Benefits of High Technology applied to Paediatric Radiation Oncology

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Incidency – Paediatric Tumors

• Incidence and mortality rates of childhood cancer differ worldwide
• ≠ How to report
  • USA (COG) – more accurate
  • 125 per million persons
  • More males and white

• Leukemias (25%)
• CNS Central Nervous System (17%)
• Neuroblastoma (7%),
• Non-Hodgkin lymphoma (NHL 6%),
• Hodgkin Disease (6%)
• Wilms tumor (6%),
• Rhabdomyossarcoma (3%), retinoblastoma (3%), osteosarcoma (3%) and Ewing sarcomas (2%)
Survival Rates of Children and Young Adults Suffering from Cancer

- acute lymphoblastic leukaemia
- acute myeloid leukaemia
- Hodgkin lymphomas
- Non-Hodgkin lymphomas
- Nephroblastoma
- Osteosarcomas
- Ewing sarcomas
- Rhabdomyosarcomas
- Brain tumours
- Germ cell tumours
- Neuroblastoma and ganglieneuroblastoma
Improved survival for children with cancer

- Paediatric cancer = a success story in oncology
- Overall 5-year relative survival rate has increased from 58.1% for 1975-1977 to 82.5% for 2001-2007
- Due to
  - Improvements in diagnosis
    - Imaging, pathology
  - Improved treatments
    - Surgery and perioperative care, radiotherapy, chemotherapy
    - Better supportive care
  - Better integration of all modalities into the therapeutic plan
    - National and international clinical trials

http://seer.gov
# Cause of Mortality in 5-Year Survivors of Childhood Cancer

<table>
<thead>
<tr>
<th></th>
<th>Recurrent Cancer</th>
<th>Second Malignancy/Neoplasm</th>
<th>Cardiac Toxicity</th>
<th>Pulmonary Disease</th>
<th>Other Sequelae</th>
<th>Non-Treatment Related</th>
</tr>
</thead>
</table>
| **Childhood Cancer Survivor Study**  
N = 2823                  | 57%              | 15%                       | 7%               | 2%                | 4%            | 15%                  |
| **Piedmont Region, Italy**  
N = 143                   | 62.2%            | 12.6%                     | 1.4%             | NA                | 8.4%          | 15.4%                |
| **British Columbia, Canada**  
N = 181                   | 69.1%            | 7.7%                      | 4.4%             | 2.2%              | 5.5%          | 11.1%                |
Radiotherapy for children with cancer

- Radiotherapy an important component of treatment
  - Local control
  - Progression-free survival
  - Survival

- Major concern in children = late effects
Evolution of practice in the last 10 years:

• Improved targeting
• Introduction of intensity modulated and image guided radiotherapy
  • Improved conformality, sparing of organs at risk
    • New considerations in contouring
    • Competing risks high vs low dose exposure
    • Quality assurance issues
High technology on central nervous system tumors (CNS)
Target volume definition for CSI – cranium-spinal irradiation

- Clinical target volume = whole brain + spinal cord with overlying meninges
- Problem areas:
  - Frontal region/cribriform plate
  - Caudal extent of thecal sac
Why is this important?

• Attention to coverage of the frontal region
  • Reduces risk of geographic miss/recurrence

• Attention to the width of the spine field
  • Reduces dose to the heart and lungs, other organs at risk

• Attention to lower limit of the spine field
  • Reduces risk of geographic miss/recurrence
  • Minimizes dose to OARs, especially the ovaries

• >>Improved RT technique may have contributed to improved survival in patients with medulloblastoma
2D → 3D conformal radiotherapy

- Early 1990s
- Introduction of CT simulation, improved treatment planning and delivery systems
- End result
  - Better conformity
Improved sparing of critical structures

“Conventional” RT

3D CRT

Decreased dose to cochlea and hypothalamus/pituitary, decreased volume of supratentorial brain in treated volume
3D CRT → intensity modulated RT

- Early 2000s
- Advantages
  - Improved dose distribution for an irregularly shaped target volume
  - Possibility of delivering differential doses within the treated volume
  - Further improved sparing of critical structures/selective avoidance
IMRT for improved sparing of critical structures

Further decreased dose to cochlea and hypothalamus/pituitary, decreased volume of supratentorial brain in treated volume.
Reducing High Dose Radiotherapy Volume with Newer Technology
Ototoxicity and Medulloblastoma

IMRT in arc or VMAT to treat the CSI

- Conventional techniques – matched junctions
- Cover optimally PTV – imperfect
- Marginal failures cribriform plate, posterior fossa, spine deformity

- VMAT, RapidArc – great advantage
- Reduce geometrical uncertainties
- Reduce integral dose
- Delivering optimal conformal RT
VMAT to CSI

- CSI conventional - Inhomogeneous dose distributions
  120%-130% of dose prescription within and outside of target – irregularities of body and natural spine curvature

- VMAT – more homogeneous dose, lower dose to OAR, lower MU than IMRT with fixed beams
CSI - Conventional technique

Gap junction

Hot spot

Heterogeneous dose in spine
CSI - VMAT technique

Homogeneous dose in spine
Better cover PTV
Lower dose OAR
Other indications IMRT – CNS tumors
Germinoma-irradiation of all ventricles

IMRT – unquestionably – best compliance
Reirradiation: rigid constraints chiasm (6Gy/50Gy)
Possibility with IMRT - VMAT

Other indications IMRT – CNS tumors
Reirradiation
Case example - 2010 / First RT – Localized Ependymoma
54Gy posterior fossa IMRT
Reirrrradiation

Base dose did not originate on displayed images and structures
Dose was resampled due to different calculation properties
2015 / 2nd RT – Localized Ependymoma recurrence

Possibility with IMRT – VMAT
Localized Ependymoma recurrence
Given more 54Gy close Brainstem
Reirrradiation

2017 – 2\textsuperscript{nd} recurrence
Chiasm and 3\textsuperscript{rd} ventricle

3\textsuperscript{rd} RT - CSI without dose to posterior Fossa + boost to tumor area

VMAT technique
Possibility with IMRT - VMAT
Reirrradiation

2017 – 2\textsuperscript{nd} recurrence
Chiasm and 3\textsuperscript{rd} ventricle

3\textsuperscript{rd} RT - CSI without dose to posterior Fossa + boost to tumor area

VMAT technique
Possibility with IMRT - VMAT
2017 – 2nd recurrence
Chiasm and 3rd ventricle

3rd RT - CSI without dose to posterior Fossa + boost to tumor area

VMAT technique – plan sum
High technology on sarcomas head and neck abdominal
Rhabdomyosarcoma in the face and left cervical VMAT
Retinoblastoma – Boldrini’s Experience
Orbit tumour – plannings comparison
Drini’s Hospital Experience

MRT and VMAT abdominal fields

Geneity

Comparing with 3D Philips or junctions

Covering kidneys and ovaries
A 3-month-old child presented with pallor and a palpable retroperitoneal mass on abdominal scanning. Biopsy showed a large cell lymphoma. Figure 1. CT-generated isodose plans for tomotherapy — (a) axial plane, (b) coronal plane, and (c) sagittal plane — demonstrating the spread of low-dose isodoses in tomotherapy.

Figure 2. Case 1. Dose-volume histogram of (a) tomotherapy and (b) linac plans. Note, in particular, the similarity in doses to distant structures away from the axial planes of therapy (e.g. the iliac crest). PTV, planning target volume.
Irini’s Hospital Experience

RT and VMAT- extended fields

Yers
- Stom alveolar
- chemo + surgery
- Consolidation

OARs
- Kidneys
- Femur
- Ischium metastases
- Tumor bed + pelvis nodes
- Ovaries (clips)
- Genitalia

Tolerance: 10Gy

OPTION:
T e VMAT extended fields

- T e VMAT extended fields
- T e VMAT extended fields
- T e VMAT extended fields
- T e VMAT extended fields

1 Arc
223MU
time 1,5min.
Radiotherapy Ewing - High technology

Advantage of technique

Technology conformal, IMRT modulated beam - desirable

(RT, RapidArc) - more conformed and faster

Acute and late side effects

Delaney et al, Cancer Control, 2005
Pisters et al, JCO, 2007
Donaldson, Pediatr Blood Cancer, 2004
MSK reviewed 60 patients treated with modern RT

- Median F/U = 41 months
- 49% received IMRT
- 49% had tumors in unfavorable sites
- Actuarial 3-year LC was 77%

Majority of patients w/o complications

La, IJROBP 2006
Whole lung irradiation – heart protection - VMAT
High technology on lymphomas
Change in Treatment Techniques? IMRT vs Conformal Radiotherapy

Opposed field RT vs IMRT
INVOLVED-NODE RADIOTHERAPY AND MODERN RADIATION TREATMENT TECHNIQUES IN PATIENTS WITH HODGKIN LYMPHOMA

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*Department of Radiation Oncology and †Physics Unit, Institut Gustave Roussy, Villejuif, France

Purpose: To assess the clinical outcome of the involved-node radiotherapy (INRT) concept using modern radiation treatments (intensity-modulated radiotherapy [IMRT] or deep-inspiration breath-hold radiotherapy [DIBH]) in patients with localized supradiaphragmatic Hodgkin lymphoma.

Methods and Materials: All but 2 patients had early-stage Hodgkin lymphoma, and they were treated with chemotherapy prior to irradiation. Radiation treatments were delivered using the INRT concept according to European Organization for Research and Treatment of Cancer guidelines. IMRT was performed with the patient free-breathing. For the adapted breath-hold technique, a spirometer dedicated to DIBH radiotherapy was used.

Results: Fifty patients with Hodgkin lymphoma (48 patients with primary Hodgkin lymphoma, 1 patient with recurrent disease, and 1 patient with refractory disease) entered the study from January 2003 to August 2008. Thirty-two patients were treated with IMRT, and 18 patients were treated with the DIBH technique. The median age was 28 years (range, 17–62 years). Thirty-four (68%) patients had stage I (I-IIA) IA disease, and 16 (32%) patients had stage I (I-IIIB) IB disease. All but 3 patients received three to six cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). The median radiation doses to patients treated with IMRT and DIBH were, respectively, 40 Gy (range, 21.6–40 Gy) and 36.6 Gy (range, 19.8–40 Gy). Protection of various organs at risk was satisfactory. Median follow-up was 33.4 months (range, 19.1–93 months). The 5-year progression-free and overall survival rates for the whole population were 92% (95% confidence interval [CI], 80%–97%) and 94% (95% CI, 75%–98%), respectively. Recurrences occurred in 4 patients: 2 patients had in-field relapses, and 2 patients had visceral recurrences. Grade 3 acute lung toxicity (transient pneumonitis) occurred in 1 case.

Conclusions: Our results suggest that patients with localized Hodgkin lymphoma can be safely and efficiently treated using the INRT concept and modern radiation treatment techniques such as IMRT and DIBH. © 2011 Elsevier Inc.

Involved node – recommendation IMRT

Fig. 2. Three-dimensional view of the heart, the origin of the coronary arteries, and the mediastinal tumor mass with free-breathing (a) and DIBH (b) modalities, illustrating the greater distance between the tumor and the OARs in a patient in deep inspiration.
Result - Better Plan - VMAT

V12 HEART
V20 LUNGS
IMRT in children?

IMRT – increased risk of second cancer?

E J Hall, Int J Radiat Oncol Biol Phys 65(1) 1-7, 2006

Effect “low dose bath”
Largest volume exposed to low dose
Dose Monitors Higher
Escape from the larger head of linac is higher
Neutrons in the room (> 10MV)
In child-rest of the body would be closer to the target of treatment (PTV)
Greater susceptibility of children to cancer
IMRT in children?

- studies of survivors of the Hiroshima bomb
  - greater volume receiving low doses - would be sufficient
  - Carcinogenesis: stochastic event
### Some of literature on Paediatric SM

<table>
<thead>
<tr>
<th>Reference</th>
<th>Group</th>
<th># children</th>
<th>#SM reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonn-Tapper 2006</td>
<td>Nordic countries</td>
<td>25.150</td>
<td>196</td>
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<tr>
<td>Hein 2003</td>
<td>Germany</td>
<td>24.203</td>
<td>238</td>
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<tr>
<td>IARC 1973-2000</td>
<td>SEER (NCI)</td>
<td>23.819</td>
<td>352</td>
</tr>
<tr>
<td>Bass 2006</td>
<td>CCSS</td>
<td>20.720</td>
<td>677</td>
</tr>
<tr>
<td>Warkentin 2004</td>
<td>Great Britain</td>
<td>16.541</td>
<td>278</td>
</tr>
<tr>
<td>Hyen 2008</td>
<td>France, Great Britain</td>
<td>4401</td>
<td>124</td>
</tr>
<tr>
<td>Stutia 2003</td>
<td>LESG</td>
<td>1380 (HD)</td>
<td>212</td>
</tr>
</tbody>
</table>
Review of 2\textsuperscript{nd} malignancies

401 pt studied -1947- 1986

4pt SMN –in 25 years after RT – 5\% risk/25 years

lateral Retinoblastoma, non-hodgkin lymphoma, ewing tumors –

and more cases 2\textsuperscript{nd} malignancies

risk was 2.6 time higher in patients treated with RT

highest integral dose – higher the risk

significant dose-response relationship

\textit{Nguyen et al, Red J, 2008}
Review of 2nd malignancies

Fig. 2. Relative risk (and 95% confidence interval) of second malignant neoplasm associated with the integral dose restricted to the irradiated fields (left panel) and with the integral dose per kilogram (right panel).

Despite this...

- Increasing use of IMRT in children
Reason for Fear of “Low Dose Bath” during Conformal RT?

0.1Gy (100mSV) total body dose increases risk of cancer by about 1% (A-Bomb survivors data, ICRP 103)

For a 50Gy RX, the total body dose for 3D is about 0.55Gy, for IMRT is about 0.7Gy and (extra head leakage dose 3-5 x MU) not dependent of number of fields

So should we worry about extra 0.15Gy difference and the creation of “low dose bath”?
So what can we do?

Choose best equipment
- Energy <10MV
- Least MLC leakage

Demand changes to linacs
- Remove flattening filter
- Additional shielding in the head
2nd malignancies – Local of 2nd tumor

35pt re-treated with RT

50% of second tumor were in inside margin region of volume treated = 2.5cm inside and 5cm outside of margin of 1st PTV

10% inside 1st PTV

11% outside 1st PTV

Dorr and Herrmann J Radiol Prot 2002
ence against the increased risk of second pregnancy with IMRT

More beams by itself does not increase integral dose (J) vs conventional treatments

IMRT by itself does not increase integral or peripheral dose vs conventional treatments by much

IMRT does give 3-4 times higher leakage dose and increases the volume receiving ultra low dose

SM infrequently occur where head leakage dose dominates, ie, distant from medium-high dose region

Reducing the volume receiving moderate to high doses in trade for increasing the volume receiving small doses should both reduce SM risk and better protect normal structures.
IGRT – Image guided radiotherapy – in children?

Indications in Paediatrics

Localization, set ups in Paediatric Radiation Oncology - critical

Very few accessories for this public

Reduction of a few mm in PTV – results in gain in irradiated normal tissue decrease
Not so good...

Image-guided radiotherapy
• Additional dose
• Larger volume exposed
IGRT – in children?

- Exposure dose – IGRT
- Small Dose, less than portal IMRT and accurately – great gain
- VMAT – precision is required, IGRT is mandatory
- Protons – more conformed - even precise location is mandatory
SBRT Stereotactic radiation body radiotherapy

• Significant number of patients metastatic
  Some patients remain curable

• Give effective doses to radioresistant tumors
  SBRT may provide a way to overcome these obstacles

• Relatively radioresistant tumors
  Dose escalation need (i.e. osteosarcoma)
  Dose-limiting normal tissue (i.e. spine)

• Potential curability in the oligometastatic state

• SBRT currently being evaluated for the new COG high risk Ewing’s protocol

• Multi-institutional trial at JHH, Mayo, Stanford, and St. Jude
SBRT

- focused, precise delivery of high-dose to a small tumor
- 1 – 5 fractions
- Similar to intracranial – radiosurgery
- Can apply to extracranial sites - metastasis
PROTONS
Critical Review

Proton Therapy in Children: A Systematic Review of Clinical Effectiveness in 15 Pediatric Cancers

Roos Leroy, PhD,* Nadia Benahmed, MSc,* Frank Hulstaert, MD,* Nancy Van Damme, PhD,† and Dirk De Ruysscher, PhD‡

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Received Apr 8, 2015, and in revised form Oct 5, 2015. Accepted for publication Oct 13, 2015.
Protons

650pt, follow up 19-91months/ 23 studies, non randomized, 20 retrospectives

For retinoblastoma, very low-level evidence - PT decrease second malignancies.

For chondrosarcoma, chordoma, craniopharyngioma, ependymoma, esthesioneuroblastoma, Ewing sarcoma, CNS (germinoma, glioma, medulloblastoma), osteosarcoma, rhabdomyosarcoma - insufficient evidence to either support or refute PT in children

For pelvic sarcoma (ie, nonrhabdomyosarcoma and non-Ewing sarcoma), pineal tumor, PNET, and “adult-type” soft tissue sarcoma, no studies were identified that fulfilled the inclusion criteria.
Protons

Articles – brainstem necrosis – more severe acute brain injury in children with protons? – further investigation

Wells E at all, Neuro oncol, 2014
Kralik SF at al, AJNR, 2015

Actual secondary cancer risk related to exposure to secondary neutrons?
However Protons…

Scanned protons result in 50 to 67% reduction of integral dose reduction of the mean and mid-to-low doses to OAR.

Neutron contamination generated by proton scatter is not a risk of carcinogenesis.

Technique pencil beam delivery reduce neutron production.
COMMENTARY

Consensus Report From the Stockholm Pediatric Proton Therapy Conference

Daniel J. Indelicato, MD,* Thomas Merchant, DO, PhD,† Normand Laperriere, MD, FRCPC,† Yasmin Lassen, MD, PhD,§ Sabina Vennarini, MD,|| Suzanne Wolden, MD, FACP,*|| William Hartsell, MD, # Mark Pankuch, PhD, # Petter Brandal, MD, PhD,** Chi-Ching K. Law, MD, †† Roger Taylor, MD, †† Siddhartha Laskar, MD, §§ Mehmet Fatih Okcu, MD, MPH, |||| Eric Bouffet, MD, †† Henry Mandeville, MBChB, MRCP, FRCR, MD, ## Thomas Björk-Eriksson, MD, PhD, *** Kristina Nilsson, MD, PhD, *** Hakan Nyström, PhD, *** Louis Sandy Constine, MD, †††
Protons indications - Experts

Majority agree indication of CNS, skull base tumors and retinoblastoma

Exception high-grade gliomas of the brain and brainstem

For wilms, whole brain, no benefit

Diversity of opinion: Hodgkin, neuroblastoma, rhabdomyosarcoma, ewing
Protons Ependymoma posterior fossa: lower dose cochlea, temporal lobe, pituitary-hypothalamic.

Fig. 2. Posterior fossa ependymoma photon (IMRT, top) and proton (IMPT, bottom) comparison plans in 3 planes.
Protons

Craniopharyngioma reduced low- moderate dose to supratentorial brain

Fig. 3. Craniopharyngioma photon (IMRT, top) and proton (bottom) comparison plans in 3 planes.
Protons - Medulloblastoma – lower dose to Heart, lung, face, pelvis but higher to scalp and paraspinal soft tissue

**Fig. 4.** Medulloblastoma proton and photon comparison plans. Left: Proton pencil beam (PBS) plan. Middle: Photon tomotherapy. Right: A dose subtraction image to highlight differences between the 2 modalities.
Protons - Rhabdo – lower dose to cochlea, face, oral cavity, infratentorial brain but higher to the frontal lobe and larynx

Fig. 5. Parameningeal rhabdomyosarcoma proton and photon comparison plans. Left: Proton pencil beam (PBS) plan. Middle: Photon tomotherapy. Right: A dose subtraction image to highlight differences between the 2 modalities.
Take home messages

• IMRT - Benefit in CNS tumors, sarcomas, head and neck, Lymphomas, neuroblastomas (increasing)

• VMAT, most plans conformed faster and with less MU, better plan CSI

• IGRT - highly recommended with IMRT, mandatory with VMAT and protons

• Protons - good indication to CNS, skull base tumors, retinoblastoma

• Controversy indication hodgkin, sarcomas, ewing, neuroblastoma

• 2nd malignancy - no increased
Thank you

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