) compared gastrostomy tube rates between 13 patients with nasopharyngeal cancer treated with IMPT matched in a 2:1 ratio with 26 control patients, treated with IMRT, taking into account tumor and patient characteristics. The median follow-ups were 13.5 months for the IMPT group and 19.8 for the IMRT group. There were significant differences between the rate of gastrostomy tubes between the IMPT and IMRT groups: 23.1% and 57.7%, respectively, but not in median duration. Similarly, the IMPT group, when compared to the IMRT group, showed significantly lower rates of median percent body weight loss (5.3% and 7.4%, respectively) and the incidence of oropharyngeal dysphagia (7.7% and 19.2%).

Sasahara et al (72) reported on the frequency of osteoradionecrosis of the maxilla, a serious known complication of hadrontherapy in head and neck cancers. They retrospectively analyzed 63 patients with head and neck tumors treated with carbon-ion therapy. All patients received more than 10% of the prescribed total dose (57.6 Gy_{RBE} in 16 fractions) to the maxilla. Twenty-one patients (41.3%) developed osteoradionecrosis of grade 1 or higher, with no

grade 4 cases reported. The main risk factors were the volume of maxilla receiving more than 50 Gy_{RBE} and the presence of teeth in the target planning volume.

Cost-effectiveness

A Dutch study by Ramaekers et al (73) compared the cost-effectiveness of IMPT and IMRT in patients with locally advanced head and neck cancers, assuming equal survival rates. IMPT for all patients would yield 6.620 quality-adjusted life years and cost €50 989, whereas IMRT for all patients would yield 6.520 QALY and cost €41 083. If IMPT were to be chosen only for patients when IMPT was believed to be more efficient (based on the probabilities of complications), the results were 6.563 QALY and a cost of €43 650. Therefore, with the appropriate selection of patients, choosing IMPT could improve quality of life for patients with almost the same cost as choosing IMRT for all patients. Another cost-effectiveness analysis (74) compared IMRT and IMPT for patients with stage IVa oropharyngeal squamous cell carcinoma. Proton therapy was not cost-effective in most scenarios, with ICER above $150 000/QALY (in the payer perspective). Indeed, only assuming a significant reduction in the incidence of long-term complication in HPV-positive young patients led to an ICER lower than $100 000/QALY.

Skull Base Tumors

Tumors of the skull-base, due to their proximity to key nerve structures (such as brainstem, optic pathway or auditory pathway), are difficult to treat. Although they are mostly indolent, surgical resection often cannot remove the totality of the tumor or is associated with neurological complications.

Though skull-base tumors are rare, it is hoped that the advantages in the dosimetry of hadrontherapy can provide an effective and safe treatment option for these malignancies.

Eighteen studies were included. (75-92) Primary outcomes were clinical outcomes in twelve publications, adverse events for five publications, and one was a cost-analysis. In terms of study design, seven studies were prospective and fourteen were retrospective. Median ages ranged between 42 and 76 years, with total dose received varying between 48.0 and 79.4 Gy_{RBE}. Cohorts varied from 20 to 260 patients, with a median follow-up from 11 months to 88.0 months.

Clinical outcomes

Guan et al (75) reported the preliminary results of 91 patients treated with either proton or carbon ion therapy, diagnosed with primary or recurrent chordoma and chondrosarcoma of

the skull-base or cervical spine. They reported 2-year local control, progression free survival and OS rates of 86.2%, 76.8% and 87.2%. Predictive factors for OS were tumor volume and re-irradiation, but only tumor volume correlated with PFS. 25 patients developed acute adverse events, with one grade 3 adverse event (mucositis). No patients experienced late adverse events grade 3 or higher.

A recent feasibility phase I/II clinical trial by Baumann et al (76) reported on 20 patients with chordomas or chondrosarcomas treated with proton therapy (as adjuvant or definitive treatment). They report 3-year local control and PFS rates of 86% and 81%. There were two patients with grade 3 adverse events (both fatigue) and one patient with late grade 3 osteoradionecrosis.

El Shafie et al (77) followed 110 patients with skull-base meningiomas treated with proton or carbon-ion therapy. Median total dose was 54 Gy_{RBE} (range: 50-60 Gy_{RBE}) for proton therapy and an 18 Gy_{RBE} carbon ion boost after a median 50 Gy_{RBE} (range: 48.4-55.8 Gy_{RBE}) of photon therapy. The 3- and 5-year PFS rate were 100% and 96.6%. The 5-year OS rate was 96.2%. No grade 4 or higher adverse events were reported. Only 4 grade 3 late adverse events were reported: three brain radionecrosis and one radio-induced hypopituitarism.

Deraniyagala et al (78) followed 33 patients with skull-base chordomas who received adjuvant proton therapy. They found that 2-year local control and OS rates were 86% and 92%. The only adverse event with grade 2 or higher reported was unilateral hearing loss (18%). However, they could not assess endocrine toxicity.

Rombi et al (79) assessed the outcomes in a pediatric population of 26 patients with chordoma or chondrosarcoma treated with proton therapy. Mean age at the time of treatment was 13.7 years. They report good clinical outcomes: 5-year control rates and OS rates were 81% and 89% for chordomas and 80% and 75% for chondrosarcomas, with no late adverse events grade 3 or higher nor secondary malignancies.

Holtzman et al (80) reviewed the medical records of 43 patients with skull-base chondrosarcoma, treated with conformal proton therapy. The 4-year local control, OS, and cause-specific survival rates were, respectively, 89%, 95% and 100%. They reported no severe acute adverse events. Four years after treatment, only 5% of patients had a grade 3 late adverse event (mostly temporal lobe necrosis and hearing loss).

A large retrospective study by Weber et al (81) assessed the outcomes of 251 patients with skull-base chondrosarcoma treated with proton therapy or a combination of proton and photon therapy. The 7-year failure-free survival and OS rates were 93.1% and 93.6%. Risk factors for treatment failure were tumor volume and compression of the optic pathway. At 7 years after treatment, 84.2% of patients did not have adverse events grade 3 or higher. The majority of

adverse events were pituitary disfunctions and the most common severe adverse events were brain and spinal cord necrosis, hearing loss and bone necrosis.

A similar study (82) which included 101 patients with skull-base chondrosarcoma treated with proton or carbon-ion therapy found similar results, with a median total dose of 60 Gy_{RBE} for carbon ions and 70 Gy_{RBE} for protons. The 1- and 4-year LCR were 100% for protons and 98.6% and 90.5% for carbon ions, respectively. The OS rates were 100% for protons (both time points) and 100% and 92.9% for carbon ions.

Takagi et al (83) analyzed the outcomes of 24 patients with skull-base chordoma treated with either proton therapy or carbon ion therapy. They reported a 5-year local control, PFS and OS rates of 85%, 81% and 86%, respectively. All of these rates were significantly higher if the patient had undergone surgery previous to the hadrontherapy. There were no reports of acute adverse events grade 3 or higher, with twelve patients experiencing late adverse events grade 2 or higher. The most severe of them were brain necrosis, unilateral blindness in a case with a tumor infiltrating the optic canal and one case of hemorrhage of a nasopharynx ulcer.

A Korean study (84) investigated the clinical outcomes of 58 patients with chordoma of the skull-base, cervical spine or sacrum treated with proton therapy. The 5-year local control, distant metastasis-free survival, OS and specific survival rates were, respectively, 87.9%, 86.7%, 88.3% and 92.9%. Cervical and sacral tumors were associated with worse survival outcomes. The most common acute adverse events were dermatitis and/or mucositis (70%). No patient experienced acute adverse events grade 3 or higher. Three patients experienced grade 3 late adverse events, including a brain stem lesion with hemiparesis in case of skull-base chordoma. No patient experienced late adverse events grade 4 or higher.

Uhl et al (85) investigated 155 patients with skull-base chordoma treated with carbon ion therapy. The 3-, 5- and 10-year local control and OS rates are, respectively, 82%, 72%, 54% and 95%, 85% and 75%. Improved rates were correlated with age less than 48 years and boost volume over 75 mL. 15% of patients experienced acute adverse events, mostly mucositis, xerostomia, dysgeusia and alopecia. After 10 years, common late adverse events include cranial nerve deficits (53%), dizziness (29%), headache (28%), double vision (26%), and hearing deficits (22%), with no secondary malignancies reported.

Combs et al (86), followed a cohort of 260 patients with brain and skull tumors, treated with either proton therapy (67%) or carbon ions (33%, of which 43% received photon beam radiotherapy with a carbon ion boost). All treatments were completed without severe toxicities. No local recurrences were observed for benign skull base meningiomas. For high-grade meningiomas, 1- and 2-year LCR were 54% and 33%, respectively. No adverse events grade 4 or higher were observed, and hearing impairments were the most common late adverse event.

Adverse Events

A study by Amelio et al (87) reported on the early quality-of-life post proton therapy for patients with large skull-base meningiomas. 33 patients answered two quality-of-life questionnaires (EORTC QLQ-C30 and EORTC QLQ-BN20) before treatment, immediately after treatment and in every follow-up consult. With a median follow-up of 9 months, all patients were disease- and progression-free. Quality-of-life in terms of global health, social functioning and motor disfunction improved with time, and remained stable for fatigue, cognitive and emotional functioning.

Another study by the same authors (88) reported the preliminary outcomes for elderly patients with skull-base or intracranial tumors (mostly meningiomas, chordomas and high-grade gliomas) treated with proton therapy. The cohort contained 26 patients over 70 years old and median age 76 years. No acute adverse events grade 3 or higher were reported, and the more common ones were skin erythema (62%), alopecia (53%) and fatigue (42%). With a mean follow-up of 8 months, no late adverse events grade 3 or higher were reported, and the most common ones were alopecia (54%), fatigue (15%), headache (12%) and skin hyperpigmentation (3%).

In a recent study, Kountouri et al (89) analyzed the incidence of radiation-induced optic neuropathy (RION) in 216 patients with skull base or head and neck tumors treated with IMPT. They found that 6.5% of patients developed RION, of which 92.9% were symptomatic. Age over 70 years old, hypertension and tumor bordering the optic apparatus were risk factors.

In a conference paper by Rangel et al (90), they analyzed the adverse events following proton therapy for 47 patients with skull-base tumors. They report 6 cases of cerebrospinal fluid leaks that required a surgical correction, 1 case of hearing loss, 1 case of osteoradionecrosis and 1 case of refractory dizziness.

A study by Koto et al (91) analyzed the incidence of radiation-induced brain injury after carbon ion therapy. The cohort consisted of 39 patients with skull-base tumor, and 24.5% of the patients developed signs of radiation induced brain injury in MRI. 7.0% of patients were symptomatic. Brain volume receiving more than 50 Gy_{RBE} was a risk factor.

Cost-effectiveness

A German study by Sprave et al (92) compared the cost-effectiveness of carbon ion therapy and photon-based external beam radiotherapy in patients with skull-base chordomas. They based their analysis solely on the direct cost of treatment and the cost of progression, the latter being extrapolated from 10 years of outcome data. They concluded that carbon ion

therapy yielded 8.26 QALY and photon beam radiotherapy yielded 6.65 QALY, with an overall ICER of €8855.76/QALY. Hence, carbon ion therapy is cost-effective treatment option for chordomas.

Prostate Adenocarcinoma

There is a wide therapeutic arsenal available for prostate adenocarcinoma, the most common non-cutaneous cancer in men. These options range from surveillance, surgery, androgen deprivation therapy (ADT), and radiotherapy. The latter can be in the form of brachytherapy or external beam radiotherapy. However, while hadrontherapy has been used in the treatment of prostate adenocarcinoma since 1979, there is still no consensus on the role of hadrontherapy in prostate cancer. (93)

Of note, hypofractioned proton therapy (HFPT), as opposed to conventionally fractioned proton therapy (CFPT), is increasingly being considered as another treatment modality.

The prognostic risk subgroups mentioned in these studies are based on the National Comprehensive Cancer Network criteria.

The main adverse events experienced after radiotherapy for prostate cancer are gastrointestinal (GI) and genitourinary (GU). The impact of urinary, sexual or gastroinstestinal symptoms on the patient's quality-of-life is evaluated by validated tools such as the Expanded Prostate Cancer Index Composite (EPIC) or International Prostate Symptom Score (IPSS).

Twenty-two publications were selected. (94-115) Eleven studies focused primarily on clinical outcomes, nine studies in adverse events, and two were a cost-analysis. In terms of study design, twelve publications were prospective and eight were retrospective. Median ages varied between 56 and 70.4 years, and total dose received ranged between 36.25 and 82 Gy_{RBE}. The size of cohorts varied from 43 to 2157 patients, with a median follow-up from 14.5 months to 7.9 years.

Clinical Outcomes

In a phase II clinical trial, Grewal et al (95) evaluated the outcomes of (HFPT) for low- to medium-risk prostate cancer. The 184 patients were divided in low-risk, favorable intermediate-risk and unfavorable intermediate-risk subgroups, and each received 70 Gy_{RBE} in 28 fractions. The 4-year clinical or biochemical recurrence-free rate was 93.5% overall, and for each of the subgroups was 94.4%, 92.5% and 93.8%. Four-year OS was 95.8%, without significant distinctions between subgroups. For acute adverse events grade 2 or higher, 3.8% reported GI adverse events (mostly diarrhea) and 12.5% reported GU complications (mostly urinary frequency). The 4-year frequency of late adverse events grade 2 or higher was 7.6%

for urological complications and 13.6% for GI adverse events. This trial corroborated a feasibility trial by Henderson et al (93), who also assessed the outcomes of HFPT for 250 low- and intermediate-risk prostate cancer patients. Treatment consisted of either 70 Gy_{RBE} in 28 fractions or 72.5 Gy_{RBE} in 29 fractions. The 5-year biochemical and clinical recurrence-free rates were 95.9% overall (98.3% for low-risk patients, 92.7% for intermediate-risk) and the 5-year incidence of late adverse events grade 3 or higher was 0.5% for GI and 1.7% for GU.

Bryant et al (96) reviewed 1327 patients with localized prostate cancer treated with dose-escalated proton therapy, with 98% of patients receiving between 78-82 Gy_{RBE}. The 5-year biochemical recurrence-free rate were 99% for low-risk cancers, 94% for intermediate-risk and 74% for high-risk. The incidences of late grade 3 or higher GU and GI adverse events, were, respectively, 2.9% (predominantly urinary obstruction and hematuria) and 0.6% (predominantly diarrhea and rectal bleeding). Quality-of-life scores remained stable for urinary and gastrointestinal symptoms. However, sexual function scores decreased significantly for patients not receiving androgen depriving therapy (EPIC scores decreased from a baseline of 67 to 53 five years after treatment).

Nomiya et al (97) performed a multi-center analysis of the outcomes of carbon-ion therapy for localized prostate cancer. 2157 patients were included, of which 263 were low-risk, 679 were intermediate-risk and 1215 were high-risk. The 5-year biochemical recurrence-free rate was 92% for low-risk patients, 89% for intermediate-risk patients, and 92% for high-risk patients, and correlated with the Gleason score. The 5-year LCR were 98%, 96%, and 99%, and the 5-year disease specific survival rates were 100%, 100%, and 99% for the respective risk sub-groups. No late adverse events grade 3 or higher were reported, except a single case of grade 3 urinary tract bleeding. The incidences of grade 2 late GU and GI adverse events were, respectively, 4.6% and 0.4%.

Another publication assessed the outcomes of proton therapy in 218 intermediate- or high-risk prostate cancer patients (98). The 5-year PFS rates were 97% for intermediate-risk patients and 87% for high-risk patients. 5-year OS was 96% and 98% for the same risk subgroups. For GI adverse events, they report no acute adverse events grade 2 or higher, and no grade 3 or higher for late adverse events. 3.9% of patients developed grade 2 late GI adverse events, all of them rectal bleeding. In the case of GU adverse events grade 2 or higher, the incidences were 23.5% in the acute phase, and 3.4% in the late phase, mostly urinary retention or urinary frequency.

Choi et al (99) reported the outcomes of proton therapy of 2 patient cohorts. A total of 1628 patients with sufficient follow-up were analyzed. The 5-year OS rates were 98.0% for low-risk, 95.9% for intermediate-risk and 87.0% for high-risk patients. 5-year biochemical relapse-free and clinical progression-free rates for the same risk subgroups are, respectively, 95.7%,

92.3%, 80.7% and 95.9%, 92.7%, 78.0%. Grade 2 or higher acute adverse events occurred in 39.4% (GU) and 5.2% (GI) of patients. The 5-year incidence of grade 2 or higher late adverse events was 15.9% (GU) and 10.6% (GI).

Kawamura et al (100) evaluated the complications following carbon ion therapy (using a novel, more compact accelerator) for 304 patients with localized prostate cancer. They received 57.6 Gy_{RBE} in 16 fractions. 5-year biochemical relapse-free rate was 92.7% (for low-, intermediate- and high-risk patients: 91.7%, 93.4%, and 92.0%). The 5-year local control and OS rates were 98.4% and 96.6%. They report no grade 3 or higher acute adverse events. The incidence of grade 2 or higher GU late adverse events was 9.3%, and all resolved with medication except for one case. 0.3% of patients had grade 2 late GI adverse events, and no adverse events with higher grade were reported.

A large multi-center retrospective study, (101) assessed long term outcomes for 1291 patients with localized prostate cancer treated with proton therapy. They were separated in low-risk (215 patients), intermediate-risk (520 patients) and high-risk (556 patients) subgroups. The 5-year biochemical relapse free survival and OS rates were, for the respective subgroups, 97.0%, 91.1%, 83.1% and 98.4%, 96.8%, 95.2%. The incidences of adverse events grade 2 or higher were 4.1% (GI) and 4.0% (GU). Grade 3 adverse events were only reported on 10 patients.

Takagi et al (102) assessed the long-term outcomes in 1375 patients with localized prostate cancer treated with proton therapy. The 5-year biochemical relapse-free survival rate was 89% overall (low-risk: 99%, intermediate-risk: 91%, high-risk: 86% and very high-risk: 66%) and the 5-year CSS rate was 99% overall (100%, 100%, 99% and 95%, for the respective risk subgroups). The incidences of late adverse events grade 2 or higher were 3.9% (GI) and 2.0% (GU). Risk factors for failure of biochemical control were patient age, T classification, Gleason score, PSA levels and the percentage of positive biopsy cores, whereas only patient age correlated with the incidence of adverse events.

In another study, the same authors (103) reported on the outcome of proton therapy for castration-resistant prostate cancer. They reviewed 43 consecutive patients, and reported as 5-year biochemical relapse-free, clinical progression free survival and OS rates, respectively, 38%, 72%, and 67%. Predictive factors for biochemical or clinical recurrence were T stage T3b or T4 and PSA above 10 ng/mL. The 5-year incidences of adverse events grade 2 or higher were 11% (GI) and 8.1% (GU).

Choi et al (104) analyzed the outcomes of 64 patients with high-risk prostate cancer treated with proton therapy and ADT. The biochemical relapse-free rate was 96.9%. Of the 52 patients whose serum testosterone levels were available, 80.8% experienced a recovery of

testosterone levels. No adverse events grade 3 or higher were seen. Grade 2 adverse events occurred in 7.8% (GI) and 18.7% (GU) of patients.

Adverse events

Kubeš et al (105) evaluated the early results of extreme HFPT in patients with low- or intermediate-risk localized prostate cancer, including 200 patients received 36.25 Gy_{RBE} in 5 fractions. There were no cases of adverse events grade 3 or higher, either acute or late. The grade 2 acute adverse events reported were 3.5% (GI) and 19% (GU). Grade 2 late adverse events were 5.5% and 4%, respectively. In addition, they report no cases of local recurrence, and 8 cases of biochemical relapses.

Philip et al (106) reported the 3-year outcomes of a phase II trial. They used HFPT (55.5 Gy_{RBE} in 15 fractions) in 181 patients with localized prostate cancer. No adverse events grade 3 or higher were reported for 3 years after treatment, and 3-year incidences of grade 2 late adverse events were 14.41% (GU) and 4.6% (GI). Grade 2 acute adverse events occurred in 15.0% (GU, primarily hesitancy and dysuria), and 4.8% (GI, mostly diarrhea) of patients. The quality-of-life EPIC scores remained stable during treatment.

A large study by Lee et al (107) reported the outcomes of 192 patients with localized prostate cancer treated with proton therapy and with over 1 year of follow-up. No adverse events grade 4 or 5. Adverse events grade 3 were rare, 1.0% (GU) and 0.5% (GI). Quality-of-life in terms of urinary symptoms showed no change after treatment, but sexual quality of life declined up until 1-year after treatment. Younger age was associated with less sexual complications.

Ho et al (108) evaluated the long-term sexual potency (defined as erection firm enough for satisfactory intercourse) of young men with prostate cancer treated with proton therapy. They evaluated 254 men under the age of 60, by means of clinical examination and questionnaires, since before treatment until 5-years after. The dose prescribed range from 70-82 Gy_{RBE}. The 7-year biochemical recurrence-free survival was 97.8%. Sexual potency was 90% before treatment, decreased significantly in the first year and then remained stable: 72% one year after treatment and 67% five years after treatment. In addition, at 5-years 98.6% of patients did not experienced significative urine incontinence. Potency after 5 years correlated with the sexual health scores at baseline.

Chuong et al (109) reported the acute adverse events in 85 patients with non-metastatic prostate cancer, including 6 patients with lymph node involvement, who received pelvic proton irradiation. Median pelvic dose was 46.9 Gy_{RBE} (range: 39.7-56 Gy_{RBE}) with median boost dose to the prostate 30 Gy_{RBE} (range:20-41.4 Gy_{RBE}). They report no acute adverse events grade 3

or higher. The incidences of grade 2 acute adverse events were 2.4% (GI, mostly diarrhea and proctitis) and 34.1% (GU, most commonly urinary frequency).

Dutz et al (110) compared the frequency of adverse events between proton therapy and IMRT in 88 patients with localized prostate cancer. 31 patients were treated with proton therapy (median age 70.4 years, median total dose 74 Gy_{RBE} , range 74-76 Gy_{RBE}). They were matched with 57 patients treated with IMRT (median age 74.9 years, median total dose 78 Gy, range: 74-78 Gy), according to tumor and patient characteristics, resulting in 29 matched pairs. They collected data until 1 year after treatment. They reported no significant differences in the incidence of gastrointestinal or urinary adverse events, either acute or late, between groups. The exception was late urinary urgency, which was not reported in the proton group, but occurred in 25.0% of the IMRT group. In addition, quality-of-life scores showed no significant changes in both groups.

Nakajima et al (111) reported the acute adverse events for 526 patients from three phase II clinical trials in Japan. The patients were diagnosed with localized prostate cancer and treated with either HFPT (272 patients, 60 Gy_{RBE} in 20 fractions for low-risk patients and 63 Gy_{RBE} in 21 fractions for high-risk patients) or CFPT (254 patients, 74 Gy_{RBE} in 37 fractions for low-risk patients, 78 Gy Gy_{RBE} in 39 fractions for high-risk patients). They report no acute adverse events grade 3 or higher. They described an incidence of grade 2 GU adverse events of 10.3% (15.0% for CFPT and 5.9% for HFPT). For GI adverse events, only four cases of grade 1 rectal hemorrhage were reported, two in each group. The IPSS scores one month after treatment increased significantly, but returned to baseline values 6 months after treatment.

Mohamad et al (112) assessed the risk of subsequent primary cancers in patients with prostate cancer treated with carbon ion therapy. They evaluated 1455 patients treated with carbon ion therapy. 234 subsequent cancers were diagnosed, including patients with multiple cancers. Significant risk factors were age and smoking. Moreover, Mohamad et al, compared these patients with 1983 patients treated with photon beam radiotherapy (median follow-up 5.7 years) and 5948 patients who underwent prostatectomy (median follow-up 6.0 years). With propensity score-weighted analyses, they found that carbon ion therapy was associated with a significant lower incidence of subsequent primary cancers when compared to photon therapy or prostatectomy (hazard ratios were 0.81 and 0.8, respectively).

In a comparative study, Mendenhall et al (113) compared two prostate cancer patient cohorts. One consisted of 1214 patients treated with proton therapy (78 Gy_{RBE} in 39 fractions, median age 66 years, median follow-up 5.6 years) and the other consisted of 301 patients treated with IMRT (75.6 Gy in 42 fractions, median age 74 years, median follow-up 7.2 years). The 5-year incidence of adverse events were lower for the proton cohort compared with the IMRT cohort: 0.1% against 1.3% (GI) and 0.1% against 4.3% (GU). For low- and intermediate risk patients,

proton therapy had favorable outcomes in terms of 5-year biochemical relapse-free rates and OS, for patients under 75 years. High-risk patients had similar results for those rates. IMRT showed higher OS for patients over 75 years.

Cost-effectiveness

An American study by Parthan et al (114) compared the cost-effectiveness of IMRT, proton therapy and stereotactic body radiation therapy (SBRT) in patients with localized prostate cancer. They used a Markov model, and estimated the probabilities of late complications and death based on published data. The patient model is a 65-year-old prostate cancer patient that refused or is unable to undergo surgery. From both a payer and societal perspective, they report that SBRT is more cost effective than IMRT or proton therapy. Proton therapy would cost (from a payer perspective) $69 412 for a yield of 8.06 QALY, as opposed to $33 068 with a yield of 8.05 QALY for IMRT and $24 873 with a yield of 8.11 QALY for SBRT.

Another American cost-effectiveness analysis by Goyal et al (115) calculated the reduction in complications that proton therapy would need to achieve to become cost-effective in comparison IMRT, in localized prostate cancer. They assume equal disease control efficacy for both methods, in a cohort of patients over 65 years old. They also used a Markov model, with probabilities for complications based on published data (SEER-Medicare). They conclude that cost-effectiveness for proton therapy would require a 41% reduction of complication risk, under the assumption of low and high cost estimates for proton therapy and IMRT, respectively.

Discussion

We identified a broad overview of some recent studies that reported outcomes of hadrontherapy in several different cancers and this is, by no means, an exhaustive review. Aside from the tumors mentioned in this work, hadrontherapy has been used in the treatment of primary tumors in several other locations, for instance, non-small cell lung cancer, breast cancer, hepatocarcinoma, esophageal and rectal cancer. (116-118)

This review has several limitations. Most of the studies were retrospective analyses from a single institution, and hence vulnerable to selection bias and often faced with unavailable clinical data. Of the prospective studies identified for this work, most are not randomized.

There is a wide heterogenicity between studies. Most of them have small sample sizes, sometimes with patient overlap in different studies, and follow-ups are usually short. Moreover, many confounding factors are present such as age, type of tumor and its location or co-morbidities present. In addition, as part of the treatment protocol for most cancers, patients also undergo other treatment modalities, such as surgery, chemotherapy or hormone therapy. All these factors make meta-analyses of the data unfeasible, and it is hard to accurately assess know how much of the reported benefits are attributable to hadrontherapy alone.

As a further complication, more recent studies make use of newer techniques for planning and dose delivery, which certainly affect outcomes and make it harder to compare data even within a single institution. In an attempt to mitigate this, we selected publications from the last decade, but even so there is a remarkable disparity in the techniques used, including factors such as total dose delivered or fractioning. Moreover, comparisons with photon based external beam radiotherapy are indirect, as different cohorts are used and hence basal characteristics may differ.

Nevertheless, and using appropriate caution in the interpretation of results, there is enough clinical experience available to permit a few simple conclusions.

Uveal melanoma

Hadrontherapy provides excellent LCR, OS and eye retention rates in uveal melanomas. The 5-year LCR are typically above 92%, 5-year eye retention rates usually are above 80% and 5-year OS over 70%.

The most common adverse events are cataracts, radiation-induced retinopathy or neuropathy and neovascular glaucoma. While cataracts can usually be satisfactorily corrected with surgery, the other adverse events lead to poor visual acuity. Neovascular glaucoma is particularly difficult to control, and is one of the main reasons for secondary enucleation after hadrontherapy.

The incidence of adverse events is strongly associated with tumor location and dose administrated to different structures of the eye. Hence, improvements in dose delivery may lead to a lower incidence of adverse events.

Thariat et al (21) showed that proton therapy achieves excellent results in parapapillary tumors, with high local control and OS rates, and visual acuity 20/200 or better in 47.2% of patients at last-follow up. Indeed, parapapillary tumors are the main indication for proton therapy in uveal melanoma. (119)

It appears that hadrontherapy outperforms brachytherapy in uveal melanomas. A phase III trial (19) showed the supremacy of helium ions in relation to iodine-125 plaques, and cost analysis also favor hadrontherapy over brachytherapy (though not over primary enucleation). Hence, hadrontherapy can be presented as the standard, eye-preserving option for the management of uveal melanoma. It should be noted, however, that the prescribed brachytherapy dose was below international standards (85 Gy). (119)

Further randomized clinical trials, comparing hadrontherapy to brachytherapy, are needed to solidify the role of hadrontherapy in these tumors.

Pediatric CNS tumors

There is a wide heterogenicity in these studies. For instance, the age of patient cohorts varies from small children to young adults under 21 years of age. Naturally the patient cognitive, behavioral or functional stage and their development is remarkably different for this age range. Most studies did not discuss outcomes separately for patients in the same stage of neurocognitive development or age. Furthermore, some cohorts include non-CNS tumors, such as head and neck or skull-base tumors.

In addition, most patients received either previous or concomitant surgery, chemotherapy or photon radiotherapy, as part of the standard protocol for the specific neoplasm at hand.

Follow-ups also varied, and were in most cases, under 5 years. This makes the late adverse events very difficult to analyze, in particular, the incidence of long-term neurocognitive effects and the feared radiation-induced secondary neoplasms is still uncertain. More studies, with follow-ups of several years, are needed to confidently evaluate hadrontherapy in terms of long-term outcomes.

With all of this in mind, the data still allow for some careful considerations. The clinical outcomes are excellent, with high LCR and OS and, at least, they are non-inferior when compared to photon beam radiotherapy. In addition, there is a reduced incidence of acute adverse events and, at least for the follow-up of the studies, there is a reduced incidence of

late adverse events as well. Furthermore, the reported quality-of-life of the patients remained stable or improved after treatment.

Cost-effective analysis of proton therapy in pediatric CNS tumors are scarce, and is focused on medulloblastomas. Evidence points to a cost-effective superiority for hadrontherapy in pediatric medulloblastoma. Even though hadrontherapy as a higher cost compared to photon-based external beam radiotherapy, the savings observed due to a reduced incidence of adverse events and superior neurocognitive outcomes offsets this. Future analyses for other pediatric CNS tumors are needed to assess if this holds for them as well.

Hence, with the current experience, hadrontherapy is an effective and safe option for the treatment of pediatric CNS tumors. Still, long-term clinical trials, with rigorous control of confounding variables, are sorely needed to solidify this position, and to confidently assess the added value of hadrontherapy in comparison to other treatment modalities.

Head and neck tumors

There is a rising incidence in p16 positive oropharyngeal cancers, correlated with HPV infection, affecting younger patients, with less marked smoking habits and associated with better prognosis. Hence, a therapeutic option with reduced adverse events is necessary to ensure maximal quality-of-life for these patients. Hadrontherapy has favorable clinical outcomes and a good safety profile in the treatment of oropharyngeal cancers. Symptom burdens on the quality of life are comparable in proton therapy and photon beam radiotherapy.

Radiation, possibly associated with chemotherapy, plays a key role in the treatment of nasopharyngeal cancer. Their location, however, requires a careful dosimetry planning, which hadrontherapy can provide. Published results show excellent control rates, and there is a low incidence of severe dysphagia or gastrostomy tube dependence. However, follow-ups are still quite short, and there is not enough data to assess long term adverse events, in particular from a neurological perspective.

Surgery is the primary treatment for sinonasal tumors, with radiation therapy taking an adjuvant role. Hadrontherapy has shown adequate outcomes for these cancers. Information on adverse events is limited, but the incidence of neuropathy and osteonecrosis is still relevant.

One drawback of hadrontherapy in the clinical setting of head and neck tumors is its sensitivity to patient positioning or anatomic variations (mainly due to weight loss) (120), that can lead to significant differences between the estimated dose and the actual dose received by the target volume, thereby compromising outcomes.

So far, hadrontherapy is only cost-effective, or nearly so, for specific subgroups of patients with head and neck cancer, namely, young patients with oropharyngeal cancer. In these

selected cases, the favorable safety profile and reduced need of gastrostomy tubes due to hadrontherapy outweighs its increased costs. More studies are needed to determine if current advances in hadrontherapy allow its cost-effective use in a broader group of head and neck cancer patients.

Skull-base tumors

Hadrontherapy shows effective control and survival outcomes for chordomas and chondrosarcomas, and show a low incidence of adverse events. Moreover, more severe adverse events, such as brain necrosis, are associated to higher doses received by the brain parenchyma. As such, innovations in target planning and dose delivery can reduce these complications even further.

The rarity of skull-base tumors means that we only have small patient populations, and most studies published are retrospective in nature. Hence, we need studies with multi-center collaboration, with a large patient cohort, to confidently prove the advantages of hadrontherapy in this class of tumors.

Hadrontherapy has showed to be cost-effective in skull-base tumors, but again, due to the rarity of these tumors, cost-effective analysis on this matter are scarce, and more studies are needed to reassure this conclusion.

Prostate Adenocarcinoma

It is clear, based on available studies, that hadrontherapy provides excellent control and survival outcomes for prostate adenocarcinoma. Less clear, however, is how these results compare with other treatment modalities. A review article by Royce at al (121) concluded that there is no reliable evidence for the superiority in clinical outcomes of proton therapy in relation to other treatment modalities. Medenhall et al (113) reported that proton therapy showed favorable outcomes for low- and intermediate-risk younger patients, and favorable results for IMRT in older patients. Unless future studies prove otherwise, hadrontherapy distinguishes itself from other modalities mainly in its safety profile.

Hadrontherapy certainly has a good safety profile. Adverse events grade 3 or higher are rate, and the incidence of grade 2 adverse events is low. However, there is still doubt on whether there is a superiority of hadrontherapy in this regard. Dutz et al (110) reported no significant differences between proton therapy and IMRT, and (113) reported less incidence of adverse events with proton therapy. Recent reviews confirm that current evidence cannot affirm the superiority of hadrontherapy in terms of adverse events. (121-122)

Hence, hadrontherapy and photon beam radiotherapy are, in a clinical perspective, on equal footing in terms of prostate adenocarcinoma. From a cost perspective, hadrontherapy is simply not cost-effective in prostate adenocarcinoma. Nevertheless, the use of rectal gel spacers or

rectum sparing anterior-oblique beam arrangements, may provide decisive differences in the safety profile of hadrontherapy, and change its current cost-effective status. Of note, since rectal gel spacers are also used in photon beam radiotherapy, so they are a cost-effective measure rather than an intrinsic advantage of hadrontherapy.

Fortunately, there are currently several ongoing clinical trials comparing hadrontherapy to photon beam radiotherapy, which may finally tip the scales for one side or the other.

Conclusion

Hadrontherapy has dosimetric superiority in relation to photon-based external beam radiotherapy, delivering less radiation to healthy tissue surrounding the tumor. Hadrontherapy has shown excellent tumor control rates, and a superior safety profile in the treatment of uveal melanoma, skull-base tumors and pediatric brain tumors and, as such, and is a cost-effective treatment option in these cases.

For prostate cancer, as well as head and neck cancers, results show that hadrontherapy is a treatment option at least equivalent to radiotherapy using photons beams. However, currently there is not enough evidence about the advantages of hadrontherapy to make it a cost-effective option, except for very particular cases, such as young, HPV-positive, oropharyngeal cancer patients, and even so the evidence is still not robust, due to the lack of studies.

In our perspective, hadrontherapy faces two major hurdles:

First, the infrastructure needed for hadrontherapy is quite expensive, which translates into a small number of facilities available, and difficult access for patients. This scarcity also makes the design of large-scale prospective trials difficult. Hopefully, technological advancements, associated with cost saving strategies such as building single-room facilities instead of larger ones, will bring costs down enough to allow a more widespread use of hadrontherapy.

Secondly, the lack of long-term, randomized controlled trials comparing the effectiveness and safety of hadrontherapy with other treatment modalities. The decision of whether or not hadrontherapy should be the standard treatment for a given neoplasm must be based on strong evidence. Fortunately, as interest in hadrontherapy grows, several comparative trials are undergoing or being planned. In the following years, the results of these trials will determine the place of hadrontherapy in radiation oncology. As for now, we need to be careful in selecting patients which might benefit from this technique, since the available data is so heterogeneous and lacks long-term validation.

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Supplement

Table I – Relevant data from the selected publications in this work

Author; Year; Country;	Number of patients; Median* age and range (years)	Tumor characteristics;	Dose characteristics (median* and range); Median* follow-up;	Clinical Outcomes**	Adverse Events***
Sikuade (18); 2015; United Kingdom;	191; SRS group: 64, (17-87); PT group: 59, (24-82);	Posterior (choroidal and ciliary body) uveal melanoma;	SRS group: 85 patients, 35 Gy to the 50% isodose line in a single session; 39* months; PT group: 106 patients, 53.1 Gy_{RBE} in 4 daily fractions; 34* months;	SRS vs. PT group: Visual acuity 6/60 or better - 33% vs. 54%; Loss of 3 or more Snellen lines - 65% vs. 45%; OS - 84% vs. 87%; Eye retention rate - 97.6% vs. 95.3%;	SRS group vs. PT group: Radiation retinopathy - 24% vs. 30%; Optic neuropathy - 28% vs. 13%; NVG - 11% vs. 5%;
Mishra (19); 2015; United States;	184; 56*, (20-85);	Uveal melanoma, excluding iris, less than 15 mm in basal diameter and less than 11 mm in thickness;	Plaque therapy (iodine-125): 98 patients, minimum dose 70 Gy; 12.3 years; Helium-ion therapy: 86 patients, minimum dose of 70 Gy_{RBE} (RBE 1.3) in 5 fractions; 14.6 years;	Helium vs. plaque group: 5- and 12-year LCR - 100% and 98% vs. 84% and 79%; 5- and 12-year eye retention rate - 89% and 83% vs. 78% and 63%; 12-year SS: 80% vs. 76%; 5- and 12-year OS - 86% and 67% vs. 76% and 54%;	–
Lane (20); 2016; United States;	3088; 61.3, (10.3-94.2);	Choroidal and ciliary body melanomas;	Proton therapy: 86.9% received 70 Gy_{RBE}; 12.3 years;	15-, 20- and 25-year: OS - 51.0%, 41.4% and 33.2%; SS - 75.4%, 74.2% and 73.6%;	–
Thariat (21); 2015; France;	865; 61.7* (13-93);	Parapapillary uveal melanoma (35.1% abutted the papilla);	Proton therapy: 57 Gy_{RBE} in 4 fractions; 69 months;	2-, 5-, 10- and 15-year: OS - 94.5%, 82.4%, 69.7% and 57.7%; MFS - 98.5%, 95.6%, 70% and 55.4%; 2-, 5-, and 10-year RFS - 96.6%, 92.7% and 88.8%; Crude eye retention rate - 88%;	Intravitreous hemorrhage or hyphema - 11%; Retinal detachment -15.2%; Cataract - 28.7%; NVG - 17.9%; Optic neuropathy - 47.5%; Maculopathy - 33.6%;

				Visual acuity 20/200 or better - 72.6% (baseline) and 47.2% (last follow-up);	
Seibel (22); 2018; Germany;	27; No age data given;	Uveal melanoma with posterior extraocular extension;	Proton therapy: 60 Gy_{RBE} in 4 daily fractions; 80 months;	No local recurrences observed;	3 patients underwent secondary enucleation due to NVG;
Caujolle (23); 2010; France;	886; 64.6 (14.7-92.7)	Uveal melanoma, 15.46% involving the ciliary body;	Proton therapy: 60 Gy_{RBE} in 4 consecutive days; 63.7 months;	5-, 10- and 15-year: OS - 79.4%, 64.1% and 54.2%; 5- and 10-year: MFS - 88.3% and 76.4%; LCR - 93.9% and 92.1%; Eye retention rate - 91.1% and 87.3%; Visual acuity 20/200 or better: 80% (baseline) and 51.2% (after treatment);	Cataract - 31.67%; Glaucoma - 17%, NVG - 11.17%; Radiation retinopathy - 27.54%; Optic neuropathy - 7.79%;
Choi (24); 2016; Korea;	20; No age data given;	Uveal melanoma;	Proton therapy: 60-71 Gy_{RBE} all in 5 fractions; 43 months;	LCR - 95%; DC - 90%; Enucleation - in one patient; Visual acuity less than 0.1 - 70%;	Acute adverse events - vitreous hemorrhage, cataract; Late adverse events - posterior synechia, NVG;
Petrovic (25); 2014; Switzerland;	43 (129 adult controls); Juvenile patients, aged 20 years or younger;	Uveal melanoma (around 20% invade the iris);	Proton therapy: 60 Gy_{RBE} in 4 fractions; 155 months (juvenile patients) and 79 months (controls);	Juvenile vs. adult groups, at 5-, 10- and 15-year time endpoints: MFS - 92%, 89%, and 81% vs. 76%, 66% and 52%; SS - 93%, 93% and 85% vs. 77%, 65% and 50%; Eye retention rate - 90%, 90%, and 90% vs. 86%, 77% and 67%; Local recurrence - 1 patient vs. 2 patients;	Juvenile vs. adult groups: Retinal ischemia requiring treatment - 37% vs. 16%; NVG - 19% in both groups; Phthisis bulbi - 5% vs. 4%; Scleral melt - 2% in both groups;
Macdonald (26); 2015; United Kingdom	147; 63.3, (27.7-89.8);	Choroidal (94.6%) or ciliary body melanoma;	Proton therapy: 53.1 Gy_{RBE} in 4 fractions; 4.4* years;	3- and 5-year: SS - 89.1% and 87.7%; Eye retention rate - 79.2% and 71.3%;	–

				Metastatic death occurred in 9.5% of all patients (median 21.3 months);	
Toyama (27); 2012; Japan;	114; 56, (22-83);	Uveal melanoma, locally advanced or with an unfavorable location	Carbon-ion therapy: 70 Gy_{RBE} (60-85 Gy_{RBE}) in 5 fractions; 4.6 years;	3- and 5-year: OS - 88.4% and 80.4%; SS - 90.5% and 82.2%; LCR - 95.7% and 92.8%; MFS - 84.6% and 72.1%; Eye retention rate - 94.1% and 92.8%; Visual acuity 20/200 or better preserved in 55.1%;	3- and 5-year NVG incidence - 29.7% and 35.9%;
Lee (28); 2019; United States;	92; 66, (13-93);	Uveal melanoma;	Proton therapy: 50-56 Gy_{RBE} in 4-5 fractions; Follow-up data collected 6 months after treatment;	No reported local recurrence or enucleation; One patient had liver metastasis;	Corneal toxicity grade ≥2 - 10.9% (53.8% incidence in anterior tumors, 25% in posterior tumors extending past the equator and 0% for posterior tumors); 7 patients had persistent epithelial defects;
Mishra (29); 2013; United States;	704; 60, (13-94);	Uveal melanoma;	Proton therapy: 56 Gy_{RBE} in 4 fractions; 58.3 months;	–	5-year NVG incidence - 12.7%, with enucleation rate 4.9%;
Lanteri (30); 2016; France;	1445; No age data given;	Uveal or conjunctival melanoma. 7.6% with temporal superior location;	Proton therapy: 52 Gy_{RBE} in 4 fractions; No FU data given;	–	Dry-eye syndrome - 14.7%, 2.0% severe; 2- and 5- year dry-eye syndrome free survival incidence: 88.9% and 83.6%; No patient underwent enucleation due to dry-eye syndrome;
Seibel (31); 2016; Germany;	258; 50*, (16-72);	Uveal melanoma;	Proton therapy: Median dose to the lens, fovea and optic disk (Gy_{RBE}) of 2.0, 59.0 and 7.0 (patients without cataracts) and 3.5, 58 and 50 (patients with cataracts); 72.6 months;	Local recurrence - 9 patients; Metastasis - 33 patients;	Cataract at last FU - 66.3%, 20.4% requiring surgery, with median time for development 31.3 months (0.7-142.4); 5- and 10-year cataract incidence - 74.3% and 97.7%; Radiation retinopathy - 85.3%; Optic neurophathy - 64.7%;
DeNunzio (33); 2019;	100; 8.0;	Glial tumor (23 patients);	Proton therapy: 50.4-59.4 Gy_{RBE};	5- year EFS - 84% (94% for gliomas, 68% for ependymoma,	9 patients had hearing loss both at baseline and at last follow-up;

United States;		Ependymoma (41); Craniopharyngioma (20); Other (16);	4.0 years;	100% for craniopharyngioma and 89% for other tumors); 5-year OS - 94%; Mean change in FSIQ: +0.84;	29 patients had endocrine deficiency at baseline and 13 at last follow-up;
Pulsifer (34); 2018; United States;	155; 8.9*, (1-22.5);	Medulloblastoma (34.8%); Craniopharyngioma (18.1%); Ependymoma (16.1%); Glial tumor (14.2%); Germ cell tumor (7.7%); Other (9.0%);	Focal proton therapy: 95 patients, 52.2 Gy_{RBE} (30.6-57.6 Gy_{RBE}); CSI: 60 patients, 23.4 Gy_{RBE} (18.0-36.0 Gy_{RBE}), with total dose 54.0 Gy_{RBE} (30.6-54.0 Gy_{RBE}); 3.6* years for both groups;	Mean FSIQ score declined by –2.9 points from a score of 105.4 at baseline, with decline of –6.3 points for patients under 6 years old and –0.9 for older patients; Rate of impairment - 7.9% (baseline) and 12.3% (last FU); SIB-R scores were in the average range both at baseline and at follow-up, with no significant change;	–
Antonini (35); 2017; United States;	39; CSI group: 10.9, (3.01-15.54); Focal group: 9.91, (1.56-16.27);	Medulloblastoma/PNET (14 patients); Glioma (10); Germ cell tumor (9); Craniopharyngioma (4); Other (2);	Focal proton therapy: 18 patients, 50.40 Gy_{RBE} (45.00-60.00 Gy_{RBE}); 2.20 years; CSI: 21 patients, with total dose 55.80 Gy_{RBE} (45.00-55.80 Gy_{RBE}); 2.92 years;	Attention, processing speed and executive functioning were not significantly different from population norms for both groups, but the CSI group had relatively worse results in some executive and processing speed subtests;	–
Grieco (36); 2015; United States;	35; 2.5*, (1.0-3.8);	Ependymoma (51%); Medulloblastoma (23%); Craniopharyngioma (9%); Glial tumor (6%); Other (11%);	Proton therapy, either CSI or partial-brain irradiation (80%): No dose data given; 2.1* years;	Mean FSIQ and SIB-R scores - within normal range at baseline (103.9 and 97.3) and at last FU (107.3 and 96.0), with no significant change; CSI was associated with change in FSIQ when compared to partial-brain irradiation: -12.6 vs. +8.5 points. Functional skills - lower in the CSI group;	Sensory deficit (hearing, motor) at last FU - 66%;

Gross (37); 2019; United States;	125; Proton group: 8.50, (5.75-11.81); Photon group: 7.35, (4.57-11.03);	Medulloblastoma/PNET (67 patients); Ependymoma (16); Glioma (16); Germ cell tumor (14); Craniopharyngioma (6); Other (5);	Proton therapy: 58 patients, 22.4% and 20.7% of patients received CSI of 23.4 Gy_{RBE} and 36 Gy_{RBE}, respectively; 2.6 years; Photon radiotherapy: 67 patients, 35.8% and 25.4% of patients received CSI of 23.4 Gy and 36 Gy, respectively; 6.7 years;	Proton vs. photon radiotherapy: FSIQ - 96.0 vs. 88.6; Processing speed index - 87.1 vs. 80.0; Verbal intelligence quotient - 99.7 vs. 92.8;	Proton vs. photon radiotherapy: Posterior fossa syndrome - 13.8% vs. 17.9%; Hearing loss - 25.9% vs. 32.8%; Visual impairment - 13.8% vs. 17.9%;
Indelicato (38); 2017; United States;	166; 7, (1-19);	Ependymoma (34%); Low-grade glioma (33%); Craniopharyngioma (27%); Germ cell tumor (2%); Meningioma (2%); Medulloblastoma/PNET (1%); Pituitary adenoma (1%);	Proton therapy: 45-59.4 Gy_{RBE}; 2.6 years;	Overall, ependymoma, low-grade glioma and craniopharyngioma 3-year: OS - 96%, 92%, 95%, and 100%; PFS - 87%, 77%, 87%, and 100%; LCR - 91%, 85%, 88%, and 100%;	New-onset seizures - 1.8%; Symptomatic vasculopathy - 1.8%; Symptomatic brainstem necrosis - 0.6%; Endocrine deficiency - 9%; New-onset hearing loss - 0.9% of ears; 13 of the patients with craniopharyngioma had cyst expansion, resulting in vision loss in 1 case;
Kahalley (39); 2016; United States;	150; Proton group: 9.2*, (1.7-18.2); Photon group: 8.1*, (1.2-18.0);	Medulloblastoma/PNET (62 patients); Glioma (28); Germ cell tumor (20); Ependymoma (17); Other (23);	Proton therapy: 90 patients, 54.0 Gy_{RBE} (30.0-60.0 Gy_{RBE}), 56.7% of patients underwent CSI, 23.4 Gy_{RBE} (21.0-39.6 Gy_{RBE}); 0.7* years; Photon radiotherapy: 60 patients, 54.0 Gy (30.6-59.4 Gy), 51.7% of patients underwent CSI, 23.4 Gy (21.0-39.6 Gy); 0.9* years;	Proton vs. photon radiotherapy: FSIQ - lower in the photon group by 8.7 points; Change in FSIQ overtime - no change vs. decrease of 1.1 points per year, however with no significant difference in slope; CSI subgroup: FSIQ - stable in both groups, with the photon group having mean FSIQ lower by 12.5 points;	–

				Focal therapy subgroup: FSIQ - stable vs. decline of 1.57 points per year;	
Ondrová (40); 2018; Czech Republic;	99; 6, (2-15);	CNS tumors (89 patients); Other (10);	Intensity modulated proton therapy: All patients received more than 50 Gy_{RBE} to the CNS; 24 months;	–	Radiological signs of CNS toxicity - 17.2%; Grade ≥2 toxicity - 5.05%; One death due to brainstem and cervical spine necrosis;
Yock (41); 2014; United States;	120; Proton group: 7.0, (2.0-14.0); Photon group; 7.7, (2.3-18.0);	Medulloblastoma/PNET (33.3% in proton group, 46.0% in photon group); Ependymoma/high-grade glioma (26.3% and 19.1%); Low-grade glioma (10.5% and 19.1%); Germ cell tumor (12.3% and 11.1%); Other (17.5% and 4.8%);	Proton therapy: 57 patients, 71.9% received 50-54 Gy_{RBE}; Data was collected at the 3-year FU; Photon radiotherapy: 63 patients, 71.4% received 50-54 Gy; 2.9 years;	–	Proton vs. photon radiotherapy: Mean PedsQL - 75.9 vs. 65.4, 5.0 and 13.3 points lower than the normative, respectively. The proton group scored better in both physical and psychological domains;
Song (42); 2014; Korea;	30, (13 controls); 10, (2-18); Controls: 11, (3-18);	Medulloblastoma (13 patients); Mixed germ cell tumors (8); Germinoma (7); Non-germinomatous germ cell tumors (4) Other (8);	Proton therapy: 30 patients, CSI dose 29.4 Gy_{RBE} (19.8-39.6 Gy_{RBE}), with dose to the primary site 51.8 Gy_{RBE} (30.6-61.2 Gy_{RBE}), with 1.5 or 1.8 Gy_{RBE} fractions; Photon radiotherapy: 13 controls, CSI dose 32.1 Gy (23.4-39.6 Gy), with dose applied to the primary site 53.2 Gy (39.6-60.6 Gy), with 1.8 Gy fractions; 22 months for both groups;	–	Proton vs. photon radiotherapy: Grade ≥3 leukemia - 64% vs. 77%; Grade ≥3 anemia - 0% vs. 15%; Grade ≥3 thrombocytopenia - 23% vs. 54%; Grade 3 non-hematological adverse events - 2 patients vs. 1 patient;

Frakuli (43); 2019; Germany;	63; 5.1, (1.7-20.8);	Medulloblastoma (87.3%); Atypical rhabdoid teratoid tumor (3.2%); Other (9.5%);	Proton therapy: CSI dose 24 Gy_{RBE} (18-36 Gy_{RBE}) followed by boost dose 30.6 Gy_{RBE} (10.3-36 Gy_{RBE}); 1.4 years;	–	1-year grade ≥3 hearing loss - 6 patients, present at baseline in 4 of them;
Kralik (44); 2018; United States;	100; 8.1*, (0.75-18);	Medulloblastoma/PNET (28 patients); Ependymoma (19); Craniopharyngioma (17); Pilocytic/pilomyxoid astrocytoma (9); Germinoma (7); Other (20);	Proton therapy: Total cranial dose 54.6 Gy_{RBE} (30-59.4 Gy_{RBE}); 57 months;	–	Incidence of cerebral microbleeds at 1-, 2-, 3-, 4-, 5- and more than 5 years - 43%, 66%, 80%, 81%, 83% and 81%; Median time to development - 8 months (3-28 months);
Kralik (45); 2017; United States;	75; 7.9*, (1.5-18);	Medulloblastoma/PNET (25 patients); Craniopharyngioma (14); Pilocytic/pilomyxoid astrocytoma (10); Germinoma (6); Ependymoma (4); Other (16);	Proton therapy: 53.7* Gy_{RBE} (30-59.4 Gy_{RBE}); 4.3 years;	–	RLVCV incidence - 6.7%; Median time to development - 1.5 years (1.0-7.5); 3-, 4- and 5-year RLVCV-free survival - 96%, 95%, and 95%;
Hall (46); 2018; United States;	644; 7.6, (0.7-21.8);	Craniopharyngioma (135 patients); Ependymoma (135); Low-grade glioma (131);	Proton therapy: 54 Gy_{RBE} (25.2-75.6 Gy_{RBE}); 3.0 years;	–	3- year incidence of vasculopathy, severe vasculopathy, transient ischemic attacks and cerebrovascular accidents - 6.4%, 2.6%, 0.5% and 1.2%; Asymptomatic vessel narrowing - 30 patients;

		Medulloblastoma/PNET (80); Other (163);			
Bojaxhiu (47); 2017; Switzerland;	171; 3.3, (0.3-17.0);	Ependymoma (37%); Low-grade glioma (12%); Craniopharyngioma (9%); Medulloblastoma/PNET (7%); Chordoma (9%); Other (25%);	Proton therapy; 54 Gy_{RBE} (40.0-74.1 Gy_{RBE}); 49.8 months;	–	RN incidence - 17% (59% grade 1, 28% grade 2, 6.5% grade 4 and 6.5% grade 5); Median time to develop RN - 5 months; WML incidence - 11% (72% grade 1, 22% grade 2 and 6% grade 3); Median time to develop WML - 14.5 months; 5-year RN-free and WML-free survival - 83% and 87%;
Gentile (48); 2017; United States;	216; 6.6, (0.5-23.1);	Medulloblastoma (71.3%); Ependymoma (25.9%); Atypical rhabdoid teratoid tumor (2.8%);	Proton therapy: 54 Gy_{RBE} (46.8-59.4 Gy_{RBE}); 4.2 years;	3- and 5-year: PFS - 87.2% and 82.6%; OS - 95.0% and 87.3%;	Brainstem injury - 5 patients, 1 with grade 2, 3 with grade 3, and 1 with grade 4; Median time to symptom onset - 8.5 months (5.3-82.3); 5-year incidence of brainstem injury - 2.0%;
Indelicato (49); 2014; United States;	313; 5.9, (0.5-17.9);	Ependymoma (73 points); Craniopharyngioma (68); Low-grade glioma (66); Medulloblastoma/PNET (38); Parameningeal rhabdomyosarcoma (13); Other (55);	Proton therapy (combined proton and photon radiotherapy in 9.9%): 54 Gy_{RBE} (48.6-75.6 Gy_{RBE}), with fractions of 1.8 Gy_{RBE} daily (1.2 Gy_{RBE} twice daily in 2 patients); 2 years;	2-year OS: 90.5%;	Brainstem necrosis - 11 (3.1%) patients, 7 with grade 2, 1 with grade 3, 2 with grade 4, and 1 with grade 5; 2-year incidence of brainstem necrosis - 3.8%, 2.1% for grade ≥3; Median time to symptom onset - 3 months (2-12);
Fukushima (50); 2017; Japan;	60; 6.2, (0.7-15.6);	Brain tumors (18 patients); Rhabdomyosarcoma (20);	Proton therapy: 54.0 Gy_{RBE} (18.0-80.0 Gy_{RBE}); 63 months;	24 patients died, 20 of which from the primary tumor; 29 patients were alive without tumor progression, 2 were alive	Of 32 living patients, 10 patients have grade 1 co-morbidities, 7 have grade 2, 8 have grade 3, 1 has grade 4 and 6 have none;

		Erwin sarcoma (6); Other (16);		with tumor present, and 1 has an unknown tumor status; 4 patients have unknown status;	Asymptomatic RN - 3 patients; Facial deformity - 8 patients; Average PedsQL scores were above normative values;
Eaton (51); 2016; United States;	40; 2.5, (0.3-3.8);	Ependymoma (55%); Medulloblastoma (18%); Other (27%);	Proton therapy, 12.5% with CSI: 54 Gy_{RBE} (504.-57.6 Gy_{RBE}); 5.6 years;	_	35 patients functioned in a regular classroom, 18 had an individualized education program, 14 a classroom aid and 9 an outside tutor;
Suneja (52); 2013; United States;	48; 10.8*, (1-22);	Glial tumors (16 patients); Medulloblastoma (9); Germinoma (6); Ependymoma (5); Craniopharyngioma (4); Atypical teratoid rhabdoid tumor (3); Other (5);	Proton therapy, 25% with CSI: 54.00 Gy_{RBE} (45.00-63.00 Gy_{RBE}); Acute adverse events were recorded weekly by the care team;	_	Acute adverse events (grade 1, 2, 3): Fatigue - 67%, 10%, 0%; Headache - 44%, 2%, 2%; Insomnia - 10%, 4%, 0%; Anorexia - 23%, 23%, 4%; Nausea - 46%, 4%, 0%; Vomiting - 21%, 2%, 0%; Alopecia - 31%, 42%, 0%; Dermatitis - 48%, 13%, 0%; Mean change in weight 1.1% gain;
Viswanathan (53); 2011; United States;	38; 11.9*, (3.6-17.4);	Craniopharyngioma (7 patients); Medulloblastoma (6); Glioma (4); Rhabdomyosarcoma (3); Ependymoma (2); Astrocytoma (2); Other (7);	Proton therapy (12 patients received a combination of conventional and proton radiotherapy): 57.75* ± 2.26 Gy_{RBE} for patients treated only with proton therapy and 53.84* ± 2.68 Gy_{RBE} for combined therapy; 1.8* years;	_	Proton only vs. combined therapy: Endocrine dysfunction - 13 patients (9 vs. 4); Endocrine dysfunction onset - 1.17 years vs. 0.33 years;
Uezono (56); 2019; United States;	17; 15.3, (7-21);	Nonmetastatic, nonkeratinizing undifferentiated/ poorly differentiated	Proton therapy: 61.2 Gy_{RBE} (59.4-61.2 Gy_{RBE}), with 1.8 Gy_{RBE} fractions; 3.0 years;	OS - 100%; PFS - 100%; LCR - 100%;	Acute adverse events: Grade 3 mucositis - 88%, all requiring enteral or total parenteral feeding; Grade 3 dermatitis - 18%; Late adverse events:

		nasopharyngeal carcinoma;			Grade 3 hearing loss (bilateral) - 6%; Unilateral cataract - 6%; Grade 3 esophageal stenosis - 6%; Grade 2 hormone deficiency - 35%;
Williams (57); 2019; United States;	21; 57, (19-73);	Locally advanced nasopharyngeal carcinoma, 71% EBV positive;	Pencil beam proton therapy: Majority received 69.96 Gy_{RBE} in 33 fractions once daily, two patients underwent hyperfractioned treatment twice daily; 16 months;	LCR - 95%; MFS - 90%; OS - 90%;	Acute adverse events: Grade 3 mucositis - 14 patients; Grade 3 dermatitis - 9 patients; Late adverse events: Hearing loss - 3 patients; Grade 2 xerostomia - 2 patients; Feeding tube dependence - 1 patient;
Gunn (58); 2016; United States;	50; 61, (37-84);	Oropharyngeal cancer, 88% p16 positive;	Intensity modulated proton therapy: 70 Gy_{RBE} (60-70 Gy_{RBE}); 29 months;	2-year OS - 94.5%; 2-year PFS - 88.6%;	Median weight loss - 7.4%; 11 patients needed feeding tube during treatment, with median duration 82 days; Persistent grade 3 or higher dysphagia at last FU - 0%;
Koto (60); 2018; Japan;	458; 63, (21-91);	Sinonasal malignant tumors stage N0-1M0; Mucosal melanoma: 48%; Adenoid cystic carcinoma: 26%; Squamous cell carcinoma: 7%; Olfactory neuroblastoma: 7%; Adenocarcinoma: 5%; Others: 7%;	Carbon-ion therapy: Doses: 57.6-70.4 Gy_{RBE} in 16-32 fractions; 25.2 months;	2- and 5- year: LCR - 84.1% and 71.2%; Regional recurrence rates - 10.9% and 15.2%; OS - 79.6% and 59.7%; PFS - 52.8% and 35.5%;	Acute adverse events: Grade 3 mucositis - 19%; Grade 3 dermatitis - 3%; Late adverse events: Ipsilateral blindness - 5%; Cataract - 3%; Grade 3 osteonecrosis of the maxilla - 4%;

Toyomasu (61); 2018; Japan;	59; 60, (35-92);	Sinonasal squamous cell carcinoma: Maxillary sinus: 49%; Ethmoid sinus: 31%; Nasal cavity: 10%; Frontal sinus: 7%; Sphenoid sinus: 3%;	Proton therapy (38 patients) and carbon-ion therapy (21 patients): 57.6-70.2 Gy_{RBE} in 16-28 fractions; 30 months;	3- and 5-year: OS - 56.2% and 41.6%; PFS - 42.9% and 34.7%; LCR - 54.0% and 50.4%; 5-year rates for resectable vs unresectable tumors: OS - 40.3% vs. 43.7%; PFS - 33.2% vs. 45.1%; LCR - 46.9% vs. 53.7%;	Acute grade 3 dermatitis - 12%; Late adverse events grade 3 or higher - 22%, including a grade 5 brain necrosis; Unilateral blindness - 7 patients; Bilateral blindness - 2 patients;
Dagan (62); 2016; United States;	84; 59, (28-81);	Sinonasal tumors: Olfactory neuroblastoma: 27%; Squamous cell carcinoma: 26%; Adenoid cystic carcinoma: 17%; Adenocarcinoma: 8%; Others: 20%;	Proton therapy, either primary (13%) or adjuvant (87%): 73.8 Gy_{RBE} (62.4-74.4 Gy_{RBE}), in 1.2 Gy_{RBE} fractions twice daily (one patient received 2 Gy_{RBE} fraction once daily); 2.4 years;	3-year: LCR - 83% (90% with gross total resection and proton therapy, and 59% for patients with gross disease); Neck control rate - 94%; MFS - 73.2%; DC - 63%; SS - 70%; OS - 68%;	Grade ≥3 adverse events - 24%; Unilateral blindness - 2 patients; Bone of soft-tissue necrosis - 7 patients, including 1 death due to brain necrosis;
Russo (63); 2016; United States;	54; 56, (18-82);	Sinonasal squamous cell carcinoma stage III and IV;	Proton therapy: 72.8 Gy_{RBE} (59.4-79.4 Gy_{RBE}); 82 months;	2- and 5-year: LCR - 80% and 80%; Regional control rate - 89% and 83%; Loco-regional control rate - 76% and 73%; MFS - 78% and 78%; OS - 67% and 47%; DC - 57% and 48%;	Grade ≥3 adverse events - 15 patients; Grade 3 or 4 sinonasal cutaneous fistulas - 6 patients; Grade 3 bone necrosis - 1 patient; Grade 3 hearing loss - 2 patients; Grade 3 trismus - 1 patient;
Bagley (64); 2019; United States;	69; 64, (37-84);	Oropharyngeal carcinoma stage III and IV;	Intensity modulated proton therapy: 60–70 Gy_{RBE}; Data was collected at	–	Mean xerostomia related quality-of-life score at baseline, 6 weeks during treatment, and follow-up visits at 10 weeks

		84% are p16 positive;	baseline and up until 2 years after treatment;		and at 6, 12, and 24 months: 0.24, 2.00, 1.03, 0.97, 0.82 and 0.70;
Hutcheson (65); 2017; United States;	66; 62*;	Oropharyngeal carcinoma, 96% with stage III/IV; 84% are p16 positive;	Intensity modulated proton therapy: No dose information given; Data was collected at baseline, end of treatment and 10 weeks, 6-, 12- and 24-months after treatment;	–	Poor MD Anderson Dysphagia Inventory score at baseline, end of treatment, 10-weeks and 2-year after treatment: 7%, 61%, 20%, and 13%;
Bahig (66); 2019; United States;	103; 61, (37-84);	Oropharyngeal carcinoma; 92% were p16 positive;	Intensity modulated proton therapy: No dose information given; 3.3 years;	3- and 5-year: OS - 96% and 80%; Loco-regional control rate - 93% and 90%; DFS - 93% and 77%;	Grade 3 mucositis - 46%; Grade 3 dermatitis - 43%; Grade 3 dysphagia - 15%; Feeding tube - 26%, median duration 106 days; Aspiration pneumonia - 16%; Very severe dysphagia - 7%;
Goldsmith (67); 2012; United States;	24; 48.9, (31-66);	Nasopharyngeal carcinoma stage III-IV;	Proton therapy combined with cisplatin and 5-fluoracil chemotherapy: 70 Gy_{RBE}; 2.3 years;	Loco-regional control rate - 100%;	Abnormal swallowing for semi-solids/solids at baseline, 3 months and 12-14 months - 10%, 43% and 38%; Penetration-aspiration - 2 patients; Nasal regurgitation - 1 patient; Pharyngeal residue - normal;
Sio (68); 2016; United States;	81; Proton group: 59.1*; Photon group: 58.2*;	Oropharyngeal carcinoma; p16 was positive in 74.3% of the proton group and 13.0% of the photon group;	Intensity modulated proton therapy: 36 patients, 70.0 Gy_{RBE} (59.0-70.0 Gy_{RBE}); 7.7 months; Intensity modulated radiotherapy: 46, patients, 70.0 Gy (58.0-70.0 Gy); 2.68 months;	–	Acute adverse events - comparable in both groups; Subacute and chronic dysgeusia and anorexia - favorable for the proton group; Symptom burden - similar for both groups in the acute and chronic phases, but higher in the subacute phase for the photon group;
McDonald (69); 2016; United States;	40; Proton group: 46.7;	Nasopharynx tumor: 57.7%; Nasal/paranasal	Proton therapy: 14 patients, 71.4 Gy_{RBE} (63-75.6 Gy_{RBE});	–	Proton therapy was associated with lower need for opioids and feeding tube dependence at the

	Photon group: 54.1;	sinuses tumors: 42.3%;	Photon radiotherapy: 26 patients, 71.8 Gy (66-76.4 Gy); Data was collected at baseline, end of treatment, 1- and 3-months after treatment;		end of treatment and at 3 months after treatment;
Zenda (70); 2014; Japan;	90; 57, (17-84);	Sinonasal and skull-base tumors: Olfactory neuroblastoma: 27 patients; Squamous cell carcinoma: 22; Adenoid cystic carcinoma: 15; Melanoma: 14; Others: 12;	Proton therapy; 60-70 Gy_{RBE} in 15-33 fractions; 57.5 months;	5-year PFS - 44.5%; 5-year OS - 64.2%;	Grade 3 late adverse events - 17 patients (5 cataracts, 2 hearing losses, 4 necrosis of brain, soft tissue or bone, 2 nerve disorders); Grade 4 late adverse events - 6 patients (4 optic nerve disorders, 2 encephalomyelitis);
Holliday (71); 2014; United States;	39; No age data given;	Nasopharyngeal cancer;	Intensity modulated proton therapy (13 patients) or intensity modulated radiotherapy (26): No dose data given; 13.5 months (proton group) and 19.8 months (photon group);	–	Proton vs. photon group: Feeding tube during or after treatment - 23.1% vs. 57.7%; Median weight loss: 5.3% vs. 7.4%; Swallowing dysfunction: 7.7% vs. 19.2%;
Sasahara (72); 2014; Japan;	63; 59, (16-80);	Sinonasal tumors: Adenoid cystic carcinoma: 24 patients; Melanoma: 24; Adenocarcinoma: 9; Squamous cell carcinoma: 2; Others: 4;	Carbon-ion therapy: 57.6 Gy_{RBE} in 16 fractions, with the maxilla receiving more than 10%; 79 months;	–	Maxillary necrosis - 41.3%, with maximum grade 3 (in 3 patients); Median development time of maxillary necrosis - 23 months (6-107);
Guan (75); 2019; China;	91; 38, (4-70);	Skull-base chordoma: 84.6%;	Intensity modulated proton therpay:	2-year: LCR - 86.2%; PFS - 76.8%;	Grade 3 mucositis - 1 patient; Grade 1 and 2 late adverse events - 19 patients;

		Skull-base chondrosarcoma: 15.4%;	8 patients, 70 Gy_{RBE} in 35 fractions; Carbon-ion boost: 69 patients, total dose 63-71 Gy_{RBE} in 21 to 38 fractions; Salvage re-irradiation: 14 patients, 57 to 69 Gy_{RBE} in 19-31 fractions; 28 months;	OS - 87.2% (93.8% for first-time radiation, 50.3% for re-irradiation);	Grade 3 late adverse events - 0 patients;
Baumann (76); 2019; United States;	20; 57, (38-83);	Skull-base chordomas: 10 patients; Sacrum chordomas: 5; Cervical spine chordomas; 3; Skull-base chondrosarcomas: 2;	Proton therapy (adjuvant in 17 patients, definitive in 3); 73.8 Gy_{RBE} (68.4-79.2 Gy_{RBE}); 37 months;	Feasibility endpoints of no treatments delays over 10 days and rate of acute adverse events less than 20% were met; 2- and 3-year: LCR - 95% and 86%; PFS - 90% and 81%;	Grade 3 acute adverse events - 2 patients, both fatigue; Grade 3 late adverse events - 1 patient, with sphenoid osteonecrosis and epistaxis; No significant difference on patient reported quality-of-life;
El Shafie (77); 2018; Germany;	110; 52, (45-59);	Skull-base meningioma: Sphenoid wing: 42 patients; Petroclival region: 23; Cavernous sinus: 4; Sella: 10; Olfactory nerve: 4; Other: 27;	Proton therapy: 104 patients, 54 Gy_{RBE} (50-60 Gy_{RBE}) in 1.8-2 Gy_{RBE} fraction; Carbon-ion therapy: 6 patients, 18 Gy_{RBE} in 3 Gy_{RBE} fractions; 46.8 months for both groups;	3- and 5-year PFS - 100% and 96.6%; 5- and 6-year OS - 96.2% and 92.0% (no death was meningioma related);	Grade 3 acute adverse events - 2 patients, one case of ulcerative mucositis and one case of prolonged nausea; Grade 3 late adverse events - 4 patients, one case of hypopituitarism and three cases of necrosis;
Deraniyagala (78); 2013; United States;	33; All patients over 18 years of age;	Skull-base chordoma;	Adjuvant proton therapy: 74 Gy_{RBE} (70-79 Gy_{RBE}); 21 months;	2-year LCR - 86%; 2-year OS - 92%;	Grade ≥2 unilateral hearing loss - 18%;
Rombi (79); 2013; Switzerland;	26; 13.2*, (3.7-20.8);	Skull-base chordoma: 12 patients; Axial skeleton chordoma: 7;	Proton therapy: 74 Gy_{RBE} (73.8-75.6 Gy_{RBE}) for chordomas and 66 Gy_{RBE} (54-72 Gy_{RBE}) for chondrosarcomas;	5-year rates for chordoma and chondrosarcoma: LCR - 81% and 80%; OS - 89% and 75%;	Grade 2 acute adverse events - 46%; Grade 2 late adverse events - 19%;

		Skull-base chondrosarcoma: 5; Axial skeleton chondrosarcoma: 2;	46 months;		No higher-grade adverse events were reported;
Holtzman (80); 2019; United States;	43; 49, (23-80);	Skull-base chondrosarcoma;	Proton therapy: 73.8 Gy_{RBE} (64.5-74.4 Gy_{RBE}); 3.7 years;	4-year: LCR - 89%; OS - 95%; SS - 100%; Toxicity-free survival rate - 95%;	Grade 3 acute adverse events - none; Grade 3 late adverse events - 6 patients, including one bilateral temporal lobe necrosis and four cases of hearing loss;
Weber (81); 2018; Switzerland and France;	251; 42.0*;	Skull-base chondrosarcoma;	Proton therapy, alone (116 patients) or combined with photon radiotherapy (135 patients): 70.2 Gy_{RBE} (62.0-76.0 Gy_{RBE}), with 1.8-2.0 Gy_{RBE} fractions; 88.0 months;	LCR - 95.2%; MFS - 98.4%; 7-year EFS - 93.1%; 7-year OS - 93.6%; 7-year toxicity-free survival - 84.2%;	Grade ≥3 acute adverse events - none; Grade ≥3 late adverse events - 15.1%, mostly hearing loss and brain and spinal cord necrosis, including 1 grade 5 brain necrosis; Two cases of secondary brain tumors were probably radiation induced;
Mattke (82); 2018; Germany;	101; 44*, (19-77);	Skull-base chondrosarcoma;	Carbon-ion therapy: 79 patients, 60 Gy_{RBE} with 3 Gy_{RBE} fractions; Proton therapy: 22, patients 70 Gy_{RBE} with 2 Gy_{RBE} fractions; 40 months for both groups;	Carbon-ion vs. proton therapy, at 1-, 2- and 4-year time endpoints: LCR - 98.6%, 97.2% and 90.5% vs. 100%, 100% and 100%; OS - 100%, 98.5% and 92.9% vs. 100%, 100% and 100%;	Adverse events at baseline, 0-1 years, 1-3 years and 3-5 years, carbon-ion vs. proton therapy: Hearing loss - 25%, 43%, 30% and 40% vs. 27%, 68%, 79%, and 33%; Cranial nerve deficit - 71%, 63%, 41% and 19% vs. 59%, 64%, 63%, and 33%; Double vision - 42%, 37%, 24% and 21% vs. 32%, 41%, 37%, and 33%;
Takagi (83); 2018; Japan;	24; 55.5, (24-79);	Skull-base chordoma;	Proton therapy (11 patients) or carbon-ion therapy (13): 57.6-74.0 Gy_{RBE} in 16-37 fractions; 71.5 months;	5- and 8-year: LCR - 85% and 71%; PFS - 81% and 65%; OS - 86% and 76%;	Grade ≥3 acute adverse events - none; Grade ≥3 late adverse events - 7 patients, including 2 cases of grade 3 brain necrosis and 1

					case of grade 4 pharyngeal hemorrhage;
Youn (84); 2018; Korea;	58; 54, (18-77);	Skull-base chordoma: 58.6%; Cervical spine chordoma: 12.1%; Sacrum chordoma: 29.3%;	Proton therapy: 69.6 Gy_{RBE} (64.8-79.2 Gy_{RBE}) in 2.4 Gy_{RBE} fractions; 42.8 months;	5-year: LCR - 87.9%; MFS - 86.7%; OS - 88.3%; SS - 92.9%;	Grade ≥3 acute adverse events - none; Grade ≥3 late adverse events - 3 patients, including 1 case of hemiparesis due to brainstem necrosis;
Matthias (85); 2014; Germany;	155; 48, (15-85);	Skull-base chordomas;	Raster scan carbon-ion therapy: 60 Gy_{RBE} at 3 Gy_{RBE} per fraction; 72 months;	3-, 5- and 10-year: LCR - 82%, 72% and 54%; OS - 95%, 85%, and 75%;	Acute adverse events -15%; At baseline and at 7-10 years: Hearing loss - 17% and 22%; Double vision - 45% and 26%; Cranial nerve deficits - 62% and 53%; Dizziness - 22% and 29%; Fatigue - 8% and 4%; Seizures - 2% and 4%;
Combs (86); 2013; Germany;	260; 48, (1-85);	Skull-base meningioma: 107 patients; Gliomas: 106; Pituitary adenomas: 14; Others: 33;	Proton therapy (67%) and carbon-ion therapy (33%): low-grade meningiomas received a median dose of 57.6 Gy_{RBE} high-grade meningiomas received photon radiotherapy with a carbon-ion boost; 12 months;	Low-grade meningiomas: LCR - 100%; OS - 100%; High-grade meningiomas: 1- and 2-year LCR - 54% and 33%;	No severe adverse events were reported;
Amelio (87); 2018; Italy;	33; 53, (28-82);	Large skull-base meningiomas;	Proton therapy: 50 Gy_{RBE} for newly diagnosed tumors and 54 Gy_{RBE} with 2 Gy_{RBE} fractions for progressing tumors; 9 months;	PFS - 100%;	Health-related quality-of-life scores improved compared with the baseline in the global health, social functioning and motor dysfunction domains; Cognitive, emotional function and fatigue domains remained stable;
Scartoni (88); 2018; Italy;	26; 76, (70-87);	Meningioma: 61%; Chordoma: 12%;	Active scanning proton therapy: 54 Gy_{RBE} (50-72 Gy_{RBE}), with 1.8-2 Gy_{RBE} fractions;	One patient experienced tumor progression;	Grade 1 and 2 acute and late adverse events: Skin erythema - 62% (acute only);

		Glioma: 15%; Other: 12%;	8 months;		Alopecia - 53% and 53%; Fatigue - 42% and 15%; Conjunctivitis - 19% (acute only); Pain - 41% (acute only); Headache - 27% and 12%; Skin hyperpigmentation - 14% and 3%; grade 3 adverse events - none;
Kountouri (89); 2019; Switzerland;	216; 47, (18-77);	Chordoma: 52.8%; Chondrosarcoma: 22.2%; Meningioma: 18.1%; Adenoid cystic carcinoma: 3.2%; Others: 3.7%;	Pencil beam proton therapy: 74.0 Gy_{RBE} (54.0-77.4 Gy_{RBE}); 5.3 years;	3- and 5-year: OS - 99% and 90.7%; LCR - 91.8% and 84.3%;	Radiation induced optic neuropathy - 6.5%, 78.6% of which were unilateral. Cases were grade 3 and 4, except in two patients; Median time to symptom onset - 13.2 months (4.8-42.6); 5-year optic neuropathy-free survival - 93.3%;
Rangel (90); 2019; Treatment location not given;	47; No age data given;	Skull-base chordoma; Skull-base chondrosarcoma;	Proton therapy: No dose or FU data were given;	–	Cerebrospinal fluid leak - 6 patients; Osteoradionecrosis of skull-base - 1 patient; Refractory dizziness - 1 patient; Hearing loss - 1 patient;
Koto (91); 2013; Japan;	39; 47. (16-76);	Skull-base chordoma: 25 patients; Skull-base chondrosarcoma: 5; Olfactory neuroblastoma: 4; Meningioma: 4; Giant cell tumor: 1;	Carbon-ion therapy: 48.0-60.8 Gy_{RBE} in 16 fractions; 67 months;	–	5-year incidence of brain lesion grade 2 or higher - 24.5%; 5-year incidence of symptomatic brain lesion - 7.0%; Median time between treatment and development of brain lesion - 26 months (5-103);
Henderson (94); 2017; United States;	215; 65, (41-82);	PCa: Low-risk: 120 patients;	Hypofractioned proton therapy:	5-year rates for low- and intermediate risk patients: OS - 96.0% and 96.4%; BCS - 98.3% and 92.7%;	No grade ≥3 adverse events occurred in the first 6 months of FU;

		Intermediate-risk: 95;	70 Gy_{RBE} in 28 fractions (low-risk patients), 72.5 Gy_{RBE} in 29 fractions (intermediate-risk); 5.2 years;	MFS - 98.5% (low- and favorable intermediate-risk patients) and 88.5% (unfavorable intermediate-risk patients);	5-year late GU adverse events grade ≥3 - 1.0%; 5-year late GI adverse events grade ≥3 - 0.5%;
Grewal (95); 2019; The Netherlands;	184; Low-risk: 64. (53-75); Favorable intermediate-risk: 67. (50-80); Unfavorable intermediate-risk: 68 (50-83);	PCa: Low-risk: 18 patients; Favorable intermediate-risk: 78; Unfavorable intermediate-risk: 88;	Hypofractioned proton therapy: 70 Gy_{RBE} in 28 fractions; 49.2 months;	4-year: BCS - 93.5%, (94.4% for low-risk, 92.5% for favorable intermediate-risk and 93.8% unfavorable intermediate-risk); OS - 95.8%;	Acute GU adverse events grade ≥2 - 12.5%; Acute GI adverse events grade ≥2 - 3.8%; 4-year late GU adverse events grade ≥2 - 7.6%; 4-year late GI adverse events grade ≥2 - 13.6%; IPSS and EPIC quality-of-life scores showed no significant changes;
Bryant (96); 2016; United States;	1327; 66, (41-88);	PCa: Low-risk: 41%; Intermediate-risk: 42%; High-risk: 17%;	Proton therapy: 98% of patients received 78-82 Gy_{RBE}; 5.5 years;	5-year rates for low-, intermediate- and high-risk patients: BFS - 99%, 94% and 74%; MFS - 99%, 99%, and 98%; Nodal metastasis-free survival - 99%, 99%, and 96%; SS - 98%, 97%, and 95%;	5-year overall GU adverse events grade ≥3 - 3.0%; 5-year late GU adverse events grade ≥3 - 2.9%; 5-year late GI adverse events grade ≥3 - 0.6%; IPSS scores remained stable, but EPIC sexual function scores significantly decreased for non-castrated patients;
Nomiya (97); 2016; Japan;	2157; 67, (45-92);	PCa: Low-risk: 12%; Intermediate-risk: 31%; High-risk: 56%;	Proton therapy: 51.6-66 Gy_{RBE} in 12-20 fractions; 29 months;	5-year rates for low-, intermediate- and high-risk patients: BFS - 92%, 89% and 92%; LCR - 98%, 96%, and 99%; SS - 100%, 100%, and 99%; OS - 100%, 99%, and 96%;	5-year GI adverse events grade 2 - 0.8%, all of them rectal hemorrhage. 5-year GU adverse events grade 2 - 6.1%, mostly hematuria; 5-year GU/GI adverse events grade ≥3 - 0%;
Arimura (98); 2018; Japan;	218; 65, (39-86);	PCa: Intermediate-risk: 55%; High-risk: 45%;	Proton therapy: 70-78 Gy_{RBE} in 28-39 fractions; 52 months;	5-year rates for intermediate- and high-risk patients: OS - 96% and 98%; PFS - 97% and 83%;	Acute GU adverse events grade ≥2 - 23.5%; Acute GI adverse events grade ≥2 - 0%; Late GU adverse events grade ≥2 - 3.4%;

					Late GI adverse events grade ≥2 - 3.9%;
Choi (99); 2017; United Sates;	1628; No age data given;	PCa: Low-risk: 31.7%; Intermediate-risk: 60%; High-risk: 8.2%;	Proton therapy: 76 Gy_{RBE} (75.6-78 Gy_{RBE}) in 2 Gy_{RBE} fractions; 4.1 years;	2- vs. 5-year rates for low-, intermediate- and high-risk patients: OS - 100%, 98.0% and 99.2% vs. 98.0%, 95.9% and 87.0%; BFS - 99.6%, 97.9%, and 98.4% vs. 95.7%, 92.3% and 80.7%; PFS - 99.8%, 98.6%, and 98.0% vs. 95.9%, 92.7% and 78.0%;	Acute GU adverse events grade ≥2 - 39.4%; Acute GI adverse events grade ≥2 - 5.2%; 2- and 5-year late GU adverse events grade ≥2 - 10.4% and 15.9%; 2- and 5-year late GI adverse events grade ≥2 - 8.3% and 10.6%;
Kawamura (100); 2020; Japan;	304; 66, (48-80);	PCa: Low-risk: 5%; Intermediate-risk: 47%; High-risk: 48%;	Carbon-ion therapy: 57.6 Gy_{RBE} in 16 fractions; 60 months;	5-year rates: BFS - 92.7% (91.7%, 93.4% and 92.0% for low-, intermediate- and high-risk patients, respectively); LCR - 98.4%; OS - 96.6%;	Acute GU adverse events grade ≥2 - 4.0%; Acute GI adverse events grade ≥2 - 0%; Late GU adverse events grade ≥2 - 9.3%; Late GI adverse events grade ≥2 - 0.3%;
Iwata (101); 2018; Japan;	1291; 68;	PCa: Low-risk: 215 patients; Intermediate-risk: 520; High-risk: 556;	Proton therapy, conventionally fractionated (98.8%) or hypofractionated (1.2%): 70-80 Gy_{RBE} in 35-40 fractions or 63-66 Gy_{RBE} in 21-22 fractions; 69 months;	5-year rates for low-, intermediate- and high-risk patients: BFS - 97.0%, 91.0% and 83.1%; OS - 98.4%, 96.8%, and 95.2%; SS - 100%, 100% and 99.6%; Clinical relapse-free survival - 100%, 98.2%, and 95.9%;	Late GU adverse events grade ≥2 - 4.0%; Late GI adverse events grade ≥2 - 4.1%;
Takagi (102); 2017; Japan;	1375; 69, (44-92);	PCa: Low-risk: 18%; Intermediate-risk: 44%; High-risk: 33%; Very high-risk: 5%;	Proton therapy: 99% of patients received 74 Gy_{RBE}, and the remaining patients received 78 Gy_{RBE}; 70 months;	5- vs. 8-year rates for low-, intermediate-, high- and very high-risk patients: BFS - 99%, 91%, 86%, and 66% vs. 95%, 87%, 71%, and 55%;	5-year late GU adverse events grade ≥2 - 2.0%; 5-year late GI adverse events grade ≥2 - 3.9%;

				OS - 98%, 96%, 96%, and 90% vs. 94%, 90%, 89%, and 86%; SS - 100%, 100%, 99%, and 95% vs. 100%, 99%, 98%, and 92%;	
Takagi (103); 2018; Japan;	43; No age data given;	Castration resistant PCa;	Proton therapy: 98% of patients received 74 Gy_{RBE} in 37 fractions; 68 months;	5-year rates: BFS - 38%; PFS - 72%; SS - 75%; OS - 67%;	5-year late GU adverse events grade ≥2 - 8.1%; 5-year late GI adverse events grade ≥2 - 11%;
Choi (104); 2015; United States;	64; 69, (45-89);	High-risk PCa;	Scanning beam proton therapy: 78 Gy_{RBE} (76-78 Gy_{RBE}) in 2 Gy_{RBE} fractions; 41.5 months;	BFS - 96.9%; 80.8% patients showed a recovery of serum testosterone levels to >200 ng/dL;	GU adverse events grade ≥2 - 18.7%; GI adverse events grade ≥2 - 7.8%;
Kubeš (105); 2019; Czech Republic;	200; 64.3*;	Early stage PCa: Low-risk: 46.5%; Intermediate-risk: 53.5%;	Extreme hypofractionated proton therapy: 36.25 Gy_{RBE} in 5 fractions; 36 months;	Biochemical relapse occurred in 8 patients; No local recurrences were observed; No patient died of prostate cancer;	Acute GU adverse events grade 2 - 19.0%; Acute GI adverse events grade 2 - 3.5%; Late GU adverse events grade 2 - 4%; Late GI adverse events grade 2 - 5.5%; No adverse events grade ≥3 were observed;
Philip (106); 2019; United States;	181; 66*;	PCa;	Hypofractionated proton therapy: 55.5 Gy_{RBE} in 15 fractions of 3.7 Gy_{RBE}; 2.6 years;	–	Acute GU adverse events grade 2 - 15.0%; Acute GI adverse events grade 2 - 4.8%; 1-, 2-, and 3-year late GU adverse events grade 2 - 9.0%, 12.4% and 14.41%; 1-, 2-, and 3-year late GI adverse events grade 2 - 2.7%, 3.6% and 4.6%; No adverse events grade ≥3 were observed;

					At 3 years, 95% of patients reported no use of urinary pads, and 58% reported erections firm enough for intercourse;
Lee (107); 2018; United States;	231; 68, (50-85);	PCa: Low-risk: 19.8%; Intermediate-risk: 54.2%; High-risk: 26.0%;	Proton therapy: Over 95% of patients received 75.6-81 Gy_{RBE} in 1.8-2.0 Gy_{RBE} fractions; 1.7 years;	–	Quality-of-life scores: IPSS - remained stable; EPIC bowel domain and SHIM erectile function scores - median decrease of 5.4 and 3.7 points, respectively, at 1 year, and remained stable thereafter; 2-year GU adverse events grade ≥2 - 26.4%; 2-year GI adverse events grade ≥2 - 21.3%; 2-year erectile dysfunction grade ≥2 - 23.0%;
Ho (108); 2018; United States;	254; 56, (41-60);	PCa: Low-risk: 56%; Intermediate-risk: 42%; High-risk: 2%;	Proton therapy: 76-82 Gy_{RBE} in 2 Gy_{RBE} fractions or 70-72.5 Gy_{RBE} in 2.5 Gy_{RBE} fractions; 7.1 years;	7-year BFS - 97.8%; 7-year OS - 98.7%;	Baseline, 1-, and 5-year: Sexual potency - 89.7%, 71.9% and 68.1%; 1-, and 5-year urinary incontinence-free: 99.6% and 98.6%; Bowel symptoms quality-of-life mean scores decreased at 1-year FU, and improved thereafter;
Chuong (109); 2017; United States;	85; 69, (53.9-79.9);	Non metastatic PCa, 78.8% of patients had Gleason score ≥8;	Proton therapy, prostatic and pelvic irradiation: Pelvic - 46.9 Gy_{RBE} (39.7-56 Gy_{RBE}) in 24-30 fractions; Boost to prostate - 30 Gy_{RBE} (20-41.4 Gy_{RBE}) in 10-24 fractions; 14.5 months;	–	Acute GU adverse events grade 1 and 2 - 60% and 34.1%; Acute GI adverse events grade 1 and 2 - 16.4% and 2.4%; No acute adverse events grade ≥3 were observed;
Dutz (110); 2019; Germany;	88; Photon group: 74.9, (65.9-83.8);	PCa: For the proton and photon group,	Proton therapy: 31 patients, 74 Gy_{RBE} (74-76 Gy_{RBE});	–	Photon vs. proton radiotherapy: Acute GU adverse events grade ≥2 - 44% vs. 27%;

	Proton group: 70.4, (49.3-83.6);	low-risk: 6.9% and 0%; intermediate-risk: 75.9% and 79.3%; high-risk: 17.2 and 20.7%;	Intensity modulated radiotherapy: 57 patients, 78 Gy (74-78 Gy); Data collected at baseline, weekly during treatment, at the end of treatment and at 3-6 month intervals after;		Acute GI adverse events grade ≥2 - 17% for both groups; Late GU adverse events grade ≥2 - 32% vs. 23%; Late GI adverse events grade ≥2 - 9% vs. 14%; Global health scores 1-year after treatment: 8.3 vs. –2.8 points; Only late urinary urgency was significantly different between groups (favorable in proton therapy);
Nakajima (111); 2017; Japan;	526; Conventionally fractionated group: 70. (52-88); Hypofractionated group: 69, (47-86);	PCa: For the conventionally fractionated and hypofractionated group, low-risk: 19% and 15%; intermediate-risk: 38% and 46%; high-risk: 43% and 39%;	Conventionally fractionated (254 patients) or hypofractionated proton therapy (272): Low-risk - 74 Gy_{RBE} in 37 fractions or 60 Gy_{RBE} in 20 fractions; Intermediate- and high-risk - 78 Gy_{RBE} in 39 fractions or 63 Gy_{RBE} in 21 fractions; Data collected at baseline, and at FU in 1-6-month intervals after treatment;	–	For conventionally fractionated vs. hypofractionated groups: Acute GU adverse events grade 2 - 15% vs. 5.9%; Acute GI adverse events grade 2 - 0% for both groups; Acute adverse events grade ≥3 - none; Baseline, 1- and 6-month IPSS scores - 7, 9 and 7 vs. 6, 11 and 7;
Mohamad (112); 2019; Japan;	9386; Carbon-ions: 68, (63-73); Photons: 71; Surgery: 68;	PCa: For the carbon-ion group: Low-risk- 13%; Intermediate-risk - 34%; High-risk - 53%;	Carbon-ion therapy: 1455 patients, 57.6 Gy_{RBE} with a median of 16 fractions; 7.9 years; Photon radiotherapy: 1983 patients, no data bout dose given; 5.7 years; Surgery: 5948 patients; 6.0 years;	–	9.9-year subsequent primary cancers cumulative incidence: Carbon-ions - 16.1%; Photons - 24%; Surgery - 18.7%;
Mendenhall (113); 2017; United States;	1515; Proton group: 66;	PCa;	Proton therapy: 1214 patients, 78 Gy_{RBE} in 39 fractions; 5.6 years;	Proton vs. photon groups for low-, intermediate- and high-risk patients:	Photon vs. proton groups: Late GU adverse events grade ≥3 - 4.3% vs. 0.1%;

	Photon group: 74;		Photon radiotherapy: 301 patients, 75.6 Gy in 42 fractions; 7.2 years;	OS (under 75 years) - 97.5%, 95.5%, and 90.0% vs. 91.6%, 92.1%, and 92.0%; BFS - 98.9%, 94.5%, and 74.4% vs. 92.2%, 87.3% and 80.3%; OS for men over 75 years - 88.7% vs. 90.8%;	Late GI adverse events grade ≥3 - 1.3% vs. 0.1%;

Abbreviations key: BCS: Biochemical and/or clinical relapse-free survival; BFS: Biochemical relapse-free survival; CNS: Central nervous system; CSI: Craniospinal irradiation; DC: Disease control rate; DFS: Disease free survival rate; EBV: Epstein-Barr virus; EFS: Event-free survival; FSIQ: Full Scale Intelligence Quotient; FU: follow-up; GI: Gastrointestinal, GU: Genitourinary; LCR: local control rate; MFS: metastasis-free survival rate, NVG: neovascular glaucoma; OS: overall survival rate; PCa: Prostate adenocarcinoma; PFS: progression-free survival rate; PNET: primitive neuroectodermal tumor; PT: proton therapy; RFS: relapse-free survival rate; RLVCV: Radiation induced large vessel cerebral vasculopathy; RN: radiation necrosis; SIB-R: Scales of Independent Behavior-Revised; SRS: stereotactic radiosurgery; SS: specific survival rate; WML: white matter lesions;

* Mean value given instead of median;

** Rates estimated with Kaplan-Meier methods;

*** Adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Table II – Ongoing, non-recruiting, trials on hadrontherapy

Clinicaltrials.gov Identifier	Title	Primary Outcome	Start and Estimated Completion year	Study design
NCT03696355;	Study of GDC-0084 in Pediatric Patients With Newly Diagnosed Diffuse Intrinsic Pontine Glioma or Diffuse Midline Gliomas;	Characterize the maximum/recommended phase 2 dosage, toxicity and pharmakinetics of GCD-0084 after radiation therapy in pediatric patients with diffuse midline glioma;	2018-2024;	Phase I interventional non-randomized clinical trial;
NCT03520504;	Study of Proton Radiation to the Brain and Spinal Cord for Patients With Leptomeningeal Metastases;	Assess the number of patients with dose-limiting toxicity (time frame: 2 years);	2019-2020;	Phase Ib single-arm, prospective trial with 3+3 dose de-escalation and dose expansion cohort.
NCT03159676;	Proton-Based Stereotactic Ablative Body Radiotherapy for Prostate Cancer;	Assess the effect of proton-based stereotactic ablative body radiotherapy in the quality-of-life of patients with localized prostate adenocarcinoma;	2017-2029;	Observational case-only prospective trial;
NCT02874014;	Prospective Evaluation of Hypofractionation Proton Beam Therapy With Concurrent Treatment of the Prostate and Pelvic Nodes for Clinically Localized, High Risk or Unfavorable Intermediate Risk Prostate Cancer;	Evaluate the late grade 3 or higher gastrointestinal and genitourinary toxicity in a moderate hypofractionated proton therapy regime for unfavorable intermediate- or high-risk prostate cancer;	2016-2023;	Interventional single-arm prospective trial;
NCT02795195;	Trail Evaluating Carbon Ion Radiotherapy (3 GyE Per Fraction) for Locally Recurrent Nasopharyngeal Carcinoma;	Assess the number of patients with treatment related adverse events (time frame: from start of radiotherapy to 4 months after treatment);	2016-2020;	Phase I/II interventional single-arm clinical trial;
NCT02736786;	A Study of Mucosal Sparing Proton Beam Therapy (PBT) in Resected Oropharyngeal Tumors;	Assess the local control rate in patients treated with proton therapy after surgical resection (time frame: 2 years);	2016-2021;	Observational cohort prospective trial;
NCT01627093;	Medical Data Collection of Patients With Head and Neck Cancer Treated With Proton Therapy;	Assess outcomes in patients who received proton therapy for head and neck cancer;	2012-2024;	Observational cohort prospective data collection;
NCT01368055;	Hypofractionated Proton Radiation Therapy for Low and Intermediate Risk Prostate Cancer (PR07);	Assess the cumulative incidence of treatment related grade 2 or higher rectal bleeding (time frame: 2 years);	2011-2036;	Phase II interventional non-randomized clinical trial;
NCT01338389;	Influence of Oral Treatment With Citicoline for the Prevention of Radiation	Assess the effect of citicoline in the occurrence and delay of radiation optic neuropathy in patients	2011-2023;	Interventional randomized, double blind, clinical trial;

	Optic Neuropathy in Patients Treated for Uveal Melanomas With Proton Beam Therapy;	treated with proton therapy (time frame: every 6 months);		
NCT01288235;	Proton Radiotherapy for Pediatric Brain Tumors Requiring Partial Brain Irradiation;	Assess the incidence of endocrine dysfunction and neurocognitive sequalae after proton therapy (time frame: 5 years);	2011-2022;	Phase II interventional single-arm clinical trial;
NCT01180881;	Neurobehavioral Functioning in Pediatric Brain Tumor Patients After Proton Beam Radiation Treatment;	Assess the neurobehavioral function outcomes and use of special education services in pediatric brain tumor patients treated with proton therapy (time frame: 1 year);	2010-2020;	Observational prospective cohort;
NCT01115777;	Prospective Assessment of Quality of Life (QOL) in Pediatric Patients Treated With Radiation Therapy for Brain Tumors and Non-central Nervous System (Non-CNS) Malignancies;	Assess the quality-of-life outcomes in pediatric patients treated with radiotherapy (time frame: 10 years);	2005-2029;	Observational prospective cohort;
NCT01067196;	Outcomes Study of Late Effects After Proton RT for Pediatric Tumors of the Brain, Head, and Neck (CN01	Assess the late adverse events of proton therapy in pediatric patients (time frame: 5.4 years);	2010-2022;	Observational prospective cohort;
NCT01063114;	Proton Beam Radiotherapy for Medulloblastoma and Pineoblastoma;	Assess the incidence and severity of ototoxicity, endocrine dysfunction and neurocognitive effects after radiation therapy for pediatric patients (time frame: 3 years);	2010-2021;	Interventional single-arm clinical trial;
NCT01049230;	Proton Beam Radiation Therapy for Central Nervous System (CNS) Germ Cell Tumors;	Assess the acute, subacute and late adverse events of craniospinal, whole ventricle and involved field proton radiation therapy in place of photon therapy for pediatric patients (time frame: 2 years);	2010-2020;	Phase II interventional single-arm clinical trial;
NCT01045226;	Proton Radiation Therapy in Treating Patients With Prostate Cancer;	Assess the feasibility of proton radiation therapy with standard fractionation in prostate cancer (time frame: 5 years) and evaluate acute adverse events (time frame: 90 days);	2010-2020;	Phase II interventional single-arm clinical trial;
NCT01040624;	Docetaxel, Androgen Deprivation and Proton Therapy for High Risk Prostate Cancer (PR05);	Assess acute grade 3 or higher treatment-related adverse events (time frame: 6 months);	2015-2035;	Phase II interventional non-randomized clinical trial;
NCT00693238;	Proton Therapy for Low and Intermediate Risk Prostate Cancer (PR04);	Assess acute grade 3 or higher treatment-related adverse events (time frame: 6 months);	2013-2033;	Phase II interventional non-randomized clinical trial;

NCT00489814;	Study of Quality of Life for Prostate Proton Therapy;	Collect information of the adverse events of proton therapy and its effects on quality-of-life (time frame: 4 years);	2006-2020;	Observational prospective cohort;
NCT00105560;	Proton Beam Radiation Therapy in Treating Young Patients Who Have Undergone Biopsy or Surgery for Medulloblastoma or Pineoblastoma;	Assess the cumulative incidence of ototoxicity (time frame: 3, 5, 7, and 10 years);	2017-2021;	Phase II interventional single-arm clinical trial;