HITRI plus

Heavy Ion Therapy Research Integration

18–19 Oct 2024
Thessaloniki

Hadron Therapy Workshop: status and perspectives, plans for next generation facilities

Clinical profile of pediatric oncology patients managed and treated in Pediatric Haematology and/or Oncology Unit Hospital Hippoktateio Hospital

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EC Greece FOSTER

- Proton therapy is radiation treatment that uses protons to treat cancer
- Advantages: Greater precision, reduced damage to healthy tissues, important in pediatric cancer

The labyrinth of treatment options in pediatric oncology demands precise, innovative solutions, and proton therapy is proving to be a critical tool for pediatric oncologists

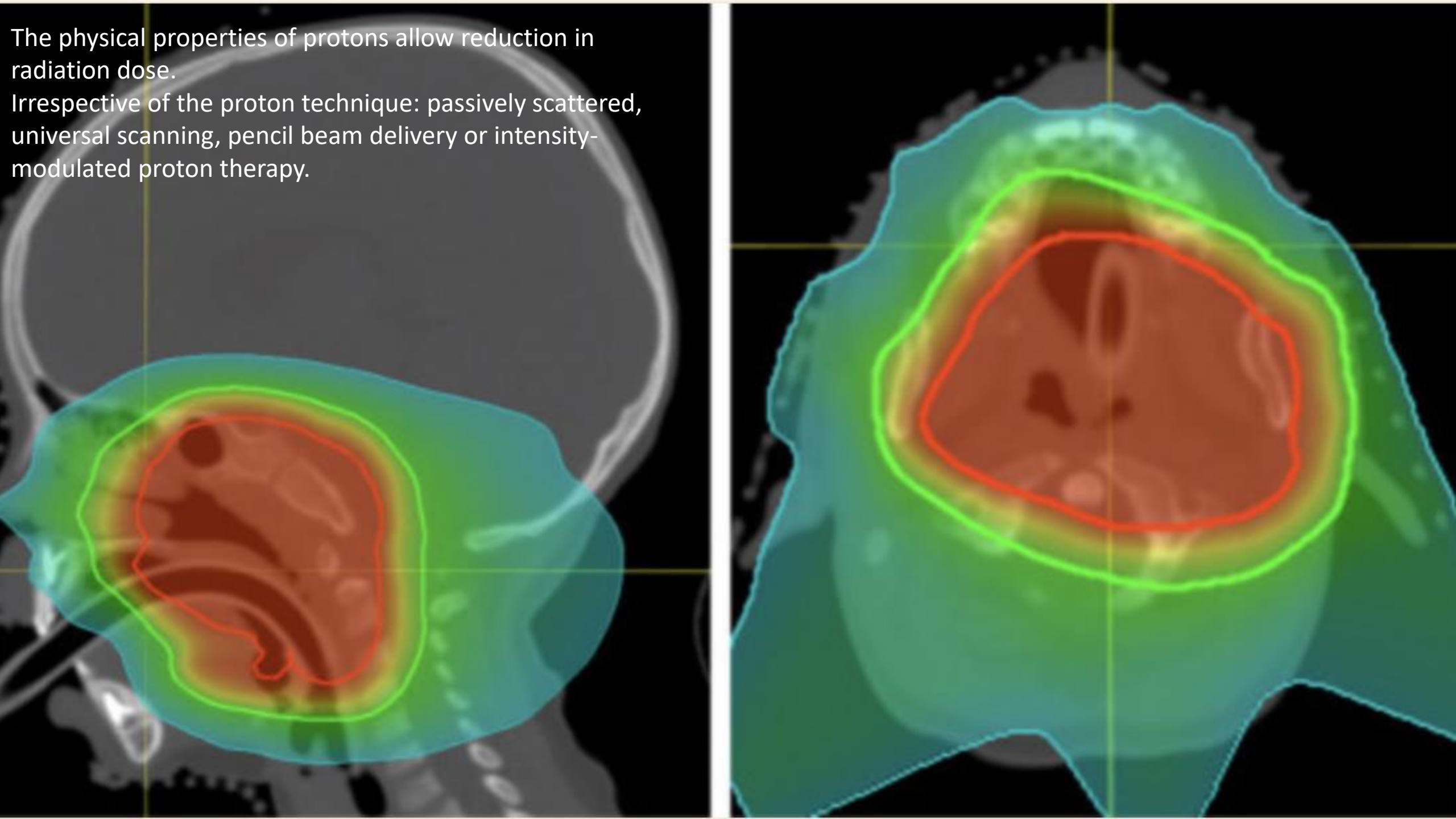
- In pediatric patients, developing bodies are particularly sensitive to conventional radiotherapy
- Targeted radiation to tumors with sparing of surrounding healthy tissues, reduces the risk of long-term side effects
- Studies comparing outcomes of proton and photon in brain tumor pediatric patients showed an improvement in Quality of Life. This demonstrates the great potential of proton radiotherapy to mitigate late-effects in the pediatric population.

Baliga S, *Curr Opin Pediatr*. 2019

- In 2010 →24 proton therapy centers existed worldwide.
- By 2024 >100 centers in operation in Europe.
- In USA the number of pediatric patients receiving proton therapy is expanding
- 50% of pediatric patients CNS (medulloblastoma, ependymoma) and 25% sarcomas (RMS, Ewing sarcoma)

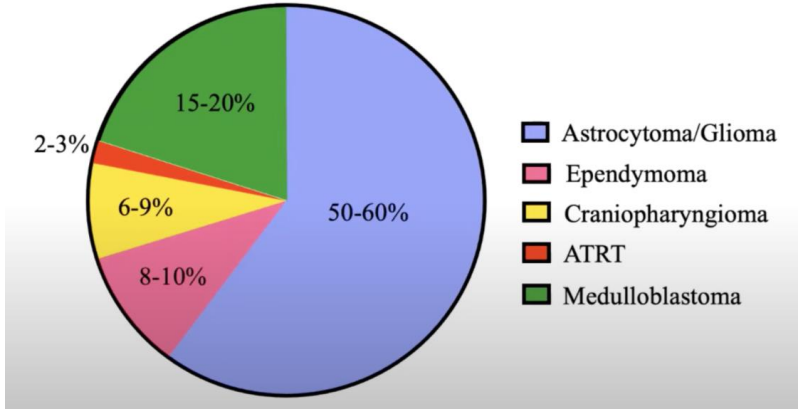
Berrington de González A, *Adv Radiat Oncol*. 2023

The physical properties of protons allow reduction in radiation dose.
Irrespective of the proton technique: passively scattered, universal scanning, pencil beam delivery or intensity-modulated proton therapy.

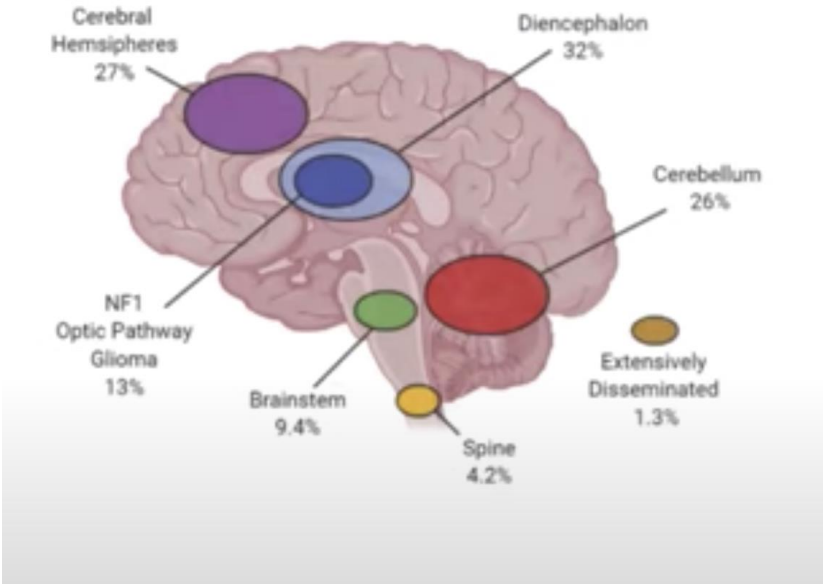


Low-grade gliomas LGG

- The most common CNS tumors of childhood



- Their current treatment:
  - Surgery. Maximum safe resection
  - If residual tumor, chemotherapy or RT



Low-grade gliomas LGG

- Radiation therapy is necessary for unresectable tumors.
- Photon therapy reveals 65% toxicities grade-3, with 30% serious cognitive disability.
- A dosimetric study of 74 patients treated with PBT demonstrated reduction in radiation therapy dose to the optic nerve, optic chiasm, thalamus, hippocampus, hypothalamus and inner ear.
- Greenberger reported 32 pediatric LGG patients. IQ, verbal comprehension and perceptual reasoning indices remained stable, but patients treated at age less than 7 years did suffer declines in IQ and VCI. 8-y OS was excellent at 100%.
- After Proton therapy in 166 LGG patients only 9% required hormone replacement and none experienced significant toxicity

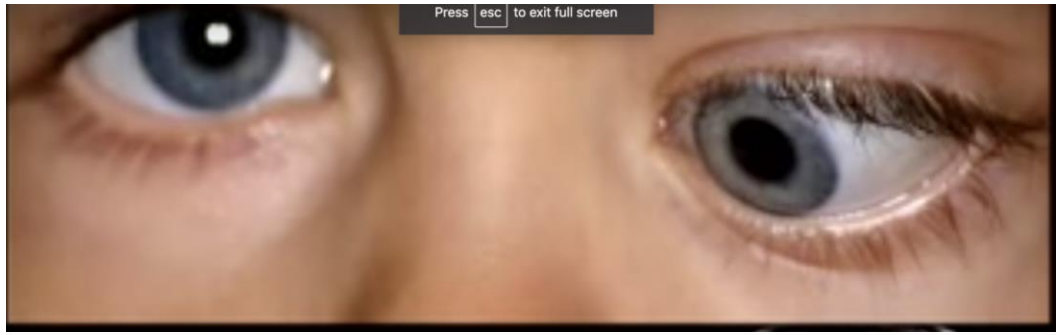
Baliga S, *Curr Opin Pediatr*. 2019

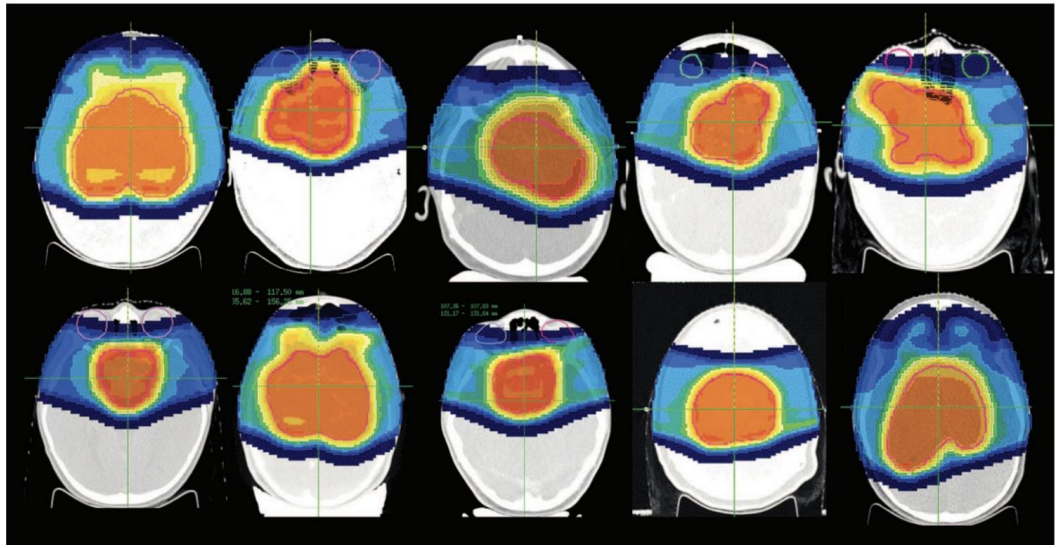
OPTIC GLIOMA OPG

- The effect on vision guides our treatment
- Delay in treatment: danger of permanent loss of vision
- Surgical intervention: Only in painful eye prolapse with blindness
- Radiotherapy: To be avoided
- Indication for PBT

Decline in visual acuity usually occurs slowly and gradually and may not be noticed

Exophthalmos

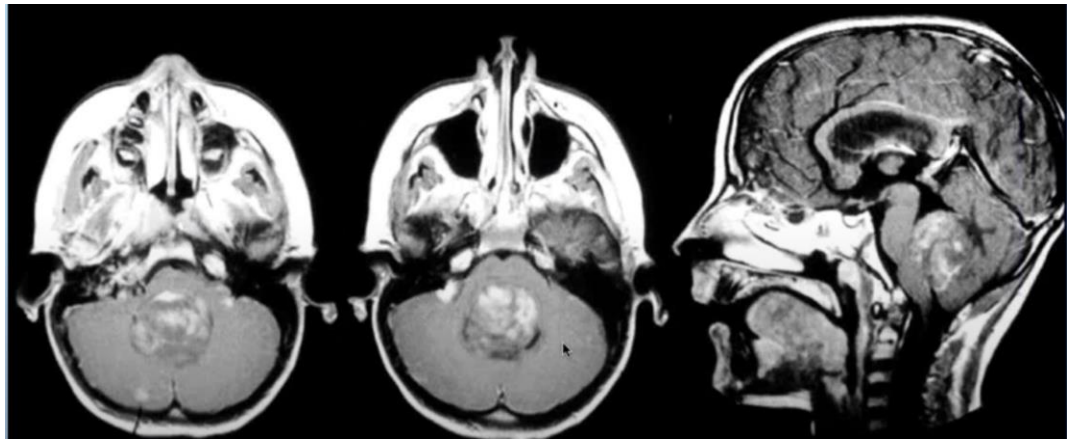




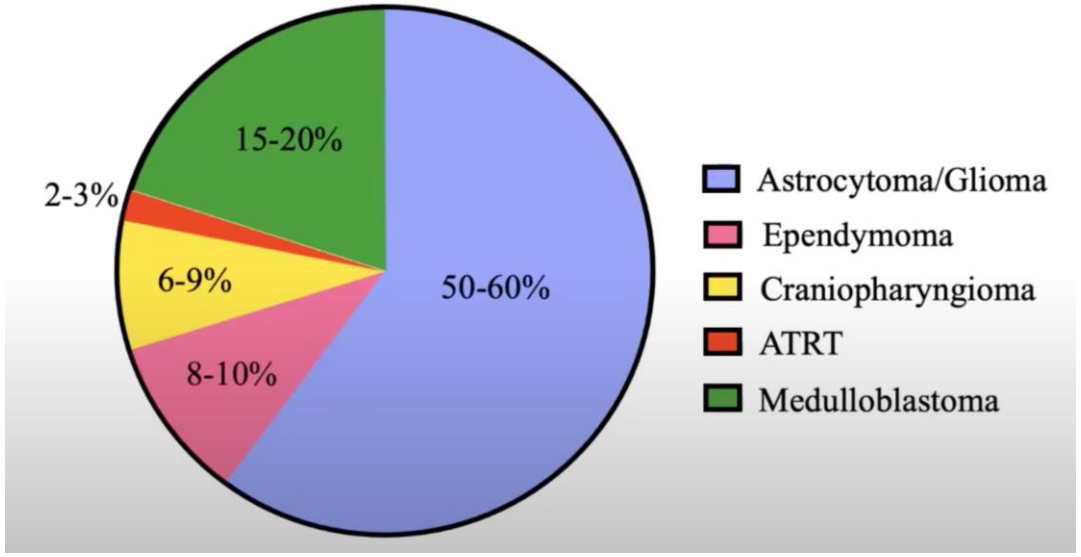
De Bella Pediatrics 2000, Lohkamp Front-Surg 2022

Medulloblastoma

- The 2nd most common malignant CNS tumor
- Age 4-5 years



- Treatment
- Maximum safe excision
- Brain and spinal radiation therapy with concurrent chemotherapy followed by maintenance chemotherapy



Medulloblastoma treatment

- Standard risk patients are treated with 23.4 Gy craniospinal irradiation (CSI) followed by a tumor bed boost to 54 Gy
- High-risk patients receive higher CSI dose of 36 Gy followed by a similar boost

- Treatment-related neurocognitive impairment and adverse effects on QoL are common and more severe in the youngers. More than 50% of children have cognitive impairment.
  Only 28% of patients >20 years of age able to live and function independently

- Ototoxicity may be reduced with the use of PBT due to capability of sparing dose to the cochlea. Massachusetts General Hospital reports a 5-y incidence of grade 3–4 ototoxicity of 16%, lower than with photon radiation (approximately 18–25%).
- PBT can improve neurocognitive and psychosocial outcomes due to less dose to the supratentorial brain during the tumor bed boost.

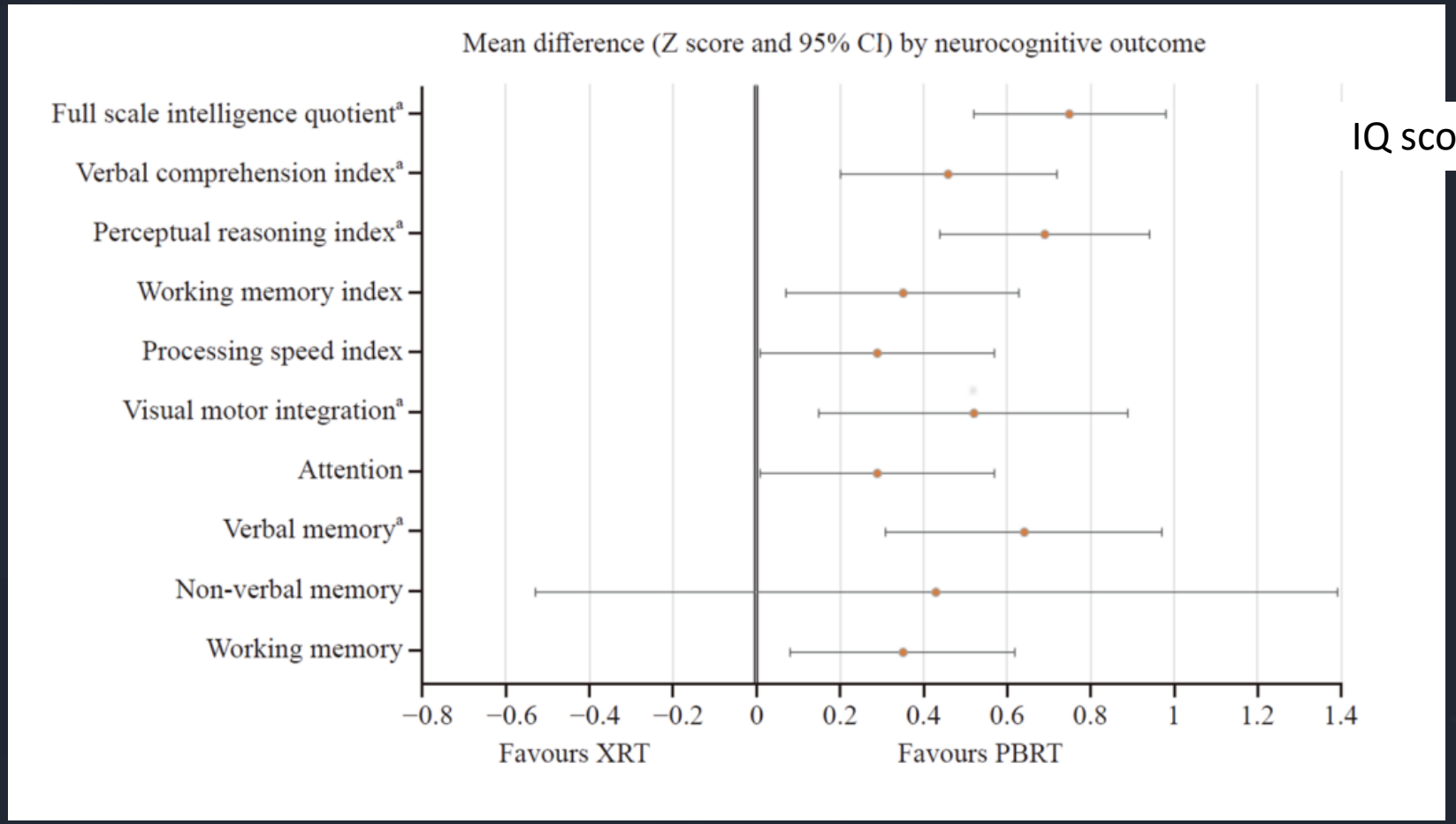
Baliga S, *Curr Opin Pediatr*. 2019

Neurocognitive Outcomes in Multiethnic Pediatric Brain Tumor Patients Treated with Proton vs Photon Radiation

Evolution of Proton Radiation Therapy Brainstem Constraints on the Pediatric Proton/ Photon Consortium Registry

Significant reduction of radiation therapy dose to pituitary and hypothalamus, cochlea

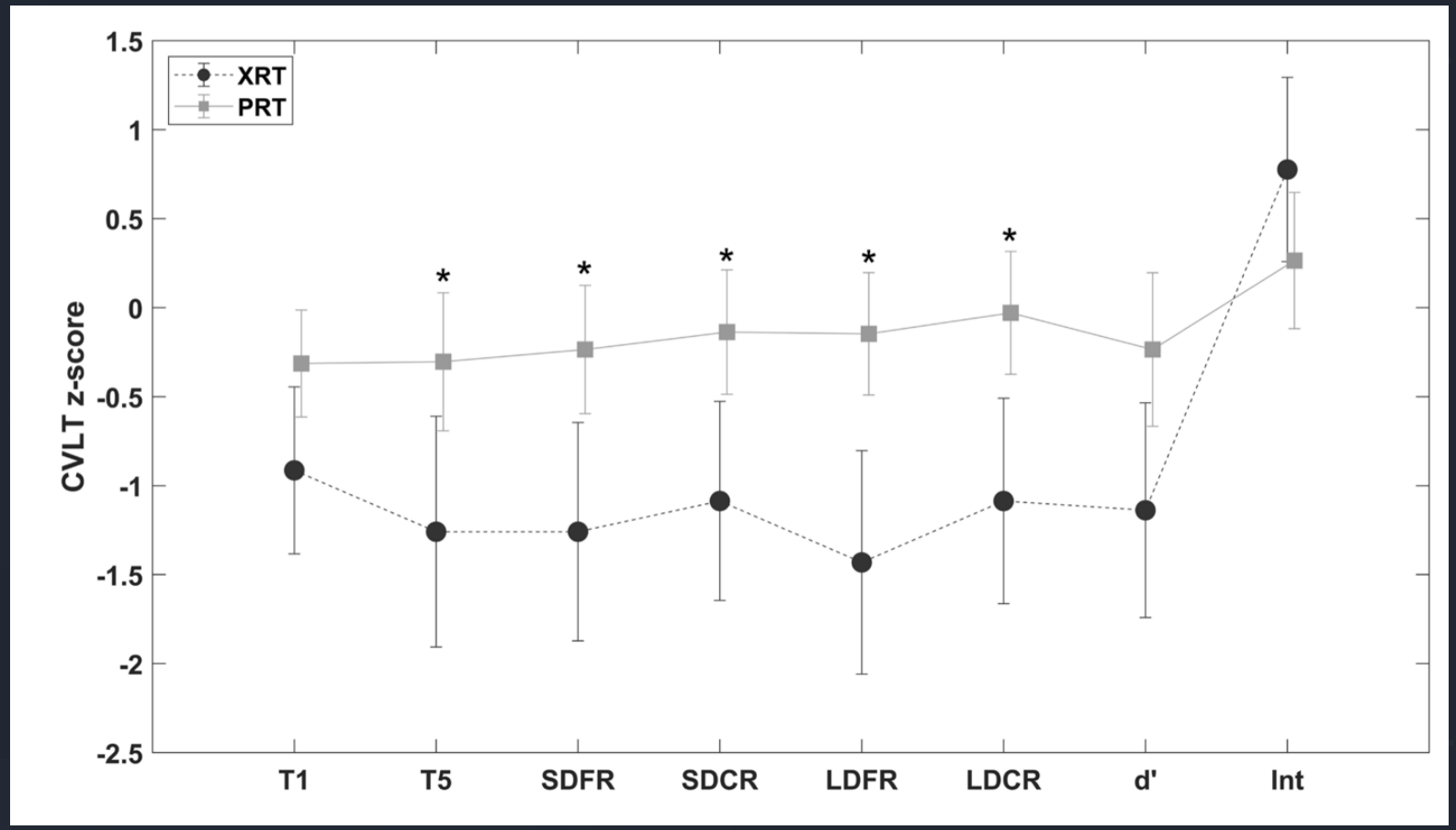
Neurocognitive outcomes in pediatric brain tumors after treatment with proton versus photon radiation: a systematic review and meta-analysis



IQ score was 10% higher with PBT

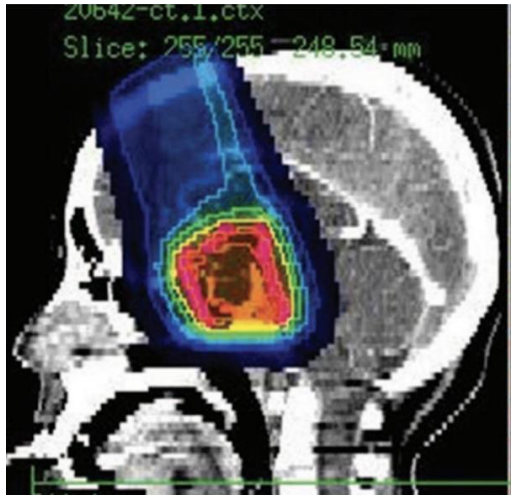
Fig. 1 Comparison of neurocognitive outcomes in children and adolescents with brain tumors treated with photon radiation (XRT) or proton therapy (PBRT). [a]This outcome did remain significant in sensitivity analyses. *CI* confidence interval

Superior Verbal Learning and Memory in Pediatric Brain Tumor Survivors Treated with Proton Versus Photon Radiotherapy



CENTRAL NERVOUS SYSTEM TUMORS

- Significant impairments in psychosocial functioning, attention, processing speed and measures of intelligence for survivors of medulloblastoma who received RT
- Proton BT reduces dose to normal tissues, and spares brainstem, hypothalamic–pituitary axis and cochlea
- Benefits of Proton Therapy: Reduced neurocognitive outcomes, endocrine deficits and hearing loss.



Baliga S, *Curr Opin Pediatr*. 2019

Rhabdomyosarcoma

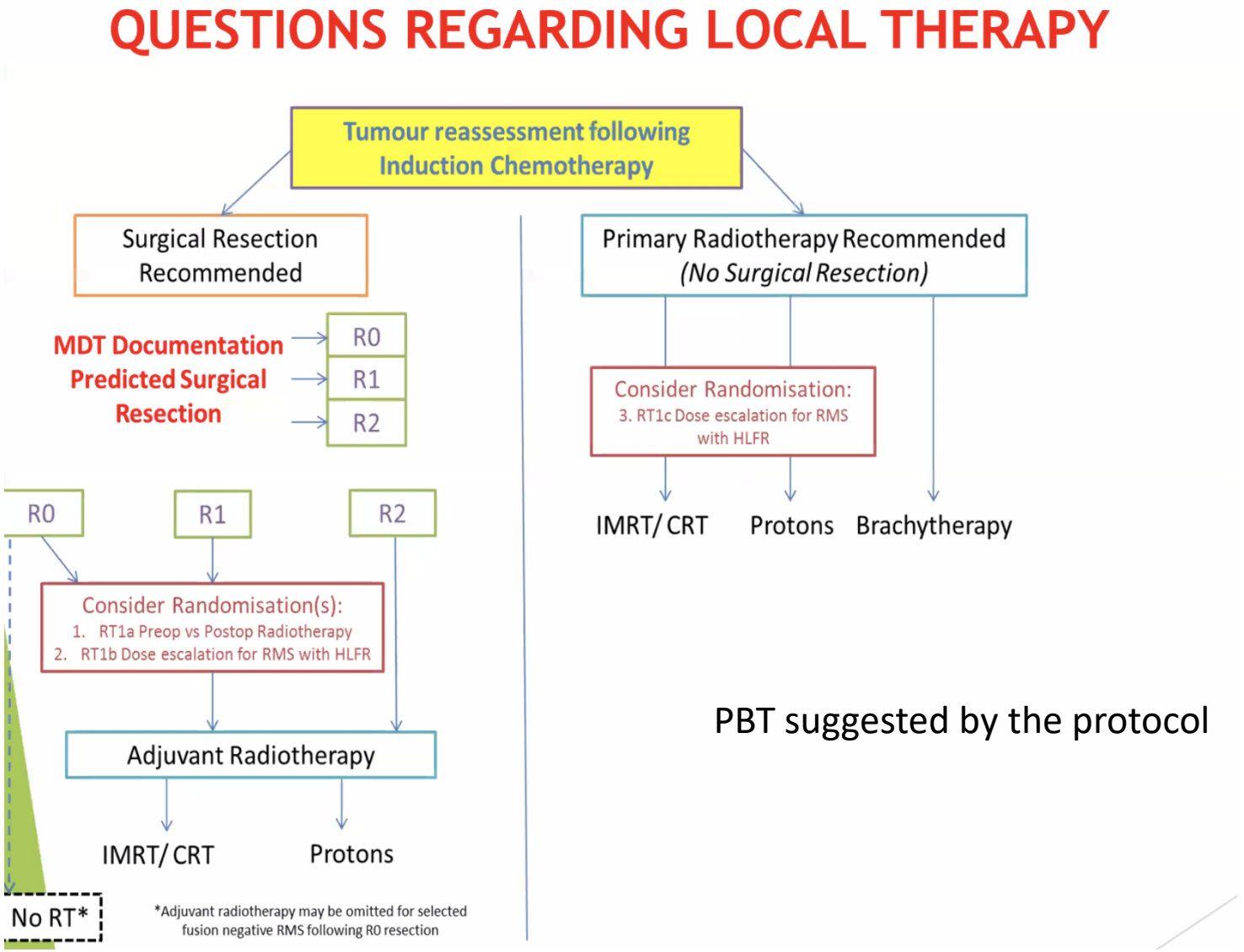
- Malignant tumor originating from striated muscle cells Located where there are striated muscles
  - Head and neck region 40%
  - Genitourinary 25%
  - Extremities 20%
- 2 age groups, the first 1-7 years and the 2nd 12-20 years.
  - In the first group, located in the vagina, bladder
  - In the 2nd group in the male genitourinary system and chest wall

Rhabdomyosarcoma

- Radiation therapy is associated with facial deformities, endocrine deficiencies, bone growth impairment, wound healing complications and peripheral nerve damage in extremity tumors.
- PBT for 83 RMS patients (follow-up of 4.6 ys) demonstrated 5y local control rate of 78.5%. Only 15% of patients experienced grade 3 toxicities, the majority mucositis. The late ocular toxicity grade 3 for orbital RMS was 58.8%, only 6.5% for parameningeal RMS.
- Endocrinopathies were more common in parameningeal RMS (37% vs 29% for orbital RMS).
- In urogenital RMS no grade 3 late toxicities, gastrointestinal and urinary complications grade 1, 2 were 20 and 30%, respectively

Baliga S, *Curr Opin Pediatr*. 2019

FaR-RMS protocol



PBT suggested by the protocol

Non-rhabdomyosarcoma soft-tissue sarcomas (NRSTS)

Large group of histologic subtypes with different grades of malignancy

Liposarcoma

Infantile fibrosarcoma

Synovial sarcoma

Alveolar sarcoma

Dermatofibrosarcoma

Angiosarcoma

Malignant fibrous histiocytoma

Malignant schwannoma

Hemangiopericytoma

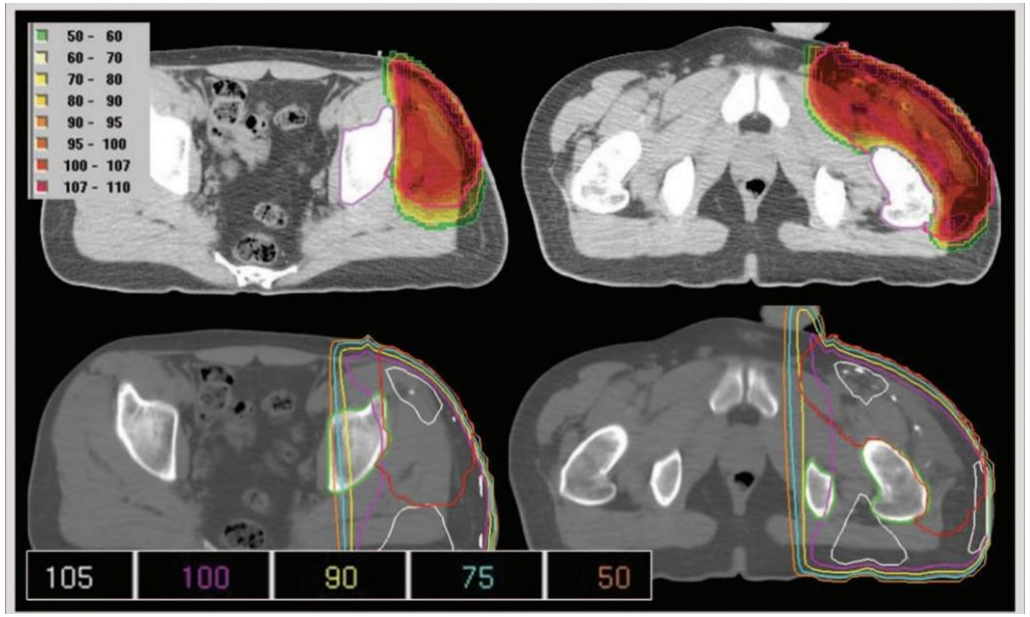
NRSTS Role of radiotherapy

- Radiotherapy: Critical role in the management of NRSTS
- Indicating in patients at higher risk of local failure: marginally resected high-grade NRSTS, high-grade tumors >5cm, unresectable disease
- Neoadjuvant RT has been increasingly used for borderline or unresectable NRSTS, often combined with systemic therapy with the goal of shrinking the tumor to allow for resection
- A clinical challenge arises when patients receive preoperative RT and then undergo surgical resection with positive margins (boost of 10-20Gy?)

Ewing Sarcoma

Radiotherapy: Poor responders or Resections with positive margins

- PBT in 30 children with Ewing sarcoma: (follow-up of 38.4 months) showed excellent 3-y local rate of 86% and minimal serious late effects.
- Weber, reported 38 patients treated with PBT (follow-up of 50 months) 5-year OS was 83%. Toxicity: only two grade 2 toxicities, including endocrine dysfunction and kyphoscoliosis.



Outcomes: Reduced radiation to healthy surrounding tissues, minimizing growth issues and fractures

Merchant TE, *Cancer J*. 2009 Baliga S, *Curr Opin Pediatr*. 2019

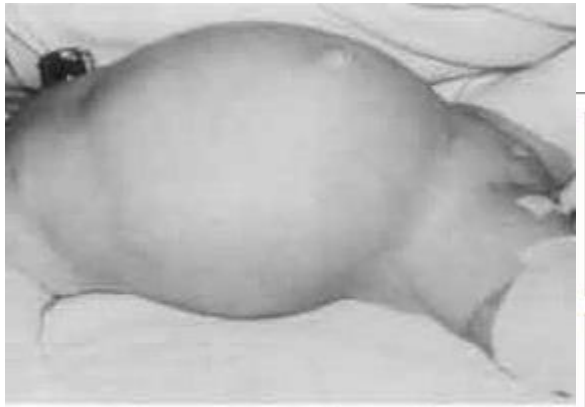
Osteosarcoma

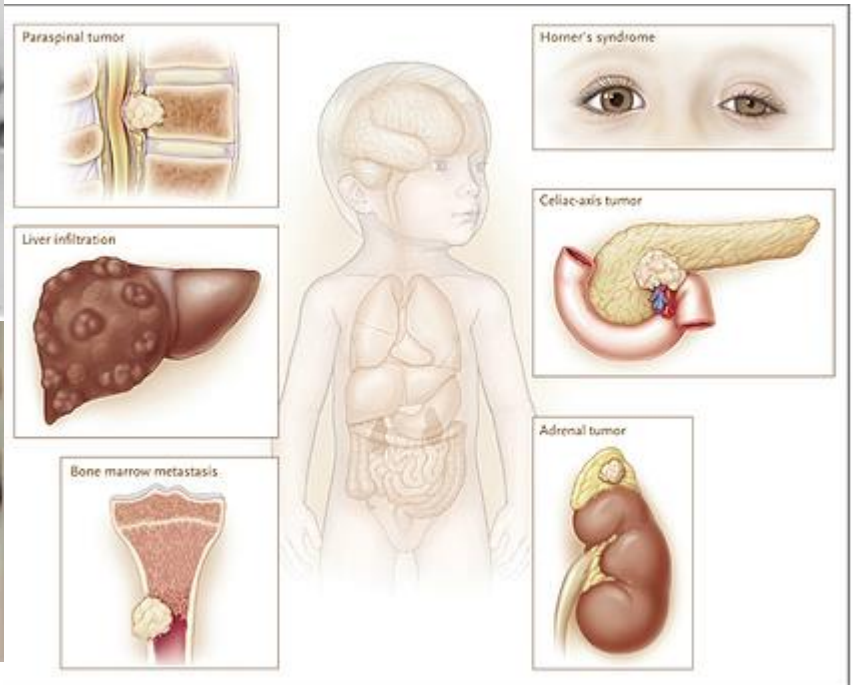
- Indication for RT
  - Inoperable
  - Resected with positive margins
- PBT allows for dose escalation to the tumor with a lower rate of toxicities to the normal tissues and is thus an attractive modality in unresectable osteosarcoma.
- Ciernik reported 55 patients treated with either PBT alone or with photon RT (dose of 68.4 Gy) demonstrated a 5-year local control of 72% with a 30% rate of grade 3 and 4 late toxicities.
- Proton radiotherapy (68.4 Gy) local control at 3 and 5 years: 82% and 72%

Marie-Anaïs Locquet BMC 2023

Neuroblastoma

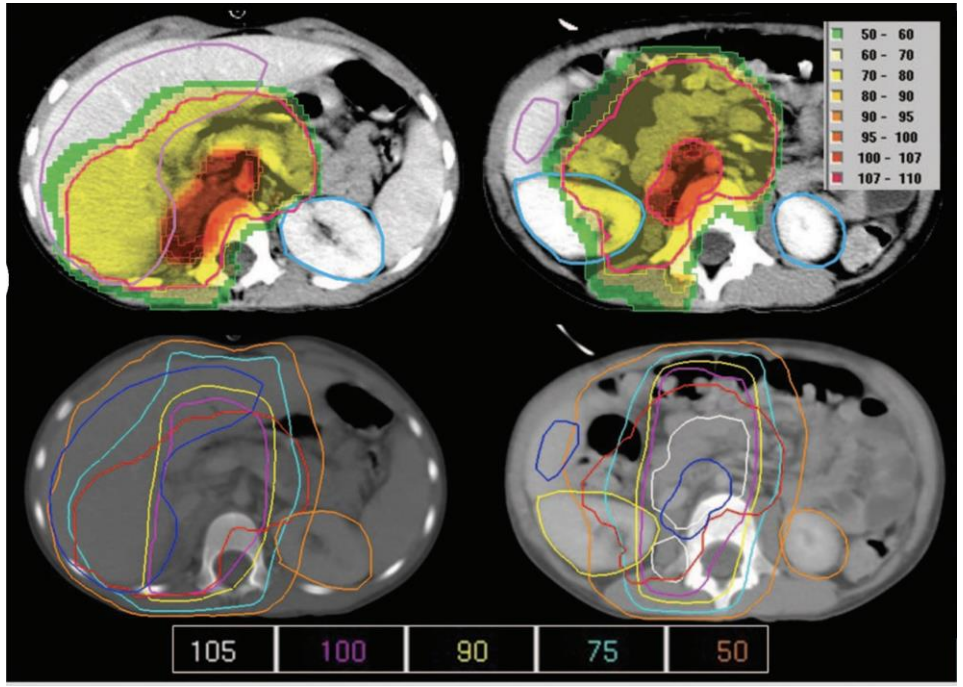
- Average age 2-4 years
- The most common tumor of infancy
- The most common extracranial tumor
- 8-10% of childhood cancer
- 50% metastases at diagnosis
- M>F





Neuroblastoma

Radiation therapy continues to play an important role in local therapy for high-risk NBL for the primary site, and metastases.
PBT can spare normal structures and improve late toxicities.
A dosimetric study of protons vs IMRT for NBL demonstrated lower mean doses to the liver, stomach, small intestine, bone, pancreas and colon.
Hattangadi reports 100% local control (follow-up of 38 months) and minimal acute side effects with no serious late-effects in 9 patients.
A study of 14 patients treated with PBT for neuroblastoma demonstrated 3-year local control of 82% with no severe acute toxicities and 7% grade 3 and 4 late toxicities

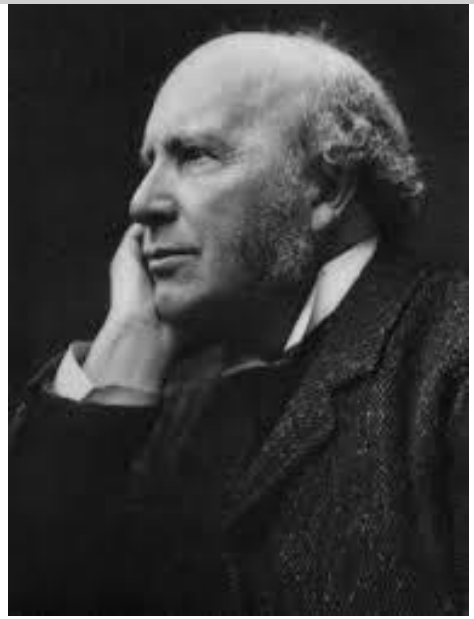


Merchant TE, *Cancer J*. 2009

Baliga S, *Curr Opin Pediatr*. 2019

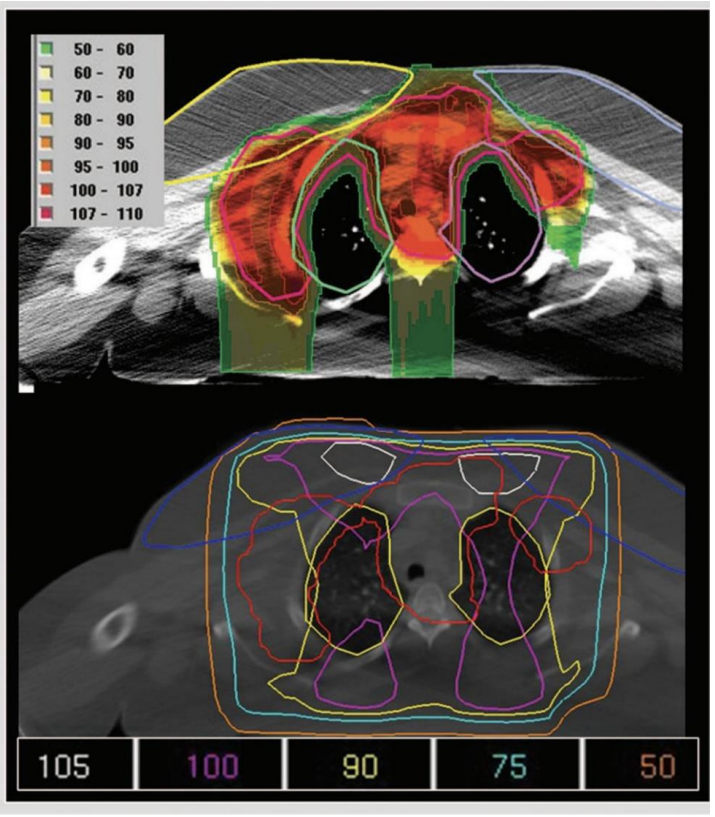
Hodgkin Lymphoma

- Described by Hodgkin 1832
- 40% of pediatric lymphomas
- Age distribution 2-3rd decade and 5th-6th
- Cure rate 70-99%



Hodgkin Lymphoma

Reductions in dose to heart, lungs, and breasts are significant



Radiotherapy in Hodgkin's disease is employed depending on the response of the patient's disease to chemotherapy.

PBT is being evaluated as a tool to further mitigate the risks of late-effects, including cardiac disease and second malignancies.

Wray reports 22 pediatric Hodgkin's disease patients treated with PBT to a dose of 21 Gy. The overall 3-year PFS and OS was 83% and 94%, with no significant acute or late toxicities.

Another study investigated outcomes for patients treated with consolidative PBT to a median dose of 30.6 Gy. 3-year relapse-free survival (RFS) was 87% in pediatric patients with no grade 3 toxicities.

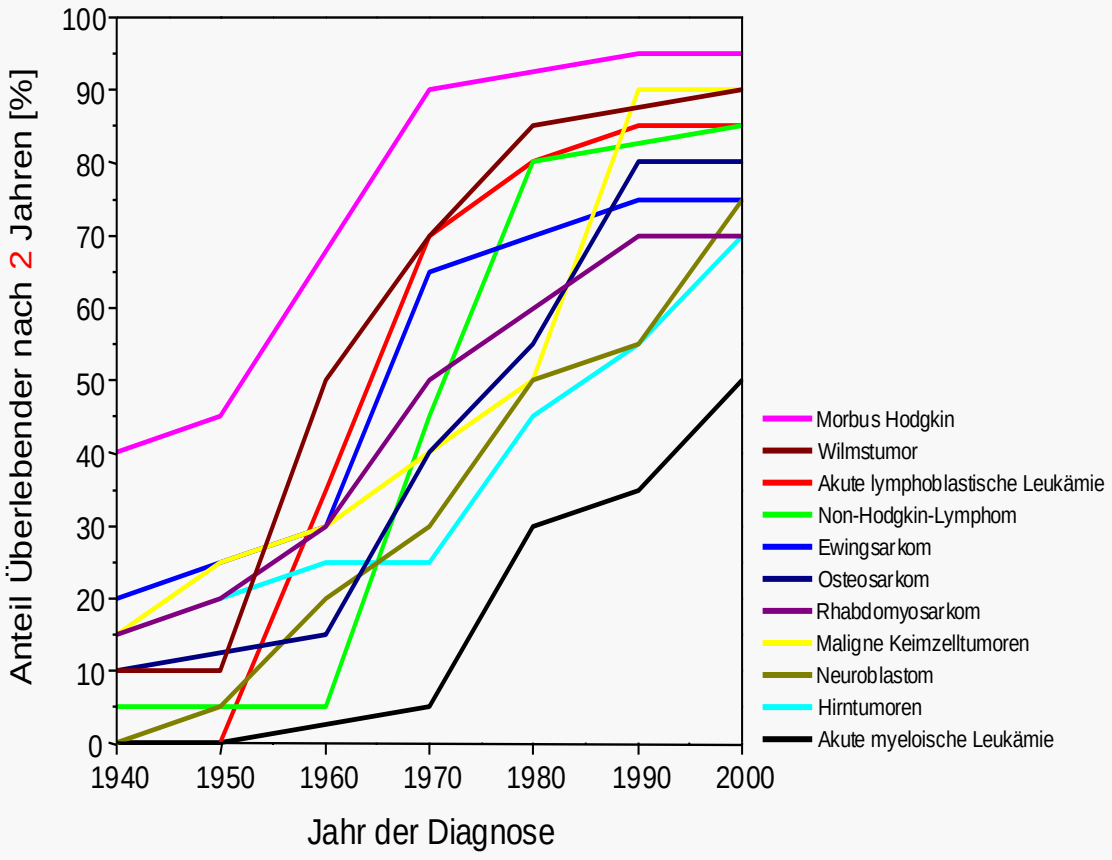
Merchant TE, *Cancer J*. 2009

Baliga S, *Curr Opin Pediatr*. 2019

Pediatric Cancer in Greece

300 new diagnoses
<15 years of age/year

Increasing the survival of children with cancer
8 out of 10 children are cured

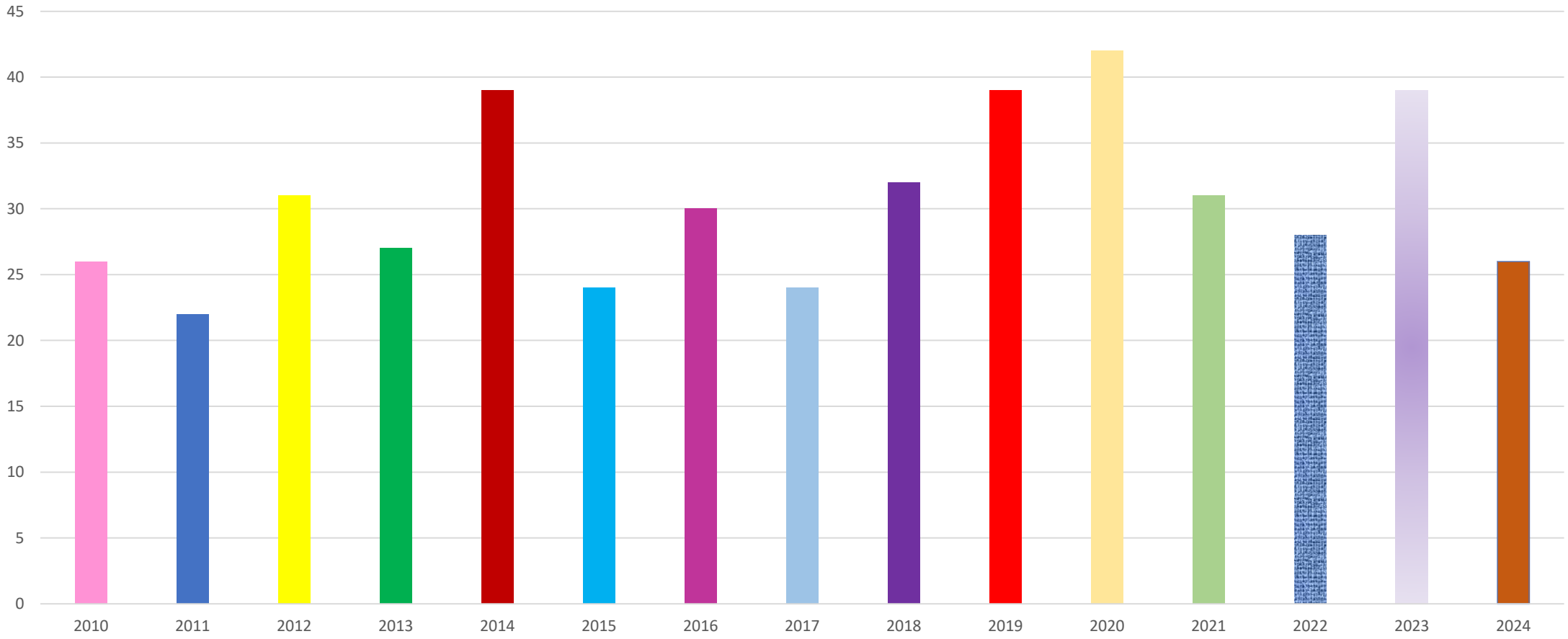


Report of pediatric oncology patients treated in Thessaloniki

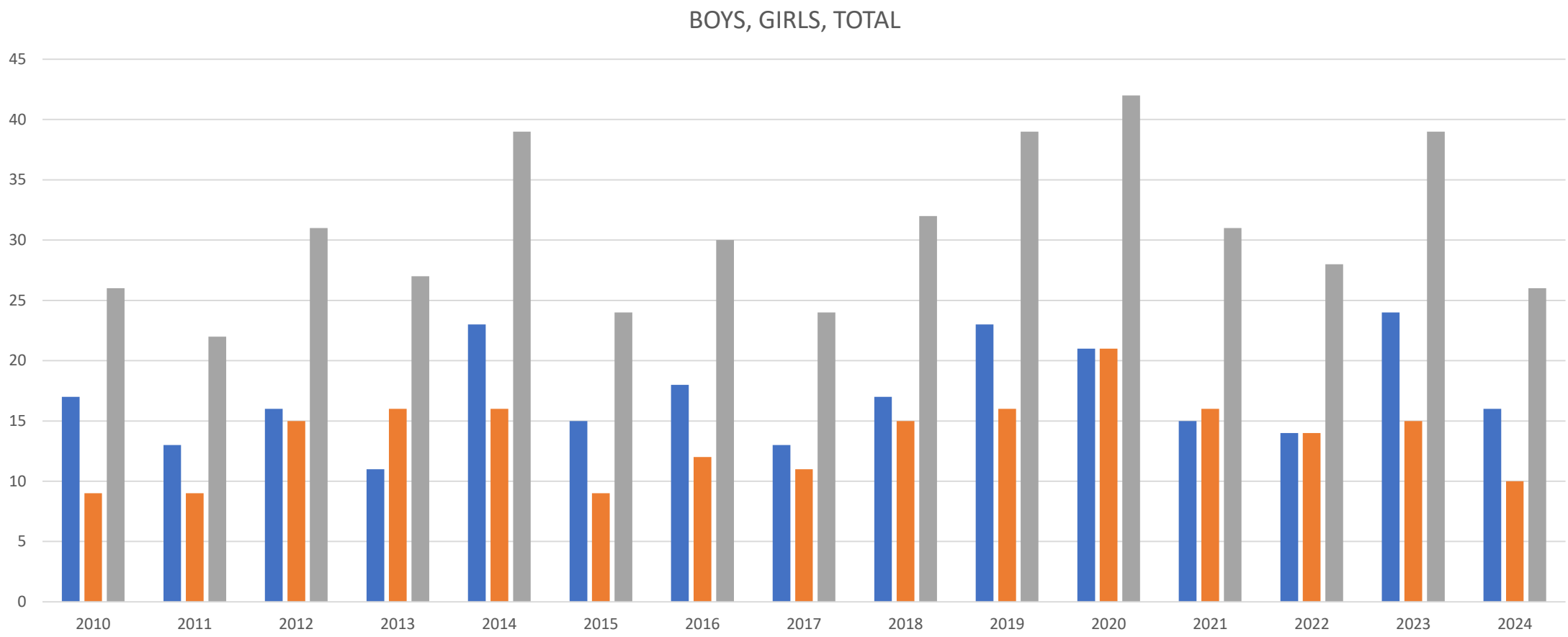
Report of pediatric oncology patients treated in Ippokratio Hospital

Pediatric Oncology Department Ippokratio Hospital 2010-2024

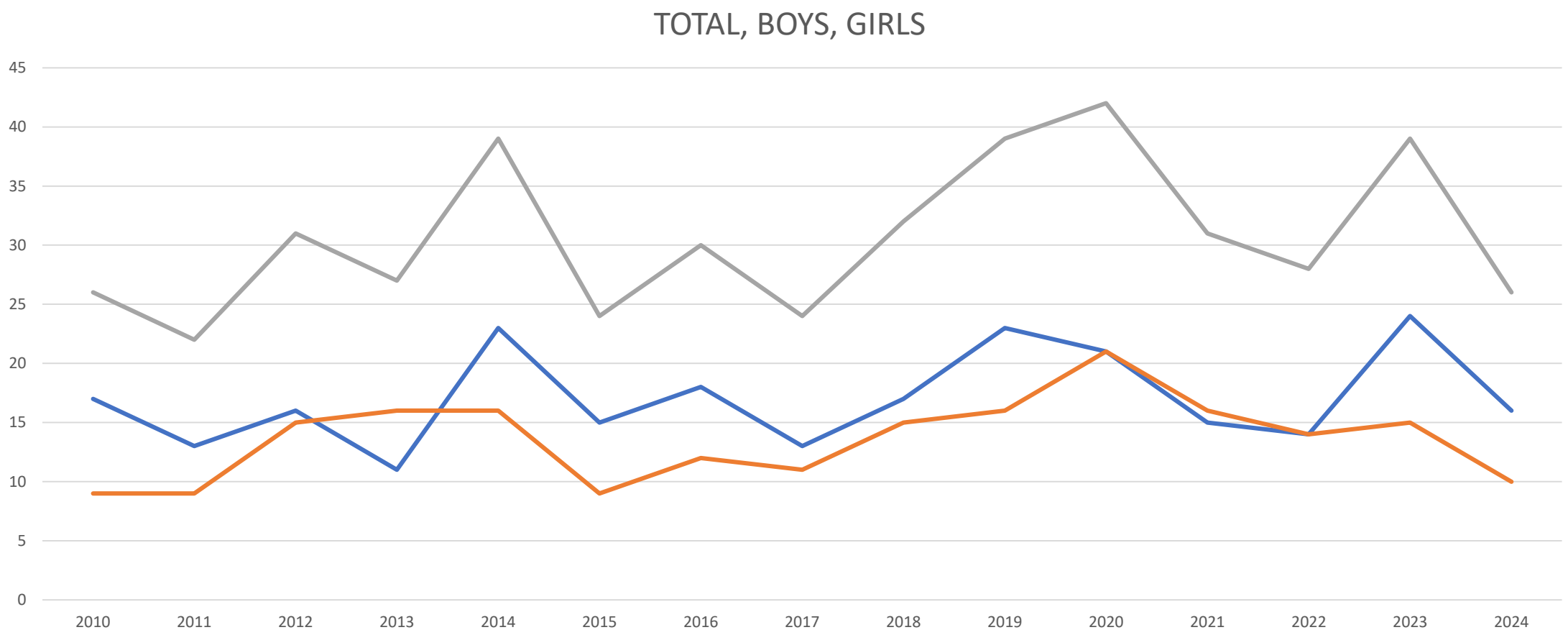
Pediatric Oncology Patients Ippokratio Hospital 2010-2024



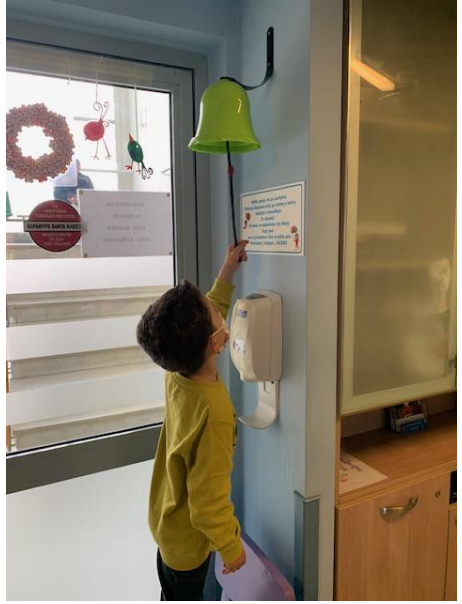
Pediatric Oncology Patients Ippokratio Hospital 2010-2024

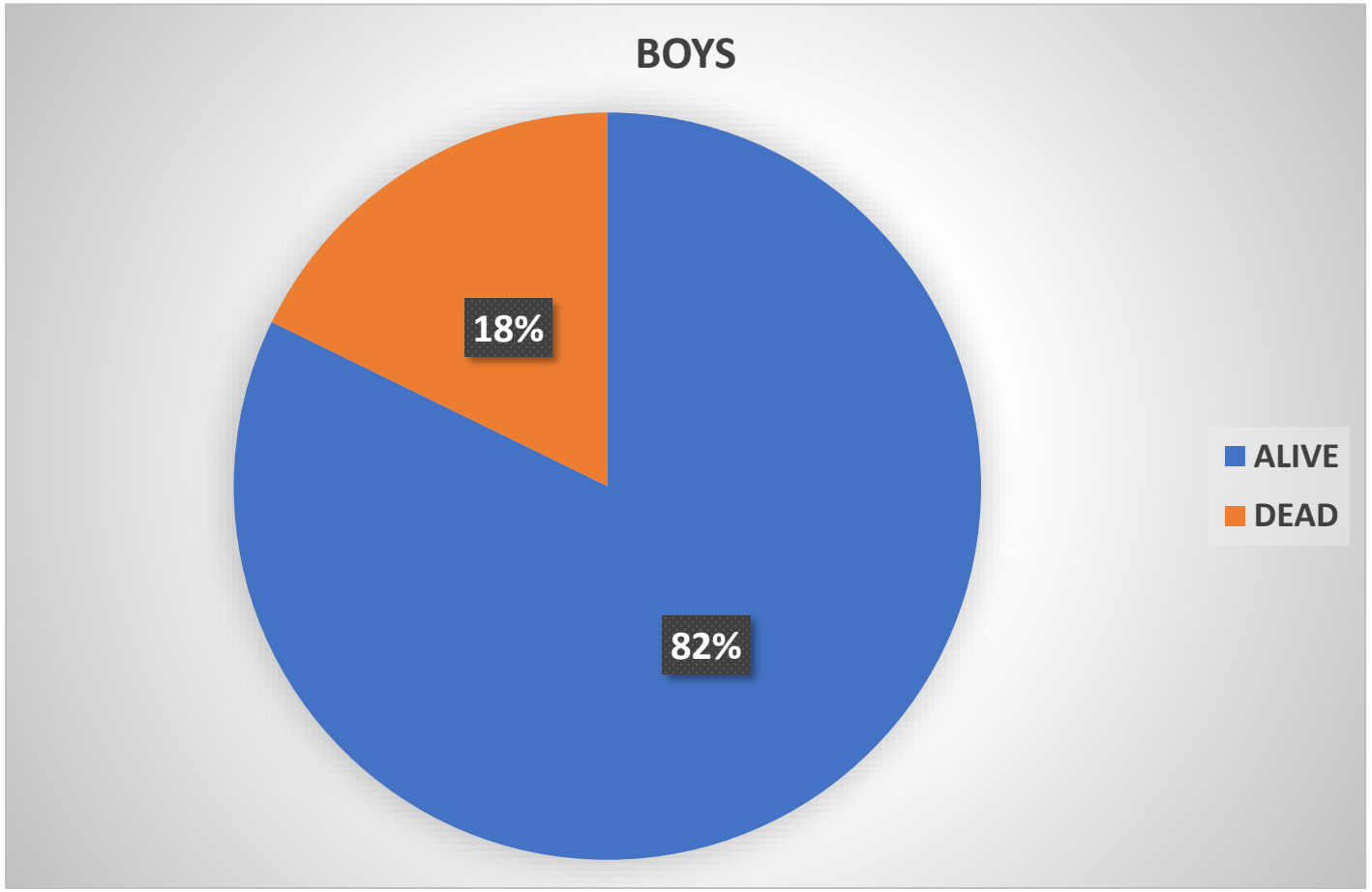


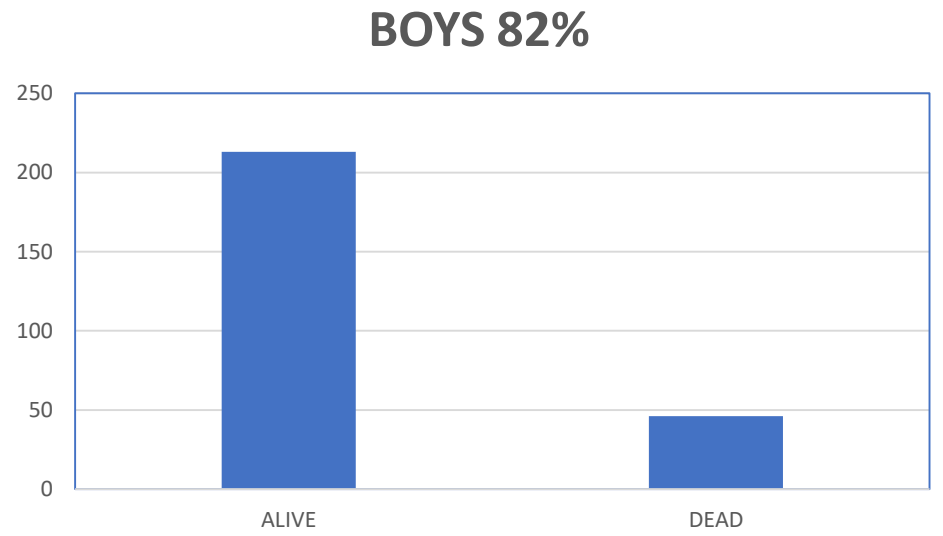
Pediatric Oncology Patients Ippokratio Hospital 2010-2024



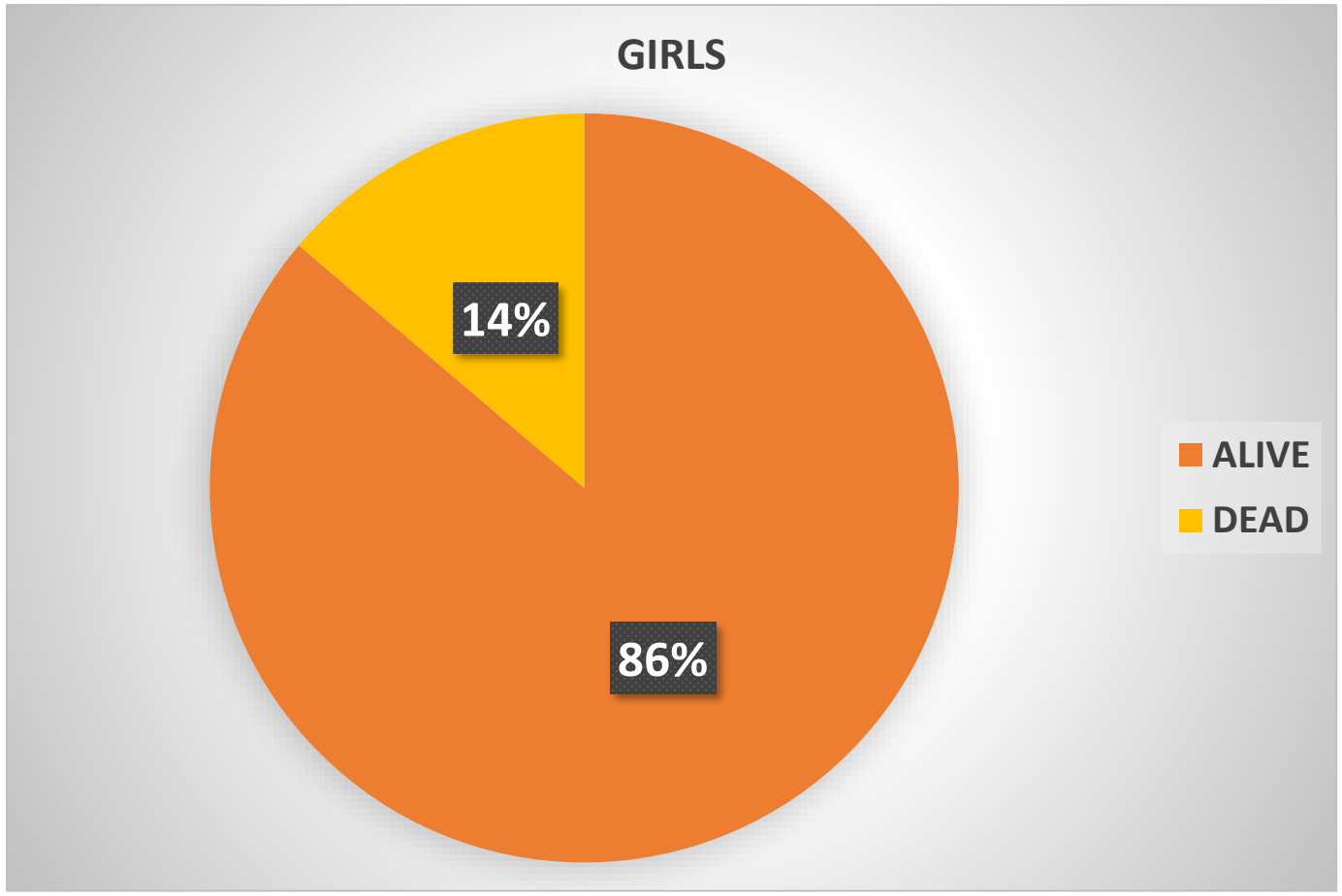
Overall survival of male patients 82%

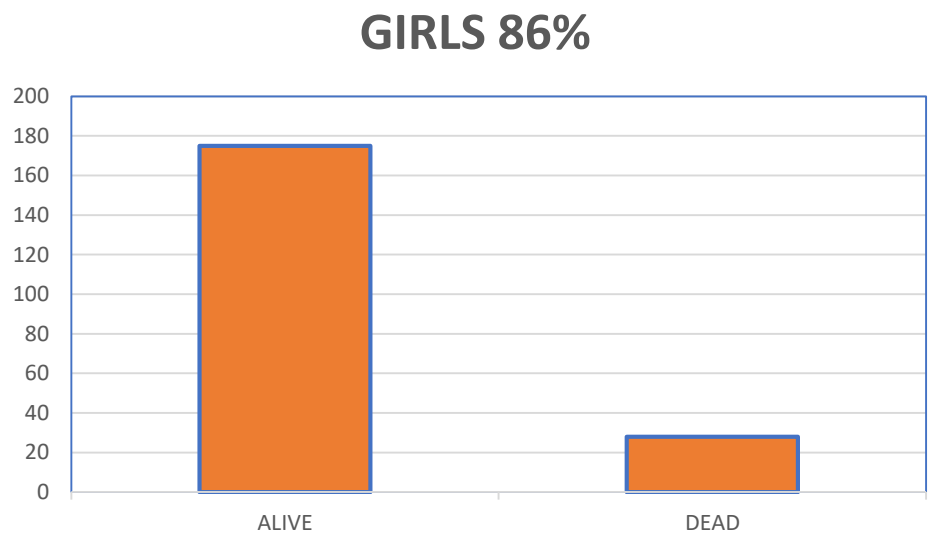




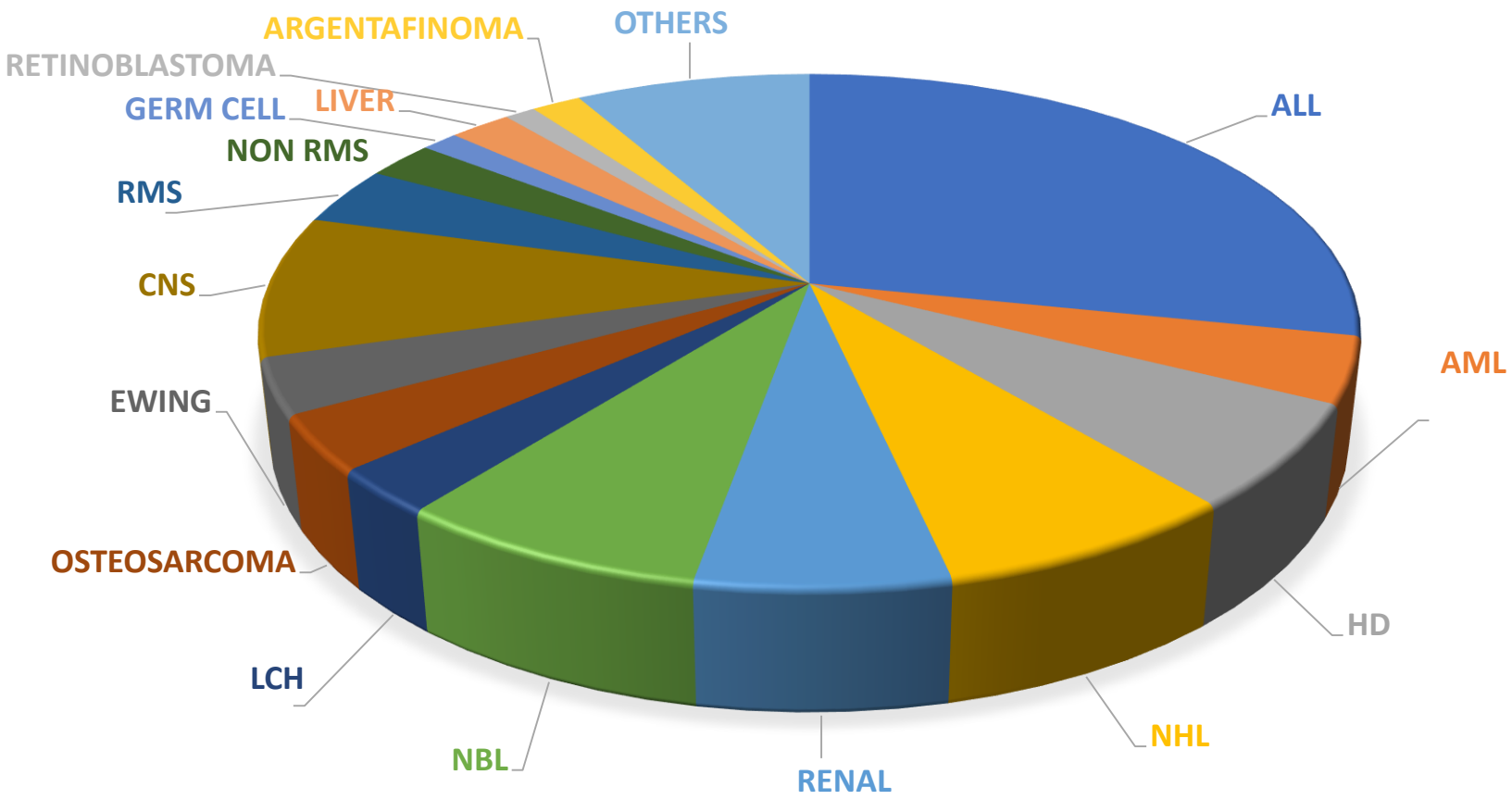


Overall survival of female patients 86%

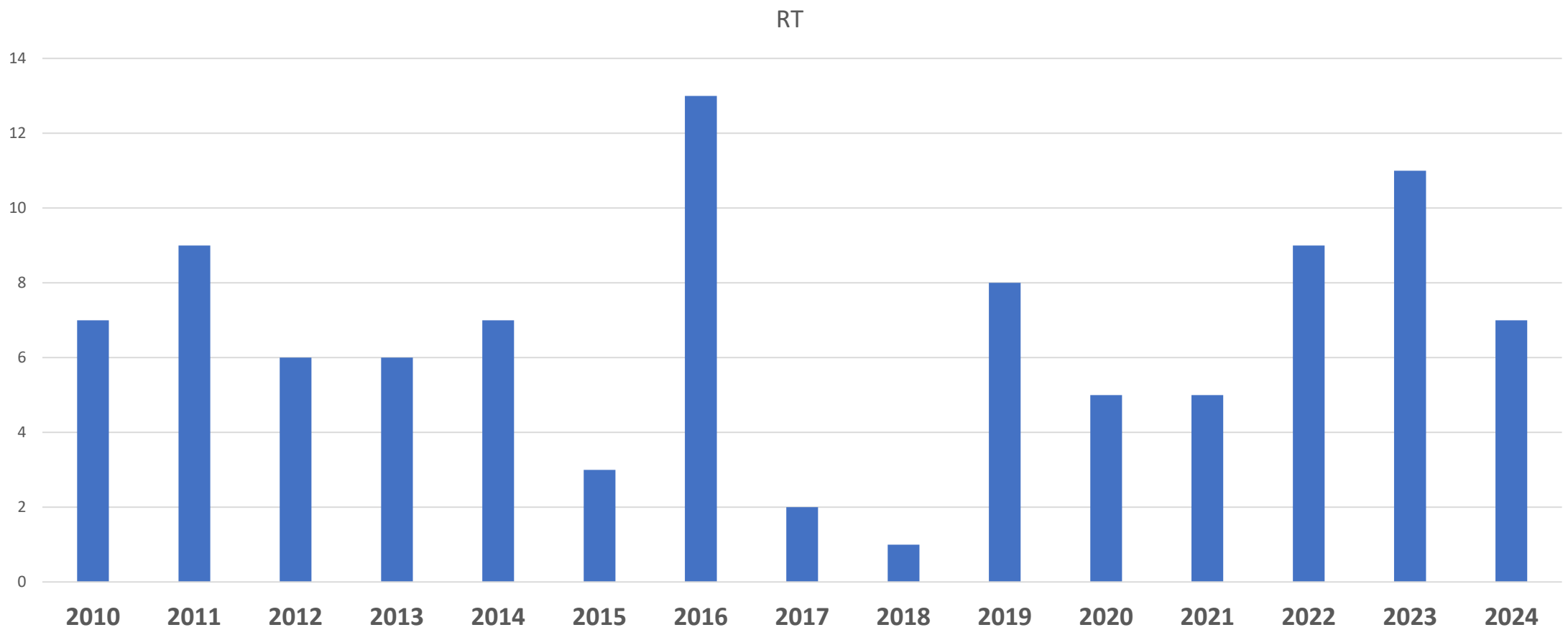




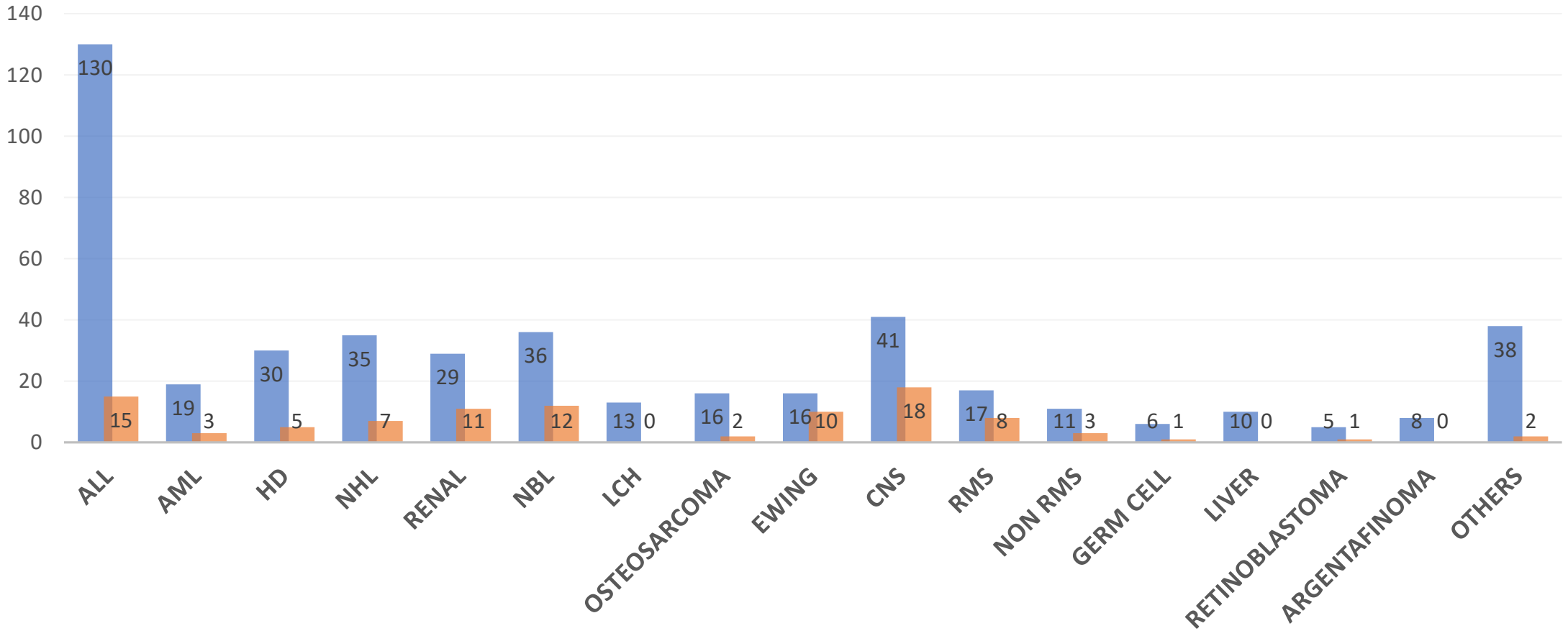
Frequency of pediatric tumors 2010-2024



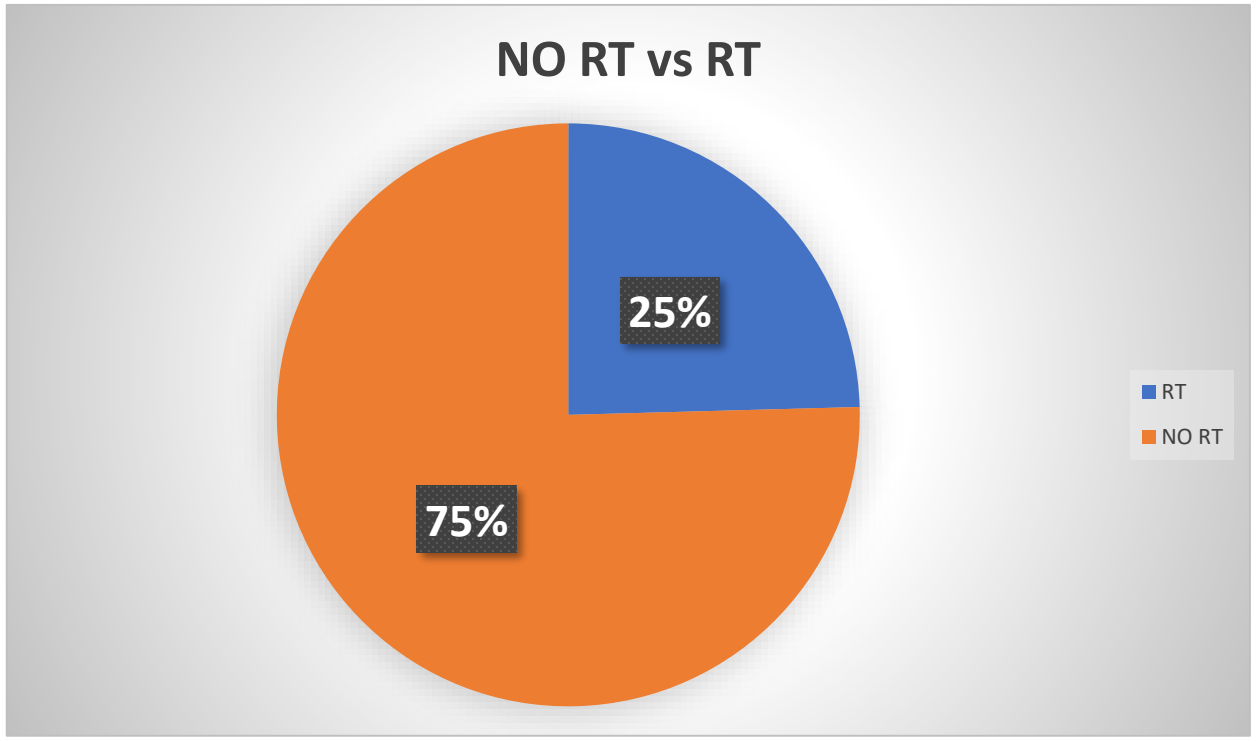
Patients who received RT 2010-2024

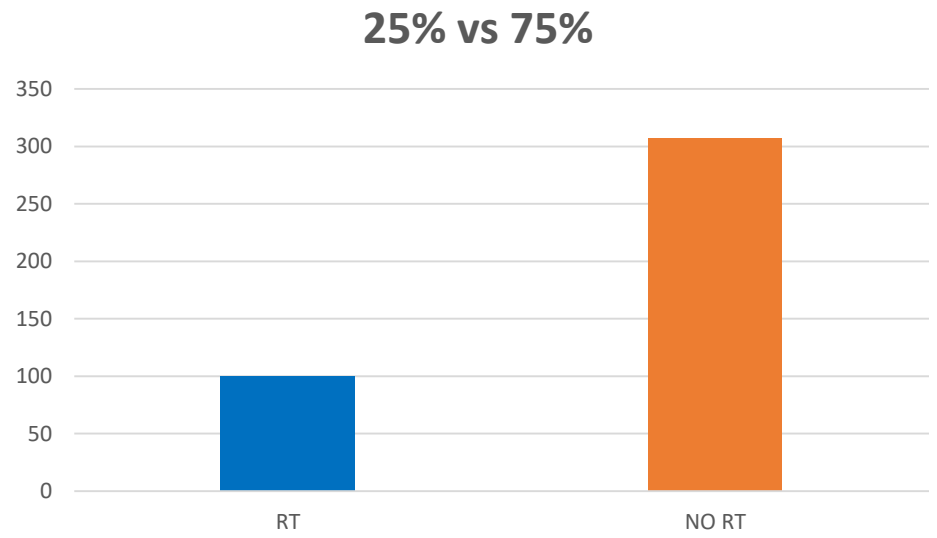


Patients who did not receive RT vs RT 2010-2024

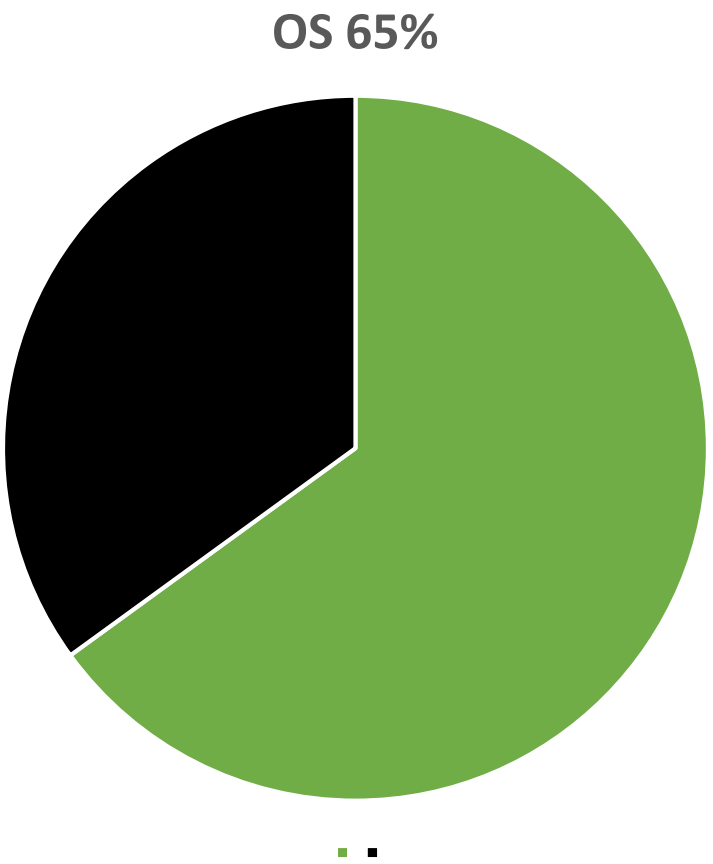


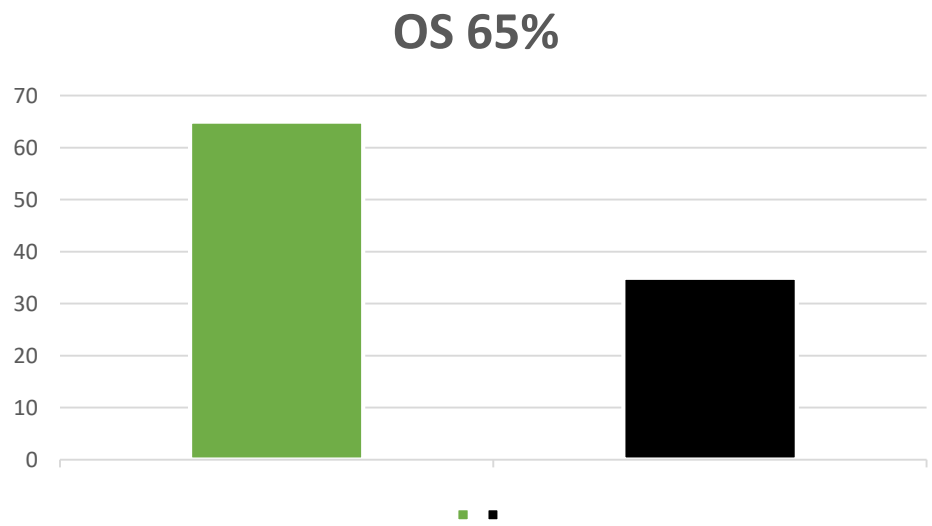
Patients who did not receive RT vs RT 2010-2024





Survival of patients who received RT 65%





Overall Benefits and Challenges to Proton Therapy

Benefits: Precision, reduction in side-effects, preservation of organ function, lower long-term risks

Challenges: High cost, limited availability, not suitable for all types of cancers

Future directions: Expanding access, and ongoing clinical trials to minimize toxicities further

Home message

Proton therapy offers significant benefits in the treatment of pediatric malignancies, particularly for tumors in critical or radiosensitive locations

Future of Proton Therapy: Expanding access, refining radiobiological models, and integrating novel imaging techniques to optimize outcomes


Never Never Never Never Never
EVER EVER EVER
EVER EVER EVER
EVERREVER
GIVE UP
Stay strong

Thank you

for your attention