PARTICLE THERAPY EXPERIENCE ON PEDIATRIC PATIENTS

Project meeting and hadrontherapy workshop from innovation to implementation
24-25 MARCH 2025, PODGORICA

FRANCESCA COLOMBO, MD
Radiation oncologist
Fondazione CNAO, Italy

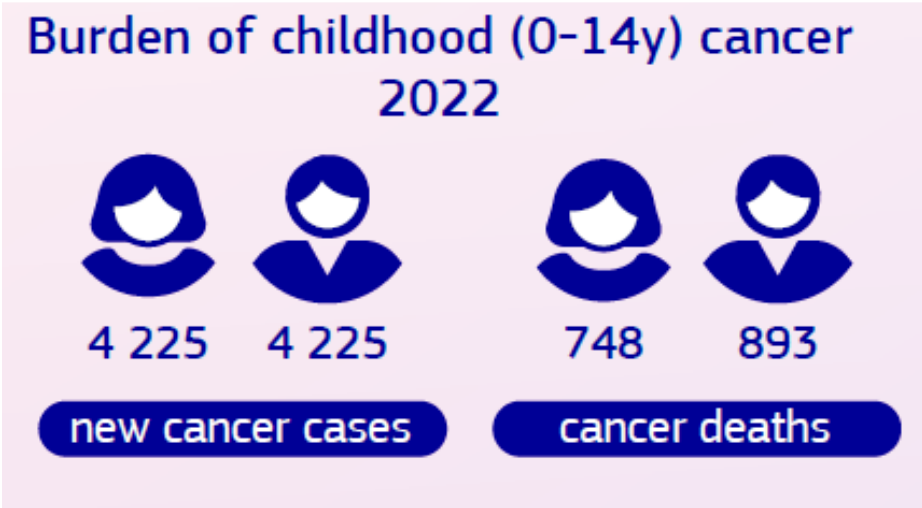
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

OVERVIEW

- Childhood cancer is a **rare disease**

- It is estimated that in 2022 in <u>Europe</u>:
  - > 9 thousand children aged 0 to 14 years were diagnosed with cancer
  - > 1.6 thousand died from cancer

  → approximately a quarter of all deaths in children are due to cancer



Eurostat - Being young in Europe today (2020)
ECIS - European Cancer Information System

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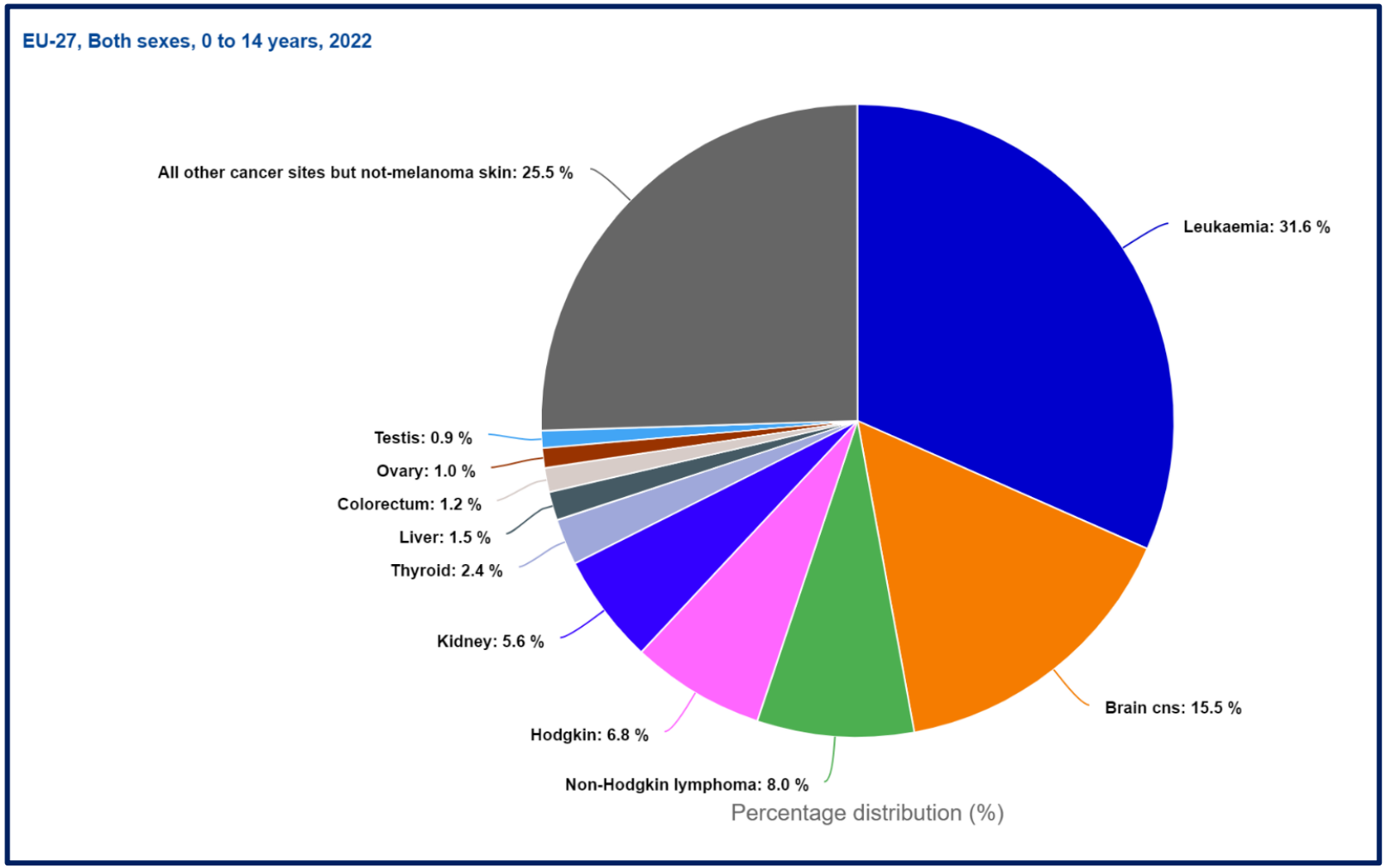

The most common cancer diagnoses among children between 0 to 14 years were:

- Leukaemias
- cancers of CNS
- lymphomas

But there are more than 60 different paediatric malignancies.

Source: ECIS - European Cancer Information System

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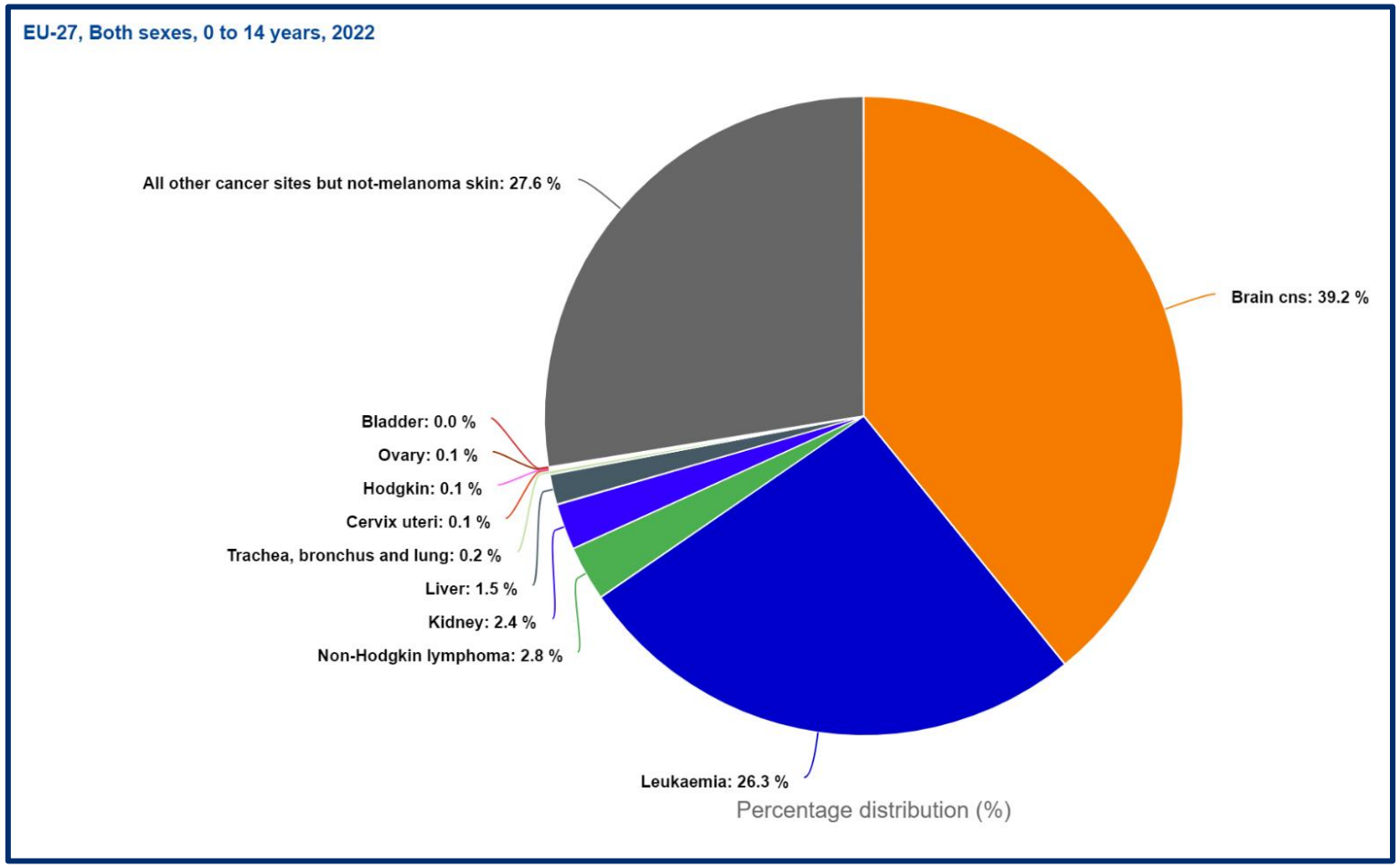

Nearly 40% of cancer deaths were due to CNS tumors.

Source: ECIS - European Cancer Information System

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- The 5-year survival rate is **81%,** an ⇧ from previous years.
  Cure rates range from 99% for retinoblastoma to 60% for CNS tumours.

- Increased survival rates lead to an increase in the number of long-term survivors

- + 500,000 childhood cancer survivors in Europe

➡ Greater interest in: **LATE TOXICITY** and **QoL**

LATE SIDE EFFECTS

- Neurological deficits
- *Neurocognitive decline*
- *Endocrinopathies*
- *Growth alterations*
- Hearing-Visual loss
- Vascular deficits
- Permanent alopecia
- Psycho-social issues
- Infertility
- Secondary tumours

→ The impact of late sequelae not only affects quality of life, but can also influence overall survival

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› Cancer. 2020 Aug 1;126(15):3560-3568. doi: 10.1002/cncr.32938. Epub 2020 May 19.

Second cancer risk after primary cancer treatment with three-dimensional conformal, intensity-modulated, or proton beam radiation therapy

Michael Xiang [1 2], Daniel T Chang [1], Erqi L Pollom [1 2]

TABLE 2. Overall Second Cancer Risk for Intensity-Modulated Radiation Relative to Three-Dimensional Conformal Radiation and Proton Beam Radiation Relative to Intensity-Modulated Radiation[a]

Abbreviations: 3DCRT, 3-dimensional conformal radiation, IMRT, intensity-modulated radiation; OR, odds ratio; PBRT, proton beam radiation; CI, confidence interval.
[a]Values were estimated using multivariable adjustment, matching, or both (with the same covariates used in Table 1).

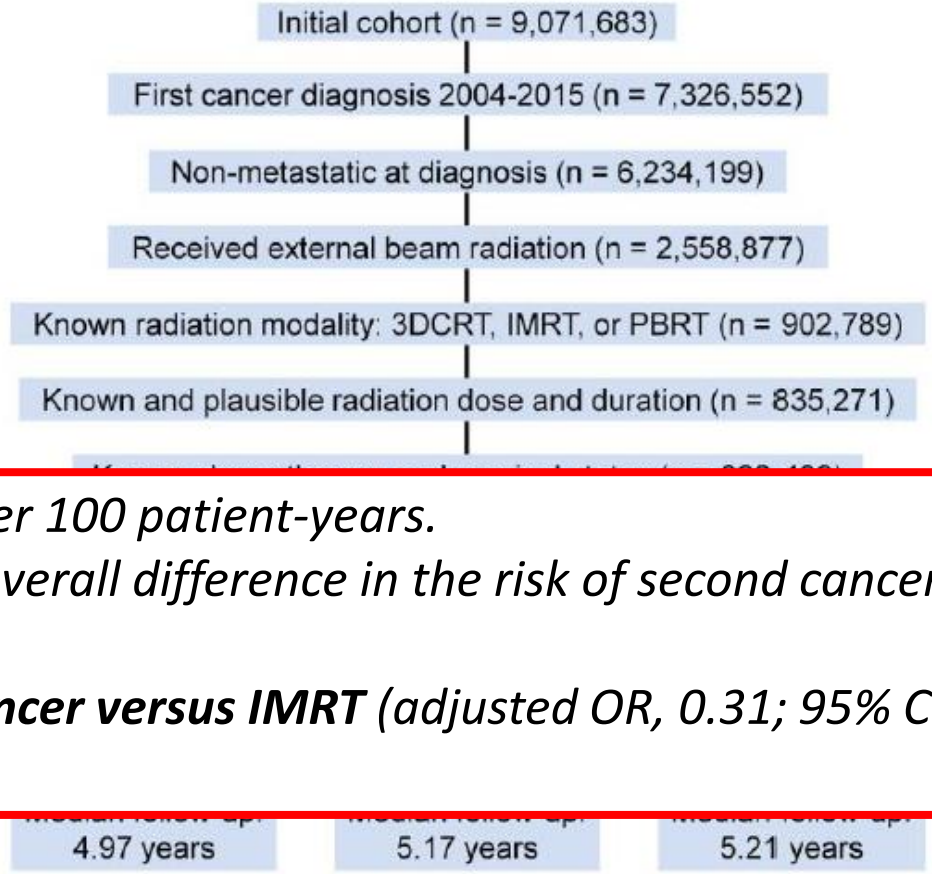

FIGURE 1. This is a Consolidated Standards for Reporting Trials (CONSORT)-style diagram for cohort identification. 3DCRT indicates 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBRT, proton beam radiation therapy.

Overall, the incidence of second cancer diagnosis was 1.55 per 100 patient-years.
In a comparison between IMRT versus 3DCRT, there was no overall difference in the risk of second cancer (adjusted odds ratio [OR], 1.00; 95% CI, 0.97-1.02; P = .75).
*By comparison, **PBRT had an overall lower risk of second cancer versus IMRT** (adjusted OR, 0.31; 95% CI, 0.26-0.36; P < .0001).*

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The Pediatric Proton and Photon Therapy Comparison Cohort: Study Design for a Multicenter Retrospective Cohort to Investigate Subsequent Cancers After Pediatric Radiation Therapy

Methods and Materials: We are developing a record-linkage cohort of 10,000 proton and 10,000 photon therapy patients treated from 2007 to 2022 in the United States and Canada for pediatric central nervous system tumors, sarcomas, Hodgkin lymphoma, or neuroblastoma, the pediatric tumors most frequently treated with protons. Exposure assessment will be based on state-of-the-art dosimetry facilitated by collection of electronic radiation records for all eligible patients. Subsequent cancers and mortality will be ascertained by linkage to state and provincial cancer registries in the United States and Canada, respectively. The primary analysis will examine subsequent cancer risk after proton therapy compared with photon therapy, adjusting for potential confounders and accounting for competing risks.

A. Berrington de Gonzalez et al, 2023

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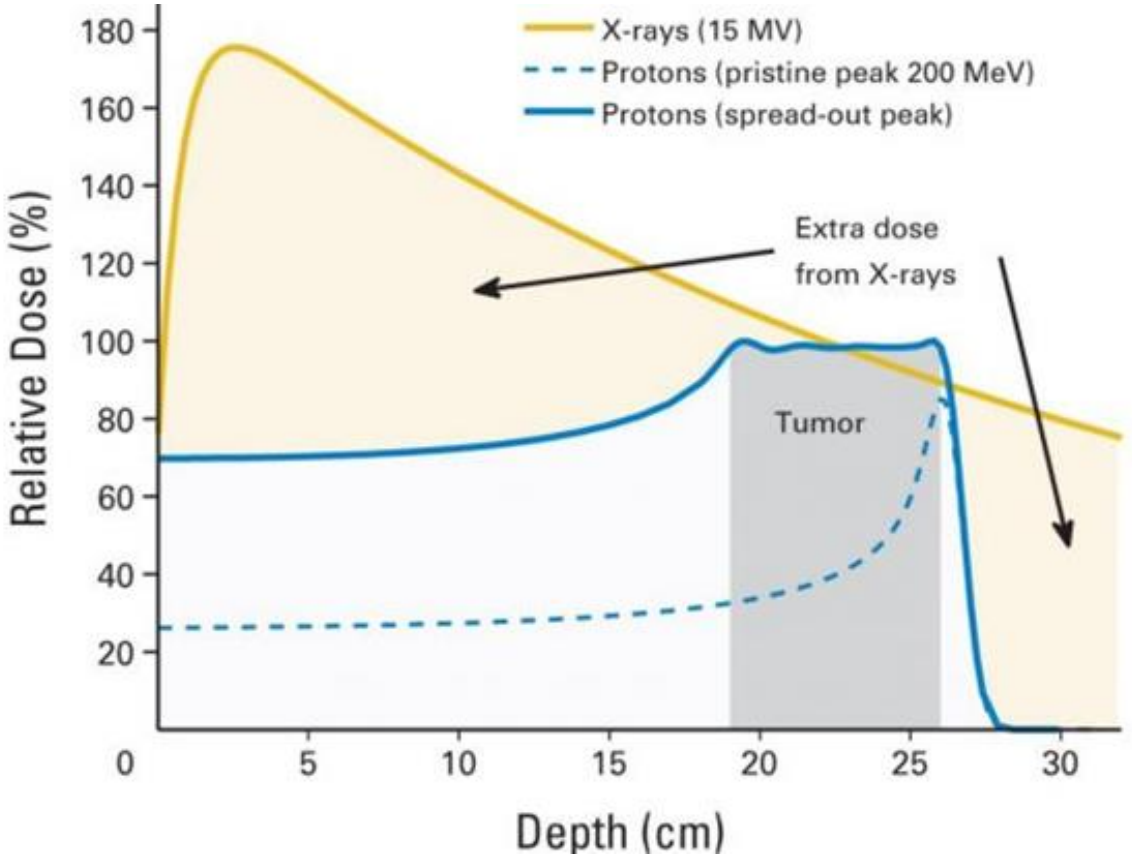
PROTON THERAPY: dosimetric properties and physical selectivity



Dose to OARs

- Potential optimization of local tumor probability by increasing dose to the tumor without increasing the dose to OAR.
- No changes in dose prescription but reduction of the likelihood of radiation induced toxicity.
- Dose escalation to the tumor.

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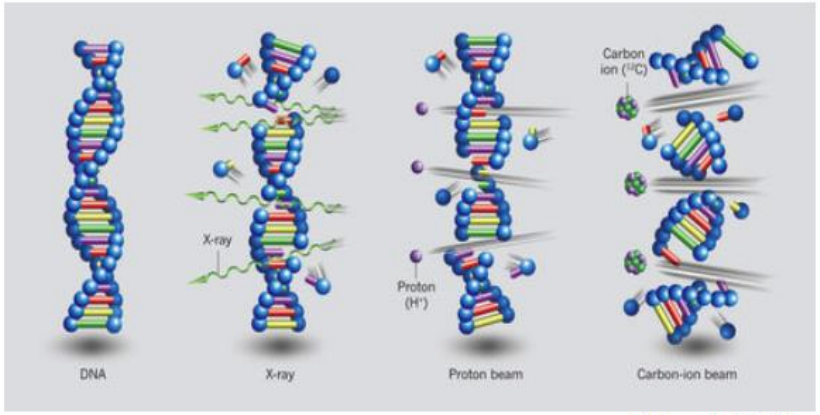
CARBON ION THERAPY: 3Rs (Rare), Radioresistant, Recurrent

1.

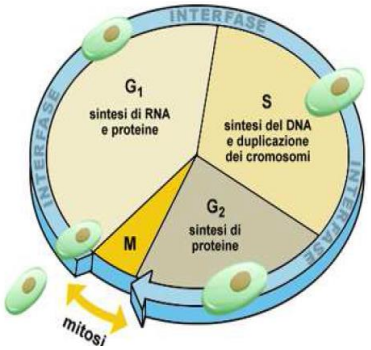


Nature, April 2014

- C-ions: **High Linear Energy Transfer** (LET) radiation
- X-rays and protons cause similar DNA damage → similar tumor killing → Repair
- C-ions cause complex DNA damage → greater tumor killing → **No Repair**

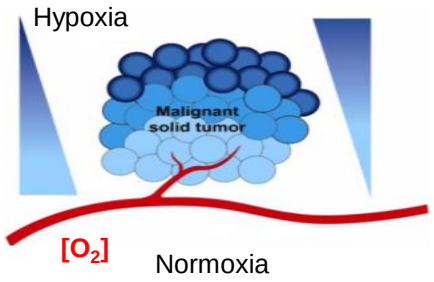
High radiobiological effectiveness (RBE) → > Effective for radioresistant tumors

2.



Low cell-cycle dependence → increased lethality in the target because cells in radioresistant phase (S) are sensitized

3.



Low OER → Effective against hypoxic tumor cells

Tinganelli , Cancers, 2020

BIOLOGICAL EFFECTS OF PARTICLE THERAPY

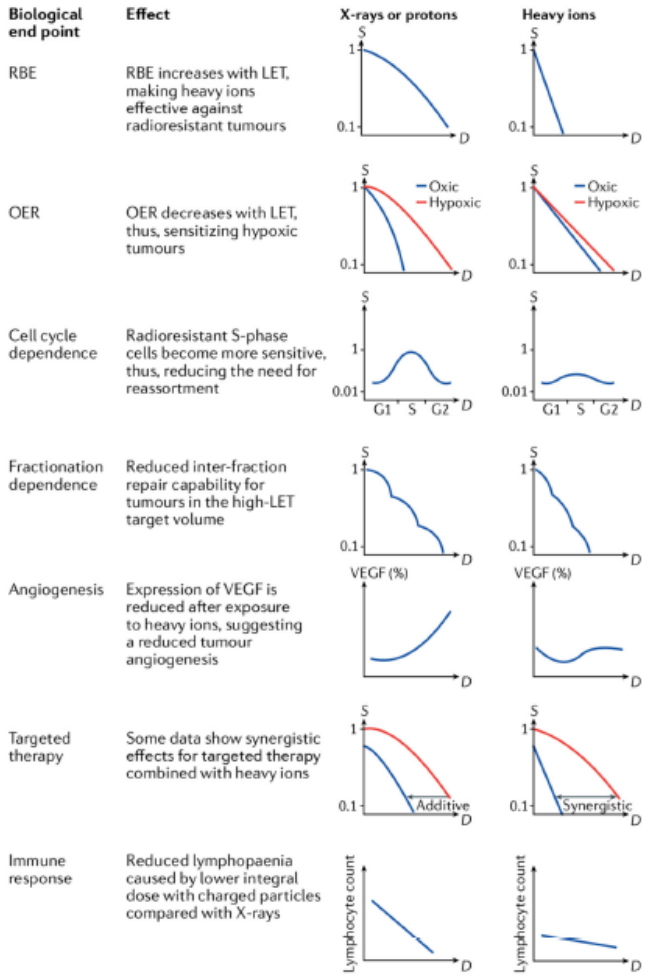


Figure 5. Biological advantages of heavy ions.
D, dose; G1, pre-DNA replication (S) cell cycle phase; G2, post-DNA replication (S) cell cycle phase; LET, linear energy transfer; OER, oxygen enhancement ratio; RBE, relative biological effectiveness; *S*, survival; VEGF, vascular endothelial growth factor[89].

The preclinical studies had already demonstrated that, in addition to the increased RBE for cell killing, heavy ions have:

- reduced oxygen enhancement ratio (OER),
- reduced dependence from the cell cycle phase
- reduced dependence on dose rate or fractionation.

More modern observations have shown:

- reduced angiogenesis,
- as well as synergistic effects in combination with targeted therapy and immunotherapy.

Most of the patients are treated with protons, but heavy ions present additional biological advantages.

Durante M, 2021

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CLINICAL INDICATIONS FOR PARTICLE THERAPY

Consequently, PT is increasingly used worldwide:

- for all pediatric cancers
- with a high priority for very young children
- in curative scenarios
- If very high doses are necessary

INDICATIONS AND LIMITATIONS OF COVERAGE AND/OR MEDICAL NECESSITY

Indications for Coverage

PBT is considered reasonable in instances where sparing the surrounding normal tissue is of adde
and cannot be adequately achieved with photon-based radiation therapy. Examples of such an adv
limited to:

1. The target volume is near one or more critical structures and a steep dose gradient outside the
avoid exceeding the tolerance dose to the critical structure(s), which would portend a higher
2. A proton-based technique would decrease the probability of clinically meaningful normal tiss
integral dose-based metric and/or organ at risk dose volume constraint associated with toxicit
3. The same or an immediately adjacent area has been previously irradiated, and the dose distrib
be sculpted to avoid exceeding the cumulative tolerance dose of nearby normal tissue.

Group 1

Based on the medical necessity requirements and published clinical data that meets the selection criteria above, disease sites that frequently support the use of PBT include the following:

GENERAL
Benign or malignant tumors or hematologic malignancies in children aged 21 years and younger treated with curative intent and occasionally palliative intent treatment of childhood tumors when at least one of the three criteria noted above under "indications for coverage" apply
Benign or malignant tumors or hematologic malignancies in the adolescent/young adult (AYA) population aged 22 years to 39 years treated with curative intent when at least one of the three criteria noted above under "indications for coverage" apply
Patients with genetic syndromes making total volume of radiation minimization crucial, such as but not limited to NF-1 patients, deleterious ATM mutations, Li-Fraumeni, retinoblastoma patients, and patients with known or suspected genetic mutations. In addition, patients with other genetic mutations who are at increased risk of developing second cancers at or near the same body location such as but not limited to BRCA 1/2, Lynch syndrome, etc.
Medically inoperable patients with a diagnosis of cancer typically treated with surgery where dose escalation is required due to the inability to receive surgery
Re-irradiation cases (where cumulative critical structure dose would exceed tolerance dose)
Primary malignant or benign bone tumors

ASTRO Proton Beam Therapy Model Policy 2022

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CLINICAL INDICATIONS FOR PROTON THERAPY

An international survey found that in children, PT was most commonly used for treating CNS tumours, followed by extracranial sarcomas, neuroblastomas, and haematopoietic tumours. *(N. Journy et al, 2019)*

- **SNC Tumors**
  - Craniopharyngioma
  - Glioma (Low-grade glioma, Optic pathway glioma)
  - Germ cell tumors
  - Medulloblastoma-PNET
  - Ependymoma
  - ATRT
  - CNS sarcoma
- **Skull Base Tumors**
  - Chordoma/chondrosarcoma
- **Soft tissue and Bone Tumors**
  - Rhabdomyosarcoma
  - Ewing's tumor
  - Osteosarcoma
  - NRSTS
- Head and Neck Tumours
- Retinoblastoma
- **Neuroblastoma**
- Lymphoma
- Re-RT

1. Historically radio-resistant tumors
   → Increase the proportion of long-term survivors

2. Tumors that respond favourably to RT → Maintain favourable outcome and improve QoL

3. CSI → Complex and large volumes

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WHAT ABOUT ITALY?

PATOLOGIE TUMORALI INSERITE NEI LEA

CONDROSARCOMI E CORDOMI DELLA BASE DEL CRANIO E DEL RACHIDE

TUMORI DEL TRONCO ENCEFALICO E DEL MIDOLLO SPINALE

SARCOMI DEI TESSUTI MOLLI

SARCOMI OSSEI INCLUSI OSTEOSARCOMI E CONDROSARCOMI

MENINGIOMI INTRACRANICI IN SEDI CRITICHE

TUMORI ORBITARI E PERIORBITARI INCLUSO IL MELANOMA OCULARE

CARCINOMI ADENOIDEO-CISTICI DELLE GHIANDOLE SALIVARI

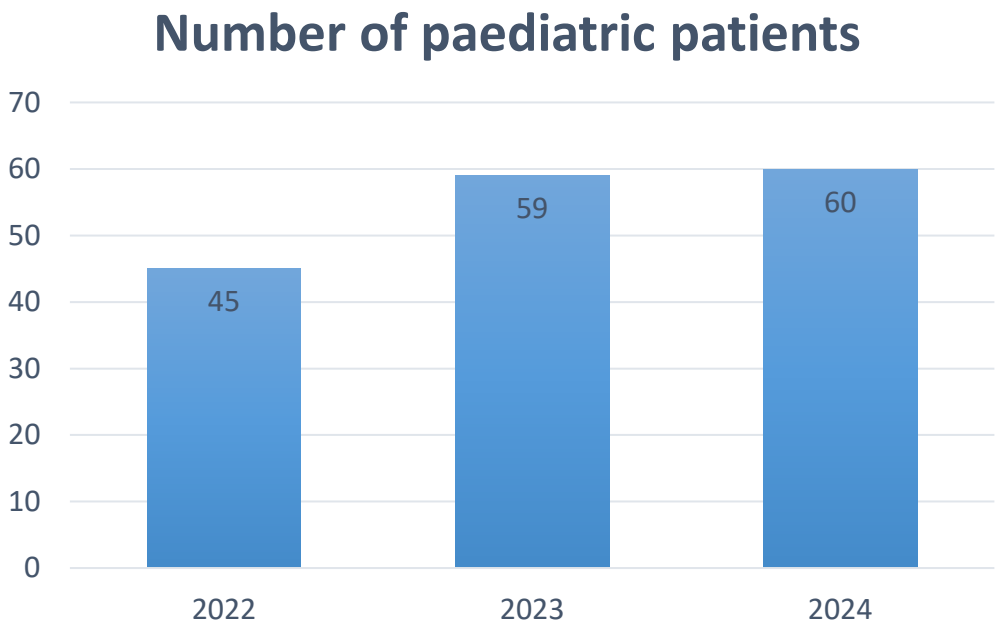
TUMORI SOLIDI PEDIATRICI

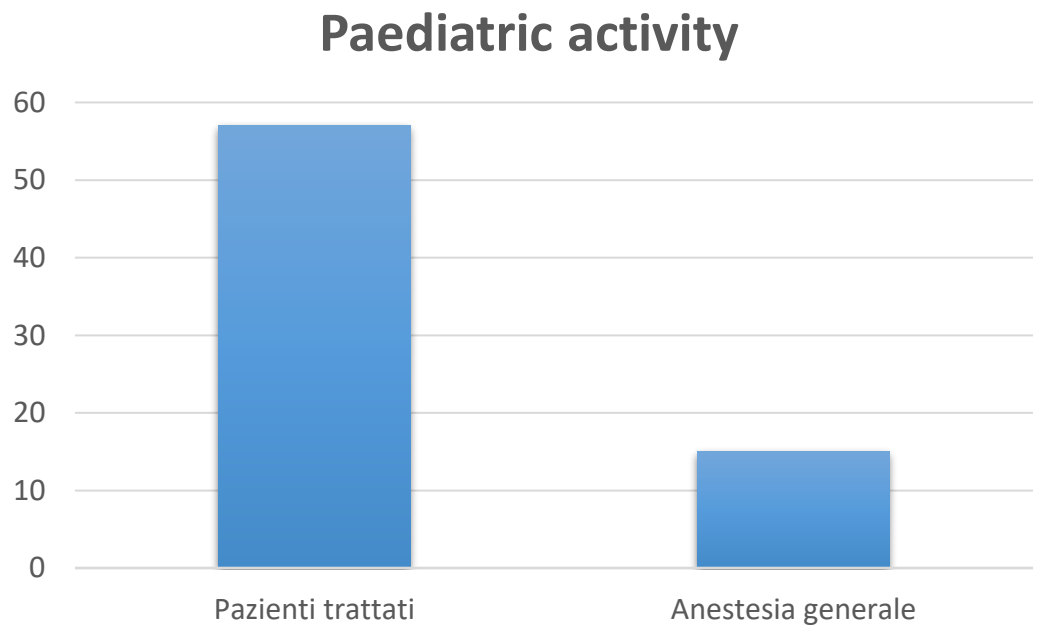
TUMORI IN PAZIENTI AFFETTI DA SINDROMI GENETICHE

RITRATTAMENTI DI TUMORI IN SEDI GIÀ IRRADIATE

CNAO EXPERIENCE - Paediatric patients

Età media: 11,8 anni (1-29 anni)





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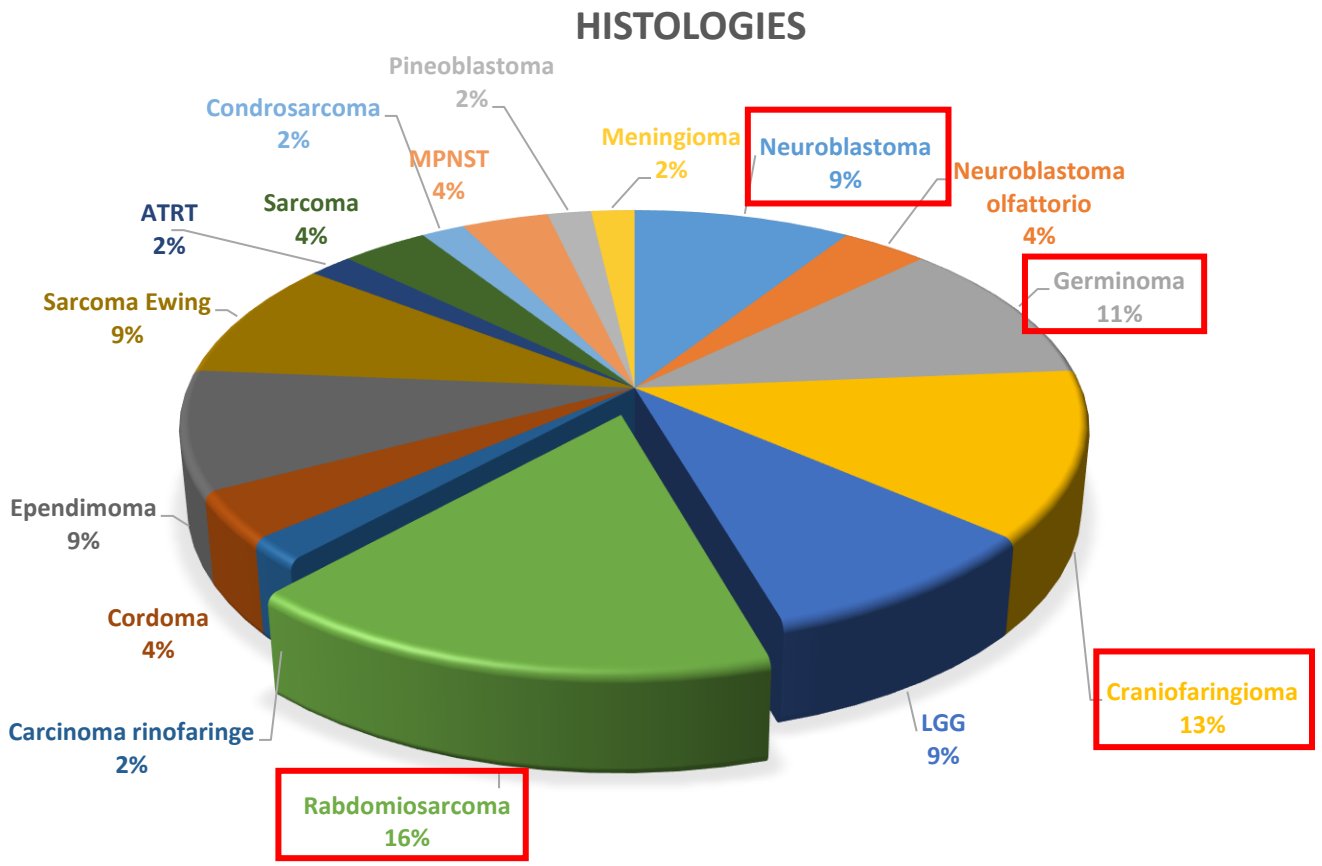
Histologies	n°
Neuroblastoma	5
Neuroblastoma olfattorio	2
Germinoma	6
Craniofaringioma	7
LGG	5
Rabdomiosarcoma	9
Carcinoma rinofaringe	1
Cordoma	2
Ependimoma	5
Sarcoma Ewing	5
ATRT	1
Sarcoma	2
Condrosarcoma	1
MPNST	2
Pineoblastoma	1
Meningioma	1



Total fractions (average): 30 fractions
Total dose (average): 54 Gy

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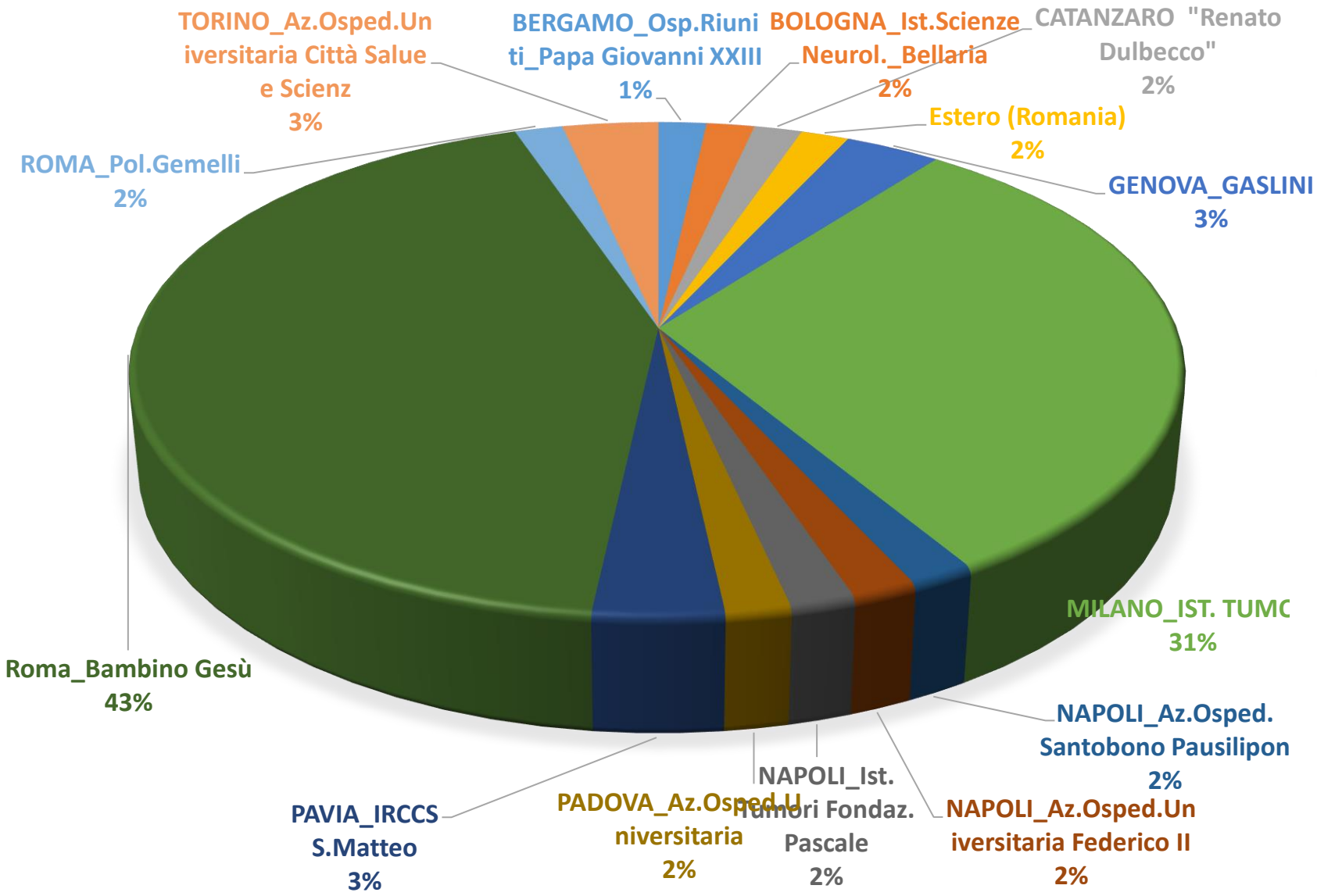

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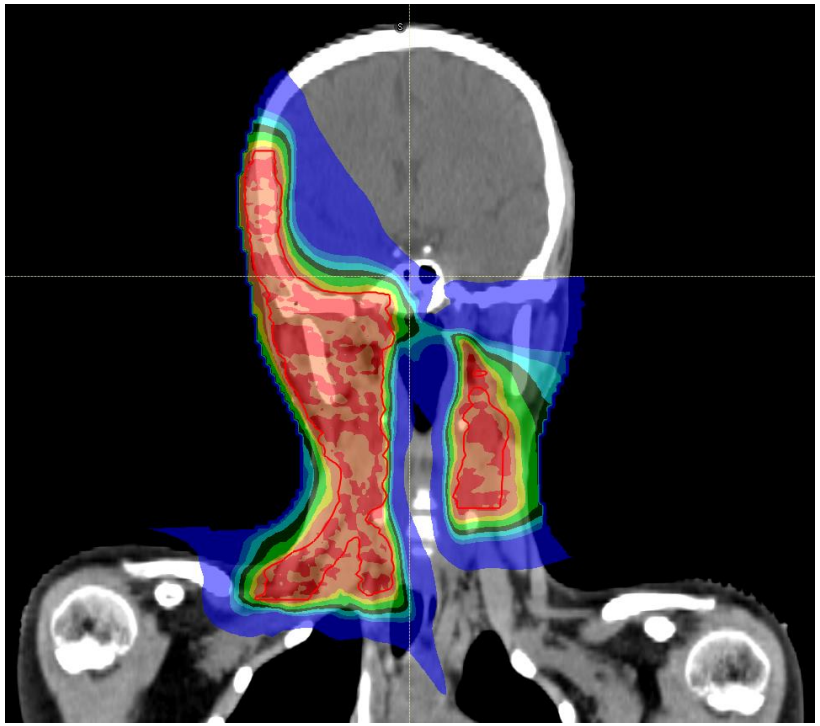
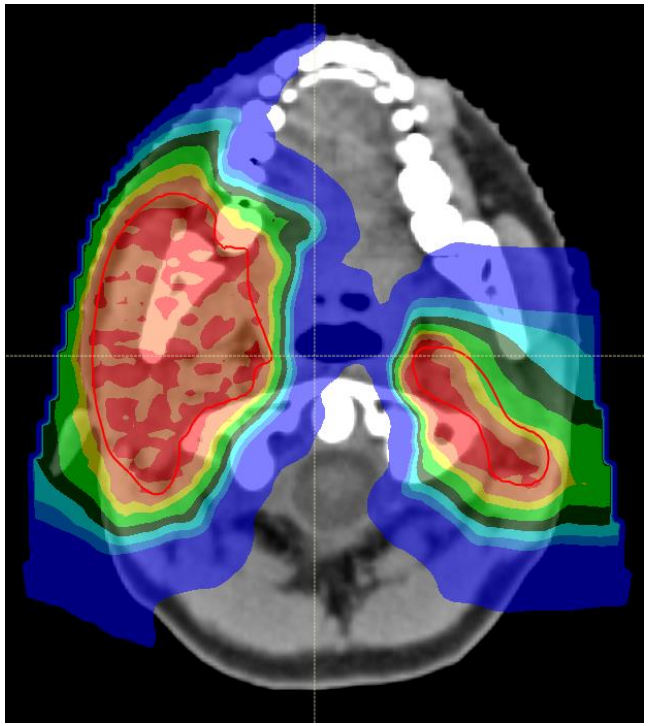
CLINICAL CASE

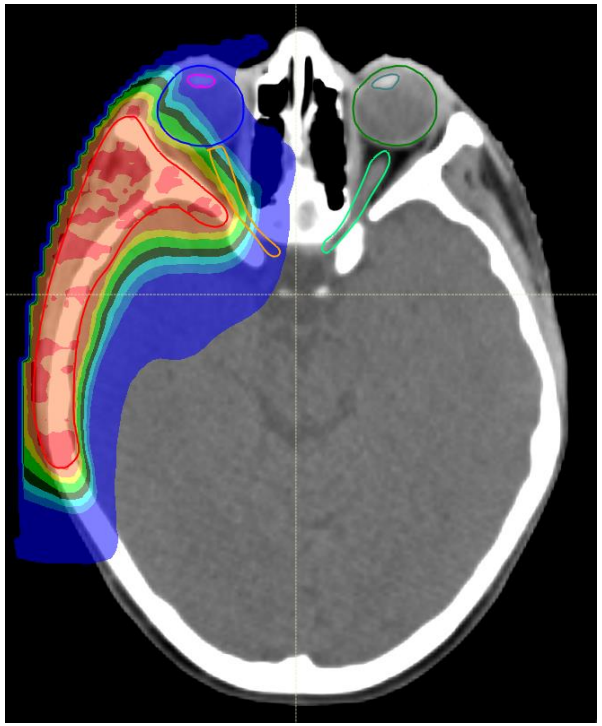
PM RMS (F, 10yr) treated according to RMS 05 protocol.

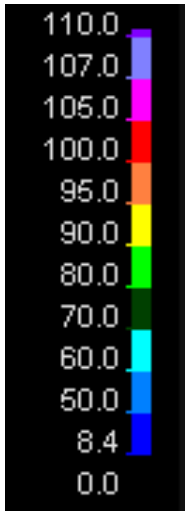
<u>RT doses:</u>
41.4 Gy in 23 fractions at the level of positive lymph nodes at diagnosis
sequential boost of 12.6 Gy in 7 fractions at the level of initial diagnosis of disease (T)
sequential boost of 5.4 Gy in 3 fractions for residual disease

<u>Acute tocixity:</u> erythema g1, mucositis g2









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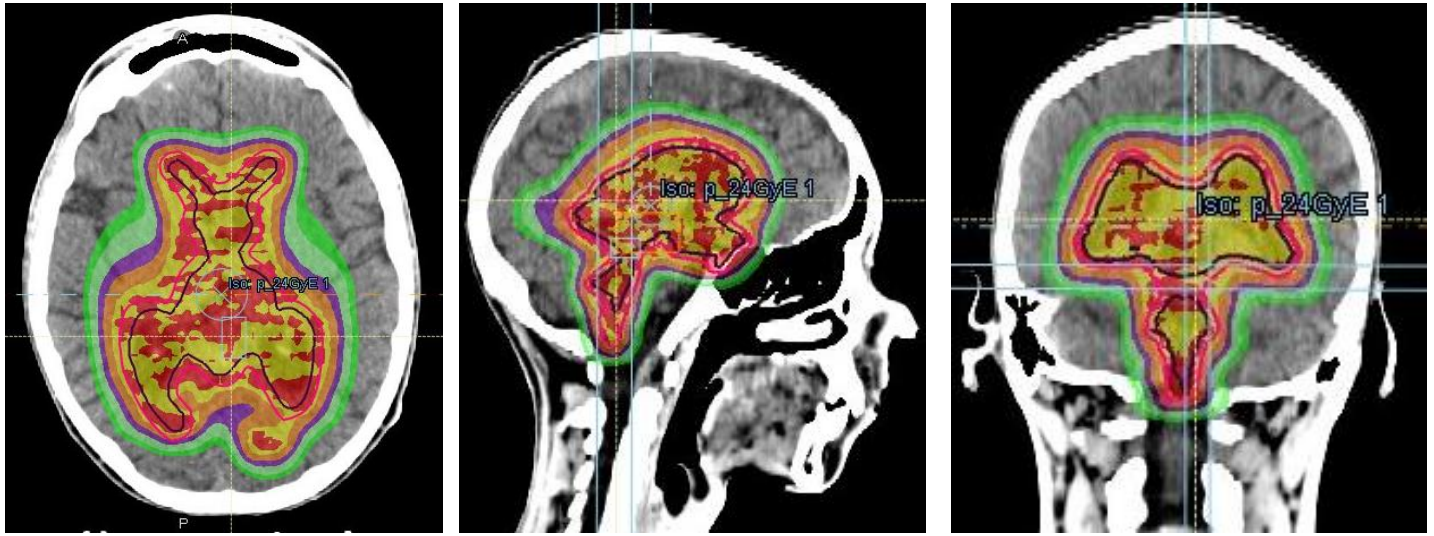
12-year-old boy with Pineal Germinoma

Robust PBS-IMPT dose plan in coronal view; 2 opposing side fields and a vertex field for the WVI, and 2 30-degree inclined fields for the boost
Color wash represents 100% prescription dose (red); 98% (yellow); 90%(orange); 60% (green), 50% (light green)

ROI	ROI vol. [cm³]	Dose [Gy (RBE)] D99	D98	D95	Average	D50	D2	D1
Basilare	0.19	0.88	0.88	1.07	3.17	2.36	7.52	7.91
Brain (1)	1330.90	0.04	0.12	0.73	14.51	11.81	39.66	39.98
Brainstem	22.11	9.68	10.99	13.62	28.56	28.82	40.12	40.17
Cochlea_L	0.16	1.43	1.43	1.47	2.85	2.76	4.95	5.52
Cochlea_R	0.24	2.35	2.35	2.56	5.50	5.44	11.12	11.95
Eye_L	7.80	0.00	0.00	0.00	0.03	0.01	0.16	0.19
Eye_R	7.84	0.00	0.00	0.00	0.04	0.01	0.23	0.27
ippocampo dx	1.86	23.87	23.95	24.05	30.87	29.47	40.10	40.17
ippocampo sx	1.95	23.79	23.87	23.93	30.89	29.13	40.04	40.11
Lens_L	0.20	0.00	0.00	0.00	0.00	0.00	0.01	0.01
Lens_R	0.21	0.00	0.00	0.00	0.00	0.00	0.01	0.01
Lobe_Temporal_L	112.23	2.60	3.70	6.23	17.21	16.43	37.67	39.55
Lobe_Temporal_R	106.91	6.02	6.57	7.25	18.30	18.36	38.13	39.56
OpticChiasm	0.38	23.79	23.81	23.81	24.07	24.02	24.70	24.82
OpticNrv_L	0.69	0.20	0.23	0.28	5.40	1.96	24.34	24.39
OpticNrv_R	0.81	0.41	0.43	0.49	7.41	3.83	24.25	24.35
SpinalCord	3.43	0.00	0.00	0.00	2.20	0.04	18.87	19.24
tratti ottici posteriori	0.42	24.34	24.39	24.54	26.46	26.22	29.83	29.98

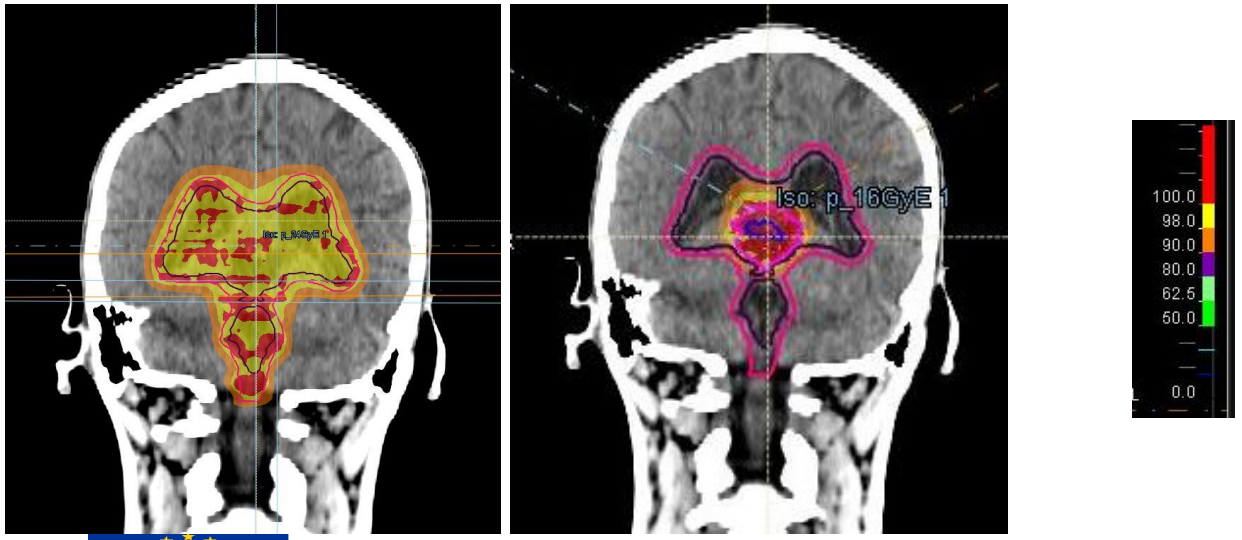
Dose statistics – Sum plan (24 + 16 = 40 Gy)



WVI 24 Gy in 15 fr (1,6 Gy/fr)

WVI

Boost TB 16 Gy



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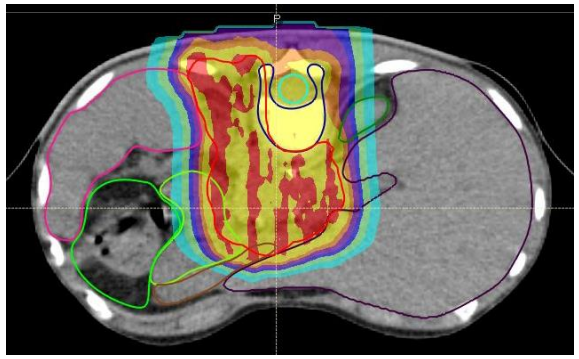
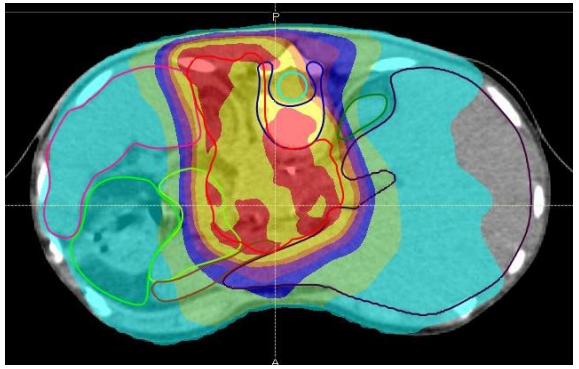
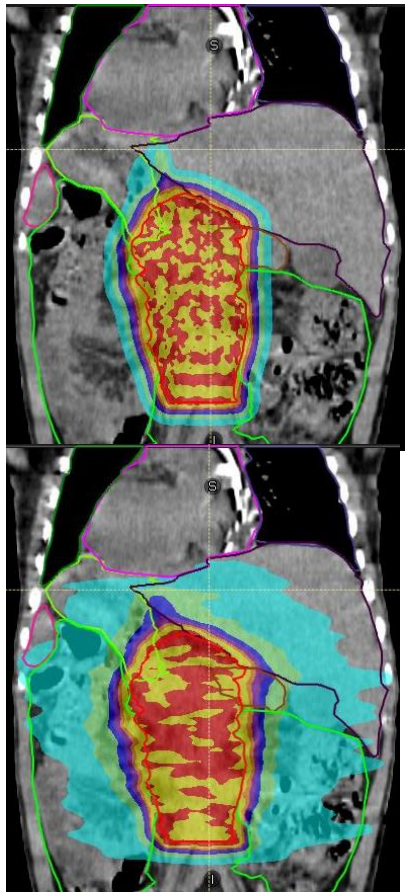
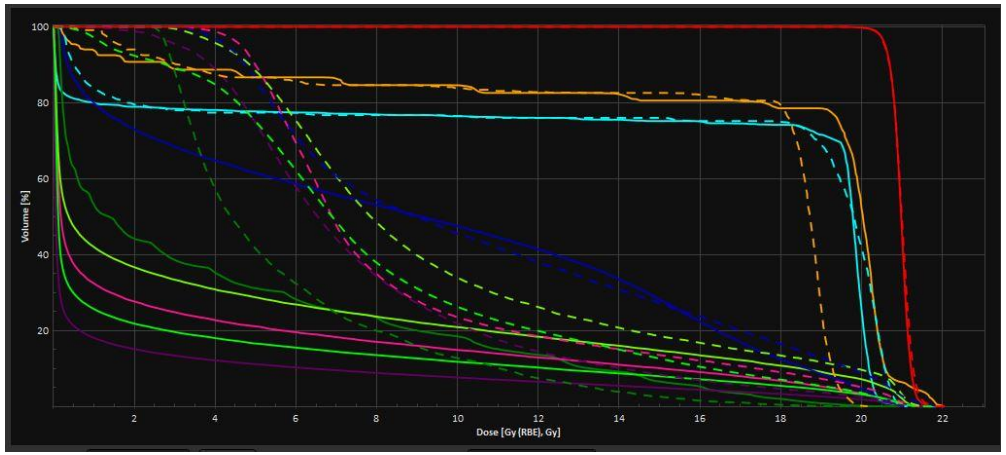
2-year-old patient with abdominal neuroblastoma, stage M, MYCN not amplified, treated according to HR-NBL-1/SIOPEN Protocol.

Dosimetric comparison of proton plane (PBS-IMPT) vs photon plane (IMRT-VMAT) in axial and coronal view.









The data show optimal target coverage with both radiotherapy techniques, and the clear advantage of protons in reducing the dose to all examined OARs. Major advantage at: Liver, Kidneys, Spleen, Stomach, and Peritoneal cavity

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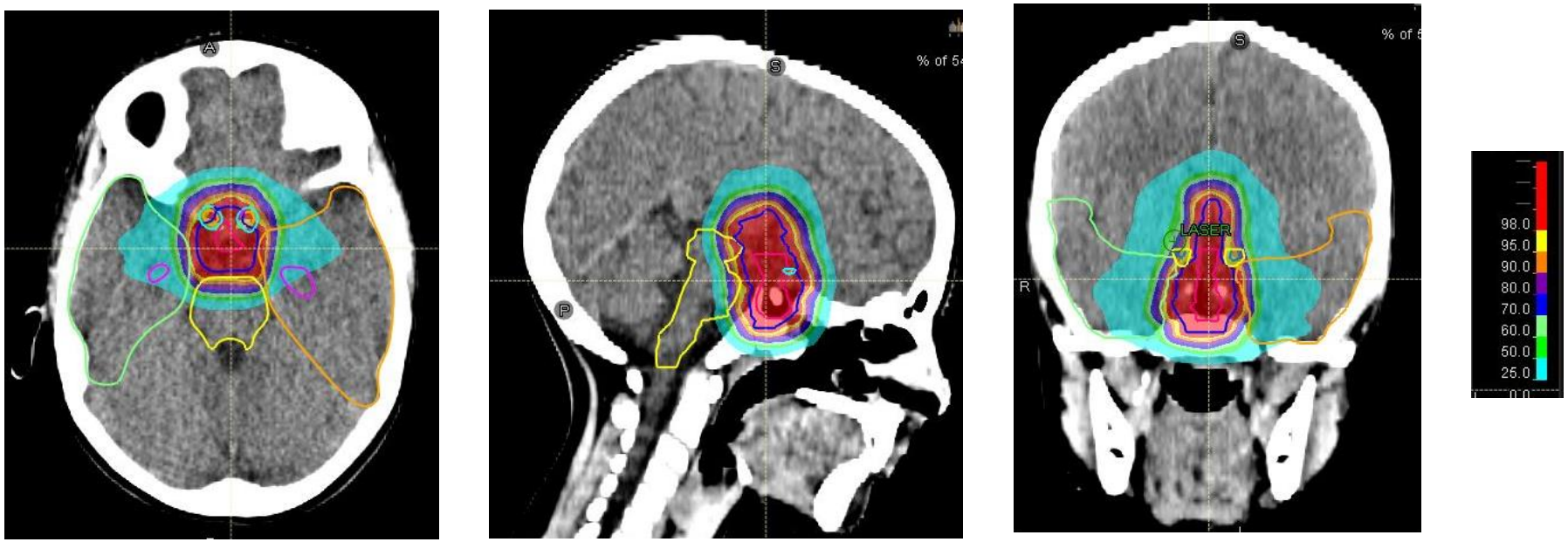
6-year-old girl with Craniopharyngioma

Robust PBS-IMPT dose plan in coronal view; 2 opposing side fields and a vertex field.
Blue contour: CTV 54Gy
GTV = cystic, solid, and calcific components; CTV = GTV + 3-5mm

Color wash represents 100% prescription dose (red); 95% (yellow); 90%(orange); 80% (purple) 70% (blue); 60% (green), 50% (light green) and 25% (light blue) respectively



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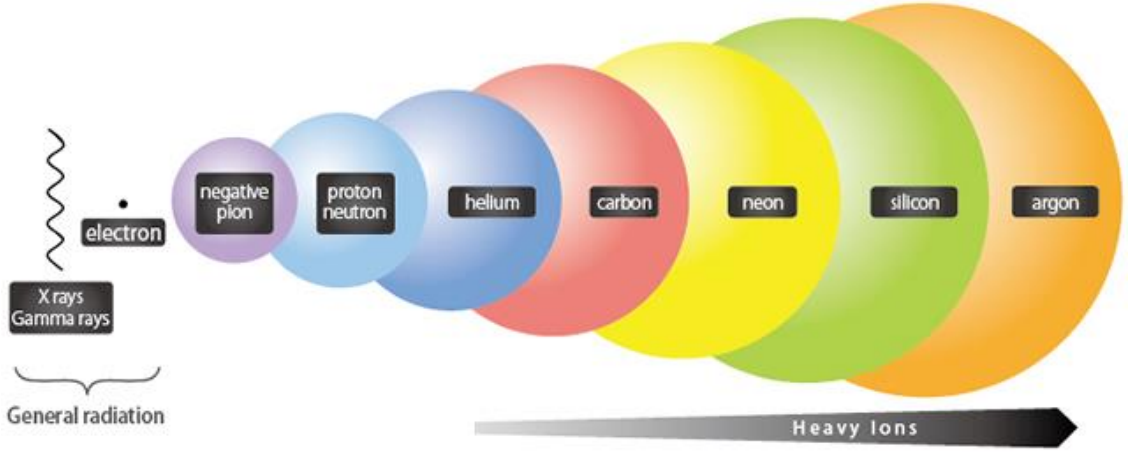
CARBON ION RT IN PAEDIATRIC PATIENTS

Contrary to expectations, there were no high-quality or independently focussed studies on CIRT for paediatric patients.

Carbon ion radiotherapy is most commonly used to treat photon-resistant bone and soft tissue tumours, including:

- osteosarcomas,
- chordomas,
- chondrosarcomas,
- chemotherapy-resistant soft tissue sarcomas
- re-irradiation



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Carbon Ion Radiotherapy for Pediatric Patients and Young Adults Treated for Tumors of the Skull Base

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- 17 patients were aged 6-21 years (median 18 years) treated between 1997 and 2007
  - 14 pts (82%) primary diagnosis,
  - 3 pts (18%) recurrent disease
- Skull base chordomas (7 pts) and chondrosarcomas (10 pts)
- Median total dose of 60 (GyE) (range, 60-66.6 GyE) in a fractionation of 3 GyE (7 days per week) of CIRT

Results:

- Median fup 49 months (range 3-112 months)
- RT was well tolerated → No severe treatment-related toxicities
- Only 1 tumor progression at 60 months after CIRT → LC 94%

SE Combs et al, 2009 - HIT

HITRI plus
Heavy Ion Therapy Research Integration

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Carbon ion radiotherapy for inoperable pediatric osteosarcoma

Osama Mohamad[1,2], Reiko Imai[1], Tadashi Kamada[1], Yuki Nitta[1], Nobuhito Araki[3] and the Working Group for Bone and Soft Tissue Sarcoma

- 26 patients aged 11–20 years (median 16) treated between 1996 and 2014
- inoperable osteosarcoma of the trunk (24 pelvic, 1 mediastinal and 1 paravertebral) without any other lesion at initial examination.
- Median CIRT dose was 70.4 Gy RBE delivered in 16 fractions.
- Median follow-up was 32.7 months.

Conclusions: CIRT was safe and efficacious in the treatment of inoperable pediatric osteosarcoma with improved local control and overall survival compared to conventional treatments.

- PFS was 34.6% at 3 and 5 years.
  → Only largest tumor diameter correlated with 5-year OS and LC

- There were 4 grade 3-4 CIRT-related late toxicities, 1 case of bone fracture and no treatment-related mortalities. All patients (except 1) were able to ambulate after CIRT.

Mohamad O, 2018 - Japan

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The role of combined ion-beam radiotherapy (CIBRT) with protons and carbon ions in a multimodal treatment strategy of inoperable osteosarcoma

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- 20 pts aged 10.8–49.8 yr (median 20 yr)
- Inoperable pelvic (70%) or craniofacial (30%) osteosarcoma

Conclusion: CIBRT shows a favorable toxicity profile and promising results particularly for patients with inoperable craniofacial osteosarcoma.

Results

- 1yr-PFS was 60% and 1-yr OS was 75%; 2yr-PFS was 45% and 1-yr OS was 68%
- Median OS 34 months.
- 7 in-field local progression (6 in pelvic localization) and 8 distant progression
- No acute toxicities > G3
- We observed one case of secondary acute myeloid leukemia (AML) seven months after CIBRT for recurrent disease and one case of hearing loss.
- Craniofacial localization, lower uptake of FDG in PET/CT and boost plan CTV < median were associated with improved overall survival

K Seidensaal, 2021 - HIT

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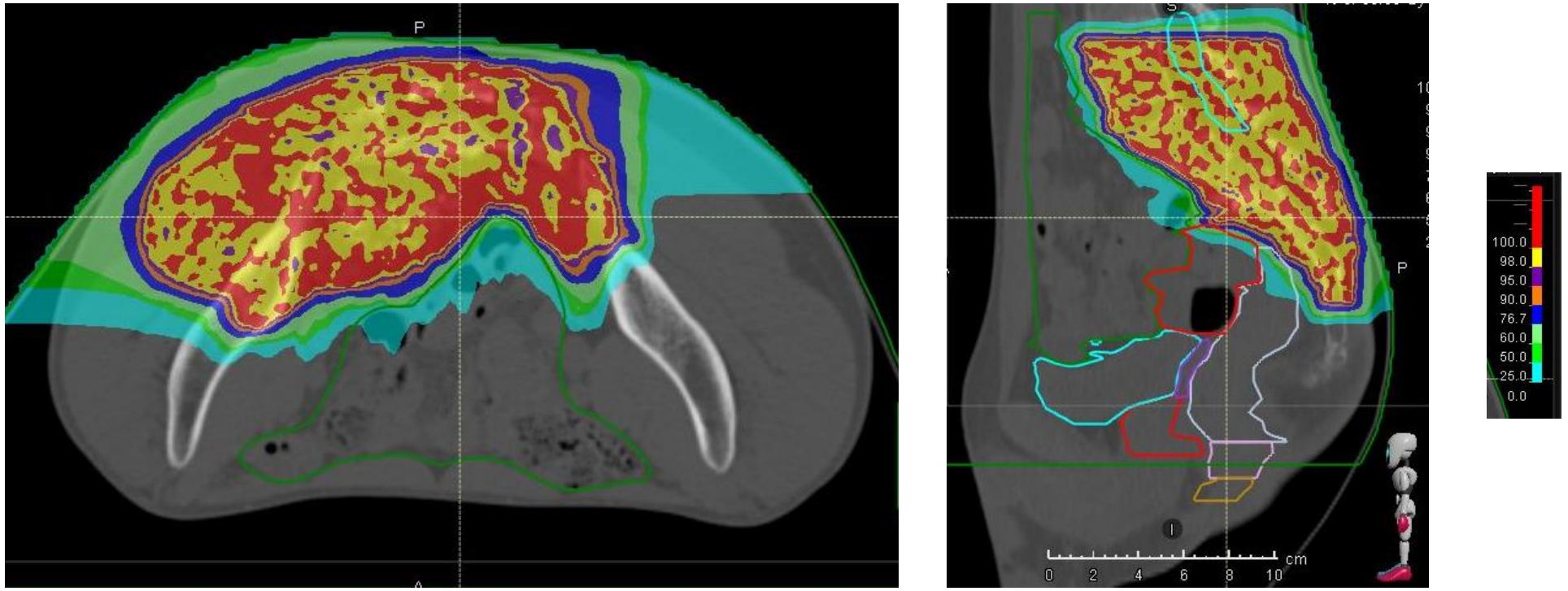
15-year-old boy with local recurrence of osteosarcoma of the pelvis. Previous RT terminated in May 2022.

CIRT 60Gy(RBE) (4Gy(RBE)/fraction, 15 fractions, 4 fractions/week

Well-tolerated treatment. Acute toxicities: erythema G1



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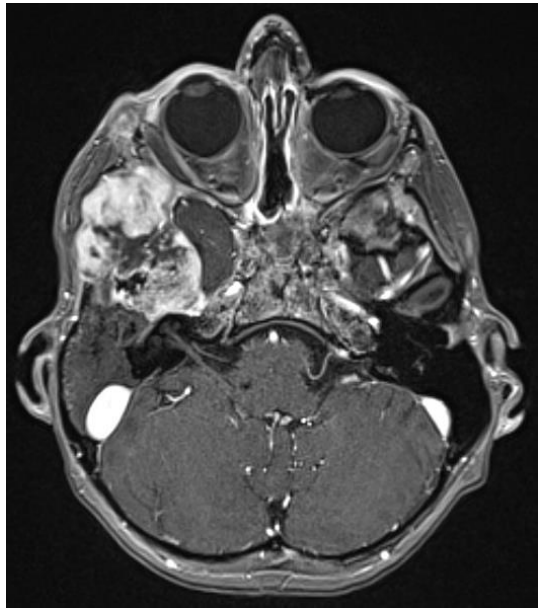

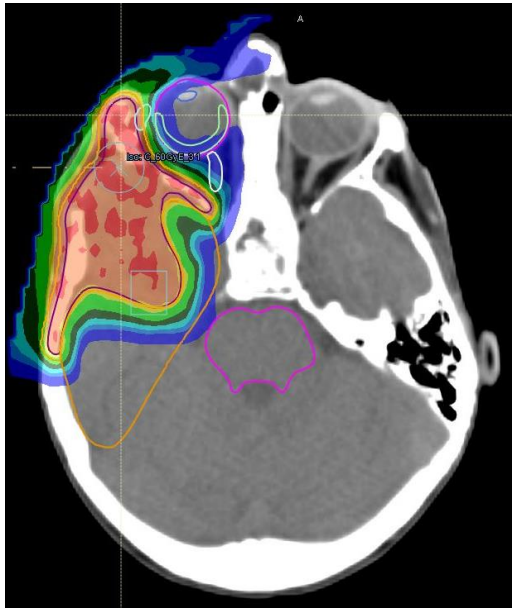

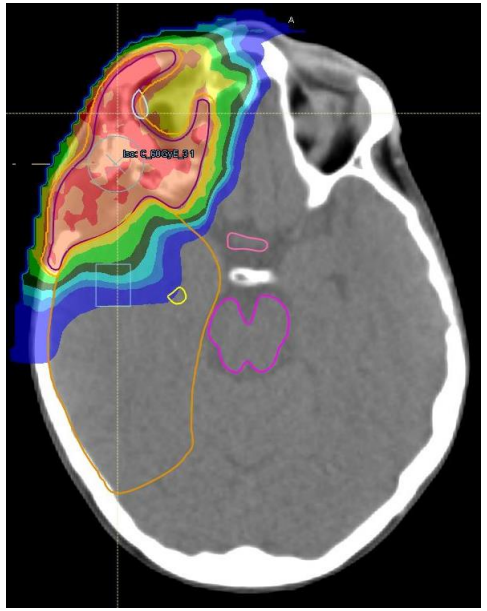

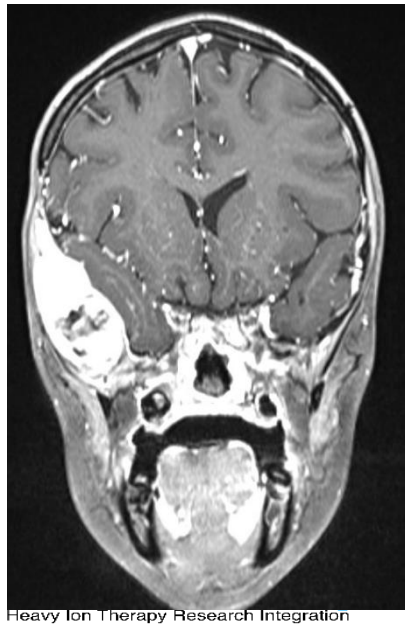

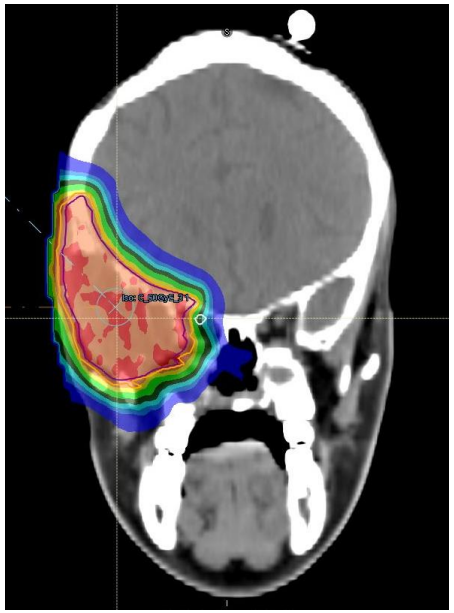

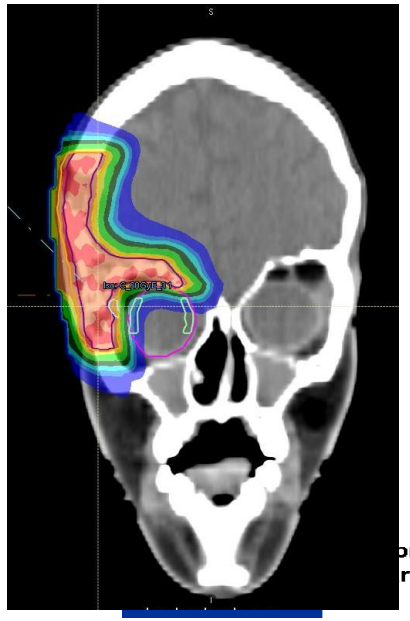

A 15-year-old patient with grade 2 sarcoma of the right temporal region undergoing chemotherapy in a patient with a history of embryonal rhabdomyosarcoma of the skull base treated with chemo-radiotherapy (2013 IMRT 54 Gy).

08/2024 CIRT
60 Gy in 20 fractions (3Gy/fraction) at CTV 2024 (=GTV + 2mm)

Well-tolerated treatment.
Acute toxicities: erythema G1, oedema G2.

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Good Pratice guide for paediatric RT: TEN KEY THEMES

1. Top quality clinical outcomes
2. Excellent patient safety
3. Good patient experience
4. Information and communication with families
5. Communication and multiprofessional relationships
6. Child- and family-friendly environment
7. Radiotherapy equipment and techniques
8. Human and financial resources
9. Education and training
10. Research and development

Good practice guide for paediatric radiotherapy, 2° ed, 2018

HITRI plus
Heavy Ion Therapy Research Integration

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THANKS