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TITOLO TESI

# PROTON RADIOTHERAPY: A THERAPEUTIC OPPORTUNITY FOR PEDIATRIC BRAIN TUMOR PATIENTS

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**ABSTRACT**

Proton radiation therapy is a form of external radiation that uses charged particles which have distinct physical advantages to deliver the majority of its dose in the target while minimizing the dose of radiation to normal tissues. In children who are particularly susceptible even at low and medium doses of radiation, the significant reduction of integral dose can potentially mitigate the incidence of side effects and improve quality of life. The aim of the first part of the thesis is to describe the physical and radiobiological properties of protons, the Proton Therapy Center of Trento (TCPT) active for clinical purpose since 2014, which use the most recent technique called active pencil beam scanning. The second part of the thesis describes the preliminary clinical results of 23 pediatric patients with central nervous system tumors as well as of two aggressive pediatric meningiomas treated with pencil beam scanning. All the patients were particularly well-suited candidates for proton therapy (PT) for possible benefits in terms of survival and incidence of acute and late side effects. We reported also a multicentric experience of 27 medulloblastoma patients (median age 6 years, M/F ratio 13/14) treated between 2015 and 2020 at TPTC coming from three Pediatric oncology centers: Bologna, Florence, and Ljubljana, with a focus on clinical results and toxicities related to radiotherapy (RT). Proton therapy was associated with mostly mild acute

and late adverse effects and no cases of CNS necrosis or high grade of neuroradiological abnormailities. Comparable rates of survival and local control were obtained to those achievable with conventional RT. Finally, we performed a systematic review to specifically address the safety of PT for pediatric CNS patients, late side effects and clinical effectiveness after PT in this patient group.

## 1. INTRODUCTION

Tremendous progress in the field of pediatric oncology has been made over the past two decades so that the 5-year overall survival rates improved from 39% in 1960 to more than 80% in 2004 [1]. RT is an integral component in the curative treatment of many childhood tumors. Unfortunately, radiation exposure is a major contributor to treatment related late morbidity for long-term survivors. Children are particularly susceptible to the late effects of radiation, even at low and medium doses, as demonstrated in epidemiologic studies of exposed populations [2]. The normal growing tissues are more sensitive to radiation so they can develop more frequently late side effects and chronic conditions, and the longer life expectancy can result larger window of opportunity for expressing radiation damage. Several approaches have been used to decrease the morbidity of radiation delaying radiation using chemotherapy or surgery to avoid or reduce the dose of RT. Despite these approaches, many children require radiation and remain at high risk of developing a multitude of serious long-term sequelae including but not limited to secondary cancers, cardiac disease, endocrinopathies, neuro-cognitive dysfunction, cosmetic damage [3].

## 2. RATIONALE FOR PROTON RADIOTHERAPY

Although photon-based RT is used worldwide for the treatment of CNS tumor with different techniques which include three-dimensional conformal photon radiotherapy (3DCRT), intensity modulated radiation therapy (IMRT) and thomotherapy, Proton therapy (PT) could reduce the risk of the adverse radiation effects caused by photon-based radiotherapy. Dosimetric studies continue to show the benefits of PT over these photons techniques [4,5] and as a result, medical centers around the world are working to open more facilities and improve patient access. Protons radiation therapy is a high-precision form of irradiation which guarantees optimal coverage of the tumor region with a high conformality and homogeneity while sparing the surrounding organs at risk (OAR) [6].

### 2.1 Physics of Protons

Proton radiation therapy is a form of external radiation that uses charged particles produced by particle accelerators i.e., cyclotron or synchrotron. PT offers the possibility to reduce inadvertent dose deposition in non-target tissue (absorbed dose) of healthy brain, mainly because of the advantageous physical properties of protons. The figure 1 shows a

comparison of dose-deposition curves in the matter of 15 MV photons and SOBP (spread out break peak) proton. High energy photons deposit the maximum dose within a few centimeters of the skin surface and continue to irradiate tissues beyond the target delivering dose throughout the entire volume of the irradiated tissue and decreasing exponentially until exiting the body. For targets deeper than three cm, each photon beam will deliver more dose proximal to the target than in the target. For this reason, photon therapy is generally delivered with multiple beam directions. Protons enter the body and deliver a small and constant dose until near the end of range. This dose distribution is known as the Bragg peak, beyond which, no dose is delivered (Fig.1).

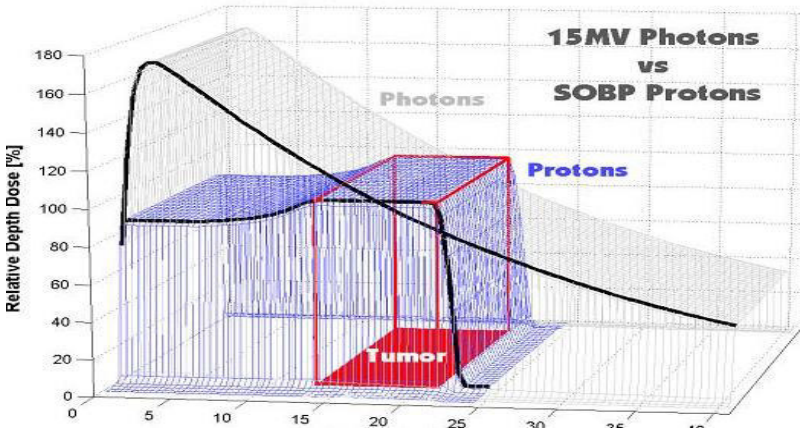


Fig.1 Comparison between spread out bragg peak (SOBP) protons and 15 MV photons

Because a single mono-energetic Bragg peak called pristine peak (Fig.2) is too narrow to cover the entire volume of most tumors, several peaks with different energies are used to cover all the tumor with uniform dose area named spread out Bragg peak (SOBP).

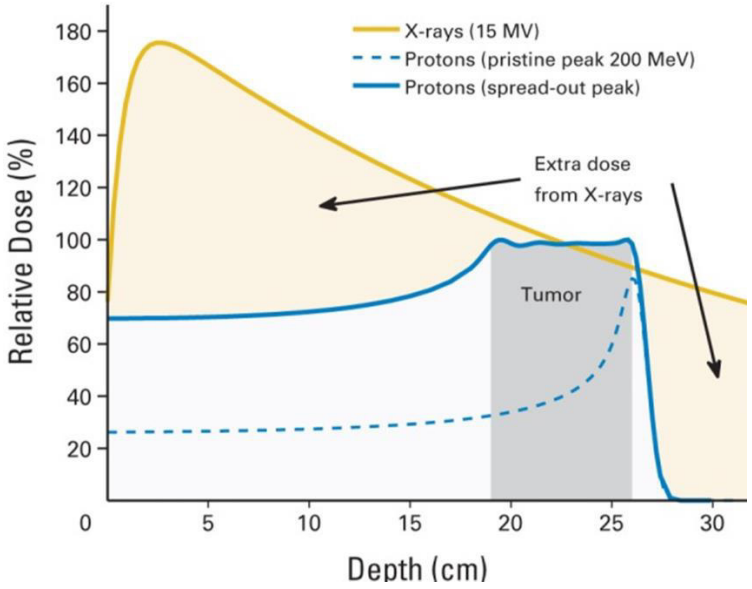


Fig. 2 Pristine peak in light blue dashed line

Therefore, with protons less normal tissues are irradiated and the integral dose is minimized, decreasing the dose to non-target tissues by more than one-half [7].

Protons interact with matter primarily through Coulomb interactions with atomic electrons; Coulomb interactions with nuclei; and nuclear

interactions. They lose most of their energy through interactions with electrons. Secondary electrons travel a short distance from the path of the proton while ionizing and depositing energy. Because a proton is much heavier than an electron, its interactions with electrons do not result in an appreciable deviation from its original direction. The energy deposited by a proton per unit distance called Linear Energy Transfert (LET) increases inversely as the square of the proton velocity. In uniform monoenergetic protons will travel to a well-defined distance, losing linearly energy at an increasing rate as they slow down, before coming to a stop. This leads to the formation of the characteristic Bragg curve shown in Figure 1.

### 2.2 Biological Effectiveness of Protons

Based on numerous in-vitro and animal experiments, protons have been assumed to have a 10% higher biological effectiveness relative to photons (i.e., RBE of 1.1) [8]. In clinical practice, the physical dose, in units of Gy, delivered by protons is multiplied by 1.1 to obtain the biologically effective dose in units of Gy (RBE). Is true that the RBE is, in fact, variable. It may be close to 1 in the entrance regions and be higher than 1.1 at larger depth depending on the LET (which is a function of the

residual range of protons), dose per fraction, tissue type, end point, etc. infact several studies in vitro and vivo defined RBE around 1.3-1.4 proximally to the distal edge of bragg peak [9].

## 3. THE TRENTO PROTON THERAPY CENTER

The Trento facility is equipped with active beam delivery based on spot scanning which use is a more efficient and potentially clinically more effective alternative technique. Protons are accelerated to the maximum of the energy of 228 MeV of the cyclotron (Proteus Plus, IBA, Belgium) (Fig. 3, Fig. 4 A), and the required lower energies are achieved by a electromechanically inserting energy degraders (fig. 4 D) in the path of protons called Trasportation system (TS) between the accelerator and the treatment rooms (Fig. 4 B, C) or to the experimental room (Fig. 4 E).

The gantry is used to aim the beam at the target in the patient lying on a treatment couch. The couch can also be rotated and shifted to achieve optimum beam directions to avoid as much normal tissue as possible.

The Trento's proton accelerator serves multiple rooms. The beam is switched automatically from one room to the next based on the order of request and priority.


Fig. 3 Cyclotron

TS (fig. 4 D) transforms the 230-MeV fixed energy beam extracted from the cyclotron into a beam having an energy level that is variable between 230 MeV and 70 MeV. In addition, the energy selection devices in the TS also stop unwanted beam particles from traveling down the beam line. The absolute energy, energy spread, and emittance of the beam exiting the energy selection section of the TS and entering the static beam line are verified and controlled. Control is made possible using a series of quadrupole and dipole magnets used in conjunction with an energy degrader, collimators, and slits.

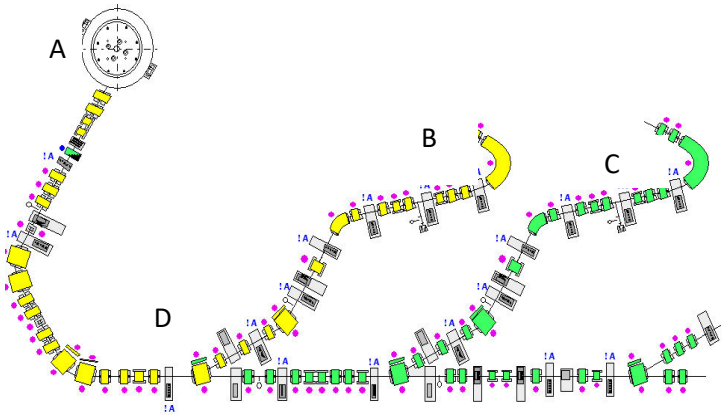


Fig. 4 Beam line

Each treatment room (Fig. 5, 6) is equipped with a gantry which allows 360° rotation of the beam line, 6 degrees of freedom robotic treatment table, two orthogonal X-ray devices, a CT on-rails in one room and a cone-beam CT in the other. Two horizontal beam lines are placed in a third experimental room (Fig. 7).

Fig. 5 Treatment room 1

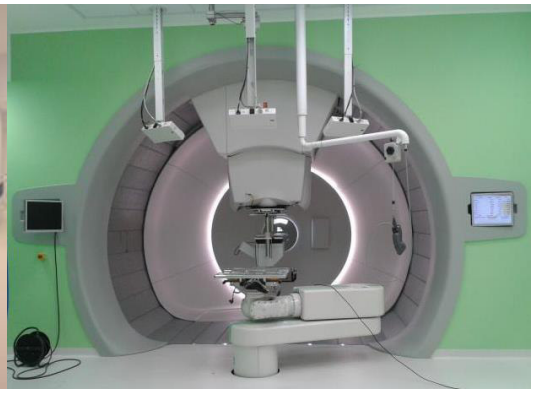

Fig. 6 Treatment room 2

Fig. 7 Experimental room

The center is equipped also with a dedicated CT and 1.5T MRI and an anesthesia area. In October 2014, the facility started clinical activity on adult and, one year after, with pediatric patients.

In the proton therapy center available in Trento the pencil beam scanning technique was made by multiple beams incident from different directions, each comprising the scanning beamlets of a sequence of energies, are used to produce the desired pattern of dose. For each scanned beam, the treatment is delivered in "layers," one layer per energy. Upon completion of one layer, the energy is changed to the next in the sequence. For scanning beams, proximal and lateral field shaping is achieved by limiting the positions of the spots to within the target regions only. Further advances such as pencil beam scanning and intensity modulated proton therapy can allows usually better dose conformality, lower normal tissue dose and lower neutron dose contamination.

## 3.1 Cranio-spinal irradiation with pencil beam scanning: Trento's technique

Craniospinal spinal irradiation (CSI) continues to play a significant role in the multidisciplinary management of brain tumors in children and adults. Postoperative CSI with chemotherapy is the current standard of care of medulloblastoma and for brain tumors with proven spread in the cerebrospinal fluids [10].

Late toxicity is a major problem in long-term survivors and significantly affects their quality of life.

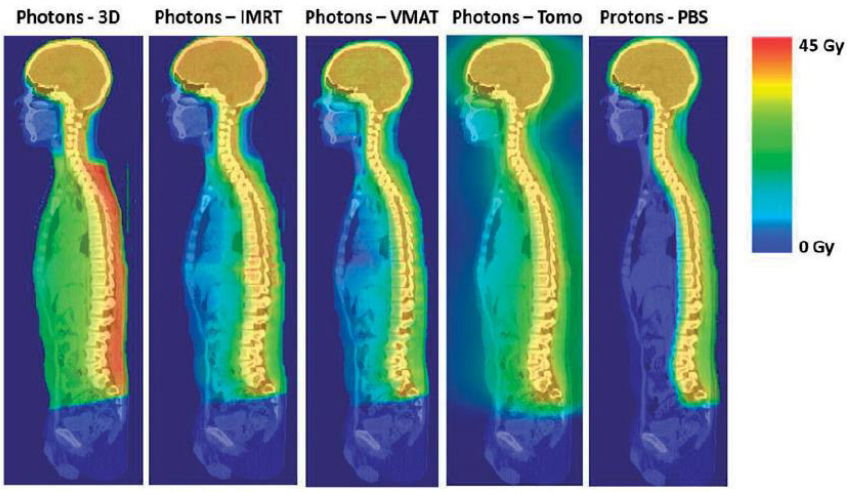


Fig. 8 CSI dose distribution with (3D-CRT, IMRT, VMAT, Tomo-therapy and protons

Serravalli and colleagues [11] from SIOP society of radiotherapy brain tumor working group evaluated a comparative analysis of multicentric dosimetric CSI plans (N.15) of five different techniques for CSI (3D-CRT, IMRT, VMAT, Tomo-therapy, Pencil beam scanning); 3 centers per technique. CSI plan was performed using the same patient data, set of delineations and dose prescription (36, 1.8 Gy per day). Different treatment plans were optimized based on the same planning target volume margin.

Authors showed that modern radiotherapy techniques i.e., IMRT, VMAT, Tomo-therapy and PBS resulted in superior conformity/homogeneity-indices (CI/HI), particularly in the spinal part of the target and

demonstrated a decreased dose to the thyroid, heart, esophagus and pancreas. Dose reductions of >10 Gy were observed with PBS compared to modern photon techniques for parotid glands, thyroid and pancreas. Overall, the lowest mean dose for organs at risk obtained with proton therapy (Fig. 8) thanks to the lack of exit dose in the organs placed anteriorly to the vertebral body.

Nowadays there are few published studies that comprehensively describe the clinically applied treatment techniques for proton CSI [12] and most of them mentioned passive scattering which represent the standard method for protons. Particularly, in pediatric medulloblastoma the compelling dosimetric data as well as published clinical results presented by Yock et al. [13], suggested that proton therapy allows equivalent disease control with respect to conventional photon radiation therapy but with less toxicity [14] and PT must be considered as preferred irradiation modality in pediatric patients.

In our proton center we implemented a very peculiar CSI technique in supine position with proton pencil beam scanning which is useful also for sedated patients under anesthesia [15].

The clinical target volume for CSI is defined by a CT performed in supine position with 2-3 mm slices through the entire cranium and spinal region including all organs and structures of the pelvis.

For skeletally immature children, CTV includes whole brain with the cribriform plate, optic nerves, dural cuffs of cranial nerves as they pass through the skull base foramina [16]. In the spine, the subarachnoid space, and spinal nerve roots are part of CTV as well as whole vertebral body in order to avoid long-term spinal problems, including kyphosis, lordosis, scoliosis, and hypoplasia [17]. For skeletally mature patients, the CTV includes only the subarachnoid space and spinal nerve roots. The inferior border of CTV was identified at the end of dural sac (generally to S3 vertebral level) by high resolution pre-irradiation sagittal spine MRI [16]. A PTV (planning target volume) created as a 3/5 mm uniform expansion of the CTV. In addition, the following organs at risk (OARs) are outlined: lens, cochleae, eyes, thyroid gland, larynx, esophagus, heart, lungs, bowel, spleen, liver and kidneys. For standard clinical risk patients, the prescribed dose is 23.4 Gy RBE in 13 fractions. For high-risk patients, CSI dose is 36 Gy RBE in 20 fractions.

CSI is delivered by active scanning using two or three isocenters depending on the PTV length. For brain-CTV two lateral cranial opposed beams were used with couch angle ±15° to minimize the overlap between the cribriform plate and the lens. An additional posterior beam and two postero-anterior spinal beams were used for spine-CTV. Single-field-optimization of the three equally weighted beams is performed. Cranial

and caudal field junctions are planned by the ancillary-beam technique [18] (Fig 9) which consists of high energy layers of pencil beams at the maximum energy (226 MeV) with variable monitor units along the cranio-caudal direction to produce a linear dose gradient (from zero to full dose) in the overlapping region between adjacent treatment beams.

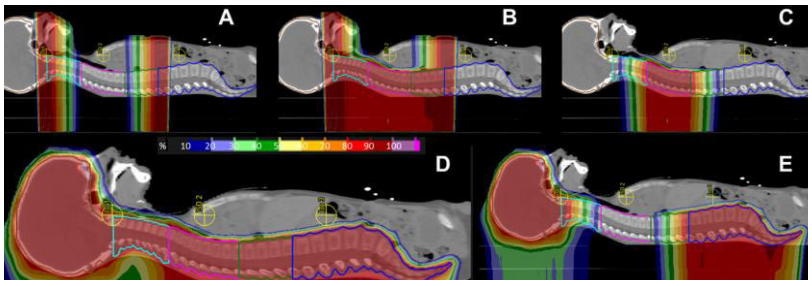


Fig. 9 Planning field-junction by the ancillary beam technique. The ancillary beams (A) are used to inversely plan the upper spinal beam (B) and then deleted. The resulting upper spinal beam (C) is switched on during the optimization of the cranial and lower spinal beams to obtain the final dose distribution (D). The dose distribution of the resulting cranial and lower spinal beams is shown in (E). The positions of the three isocenters are also shown. The dose scale refers to all the image and it is reported in % of the prescription dose (36 Gy RBE).

Whole brain irradiation as part of CSI planning, is performed by a lens-sparing three beam technique [Fig.10] which allowed to markedly decrease the dose to the lenses.

Such three-beam arrangement for brain irradiation includes two lateral opposed beams (gantry angle 90 and 270), with couch angle ±15 to minimize the overlap between the cribriform plate and the lens, and an additional 180_ posterior beam. During SFO of the three equally weighted

beams, coverage of the cribriform plate is assumed as the primary goal and lens sparing as a secondary objective.

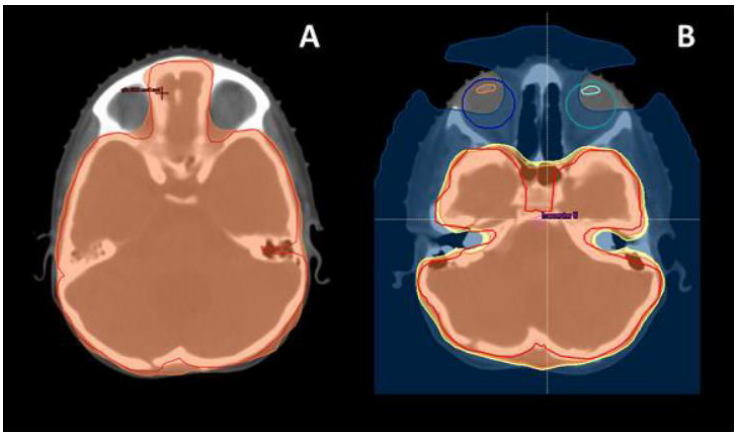


Fig.10 Dose distribution obtained by the lens-sparing technique at the cribriform plate (A) and of the lens (B). The PTV is the red line, right lens in orange, left lens in cyan, right ocular globe in blue and left ocular globe in light blue are shown.

A kidney-sparing technique is also reported in Fig. 11. The splitting technique and snout extension allow to improve kidney sparing is very well reported by Farace and colleagues from Trento's proton center.

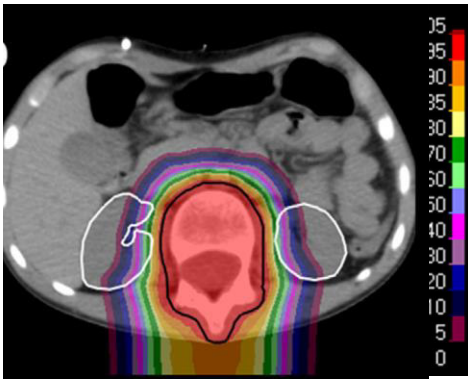


Fig. 11. Kidney sparing by splitting technique and snout extension. Two posterior beams splitting technique, with snout extension (air gap = 12 cm) of the beam with the range shifter, delivering a kidney mean dose = 8.5 Gy. The dose scale reported in % of the prescription dose (36 Gy).

## 4. OUR EXPERIENCE

### 4.1 Late effects treatment-related after radiotherapy in CNS pediatric tumors

Approximately 20% of pediatric cancers occur within the central nervous system (CNS). The incidence is highest in children aged 1 -4 years and lowest in those aged 10 – 14 years. The most common type of tumors in children aged 0-14 years are pilocytic astrocytomas (17.6%), other low-grade gliomas (14.3%), malignant gliomas (11.1%), and medulloblastomas (9.3%) [19]; in children aged 15-19 years, the most common are pituitary tumors (21.6%), pilocytic astrocytomas (11.5%) and glioneuronal tumors (8.7%) [20].

Fortunately, approximately 70% of children survive at least 5 years [21]. The greatest challenge for long-term childhood cancer survivors remains the balance between cure and long-term morbidity. 62% of people who survive any type of childhood cancer report at least one long-term treatment-related effect; one-third of survivors report three or more, and approximately one-third of the effects are graded as life-threatening or severe [22]. Treatment options for childhood CNS tumors include radiation therapy, surgery and chemotherapy, often given in combination. Brain RT continues to pose a challenge to radiation

oncologists because of the negative effects in neurocognitive, neuroendocrine function, growth and musculoskeletal anomalies, sensorineural hearing loss, vasculopathy and secondary malignancies. Neurocognitive damage is demonstrated by a development of deficits in several areas including mathematic ability, language, attention, memory, sleep-wake rhythm, and Intelligence Quotient (IQ) [23,24]. Negative neurocognitive effects are the result of several factors including the brain tumor itself disrupting neurocognitive functioning, hydrocephalus, operative approaches, and peri-operative complications. Chemotherapy can also influence neurocognitive functioning, and additionally, host factors such as age at the time of treatment, gender, irradiated brain volume and dose delivered [25].

The pathophysiology of radiotherapy-related neurocognitive toxicities is multi-factorial. One important factor seems to be the vulnerability of cerebral white matter to radiotherapy injury. Survivors of childhood medulloblastoma had smaller volumes of cerebral white matter, larger volumes of cerebrospinal fluid, and equivalent volumes of grey matter [26]. Importantly, the volume of cerebral white matter seemed to correlate with IQ scores. Another study [27] revealed a pattern of cortical thinning in selected brain areas — predominantly in the posterior part of the brain — in patients with medulloblastoma that was not seen in

healthy controls matched for age and sex. Another possible mechanism of radiotherapy-related cognitive toxicity involves the hippocampal dentate gyrus, which is the source of neural progenitor cells that are important for memory formation and consolidation and are particularly sensitive to radiation [28-30]. Evidence from a cross-sectional comparative study indicates that the rate of decline in IQ is affected by the volume of supratentorial brain irradiated [25] and was observed with high dose (30.6-36.0 Gy) CSI or with a boost to the entire posterior fossa.

Neuro-endocrine deficits were reported by 43% of paediatric CNS tumour survivors, in whom the risk of growth hormone deficiency, hypothyroidism, osteoporosis and a need for medical induction of puberty was higher than in their siblings [31]. Higher total doses of radiation delivered to the hypothalamic–pituitary axis and younger age at the time of radiotherapy have been shown to decrease the time to onset of endocrine effects and increase their likelihood and severity. Selective radiosensitivity of pituitary cell populations accounts for the differential incidence of endocrine deficits. Growth hormone deficiency is the most common endocrine deficit after cranial irradiation: radiation doses of 30 Gy to the pituitary leads to the development of growth hormone deficiency in ~30% of patients [32]. Lower doses are associated with smaller risk, although the deficit can develop with doses of 18–24

Gy [33]. Levels of gonadotropins, adrenocorticotropic hormone and thyroid stimulating hormone can also be affected, but less often and with a longer latency [34].

Regarding the cerebrovascular complications, evidence indicates that late-occurring stroke is also associated with treatment of pediatric CNS tumours. In one study of survivors of pediatric CNS tumors that were treated with cranial irradiation, 36% developed a cerebrovascular complication over a median follow-up of 16.7 years; microbleeds and cavernomas were the most common complications [35]. Cerebrovascular complications were symptomatic in 7% of the survivors and occurred more commonly in children who were treated with whole-brain radiotherapy. The risk of stroke increased with the dose of cranial irradiation, specifically in areas of the brain containing the temporal lobes, circle of Willis, and origin of larger arteries and when the radiation dose delivered to the prepontine cistern. Radiotherapy induced vascular injury to the circle of Willis has been proposed as the mechanism that underlies this association [36].

Radiation-induced secondary malignancies are a rare late effect of radiation treatment among cancer survivors. Secondary malignancy is the second-most common cause of death among survivors of pediatric CNS tumours [37], and the most common cause of death among those

who survive for ≥10 years [38]. Chemotherapy typically induces haematological malignancies after a median of 5 years, whereas radiotherapy typically leads to solid malignancies with a highly variable latency. The second malignancy risk is dependent upon the patient's age, the radiation dose received, and volume of normal tissue irradiated, as well as the patients' family history of cancer and unique biological risk for malignancy.

This is of particular concern with the use of IMRT that has the potential to increase whole body radiation exposure. IMRT employs multiple treatment fields, has longer treatment time with an increase of the leakage from the treatment 'head' exposing a greater volume of normal tissue to low dose radiation. An epidemiological study on a comparison of second cancer risk between a photon and proton-treated group was published by Chung et al. [39]. They found that the use of proton radiation therapy using passively scattered protons was not associated with a significantly increased risk of secondary malignancies compared with photon therapy. In a study published in 2014, Sethi et al. [40] examined in-field and out-of-field cancer incidence in proton vs. photon-treated patients with retinoblastoma. In-field cancer was significantly higher in photon-treated patients. With a 7-year median follow-up, the incidence of out-of-field cancer did not significantly differ in the proton-

vs. photon-treated patients. These results are in accordance with the integral dose advantage of protons vs. photons.

### 4.2 Preliminary clinical results of CNS pediatric patients treated with PT in Trento

We recently reported at several pediatric oncology national and international meetings early multi-institutional retrospective clinical results of 23 pediatric (13 males and 10 females, 17 in daily anesthesia) CNS tumors treated with proton pencil-beam scanning in the period between 2015 and 2019 [41]. We also evaluated potential late effects occurred as well as neuro-radiological sequelae in the same cohort of patients. Median age at PT was 6 years [13 months – 18 years]. Median total dose to the primary tumor site was 54 Gy RBE; 14 received craniospinal irradiation (23.4/36 Gy RBE). Histologies were: 11 medulloblastomas, 2 pilocytic astrocytomas, 4 AT/RTs, 3 germinomas, 2 meningiomas and 1 choroid plexus carcinoma. In 22 surgery was performed (5 total resections, 13 partial, 4 biopsies). Twenty patients received chemotherapy (before/after PT) and 9 patients had autologous stem-cell rescue before PT. Toxicities were recorded according to CTCAEv4. Regarding any potential neuroradiological toxicity, for all pts

MRI including susceptibility weighted (SW) and/or T2 imaging were performed at diagnosis, 1 month after PT, every 3 months for the first year and later every 6 months. At a median follow-up of 23 months [8 – 51 months], 21 patients are alive (12 complete remission, 1 partial response, 7 stable disease, 3 progressive disease). Among 3 patients with disease progression two eventually died. Hematological toxicity during PT was limited: 12 patients developed neutropenia and/or thrombocytopenia G1-G2, 5 patients G3. In three patients G3 acute side effects were observed: two persistent of fatigue and severe headache; all recovered completely after treatment. Two patients developed early (<6 months) neuroradiological toxicities. One MBL patient suffered from PRES (G3) during chemotherapy and after PT which resolved completely; one year old meningioma developed symptomatic perilesional edema (G3), with full recovery after medical therapy. one of which led to a small bleeding.

Six patients experienced late toxicities: one had a self-limiting intracranial bleeding (G2) with headache 46 months after PT from an isolated cavernoma developed close to the pituitary region, an asymptomatic Moyamoya arteriopathy, and other three cases developed asymptomatic small cavernomas [42,43].

Our preliminary experience in pediatric patients treated in our Institution shows that PT can be an interesting option for pediatric CNS tumors, achieving good disease control with limited toxicity. Neuroradiological toxicity was limited, with no cases of radio-necrosis. Cavernomas seem more frequent in patients treated with whole brain irradiation as part of craniospinal irradiation but more data with longer follow up are needed. More data and longer follow-up needed to better evaluate long-term results.

### 4.3 Protontherapy of two aggressive pediatric Meningiomas

While in the adult meningiomas account for 30% all primary brain tumors and are the most common benign primary neoplasm of the brain [44]. in the pediatric population they are considerably rarer, making up roughly 2% of all pediatric central nervous system (CNS) tumors [45,46]. The majority of meningiomas are benign [47], but atypical (WHO grade II) or malignant meningioma (WHO grade III) can be observed in approximately 5–34% [48] and 1–3% of cases [49], respectively.

These non-benign meningiomas are associated with less favorable clinical outcome [50] and are locally more aggressive, with early recurrence or tumor progression: immediate radiotherapy may be of benefit [51].

Moreover, in the pediatric age group there is no clear sex preponderance in the incidence of meningiomas, even if some studies suggest a higher incidence in males [45,46,52]. Moreover, meningiomas in infants are exceedingly rare [45].

The most important risk factors for the development of a meningioma in the pediatric population are genetic cancer-predisposing syndromes, such as Type 2 Neurofibromatosis (NF2) and Gorlin syndrome, and past cranial irradiation. Clear cell meningiomas are often associated with SMARCE1 mutation [53].

The clinical presentation of meningiomas depends on the age of the patient and on tumor location, with symptoms and signs ranging from those of elevated intracranial pressure to focal neurological deficits and seizures [52].

Imaging studies usually show a clearly defined, contrast-enhanced lesion with surrounding brain edema, sometimes with calcification [45]. Cystic lesions have been described more commonly in children [54] and sometimes pediatric meningiomas lack a dural attachment (13-30% of cases) [55,56].

Many tumors express somatostatin receptors. Among brain tumors, meningiomas have shown the highest frequency in somatostatin receptor expression detected by octreotide scintigraphy (up to a 90% positive rate of detection). The largest trial on the use of somatostatin in meningiomas performed in 16 patients with recurrent meningiomas by Chamberlain et al. showed that 31 % of patients had partial radiographic response and 44% achieved PFS at 6 months with minimal toxicity [57].

Meningiomas are classified according to the WHO grading system and the most recent revision was published in 2016 [58]. Even if the majority of pediatric meningiomas are WHO grade I [52], there is a higher incidence of grade II and grade III tumors compared to adults; furthermore, some variants, such as the clear cell meningioma we encountered, are more common in children [45].

WHO grade correlates with recurrence-free survival, but does not correlate clearly with overall survival [45,52]. Clear cell meningioma is a variant recognized as WHO grade II and only constitutes 0.2% of all subtypes of meningioma [56].

PT has been shown to offer significant advantages compared to conventional photon-based radiotherapy in terms of reduction of radiation-related long-term side-effects and incidence of secondary malignancies [39,40]. The high survival associated with meningiomas

leads to an increased emphasis on sparing OARs, in efforts to maintain neuronal function and QoL in a population that may experience substantial detriment if this is not achieved. Some small retrospective studies [59,60] have shown that administering higher doses of radiation could optimize outcome for WHO grade II and III tumors. A non-randomized clinical trial 22 found a 70% 3-year PFS in WHO grade II meningioma patients undergoing a complete resection (Simpson I–III) plus high-dose (60 Gy) radiotherapy.

In our proton center two pediatric meningioma's patients located intracranially were treated with proton irradiation in 2018.

*Description of the first case*

The first case was a 4-months old male infant who was diagnosed with an invasive clear cell meningioma of the brainstem and of 3rd right cranial nerve. A mild right ptosis developed at 1 month of age and the child was closely monitored. At 4 months an ophthalmological check-up also found a fixed mydriasis, with partial deficit of the 3rd cranial nerve and heterocromia iridis. A subsequent brain MRI (see Fig. 12) revealed an expansive process adjacent to the 3rd right cranial nerve and in the interpeduncular and ambiens cistern. A surgical biopsy of the lesion was performed, and histology showed an invasive clear-cell meningioma

(WHO grade II) with a Ki67 proliferative index of 7%. Tumor cells were positive for EMA and vimentin, negative for GFAP, Olig2 and SYN. The protein INI1 was expressed. The diagnosis was confirmed by the Italian central pathology reference center for pediatric CNS tumors. Given the rarity of the disease and family

Due to his history of hypoacusis the child was investigated for mutations of the NF2 gene, as well as for germ-line mutations of SMARCE1: both tests were, however, negative. A surgical removal of the tumor was deemed not feasible. At 12 months of age, a follow-up MRI showed signs of disease progression (dimension 14x18x23 mm versus 12x14x16 mm expanding into the ambiens cistern with signs of infiltration of the homolateral cerebral peduncle. A slight contrast enhancement along the border of the contralateral cerebral peduncle was also observed, as well as a significant increase of the perilesional edema, with marked involvement of the midbrain. The tumor was again deemed not operable, so he was referred to Trento's proton facility.

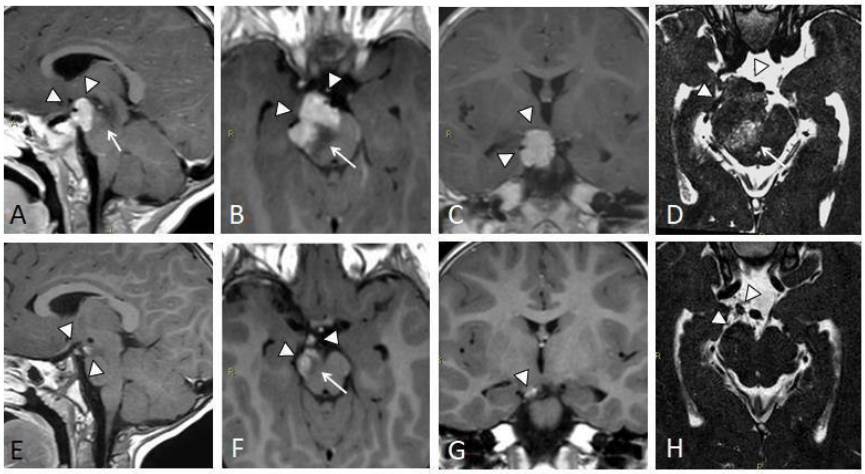


Fig.12 MRI of an infant with invasive clear-cell meningioma of the brainstem. Post-surgical/Pre-protontherapy MRI: (**A**), (**B**), (**C**) sagittal, axial, and coronal 3D T1-weighted multiplanar reconstructions (MPR); (**D**), axial 3D T2 DRIVE. Meningioma arising from the right third cranial nerve, infiltrating adjacent ventral portion of the mesencephalon (arrowheads); perilesional vasogenic edema is evident (arrow). (**E**), (**F**), (**G**) Post-protontherapy MRI, 39 months after treatment: sagittal, axial, and coronal 3D T1-weighted MPR; (**H**), axial 3D T2 DRIVE. Noticeable volume reduction of the treated meningioma (arrowhead) along with perilesional edema (arrow).

Proton treatment phase

Patient received active-scanning fractionated PT using 3 beam arrangements. He received a total dose of 54 Gy RBE in 30 fractions, 1.8 Gy daily, to the gross tumor volume (GTV) with 5 mm of isotropic margins, in daily anesthesia (Fig. 13).

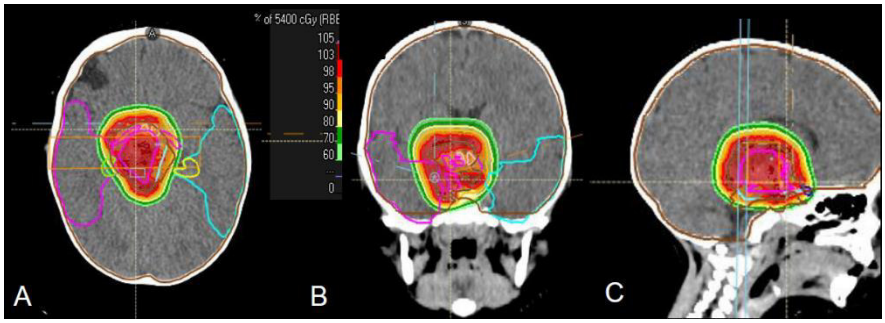


Fig. 13 Proton therapy plan of the brainstem invasive meningioma. (A), (B), (C): Axial, coronal, and sagittal spot-scanning proton therapy plan for brainstem/3rd cranial nerve meningioma showing 3-field beam arrangements (2 LL fields and 1 Sup-Inf). Red line contour = PTV (planning target volume) and within it, in pink = GTV (gross tumor volume); pink contour = right temporal lobe; light blue contour = left temporal lobe.

Proton treatment was well tolerated, and no supportive therapies were necessary; no hematological or other toxicities (i.e., neurological symptoms) were observed, except for alopecia and a mild skin reaction (grade 1 CTCAE v4) of the treated region.

Two months after PT, the parents complained about a significant loss of muscle strength on the left side. A first MRI was performed, showing slightly increased perilesional edema; two months later, a second MRI showed an increase of the edema and the appearance of small cavernomas adjacent to the irradiated area. The meningioma, however, appeared smaller and with more contrast inhomogeneity. Dexamethasone was initiated and after one month a control MRI showed a significant reduction of the edema. Therefore, steroid therapy was reduced and discontinued. Clinically, the hyposthenia improved, with only a slight difficulty with the grasping motion of the left hand remaining. Regular MRI scans showed a steady reduction in size of the meningioma (Fig. 12). At 39 months of follow-up after PT, no other toxicities were observed. The child undergoes regular physical therapy for residual minimal impairment of the left hand. During follow-up, the child's cognitive development was regularly evaluated using age-adjusted

neuropsychological scales and no significant deviations from the normal range were found.

*Description of the second case*

A second one was a 7-year-old child who experienced repeated episodes of severe headache with falls, tremors, and loss of urine. An MRI was performed, which showed a frontal lobe mass of 50x70x50 mm with signs of intralesional hemorrhage. The patient underwent surgery, with a frontal paramedian approach. Histologically the tumor was composed of a proliferation of meningothelial cells with prominent nucleoli, which invaded the adjacent brain parenchyma.

Mitoses were present as well as areas of necrosis. The Ki67 proliferative index in the most positive areas was 18%. Based on these features the tumor was identified as an atypical meningioma (WHO grade II).

Due to a post-operative obstructive hydrocephalus, a ventriculoperitoneal shunt was implanted. Post-operative MRI showed a partial resection, with a tumor residue of 47x45x45 mm in the anterior part of the corpus callosum. For this reason, a second surgery was performed with the goal of achieving a total resection. The post-operative contrast-enhancement MRI scan showed a 7 mm of small nodule confirmed by a Gallium-68 DOTATOC PET-CT (Fig. 14).

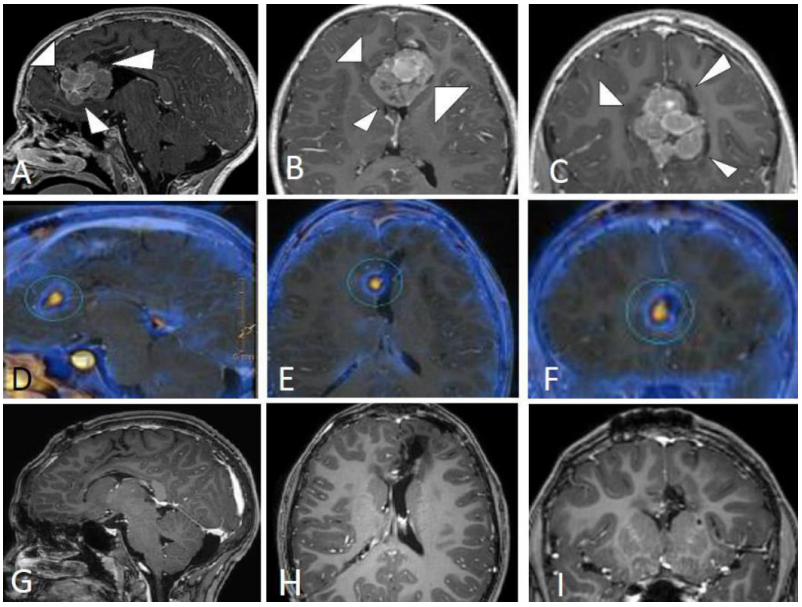


Figure 14. MRI of a child with frontal lobe atypical meningioma. Pre-surgical MRI: (A), (B), (C): sagittal, axial, and coronal 3D T1-weighted multiplanar reconstructions (MPR). Meningioma arising from the frontal lobe with signs of intralesional hemorrhage (arrowheads); Post-surgical/Pre-protontherapy MRI/PET: (D), (E), (F): sagittal, axial and coronal Gallium-68 DOTATOC PET fused with 3D T1-weighted post-operative MRI; Noticeable small hypercaptating nodule in the frontal tumor bed (ring). Post-protontherapy MRI 30 months after treatment: (G), (H), (I): sagittal, axial, and coronal 3D T1-weighted. No evidence of residual tumor.

*Proton treatment phase*

PT was performed 45 days after second surgery to a total dose of 59.4 Gy RBE in 33 fractions, 1.8 Gy RBE per day (Fig. 15).

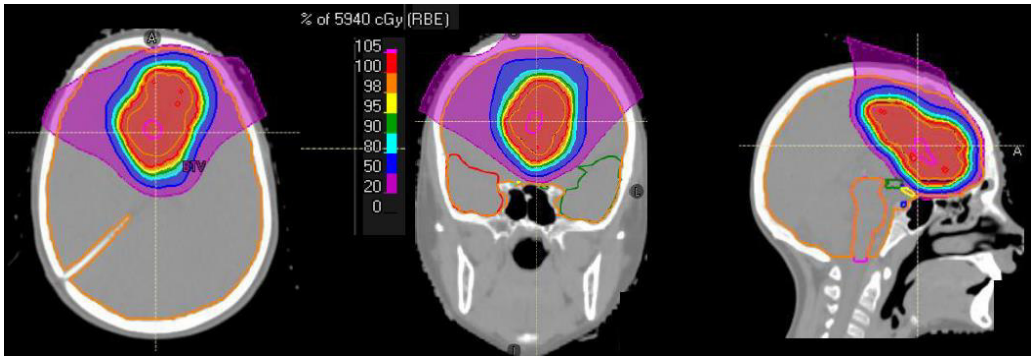


Fig. 15 Proton therapy plan of the frontal lobe atypical meningioma. Axial, coronal, and sagittal spot-scanning proton therapy plan for frontal lobe patient showing 3-field beam arrangements (1 AP and 2 Sup-Inf obliques). Red line contour = PTV (planning target volume); orange line contour = CTV (clinical target volume); red contour = right temporal lobe; green contour = left temporal lobe.

Proton treatment was well tolerated, no toxicities (i.e., neurological symptoms) were observed, except for partial alopecia of the treated region. The clinical target volume (CTV) was defined as the tumor bed area seen on postoperative MRI, planning CT/MRI and additional PET-imaging with 68Ga-Dotatoc, plus 5 mm of margins. CTV included also the BTV defined as biological target volume, that is areas with increased focal uptake as seen in the DOTATOC PET-CT.

The MRI scans after PT showed only mild contrast enhancement in the frontal meninges of the surgical cavity. Subsequently, the child started follow-up with surveillance MRIs. At 33 months of follow-up after PT, the last MRI showed an unchanged post-surgical malacic area with hemosiderin residues of the left parasagittal frontal lobe. The contrast enhancement of the frontal meninges was unchanged. Clinically, he did not develop any late toxicity and at the last FU he is physically and cognitively normal.

Management of pediatric meningiomas is often extrapolated from knowledge of the adult counterparts [45,46]. As for many other CNS tumors in children and adolescents, gross-total resection (GTR) should be attempted whenever possible: a large meta-analysis showed that patients who had an initial GTR had better relapse-free survival (RFS) and overall survival than those with only subtotal resections [52]. In the

event of an incomplete resection, the possibility of a second surgery should be evaluated. It should be noted, however, that aggressive surgery is associated with higher perioperative mortality and long-term neurological morbidity, therefore a careful risk-benefit analysis should be done for each patient. A meta-analysis of Kotecha et al. Reported a relatively high mortality rate of 12.7% after 5-7 years of follow-up [52], with a Dutch study showing similar results (16.1% mortality, mean follow-up: 4.8 years) [59]. Children with NF2 tend to have worse RFS and overall survival (especially over longer periods of time). Patients under 3 years of age may have worse overall survival, with the already cited meta-analysis finding a borderline significant correlation [52]. However, since these two studies only included children who underwent surgery, they may be biased towards more aggressive tumors. In fact, other studies show no difference in mortality between children/adolescents and young adults and warn against over-treatment due to a perceived aggressive nature of pediatric meningiomas [46].

The evidence for the use of radiotherapy in pediatric meningiomas is limited and current recommendations are based on adult retrospective series [45,61]. Children, especially infants, are more vulnerable to the effects of radiotherapy [62] and of developing late sequelae. The St. Jude Lifetime Cohort Study (SJLIFE) showed a higher incidence of severe

chronic disease in children with brain tumors who received a higher radiation dose [63]. Thus, the decision to use radiation therapy for pediatric meningioma should be carefully evaluated: The Children's Cancer and Leukemia Group (CCLG) suggests consideration of radiotherapy for grade I-II meningiomas after multiple relapses that can't be operated or after evidence of clinically relevant progression after incomplete resection, and in all grade III meningiomas at time of diagnosis, irrespective of surgical outcome [64]. Gamma knife and conventional radiotherapy are also used as adjuvant therapies for pediatric meningiomas that cannot be completely resected due to their location [65]. A retrospective analysis by Dudley et al. showed that a higher percentage of children/adolescents and young adults with meningioma are treated with radiotherapy compared to adults [46], even if its role and impact on prognosis are not clear. Upfront radiotherapy leads to worse RFS but does not appear to have a significant effect on overall survival; it should be noted that in the meta- analysis by Kotecha et al. the number of patients who underwent upfront radiotherapy was small and the dose, type and rationale behind the decision to irradiate were unknown [52].

During the treatment planning process, the definition of the target volume remains challenging even when using MRI and CT imaging

combined: Kessel et al. [66] showed that the addition of PET-imaging for target volume definition led to a significantly enhanced LC after high-precision RT. Thus, PET improves the detection of tumor cells and helps distinguish between healthy tissue and meningioma tissue [66].

In our patients a very few acute and late toxicity has been reported: in patient 1 the post PT perilesional edema resolved completely after standard steroid therapy, with minimal residual hyposthenia of the left hand, while the small cavernomas remained asymptomatic. The development of cavernomas following CNS radiotherapy is well-documented with photons [67, 68]. Patient 2 had no significant acute or late toxicities related to PT and remains in good physical and cognitive conditions at the last follow-up evaluation.

In conclusion adjuvant radiotherapy should be carefully considered for higher grade tumors or in clinically aggressive, and potentially relapsing meningioma. Given the vulnerability of children to the effects of radiation, they are particularly well-suited candidates for proton therapy with possible benefits in terms of survival and quality of life of survivors and our two cases confirm this positive trend.

## 4.4 Clinical results after PT for pediatric medulloblastoma patients: a multi-centric study

Medulloblastoma is among the most common brain tumors in the pediatric age group. The peak age at diagnosis is ~6-8 years of age, although MB can occur during the first year of life or during adulthood in some individuals [69]. Standard-of-care treatment for MB includes surgical resection, cytotoxic chemotherapy, and CSI radiotherapy since medulloblastomas have a high tendency for leptomeningeal spread, which is the main cause of death from this disease [70]. Variable CSI doses were indicated depending on the clinical risk [71] plus additional dose to the primary tumor region and to any metastatic sites. Under the age of 3 only radiation-sparing protocols are used, because of the devastating long-term sequelae of CSI on infants. There are two main risk categories: high-risk and standard risk (SR) clinical group. High-risk is defined by residual disease >1.5 $cm^2$, metastatic dissemination, CSF liquor cytology positive for tumor cells, and, in some studies, large-cell anaplastic histology. After surgery, SR patients currently receive low dose of CSI (23.4 Gy) plus a boost to the tumor bed up to 54 Gy, followed by adjuvant chemotherapy with cisplatin, CCNU and vincristine. SR patients achieve 5 to 10 years overall survival of approximately 80% [72].

Currently, high-risk patients receive 36-39.6 Gy CSI with a boost to 54-55.9 Gy in 1.8 Gy fractions to the tumor bed in the posterior fossa, followed by cisplatin-cyclophosphamide-based chemotherapy. This results in 5-year survivals of <70% across most studies [73]. Multiple clinical trials evaluating risk-adapted approaches based on molecular genetics, the role of high-dose chemotherapy and of hyperfractionated accelerated radiotherapy are underway. This results in 5-year survivals of <70% across most studies [74]. Even if with current treatment options the prognosis for this neoplasm has improved, the survivors often develop long-term sequelae because of oncological treatments. Several papers show that more than 50% of children treated for medulloblastoma later developed cognitive deficits, and only 28% of those who survived more than 20 years was able to live an autonomous, independent life [75,76].

Hearing loss is frequent in patients treated with radiation and/or after chemotherapy platinum -based agents, and growth failure is nearly ubiquitous in prepubertal patients. Secondary malignancies, including secondary glioblastoma and leukemias, approach 3 to 5%. The dose of CSI and boost volume have a tremendous effect on neurocognitive outcome, which worsens over time. Reducing the boost volume to the tumor bed and introducing proton radiotherapy have seemed to

significantly improve some sequelae, without compromising survival [77]. PT has similar efficacy in terms of survival compared to photon-based radiotherapy but might achieve lower toxicity rates. It can improve neurocognitive and psychosocial outcomes by lowering the dose received by healthy tissues during the posterior cranial fossa or tumor bed boost [78].

Proton exit dose drops to almost zero already a few millimeters distally to the Bragg's peak: healthy organs (i.e., thyroid gland, heart, lungs, bowel, ovaries, mammary glands and uterus) located ventrally to the vertebral bodies receive a negligible dose during CSI with protons, as shown in Fig.16. Zhang *et al.* (79) studied the relative risk (RR) of cardiac toxicity in a 4-year-old with medulloblastoma: protons had a RR of 1.28 compared with 8.39 for photons. In a similar way, Pérez-Andùjar et al. (80) found that protons are associated with the lowest risk of premature ovarian insufficiency induced by CSI if compared with photons and IMRT. Incidence of secondary neoplasms were reduced by protons as reported by Chung and colleagues [39].

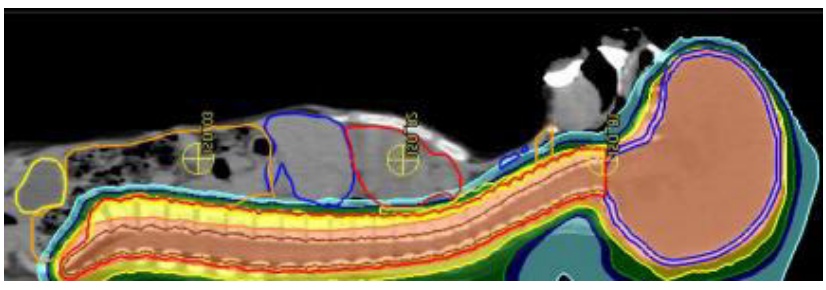

Fig.16 Active scanning CSI

We report on our multicentric experience of 27 children (14 males, 13 females) with medulloblastoma treated with PT between 2015 and 2020, focusing on clinical results and toxicities related to PT. The median age at diagnosis was 5.8 years [1.8 – 18.5 years], while median age at PT was 6.2 years [3.1 – 19.0 years]; median follow-up is 26.5 months [1 – 62 months]. Nine patients were SR medulloblastoma, 18 HR. Of the HR patients, 5 were M0, 2 M1, 2 M2, 9 M3. Pathology was reviewed by the central Italian institution to confirm the diagnosis. Histologies were as follows: 22 classic, 2 desmoplastic-nodular, 1 large-cell anaplastic, 1 extensive nodularity; in one case, there was not enough material available for pathological examination (table 1 for Patient characteristics).

All patients in this study received PT at the TPTC and come from three centers: Bologna, Florence, and Ljubljana. Proton therapy was performed with Pencil-Beam Scanning (PBS). All patients had a CT scan in supine position with 2-3 mm slices through the entire cranium and spinal region including all organs and structures of the pelvis to define the CTV for CSI [16]. All patients had surgery before PT. 15 partial resections, 12 gross-total or near-total resections. All patients received adjuvant

chemotherapy, either upfront after surgery or after PT according to local institutional protocol and following the clinical risk, 8 HR patients received concurrent every-two-weeks chemotherapy during PT with vinorelbine based on mono-institutional protocol and three had concurrent vincristine.

| Table 1: Patient characteristics | | | | | | | |
|---|---|---|---|---|---|---|---|
| # | HR/ SR | Stage, Pathology | Sex | PT-Age (years) | Target | CSI Gy (RBE) | Primitive /Mets Gy (RBE) |
| 1 | HR | M3, classic, non-SHH/non-WNT | M | 12,6 | CSI + Boost on primitive | 36 | 54 |
| 2 | HR | M1, classic, non-SHH/non-WNT | M | 13,4 | CSI + Boost on primitive | 36 | 54 |
| 3 | HR | M3, large-cell anaplastic | M | 12,7 | CSI + Boost on primitive and metastases | 36 | 54/45/50.4 |
| 4 | HR | M3, classic, non-SHH/non-WNT | M | 10,6 | CSI + Boost on primitive and metastases | 36 | 54/50.4 |
| 5 | HR | M1, classic, non-SHH/non-WNT | F | 19,0 | CSI + Boost on primitive | 36 | 54 |
| 6 | HR | M3, classic, non-SHH/non-WNT | M | 17,5 | CSI + Boost on primitive and metastases | 36 | 54/45 |
| 7 | HR | M0, classic, non-SHH/non-WNT | F | 3,8 | CSI + Boost on primitive | 36 | 55,8 |
| 8 | HR | M3, classic, non-SHH/non-WNT | F | 5,8 | CSI + Boost on primitive and metastases | 39,6 | 54/50.4 |
| 9 | HR | M0, classic, non-SHH/non-WNT | M | 13,3 | CSI + Boost on primitive | 36 | 55,8 |
| 10 | HR | M3, extensive nodularity | F | 3,8 | CSI + Boost on primitive and metastases | 23.4 whole brain, 36.0 whole spine | 54/50.4 |
| 11 | HR | M2, classic, non-SHH/non-WNT | M | 5,9 | CSI + Boost on primitive | 36 | 54 |
| 12 | HR | M0, classic, non-SHH/non-WNT | M | 10,3 | CSI + Boost on primitive | 36 | 54 |
| 13 | HR | M2, classic, non-SHH/non-WNT | F | 4,2 | CSI + Boost on primitive | 36 | 54 |
| 14 | HR | M0, classic, non-SHH/non-WNT | M | 10,4 | CSI + Boost on primitive | 36 | 55,8 |
| 15 | HR | M0, desmoplastic | F | 3,6 | CSI + Boost on primitive | 36 | 54 |
| 16 | HR | M3, classic, non-SHH/non-WNT | M | 4,8 | CSI + Boost on primitive | 36 | 54 |
| 17 | HR | M3, classic, non-SHH/non-WNT | F | 3,1 | CSI + Boost on primitive and metastases | 23.4 whole brain, 36.0 whole spine | 54/50.4 |
| 18 | HR | M3, classic, non-SHH/non-WNT | M | 6,3 | CSI + Boost on primitive | 36 | 54 |
| 19 | SR | M0, classic, non-SHH/non-WNT | M | 4,3 | CSI + Boost on primitive | 54 | 23,4 |
| 20 | SR | M0, classic, non-SHH/non-WNT | F | 4,1 | CSI + Boost on primitive | 55,8 | 25,2 |
| 21 | SR | M0, classic, non-SHH/non-WNT | M | 7,0 | CSI + Boost on primitive | 54 | 23,4 |
| 22 | SR | M0, classic, non-SHH/non-WNT | F | 5,3 | CSI + Boost on primitive | 54 | 23,4 |
| 23 | SR | M0, classic, WNT | F | 6,2 | CSI + Boost on primitive | 54 | 23,4 |
| 24 | SR | M0, classic, non-SHH/non-WNT | M | 7,5 | CSI + Boost on primitive | 54 | 23,4 |
| 25 | SR | M0, unavailable | F | 10,6 | CSI + Boost on primitive | 54 | 23,4 |
| 26 | SR | M0, classic | F | 5,7 | CSI + Boost on primitive | 54 | 23,4 |
| 27 | SR | M0, desmoplastic | F | 5,6 | CSI + Boost on primitive | 54 | 23,4 |

Every patient was followed by a Follow-up program which includes radiological examination (brain/spine MRI), audiological, endocrinological, ophthalmological and psychological evaluations as the following timing (baseline, every 6 months for the first two years, and then every year).

The most common observed acute toxicities (see Table 2) were radiation dermatitis (20, 74,1%), pharyngitis (19, 70,4%), fatigue (12, 44,4%), and alopecia (10, 37,0%): these toxicities appeared in the first month of PT and were usually G1-G2, with only one case of G3 dermatitis and one case of G3 pharyngitis with dysphagia. Other common acute toxicities were nausea and vomiting, anorexia and herpes virus infection or reactivation. We observed 1 G3 case of anorexia 5 months after PT start, which resulted in a 20% body weight loss: the patient was receiving chemotherapy with CCNU, which was suspected to be the main cause of the symptoms. In accordance with the treatment protocol, the CCNU dose was halved, and the patient received total parenteral nutrition at home, eventually recovering.

Table 2. Acute toxicity

| Toxicity | No. | G1-G2 | G3 | Median latency (months) |
|---|---|---|---|---|
| Dermatitis | 20 (74,1%) | 19 | 1 | 1 |
| Pharyngitis | 19 (70,4%) | 17 | 1 | 1 |
| Fatigue | 12 (44,4%) | 12 | 0 | 1 |
| Alopecia | 10 (37,0%) | 10 | 0 | 1 |
| Nausea | 8 (29,6%) | 8 | 0 | 2 |
| Anorexia | 7 (25,9%) | 6 | 1 | 1 |
| Herpes | 6 (22,2%) | 6 | 0 | 2 |
| Vomiting | 5 (18,5%) | 4 | 1 | 2,5 |
| Headache | 4 (14,8%) | 3 | 1 | 1,5 |
| airway infection | 3 (11,1%) | 3 | 0 | 1 |
| Insomnia | 2 (7,4%) | 2 | 0 | 3,5 |
| Fever | 2 (7,4%) | 2 | 0 | 1,5 |
| Cough | 1 (3,7%) | 1 | 0 | 1 |
| Diarrhea | 1 (3,7%) | 1 | 0 | 3 |
| Myalgia | 1 (3,7%) | 1 | 0 | 3 |
| PRES | 1 (3,7%) | 0 | 1 | 3 |
| Cavernoma | 1 (3,7%) | 1 | 0 | 3 |
| CMV Encephalitis | 1 (3,7%) | 0 | 1 | 5 |

PRES: posterior reversible encephalopathy syndrome; CMV: Cytomegalovirus;

Regarding late side effects (Table 3) one patient developed an intracranial bleeding (G2) 24 months after PT and acutely developed panhypopituitarism (a pituitary deficit was already present at diagnosis,

but gradually worsened over time) plus asymptomatic cavernomas, another patient developed at 31 months after PT a stroke in the left lenticular nucleus, one developed multiple tiny asyntomatic cavernomas, one CMV infection, one epileptic seizures with supratentorial neuroradiological abnormalities.

Table 3 Late toxicity

| Table 4: Late toxicity | | | |
|---|---|---|---|
| N- pt/Toxicity | Frequency/Grade | Latency * | Notes |
| 1/Seizure and headache | 1 / G2 | 45 | Self-limiting, brief generalized seizure.moderate pain with good response to medical therapy |
| 1/TIA | 1 / G1-G2 | 24 | |
| 1/Intracranial bleeding and panhypopituitarism and cavernomas | 1 / G2 | 24 | The bleeding occurred in the pituitary region, where the patient received a PT boost on a metastasis |
| 1/Cavernomas | 1 / G1 | 9 | |
| 1/Stroke | 1 / G2 | 21 | Left lenticular nucleus |
| 1/Hearing impairment | 1 / G2 | 6 | Mild impairment for high and very high frequencies, which appeared after 1 cycle of cisplatin chemotherapy |

Using the Kaplan-Meier method, the overall Progression-Free Survival (PFS) was 88,9% with a median follow-up of 26.5 months [11 – 62 months] and a median time to progression of 14 months [12 - 23 months]. If we only consider the high-risk group, PFS was 83,3% (see Fig. 17). Three HR patients had tumor recurrence, but none of these inside the tumour bed boost volume. In one case, a single temporo-parietal macroscopic

metastasis was found; two patients relapsed instead with both intracranial and spinal metastases. In the SR group, all are in CR at the most recent follow-up. All 27 patients were alive at the latest follow-up visit.

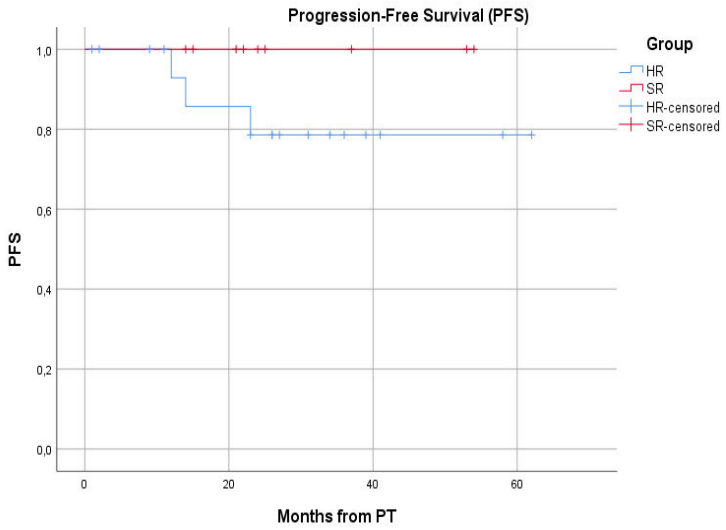


Figure 17. Progression-Free Survival analysis of the HR and SR patients using the Kaplan-Meier method.

Results of this retrospective case series of protons for medulloblastoma confirm good tumor control while demonstrating low incidence of acute and late adverse effects. A longer follow-up may provide more data on late toxicity. Only one patient developed a mild hearing impairment (G2), for high frequencies, 6 months after PT and after 1 cycle of cisplatin chemotherapy. Subsequent chemotherapy cycles were adapted according to the treatment protocol, switching from cisplatin to

carboplatin. The hearing impairment remained stable in all following audiometric exams.

There were no cardiac effects, pulmonary disorders, gastrointestinal toxicity effects i.e., dry mouth syndrome, and no cases of CNS necrosis were reported.

## 5. PROTONTHERAPY IN PEDIATRIC PATIENTS WITH CENTRAL NERVOUS SYSTEM TUMORS: A SYSTEMATIC REVIEW

PT offers significant advantages over conventional photon-based radiotherapy due to reduced long-term side-effects and second tumors incidence (81,82). However, there are few data on the PT specific toxicity. In particular, randomized studies and literature reviews addressing this topic are lacking. However, ere we performed a systematic review to specifically address the safety of PT for pediatric CNS patients. We aimed to describe late side effects (LSE) and clinical effectiveness after PT in this patient group.

### MATERIALS AND METHODS

The analysis of this systematic review was performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (83). Primary endpoint of the analysis was treatment-related toxicity after PT and local control, progression free survival, and overall survival (Table 4, 5).

**Table 4**. Studies and treatment characteristics

| Author, year | Study design/End point | N° of pts | Median age, years (range) | Primary site (N) and Histology (N) | Tumor site definition | Median/Mean tumor dose (Gy) | #Fields/delivery technique | Additional Therapy (%) | Comorbidity/ (N) of pts | Median FU, years (range) |
|---|---|---|---|---|---|---|---|---|---|---|
| Indelicato, 2019 (84) | Prospective/Clinical outcomes and toxicity in LGG | 174 | 10.2 (2-21) | IT (50)<br>ST (117)<br>Other (7)<br>LGG (174) | CTV= 5 mm<br>PTV=CTV+3 mm | Range 50.4-54.0 | NR/Double passive scattering | Neoad. CHT (43%)<br>pre PT surgery (49%) (1) | NF1/3 | 4.4<br>(0.5-11.4) |
| Hall, 2018 (85) | Retrospective/Incidence and severity of vasculopathy | 644 | 7.6 (0.7-21.8) | IT (177)<br>ST (466)<br>ND (1)<br>Craniopharyngioma (135)<br>Ependymoma (135)<br>LGG (131)<br>MBL/PNET (80)<br>Other (163) | NR | Median 54 (25.2-75.6) | Multiple fields plans (2-6)/Double passive scattering | CHT (70.5%) | Vascular metabolic disorder /47<br>Neuroendocrine deficiency/83<br>Neurological symptoms/306<br>Hydrocephalus/302<br>NF1-NF2/8 | 3<br>(0.1-9.6) |
| Bojaxhiu, 2018 (86) | Retrospective/Rate of radiation necrosis and white matter lesions (WML) | 171 | 3.3 (0.3-17.0) | IT (70)<br>SB (25)<br>ST (67)<br>Other (9)<br>Craniopharyngioma (16)<br>Ependymoma (64)<br>GCT (8)<br>LGG (20)<br>MBL/PNET (13)<br>Other (51) | NR | Range 40.0-74.1 | NR/Active scanning | CHT overall (63%)<br>Conc.CHT (18%)<br>Adjuv.CHT (19%)<br>1-2 Surgery (85%) | NR | 4.2<br>(0.5-16.2) |
| Indelicato, 2018 (87) | Prospective/Outcomes in intracranial ependymoma | 179 | 3.5 (0.7-21.3) | IT (119)<br>ST (50)<br>Ependymoma (179) | GTV= Residual gross tumor + tumor bed;<br>CTV= GTV + 5 mm expansion modified for anatomic barriers;<br>PTV1= CTV + 3 mm;<br>PTV2= GTV + 3 mm | Range 52.2-59.4 | Multiple fields plans (mostly 3)/Double passive scattering | Neoad. CHT (53%)<br>1 surgery (73%),<br>2 surgery (22%),<br>>3 surgery (1.5%) | Hereditary prothrombin disorder/1 | 3.2<br>(0.1-9.6) |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Gentile, 2018 (88) | Retrospective/Symptomatic brainstem injury in PF tumors | 216 | 6.6 (0.5-23.1) | IT (216)<br>Ependymoma (56)<br>MBL (154)<br>Other (6) | 48 CSI + WPF boost<br>105 CSI + IF boost<br>63 focal | Median 54 (46.8-59.4)<br>Median CSI 23.4 (18-39.6) | NR/Passive scattering | CHT overall (83%)<br>Adjuv. CHT (74%)<br>Conc. CHT (58%)<br>Surgery (100%)<br>(median 1, range 1-4) | Hydrocephalus/157<br>Shunt placement/55<br>Neurologic complications/ 121<br>PEG placement/35<br>Tracheotomy/9<br>PFS/50 | 4.2<br>(0.1-15.3) |
| Kralik, 2017 (89) | Retrospective/Radiation-induced large vessel cerebral vasculopathy | 75 | 7.9 (1.5-18) | IT (35)<br>Multifocal (2)<br>ST (38)<br>Craniopharyngioma (14)<br>GCT (6)<br>LGG (10)<br>MBL/PNET (25)<br>Other (20) | GTV= any visible tumor and/or bed cavity<br><br>CTV=GTV+2/5 mm | Mean 53.7 (30-59.4) | NR/Passive scattering | CHT (100%)<br>pre PT surgery (100%) | NR | 4.3<br>(0.6-9.6) |
| Indelicato, 2017 (90) | Retrospective/Clinical outcomes | 166 | 7 (1–19) | IT (50)<br>Spinal (8)<br>ST (98)<br>ND (10)<br>Craniopharyngioma (45)<br>Ependymoma (57)<br>LGG (54)<br>Other (10) | GTV= tumor cavity + residual tumor<br>CTV = GTV + 5 mm<br>PTV= CTV + 3 mm | Median 56.7 (45-59.4) | NR/NR<br>(12 Mixed with photons for downtime PT machine) | Neoad. CHT (13%)<br>pre PT surgery (100%) | NF1/2 | 2.6<br>(0.2–7.6) |
| Greenfield, 2016 (91) | Prospective/Outcomes in CNS GCT | 20 | 12 (3-16) | ST (14)<br>Other (6)<br>GCT (9)<br>Other (11) | 6 WVRT +/- 4th ventricle<br>14 CSI + IF boost<br>GTV=tumor bed + residual disease<br>CTV= GTV + 0.5–1 cm | Median 52.2 (30-54) | CSI: 2 L-R posterior oblique + multiple P-A spinal fields/NR | Neoad. CHT (80%)<br>Surgery (70%) | Endocrinopathy/10<br>Hydrocephalus/13<br>Visual symptoms/16<br>Undefined autoimmune disease/1 | 4.9<br>(0.3-7.5) |
| Yock, 2016 (92) | Prospective/long term toxic effects I in Medulloblastoma | 59 | 6.6 (5.1-9.9) | IT (59)<br>MBL (59) | CSI + tumor bed (36) or posterior fossa boost (23) | Range CSI 18-36<br>Median dose focal boost 54 | NR/Passive scattering<br>6 Mixed with photons | overall CHT (100%)<br>Conc. CHT (88%)<br>pre PT surgery (98%) | PFS/14<br>VP Shunt/12 | 7<br>(5.2–8.6) |
| Kahalley, 2016 (93) | Retrospective/Comparison of changes in IQ in pediatric brain patients treated with Proton vs | 150 (60 photon | Photon 8.1 (1.2-18.0) | IT (68)<br>ST (80)<br>ND (2) | CTV= tumor bed + margin or posterior fossa | Mean focal XRT 54 (30.6-59.4) | NR/90 PBRT (90% passive scattering, 10% scanning | CHT (100%)<br>pre PT surgery (90%) | VP shunt/25 | NR<br>(0.7-5.4) |

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| | Photon | , 90 proton s) | Proton 9.2 (1.7-18.2) | MBL/PNET (62)<br>Ependymoma (17)<br>GCT (20)<br>Other (51) | boost<br><br>CSI | Mean focal PBRT 54 (30-60)<br>Mean CSI 23.4 (21-39.6) + boost-XRT mean 55.8 or boost-PBRT mean 54 | beam) | | | |
| Giantsoudi, 2016 (94) | Retrospective/Incidence of CNS injury in medulloblastoma patients treated with proton | 111 | 7 (1.8-22) | IT (111)<br><br>MBL (111) | CSI + PF boost (42) or focal boost (69) | Mean CSI 26.7 (18-36) + boost 54 (50.4-59.5) | NR/Passive scattering | pre PT surgery (100%) | Hydrocephalus/111 | 4.2 (NR) |
| Kralik, 2015 (95) | Retrospective/Incidence of radiation necrosis in pediatric brain tumor patients | 52 | 7.2 (0.8-18) | IT (33)<br>Multifocal (2)<br>ST (17)<br><br>Ependymoma (12)<br>MBL/PNET (19)<br>Other (21) | GTV= any residual tumor and/or resection cavity<br>CTV= GTV + 5 mm;<br>PTV= CTV+2/5 mm<br>CSI | Mean 54 (21.0-59.4)<br><br>CSI (23.4-36.0) + focal boost | NR/ NR | Neoad. or conc. or adjuv. CHT (50%)<br>pre PT surgery (98%) | NR | 1.5 (0.5-2.83) |
| McGovern, 2014 (96) | Retrospective/Outcomes in CNS AT/RT | 31 | 1.6 (0.3-4.6) | ND (31)<br><br>AT/RT (31) | GTV= surgical cavity + any gross residual disease<br>CTV= GTV + 1cm<br>PTV= CTV + 3 mm | Mean 50.4 (9-54)<br>CSI (23.4-36.0) + boost 54 (43.2-55.8) | NR/Passive scattering | Neoad or conc. or adjuv. CHT (84%)<br>pre PT surgery (84%) | NR | 2 (0.3-4.4) |
| Indelicato, 2014 (97) | Retrospective/Tolerance of Brainstem | 313 | 5.9 (0.5-17.9) | IT (114)<br>SB (35)<br>ST (164)<br>Craniopharyngioma (68)<br>Ependymoma (73)<br>LGG (66)<br>MBL/PNET (38)<br>Other (68) | GTV= gross tumor volume or tumor bed<br>PTV= CTV + 3 mm<br>129 pts had a planned field reduction/boost | Median 54 (48.6-75.6) | Multiple fields (2-6)/ Passive scattering | CHT (49%)<br>pre PT surgery (98%) | NR | 2 |
| Greenberger, 2014 (98) | Retrospective/Late effect in children with LGG | 32 | 11 (2.7-21.5) | IT (11)<br>Spinal (3)<br>ST (18)<br>LGG (32) | CTV = resection cavity and any gross tumor visible + 3-5 mm<br>PTV = CTV + 8-12 mm | Median 52.2 (48.6-54.0) | 4 (ST), 2 (IT), 1-3 (spinal)/ Passive scattering | Neoad. CHT (50%)<br>pre PT surgery (90%) | Factor V Leiden deficiency/1<br>Neuroendocrine abnormalities/9 NF1/2<br>Optic nerve/retinal related injury/23<br>Other deficits/38 | 7.6 (3.2-18.2) |
| MacDonald, 2013 | Retrospective/Neurocognitive, endocrine and auditory | 70 | 3.2 (0.3-20) | IT (51)<br>ST (19) | CTV = tumor bed and/or residual | Median 55.8 (50.4-60.0) | >3//NR | Neoad. CHT (30%) | Baseline IGF-1 deficiency/2 | 3.8 (1.0-11.7) |

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| (99) | outcomes for intracranial ependymoma patients | | | Ependymoma (70) | tumor + 0.5/1 cm | | | pre PT surgery (97%) | Hydrocephalus/ 38<br>Shunt/29 | |
| Moeller, 2011 (100) | Prospective/Clinical ototoxicity in patients with medulloblastoma | 23 | 6 (3-16) | IT (23)<br><br>MBL (23) | CTV1 = CSI<br>CTV2 = tumor bed boost + clinical margins | Median CSI: (23.4 -36.0) + boost (54.0 -55.8) | NR/Passive scattering | Neoad. or adjuv. CHT (100%)<br>pre PT surgery (100%) | Uni- or bilateral grade 3-4 hearing loss/7 | 0.9<br>(0.7-1.3) |
| Viswanathan, 2011 (101) | Retrospective/Endocrine dysfunction after proton and to compare with those treated with combined conventional and proton radiation | 31 | 11.9 +/- 3.3 | IT (6)<br>ST (7)<br>Other (18)<br>Craniopharyngioma (7)<br>MBL (6)<br>Other (18) | NR | PB group: median 57.75<br>**C**onventional + PB group: median 53.84 | NR/Passive scattering<br><br>NR/12 Mixed with photons | Neoad. CHT (71%)<br>pre PT surgery (90%) | Pituitary hormone deficiency/8 | (1.8 - +/- 0.8) |
| Hug, 2002 (102) | Retrospective/Evaluation of safety and efficacy for LLG | 27 | 8.7 (2-18) | IT (5)<br>ND (22)<br>LGG (27) | CTV = any enhancement + 0.5-1 cm | Mean 55.2 (50.4-63.0) | NR/Passive scattering (1 Mixed with photons) | CHT (100%)<br>pre PT surgery (92%) | NF1/5 | 3.3<br>(0.6-6.8) |

*Legend:* CHT: Chemotherapy; CSI: Craniospinal irradiation; CTV: Clinical target volume; GCT: Germ cell tumor; GTV: Gross tumor volume; IT: Infratentorial; LGG: Low grade glioma; MBL/PNET: Medulloblastoma/Primitive Neuro-Ectodermal Tumor; ND: Not determined; NF1/NF2: Neurofibromatosis 1/2; NR: Not reported; PBRT: Proton Beam Radiation Therapy; PEG: percutaneous endoscopic gastrostomy; PFS: Posterior fossa syndrome; PT: Proton radiation therapy; PTV: Planning target volume; P-A: Posteroanterior; ST: Supratentorial; VP: Ventriculoperitoneal; WPF: Whole Posterior Fossa; XRT: Photon radiation therapy.

**Table 5.** Toxicity and outcomes

| Author, year | Late Toxicity | | | Median late toxicity time (years) | Late findings: histology (N)/ location | OAR or normal tissue damaged/ dose received Gy | PFS/LC (%) (median) | OS (%) (median) |
|---|---|---|---|---|---|---|---|---|
| | Scale | Type (%) | Grading | | | | | |
| Indelicato, 2019 (84) | CTCAE v.4 | Brain Stem necrosis (1%)<br>Hearing toxicity (2%)<br>Hormone deficiency (22%)<br>Retinopathy (0.5%)<br>Seizure (0.5%)<br>Secondary tumor (0.5%)<br>Vasculopathy (4%) | G1 (4%)<br>G2 (24%)<br>G3 (5%) | NR | Hormone deficiency: (37)/ST<br>Symptomatic vasculopathy: (2)/ST | NR | 5-y 84%/85% | 5-y 92% |
| Hall, 2018 (85) | NR | Vasculopathy (8%) | G1 (5.7%)<br>G2 (1%)<br>G3 (0.6%)<br>3 NR | NR | Vasculopathy: Craniopharyngioma (26), Ependymoma (8), LGG (4), MBL/PNET (7), Other (6)/NR | Significant HR vasculopathy in Dmax optic chiasm ≥54 Gy and age<5 yrs | NR | NR |
| Bojaxhiu, 2018 (86) | CTCAE v.4 | RN (17%)<br>WML (11%) | G1 (18%)<br>G2 (7%)<br>G3 (0.6%)<br>G4 (1.2%)<br>G5 (1.2%) | RN 0.4 (0.1-2.7)<br>WML 1.2 (0.2-5.2) | RN/WML: Craniopharyngioma (1), Ependymoma (25), GCT (1), LGG (6), MBL (2), Other (12)/NR | Brain parenchyma/57.5 Gy (50.4-74.0) | NR | 5-y 87% |
| Indelicato, 2018 (87) | CTCAE v.4 | Hearing loss (6%)<br>Neuroendocrine deficiency (8%)<br>Brainstem toxicity 6%)<br>Vasculopathy (3%) | G1 (9%)<br>G2 (4%)<br>G3 (8%)<br>G5 (0.5%) | Vasculopathy 1.2 (0.8-7.1)<br>Median duration to brainstem toxicity 0.2 | NR | NR | 3-y 76%/85% | 3-y 90% |
| Gentile, 2018 (88) | CTCAE v.4 | Brainstem injury (2%) | G2 (0.5%)<br>G3 (1%)<br>G4 (0.5%) | 2.0 (0.4-6.9) | Brainstem injury: MBL (3), Ependymoma (2)/ IT | BS D50 54 Gy.6 (50.2- 55.1)<br>BS mean dose 51.3 Gy (45.4-54.4)<br>BS Dmax 56.2 Gy (55.0-57.1)<br>BS V55 ≥ 55 Gy 27.4% (0-59.4%) | 5-y 83%/83% | 5-y 87% |
| Kralik, 2017 (89) | NR | RLVCV (7%) | Asymptomatic (1%)<br>Symptomatic (5%) (2 had surgery) | 1.5 (1-7.5) | Large vessel cerebral vasculopathy: Craniopharyngioma (2)/ST, MBL (1)/IT, Other (3)/NR | Significant HR RLVCV when mean radiation dose to the large cerebral arteries 54.5 Gy | 20% died for PD | NR |
| Indelicato, 2017 (90) | NR | Brainstem necrosis (1%)<br>Hearing loss (2%) | Unilateral hearing loss requiring hearing aids | NR | Brainstem necrosis: Ependymoma (1)/IT | For BS necrosis: Dmax 55.1 Gy | 3-y 87%/91% | 3-y 96% |

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| | | Endocrine replacement (9%)<br>Peritumoral edema (1%)<br>Seizures (2%)<br>Vasculopathy (2%) | (2%)<br>BS necrosis-edema treated with steroids (2%)<br>Symptomatic vasculopathy (2%) | | Vasculopathy:<br>Craniopharyngioma (2)/ST,<br>Ependymoma (1)/IT | | | |
| Greenfield, 2016 (91) | CTCAE v.4 | Endocrinopathy (45%)<br>Moya-Moya Syndrome +choreoathetoid movement (5%)<br>Visual symptoms (10%) | NR | NR | NR | Hypothalamic-pituitary mean dose 48 Gy<br>Bilateral optic nerve Dmax <39 Gy, optic chiasm Dmax 31.4 Gy and 51.2 Gy | 5-y 89%/ 89% (GCT);<br>82%/82% (Other) | 5-y 100% (GCT)<br>82% (Other) |
| Yock, 2016 (92) | CTCAE v.3<br>POG Ototoxicity scale<br>Full Scale Intelligence Quotient | Alopecia/NR<br>Ataxia/NR<br>Brainstem injury/2<br>Cataracts/4<br>Chronic fatigue/NR<br>Cognitive deficit/NR<br>Depression/NR<br>Dysfasia/NR<br>Headache/NR<br>Neuroendocrine deficiency/36<br>Nystagmus/NR<br>Obesity/2<br>Ototoxicity/NR<br>Stroke/1<br>Truncal muscle/NR weakness/NR | G2 (66%)<br>G3 (22%)<br>G4 (2%) | Ototoxicity 7 | Unilateral ototoxicity grade 3-4: (3)/IT<br>Bilateral ototoxicity grade 3-4: (4)/IT<br>Full Scale Intelligence: Quotient decreased by 1.5 points/yr<br>Neuroendocrine deficiency: (36)/IT | Hypothalamus Dmax >40 GyRBE in 43 pts (73%) | 5-yr 80%/NR | 5-y 83% |
| Kahalley, 2016 (93) | NR | In CSI pts, in the XRT group IQ declined by 1.1 point/y<br>In focal pts, in the XRT group IQ declined significantly by 1.6 point/y | NR | NR | NR | NR | NR | NR |
| Giantsoudi, 2016 (94) | CTCAE v.4 | BS necrosis (4%)<br>Radiological changes (5%) | G1 (5%)<br>G2 (1%)<br>G3 (2%)<br>G4 (1%) | 0.8 (0.6-1.5) | BS necrosis: MBL (4)/IT | BS Dmax range 50.17-56.17<br>BS median dose > 52.4 | NR | NR |
| Kralik, 2015 (95) | CTCAE v.4 | Radiological changes (23%)<br>RN (8%) | G1 (23%)<br>G3 (8%) | 0.4 (0.2-0.9) | Radiological changes/RN: Craniopharyngioma (1), Ependymoma (6), LGG (1), MBL/PNET (5), Other (3)/NR | NR | NR | NR |
| McGovern, 2014 | CTCAE v.4 | RN (16%) | G2 (3%) | 0.3 (0.1-0.4) | RN: (3)/IT, (2)/ST | BS Dmax range 51.3-56.2 | 2-y 48%/NR | 2-y 68% |

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| (96) | | | G3 (6%)<br>G4 (6%) | | | BS mean dose range 20.1-52 | | |
| Indelicato, 2014<br>97) | CTCAE v.4 | BS necrosis (4%) | G2 (2%),<br>G3 (0.3%)<br>G4 (0.5%)<br>G5 (0.3%) | 0.3 (0.2-1) | BS necrosis: Ependymoma (8)/IT, LGG (1)/IT, MBL (1)/IT, Other (1)/IT | Significant HR when age <5yo, primary tumor in PF and BS V55 Gy | NR | 2-y 91% |
| Greenberger, 2014<br>(98) | WISC (VCI/ FSIQ)<br>WPPSI and WAIS scale<br>Snellen/LogMar visual acuity measurements | Decline in VCI and in FSIQ (12.5%)<br>Endocrinopathy (47%)<br>Optic nerve/retinal related injury (12.5%)<br>Other visual symptoms (28%)<br>Vasculopathy in NF1/2 (6%) | Vasculopathy in Moyamoya disease requiring pial synangiosis (6%) | Vasculopathy 0.9 | Endocrinopathy: (15)/ST<br>Vasculopathy: (2)/ST | For neuroendocrine deficiency: hypothalamus, pituitary or optic chiasm HR mean dose >40 Gy, IR 12-40 Gy and LR <12 Gy<br>For neurocognitive deficits, HR group: age <5.4 y and left temporal lobe/ hippocampus V20% >15 Gy<br>For visual symptoms: chiasm, optic nerve or retina Dmax>40 Gy | 8-y 83%/NR | 8-y 100% |
| MacDonald, 2013<br>(99) | Bayley Scales/Wechsler Preschool-Primary, Adult intelligence Scale | Endocrinopathy (11%)<br>Hearing loss (3%)<br>Vasculopathy (3%) | NR<br>2 Endocrinopathy requiring replacement therapy | Hearing loss 2.3 (0.3-9.4)<br>Endocrinopathy 3.5 | Hearing loss: (2)/IT<br>Vasculopathy: (2)/IT | NR | 3-y 76%/83%<br>5-y LC 77% | 3-y 95% |
| Moeller, 2011<br>(100) | Brock ototoxicity grading scale | Ototoxicity (57%) | G1 (17%)<br>G2 (35%)<br>G3 (4%) | 2.5 | Ototoxicity: (13)/IT | Cochlea mean dose 30 (19-43) | NR | NR |
| Viswanathan, 2011<br>(101) | NR | Pituitary dysfunction (42%) (9 proton and 4 combined) | NR | Proton group 1.17+/- 0.4 Combined group 0.33 +/- 0.11 | Pituitary dysfunction proton group: Craniopharyngioma (6), MBL (1), Other (2)/NR<br>Pituitary dysfunction combined group: MBL (3), Other (1)/NR | NR | NR | NR |
| Hug, 2002<br>(102) | LENT-SOMA | Brain changes (4%)<br>Endocrinopathy (15%)<br>Vasculopathy (4%) | Brain changes asymptomatic (4%)<br>Endocrinopathy requiring replacement therapy (15%)<br>Moya-moya vascular bypass (4%) | NR | Brain changes: (1)/NR<br>Endocrinopathy: (4)/NR<br>Vasculopathy: (1)/NR | NR | 7-y NR/ 78% | 7-y 80% |

*Legend:* *CTCAE vs 4.0: Common Terminology Criteria for Adverse Events; ** defined as areas of enhancement multifocal areas of parenchymal enhancement remote from the surgical site; # For neuroendocrine deficiency: Patients in the high-risk mean dose of >40 GyRBE, intermediate-risk between 12 and 40 GyRBE, and low- risk groups less than 12 to the hypothalamus, pituitary or optic chiasm; RLVCV: Radiation-induced large vessel cerebral vasculopathy; RN: Radionecrosis; WML: White matter lesion; CVA: Cerebral vascular accident; HR: High risk; WISC: Wechsler Intelligence Scale for Children; VCI: Verbal Comprehension Index; FSIQ: Full-Scale Intelligence Quotient; °: 2 pts who required laminectomy for cervical extension of infratentorial tumor.

**Bibliographic search**

The systematic analysis was carried out using the PubMed library from January 1st 2000 to May 20th, 2020. The following search strategy was used: ("brain"[MeSH Terms] OR "brain"[All Fields]) AND ("pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "pediatric"[All Fields]) AND ("protons"[MeSH Terms] OR "protons"). The reference lists of the selected papers were checked to identify additional publications.

**Inclusion criteria**

In this review clinical studies with available full text, published in English and reporting late toxicity in brain pediatric patients treated with PT were included. We included also both retrospective studies and prospective trials. Studies not reporting tumor response and toxicity, case reports or articles with less than 20 patients, systematic or narrative reviews, meta-analysis, letter-commentaries-editorials, planning studies, imaging studies, surveys, guidelines, recommendations, re-treatments studies, or reporting duplicate data were excluded.

**Study selection**

After removing duplicate publications at the title/abstract level, BR and LR independently reviewed titles, abstracts, and keywords to perform a preliminary selection. In case of differences in the selection, the final decision was taken through a discussion with a third author (SC). In all

articles potentially suitable for the purposes of this analysis, the full text was examined independently by MF and SCa. In the event of discrepancies, we proceeded as described above.

**Data extraction**

From the papers selected for inclusion in the review, data required for the analysis were independently extracted by BR and LR using a predefined data collection form including: authors, year of publication, study design, number of patients, median patient age, tumor site and histology, irradiation site (infratentorial, supratentorial and craniospinal irradiation), median/mean tumor dose, PT technique, comorbidity, additional therapy (i.e. surgery and chemotherapy), median follow-up (Table 6) , number of patients with LSE, toxicity rate and grade toxicity, median late toxicity time, late findings (histology and site), received normal tissue dose, local control (LC), progression free survival (PFS), and overall survival (OS) (Table 4).

Collected data were then checked by SC to identify any discrepancies among the extracted data. In the event of conflicting data, the final decision was taken by discussion.

**Quality assessment**

The quality of the papers selected was considered in terms of clear definition of the study population, treatments modality, clear level of the reported toxicity and outcomes, and missing data.

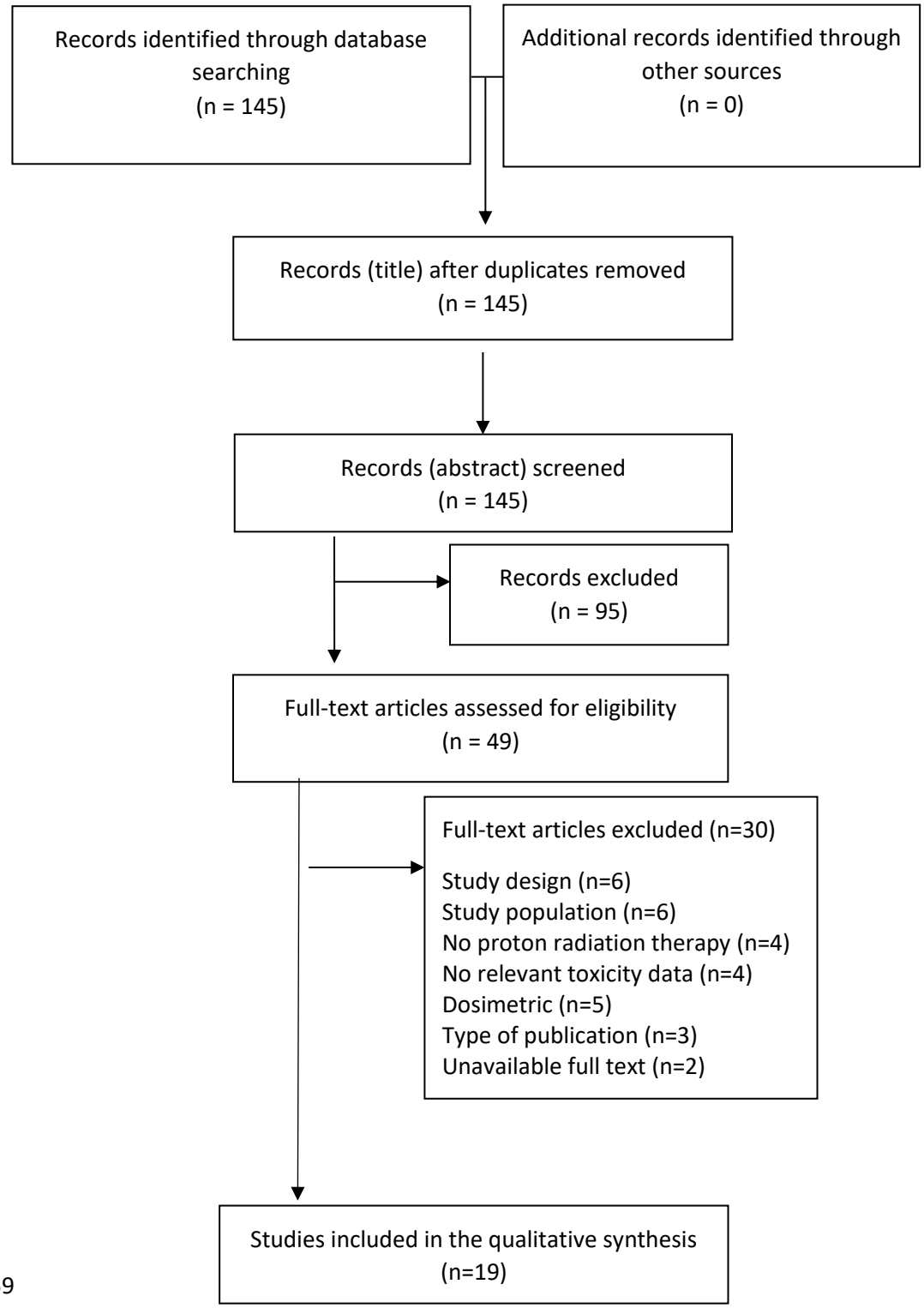
## RESULTS

### Search results

Figure 18 shows the PRISMA flowchart of the studies selection. From a total of 144 studies retrieved, through literature research, performed as previously reported, 19 papers (89-102) were suitable for analysis as illustrated in Figure 18. 96 records were excluded (abstract). 30 full-text articles were excluded because not pertinent: six because of the study design, six because of the study population, four were not pertinent to PT, four did not report relevant toxicity data, five were dosimetric studies, three because of the type of publication (two systematic reviews, one survey) and in two cases full text was not available.

A total of 19 studies fulfilled all the inclusion criteria reporting data on 2544 patients. Among the selected trials, 18 were performed in American centers and one in Switzerland. Five studies were prospective, one was a comparative analysis, and 13 were retrospective.

Figure 18. Flow chart of studies selection



**Patients characteristics**

A total of 2544 patients from 19 studies were included in the final data extraction and analysis (Table 4, 5). The most frequent histologic types were: Ependymomas (26.0%), Medulloblastoma/PNET tumors (23.1%), low grade gliomas (LGG) (20.2%), Craniopharyngiomas (11.2%), Germ cell tumors (GCT) (1.7%), other histologic types (17.6%).

Infratentorial (IT) tumor location was recorded in 1198 patients (47.1%), supratentorial (ST) site in 1155 patients (45.4%), skull base in 60 (2.3%), spinal in 11 patients (0.4%), multifocal in 4 (0.1%), other different locations in 40 (1.6%) and not reported sites in 71 patients (3.0%). In Hug and colleagues study no distinction was made between infra or supratentorial region of 22 LGG evaluated patients. In McGovern only localized ATRT tumors versus disseminated M+ ATRT disease were analyzed.

**Treatment characteristics**

All 19 trials (five prospective, one comparative and 13 retrospective) had heterogeneous characteristics in terms of tumor histology, primary tumor site, delivered dose, and combined treatments (i.e. chemotherapy and surgery were combined with different modalities and timing). Median follow-up ranged between 0.1 and 18.2 years (median: 3.7 years). In Kahalley and colleagues study, median follow up was not mentioned, but

ranged between 0.7 and 5.4 yrs. In the following papers, the follow-up range was not reported and median follow was 4.2, 2.0, and 1.8 years in Giantsoudi et al (94), Indelicato et al. (84), and in Viswanathan (101) et al. studies.

Only in 15 out of 19 studies the type of PT technique was specified (84, 85, 86,87,88,89,92,93,94,96,97,98,100,101,102). Most trials were based on the passive scattering technique and only one with active scanning; in four studies patients were treated with mixed photons-protons due to downtime PT machine or photons were used as tumor bed boost after PT (90,92,101,102).

The Gross Tumor Volume (GTV) was defined as the tumor bed plus any residual tumor in seven studies (87,89,90, 91,95,96,97,98). The Clinical Target Volume was defined in 12 studies (84,87,89,90,91,93,95,96,98,99,100,102) as the GTV plus a variable margin ranging among two and 10 mm. The Planning Target Volume (PTV) was defined in seven studies(84,87,90,95,96,97,98) as the CTV plus 2-12 mm margin. The target definition in treatments based on craniospinal irradiation (CSI) plus boost was reported only in six studies (85,88,93,94,95,96).

The mean delivered dose to the PTV local tumor site was 53.5 Gy RBE (range: 21-63 Gy) in 6 papers (89,93,94,95,96,102) while median dose was

54.3 Gy RBE in nine papers (range: 45-75.6 Gy) (85,88,90,91,92,97,98,99,100,101). In the CSI setting, mean total dose ranged between 18 Gy and 39.6 Gy RBE, depending on risk stratification. Only six papers mentioned the use of multiple beams (range 2-6 beams) (85,87,91,97).

In all studies except that of Giantsoudi et al. (94), where use of chemotherapy was not reported, chemotherapy was administered in different settings: neoadjuvant in 10 series (84,87,90,91), concurrent in five studies, (11, 13, 17, 20, 21) and adjuvant in five reports (11, 13, 20, 21, 25). In 13papers surgical resection was performed before PT (9, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27) while in five papers the specific timing was not reported (11,12,13, 14, 16) and in one study surgery was not mentioned at all (23). Overall, the rate of resected patients ranged between 49% and 100% (median: 84.2%).

**Late toxicity definition**

The most frequently used toxicity assessment tools was the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) classification [10] in 10 papers (9, 11, 12, 13, 16, 17, 19, 20, 21, 22), the LENT SOMA SCALE in one report (27), the Brock ototoxicity grading scale in one paper (25), the Pediatric Oncology Group hearing ototoxicity score in one study (17), the Bayley Scales of Infant Development and Wechsler

Intelligence Scale for Children in one report (24), and the WISC/WPPSI and Snellen Logmar visual acuity scale in one series (23).

Finally, in five studies the used toxicity scale or grading system was not reported (10, 14, 15, 18, 26).

**Toxicity**

From all 19 studies, the reported toxicities were as follows: neuroendocrine impairment in 6% (154 patients), brain/brainstem necrosis in 2.8% (72 patients), radiological changes in 1.5% (38 patients), vasculopathy in 2.9% (75 patients), ototoxicity in 2.3% (59 patients), and visual symptoms in 0.6% (16 patients). In the 10 studies reporting toxicity based on the CTCAE scale (v.4 and v.3 in nine and one reports, respectively) the adverse effects grade was as follows: G1 in 112 patients (5.9%), G2 in 126 patients (4.9%), G3 in 52 patients (2%), G4 in 9 patients (0.3%), and G5 (0.2%) in four patients ( 84,86,87,88,91,92,94,95,96,97). In Greenberger's et al. study, four patients developed both Verbal Comprehension Index (VCI) and Full-Scale Intelligence Quotient (FSIQ) decline after PT. In Yock's et al. study, IQ decreased by 1.5 points per year with worsening of processing speed and verbal comprehension index while perceptual reasoning index and working memory did not change significantly (92).

Several trials reported a low comorbidity rate before PT: neurofibromatosis (NF) type 1-2 in 18 patients (84,8590,102). Among 49 patients with vascular

metabolic disorder, one had Factor V Leiden Deficiency (98) and one hereditary prothrombin disorder (87). Ninety-three patients had neuroendocrine abnormalities before PT (85,91,98,99,101) while 427 patients had neurological clinical relevant complications after surgery and before PT (85,88) and 64 patients had Posterior Fossa Syndrome (PFS) (88,92). Thirty-five patients had PEG placement, while nine underwent tracheostomy (88). Among 742 patients with hydrocephalus, a ventriculo-peritoneal shunt (VP) was placed in 121 patients before PT as reported in four studies (88,92,93,99). Seven patients had severe uni- or bi-lateral hearing loss before PT (100) while one patient had undefined autoimmune disease (91).

**Other outcomes**

Overall, long-term outcome data were reported in 13 papers (84,86,87,88,89,90,91,92,96,97,98,99,102). PFS ranged between 47.6% and 89.7% (median 78.1%) in nine papers (84,87,88,90,91,92,96,98,99) while median LC was 83.4% as recorded in seven papers ( 84,87,88,90,91,99,102). OS was reported in twelve studies and ranged between 68% and 100% (median 88.3%) (84,86,87,88,90,91,92,96,97,98,99,102).

**Quality assessment**

A quantitative meta-analysis was not performed because of obvious heterogeneity among the analyzed studies. Therefore, no statistical analysis

was carried out due to the clear heterogeneity of toxicity scales and to the different timing of the reported outcomes.

Some papers present an intermediate risk of bias due to high heterogeneity of tumors, patients, and treatment characteristics and due to the retrospective design of most studies. Finally, in terms of missing data, long term outcomes were not reported in 6 papers (85,93,94,95,100,101) median late toxicity time not reported in 6 papers (84,85,90,91,93,96) and toxicity data and criteria were lacking in seven papers (84,87,93,95,99,101,102).

**DISCUSSION**

PT has been increasingly used to treat pediatric brain tumors, including Gliomas, Ependymomas, Germinomas, and Medulloblastomas. To the best of our knowledge, this is the first systematic review comprehensively assessing toxicity, safety, and efficacy of PT in pediatric CNS tumors.

Our analysis has several limitations, including the retrospective design of most studies, the small number of enrolled patients in some series, and the high heterogeneity in terms of tumors, patients, and treatments characteristics. However, due to the lack of evidence coming from randomized trials or meta-analyses, we though that a systematic review on this topic could have been useful to contribute to the knowledge in this field.

**Neuroendocrine deficiency**

It is well-known that tumors involving the Hypothalamus-Hypophysis axis often cause endocrinopathies themselves and chiasmal and hypothalamic tumors require high doses to the HPA for disease control. In this setting highly conformal irradiation techniques, such as PT, may allow treatment of peripheral tumors with increased sparing of the HPA.

In our analysis this complication occurred in 6% (N=154) of the whole patients population and in 20.3% (N=758) among nine studies where neuroendocrine deficit was specifically reported (84,87,90,91,92,98,99,101,102).

These figures seems lower compared to those reported in studies on photons beams-based RT. For example, in Vatner's et al. study (28), among 130 Medulloblastoma patients treated with CSI plus boost and 59 CNS brain tumor patients who received involved field RT, the 4-year actuarial rate of any hormone deficiency was 48.8%. The authors found that age at RT start, time interval since treatment, and median dose to the combined hypothalamus and pituitary region were correlated with an increased incidence of neuroendocrine impairment.

Some of the studies included in our analysis were able to identify parameters associated with increased risk of neuroendocrine adverse effects. Greenfield et al. observed cases of endocrinopathy in the patients

with suprasellar tumors where the hypothalamic-pituitary axis received a mean dose of 48 Gy RBE. Moreover, Growth Hormone deficiency was the most common new-onset endocrinopathy after PBT). Greenberger et al. (98), treated with PT 32 pediatric patients with low-grade gliomas of the brain or spinal cord. Patients in the high-risk, intermediate-risk, and low-risk groups received a mean dose of > 40 GyRBE, 12-40 GyRBE, and < 12 GyRBE, respectively, to the hypothalamus-pituitary region. The incidence of endocrinopathy was higher in patients with a mean dose ≥ 40 GyRBE to the hypothalamus/pituitary volume.

**Brain/brainstem radiation necrosis (RN) and radiological changes**

In recent years a growing awareness arose about brainstem injury and brain parenchymal alterations occurring after PT, particularly in young pediatric patients with tumors arising in the posterior fossa (PF), in close proximity to or directly infiltrating the brainstem. In pediatric series the reported RN rates seemed in some series roughly higher after PT, compared to standard RT, even though with a large inhomogeneity in terms of incidence (0%-43%) (104).

This possible negative effect of PT has been explained taking into account the proton Relative Biological Effectiveness. In particular, due to the specific linear energy transfer of protons and considering the spread-out Bragg peak, almost no radiations are delivered beyond this point.

Nevertheless, there is a potentially increased linear energy transfer in the terminal few millimeters of the spread-out Bragg peak with a consequential rise of the biologically effective range which could worsen the risk of RN. However, this hypothetical concern was not confirmed by our analysis.

In fact, these complications were not so common adverse effects recorded in this analysis, the incidence does not seem higher compared to figures recorded with photon-based RT. Indeed, RN and radiological changes were observed in 72 (2.8%) and 38 (1.5%) patients across all patients, respectively. More specifically, the incidence of radionecrosis was 4.9% in eight studies, including 1472 patients, clearly reporting this complication (84,86,89,90,91,93,94,95,102). Furthermore, radiological parenchymal changes occurred in 19 out of 527 (3.6%) patients included in three series where this adverse effect was specifically described (94,95,102).

More in detail, Gentile et al. reported 2.0% 5-year RN incidence in pediatric patients with primary PF tumors treated with PT (88). Bojaxhiu et al. (86) reported a lower prevalence of symptomatic RN (7%) and white matter lesions (WML) (3%) in children with brain tumors treated with pencil beam scanning (PBS)-PT compared to patients treated with photons-based RT. (30, 31). Indelicato et al. (97) analyzed their large pediatric series (313 patients) and were able to identify several predictive factors of brainstem injury: higher radiation dose to brainstem, peri- and post-operative

complications, multiple surgical procedures, hydrocephalus and/or shunt placement, PF syndrome, larger tumor size, infratentorial tumor site, younger age, and male gender.

As previously anticipated, the results obtained with PT in this setting, as recorded in this analysis, do not seem worse than those obtained with standard RT, as can be seen by examining some studies based on photon irradiation. In the recent study by Nanda et al. (105) the crude incidence (median follow-up: 2.8 years) of brainstem toxicity was 23.3% in children with primary posterior fossa tumors, including medulloblastoma and ependymoma, treated with IMRT. Spreafico et al. (106) reported 18.5% rate of brainstem injury in children treated with 3D-conformal RT and high-dose chemotherapy. However, the majority of patients had primary gliomas of the supratentorial region, which may have a lower risk of brainstem damages. Murphy et al. (107) treated pediatric patients with embryonal tumors with surgery, chemotherapy, and photon-based CSI (23.4 – 39.6 Gy) plus a boost on the primary tumor bed (55.8 Gy). The incidence of brain necrosis was 3.7% in the whole population and 4.4% in patients with infra-tentorial tumors. The authors observed that the dose to the infratentorial brain was more predictive of RN than the dose to the brainstem alone, probably due to devascularization or other neurologic injury from surgery. Merchant et al (108) treated 153 very young (median age: 18 months)

pediatric patients with ependymoma with photons (54-59.4 Gy) without constraints on the brainstem. They recorded three RN out of 122 patients (2.5% at 7 years) with infratentorial tumors (108). Plimpton et al. (109) retrospectively reviewed the magnetic resonance imaging of 101 children with solid brain tumors after photon radiotherapy with a median follow-up of 13 months (range 3-51). They found that RN occurred in 5% of cases with a median time to onset of 1.2 months.

**Vasculopathy**

In our analysis, late vascular damage was recorded in 75 patients (2.9%) across nine studies including 1352 patients ( 84,85,87,89,90,91,98,99,102) clearly describing this side effect. Twenty-five patients developed clinically relevant vasculopathy (2.0%) requiring surgical interventions. Three out of 18 NF type 1-2 positive patients developed the Moyamoya syndrome with need of a vascular bypass in one patient (102) and pial synangiosis in two patients (98). One patient with factor V Leiden deficiency had a veno-occlusive stroke (98).

Hall et al. (85) treated with PT 644 pediatric patients with central nervous system and skull base tumors. The authors reported the results of a multivariable analysis of factors predicting vasculopathy. The development of any vasculopathy was significantly correlated with the maximum dose (≥ vs < 54 CGE) to the optic chiasm (13.1% vs 2.2%, respectively; $p < .001$).

Also age < 5 years was significantly correlated with any vasculopathy (8.4% vs 5.4%; P < .01). Moreover, a maximum dose to the optic chiasm ≥ 54 CGE was also predictive of serious vasculopathy (3.8% vs 1.7%; p < .05). Three-year cumulative incidence of any vasculopathy and serious vasculopathy were 6.4% and 2.6%, respectively.

These results seem at least comparable if not better compared to series of patients treated with photon-based RT even though, in the latter, the rates of clinically significant vasculopathy are highly variable. For example, Ullrich et al. (110) reported 3.5% 5-year incidence of Moyamoya in 456 pediatric patients treated for brain tumors with photon therapy. Moreover, Omura et al. (111) reported 18.8% incidence of occlusive vasculopathy in a series of 32 patients with tumors near the circle of Willis treated with photon-based RT.

**Ototoxicity**

This toxicity developed in 59 (8.8 %) of 671 patients among six papers (84,87,89,92,99,100) evaluating this type of toxicity. These figures seem better compared to those reported by photon beam radiotherapy studies (18% -24%) (112,113).

Most of patients treated with PT and showing ototoxicity had infra-tentorial tumor and 47.8% received neoadjuvant chemotherapy before PT. To score ototoxicity, three papers used the CTCAE scale ()84,87,90), one paper the

Brock ototoxicity grading scale (100), one the POG hearing scale (92) while in the last one the scoring system was not specified (90,92,99).

In Indelicato and colleagues study (84), 174 of non-metastatic LGG pediatric patients treated with PT were evaluated with a minimum of 6 months of potential follow-up. They found favorably outcomes of 2% rate of hearing loss comparing with photon therapy in smaller series (113) in fact, four patients developed partial sensorineural hearing loss in 1 ear after radiation (grade 2 toxicity), 1 of whom required a hearing aid (grade 3 toxicity). Another study focusing on toxicity after PT for Ependymomas patients (87) found that 11 patients (6.1%) developed new hearing loss requiring hearing aids: seven with bilateral and four with unilateral deficits. Of note, eight of these 11 patients received cisplatin chemotherapy, including six of the seven with bilateral hearing deficits. In MacDonald and colleagues study (99) two out of 23 (18%) patients with infratentorial tumors developed hearing loss attributable to PT, at a median of 27 months (range, 4 months–9.4 years). Overall, average median dose to the right cochlea was 7.1 Gy (RBE) (range, 0–54.5), and the average median dose to the left cochlea was 6.95 Gy (RBE) (range 0–51.9). Both patients received higher doses of radiation to their cochlea than the average median dose because of tumor extension into the foramen of Luschka. In another series by Indelicato and colleagues (90) who treated different pediatric CNS tumors with PT the rate

of hearing loss is low particularly in children who did not receive chemotherapy. They concluded that in the setting where the tumor is close to Luschka foramen and ponto-cerebellar angle, PT and even more precise scanning technique may be able to further reduce the radiation dose to the cochlea beyond the PTV.

In Yock and colleagues study (92) 59 Medulloblastoma patients (39 with standard-risk disease, 6 with intermediate-risk disease, and 14 with high-risk disease) were treated with PT: the median craniospinal irradiation dose was 23.4 GyRBE and median boost dose was 54 GyRBE. Median follow-up of survivors was 7 years. Four (9%) of 45 evaluable patients had grade 3–4 ototoxicity according to Pediatric Oncology Group ototoxicity scale in both ears at follow-up, and three (7%) of 45 patients developed grade 3–4 ototoxicity in one ear, although one later reverted to grade 2. The cumulative incidence of grade 3–4 hearing loss at 3 years was 12%, at 5 years 16% which was less than the 24% of patients suffering hearing loss noted in a standard risk CCG/POG A9961 cohort treated with 23.4 Gy craniospinal irradiation and posterior fossa boost and cisplatin (112) and also less than that reported after intensity modulated radiation therapy which found that 25% of patients suffered hearing loss in one or both ears with amifostine used as an otoprotectant (113). However, these

comparisons are imperfect because of differences in radiation boost volumes.

Looking for other relevant papers in this field regarding photon world, retrospective study of prospectively collected data on 51 children consecutively diagnosed with brain tumors and treated with platinum derivatives were analyzed by Rabiço-Costa et al. (115). They also analyzed multiples variables, such as: age at diagnosis, tumor location, hydrocephalus, platinum drug type, radiotherapy, and follow-up time, the median age at diagnosis was 6 years, the median follow-up time was 75 months. The incidence of ototoxicity was 23.5%. Rates of hearing loss with carboplatin were lower than with cisplatin. A statistically significant association occurred between the presence of hydrocephalus, radiotherapy exposure, infratentorial tumor location, and ototoxicity after treatment with platinum derivatives.

**Visual deficiency**

In our analysis visual symptoms occurred in 16 of 226 pts (71%), specifically evaluated in four papers (84,91,92,98) for this complication, with an overall rate of 0.6%. The first report on postoperative PT for pediatric LGG was published in 2002 (102). In this study Hug and colleagues treated 27 progressive or recurrent low-grade astrocytomas: in 15 patients tumor was centrally diencephalic, in seven patients was in the cerebral and cerebellar

hemispheres, and in five patients in the brainstem. All six patients with optic pathway tumors had useful vision maintained or improved their visual status after PT. Also in Greenberger (98), 12 patients developed optic nerve/retinal related injury or other visual symptoms more likely when chiasm and or optic nerve or retina received Dmax dose > 40 Gy. They concluded that even though there is a risk for radiation-induced injury to the optic pathways, stabilization or improvement of visual acuity was achieved in 83.3% of patients. Regarding photon series, an interesting paper by Awdeh and colleagues (116), who enrolled 20 optic pathway glioma in children (median age 9.3 years) underwent chemotherapy (N=8) or resection (N=9) before conformal radiotherapy (54 Gy). With a median follow-up of 24 months, they showed that patients with optic pathway tumors who receive radiation therapy as their first treatment are more likely to have useful vision before and after treatment (117). These results show that stabilization of vision after radiation therapy is possible. The benefit of early intervention with radiation therapy was also demonstrated by Pierce et al. (117), who showed stable or improved visual acuity in 91% of patients for whom treatment was initiated before their vision declined severely. Similar reports that vision loss can be minimized with the early use of PT irradiation include those of Hug et al. (102), in which all optic

pathway tumors patients had useful vision maintained or improved after PT.

In Greenberger and colleagues analysis (98), 13 patients (1%) developed heterogeneous visual symptoms after PT for LGG i.e. decreased acuity (N=3), optic nerve atrophy (N=1), visual field deficit (N=1), nystagmus (N=2), ptosis (N=1), afferent pupillary defect (N=2), impaired upgaze (N=1), diplopia (N=1), exophoria (N=1) confirming a low profile of toxicity with similar incidences to those reported in other photons studies (118).

**Neurocognitive sequelae**

four papers considered cognitive impairments after PT; Macdonald et al. (99) provide the first report on the impact of focal PT for ependymoma subgroup on intelligence and adaptive functioning. Among a subset of patients in the cohort, they found stable overall intelligence and adaptive skills/functional independence adaptive skills/functional independence (SIB-R) after the completion of PT: in fact, mean SIB-R standard score was 100.1 at baseline and 100.8 at follow-up. The average total MDI /IQ (Mental Development Index/Intelligence Quotient) score across all measures was 108.5 at baseline and 111.3 at follow-up. The authors observed that patients under the age of 3 years had a lower baseline IQ but improved substantially over time. In fact in 6 patients < 3 y mean MDI/ IQ was 104.3

at baseline and 114.0 at follow-up and in 12 < 3y SIB-R was 93.3 at baseline and 96.5 at follow-up.

Similar results were obtained by Kahalley and colleagues study (93) where they compared change in IQ over time in pediatric patients with brain tumors treated with PBRT versus XRT. They found that in CSI subgroup, PT group had no change in IQ whereas in the RT group IQ declined by 1.1 point per year. Also, in focal radiotherapy group, IQ remained stable in the PT group but declined significantly in the RT group by 1.6 point per year.

In Yock and colleagues study (92), FSIQ decreased significantly by 1.5 points per year after median follow-up up of 5.2 years, driven by decrements in processing speed and verbal comprehension index. Perceptual reasoning index and working memory did not change significantly. FSIQ of patients aged younger than 8 years decreased significantly, but in older patients it was stable. Patients who received involved field boost had a greater decrease in FSIQ than did patients who received whole posterior fossa boost. However, median age in the involved field group was 5,5 years versus 7 years in the posterior fossa group.

In Greenberger and colleagues study (98), four young LGG patients (age between from 4.8 to 5.4 y) and high-risk dose group defined as receiving at least 15 GyRBE to 20% of the volume of the left temporal lobe or hippocampus, they found statistically decline in VCI and in FSIQ.

Relative cognitive stability after conformal photon therapy for patients with ependymoma has already been established (108,119).

**CONCLUSIONS**

Based on the preponderance of the available data, we posit that PT may be the best approach for offering select patients a new chance of cure with a safe manner. However, is a necessity for PT centers worldwide to report their experiences, including outcomes and toxicities, as well as dosimetric factors from composite dose–volume histograms that can help to inform the cumulative tolerance of organ at risk and their correlation to late adverse events.

# 6. GENERAL CONCLUSIONS

Multiple radiation options exist for pediatric patients, including 3D conformal photon radiotherapy, IMRT, and now, proton beam radiotherapy. The dosimetric advantages of protons which substantially decrease the radiation dose to normal tissues, promise important clinical benefits in childhood cancer survivors, by maintaining tumor control, while decreasing the deleterious late effects of radiation therapy as well as the incidence of radiation induced secondary malignancies. The medical literature is now populated with several manuscripts on the early clinical outcomes showing the real benefits of PT with regards to improved quality of life, and health outcomes. As new centers become more readily available around the world, pediatric patients with solid tumors should take precedence in receiving PT as solid tumors in childhood are more curable than adult tumors and the side effects in children due to dose to non target tissues are far graver. Additional studies with longer follow-up time will be coming soon to even better document the ameliorated long-term morbidity and incidence of radiation-induced tumors, but longer follow-ups are needed for a clinical evidence [39,40].

However, increasingly within the pediatric radiation oncology community, participation in large multi-institutional registry trials is common. Such trials will further serve to document reductions in late adverse effects. Over the last decade, this effort has been accelerating. A Gap in any case will remain due to the scant of clinical reports published using photon techniques i.e., advantaged radiotherapy techniques as IMRT or thomo-therapy.

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