Advanced radiotherapy technology in pediatrics: IMRT
Advantages and pitfalls

Dr Ajeet Kumar Gandhi
MD (AIIMS), DNB (Gold Medalist)
UICCF (MSKCC, USA)
Assistant professor, Radiation oncology
Dr RMLIMS, Lucknow
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 many 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*†‡

*Yale School of Medicine, Department of Therapeutic Radiology, New Haven, Connecticut; †Yale Cancer Center, New Haven, Connecticut; and ‡Cancer Outcomes, Public Policy, and Effectiveness Research (COPPER) Center at Yale, New Haven, Connecticut.
Optimizing outcomes!!

Our current approach to childhood cancer

Maximize Cure

Minimize Toxicities
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 cGy in 28 fractions.
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

Clinician-preferred pediatric RT technique

- IMRT/VMAT
- Proton
- 3D CRT
- TomoTherapy
- AP/PA

Tumor Types:
- Ependymoma
- Craniopharyngioma
- Medulloblastoma
- Germinoma
- Rhabdomyosarcoma
- Non-rhabdo soft tissue sarcoma
- Ewing sarcoma
- Hodgkin lymphoma
- Neuroblastoma
- Wilms tumor
- Whole brain RT for leukemia
Advantages of Pediatric IMRT
Take home message (THM-3)

- **Increased conformality**
  - Cochlear 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

- Host Factors
  - Age
  - Gender
  - Race
- Premorbid conditions
- Genetic
  - BRCA, ATM, p53 polymorphisms
- Tumor Factors
  - Histology
  - Site
  - Biology
  - Response
- Health Behaviors
  - Tobacco
  - Diet
  - Alcohol
  - Exercise
  - Sun
- Aging
- Treatment Events
- Treatment Factors
  - Surgery
  - Chemotherapy
  - Radiation therapy
Late effects of RT: Survival

IMRT may be helpful in certain scenarios
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
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.
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
<table>
<thead>
<tr>
<th>Second Malignancy</th>
<th>First Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone tumors</td>
<td>RB, other bone tumors, Ewing’s sarcoma, STS, ALL</td>
</tr>
<tr>
<td>Soft-tissue sarcoma</td>
<td>RB, STS, HD, Wilms’ tumor, bone tumors, ALL</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>HD, bone tumors, STS, ALL, brain tumors, Wilms’ tumor, NHL</td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>ALL, HD, NB, STS, bone tumors, NHL</td>
</tr>
<tr>
<td>Brain tumors</td>
<td>ALL, brain tumors, HD</td>
</tr>
<tr>
<td>Carcinomas</td>
<td>ALL, HD, NB, STS</td>
</tr>
<tr>
<td>AML/ALL</td>
<td>ALL, HD, bone tumors</td>
</tr>
</tbody>
</table>

**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.

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

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)
Second brain tumors following central nervous system radiotherapy in childhood

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

1Department of Radiotherapy, M. Skłodowska-Curie Memorial Cancer Center-Institute, Warsaw, Wawelska, Poland
2Department 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

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

**Lifetime attributable risk of cancer incidence**
Late effects: RT techniques

Mean Values of the Life Years Lost (LYL) Attributable to the Studied Endpoints

- Myocardial Infarction
- Heart Failure
- Stomach cancer
- Thyroid cancer
- Lung cancer
- Breast cancer

Life years lost (y)

3D CRT

VMAT

IMPT
Secondary cancers: Impact

**Lifetime Risk of Developing a Secondary Cancer and the Corresponding Life Years Lost (LYL)**

- Lung cancer
- Stomach cancer
- Breast cancer
- Thyroid cancer
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, i.e. distant from the medium-high dose region.
- SM risk increases with increasing dose: Reduction of moderate to high doses may be beneficial.
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

Optimizing therapeutic index in pediatric radiation oncology

Take Home Message (THM-07)
Thank you!!