HITRI plus
Heavy Ion Therapy Research Integration

THE SPECTRUM OF PAEDIATRIC PATIENTS REFERRED FOR PROTONTHERAPY

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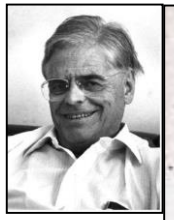
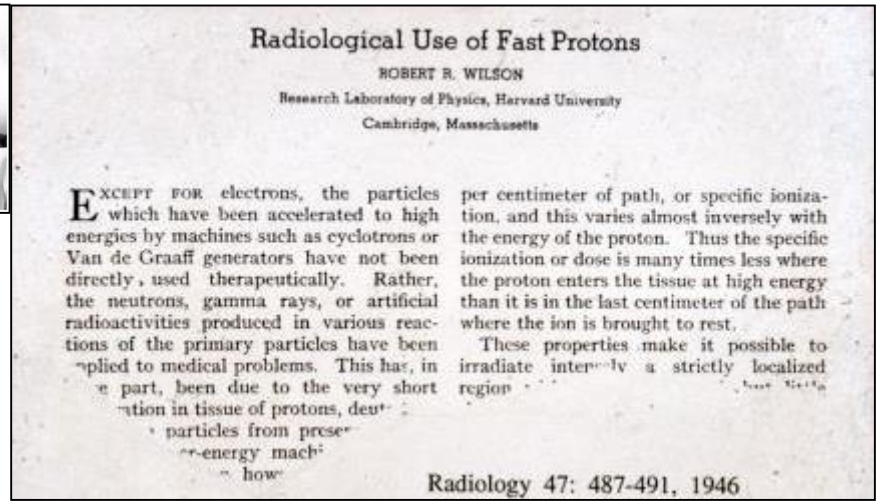
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

IMPROVE THE PHYSICAL DOSE DISTRIBUTION BY USING A DIFFERENT TYPE OF RADIATION





Radiological Use of Fast Protons

ROBERT R. WILSON

Research Laboratory of Physics, Harvard University

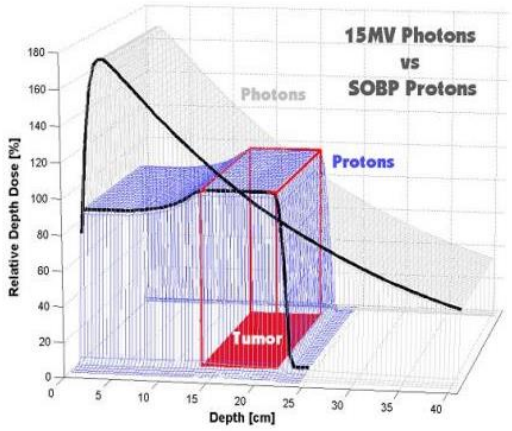
Cambridge, Massachusetts

EXCEPT FOR electrons, the particles which have been accelerated to high energies by machines such as cyclotrons or Van de Graaff generators have not been directly used therapeutically. Rather, the neutrons, gamma rays, or artificial radioactivities produced in various reactions of the primary particles have been applied to medical problems. This has, in the part, been due to the very short ration in tissue of protons, deu- particles from prese- -energy mach- how

per centimeter of path, or specific ionization, and this varies almost inversely with the energy of the proton. Thus the specific ionization or dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest.

These properties make it possible to irradiate inter-ly a strictly localized region

Radiology 47: 487-491, 1946



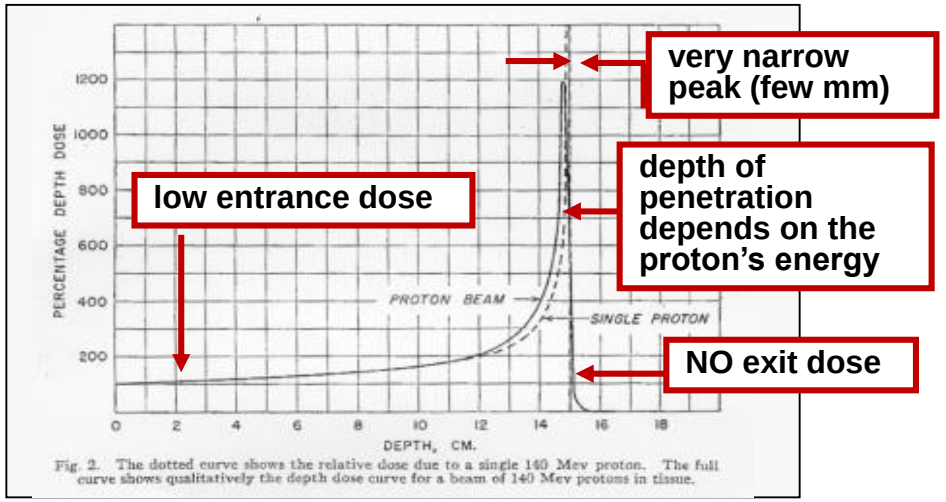


Fig. 2. The dotted curve shows the relative dose due to a single 140 Mev proton. The full curve shows qualitatively the depth dose curve for a beam of 140 Mev protons in tissue.

Relative biologic effectiveness(RBE)

→ Ratio of dose of a reference radiation quality and dose of a test radiation that produce equal effect

$$RBE = \frac{dose\ of\ reference\ radiation}{dose\ of\ test\ radiation}$$

RBE = 1.1 for protons

Dose in hadron therapy is expressed in Gy(RBE)

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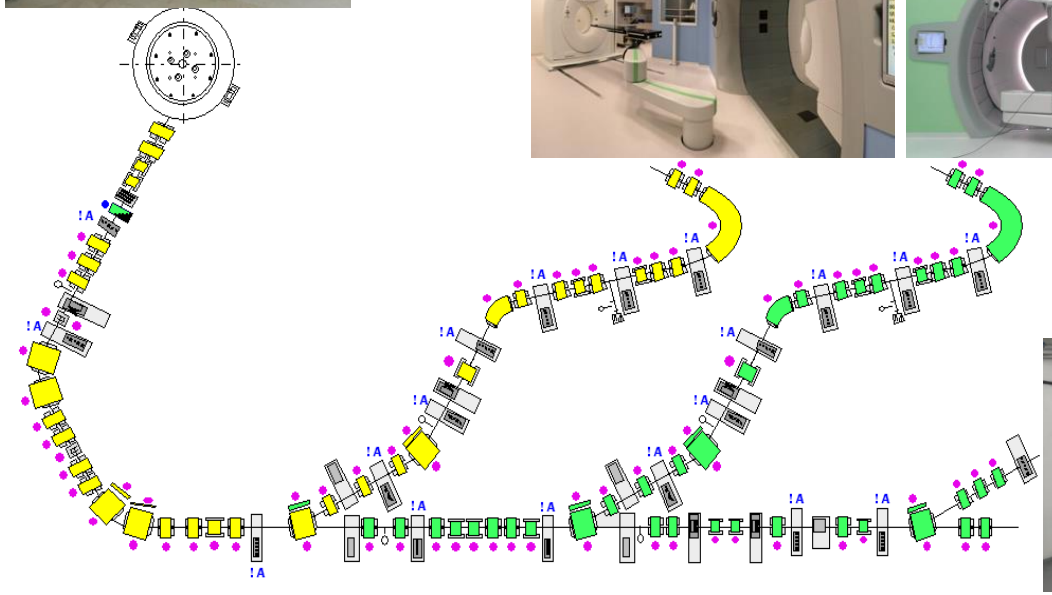
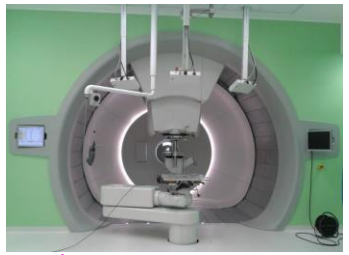
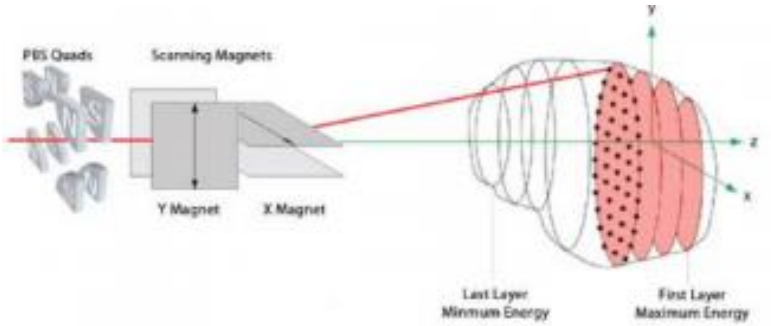
PENCIL BEAM SCANNING TECHNIQUE

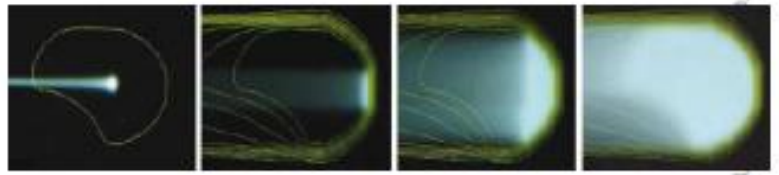
Cyclotron



Rotating gantries







Fixed line

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PEDIATRIC ONCOLOGY CLINICAL EXPERIENCE
PROTON THERAPY CENTER - TRENTO

581 pediatric patients (≤ 21 years) treated from June 2015 - September 2024
180 under daily sedation

60 patients per year (20% under daily sedation)

- 60% CNS tumors
- 7% Craniopharingiomas
- 3% SB tumors
- 29% Sarcomas
- 1% Others

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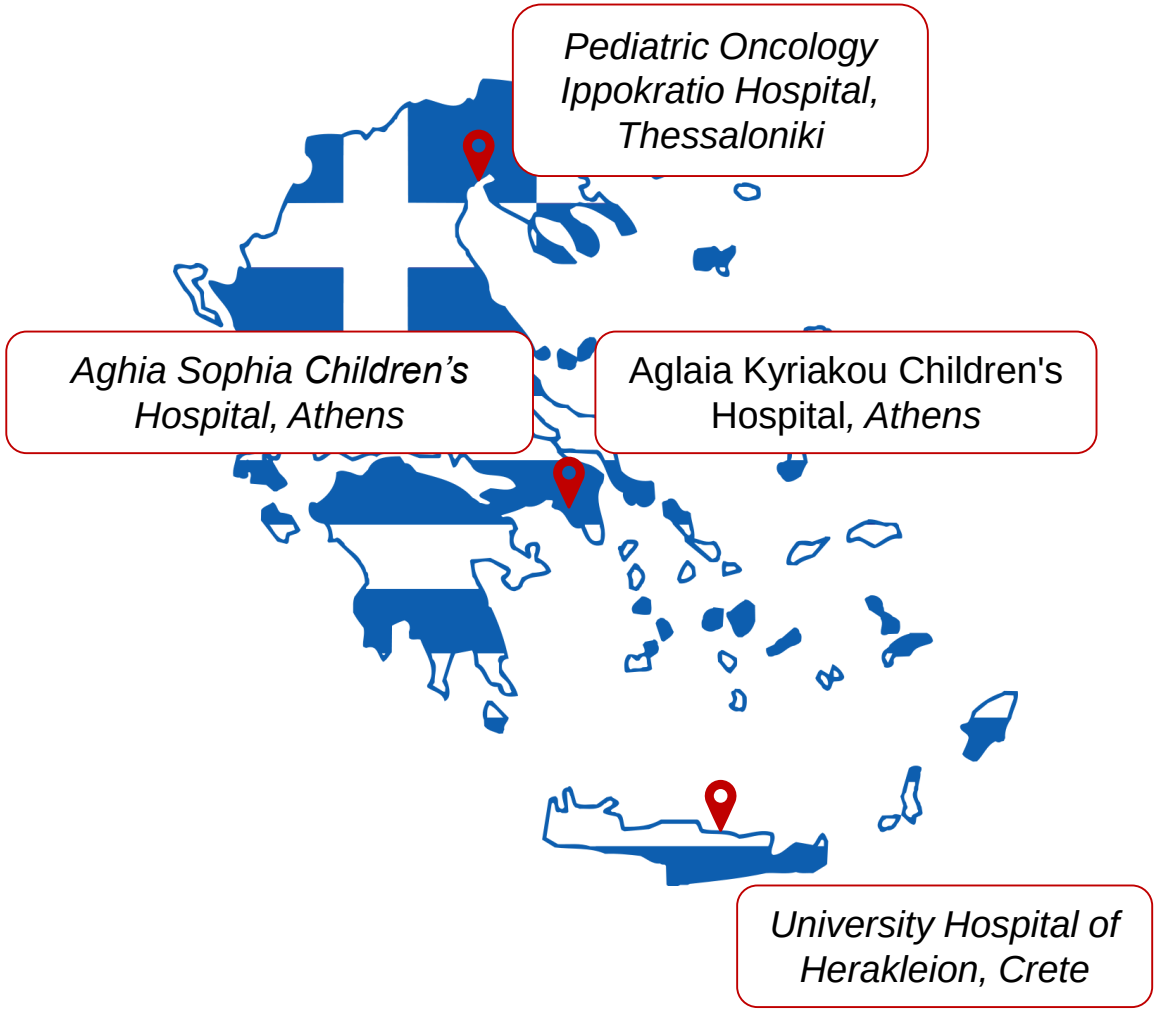
PEDIATRIC HELLENIC PATIENTS REFERRED TO TRENTO'S PROTON CENTER

FROM 2018 TO 2024
- 25 ped onc Hellenic patients
- Median age 10 yo (18 months - 20 y)
- 25% SNC tumors, 75% extra-SNC

HISTOLOGY
- 13 Rhabdomyosarcoma (Embryonal 8; alveolar 5)
  - orbital 4
  - PM 6
  - retroperitoneal 1
  - limbs 2
- 5 Sarcoma
- 2 Ependymoma
- 1 Craniopharyngioma
- 1 Adenoideocystic carcinoma
- 1 Medulloblastoma
- 1 ATRT
- 1 LGG Glioma



WORKFLOW AT PROTONTHERAPY CENTER

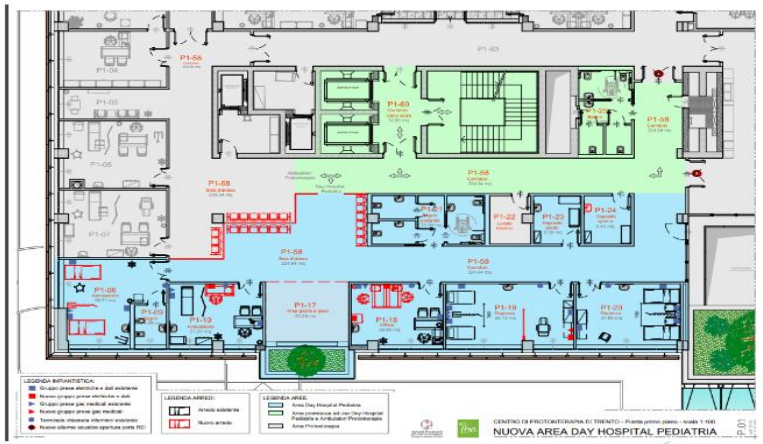
Pediatric patients in the national/international setting

Confirmation of appropriate indications for proton trough multidisciplinary meeting

S2 approval time in 10 working days

3 ROOMS WITH TWO BED
1 WAITING ROOM
1MEDICAL AMBULATORY
1 NURSE AMBULATORY

Protontherapy center
First floor



After formal acceptance for proton irradiation:

DAY 1
→ First clinical evaluation (when necessary)

DAY 2
→ Planning CT /MRI/PET with or without sedation

→ PT start in 5 days for 5 - 6 weeks

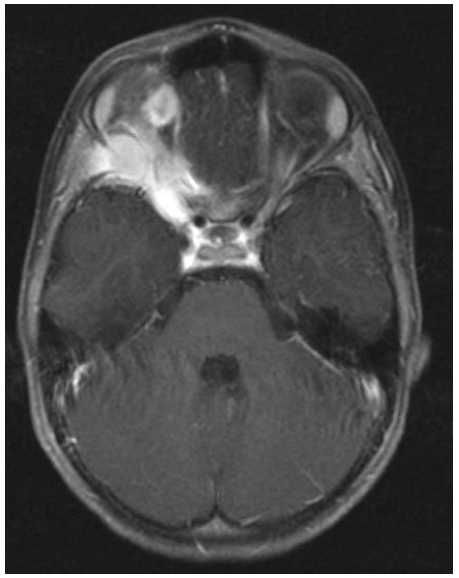
INTERNAL MULTIDISCIPLINARY DISCUSSION AND FORMAL ACCEPTANCE OF PROTON IRRADIATION

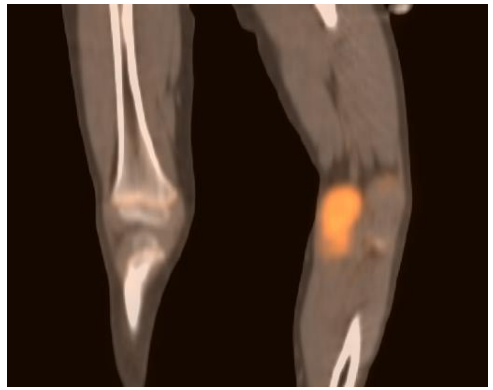
- Pediatric oncology, anesthesiology and radiation oncology consultations

- Read through all documents and viewing of all diagnostic images

- Discussion about:
  - baseline staging and restaging exams before PT
  - new assessment → ophthalmology evaluation, FKT, nutritional and psycological support
  - Need of procedural sedation during PBT
  - Opening of DH or admission to the paediatric ward
  - Scheduling of concomitant treatment

- Formal acceptance of proton irradiation → S2 form (usually ready in 2 weeks)
- Formal schedule with start date
- Logistic info

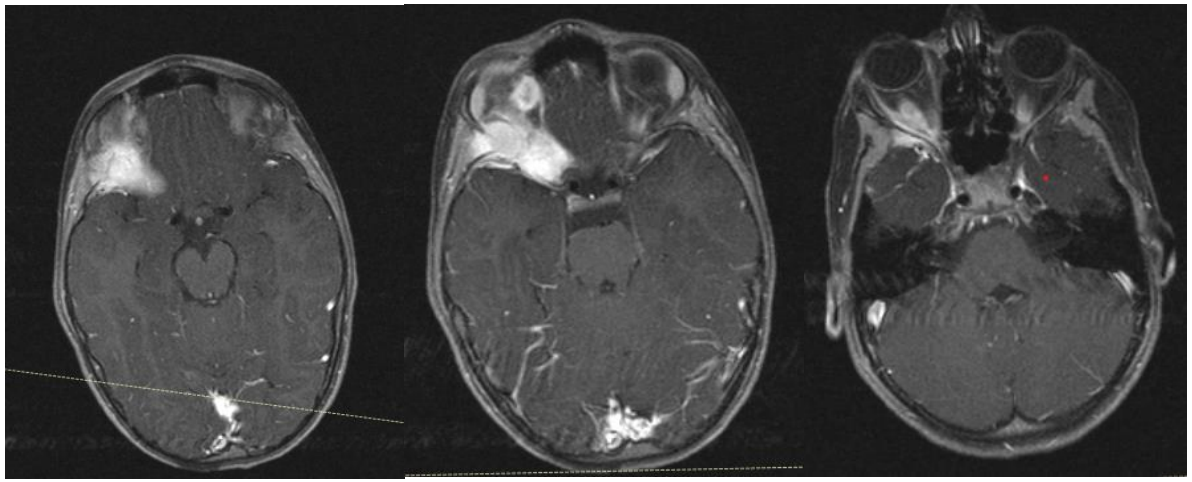




CLINICAL CASE - 1

7 yrs old, girl suffering for exophthalmos, diplopia and vision impairment (right optic nerve neuropathy)

Multifocal rhabdomyosarcoma, embryonal type, of the right orbita with involvement of sphenoid bone and parameningeal invasion



Initial MR: solid mass inside the right orbit with retrobulbar extension, infiltrating the lateral wall of the orbit and the wing of the sphenoid. Satellite lesions in the medial and top part of the orbit.

Initial CT PET (18 F- FDG): hypermetabolic lesion of the right retrobulbar space with small extension to the greater wing of the sphenoid.

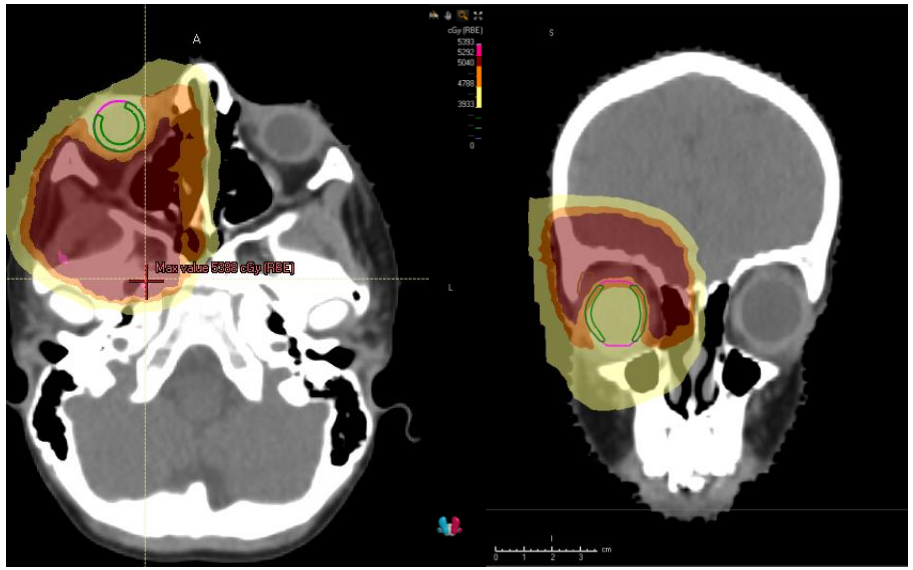
- Chemotherapy according to the FaR-RMS protocol in the high-risk arm
- In accordance with the treatment protocol, the 3 micronodules smaller than 5 mm were not considered metastases
- Doses and volumes shared with ped Onco and radiation Oncologists Greek colleagues

CONTOURING OF TARGET VOLUME(S), OARS AND DOSE PRESCRIPTION

→ PBT with the following dose prescription:

- CTV low risk (the extent of disease at diagnosis, taking into account changes in anatomy): 41.4 Gy (RBE)/1.8 Gy (RBE) daily/ 23 #

- CTV high risk (the extent of the residual primary tumour after induction chemotherapy): additional dose of 9 Gy (RBE)/1.8 Gy (RBE)daily/ # 5 → a total dose of 50.4 Gy in 28 #



	OARs dose contraints	Actual values
Optic nerve	D1% <50 Gy	left 5,7 Gy
		right 52 Gy
Lens	D1% <5Gy	left 3,9 Gy
		right 47 Gy
Optic chiasm	D1% <54Gy	52 Gy
Optic tract	D1% <54Gy	48,5 Gy
Pituitary gland	average 40 Gy	47 Gy
Hypothalamus	D1% <50Gy	41Gy

Acute toxicity

- G1 skin and eyelid toxicity
- VS reactivation 5 days before the end of PT
- 2 cycles of chemo during PT

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DOI: 10.1002/pbc.30742
Pediatric Blood & Cancer
RESEARCH ARTICLE

Radiotherapy and long-term sequelae in pediatric patients with parameningeal rhabdomyosarcoma: Results of two Cooperative Weichteilsarkom Studiengruppe (CWS) trials and one registry

Monika Sparber-Sauer[1,2] | Maximilian Dietzschold[3] | Anton Schönstein[4] | Amadeus Heinz[1] | Christian Vokuhl[5] | Kristian W. Pajtler[6,7,8] | Semi Harrabi[9,10,11,12,13,14] | Yi-Lan Lin[15] | Thekla von Kalle[16] | Rudolf Hagen[17] | Ruth Ladenstein[18] | Bernarda Kazanowska[19] | Gustaf Ljungman[20] | Thomas Klingebiel[21] | Martin Ebinger[22] | Ewa Koscielniak[1,2] | Marc Münter[23] | Beate Timmermann[15,24] | On behalf of the CWS Study Group

Treatment and outcome of 395 children with PM RMS registered within two CWS trials and one registry (1995– 2021)

Patients were IRS group II (n = 15) and III (n = 380) and received systemic treatment according to the enrolled protocols: I2VA (n = 172), VAIA/CEVAIE (n = 223).

RT was the predominant local treatment in 355/395 (90%)
- hyperfractionated accelerated photon (HART; n = 77)
- conventionally fractionated photon (n = 91)
- proton beam (n = 126)
- brachytherapy (n = 4)
- heavy ions (n = 1)
- not available (n = 56)

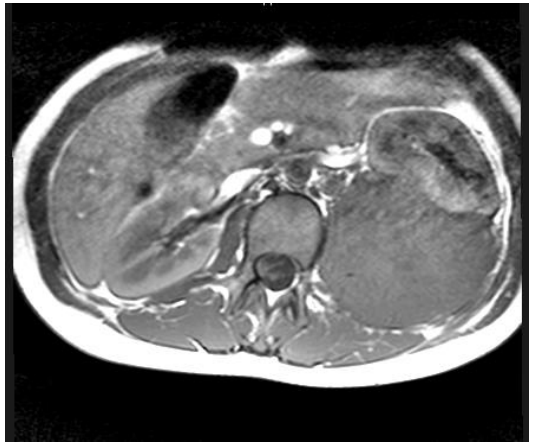
Long-term toxicity ENDOCRINOLOGICAL and VISUAL DEFICIENCIES

- proton beam RT (48%)
- HART or conventionally fractionated photon RT (71% and 72%, respectively).

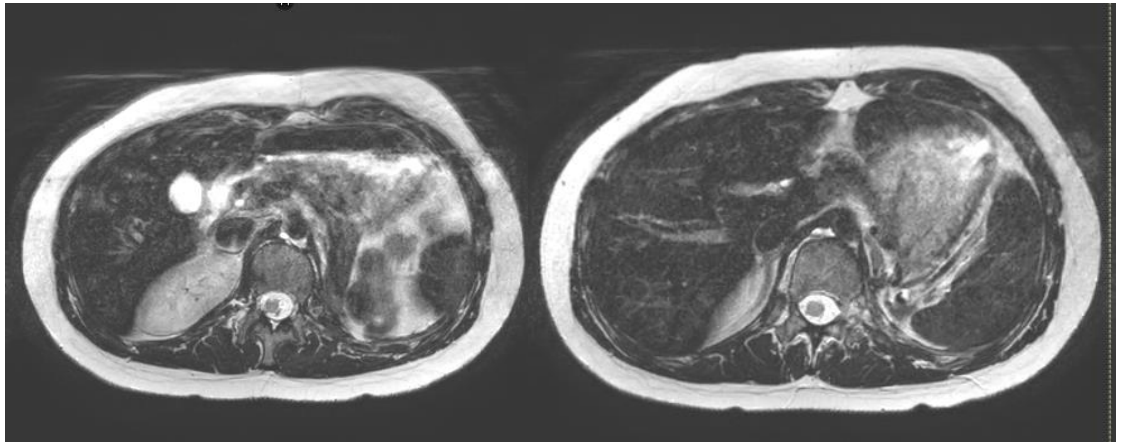
CLINICAL CASE - 2

12 yo girl affected by M+ paraspinal alveolar RMS

left paraspinal and paranephric mass; partially resected (exophytic part), left nephrectomy.
Remaining mass in the paraspinal space (max. diameter of 5.3cm).



Initial MRI



Post op- MRI

Chest- Mediastinum CT: an extrapulmonary mass of 2 cm in the back arc of the left rib
Chemotherapy according to CWS-guidance HR-group-metastatic disease
Second look surgery no possible (also asked for an international surgical opinion)

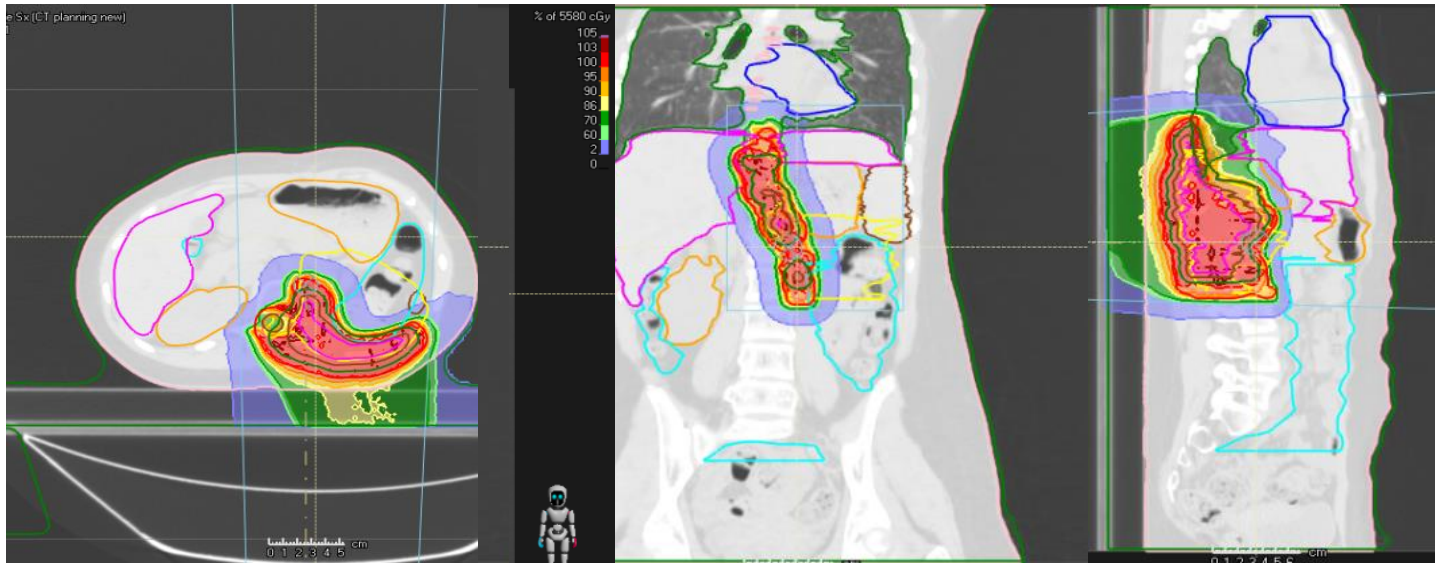
Two cycles of chemotherapy during radiotherapy (Ifosfamide and Vincristine / Carboplatin and Vincristine)

CONTOURING OF TARGET VOLUME(S), OARS AND DOSE PRESCRIPTION

→ PBT with the following dose prescription:

- CTV low risk (the extent of disease at diagnosis, taking into account changes in anatomy): 54 Gy (RBE)/1.8 Gy (RBE) daily/ 30 #

- CTV high risk (residual tumour after induction chemotherapy): additional dose of 5,4 Gy (RBE)/1.8 Gy (RBE)daily/ # 3 → a total dose of 59.4 Gy in 33 #

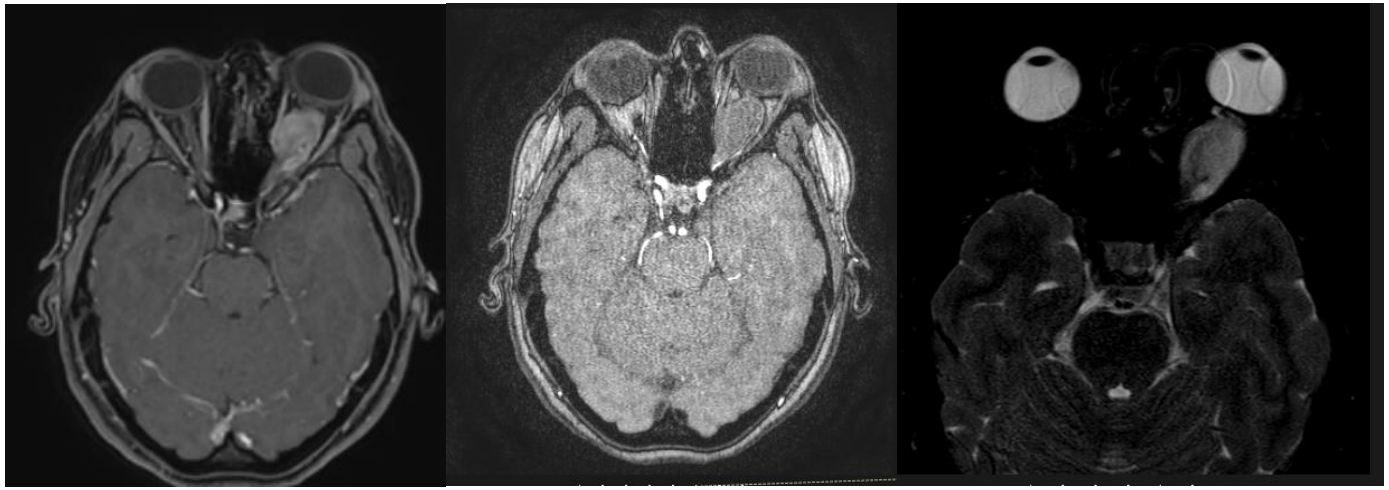


	OARs dose contraints	Actual values
Spinal cord	D1% <50 Gy	44 Gy
Right kidney	D1% <5Gy	1,8 Gy
Small bowel	195 cc at 45 Gy	38 cc
	30% volume at 50 Gy	1,62 %
	50 Gy at 1 cc	56 Gy

CLINICAL CASE - 3

15 yo girl with left optic nerve pilocytic astrocytoma, treated with VCR-Carboplatin according to the LGG protocol, clinical and radiological worsening. The left visual field had an increase in the darkening area.
Surgical partial removal. Blindness of left eye. Post operative bulbar prolapse, MRI showed an increase of the intrabulbar part of the tumor.

Indication for BRAF inhibitor → interrupted for severe (grade IV) cutaneous toxicity (generalized rash, edema, enanthema and burning sensation).
Indication for MEK inhibitor → (grade IV) cutaneous toxicity



T1 mdc 3D TOF T2 TSE FS

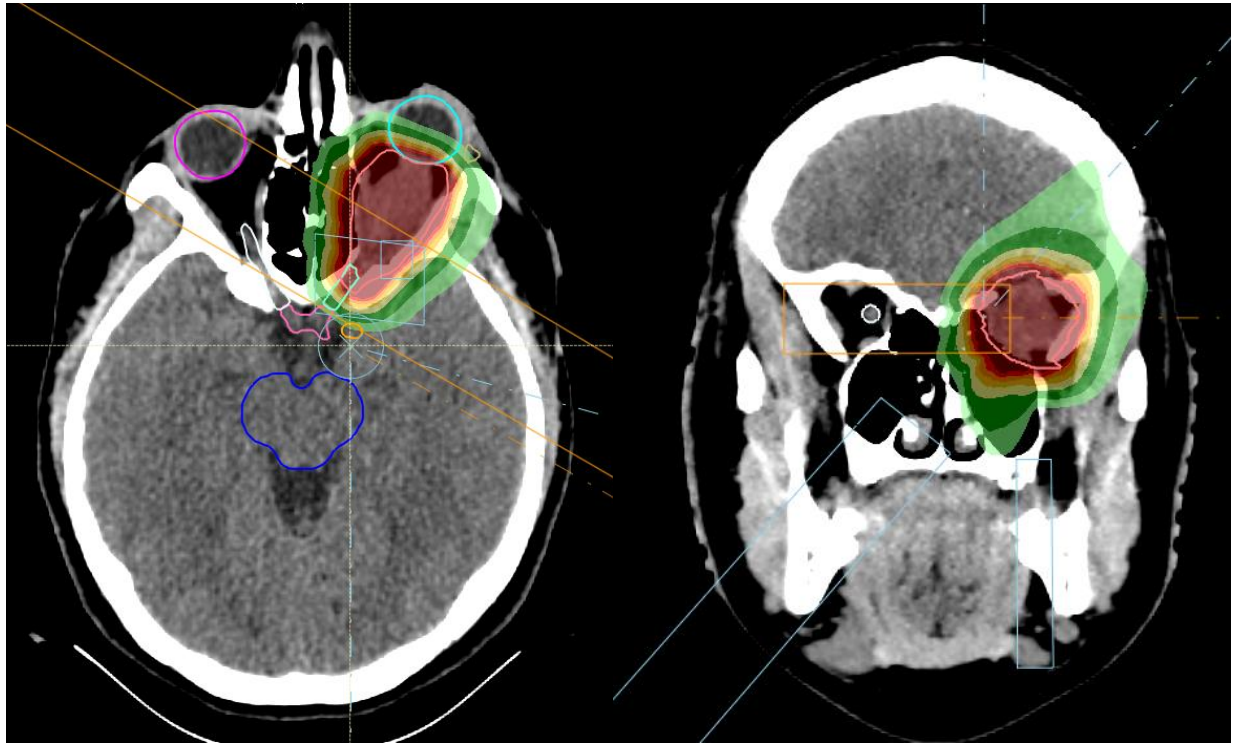
- Excellent general condition
- Left blindness (moving hand perception), right visual acuity 10/10
- Fundus: atrophy of the left optic nerve, normal appearance of the right optic nerve

CONTOURING OF TARGET VOLUME(S), OARS AND DOSE PRESCRIPTION

Dose: 54 GyRBE (1.8 GyRBE/fraction)

Technique: active beam proton therapy with 3 not coplanar beams, single field optimization (SFO) and image-guided radiotherapy (IGRT)

	OARs dose contraints	Actual values
Optic nerve	D1% <50 Gy	left 54.94 Gy
		right 2,5 Gy
Left carotid artery	D1% <55 Gy	48 Gy
Optic chiasm	D1% <54Gy	25 Gy
Optic tract	D1% <54Gy	3,34 Gy
Pituitary gland	average 40 Gy	30 Gy

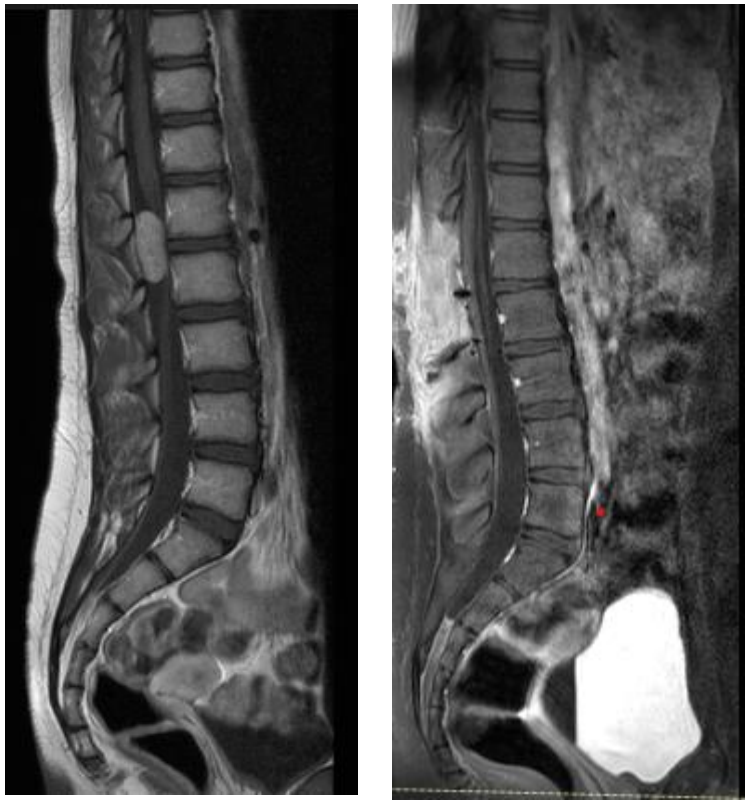


Acute toxicity
G2 headache, G1 conjunctivitis

CLINICAL CASE - 4

12 yo girl with L1-L2 GR III Ependymoma with radical resection.

Post- operative brain and whole spine MRI showed total resection in L1-L2, pathological leptomeningeal thickening in the sacral site in S2-S3, no intracranially disease. Negative CSF.



International multidisciplinary discussion

Shared proposal to irradiate whole craniospinal axis and to boost the lombosacral region

1) All tumor region (D12- S5) irradiation?
2) Whole spine irradiation?
3) CSI?

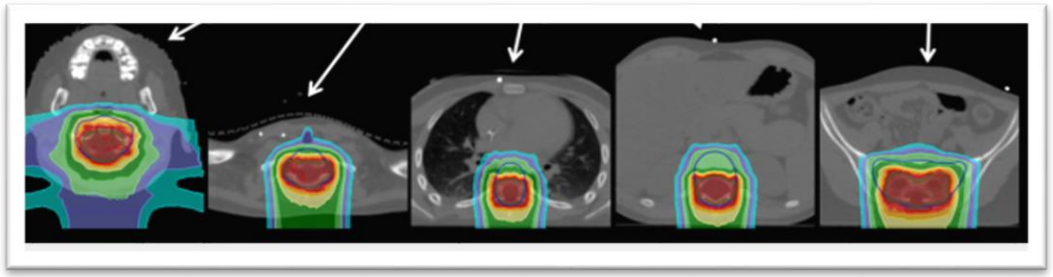
Family and patient accepted

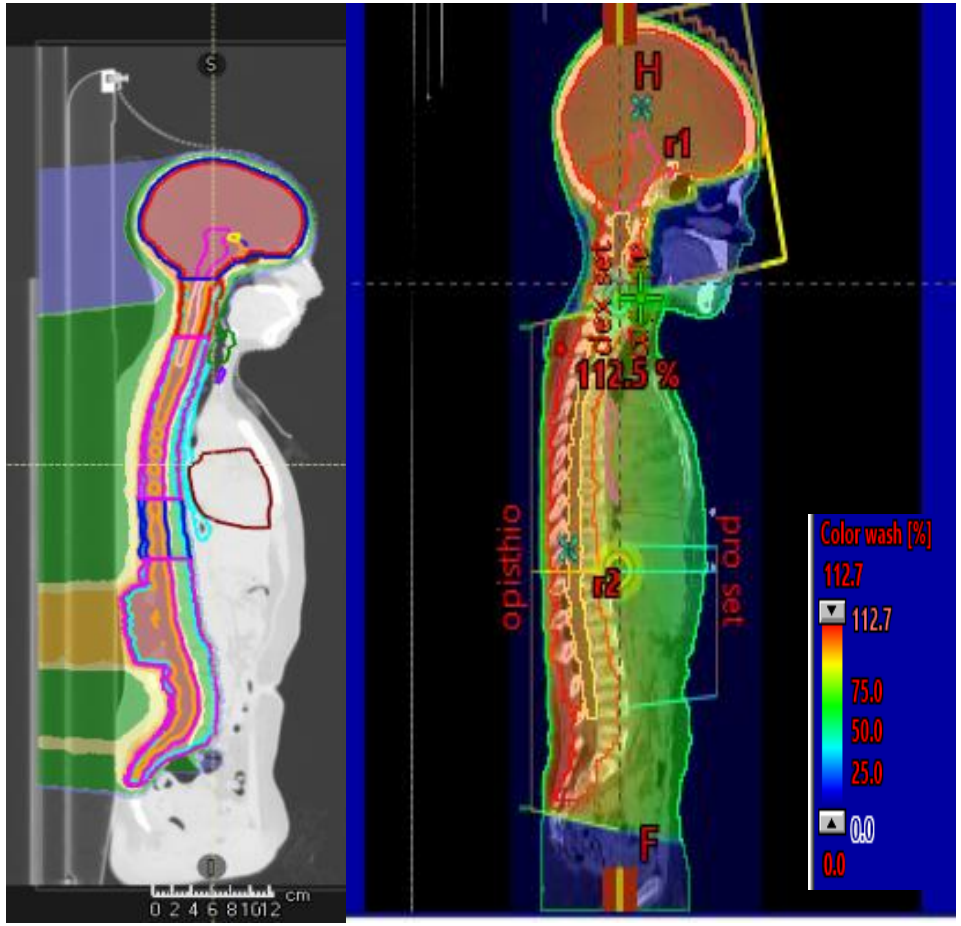
CONTOURING OF TARGET VOLUME(S), OARS AND DOSE PRESCRIPTION

CSI 36.0 GyRBE in 20 fractions (1.8 GyRBE/daily), followed by a tumor bed boost from T12-S3 up to 50,4/54 GyRBE in 30 fractions (1.8 GyRBE/fraction daily)

G1 lombo-sacral skin toxicity (where meningocele was), complete alopecia

Good quality of life until DP (Intracranially disseminated)



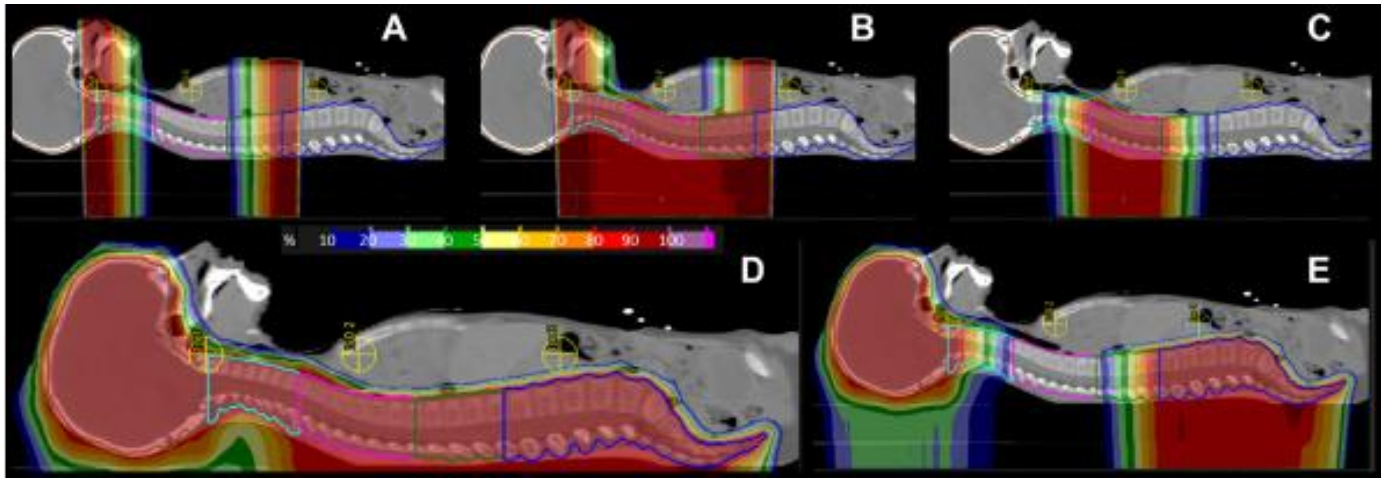


PENCIL-BEAM SCANNING - CSI

Whole brain irradiation can be performed by a lens-sparing three-beam technique

Spine irradiation can be performed with an additional posterior beam at each isocenter to the spine.

To plan the field junction, a gradient-optimized method using **ANCILLARY BEAMS** can be implemented [*].



The ancillary beam consisted 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 in the overlapping region between adjacent treatment beams.

[*] Farace P. et al. "Planning field-junction in proton cranio-spinal irradiation–the ancillary-beam technique." *Acta Oncologica* 54.7 (2015): 1075-1078.

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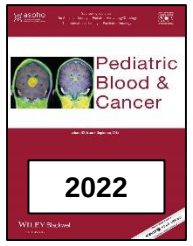
NEUROCOGNITIVE UPDATES: PT VS PHT

Cognitive predictors of social adjustment in pediatric brain tumor survivors treated with photon versus proton radiation therapy

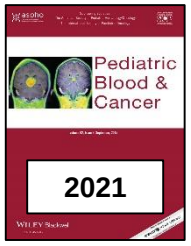
Emily A. H. Warren[1] | Kimberly P. Raghubar[1] | Paul T. Cirino[2] | Amanda E. Child[3] | Philip J. Lupo[4] | David R. Grosshans[5] | Arnold C. Paulino[5] | M. Fatih Okcu[4] | Charles G. Minard[6] | M. Douglas Ris[1] | Anita Mahajan[7] | Andres Viana[2] | Murali Chintagumpala[4] | Lisa S. Kahalley[1]



- The XRT group performed worse on measures of processing speed ($p = .01$) and verbal memory ($p < .01$)
- Social outcomes did not differ by radiation type

Long-term cognitive and academic outcomes among pediatric brain tumor survivors treated with proton versus photon radiotherapy

Amanda E. Child[1] | Emily A. Warren[2] | David R. Grosshans[3] | Arnold C. Paulino[3] | M. Fatih Okcu[4] | M. Douglas Ris[2] | Anita Mahajan[5] | Jessica Orobio[8] | Paul T. Cirino[6] | Charles G. Minard[7] | Andres G. Viana[6] | Johanna Bick[6] | Steven P. Woods[6] | Murali Chintagumpala[4] | Lisa S. Kahalley[2]



- The PRT focal group outperformed on inhibition/switching ($p = .04$)
- The PRT CSI group outperformed better inattention/impulsivity control (both $p < .05$)
- The PRT focal group performed comparably to population means on most neurocognitive measures
- CSI groups showed impairments i.e. processing speed, especially XRT CSI group

Article

Toxicity and Clinical Results after Proton Therapy for Pediatric Medulloblastoma: A Multi-Centric Retrospective Study

Alessandro Ruggi [1,†], Fraia Melchionda [2,†], Iacopo Sardi [3], Rossana Pavone [3], Linda Meneghello [4], Lidija Kitanovski [5], Lorna Zadravec Zaletel [6], Paolo Farace [7], Mino Zucchelli [8], Mirko Scagnet [9], Francesco Toni [10], Roberto Righetto [7], Marco Cianchetti [7], Arcangelo Prete [2], Daniela Greto [11], Silvia Cammelli [12,13], Alessio Giuseppe Morganti [12,13] and Barbara Rombi [7,*]

cancers
2022

POPULATION

- 43 MB (26 HR, 14 SR, 3 ex-infant)
- Histology: 31 classic, 3 desmoplastic, 7 large cell/anaplastic, 1 extensive nodularity, 1 NOS

- Median age at PT was 8.9 years; median follow-up is 26 months

- All received at least one surgical intervention before PT
- 13 (50%) HR and 5 (35.7%) SR received concurrent chemotherapy during PT
- 14 (32.6%) received an autologous HSCT before PT

- 27 HD (25 HR, 2 ex-infant) received CSI dose 36.0-39.6 GyRBE
- 16 SD (14 SR, 1 HR, 1 ex-infant) received CSI dose 23.4-25.2 GyRBE

ACUTE AND SUBACUTE TOXICITY

- No G4-G5 toxicities
- The most common (>30%) G1/G2, few cases G3
- 7 cases (16.3%) Herpes Zooster infection or reactivation
- 1 G3 of anorexia (5 months after PT)
- 1 G3 PRES (3.5 months after PT)

Type of Toxicity	Total Sample (n = 43)		High-Dose CSI (n = 27)		Standard-Dose CSI (n = 16)	
	G1–G2	G3	G1–G2	G3	G1–G2	G3
Radiation dermatitis	28 (65.1%)	1 (2.3%)	17 (63.0%)	1 (3.7%)	11 (68.8%)	-
Pharyngeal mucositis	22 (51.2%)	2 (4.7%)	15 (55.6%)	1 (3.7%)	7 (43.8%)	1 (6.3%)
Nausea/Vomiting	18 (41.9%)	1 (2.3%)	10 (37.0%)	-	8 (50.0%)	1 (6.3%)
Alopecia	17 * (94.4%)	-	3 (100%)	-	14 (93.3%)	-
Anorexia	16 (37.2%)	1 (2.3%)	8 (29.6%)	-	8 (50.0%)	1 (6.3%)
Fatigue	15 (34.9%)	-	8 (29.6%)	-	7 (43.8%)	-
Herpes Zoster	7 (16.3%)	-	4 (14.8%)		3 (18.8%)	
Upper airway infection	3 (7.0%)	-	2 (7.4%)	-	1 (6.3%)	-
Insomnia	2 (4.7%)	-	1 (3.7%)	-	1 (6.3%)	-
Fever	3 (7.0%)	-	1 (3.7%)	-	2 (12.5%)	-
Cough	1 (2.3%)	-	-	-	1 (6.3%)	-
Diarrhea	1 (2.3%)	-	-	-	1 (6.3%)	-
Myalgia	1 (2.3%)	-	-	-	1 (6.3%)	-
PRES	-	1 (2.3%)	-	1 (3.7%)	-	-
Cavernoma	1 (2.3%)	-	1 (3.7%)	-	-	-

PRELIMINARY DATA ON NEUROENDOCRINE DEFICIENCY

- 6/43 (14%) started replacement therapy after PT
- Median latency for start of replacement therapy was 9.5 months (min-max: 3- 25).
- 4 required monotherapy (3 thyroxine, 1 hydrocortisone).
- 2 receiving multidrug replacement therapy for panhypopituitarism (25 and 5 months after PT).
- 1 had PT boost on a pituitary metastasis (54 GyRBE); 5 received cumulative median dose in the pituitary/hypothalamic region of 41.24 GyRBE.

SIMILAR RESULTS REPORTED IN OTHER STUDIES
(VATNER, JCO 2018)

PRELIMINARY DATA ON OTOTOXICITY

- 7(16.3%) hearing impairment

(5 bilateral, 2 monolateral*) Grading: 1 G1, 3 G2, 3 G3
(G3-G4 16% by Yock et al, Lancet 2016)

- Median latency of hearing loss 9 months after PT (min-max: 2-37 months)
- All patients received platin-based chemotherapy (4 before radiation PT)
- Mean dose R cochlea 36 GyRBE (min-max: 23-53 GyRBE, L cochlea 34.6 GyRBE (min-max: 26-42 GyRBE)

Patient	CSI/TB dose (GyRBE)	Grade	Laterality	Cochlear D_{mean} (GyRBE)		Previous Chemotherapy
				Right	Left	
1	23.4/30.6	G1	Bilateral	35	28	No
2	36.0/18.0	G2	Bilateral	37	37	Yes
3	36.0/18.0	G2	Bilateral	37	42	Yes
4	23.4/30.6	G2	Bilateral	23	26	No
5	36.0/18.0	G3	Right	53	36	Yes
6	23.4/30.6	G3	Bilateral	32	31	No
7	23.4/30.6	G3	Right	35	42	Yes

Dmean: mean dose.

*Both patients with monolateral impairment had a first-degree relative with hearing loss and one of them is also affected by Gorlin syndrome

PRELIMINARY DATA ON LATE TOXICITIES

- 1 G4 of CMV encephalitis 6 months after PT resulted in permanent bilateral amaurosis, despite treatment with ganciclovir.
- 1 G1 stroke 21 months after PT that presented with short-lasting aphasia.
- 1 G2 intracranial bleeding 24 months after PT in the pituitary metastasis treated by 54 GyRBE

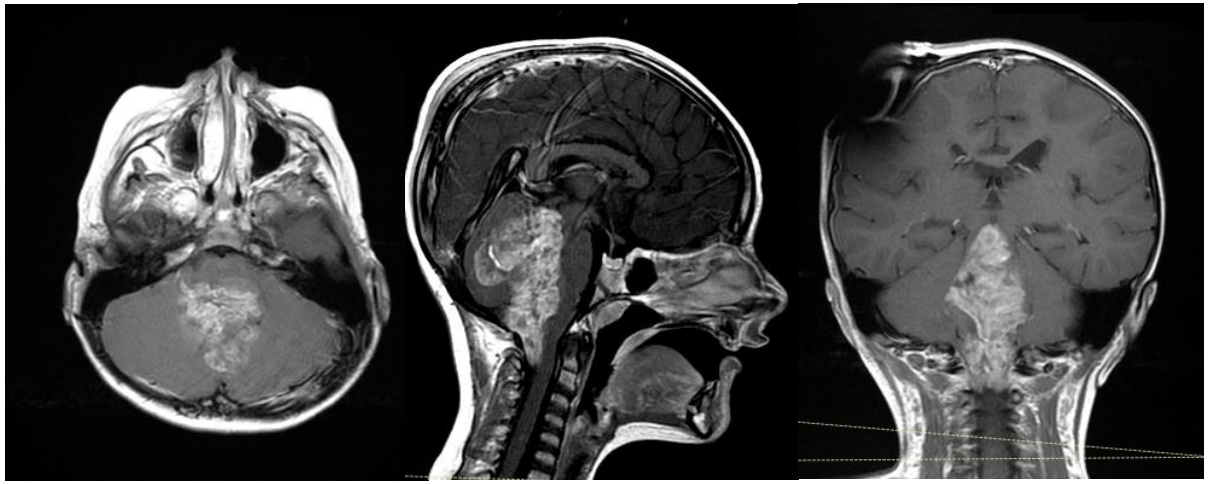
Toxicity	High-Dose CSI (n = 27)		Standard-Dose CSI (n = 16)	
	No. of Cases (%)	Grade	No. of Cases (%)	Grade
Cavernoma	8 (29.6%)	G1	1 (6.3%)	G1
	1 (3.7%)	G2	-	-
Intracranial bleeding	1 (3.7%)	G2	-	-
Loss of visual acuity	-	-	2 (12.5%)	G1
Osteoporosis	1 (3.7%)	G2		
CMV Encephalitis	1 (3.7%)	G4	-	-
Stroke	1 (3.7%)	G1	-	-
RBC Transfusion	1 (3.7%)	G3	-	-
VII CN Paralysis	-	-	1 (6.3%)	G1
Chronic headache	-	-	1 (6.3%)	G1

PRELIMINARY DATA ON DISEASE CONTROL AND SURVIVAL

- Median follow-up 26 months [2 – 67]
- 41/43 patients are alive
- Disease control: 20 CR, 3 SD, 3 PD
- Disease progression happened at 12, 15 and 23 months after PT
- 2 HR died for disease progression, 19 and 34 months after PT
- All 3 ex-infant MB CR and alive

CLINICAL CASE - 5

Fourth ventricle Anaplastic Ependymoma, group A, GTR, M0

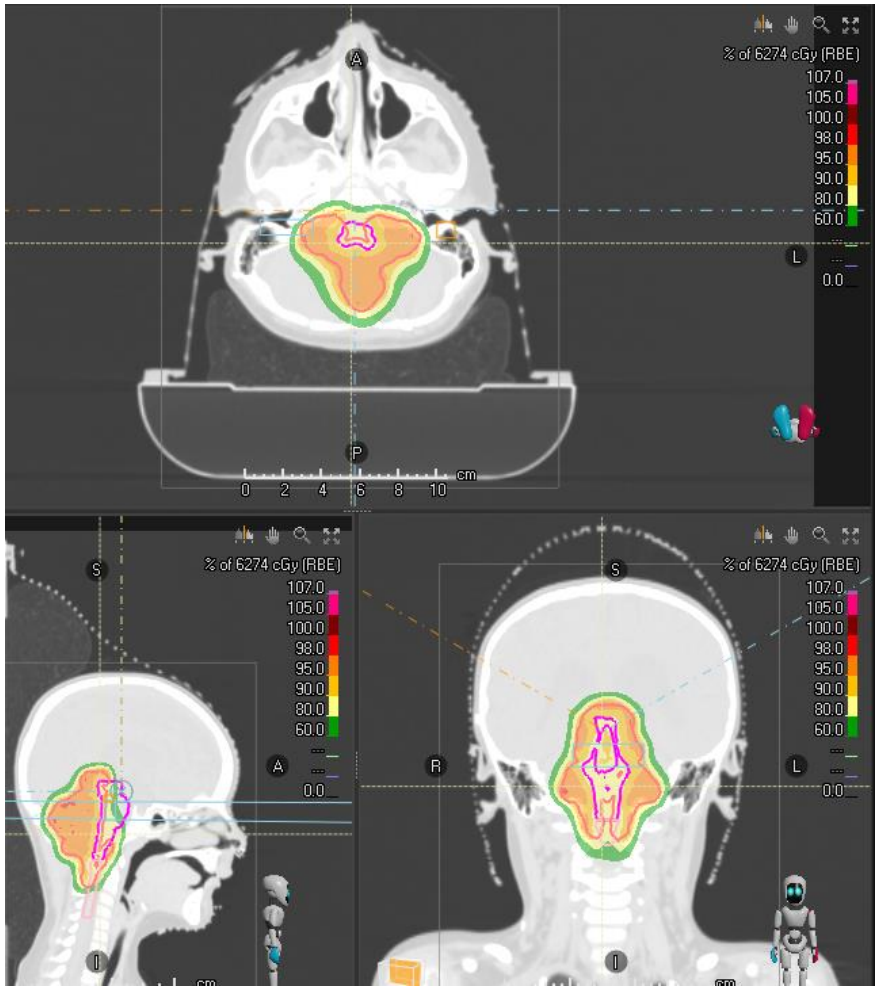


PBS, SFO tecnnique, tumor bed area treated at 59.4 Gy RBE in 33 fractions (1.8 Gy RBE daily).

Both cochleas and hypocampi partially spared (tolerance dose)

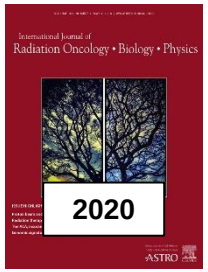
Acute side effects

Mild nausea and persisting buzzing in both ears, improvements in gait and balance



Proton Therapy for Pediatric Ependymoma: Mature Results From a Bicentric Study

Daniel J. Indelicato, MD,* Myrsini Ioakeim-Ioannidou, MD,† Julie A. Bradley, MD,* Raymond B. Mailhot-Vega, MD, MPH,* Christopher G. Morris, MS,* Nancy J. Tarbell, MD,† Torunn Yock, MD,† and Shannon M. MacDonald, MD†



386 consecutive children with nonmetastatic grade 2-3 intracranial ependymoma treated with proton therapy (PBS) at the University of Florida (UF) or the Massachusetts General Hospital (MGH)

The median prescribed radiation dose was 55.8 GyRBE (range, 50.4-59.4 GyRBE) across all patients and 54 GyRBE (range, 50.4-59.4 GyRBE) in children <3 years old

Dose constraints taken from NCI workshop, 2018.

Median follow-up was 5.0 years (range, 0.4-16.7 years)

DISEASE CONTROL OUTCOMES

- 5-yrs LC rate → 79% (CI 74.4% - 83.3%)
- 5-yrs PFS rate→ 68.4% (CI 63.3% - 73.1%)
- 5-yrs OS rate → 84.7% (CI 80.2% - 88.4%)

TOXICITY OUCOMES

- BRAINSTEM INJURY
  - Symptomatic (grade >2) brain stem injury → 4.0%
  - Grade >3 toxicity → 1%
  - Fatal grade 5 toxicity → 0.5%

Of the patients who developed brain stem toxicity, 86% were <5 years old.

- SECOND MALIGNANCY

5 patients (1.3%) developed second tumors at a median of 8 years after treatment (range, 4-14 years).

- NEUROENDOCRINE EFFECTS

45 patients (11.7%) developed hormone deficiency after radiation, typically of GH

- OTOTOXICITY

21 patients (5.4%) developed new hearing loss requiring an aid, including 3 children (0.7%) who required bilateral hearing aids.

TAKE HOME MESSAGE (1)

Consider PT:

- for curative pediatric patients: the longer the survivorship, better is the therapeutic ratio of PT
- for dose escalation
- for decreasing the likelihood of radiation induced-toxicity
- Open discussion for selected cases (i.e. retreatment, moving target)

TAKE HOME MESSAGE (2)

Suggestions:

- Multidisciplinary collaboration helps to discover potential beneficial cases and keep the right timing of PT
- After PT and during FU phase consider to share results (i.e. tumor control, temporary and permanent side effects)

Thank you to all Greek Colleagues

Ambassador of Greece Eleni Sourani to our proton Center on April 2024

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