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PROTONEN BEI KINDERN

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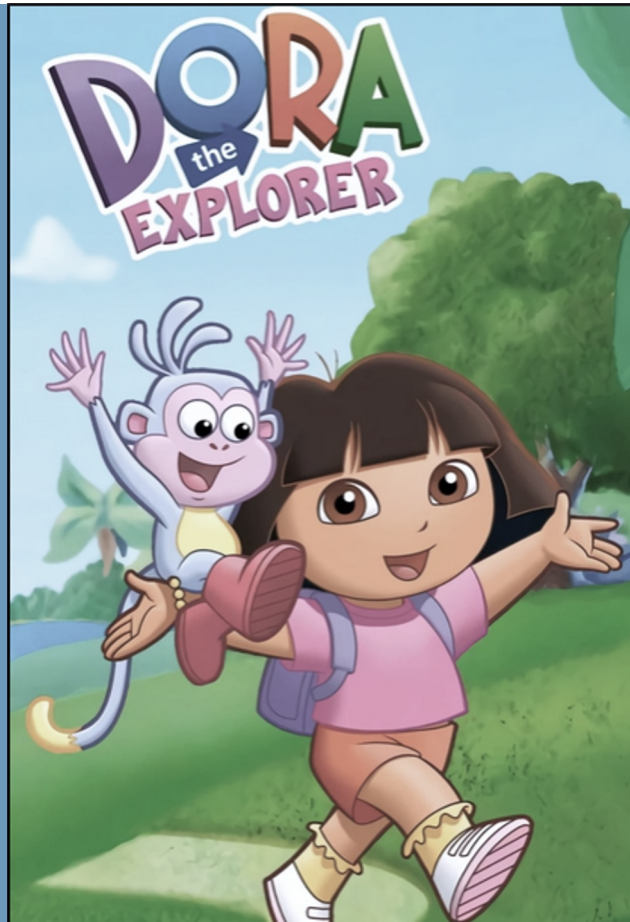

Disclosure

No conflicts of interest.

MASSACHUSETTS GENERAL HOSPITAL
RADIATION ONCOLOGY

HARVARD MEDICAL SCHOOL

krebsforschung schweiz
recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research

MGH Pediatric Radiation Oncology Clinical Research Team

Pediatric Proton/Photon Consortium Registry

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Objectives

Appreciate the spectrum of long-term late effects and importance of cancer survivorship care.

Become familiar with strategies to mitigate the burden of late effects and increase health-related quality of life.

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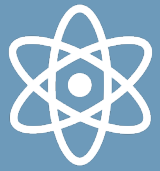
Questions



Can **proton** radiotherapy diminish radiation-related morbidities in childhood cancer survivors (CCS)?

Does proton radiotherapy increase the risk of **brainstem toxicity** in children with primary tumors of the posterior fossa?

How can we improve CCS care?

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Outline

Childhood (adolescent and young adult) cancer survivorship in high-income countries:

Epidemiology

Paediatric (radio-)oncology

Adverse effects

Mitigation strategies

Quality of life

Challenges

Lifestyle & Surveillance

Collaboration

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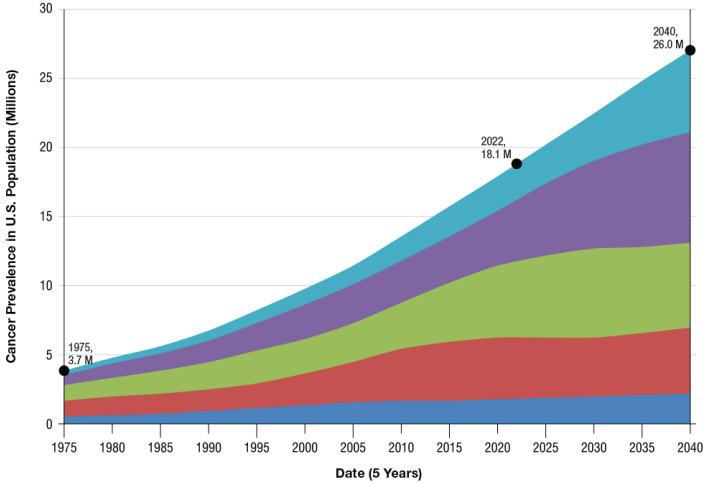
Epidemiology (high income countries)

Cancer overtakes cardiovascular disease to become leading cause of death.

BMJ 2019: Dagenais et al. Lancet, 2019 | Yusuf et al. Lancet, 2019

↗ Prevalence

Cancer Prevalence and Projections in U.S. Population from 1975–2040



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Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36.

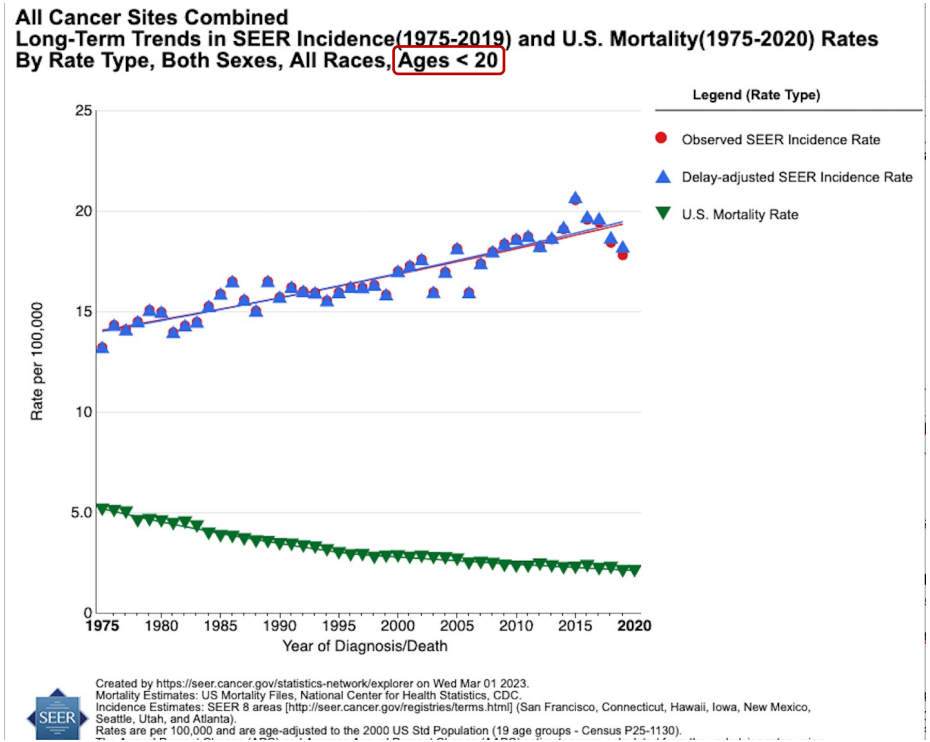
Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J and Siegel RL. Cancer Treatment and Survivorship Statistics. CA A Cancer J Clin. 2022.

Epidemiology CCS (U.S.)

Progress in pediatric cancer survival

↗ Incidence ↙ Mortality

>80% CCS will be cured. 1 CSS in 750.



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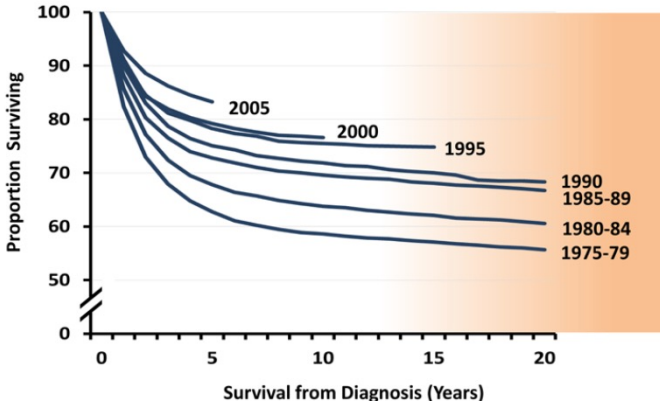
Epidemiology CCS (U.S.)

Progress in pediatric cancer survival

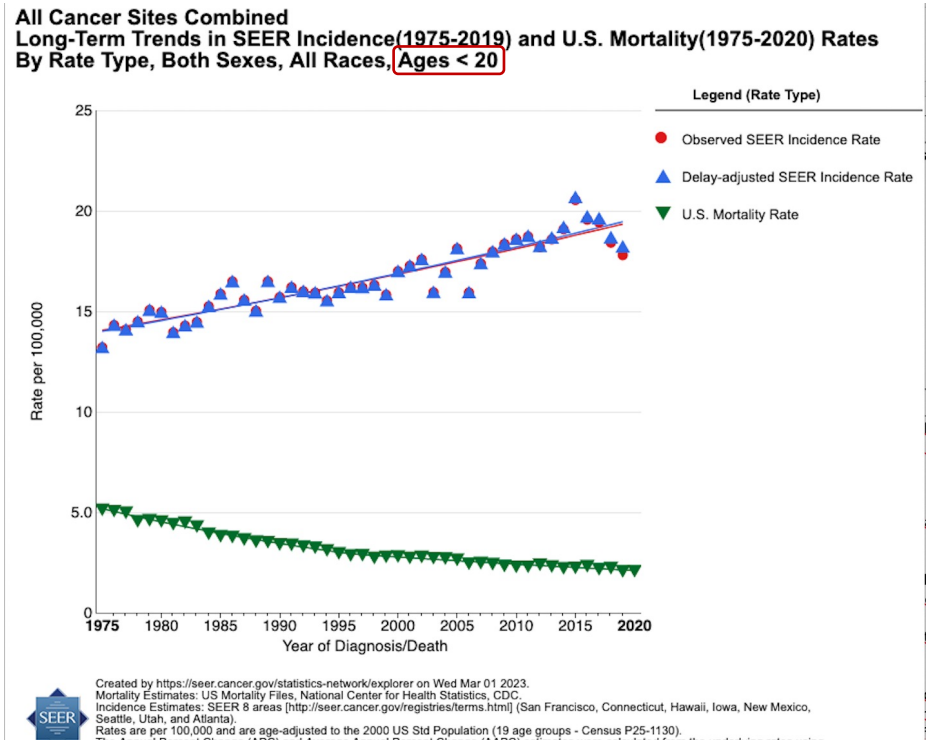
- Incidence
- Mortality

>80% CCS will be cured. 1 CSS in 750.

- OS by year of cancer diagnosis



Howlader et al, *SEER Cancer Statistics review* 1976-2012
Robison & Hudson, *Nature Reviews Cancer* 2014



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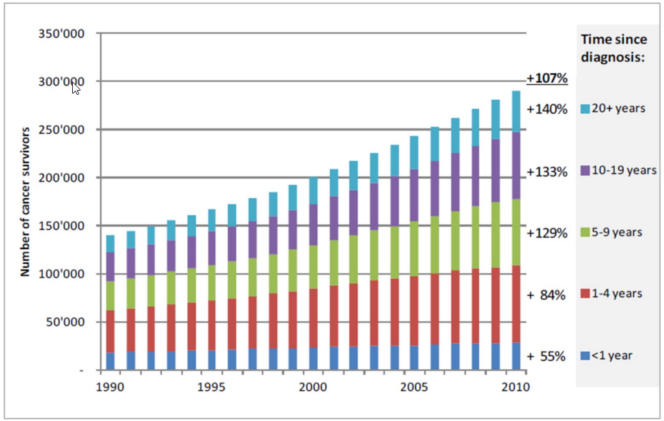
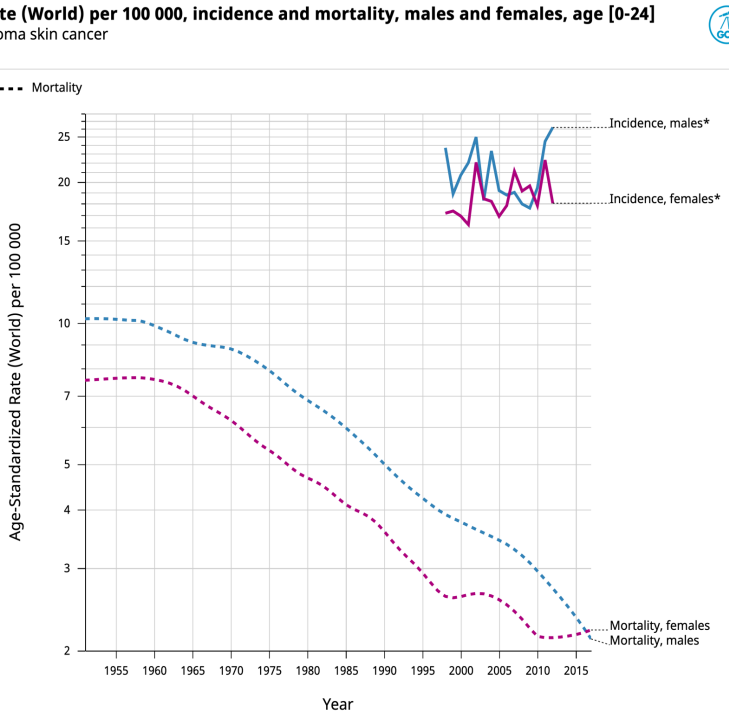
Epidemiology **CCS** (Switzerland)

Prevalence of CCS in CH

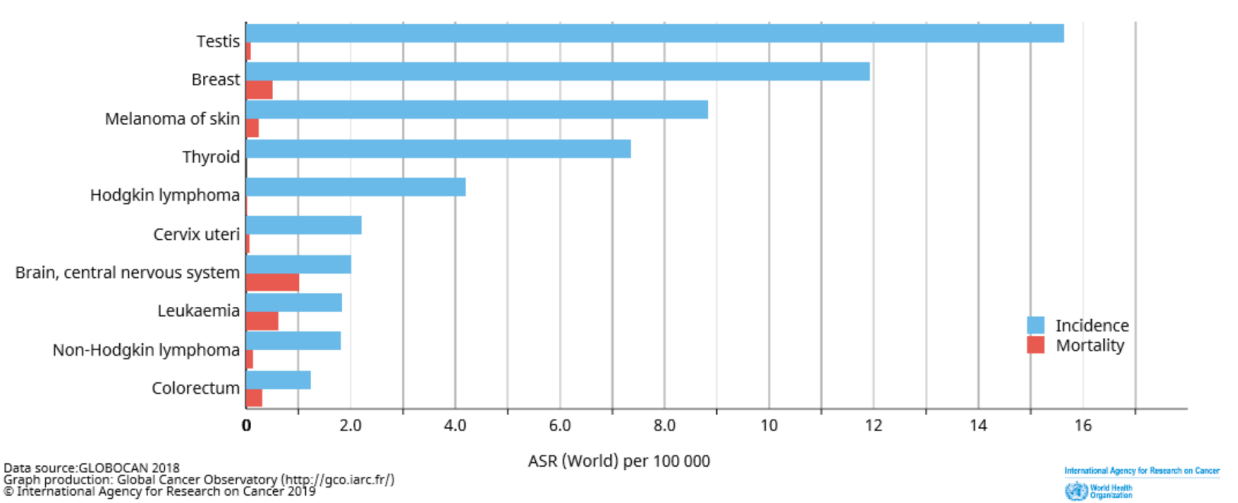


Herrmann et al, *BMC Cancer* 2013



Epidemiology AYA (Switzerland)

Adolescentes & young adults (AYA) with CNS tumours present ↗ mortality.



Age standardized cancer incidence and mortality in AYA 15-34 y.o. in CH

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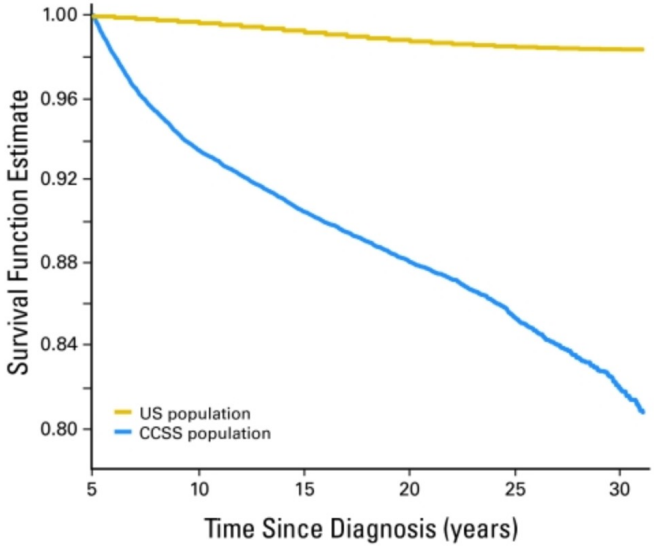
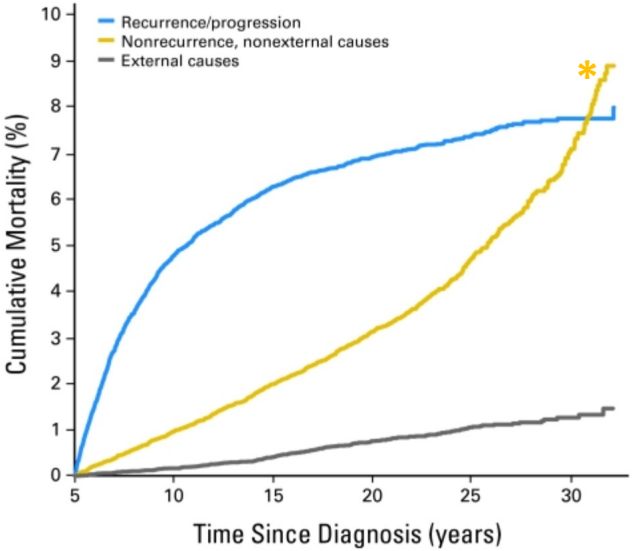
Mortality CCS

8.4x ↗ risk than standard US population

Driven by chronic health conditions - **2. malignancy**

leading cause *30 years after cancer

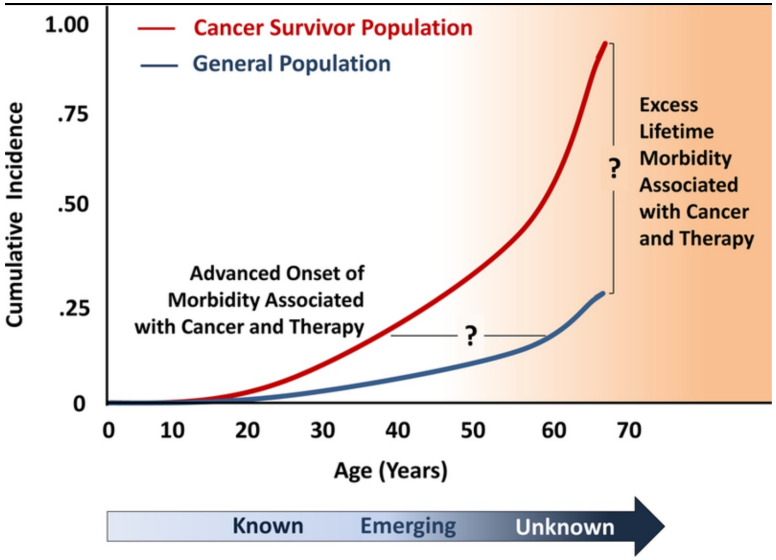




Armstrong et al, *J Clin Onc* 2009 | Mertens et al, *JNCI* 2008

Morbidity CCS

By 50 years of age the majority will have a multifactorial
serious/disabling or life-threatening chronic health condition – cancer treatment morbidity



Robison & Hudson, *Nature Reviews Cancer* 2014

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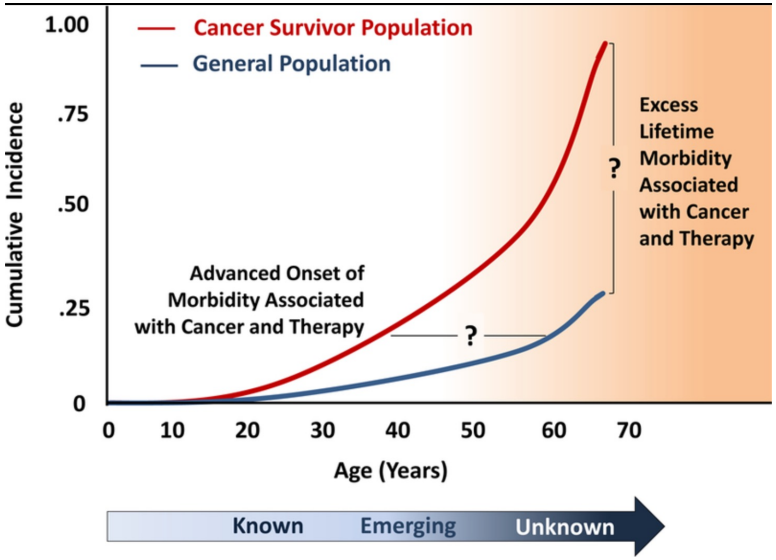


Robison & Hudson, *Nature Reviews Cancer* 2014

Cohort size	≥1	≥2	Severe	problems
290 (Birmingham, UK) *Eur J Cancer 1998*	58%	32%	-	
96 (UT Southwestern) *Cancer 2000*	69%	36%	30%	
10'397 (CCSS) *NEJM 2006*	67%	33%	33%	
1362 (Dutch LESG) *JAMA 2007*	75%	-	40%	
1'713 (St. Jude Life) *JAMA 2013*	95.5%	-	80.5%	

Modified from Shatia et al. 2006

Paediatric (Radio-)Oncology evolution

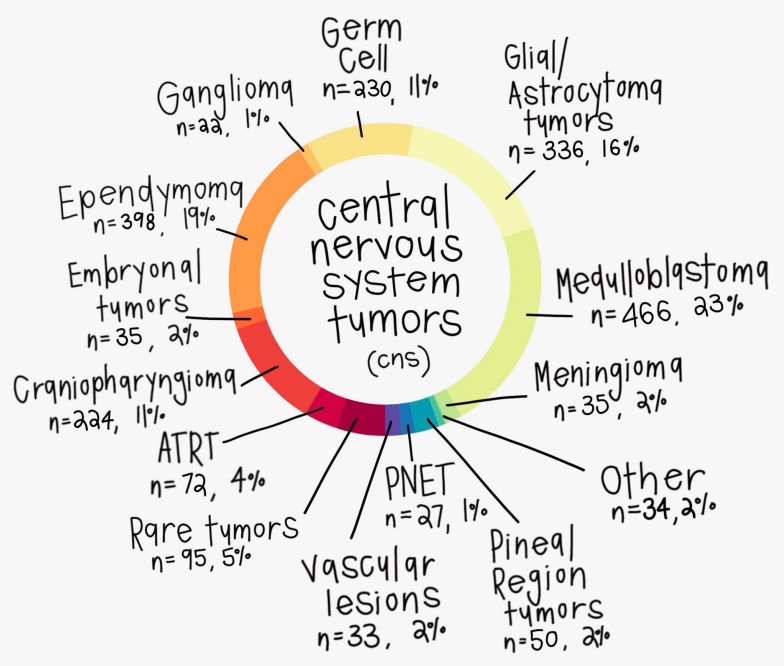
- Continue effort for maximal debulking (e.g., 2nd look surgery for ependymoma)
- Continue use of chemotherapy
- Consider use of high dose chemotherapy
- **Re-introduce radiotherapy in younger patients**
  - highly conformal planning
  - local-field radiotherapy, no craniospinal irradiation if not disseminated

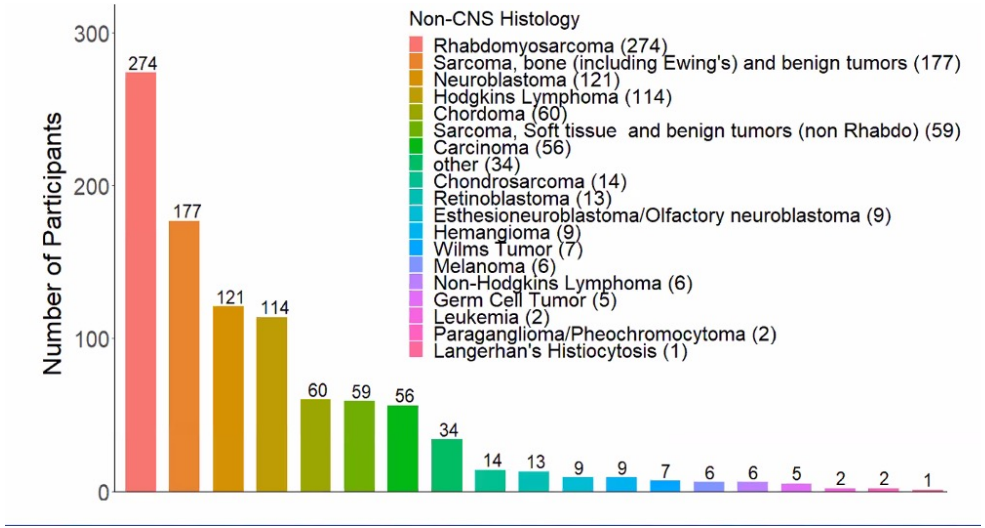
CURE: “To bring the patient back to the state prior to the actual illness” *(The Great Oxford Dictionary)*

- ✓ Eradicate cancer
- ✓ Without functional or cometic side effects
- ✓ Restoring quality of life

Paediatric solid tumours

Pediatric Proton/Photon Consortium Registry





2021 - https://www.pediatricradiationregistry.org/

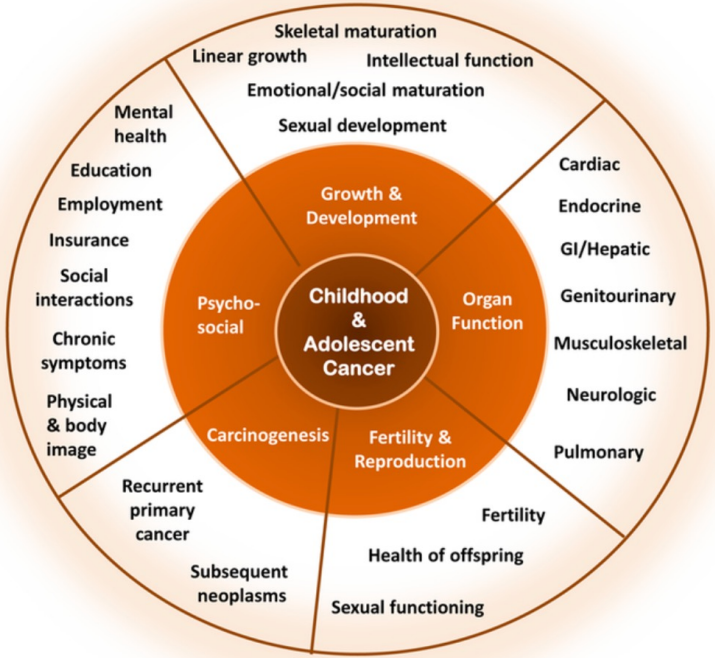
Adverse effects in CCS

Treatment phase Post treatment phase

Short-term

Long-term (persistent)

Late-effects (delayed onset)



Robison & Hudson, *Nature Reviews Cancer* 2014

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Adverse effects in CCS – multifactorial risk

Often associated with inherited conditions, **differ from those in adults** (incidence, histology, outcome, prognosis, genetic mutation type/nr…)

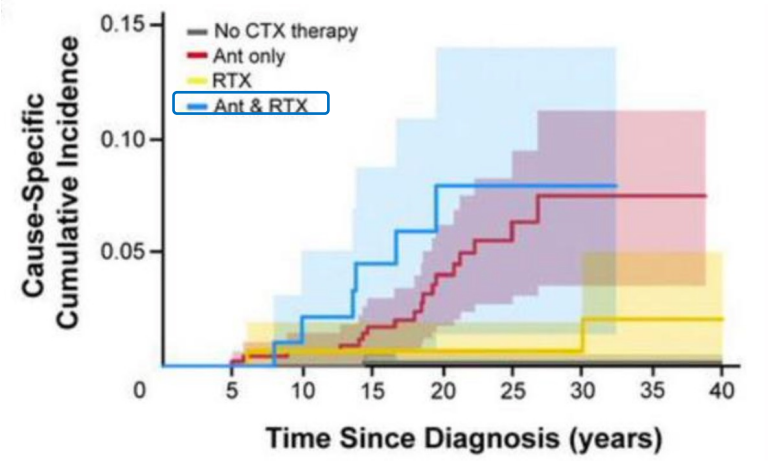
Host / Genetics

Ex.: Child with acute toxicity moist desquamation after 36 Gy_{RBE} craniospinal irradiation with protons (skin dose less!),
→ genetic workup: *Fanconi gene* variant mutation, more susceptible to side effects.

Multimodality (surgery, systemic, radiation therapy)

Risk: individual, often greater than additive

Lanzkowsky, Manual of Pediatric Hematology and Oncology, 2011



NCI Publications-Late Effects of Treatment for Childhood Cancers (PDQ).
https://www.cancer.gov/types/childhood-cancers/late-effects-hp-pdq#section/_1360

RT adverse effects

Deleterious for any normal tissue
Worse for children (under development, normal tissue growth; general long life expectancy)

Dependent on:

- Age at time of treatment
- Host (genetics, comorbidity)
- Total dose
- Dose homogeneity
- Dose per fraction
- Volume of the irradiated tissue
- Type of radiation
- Technique
- Radiosensitizers
- Time from exposure

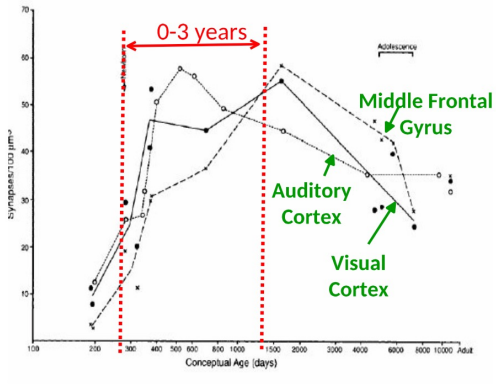
Toxicity	Main risk factors
Neurocognitive	Volume, dose
Leukoencephalopathy	Volume, dose
Endocrine	Dose
Growth	Growth hormone, dose, T4, nutrition
Hearing	Cochlear dose
Secondary malignancy	Age, genetics, tumour, volume, dose

Wang, Wilson et al., *J Clin Oncol* 2018
Armstrong et al., *J Clin Oncol* 2013
Scott et al., *JAMA Oncol* 2018
Ehrhardt et al, *Curr Oncol Rep* 2016

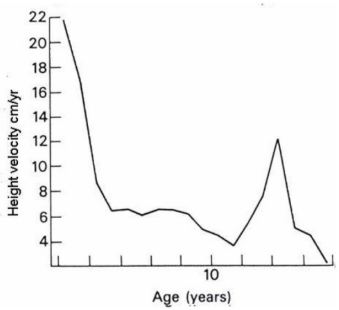
Paediatric development

Development curves of different tissues according to age

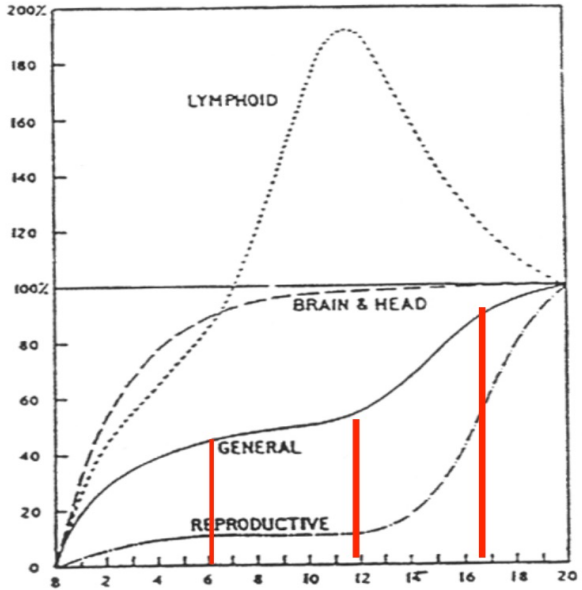
- Important time intervals | 0-6 years
  (Pre-)pubertal growing phase

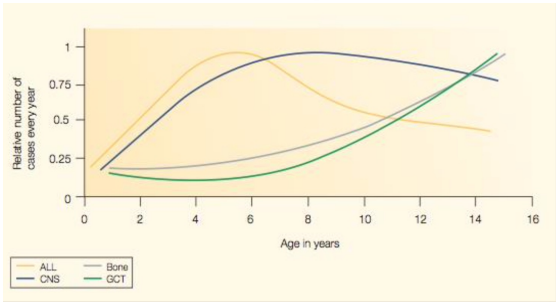


BRAIN



HEIGHT





Modified from Rubin et al., 1982

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Protons vs Photons

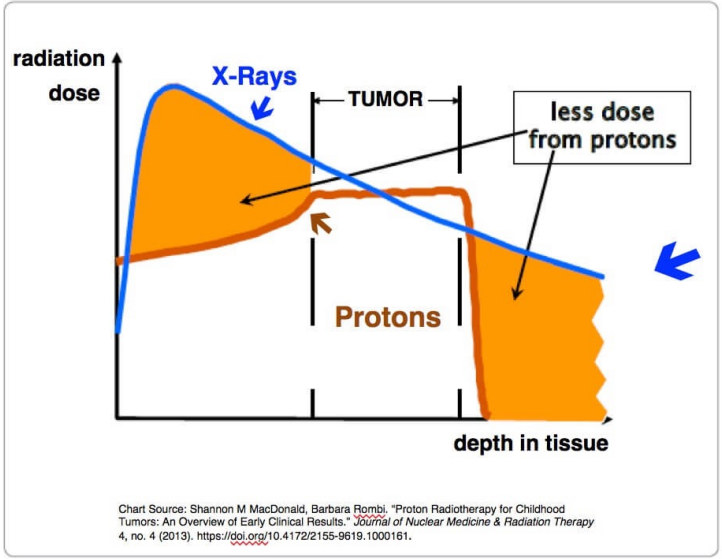
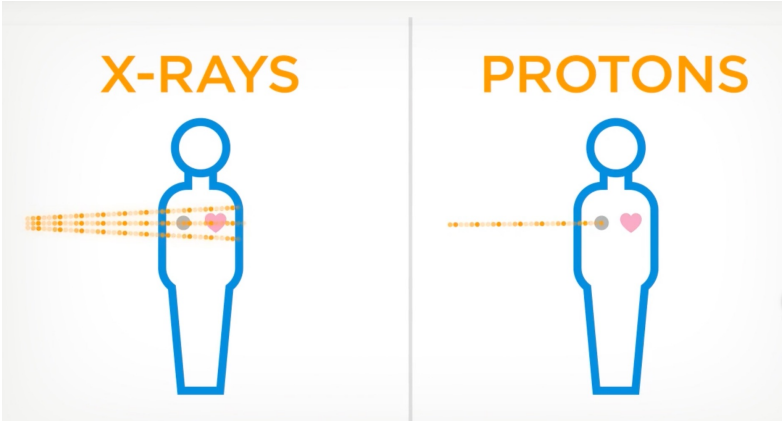


Chart Source: Shannon M MacDonald, Barbara Rombi. "Proton Radiotherapy for Childhood Tumors: An Overview of Early Clinical Results." *Journal of Nuclear Medicine & Radiation Therapy* 4, no. 4 (2013). https://doi.org/10.4172/2155-9619.1000161.

Protons STOP

X–Rays Do Not

Excess radiation to healthy tissue results in costly side effects and secondary tumors



https://www.proton-therapy.org/science/

Particle therapy advantage

- Any child where high dose is needed with curative intent.
- Tumor eccentric in the body cavity, within or next to sensitive organ.
- Recurrent disease, in selected patients.

Potential clinical relevance of dosimetric difference:

↗ RT dose in the tumour → ↗ Survival

↙ Dose to normal tissues → ↙ **Toxicity**

Special procedures (ca. 15%):

1. Total body irradiation
2. SRS
3. SBRT
4. Brachytherapy
5. IORT

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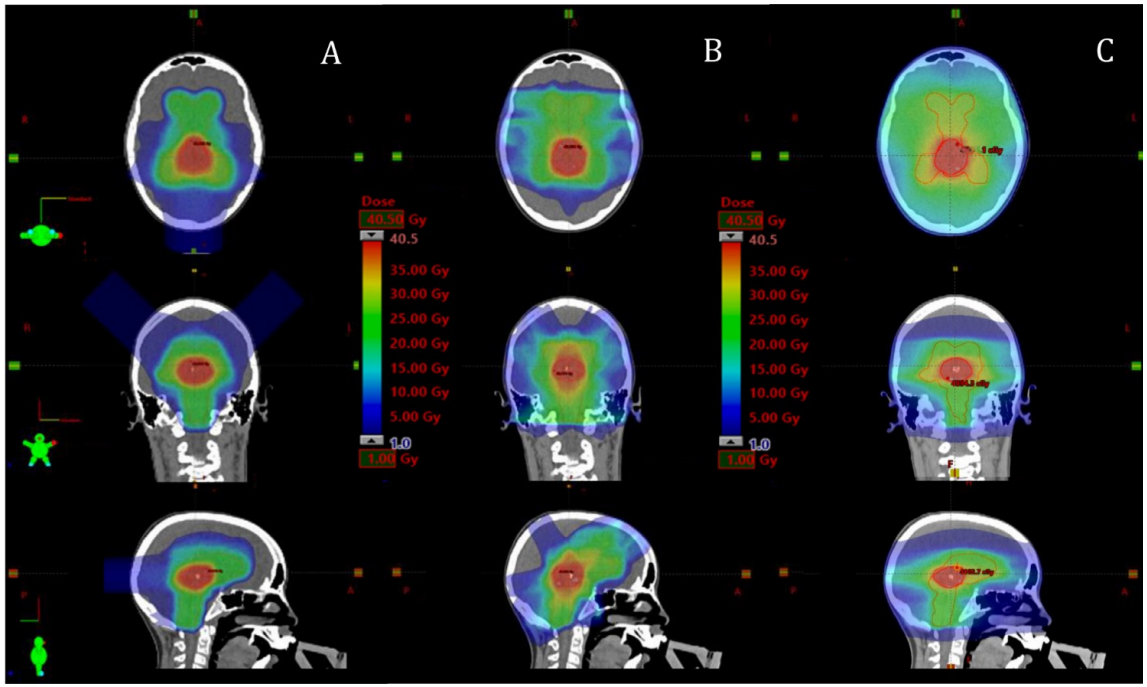
Protons (“shower”) vs Photons (“bath”)



Comparison of dose distribution in 3 ≠ modalities for a patient with intracranial germ cell tumor:

(A) PBS proton RT
(B) Intensity-modulated RT
(C) Volumetric modulated arc therapy

PTV_Low [in orange]
PTV_High [in red]

Correia et al, *Clin Transl Radiat Oncol* 2019

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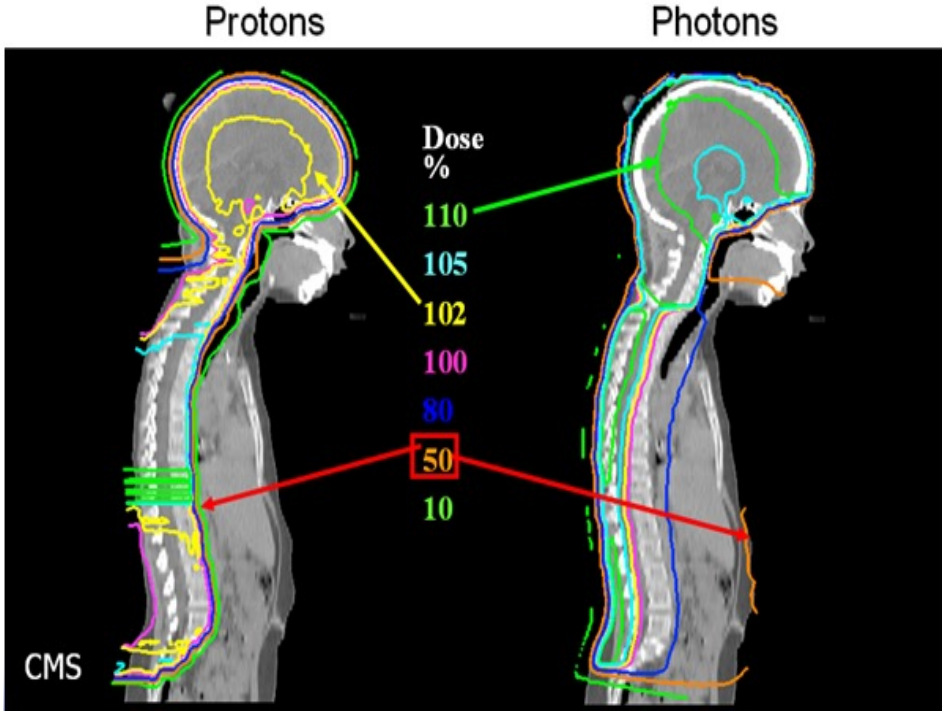
Protons vs Photons - Childhood Cancer



Dose distribution of craniospinal irradiation (CSI)
in a 5 year old paediatric patient planned with both protons and photons

(Courtesy of Prof. Yock's team, MGH, USA)

Protons in Childhood Cancer

Randomized clinical trials unethical between PRT vs XRT in children

Goitein JCO 2008, Rad Oncol 2010

49 prospective / 149 studies (1995-2022)
Nr. patients 10’674 (mean 71.6)
Median follow-up 41 months

ESTRO 2022, Prof. Timmermann, Germany

Protons can:
↑ local control rates : ↑ dose/volume,
↓ risk for late effects & secondary cancer induction
Be cost-effective
Be well embedded into medical care programs and clinical trials where available

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Clinical evidence of proton radiotherapy

↓ **Integral dose** (>3x), with greater ↓ in larger field setups like CSI

↓ lower risk for **secondary primary cancer**

↓ **Toxicities** without compromising disease control, for ≠ cancer types & ages

Xiang 2020
Lee 2005
St Clair 2004
MacDonald 2008
Leiser 2016
Peters 2020
Badelx 2019
Schneider 2014
Verma 2018
Kuhlthau 2012
Yock 2014/2016
Kamran 2018
Kahalley 2019
Eaton 2020
…

☺ Health-related **quality of life**: paediatric, head & neck, lung cancer

☺ **Cognitive outcomes** in brain tumour survivors

☺ **Cost effectiveness**: current additional costs offset by ↓ adverse events costs — Lundkvist Cancer 2005, …

☺ **Combined therapies**: ~3x ↓ in severe adverse events, (1.3x) ↓ in integral dose — Baumann JAMA 2019

☺ **Overall survival** (OS): >2x ↓ in grade 4 lymphopenia, ↑ OS — Abravan JTO 2020, Shiraishi RO 2017

Proton-related late effects

Health outcomes and quality of life in a multi-institutional prospective phase II trial of proton radiotherapy for **pediatric rhabdomyosarcoma**

Most Common

Late Toxicity	N	(%)	Grade 1	2	3	4
Musculoskeletal hypoplasia	32	(29.1)	26	5	1	0
Ocular impairment*	32	(29.1)	21	7	4	0
Hyperpigmentation	17	(15.5)	17	0	0	0
Alopecia/hair disorder	15	(13.6)	14	1	0	0
Dental disorder**	14	(12.7)	7	7	0	0

* Cataracts, vision loss, eyelid dysfunction, and other non-specific conditions
** Dental caries, cavities, and development abnormalities

Most Common

Late Toxicity	H&N RMS Non-PM (n=3)	Orbit (n=18)	PM (n=31)	p
Musculoskeletal hypoplasia	0 (0.0%)	9 (50.0%)	17 (54.8%)	0.31
Ocular impairment	0 (0.0%)	9 (50.0%)	6 (19.4%)	0.035
Hyperpigmentation	0 (0.0%)	5 (27.8%)	5 (16.2%)	1.0
Alopecia/hair disorder	1(33.3%)	18 (100%)	11 (35.5%)	<0.001
Dental disorder	1 (33.3%)	1 (5.6%)	11 (35.5%)	0.12
(Neuro-)Endocrine def.	0 (0.0%)	0 (0.0%)	8 (16.0%)	0.045

Correia et al. **[under preparation]**

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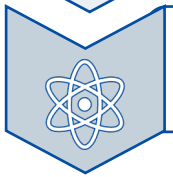
Health-related outcome & QoL in MGH CCS

Long-term treatment-related toxicity may impair the health-related quality of life of childhood cancer survivors.



Strategies to reduce toxicity include **proton** radiotherapy.

Report of mature health-related **quality of life** of children, adolescent and young adult patients treated with **proton** radiotherapy.

Correia et al. **[under preparation]**

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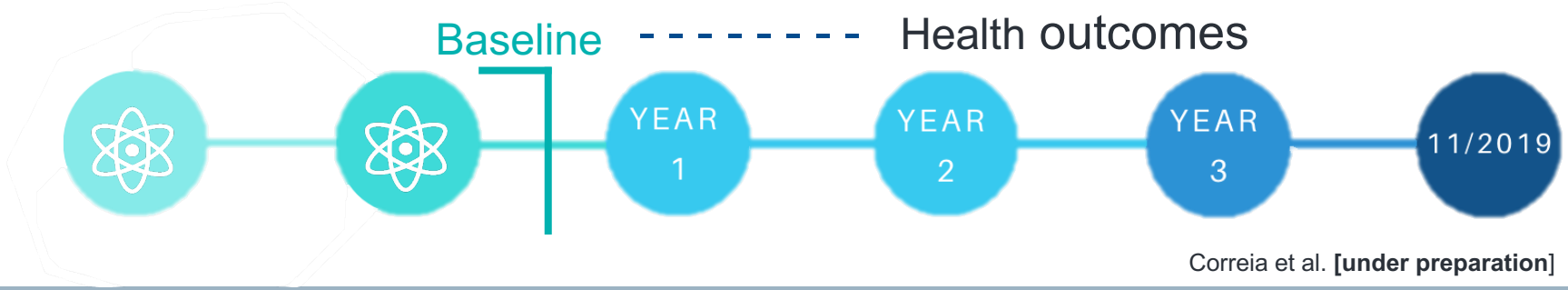
Health-related outcome & QoL in MGH CCS

- Toxicity - acute (≤90 days) / late toxicity (>90 days PRT)
- Child/parent-reported prospective **quality of life** inventory

PedsQL™ 4.0 Generic Core Scales



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Health-related outcome & QoL in MGH CCS

Data Collection Instrument	Baseline	Beg Tx Assessment	End Tx Assessment	1yr Post Tx	2yr Post Tx	3yr Post Tx	4yr Post Tx	5yr Post Tx	6yr Post Tx	7yr Post Tx	8yr Post Tx	9yr Post Tx	10yr Post Tx
CRC Notes		○	●	○	○	○	○	○	○	○	○	○	○
PedsQL Quality of Life Survey Infant 1-12 Months		○	○										
PedsQL Quality of Life Infant 13-24 Months		○	○	○									
PedsQL Quality Of Life Survey Age 2-4		●	●	○	○	○	○	○	○	○	○	○	○
PedsQL Quality Of Life Survey Age 5-7 Years		○	○	●	●	●	○	○	○	○	○	○	○
PedsQLQuality of Life Survey Age 8-12 Years		○	○	○	○	○	●	●	●	●	○	○	○
PedsQL Quality of Life Survey 13-18 Years		○	○	○	○	○	○	○	○	○	●	●	●

REDCap®

Correia et al. **[under preparation]**

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Health-related outcome & QoL in MGH CCS

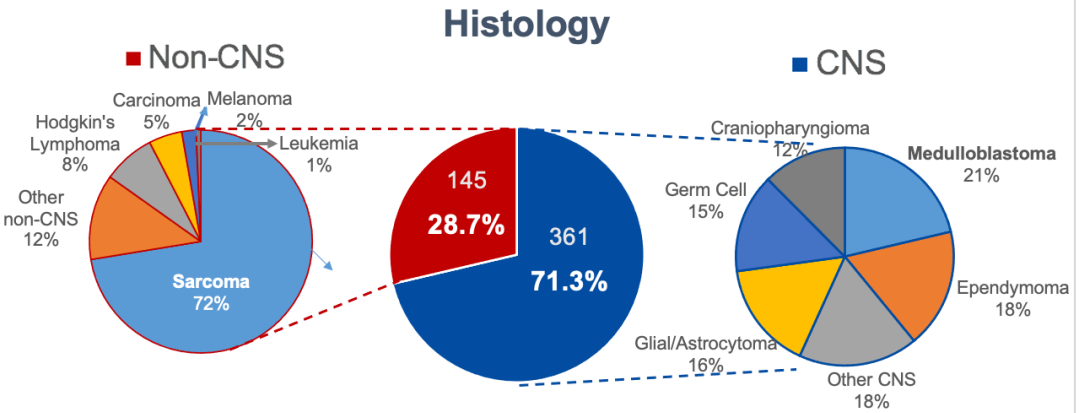
POPULATION

506 childhood cancer survivors

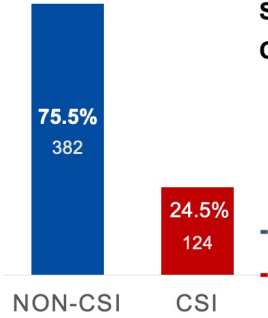
Median:

Age at PRT start	9.2 years	[0.8 - 24.0]
Follow-up	6.2 years	[0.9 - 14.6]

TUMOR



TREATMENT



Surgery: 96.2% → 37.8% GTR

Chemotherapy: 70.2% → 80.0% Neoadjuvant

2 patients with prior **irradiation**

Median:

- **total** dose 52.2 Gy_{RBE} [10.0 - 76.0]
- **CSI** dose 23.4 Gy_{RBE} [18.0 - 36.0]

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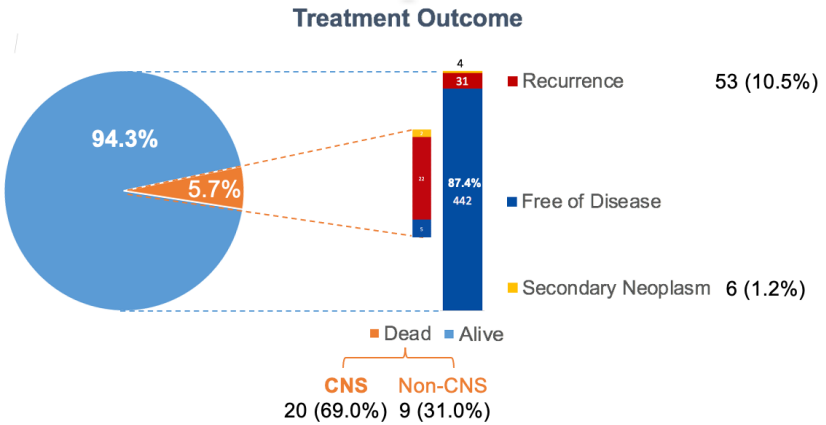
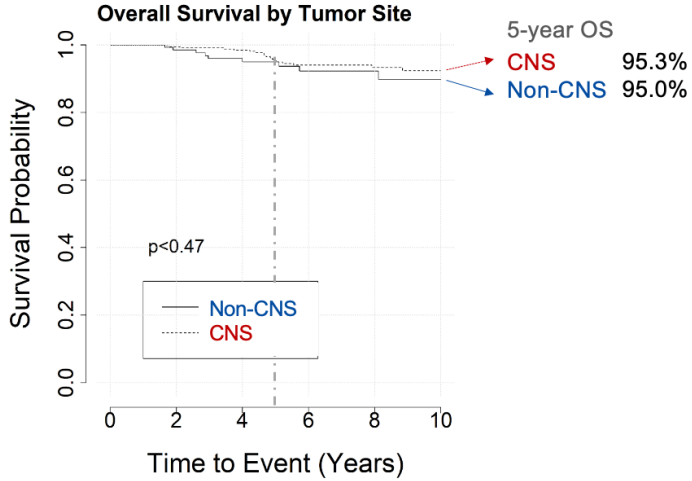
Health-related outcome & QoL in MGH CCS

SURVIVAL



SURVIVAL



Correia et al. **[under preparation]**

dora.correia@ksa.ch | @The_PT_Explorer

Health-related outcome & QoL in MGH CCS

FAILURE

Median time to disease progression: 2.4 years [0.6 – 12.4]

53 patients
- Non-CNS 13 (24.5%)
- **CNS** 40 (75.5%)
  - 37 intracranial
  - 3 spinal

Type:

Distant	24 (45.3%)
Local/Regional	33 (62.3%)

SECONDARY NEOPLASM

Median time to secondary neoplasm: 4.7 years [3.6 – 11.3]

6 patients
- Osteochondroma
- Meningioma
- Pleomorphic / high grade Sarcoma
- High Grade Glioma
- Acute Lymphoblastic Leukemia

Incidence:

- Cumulative 5- & 7-year 1.1%
- Crude 1.2%

Correia et al. **[under preparation]**

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Health-related outcome & QoL in MGH CCS

QUALITY OF LIFE – PEDSQL™ mean **PPR** TCS

Late Toxicity & **QoL** scores available for 141 patients

5 **most common** late toxicity:

Categories		**Specific Reported Toxicities**	
General	94 (66.7%)	Fatigue	47 (33.3%)
Neurological	85 (60.3%)	Pain	47 (33.3%)
Skin	73 (51.8%)	Alopecia	40 (28.4%)
Eye	62 (44.0%)	Headache	37 (26.2%)
Endocrine	48 (34.0%)	Nausea/Vomiting	35 (24.8%)

Correia et al. **[under preparation]**

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Health-related outcome & QoL in MGH CCS

Health-related **quality of life** scores **increased** over time in childhood cancer survivors treated with **proton** radiotherapy.

Survivors of CNS tumors fare worse than non-CNS tumors.

Among CNS survivors, craniospinal irradiation exposure did **not** correlate with impaired health-related quality of life compared with local-field PRT at last follow up.

Childhood cancer survivors irradiated with **protons** for non-CNS tumors reported scores approaching those of the healthy control group.

Correia et al. **[under preparation]**

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Challenges of proton radiotherapy

Efficiency of daily set up

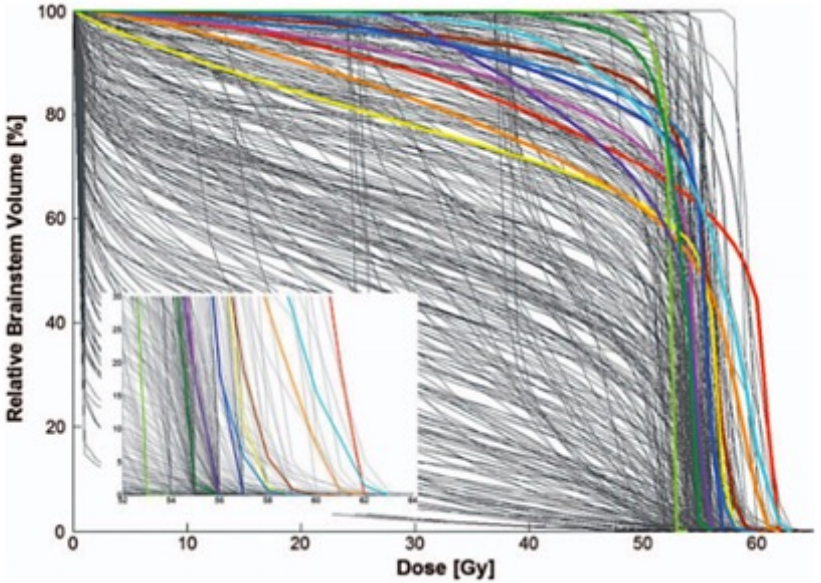
Dose of daily CBCT, KV imaging

- Surface mapping techniques may help

Incorporate MR delivery?

Radiobiology and RBE/LET planning

- Brainstem constraints/toxicity



Indelicato et al, Acta Onc 2014

Brainstem toxicity in CCS

Symptomatic **brainstem toxicity** in pediatric brain tumors: higher rates with proton radiotherapy (PRT) than photons**?**

Photons [0-6.7%] vs Protons [0-10.8%]

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Debate About Brainstem Injury Risk After Proton and Photon Therapies in Pediatric Brain Tumors

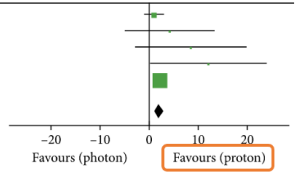
September 17, 2019

Meta-analysis **proton** vs **photon** RT ped. CNS tumors – **brainstem:**

Dmean

Study or subgroup	Photon Mean	Photon SD	Photon Total	Proton Mean	Proton SD	Proton Total	Weight	Mean difference IV, fixed, 95% CI
Correia, 2019	30.92	2.47	11	29.92	2.15	11	19.6%	1.00 [−0.94, 2.94]
Boehling, 2012	25.2	10.7	10	21	10	10	0.9%	4.20 [−4.88, 13.28]
MacDonald, 2008 (1)	31	8	2	22.5	1.5	2	0.6%	8.50 [−2.78, 19.78]
Dennis, 2013	36.36	11.86	11	24.27	16.04	11	0.5%	12.09 [0.30, 23.88]
Stoker, 2018	38	1.2	10	35.8	1	10	78.4%	2.20 [1.23, 3.17]
Total (95% CI)			*44*			*44*	*100.0%*	*2.07 [1.21, 2.93]*

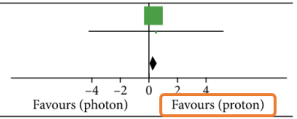
Heterogeneity: chi² = 5.48; *df* = 4 (*P* = 0.24); I^2 = 27%
Test for overall effect: *Z* = 4.74 (*P* < 0.00001)



Dmax

Study or subgroup	Photon Mean	Photon SD	Photon Total	Proton Mean	Proton SD	Proton Total	Weight	Mean difference IV, fixed, 95% CI
Correia, 2019	41.16	0.37	11	40.84	0.25	11	99.7%	0.32 [0.06, 0.58]
Boehling, 2012	52.7	6.3	10	52.2	4.2	10	0.3%	0.50 [−4.19, 5.19]
Total (95% CI)			*21*			*21*	*100.0%*	*0.32 [0.06, 0.58]*

Heterogeneity: chi² = 0.01; *df* = 1 (*P* = 0.94); I^2 = 0%
Test for overall effect: *Z* = 2.38 (*P* = 0.02)



Carbonara *et al.* J Oncol, 2019

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Brainstem toxicity in CCS

The pediatric proton community has adopted more conservative brainstem constraints over time, yet children with **ependymoma** are less likely to have these constraints met irrespective of residual disease after surgery.

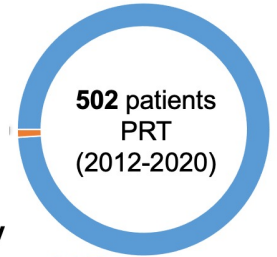
Brainstem toxicity in the PPCR cohort:
- rare, comparable to other cohorts
- 80% recovery with medical intervention

- Symptomatic brainstem toxicity: **1%** (n=5/502)

Age at PRT	4.1 years (1.9 - 8.9)
Age at toxicity	4.5 years (2.5 - 10.0)
	4.8 months (3.9 - 12.3) after PRT
Followed brainstem constraints[1,2]	**40%** (n=2/5, yet 1 relapsed)

Median:
- age at PRT 6.6 (0.47 - 21.9)
- follow-up 3.3 years (0.11 - 9.3)
- dose prescribed 54 Gy_{RBE}

(51 - 59.4 Gy_{RBE})
(54 - 59.4 Gy_{RBE})



Brainstem Toxicity
cumulative incidence at 3 & 5 years: **1.3%**

[1] Indelicato *et al.* Acta Onc, 2014
[2] Haas-Kogan *et al.* IJROBP, 2018

Correia et al [**in preparation**]

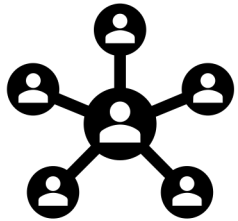
Treatment complexity

- Clinical (e.g. postop cerebellar mutism / posterior fossa syndrome)

  Diminished speech progressing to mutism, emotional lability, hypotonia, ataxia
  Prevalence 25%, 92% moderate-severely affected

  Robertson et al., *J Neurosurg*, 2006

- Patient changes (e.g., postoperative posterior fossa, tubes, weight)
- Technical/logistics/multidisciplinary (e.g., specialized anesthesia team, facility)
- Patient & Family
- Time consuming



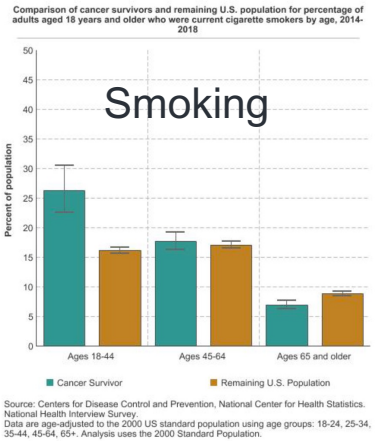
CCS Lifestyle & Surveillance

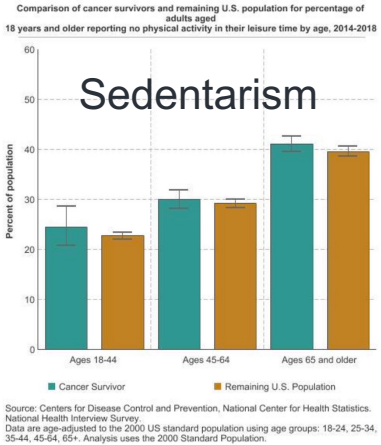
New evidence of **accelerated aging** – ongoing research on biomarkers to tailor follow-up

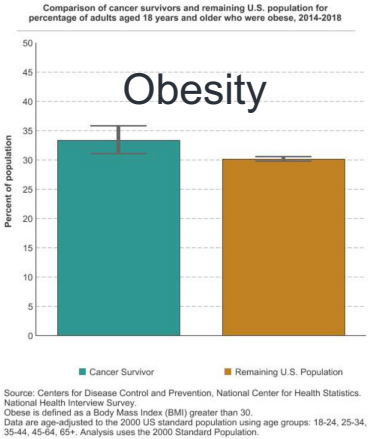
Early tailored interventions on lifestyle factors may decrease fragility over time

Song et al, *Clin Cancer Res* 2020
Ehrhardt et al, *Curr Oncol Rep* 2016

In survivorship is not the recurrence that kills:







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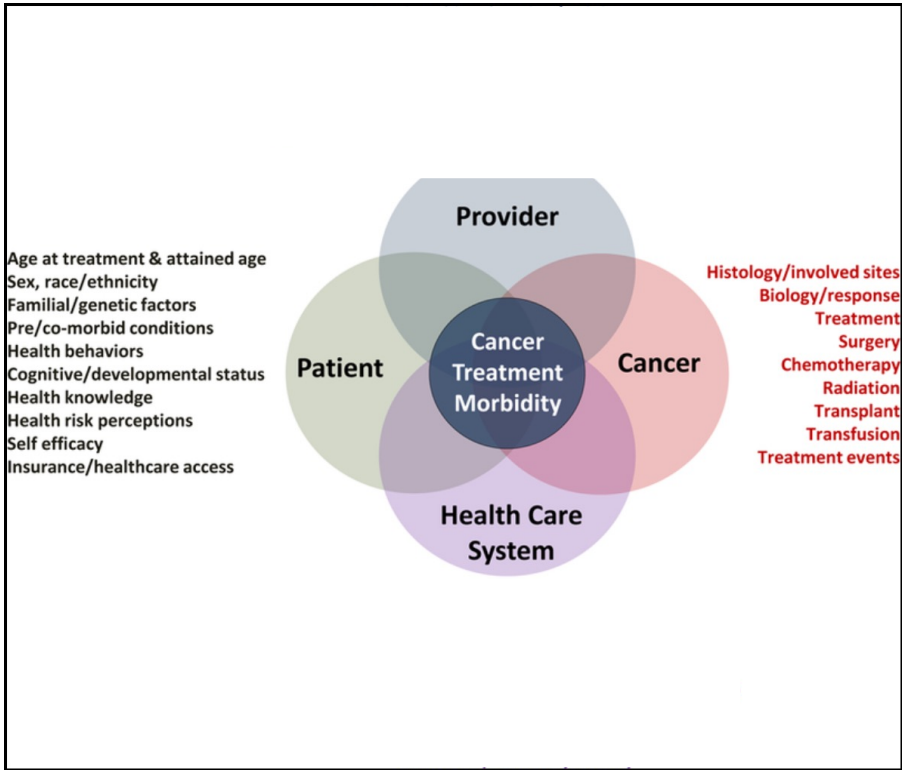
Collaboration and surveillance of CCS is key

- Institutions
- National registries
- Cooperative groups
- Long-term survivorship groups
- Patient advocacy groups
- Families

Goals

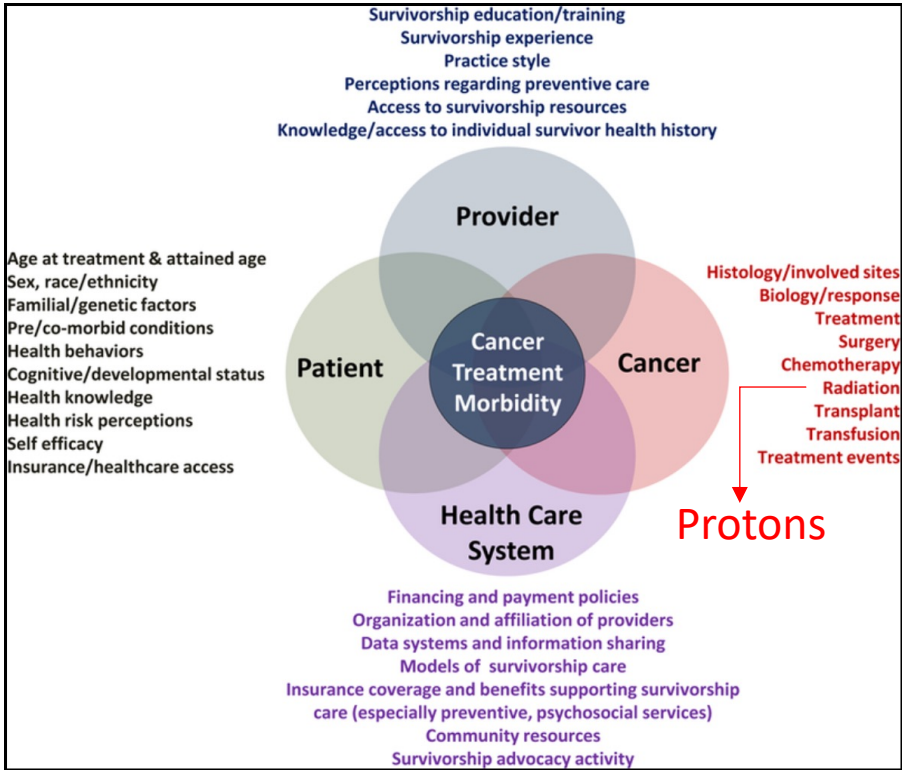
Appreciate the spectrum of long-term late effects and importance of cancer survivorship care.



Robison & Hudson, *Nature Reviews Cancer* 2014

Goals

Become familiar with strategies to mitigate the burden of late effects and increase health-related quality of life.



Robison & Hudson, *Nature Reviews Cancer* 2014

Summary

Childhood (and adolescent, young adult) cancer survivors (CCS) are increasing and living longer, yet at the expense of major risk for late adverse health events.

Improvements in treatment and supportive care have reduced the CSS morbidity and mortality.

Protons are decreasing the late effect burden in CCS compared with photons.
Clinical data supports a benefit in neurocognition, endocrine, hearing, QoL, and secondary malignancy.

Radiotherapy in children has to be performed under optimal conditions of modern imaging, modern techniques, and **experienced staff**.

Surveillance programs and ongoing research initiatives are imperative in order to continue to improve cure rates and optimise quality of life for all survivors.

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Acknowledgments

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recherche suisse contre le cancer
ricerca svizzera contro il cancro
swiss cancer research

MGH Pediatric Radiation Oncology Clinical Research Team

mim SOFTWARE

PPCR
Pediatric Proton/Photon Consortium Registry

Patients and their families

Questions?

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