Advanced radiotherapy technology in pediatrics: IMRT

Advantages and pitfalls

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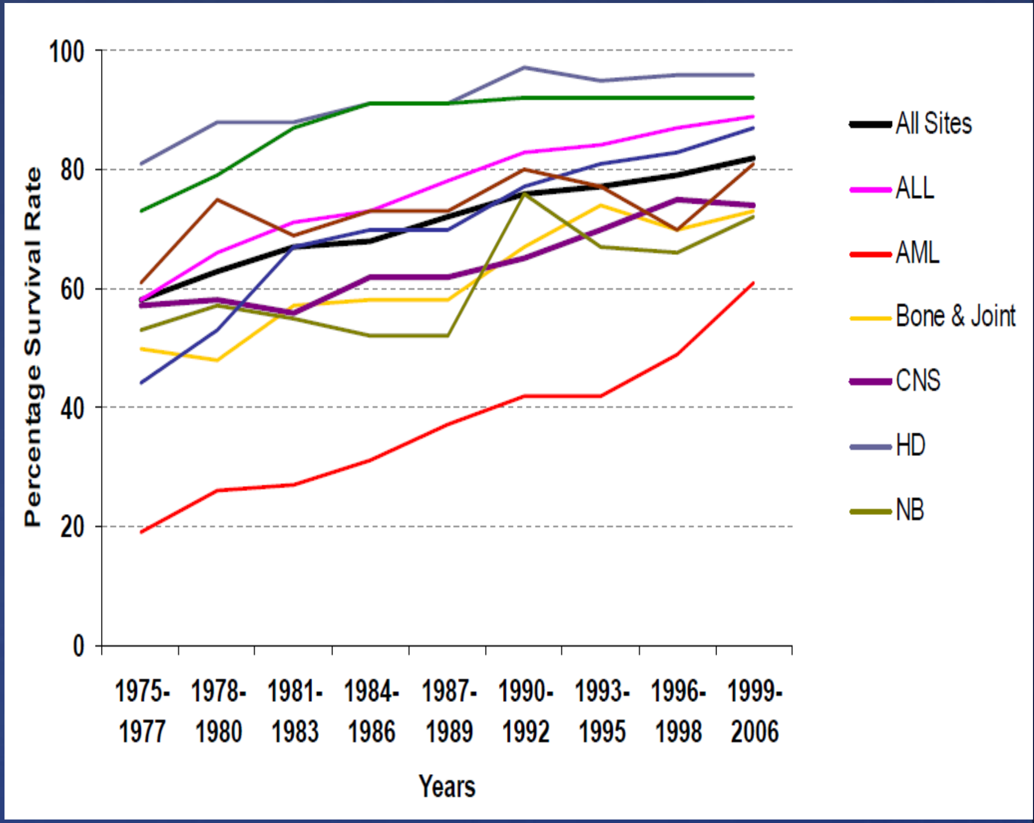
Pediatric cancer survival: Time trends

- Surgery
- Chemotherapy
- Radiotherapy
- Pathology & Genomics
- Imaging advancements
- Supportive Care
- Multidisciplinary care
- Co-operative group trials
- Childhood cancer specific institutes & Protocols
- Survivorship care



Childhood cancers: Role of RT

- ALL
- Lymphoma
- Retinoblastoma
- Medulloblastoma
- Neuroblastoma
- Ewing Sarcoma
- Rhabdomyosarcoma
- Wilm's tumor
- Supratentorial brain tumors
- Tumors of posterior fossa
- Germ cell and stromal cell tumors

Pediatric RT Paradox

- Radiation is an important part of curative therapy for may pediatric patients with tumors…… But

- Ionizing radiation even at low doses for young children may have late side effects years or decades after treatment

  - Second cancers
  - Growth disturbances
  - Decreased functional outcomes
    - Hearing
    - Vision
    - Neurocognitive
    - Vascular Anomalies
    - Endocrine
  - Cosmesis

Historical Trends in the Use of Radiation Therapy for Pediatric Cancers: 1973-2008

Vikram Jairam, BS,* **Kenneth B. Roberts, MD,*,†,‡** **and James B. Yu, MD*,†,‡**

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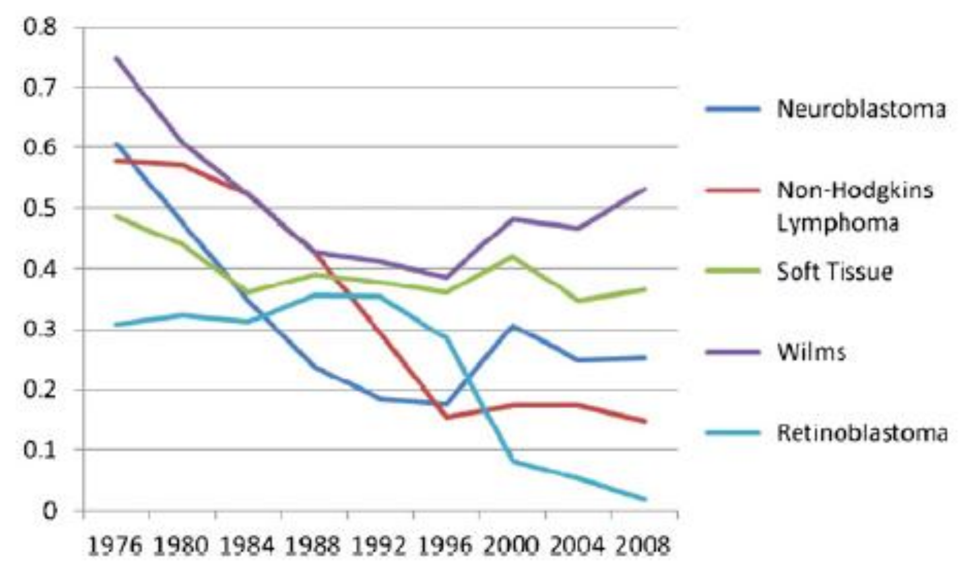
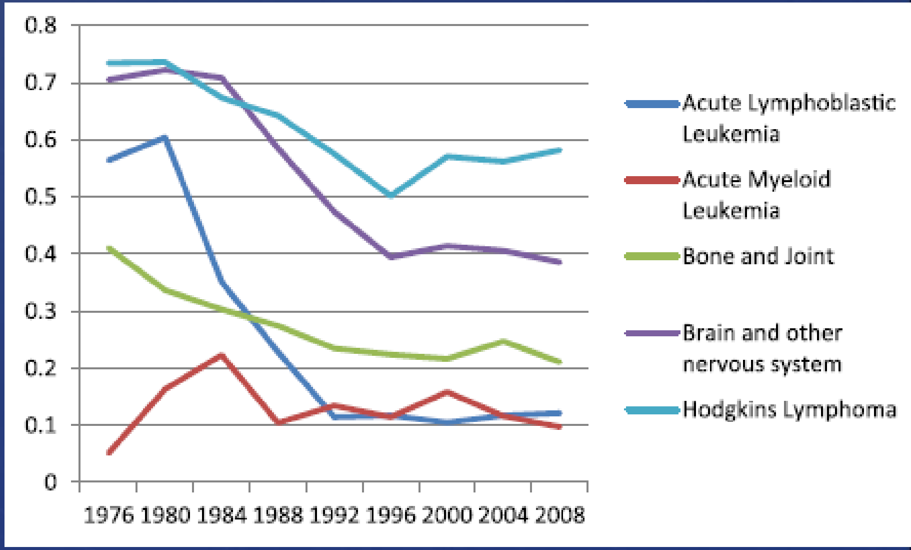
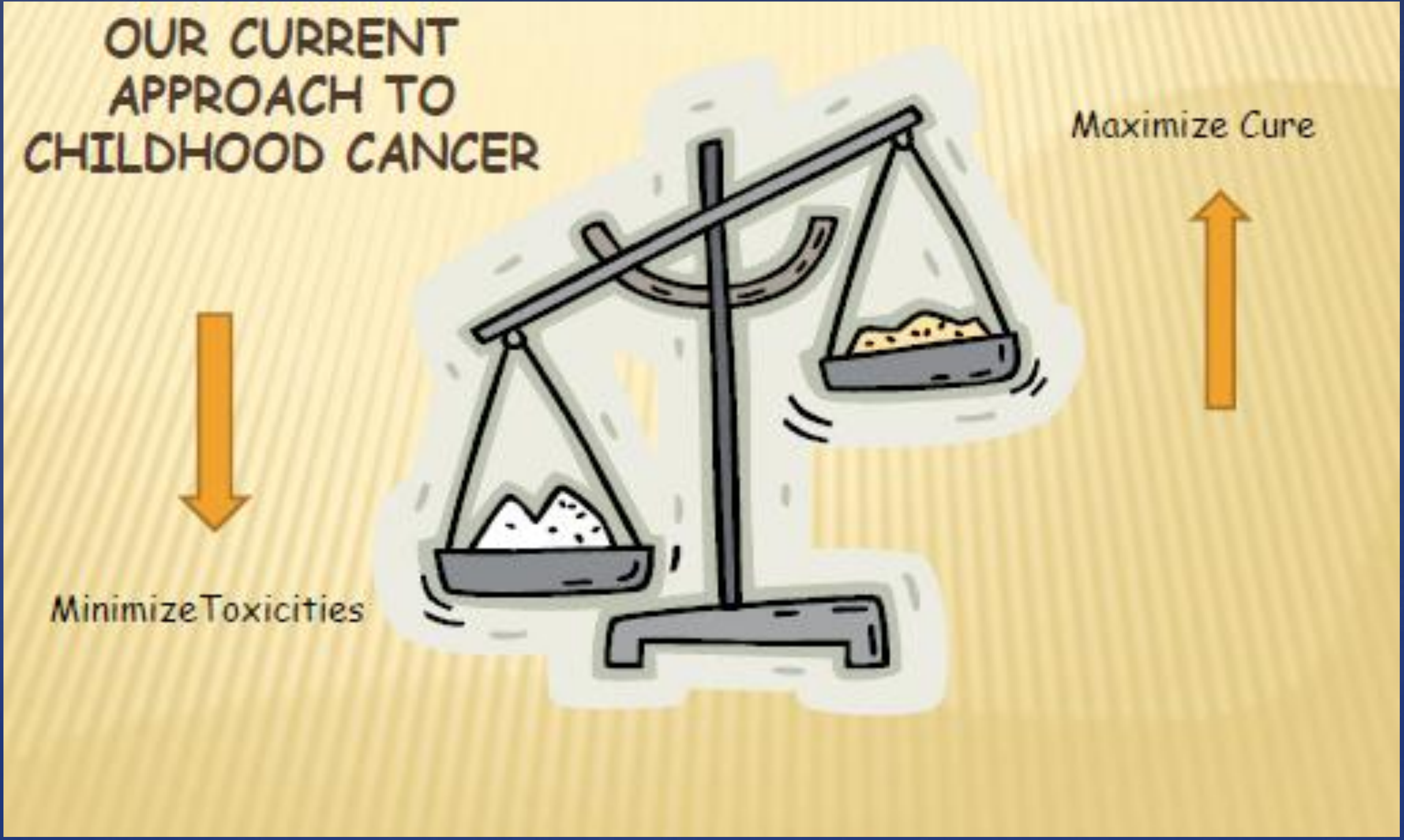




Optimizing outcomes!!

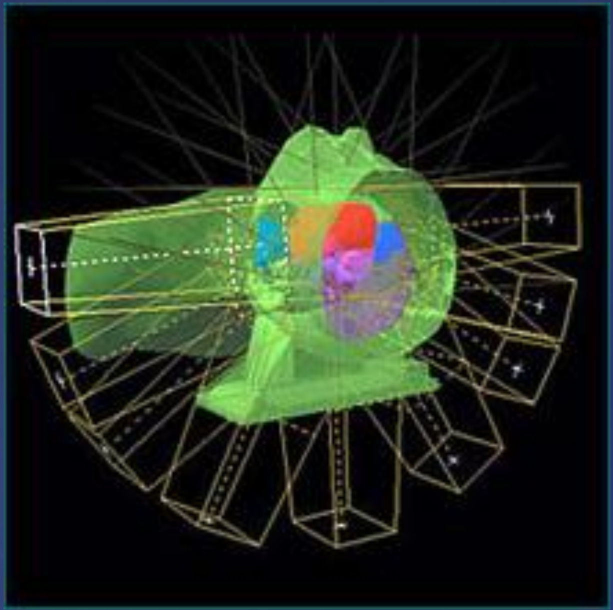


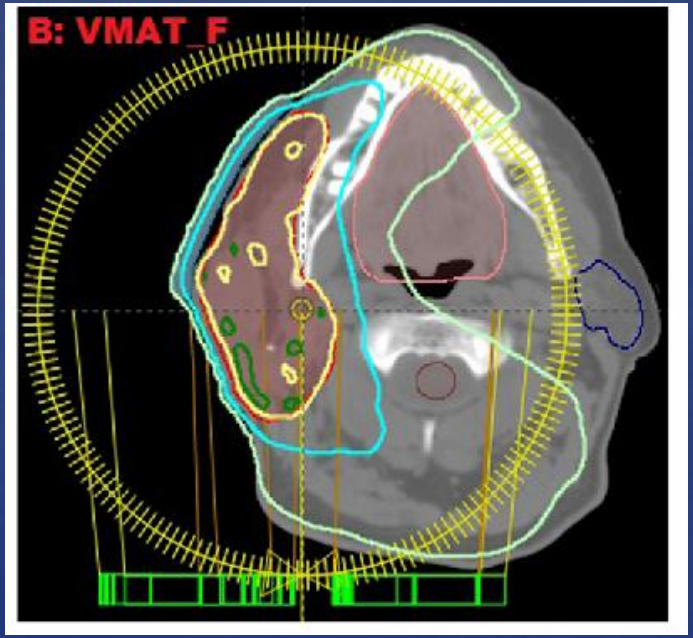
Issues with pediatric RT: General

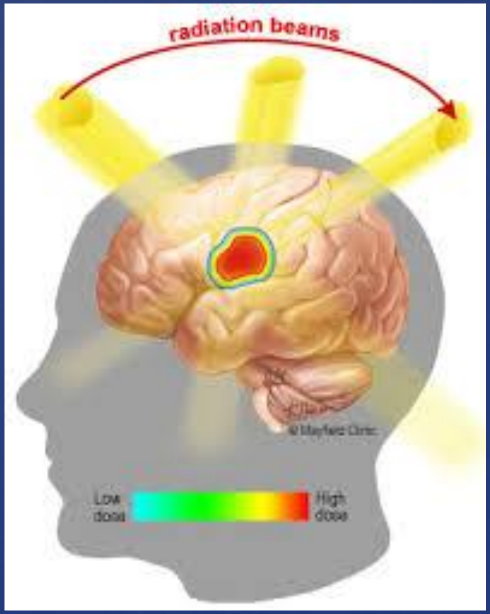
- Immobilization and need of repeated anaesthesia
- Relative treatment volume: body volume higher
- Lower tolerance to RT: Growing tissues
- More organs at risk as compared to adults like growing bones, epiphyseal plates, pituitary, thyroid etc.
- Risk of secondary malignancies and late tissue effects

IMRT/VMAT/SRT

- Better conformity
- Avoidance of OARs
- Dose escalation





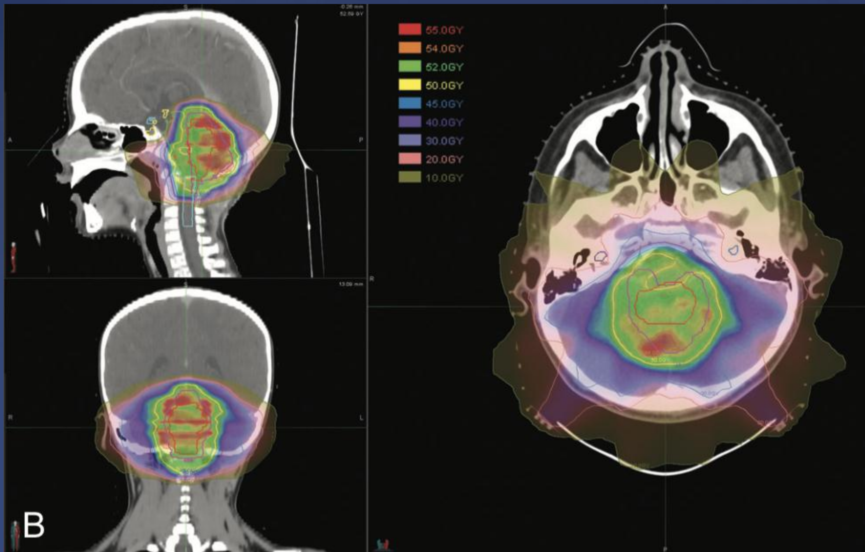


Clinical Scenarios: Need of IMRT/VMAT

- A 5-year old girl with posterior fossa anaplastic ependymoma planned for adjuvant involved field radiotherapy to the tumour bed for a total dose of 5400 cGy in 30 fractions after a gross total resection.

- A 6-year-old male with medulloblastoma planned for standard fractionation craniospinal irradiation with weekly concurrent chemotherapy, 2340 cGy in 13 fractions followed by an involved field boost to the tumour bed for an additional 3060 cGy in 17 fractions

- An 11-year-old boy diagnosed with Stage III Group 3 Parameningeal Embryonal Rhabdomyosarcoma with partial response to induction chemotherapy at week 9, planned for a total dose of 5040 cGyin 28 fractions



55.0GY
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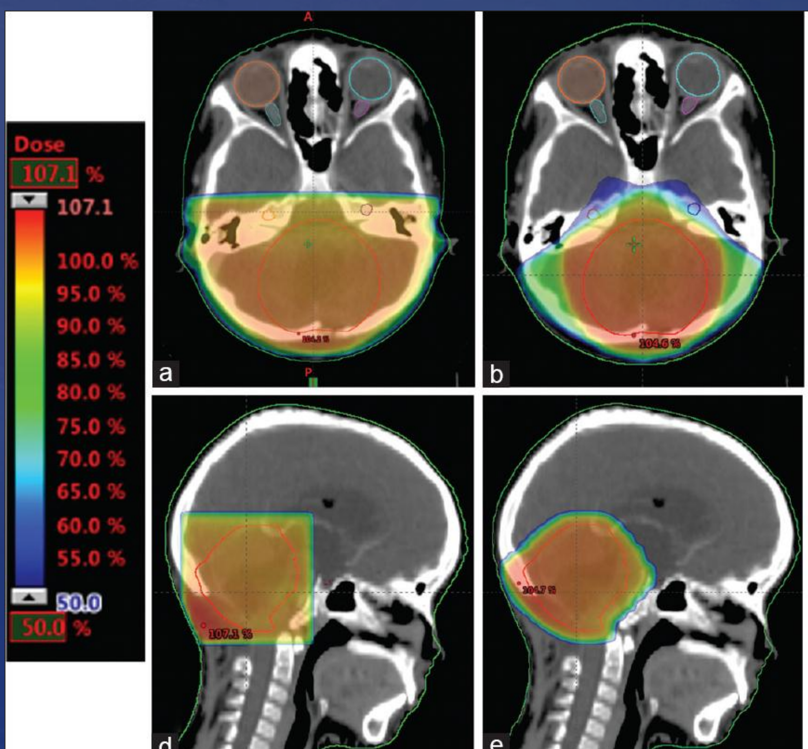
B



Dose
107.1 %
107.1
100.0 %
95.0 %
90.0 %
85.0 %
80.0 %
75.0 %
70.0 %
65.0 %
60.0 %
55.0 %
50.0
50.0 %
A
P
a
b
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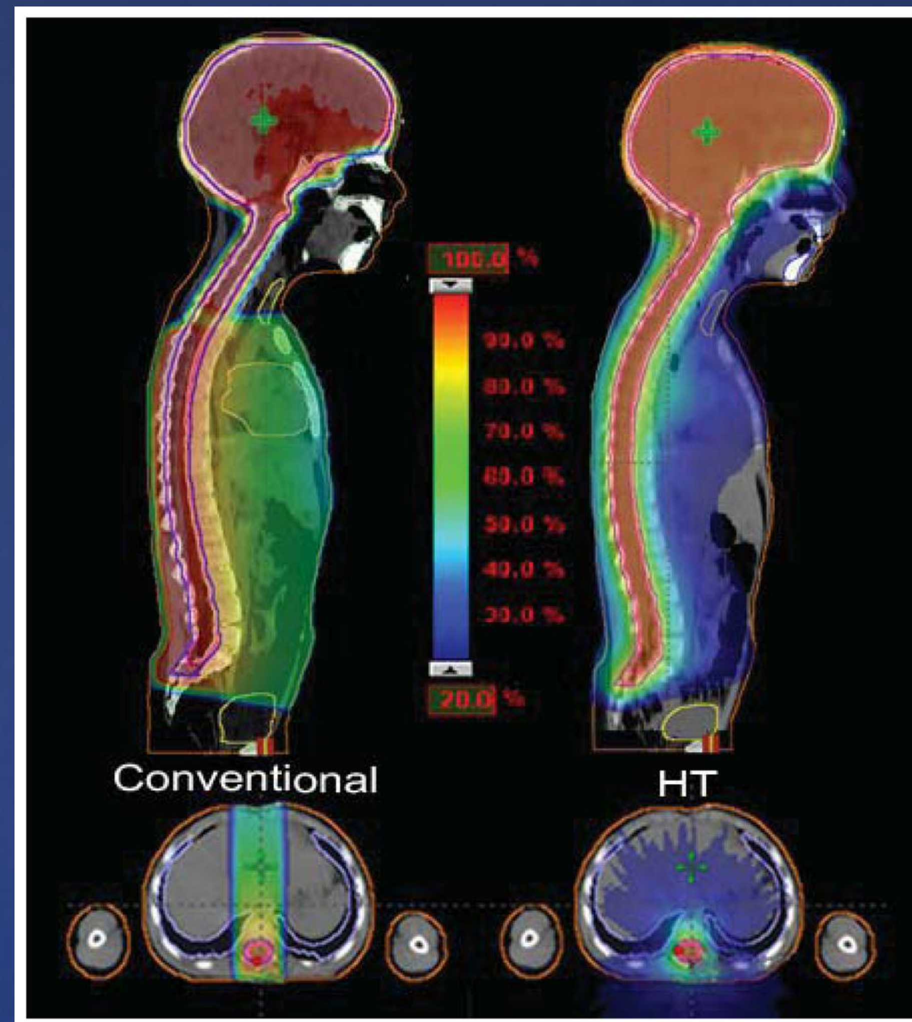
107.1 %



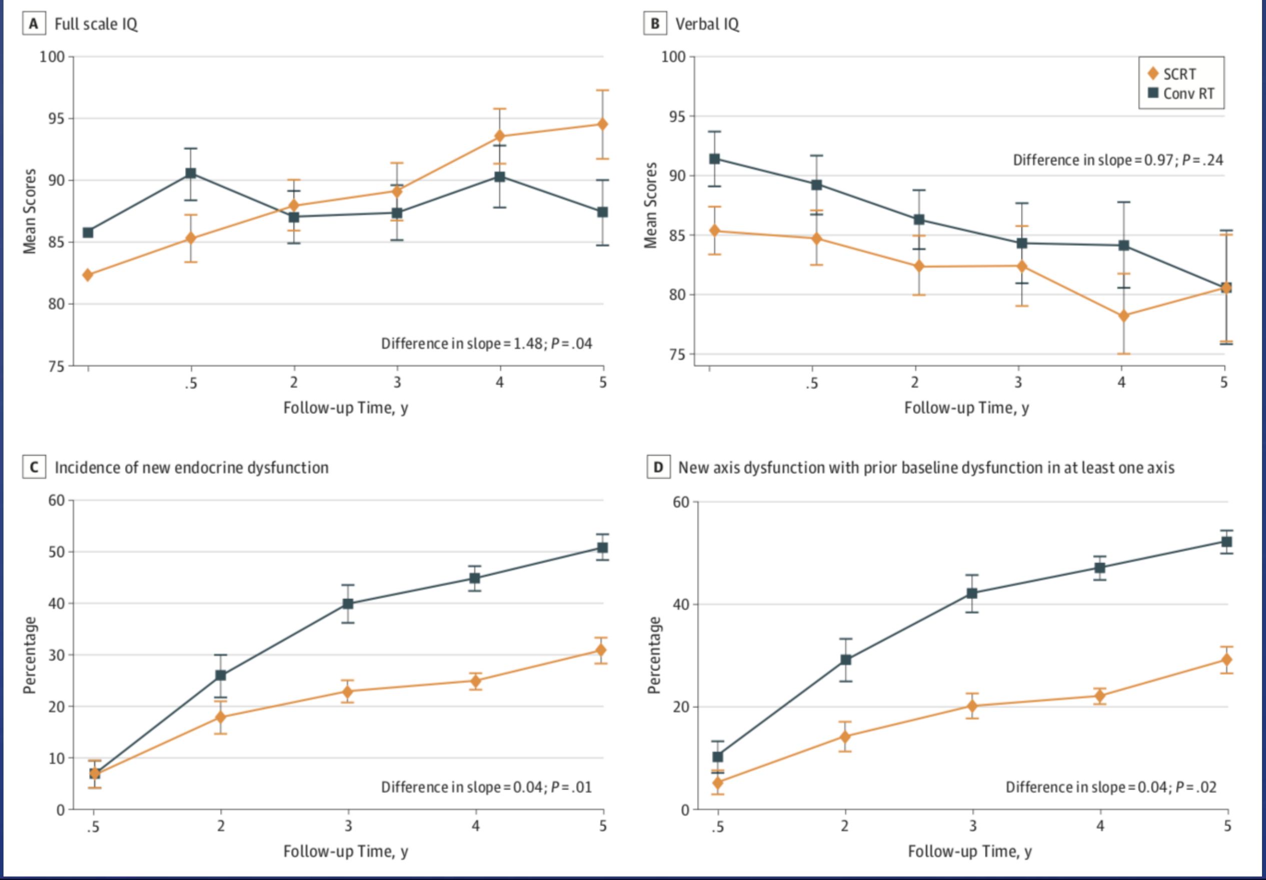
100.0 %
90.0 %
80.0 %
70.0 %
60.0 %
50.0 %
40.0 %
30.0 %
20.0 %
Conventional
HT

JAMA Oncology | Original Investigation

Efficacy of Stereotactic Conformal Radiotherapy vs Conventional Radiotherapy on Benign and Low-Grade Brain Tumors

A Randomized Clinical Trial

Rakesh Jalali, MD; Tejpal Gupta, MD; Jayant S. Goda, MD; Savita Goswami, MSc; Nalini Shah, DM; Debnarayan Dutta, MD; Uday Krishna, MD; Jayita Deodhar, MRCPsych; Padmavati Menon, DM; Sadhna Kannan, MSc; Rajiv Sarin, FRCR



Clinical Scenarios CNS tumors: Need of IMRT/VMAT

- **Goals of IMRT/VMAT treatment in CNS**
  - **Improve target coverage**
  - **Decrease high dose irradiation to neighboring organs at risk: Cochlea, optic apparatus, spinal cord and brain parenchyma**
  - **Decrease intermediate dose radiation to organs at risk: Pituitary**
  - **Avoid asymmetric bone growth: bony orbit**
  - **Improve neurocognitive/neuro-endocrine outcomes**

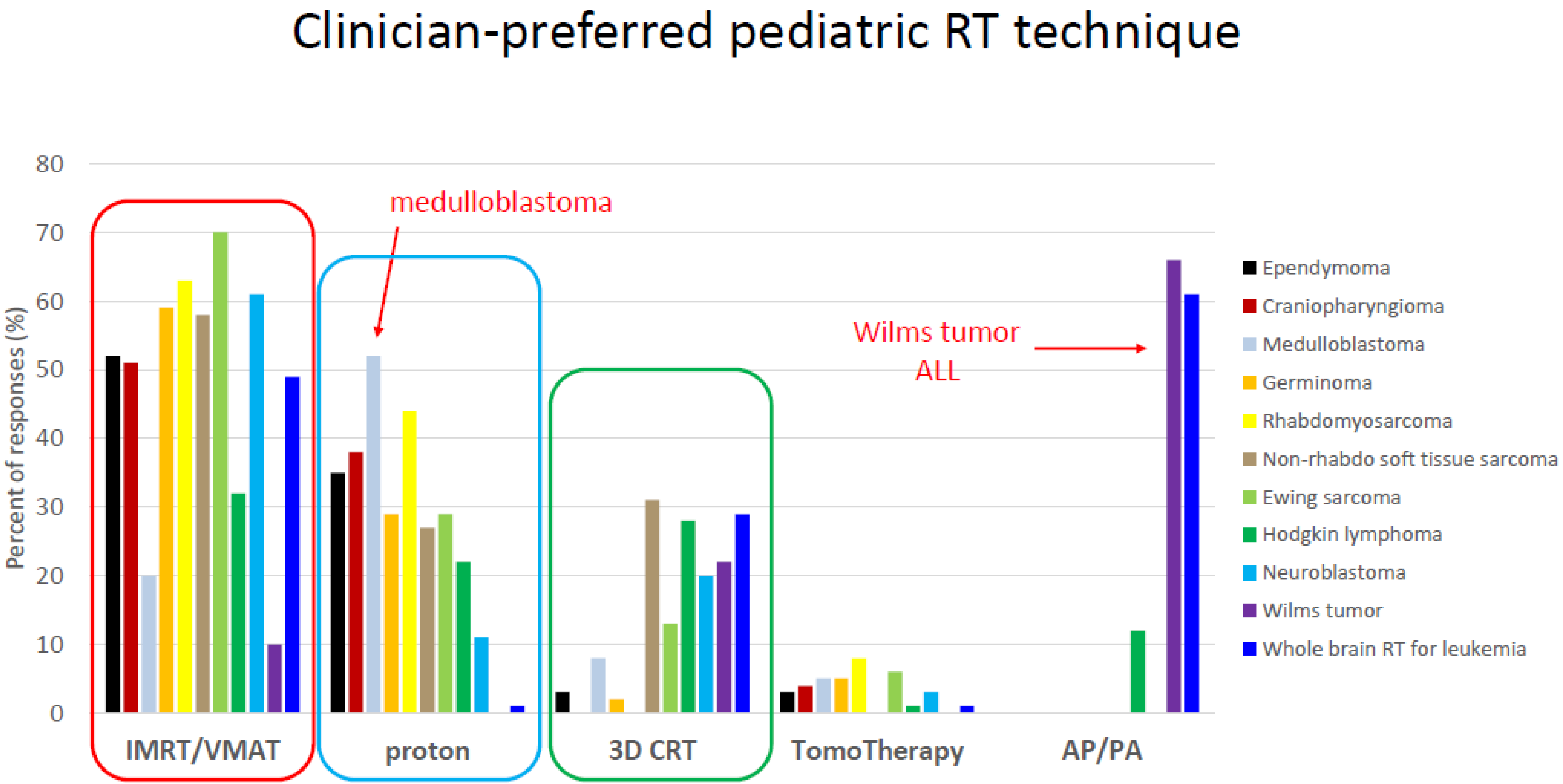
IMRT indications in pediatric tumors Take home message (THM-1)

- Brain tumors
  - Ependymoma
  - Craniopharyngioma
  - Medulloblastoma
  - Germinoma
- Complex treatment volumes
  - Para meningeal RMS
  - Non-extremity Ewing sarcoma

IMRT not needed/mandatory for certain tumor sites
Take home message (THM-2)

- Wilms tumor
- Whole brain radiotherapy for ALL
- Hodgkins Lymphoma
- Extremity Ewing sarcoma
- Retinoblastoma
- Palliative radiotherapy

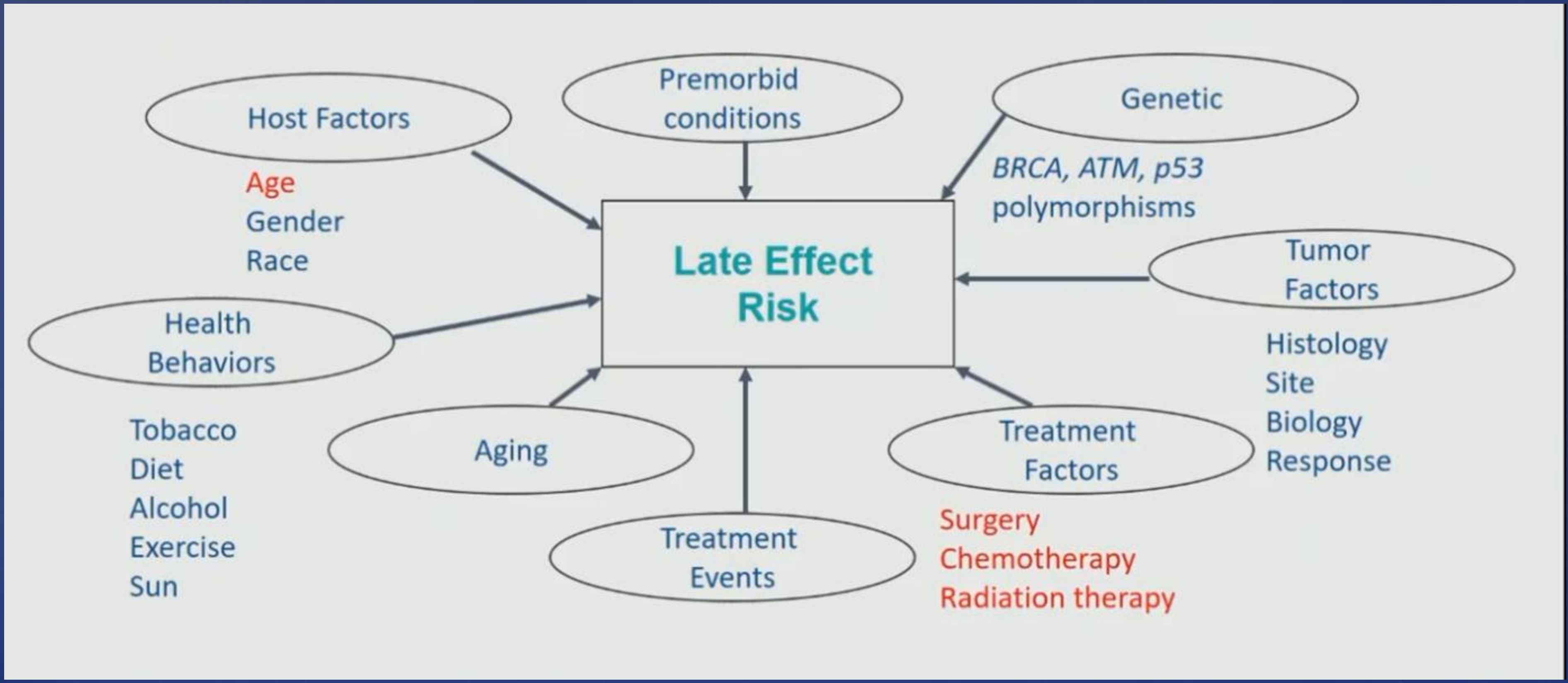
Children oncology group survey: need of RT Techniques



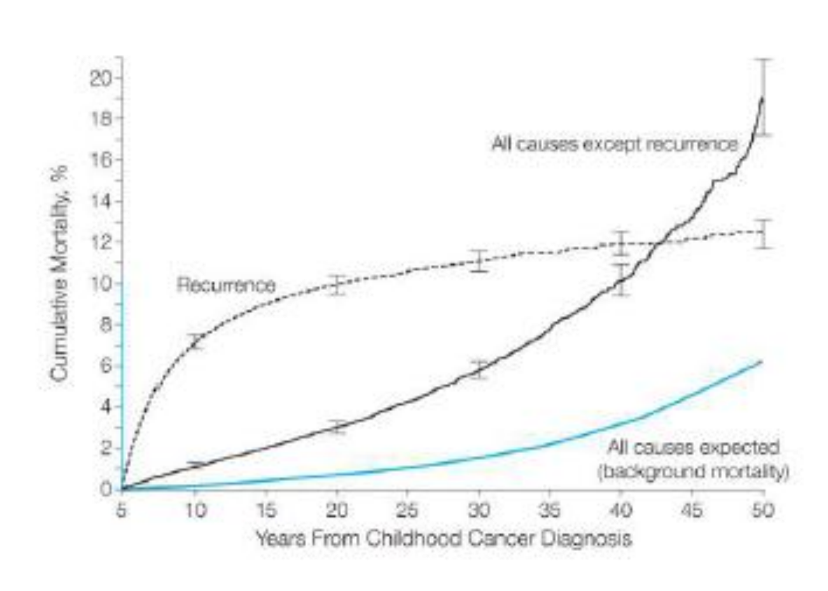
Advantages of Pediatric IMRT Take home message (THM-3)

- **Increased conformality**
  - Cochelar sparing in medulloblastoma
  - Paramenigeal RMS
- **Dose Escalation**
  - Ependymoma
- **Superior neurocognitive/neuroendocrine outcomes (SRT)**
- **Reduce medium-high dose regions**
  - ??May reduce some second malignant neoplasm risk

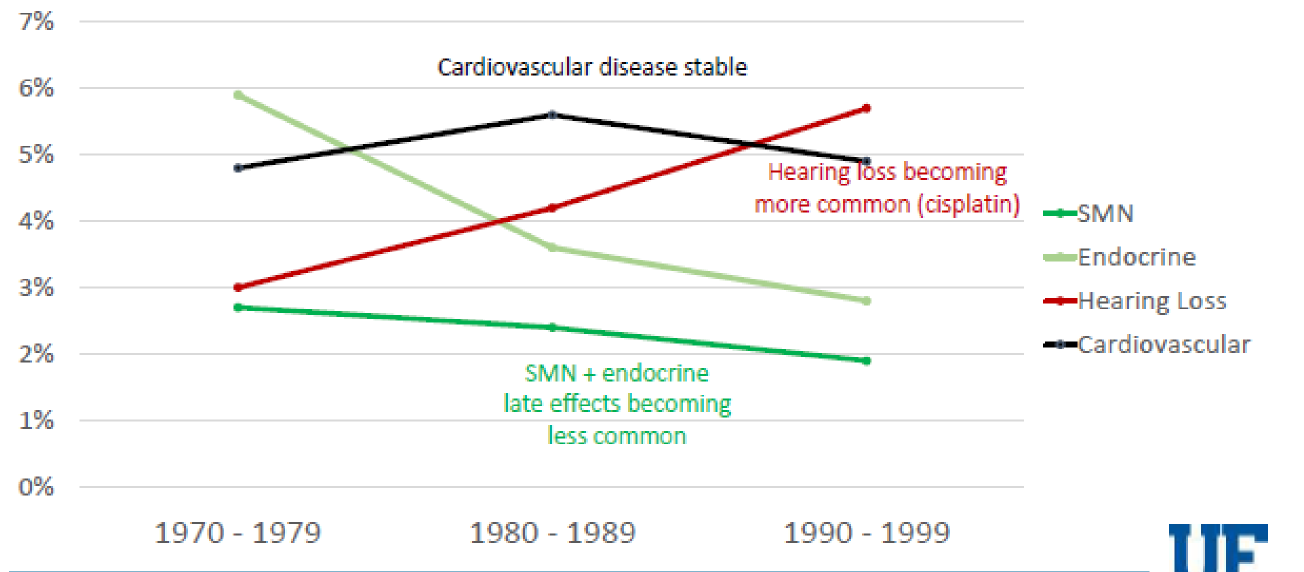
Late tissue effects: pitfalls of RT



Late effects of RT: Survival



IMRT may be helpful in certain scenarios



Adapted from Gibson TM, et al. *Lancet Oncol.* 2018. 19(12):1590-1601

IMRT/VMAT/SRT: Pitfalls Modifiable Take Home Message 04

- Modulation of intensity and other factors
  - Asymmetric dose distribution: asymmetric organ growth
- **Complex treatment set up** and immobilization
- **Increased fraction time**: Prolonged anaesthesia and strict immobilization
- Limited data on dose constraints and planning
- Limited literature and outcome results with IMRT/VMAT

Contents lists available at ScienceDirect

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journal homepage: www.clinicaloncologyonline.net

Pediatric Normal Tissue Effects in the Clinic (PENTEC): An International Collaboration to Analyse Normal Tissue Radiation Dose–Volume Response Relationships for Paediatric Cancer Patients

L.S. Constine [*], C.M. Ronckers [†‡], C.-H. Hua [§], A. Olch [¶], L.C.M. Kremer [†‡], A. Jackson [||], S.M. Bentzen [**]

- Paediatric version of QUANTEC
- Age dependence of dose tolerances for most organs
- The influence of chemotherapy (agents, doses) on radiotherapy dose tolerance for many organs.
- Dose response associations for long-term (>10 years .. >20 years . >30 years) risk of almost all the PENTEC outcomes.
- Retreatment dose tolerances.
- For most organs, substructures exist and for these we lack data on dose tolerance

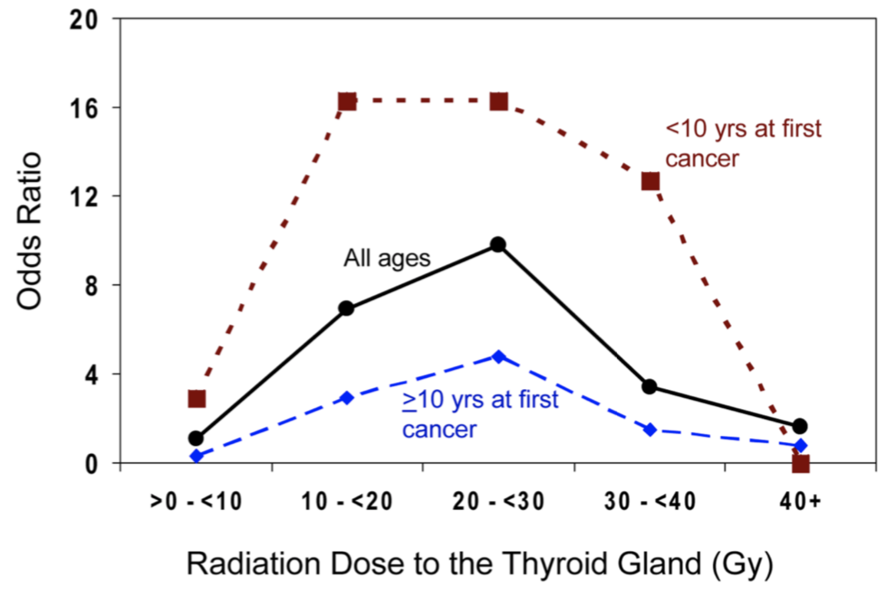
IMRT/VMAT/SRT: Pitfalls Non- Modifiable Take Home Message 05

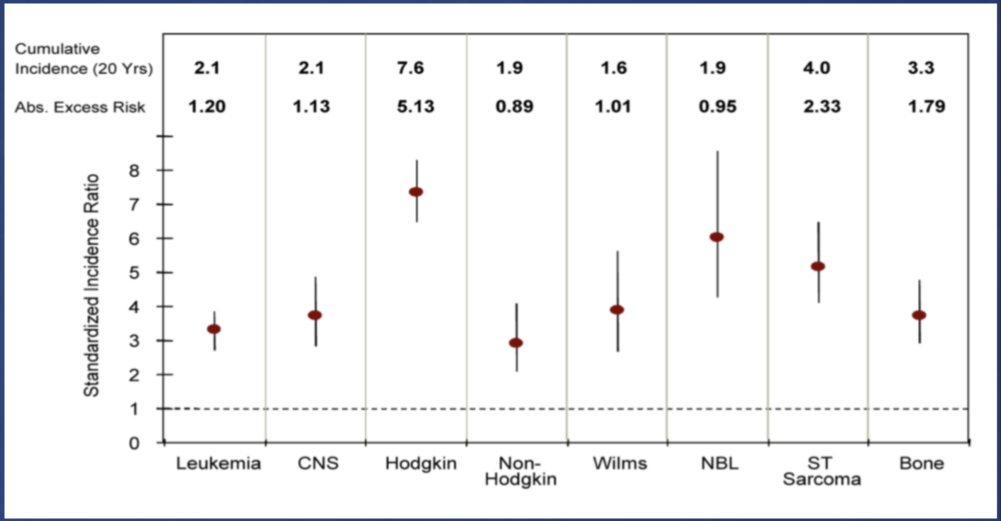
- Multiple coplanar or noncoplanar beams: Low dose spillage-Integral dose
- Increased risk of secondary malignancies
- Important, realistic, fearsome but evolving concept!!

Risk of second cancers

- A linear relationship exist between cancer and dose from about 0.1 Sv to about 2.5 Sv
- Incidence of second cancers higher in children
  - Adult: 5%/Sv
  - Children: 15%/Sv
- Radiation scatter from the treatment volume is more important in the small body of a child
- Radiation induced cancers are multifactorial:
  - Age
  - Radiation dose
  - Primary diagnosis

SMNs: Dependence on Age/Primary Site





SMN risk as per prior diagnosis

Second Malignancy	First Malignancy
Bone tumors	RB, other bone tumors, Ewing's sarcoma, STS, ALL
Soft-tissue sarcoma	RB, STS, HD, Wilms' tumor, bone tumors, ALL
Breast cancer	HD, bone tumors, STS, ALL, brain tumors, Wilms' tumor, NHL
Thyroid cancer	ALL, HD, NB, STS, bone tumors, NHL
Brain tumors	ALL, brain tumors, HD
Carcinomas	ALL, HD, NB, STS
AML/ALL	ALL, HD, bone tumors

Legend: Retinoblastoma (RB); heritable type. STS, soft-tissue sarcoma; HD, Hodgkin disease; NB, neuroblastoma; NHL, non-Hodgkin lymphoma; ALL, acute lymphocytic leukemia; AML, acute myelogenous leukemia.

Opinion split as to whether IMRT gives higher integral dose as compared to 3-D CRT

- The IMRT had higher integral dose than 3DCRT in some studies [1,2] and others reported a decrease [3,4]
- Yang et al. [6] reported that despite the increase of the volume of normal tissues receiving low dose yet, the integral doses to the normal tissues did not increase with IMRT or HT compared to 3DCRT.
- Specifically, Aoyama et al. [3] reported that IMRT and HT resulted in 5% and 4% lower integral dose to normal tissue, respectively. On the contrary, Lian et al. [1] reported a significant increase in the integral dose of normal tissues with IMRT and HT compared to 3DCRT.

1.Lian JD, Mackenzie M, Joseph K, Pervez N, Dundas G, Urtasun R, et al. Assessment of extended field radiotherapy for stage IIIC endometrial cancer using three-dimensional conformal radiotherapy, intensity-modulated radiotherapy and helical tomotherapy. Int J Rad Oncol Biol Phys 2008;70:935–43.
2.Thilmann C, Sroka-Perez G, Krempien R, Hoess A, Wannenmacher M, Debus J. Inversely planned intensity modulated radiotherapy of the breast including the internal mammary chain: a plan comparison study. Technol Cancer Res Treat 2004;3:69–75.
3. Aoyama H, Westerly DC, Mackie TR, Olivera GH, Bentzen SM, Patel RR, et al. Integral radiation dose to normal structures with conformal external beam radiation. Int J Radiat Oncol Biol Phys 2006;64:962–7.
4. Hermanto U, Frija EK, Lii MJ, Chang EL, Mahajan A, Woo SY, et al. Intensity-modulated radiotherapy (IMRT) and conventional three-dimensional conformal radiotherapy for high-grade glioma: does IMRT increase the integral dose to normal tissue? Int J Radiat Oncol Biol Phys 2007;67:1135–44.
5. Shi CY, Penagaricano J, Papanikolaou N. Comparison of IMRT treatment plans between lianac and helical tomotherapy based on integral dose and inhomogeneity index. Med Dosim 2008;33:215–21.
6. Yang R, Xu S, Jiang W, Xie C, Wang J. Integral dose in three-dimensional conformal radiotherapy, intensity-modulated radiotherapy and helical tomotherapy. Clin Oncol 2009; 21:706–12

Low dose spill: Second Malignant Neoplasm

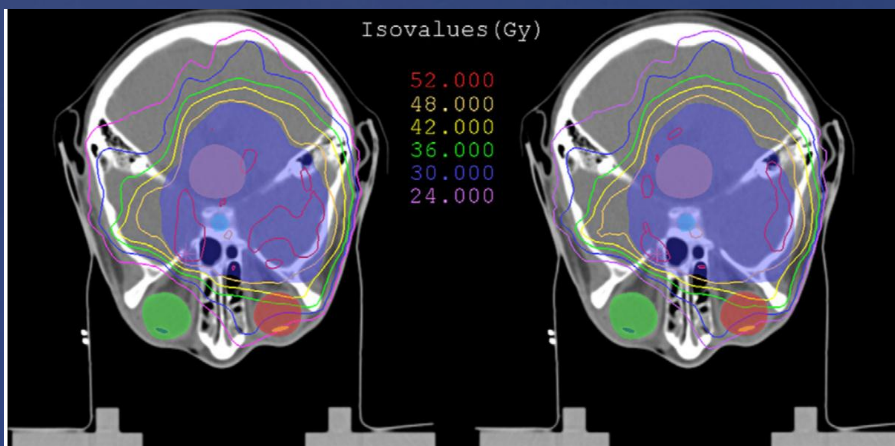
- IMRT, HT, VART may increase the incidence of SMN through increasing the volume of normal tissues receiving low dose is a subject for debate.
- This low dose is primarily caused by a leakage through the accelerator head, jaws and multi leaf collimator (MLC) together with the internal scatter within the patient.
- Secondary radiation from MLCs contributes a significant portion of low dose in IMRT plans

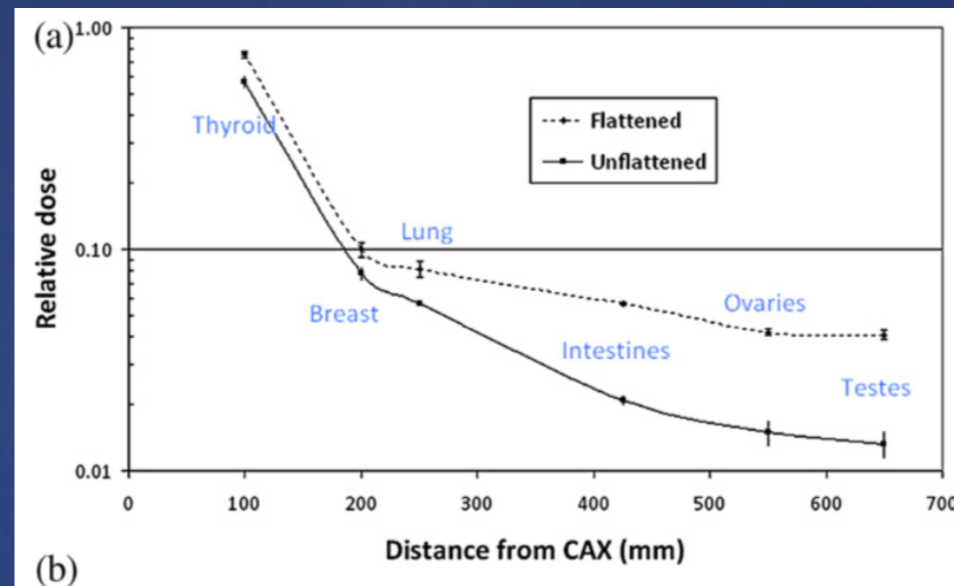
Brenner DJ. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci U S A 2003;100(24):13761–6.

LOWERING WHOLE-BODY RADIATION DOSES IN PEDIATRIC INTENSITY-MODULATED RADIOTHERAPY THROUGH THE USE OF UNFLATTENED PHOTON BEAMS

JASON CASHMORE, M.SC.,* MARK RAMTOHUL, PH.D.,* AND DAN FORD, F.R.C.R.†

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 4, pp. 1220–1227, 2011





- Average reduction in peripheral doses of 23.7%, 29.9%, 64.9% and 70% for thyroid, lung, ovaries and testes respectively with the use of Flattening filter free beams (FFF)

Low dose vs Medium/high dose: SMNs

Second brain tumors following central nervous system radiotherapy in childhood

[1]M CHOJNACKA, MD, [1]K PĘDZIWIATR, MD, [1]A SKOWROŃSKA-GARDAS, MD, PhD, [2]M PEREK-POLNIK, MD, [2]D PEREK, MD, PhD and [1]P OLASEK, MSc

[1]Department of Radiotherapy, M. Skłodowska-Curie Memorial Cancer Center-Institute, Warsaw, Wawelska, Poland
[2]Department of Pediatric Oncology, Children's Memorial Health Institute, Warsaw, Al Dzieci Polskich, Poland

ANALYSIS OF DOSE AT THE SITE OF SECOND TUMOR FORMATION AFTER RADIOTHERAPY TO THE CENTRAL NERVOUS SYSTEM

THOMAS J. GALLOWAY, M.D.,[*†] DANIEL J. INDELICATO, M.D.,[*] ROBERT J. AMDUR, M.D.,[*] CHRISTOPHER G. MORRIS, M.S.,[*] ERIKA L. SWANSON, M.D.,[*] AND ROBERT B. MARCUS, M.D.[†]

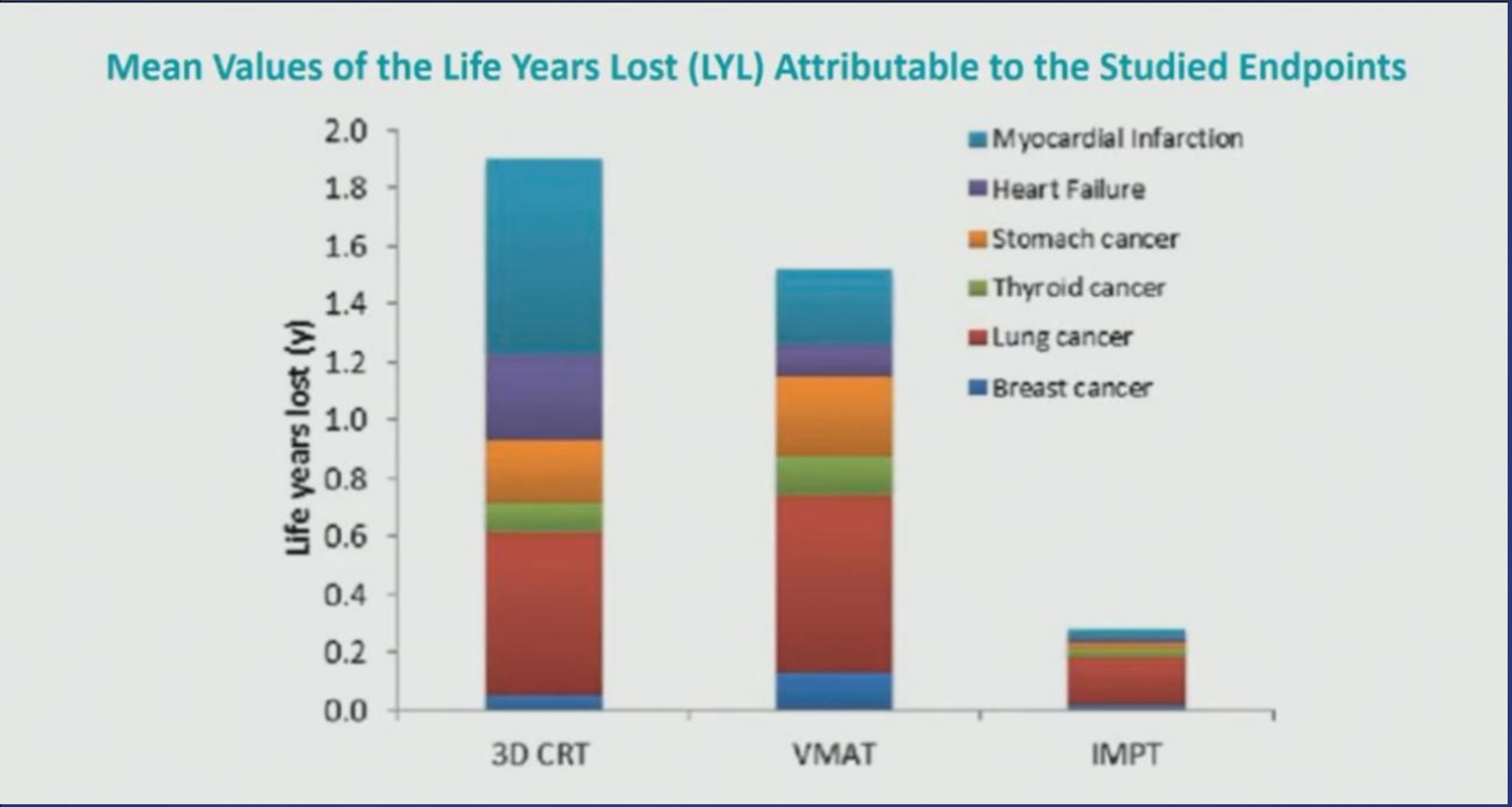
- Second tumors develop in brain tissues receiving >25 Gray
- Most second tumors develop in the region receiving moderate dose of 20-36 Gray

Pediatric CSI: 3D vs. Tomo TLD Results

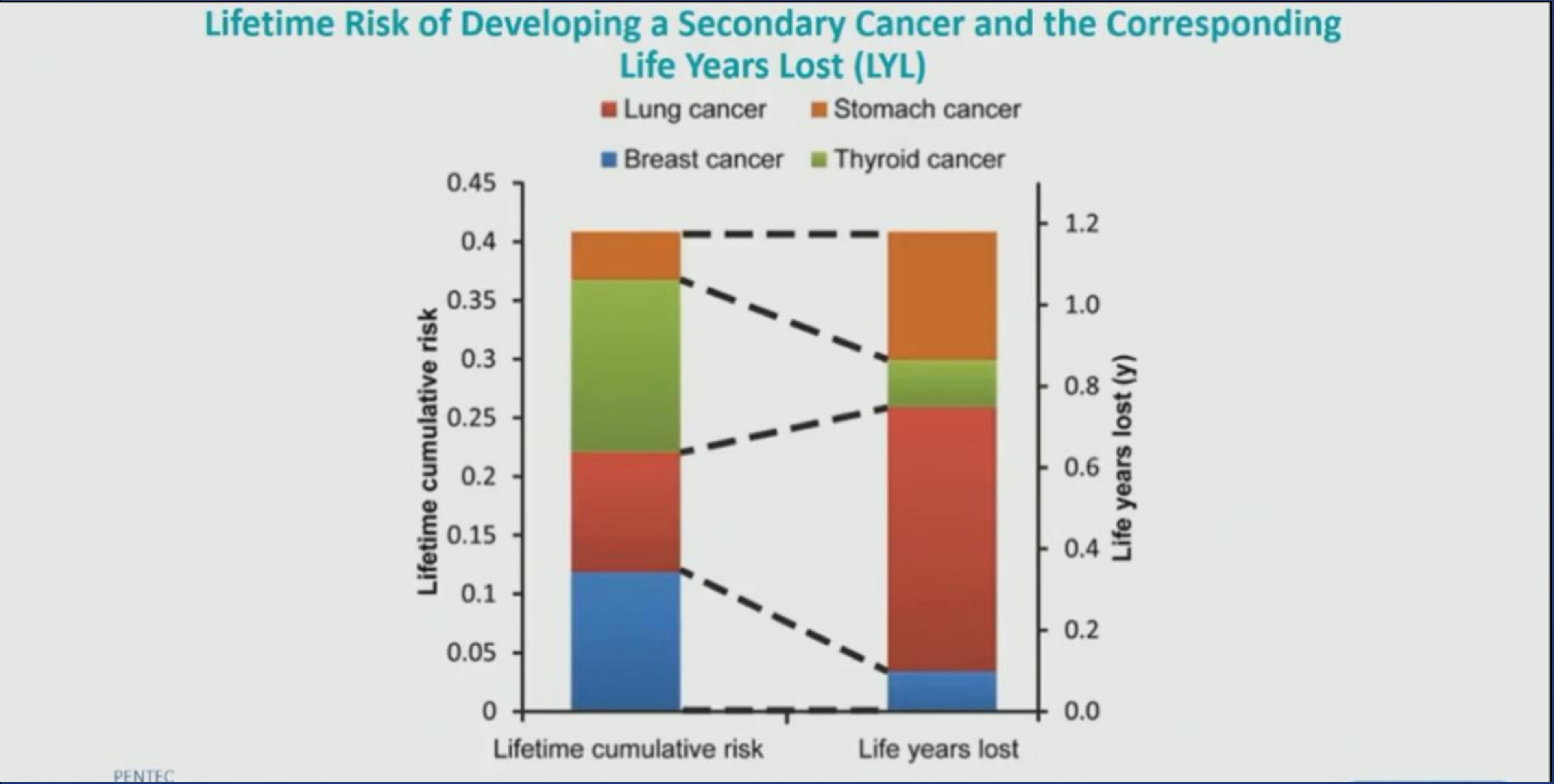
Organ site	Lifetime Risk of Cancer Mortality, %/Sv	Avg Dose from 3D trials, cGy	3D Risk, %	Avg Dose from Tomo trials, cGy	Tomo Risk, %
Thyroid	**2.5	2797.4	**69.2	362.4	**9.0
Lt. Breast Bud	2.1	151.9	3.2	437.5	9.4
Heart center		2957.4		864.9	
Heart edge		2344.9		428.0	
Lt. Lung ctr	4.0	226.4	9.0	907.3	36.2
Lt. Lung edge	4.0	242.2	9.7	446.1	17.8
Liver center	0.3	2583.4	7.4	1107.1	3.2
Liver edge	0.3	216.5	0.6	544.6	1.6
Lt. Kidney		221.1		747.8	
Bladder	0.4	194.8	0.9	76.9	0.3
Pelvic bone marrow	0.6	85.7	0.5	528.5	3.3
Lt. Ovary	0.5	322.2	1.5	135.3	0.6

**Lifetime attributable risk of cancer incidence

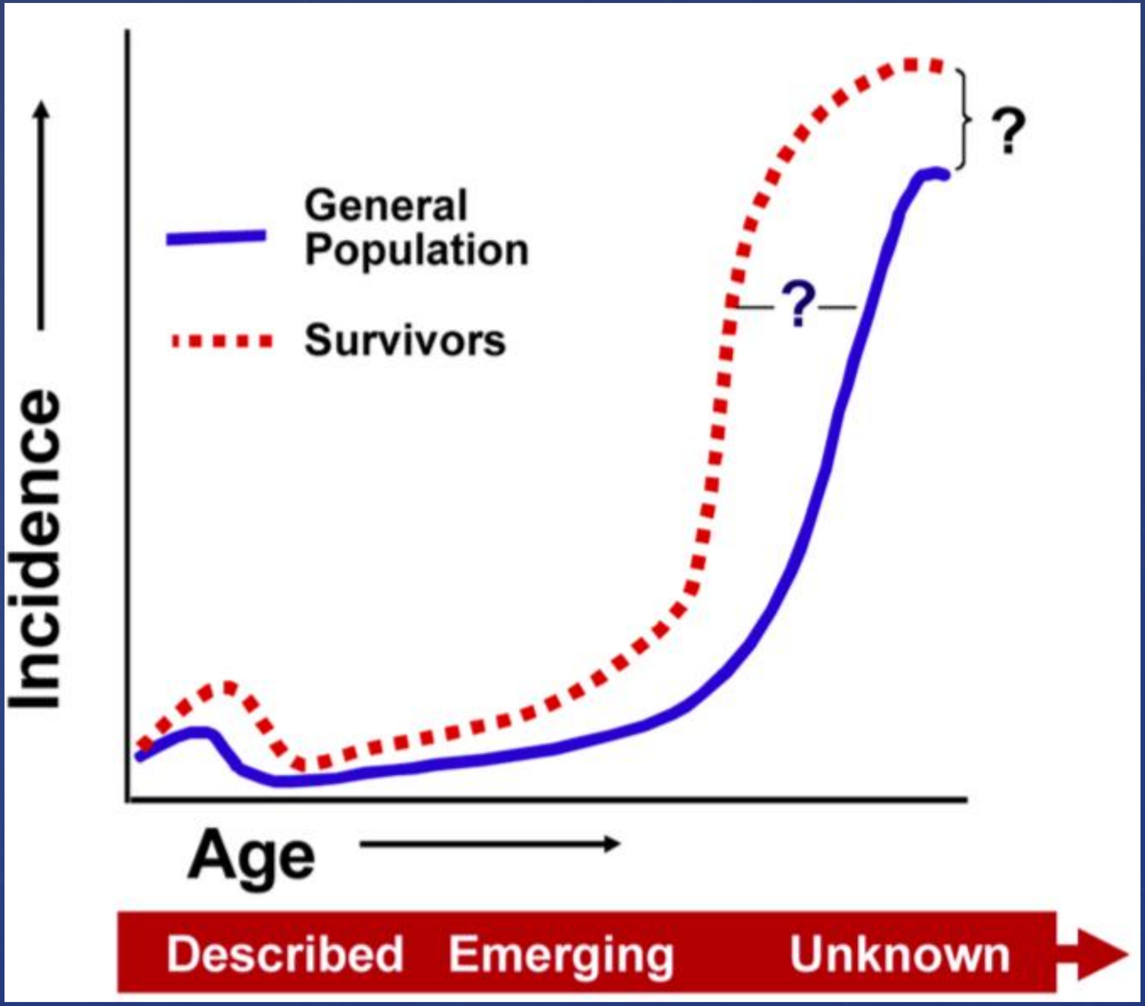
Late effects: RT techniques



Secondary cancers: Impact



Unanswered questions regarding risk of subsequent malignancies among childhood cancer survivors



Facts: SMNs from RT/IMRT Take Home Message (THM-6)

- IMRT by itself does not always increase integral or peripheral dose vs. conventional treatments.
- IMRT does give 3-4 times higher leakage dose and increases the volume receiving ultra low doses.
- SM infrequently occur where head leakage dose dominates, ie. distant from the medium-high dose region.
- SM risk increases with increasing dose: Reduction of moderate to high doses may be beneficial.

Optimizing therapeutic index in pediatric radiation oncology Take Home Message (THM-07)

- Radiation therapy: Important part of multidisciplinary care in pediatric cancers
- Given the risk of late effects adaptation of radiotherapy is evolving
  - Treating less patients (histologic and genetic subtypes)
  - Decreasing treatment volumes/dose
  - Decreasing normal tissue exposed: Image guidance/IMRT/IGRT/Protons
- Use of advanced technology like IMRT/IGRT is not "one stop solution for all pediatric patients"
- Individualized patient selection and adaptation is key for an optimal outcome

Thank you!!