HITRI plus
Heavy Ion Therapy Research Integration

Hadron therapy state-of-the art in pediatric oncology-clinical aspects

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SABINA VENNARINI

Radiologist-Paediatric Radiation Oncologist
Head of Paediatric Radiation Unit
IRCCS Fondazione Istituto dei Tumori di Milano
Milan-Italy

Senior Consultant for Paediatric Patient
National Center for Oncological Hadrontherapy
Pavia-Italy

sabina.vennarini@istitutotumori.mi.it

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

Background

- The role of paediatric radiotherapy in the treatment of paediatric tumours

- Paediatric Proton therapy (PT) and its applications in the treatment of paediatric tumours

- Presentation of clinical cases treated with Hadron Therapy

How has survival changed in the treatment of paediatric cancers?

- **Survival in Pediatric Oncology has increased, the survival rate is approximately 80%**

Improvements in survival rates of childhood cancer over the last 50 years have resulted in a growing number of long-term survivors. Current estimates indicate that nearly 400,000 survivors currently are living in the United States.

- *Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012. Bethesda, MD: National Cancer Institute; 2015.*
- *Phillips SM, Padgett LS, Leisenring WM, et al. Survivors of childhood cancer in the United States: prevalence and burden of morbidity. Cancer Epidemiol Biomarkers Prev. 2015;24:653-663.*

- **Quality of life and late effects of therapy represent a greater field of interest**

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Approach to combined Multimodal Therapeutic treatments according to precise Clinical National and International Protocols

Radiotherapy: integral part of Onc. Ped. treatment

Consolidated role upon the local control of the disease

SIOP Europe
the European Society for Paediatric Oncology

CHILDREN'S ONCOLOGY GROUP

AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

Significant Risk increase due to appearance of adverse tardive events

- RT plays a fundamental role in the development of late toxicity due to the involvement of tissue and/or organs included or in proximity to the irradiation area

- **Onset of Organ Disfunctions:**
  - Chronic pathologies
  - Secondary neoplasia either benign or malignant
  - Psycho-social sequences

Chronic Health Conditions in Adult Survivors of Childhood Cancer

Kevin C. Oeffinger, M.D., Ann C. Mertens, Ph.D., Charles A. Sklar, M.D., Toana Kawashima, M.S., Melissa M. Hudson, M.D., Anna T. Meadows, M.D., Debra L. Friedman, M.D., Neyssa Marina, M.D., Wendy Hobbie, C.P.N.P., Nina S. Kadan-Lottick, M.D., Cindy L. Schwartz, M.D., Wendy Leisenring, Sc.D., and Leslie L. Robison, Ph.D., for the Childhood Cancer Survivor Study*

N Engl J Med 2006;355:1572-82.

Photons in the treatment of pediatric tumours

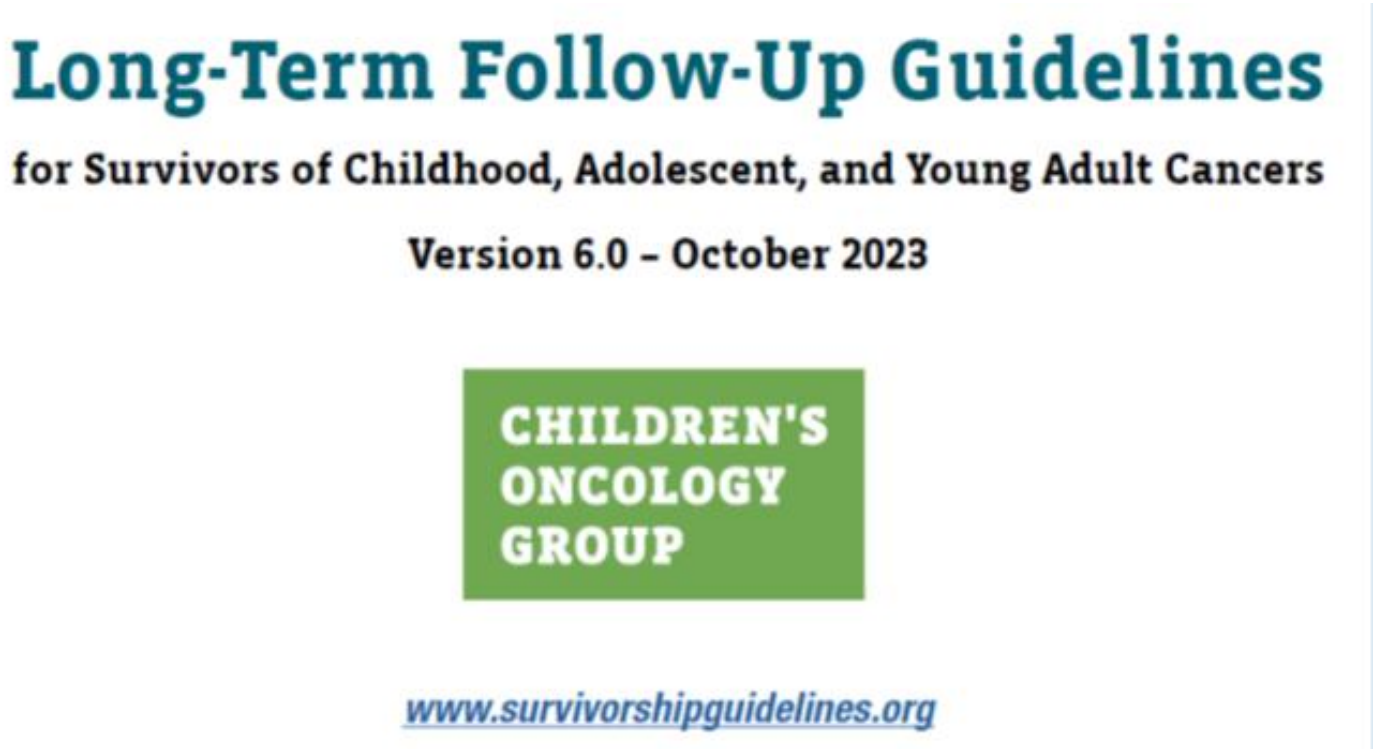
The Price of Survival:

- Neurocognitive and Neurological deficits
- Neuroendocrine deficits
- Growth alterations, Musculoskeletal Deficit
- Permanent alopecia
- Hearing-Visual loss
- Cardio-Vascular deficits
- Respiratory deficits
- Secondary tumours

Depending on:
- Age at Diagnosis
- Tumor
- Dose and Volume of RT
- Surgeries
- Chemotherapy etc.

→**The impact of these sequelae not only affect quality of life but may also influence overall survival**

- In order to monitor for late toxicity, it is important to manage and follow childhood survivors as a multidisciplinary team. To meet critical needs, the Children's Oncology Group (COG) created



Quality of Life and late effects:
are concepts of primary importance in paediatrics!

Where to go?

What are the End points to reach for modern pediatric radiotherapy?

1◦ Step CRUCIAL:
do not lose sight of resources or efforts already attained

2◦ Step CRUCIAL:

centralization of high specialization principles

create a connection with the major Paediatric Oncology Centres

Also in pediatric radio therapy

Diversification of techniques:

- <u>High precision X-RT techniques</u>

&

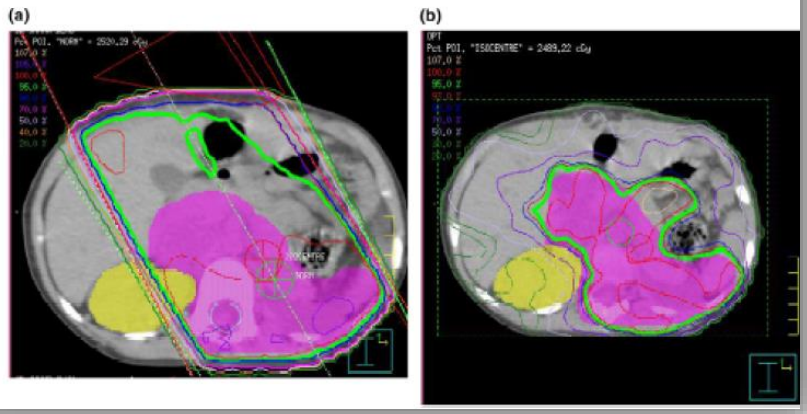
- <u>Particles Therapy</u>



- clinical experience
- optimal knowledge of diagnostic - technology

- Improved Conformality : especially for irregular targets and concavities
- Better Sparing of OARs near the targets

Conventional XRT - IMRT



IGRT

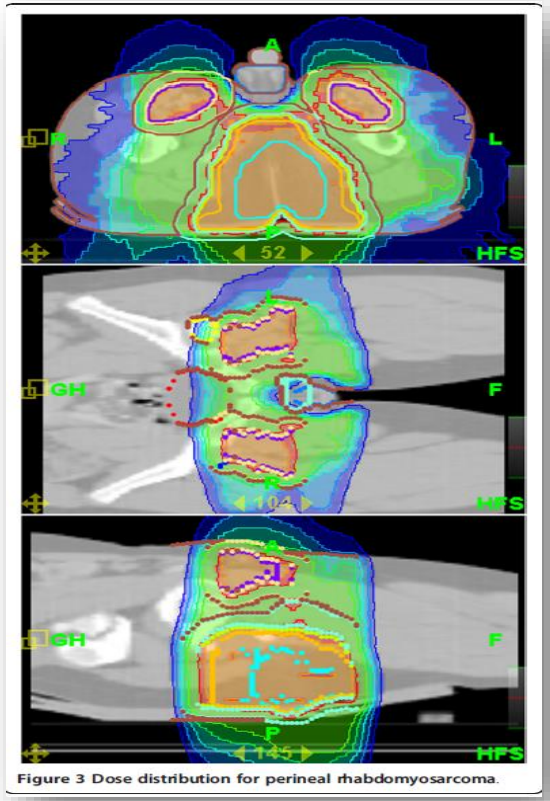


Figure 3 Dose distribution for perineal rhabdomyosarcoma.

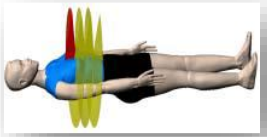
F. Saran / European Journal of Cancer 40 (2004) 2091–2105

Mesbah et al. Radiation Oncology 2011, 6:102
http://www.ro-journal.com/content/6/1/102

RADIATION ONCOLOGY

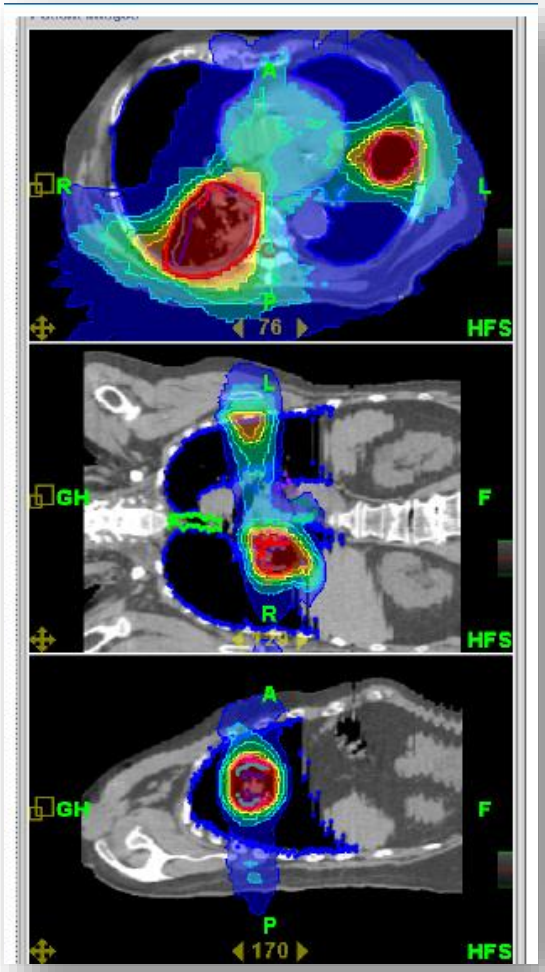
RESEARCH Open Access

Helical tomotherapy in the treatment of pediatric malignancies: a preliminary report of feasibility and acute toxicity



Conclusion: HT in pediatric population is feasible and safe treatment modality. It is characterized by an acceptable level of acute toxicity that we have seen in this highly selected pediatric patient cohort with clinical features of poor prognosis and/or aggressive therapy needed. Despite of a dosimetrical advantage of HT technique, an exhaustive analysis of long-term follow-up data is needed to assess late toxicity, especially in this potentially sensitive to radiation population.

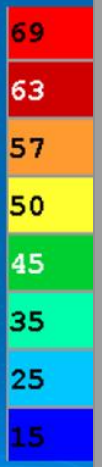
The Price :
Multiple fields & “Dose bath”



Dose Spread?

Due to

1. multiple fields
2. repeated imaging



Late Toxicity

Risk of Second Cancers

Chung, C. et al..Comparative Analysis of Second Malignancy
, Risk in Patients Treated with Proton Therapy versus Conventional Photon Therapy. IJROBP S8 (2008)

Risk of second cancers after photon and proton radiotherapy: a review of the data.

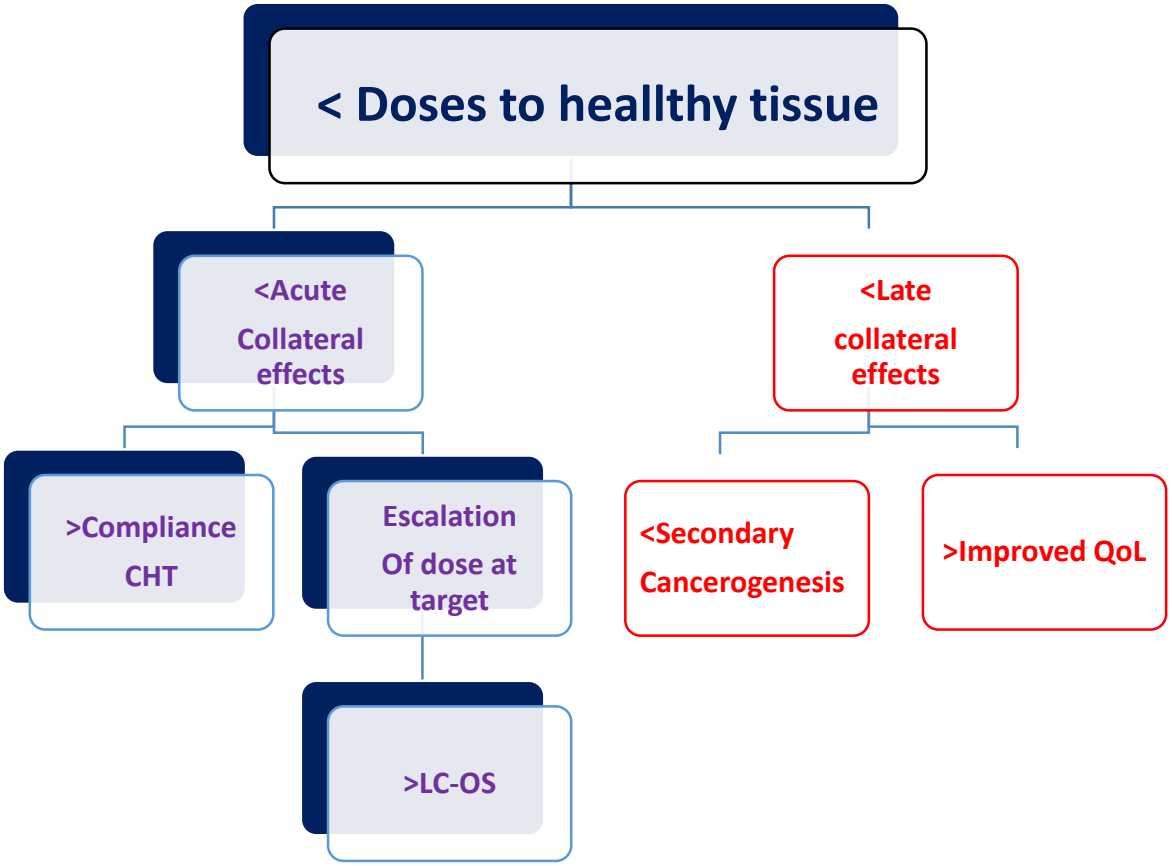
Yock TI, Caruso PA. Health Phys. 2012 Nov;103(5):577-85.

SUMMARY AND CONCLUSION

To summarize, second cancer formation after radiotherapy is an unfortunate consequence of the curative treatment. The burden of risk is greater in the pediatric cancer survivor population than in the adult populations, and this risk is related to a patient's age at treatment. In addition, risk is also proportional to dose and volume of normal tissue irradiated. Therefore, whatever techniques can be use to minimize nontarget tissue irradiation, the better the second cancer risk profile (i.e., the lower the estimated risk of developing a second cancer later in life). Proton therapy seems to mitigate this risk compared with photon therapy, with a scanned beam approach somewhat superior to the passively scattered protons. However, the advantages of scanned proton beam are not yet realized in most clinical facilities due to large spot size (i.e., lateral and longitudinal size and the minimum achievable range of the proton beam). Future technological improvements are likely to make scanning beam treatments more feasible.

Therefore…Protons

…such physical properties of PT potentially translate clinically



International Journal of Radiation Oncology biology • physics

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COMMENTARY

Consensus Report From the Stockholm Pediatric Proton Therapy Conference

Daniel J. Indelicato, MD,* Thomas Merchant, DO, PhD,† Normand Laperriere, MD, FRCPC,‡ Yasmin Lassen, MD, PhD,§ Sabina Vennarini, MD,‖ Suzanne Wolden, MD, FACR,¶ William Hartsell, MD,# Mark Pankuch, PhD,# Petter Brandal, MD, PhD,** Chi-Ching K. Law, MD,†† Roger Taylor, MD,‡‡ Siddhartha Laskar, MD,§§ Mehmet Fatih Okcu, MD, MPH,‖‖ Eric Bouffet, MD,¶¶ Henry Mandeville, MBChB, MRCP, FRCR, MD,## Thomas Björk-Eriksson, MD, PhD,*** Kristina Nilsson, MD, PhD,*** Hakan Nyström, PhD,*** Louis Sandy Constine, MD,††† Michael Story, PhD,‡‡‡ Beate Timmermann, MD,§§§ Kenneth Roberts, MD,‖‖‖ and Rolf-Dieter Kortmann, MD¶¶¶

*University of Florida Health Proton Therapy Institute, Jacksonville, Florida; †St. Jude Children's Research Hospital, Memphis, Tennessee; ‡Princess Margaret Cancer Centre/University Health Network, Toronto, Ontario, Canada; §Aarhus University Hospital, Aarhus, Denmark; ‖Agenzia Provinciale per la Protonterapia, Trento, Italy; ¶Memorial Sloan-Kettering Cancer Center, New York, New York; #Northwestern Medicine Chicago Proton Center, Chicago, Illinois; **Oslo Universitetssykhus, Oslo, Norway; ††Queen Elizabeth Hospital, Hong Kong, China; ‡‡Swansea University South West Wales Cancer Centre, London, United Kingdom; §§Tata Memorial Hospital, Mumbai, India; ‖‖Texas Children's Hospital, Houston, Texas; ¶¶The Hospital for Sick Children, Toronto, Ontario, Canada; ##The Royal Marsden NHS Foundation Trust, London, United Kingdom; ***The Scandion Clinic, Uppsala, Sweden; †††University of Rochester Medical Center, Rochester, New York; ‡‡‡University of Texas Southwestern Medical Center, Dallas, Texas; §§§Westdeutsche Protonentherapiezentrum, Essen, Germany; ‖‖‖Yale University School of Medicine, New Haven, Connecticut; and ¶¶¶Universitätsklinikum Leipzig, Leipzig, Germany

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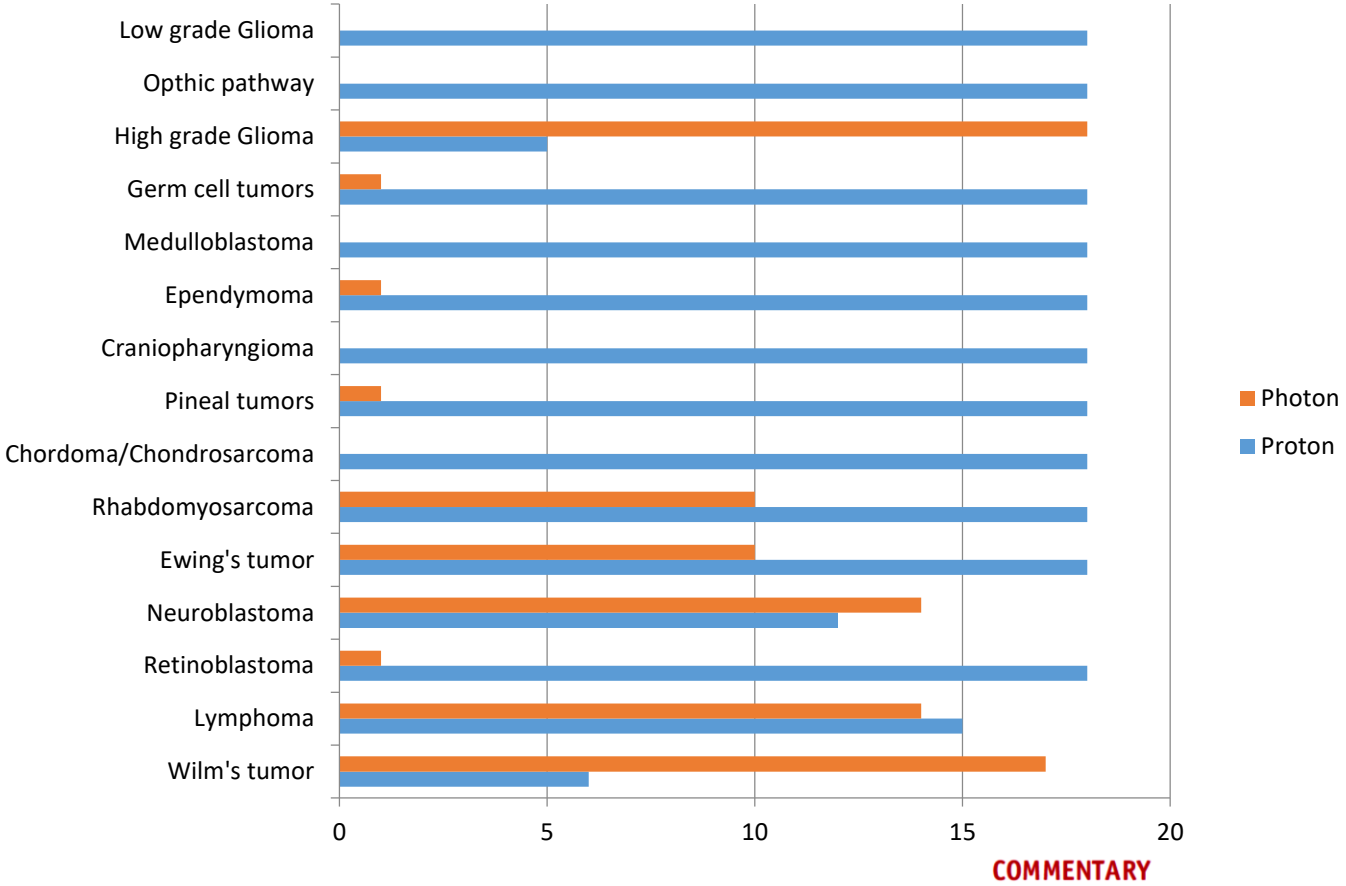

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Clinical indications for proton therapy

- **Tumours historically radio-resistant**

↓

Increase the % of survivors in the long term

- **Tumours that respond favourable to radiotherapy**

↓

Maintain favourable outcome and improve the quality of life

- **CSI:** → Complex site -large volumes; >Number of OAR
- **AGE:** → < Late Effects

Proton therapy for pediatric malignancies: Indications and challenges focusing on the oncological landscape. Vennarini S, et Al. Tumori. 2024 Oct.

INDICATIONS FOR PT

Consequently, PT is increasingly used worldwide:

- for all pediatric cancers
- with a high priority for very young children in curative scenarios

- **SNC Tumors**

Craniopharyngioma
Low-grade glioma
Optic pathway glioma
Germ cell tumors
Medulloblastoma
Ependymoma
ATRT

- **Skull Base Tumors**

Chordoma/chondrosarcoma

- **Soft tissue and Bone Tumors**

Rhabdomyosarcoma/NRSTS
Ewing's tumor/Osteosarcoma

- **Retinoblastoma**
- **Neuroblastoma**
- **Lymphoma**

What is Happening in the Pediatric Oncology Community?

pediatric proton foundation

ORIGINAL RESEARCH article

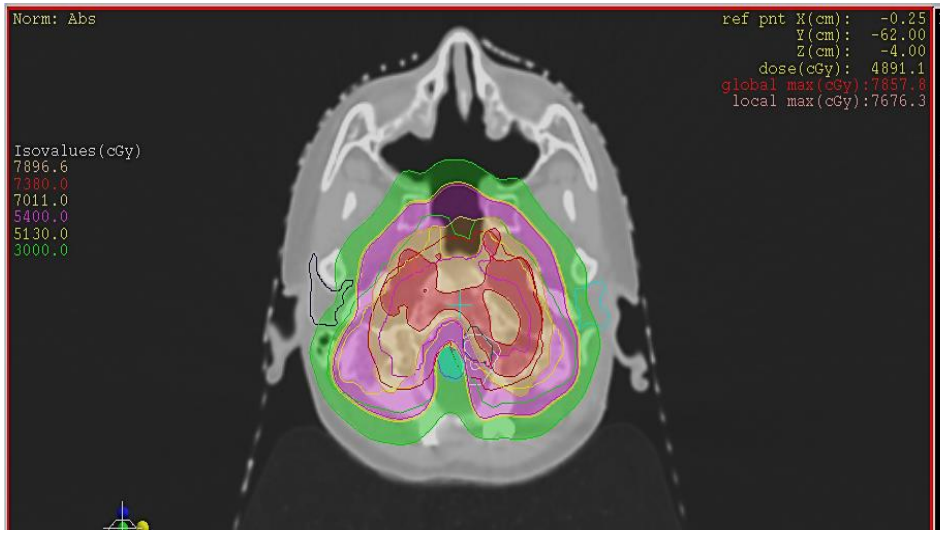
Front. Oncol., 24 May 2018 | https://doi.org/10.3389/fonc.2018.00165

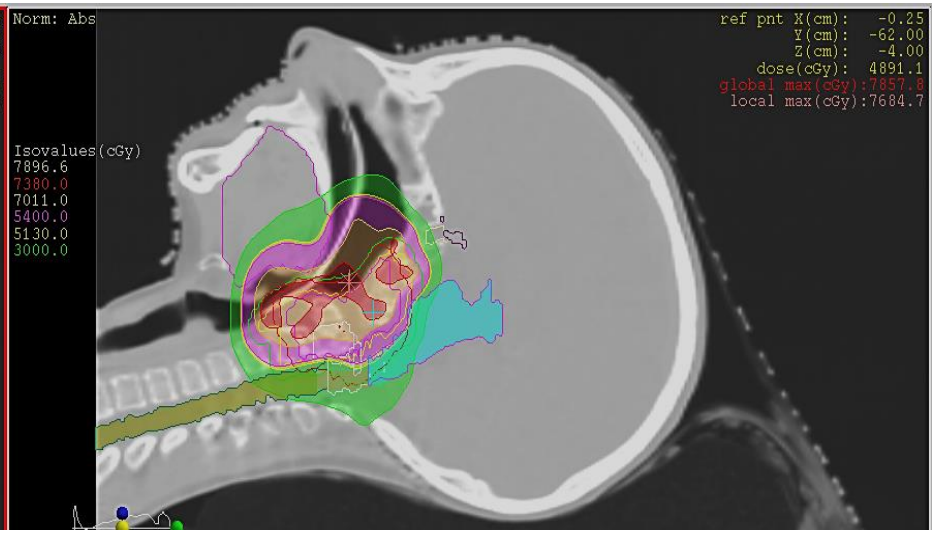
An Update From the Pediatric Proton Consortium Registry

A total of **1,854** patients have consented and enrolled in the PPCR from October 2012 until September 2017.

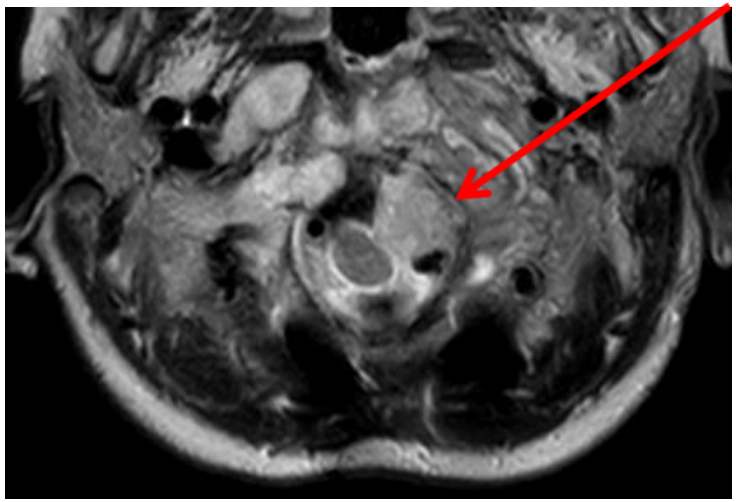
PPCR
Pediatric Proton Consortium Registry

10 year-old girl with Skull Base Chordoma





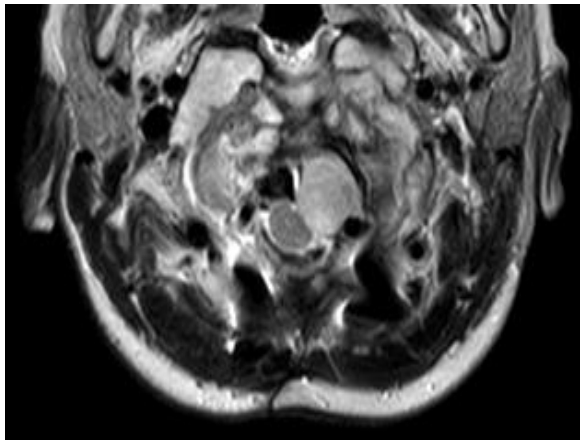
- Residual disease bilateral macroscopic to the epistropheus tooth
- Presence of a left para-bulbus spinal cord nodule with shift compression of the cord.



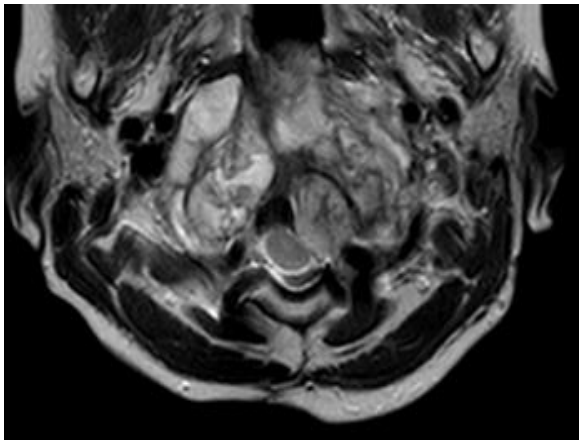
Imaging 1st session PT
04/06/2015-MR AxT2

Monitoring MRI (T2w)

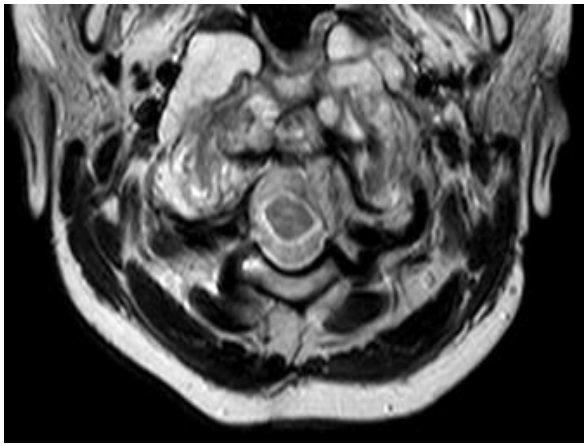
Magnetic Resonance Imaging during Proton Therapy Irradiation Allows for the Early Response Assessment of Pediatric Chordoma. Vennarini S.,et All.Diagnostics (Basel). 2021 Jun



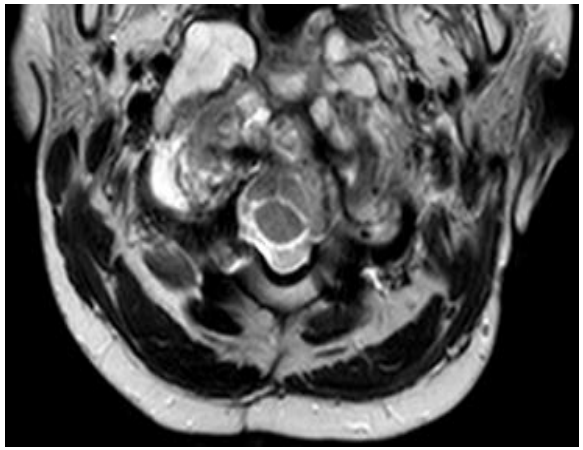
04/06 (1fx)
0 Gy RBE



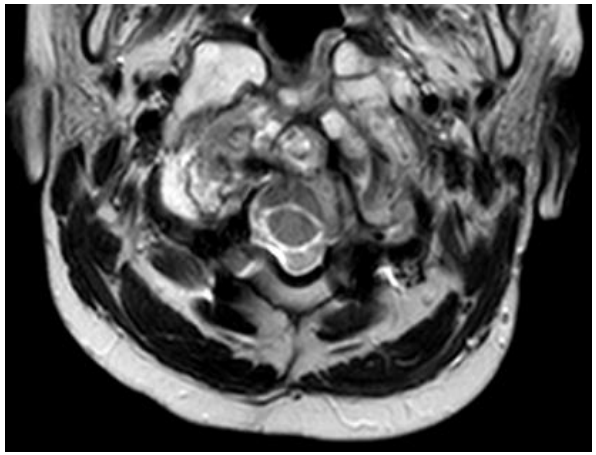
30/06 (18fx)
32,4 Gy RBE



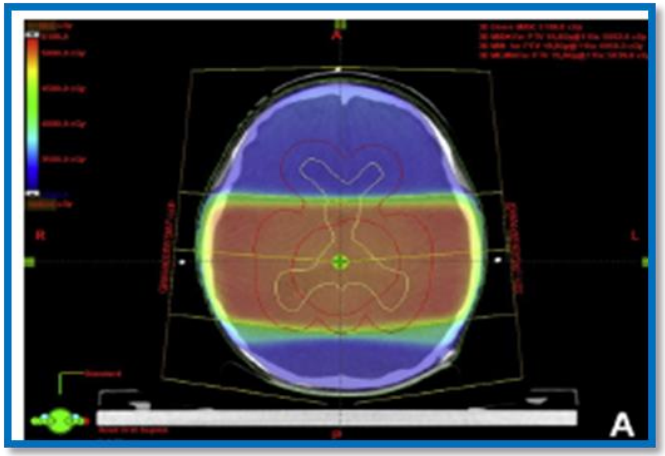
16/07 (30fx)
54GyRBE

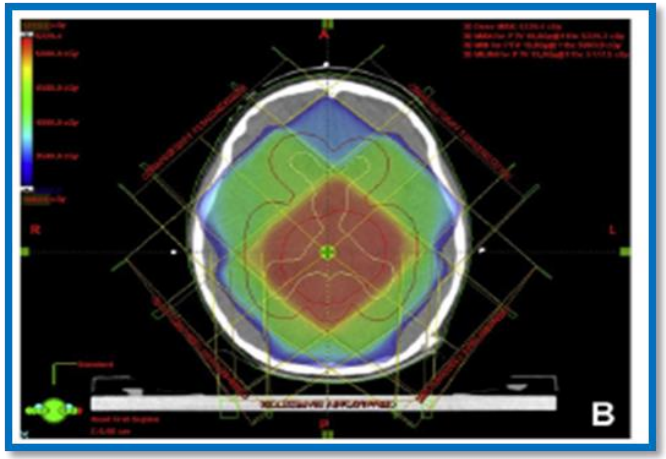


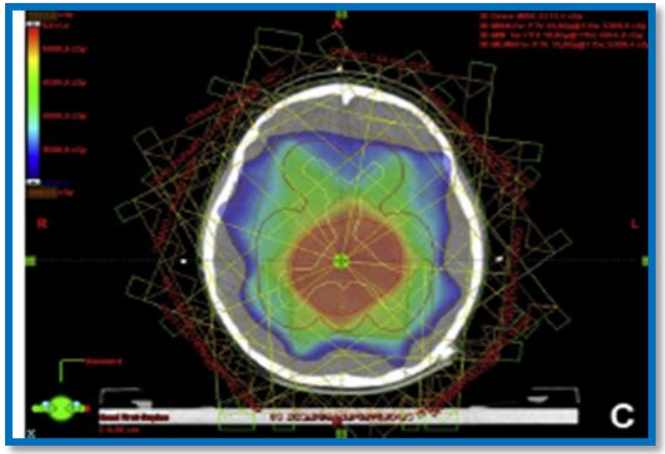
24/07 (36fx)
64,8GyRBE

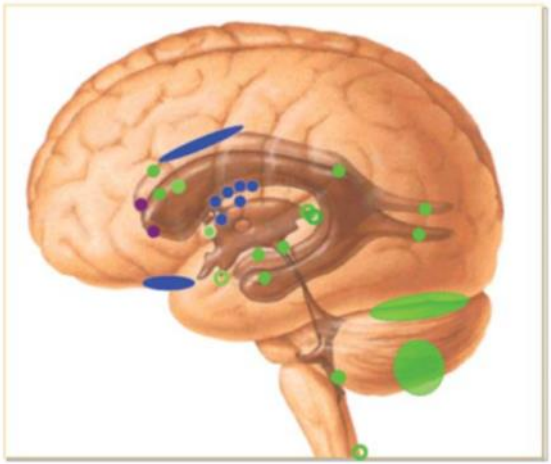


31/07 (41fx)
73,8Gy RBE



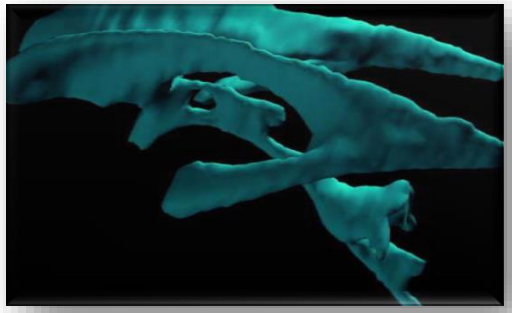


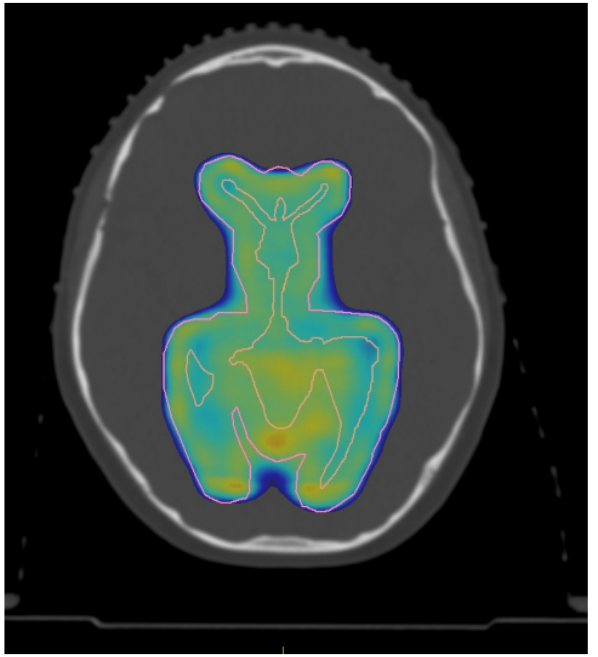




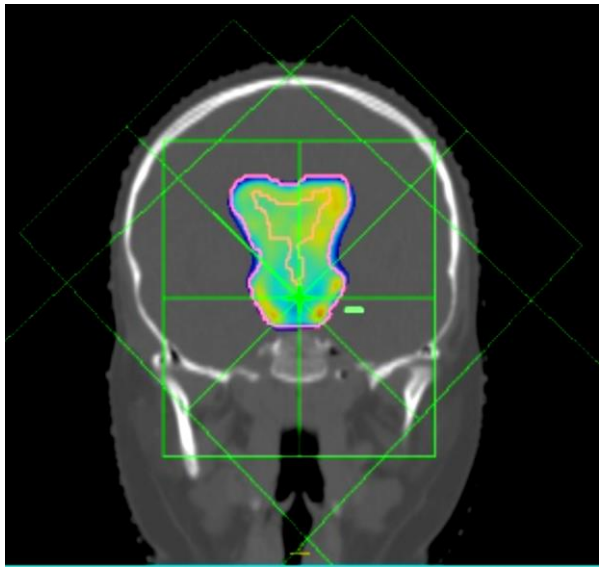
Source: Alapetite et al. SFOP experience (2010)
S.Vennarini-SIOP 2015

Whole Ventricular Irradiation

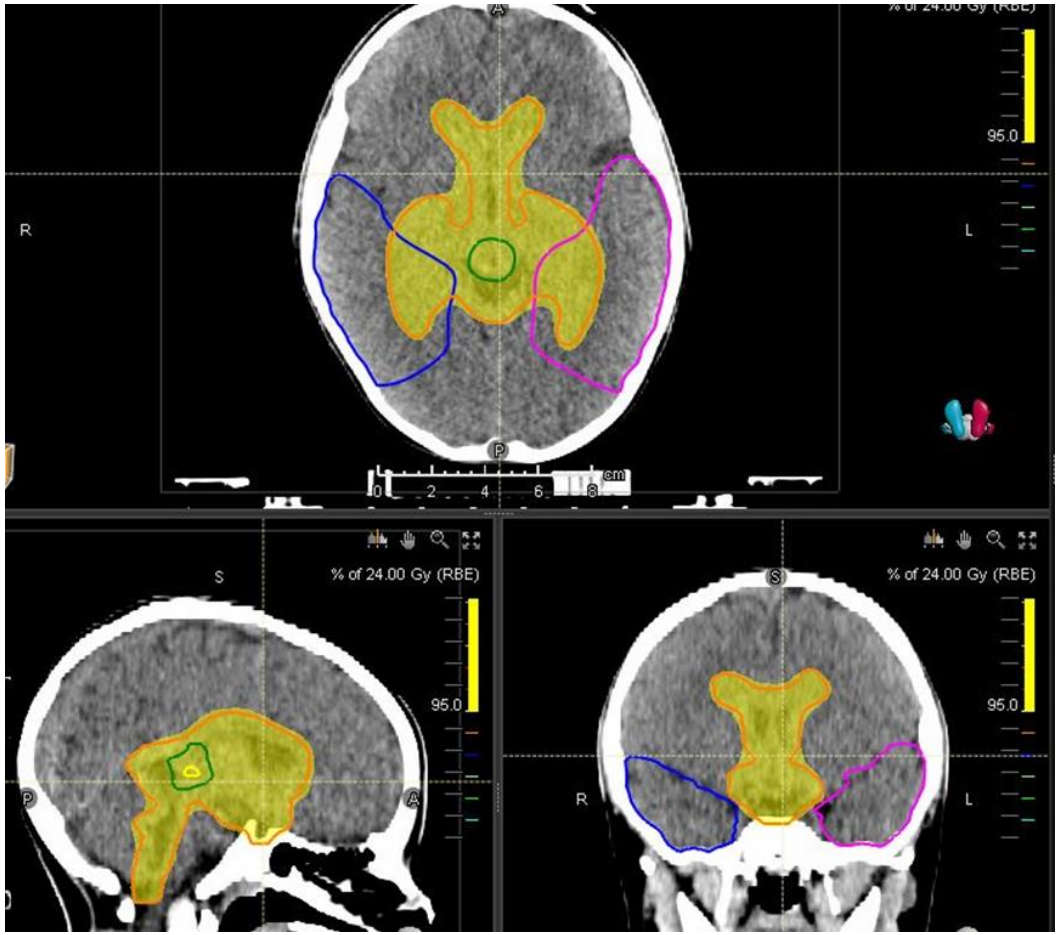


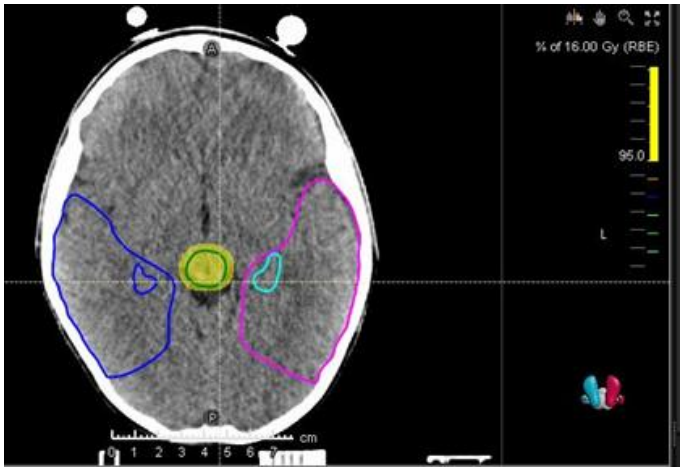


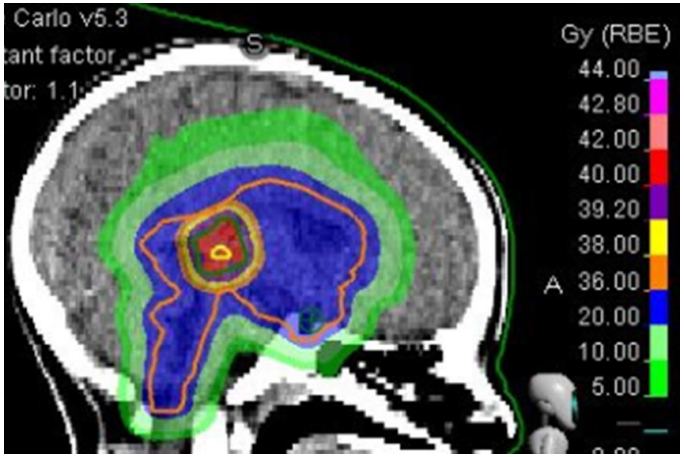
Protoni-PBS



6 year-old boy with CNS-Germinoma







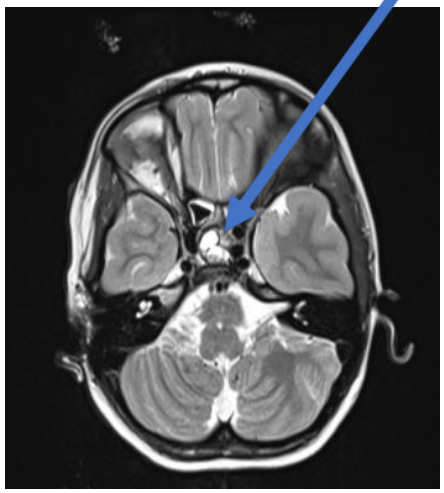
Unraveling the impact of upfront chemotherapy and proton beam therapy on treatment outcome and follow-up in central nervous system germ cell tumors: a single center experience. Del Baldo G.,Vennarini S., et Al . Front Oncol. 2023 Oct

- **It is located in the sellar-suprasellar region!**

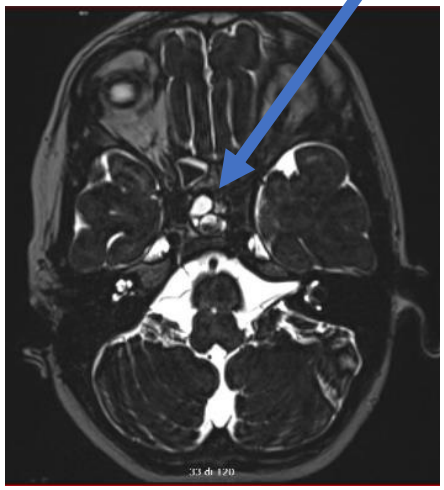
- → surrounded by **>critical OARs**, such as:
  - Optic pathway
  - Hypothalamic-pituitary axis structures
  - Vessels
  - Brainstem
  - Temporal lobes
  - Hippocampi

- Craniopharyngioma is composed of three components: ***cystic***, ***solid***, and ***calcific***.

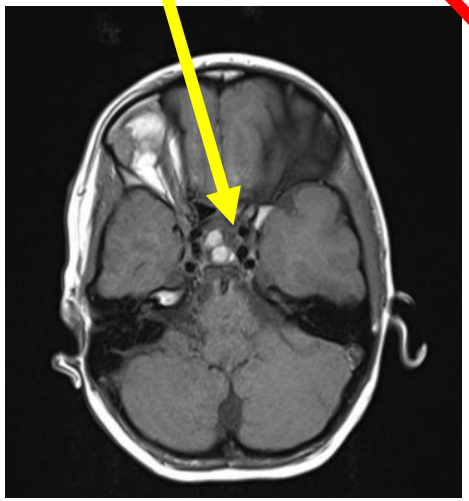
Angio-MR Ax



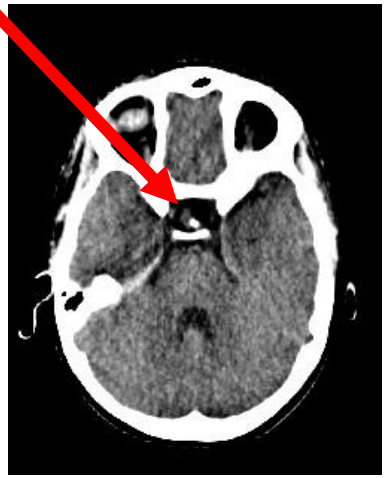
MR-AxT2



MR-AxCiss T2

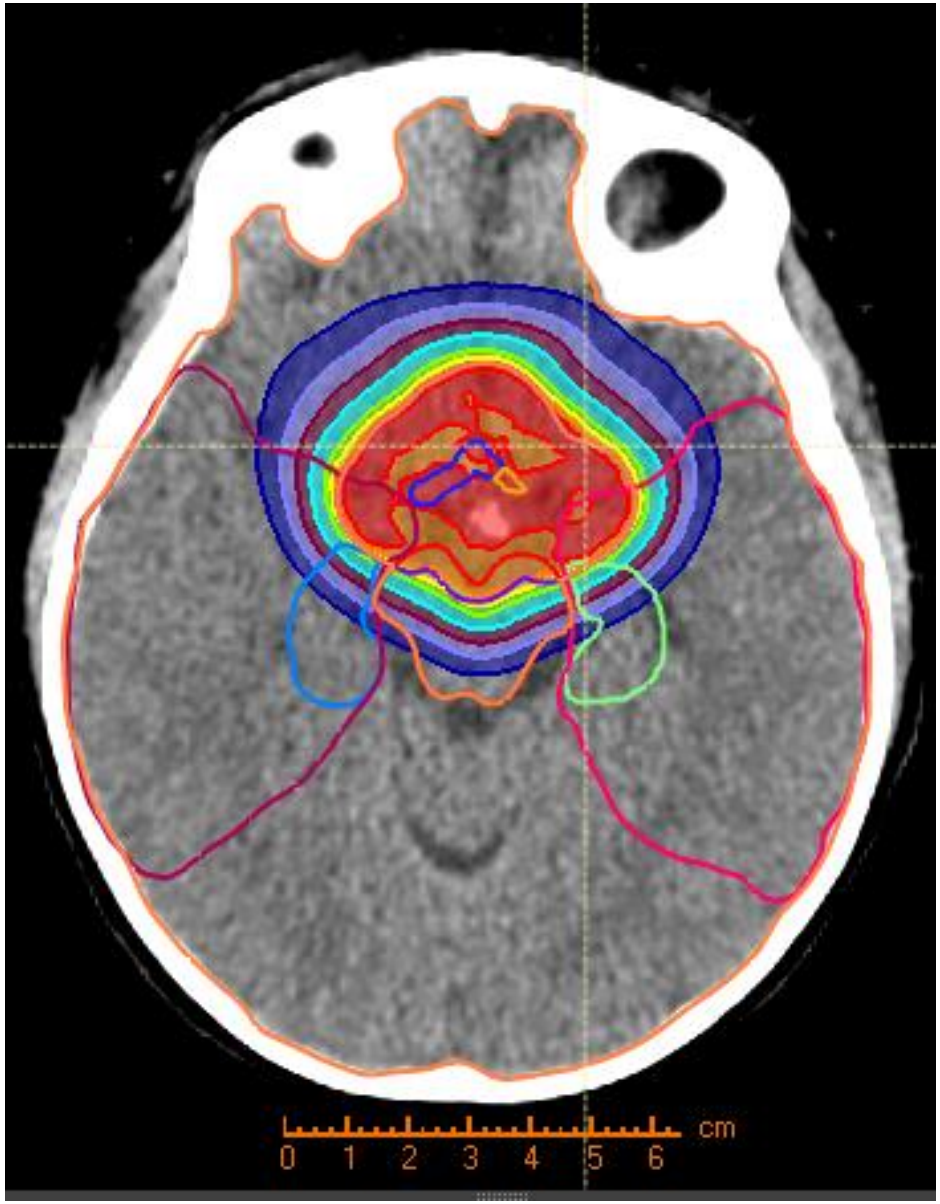


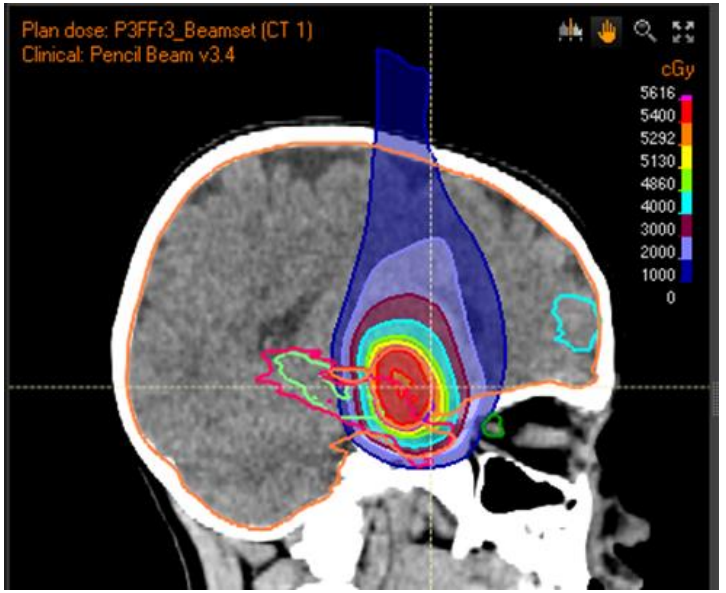
MR-Ax T1+CE

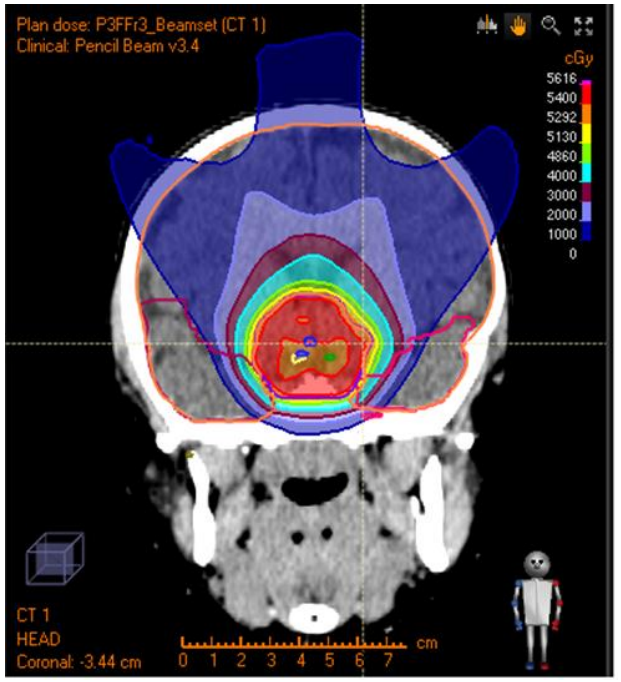


CT-Ax

5year-old girl with Craniopharyngioma and frontal congenital cavernoma

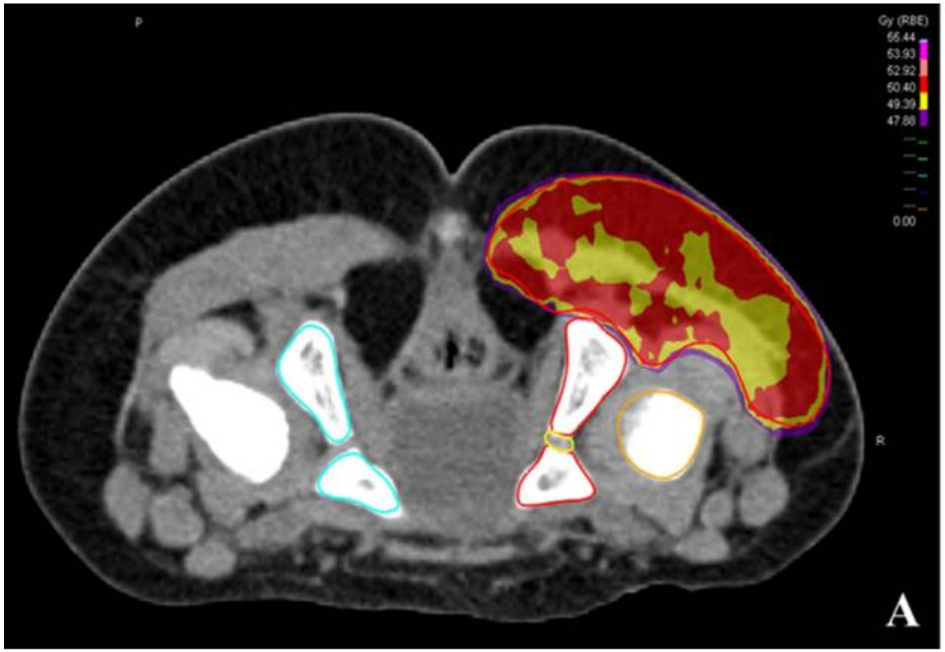


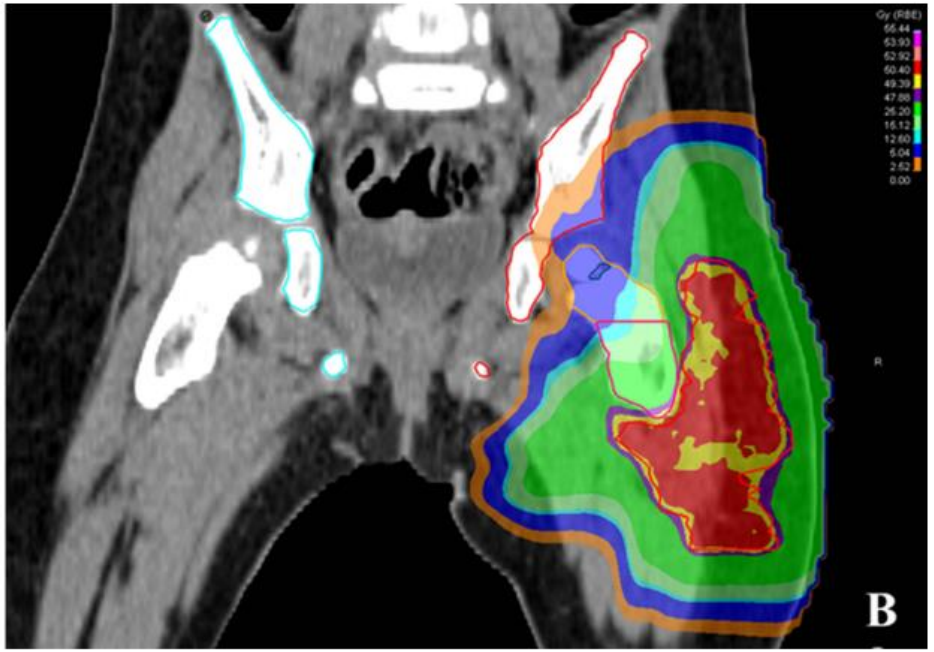




Multidisciplinary Management of Craniopharyngiomas in Children: A Single Center Experience. Del Baldo G., Vennarini S.,et All. Diagnostics (Basel). 2022 Nov

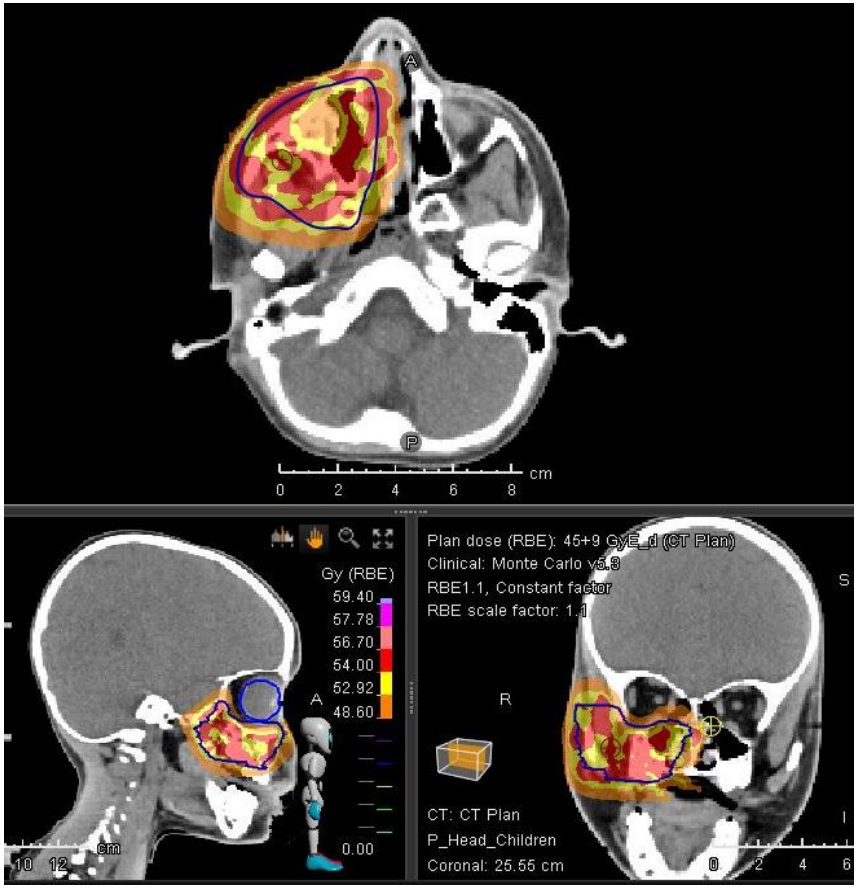
2-year-old girl with alveolar RMS of the right gluteus

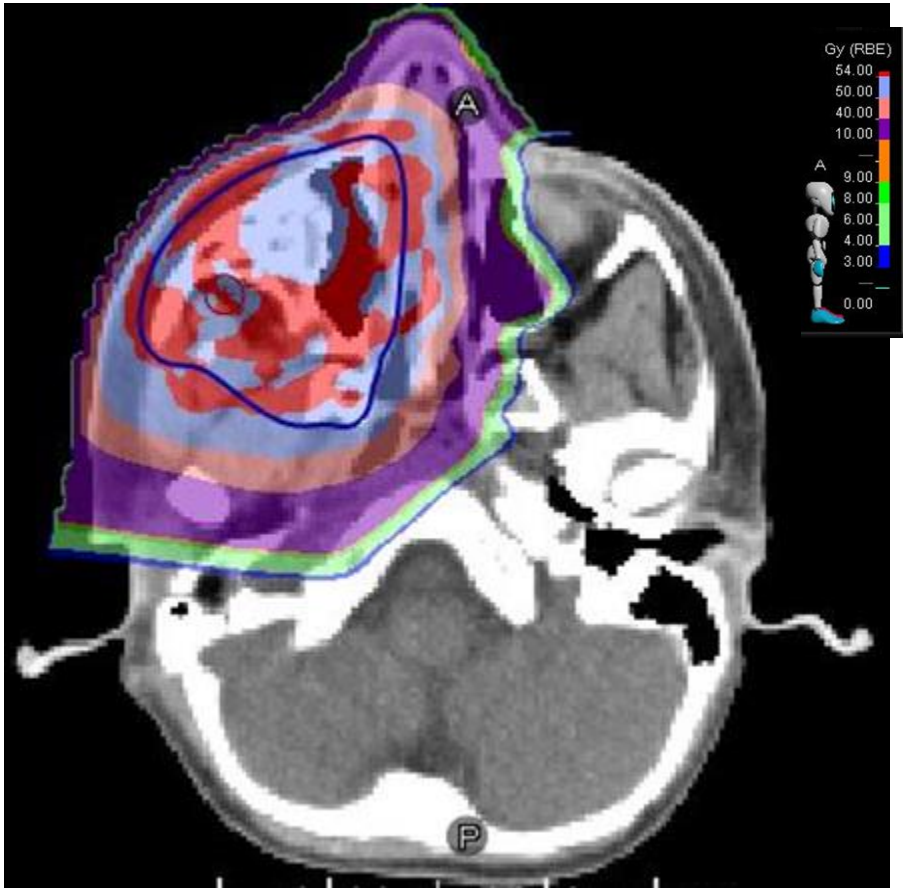




- *Proton Therapy in Non-Rhabdomyosarcoma Soft Tissue Sarcomas of Children and Adolescents. Vennarini S.,Cancers (Basel). 2024 Apr*
- *Clinical Insight on Proton Therapy for Paediatric Rhabdomyosarcoma. Vennarini S., et All.Cancer Manag Res. 2023 Oct*

4-year-old girl with PM-RMS





- ***Proton Therapy in Non-Rhabdomyosarcoma Soft Tissue Sarcomas of Children and Adolescents. Vennarini S.,Cancers (Basel). 2024 Apr***
- ***Clinical Insight on Proton Therapy for Paediatric Rhabdomyosarcoma. Vennarini S., et All.Cancer Manag Res. 2023 Oct***

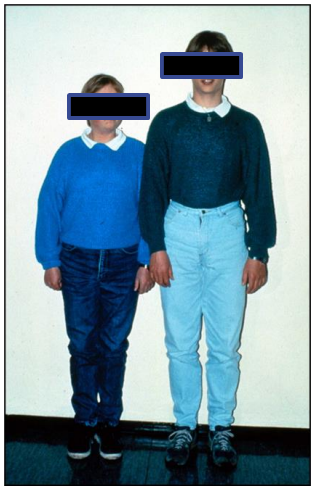
Reduce toxicity ⟷ Technique

SIOP Europe
the European Society for Paediatric Oncology

AN INTERNATIONAL PROSPECTIVE TRIAL ON HIGH-RISK MEDULLOBLASTOMA IN PATIENTS OLDER THAN 3 YEARS

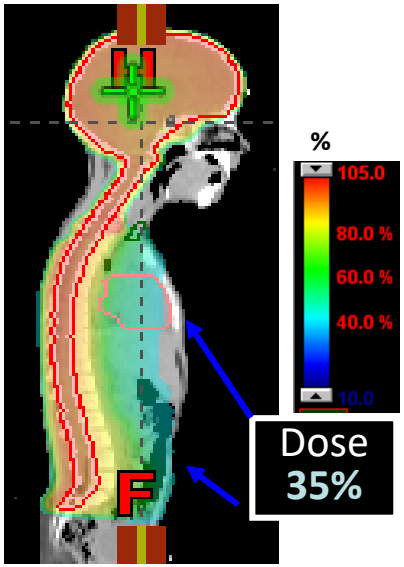
SIOP High-Risk Medulloblastoma

Protocol version 3.0
22 June 2023



Twin…after MBL

3DCRT



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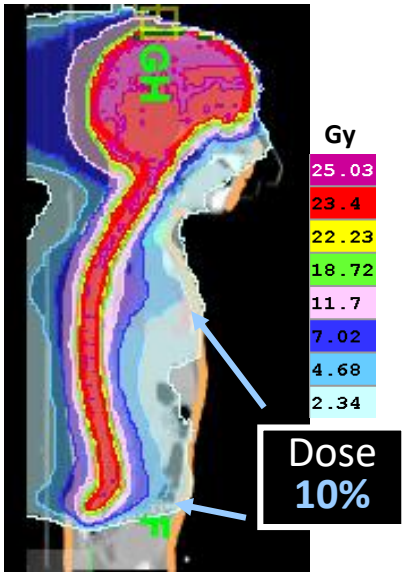

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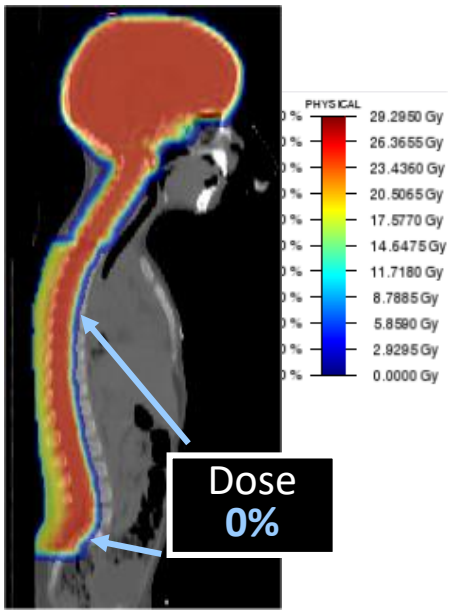

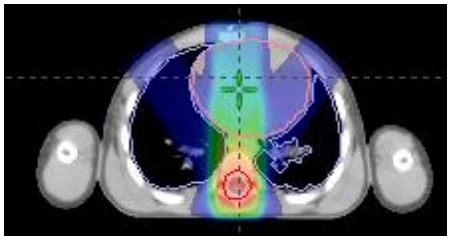

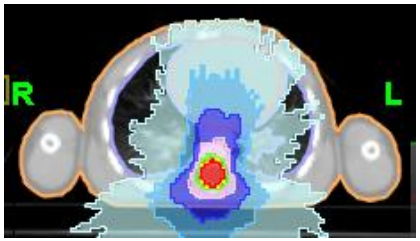

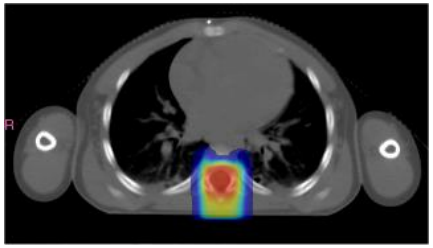

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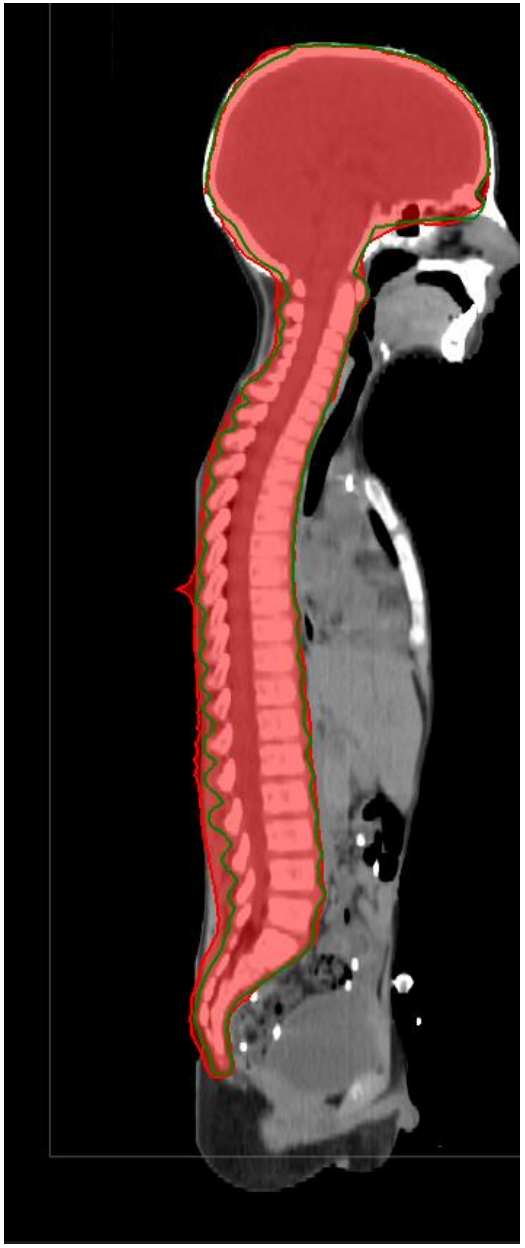

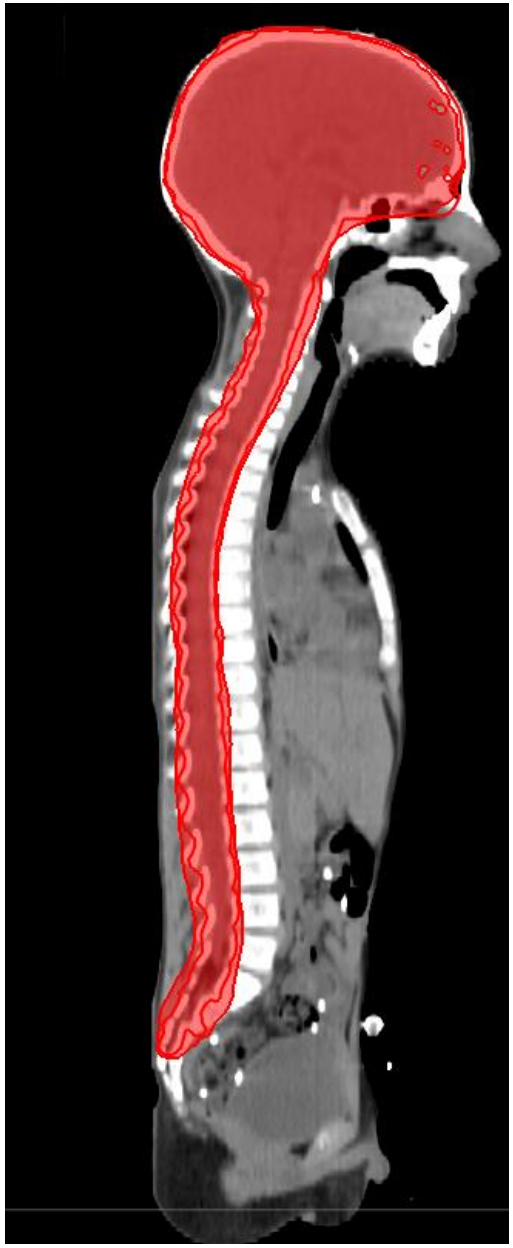

6 year-old boy with MBL

PT+Immunotherapy

PT+Radio-sensitivity multi-drug

Acute Hematological Toxicity during Cranio-Spinal Proton Therapy in Pediatric Brain Embryonal Tumors.
Vennarini S.,Cancers (Basel). 2022 Mar

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C.Diegoli -All Radiotherapists
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E.Domenegatti
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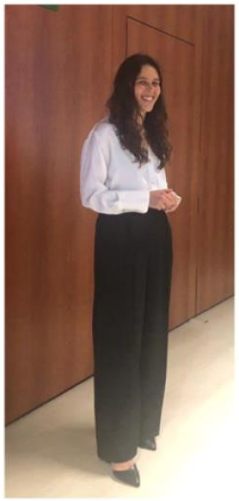

F.Colombo

HITRI
Heavy Ion Therapy Research Integration

“cure is not enough,”

Giulio D'Angio, MD

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