Curing Children with Cancer, But At What Cost? The Double-edged Sword of Cytotoxic Therapy and PENTEC: investigations into normal tissue dose constraints in children

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No conflicts of interest
Cancer Survival, 0-14 Years of Age
SEER Program 1973-2012

Survivorship Statistics

• >83% of children with a malignancy will achieve five-year survival

• In 2013, estimated 420,000 survivors of childhood cancer in the U.S.

• By 2020, estimated 500,000 survivors

• 1 in 750 in US is a childhood cancer survivor

Howlader N, SEER Cancer Statistics Review 1975-2012
Phillips et al, CEBP, 2015 NCI Office of Cancer Survivorship
Five-Year Relative Survival Rates

- Over 250,000 childhood cancer survivors in the US
- 1 in 1,000 is a childhood cancer survivor
- 1 in 570 is a childhood cancer survivor (ages 20 to 34 yr.)

Graph showing five-year relative survival rates for various cancers from 1974-1976 to 1992-1998.
Cumulative Case-Specific Mortality
5 year survivors - Childhood Cancer Survivor Study

Late Mortality Among 5+ Year Survivors
Childhood Cancer Survivor Study (N=20,483)

Causes                  SMR
Second cancers          15.2
Cardiac                 7.0
Pulmonary               8.8

Incidence of Health Conditions in 10,397 Adults in Children’s Cancer Survivor Study

Cumulative Incidence

Years Since Diagnosis

Oeffinger, NEJM, 2006
Spectrum of Treatment Effects

Life-Threatening → Life-Altering

- Cardiomyopathy
- Pulmonary fibrosis
- High grade second cancers

Obesity
- Immunodeficiency
- Chronic hepatitis
- Endocrinopathy
- Asplenia

Infertility
- Neurocognitive deficits

Seizure disorder
- Low grade second cancers

Hearing/vision loss
- Amputation

Chronic pain
- Short stature

- Short stature

- Seizure disorder
- Low grade second cancers
- Hearing/vision loss
- Amputation
- Chronic pain
- Short stature

It’s not what you don’t know that hurts you,
It’s what you know that just ain’t so.

» Mark Twain
## Comparative Risks after Radiotherapy: Children vs. Adults

<table>
<thead>
<tr>
<th>Risk</th>
<th>Levels of Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neurocognitive reduction</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>No difference</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>But consequences greater due to growth hormone suppression</td>
</tr>
<tr>
<td>Cataracts</td>
<td>More</td>
<td>Weak</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>More</td>
<td>Moderate</td>
</tr>
<tr>
<td>Heart</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevents myocyte hypertrophy and remodeling</td>
</tr>
<tr>
<td>Breast hypoplasia</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most severe during puberty</td>
</tr>
<tr>
<td>Lung</td>
<td>Less</td>
<td>Weak</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Depends on endpoint: maximum capacity decreased if chest wall growth is inhibited</td>
</tr>
<tr>
<td>Thyroid hypofunction</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td>Thyroid nodules</td>
<td>More</td>
<td>Moderate</td>
</tr>
<tr>
<td>Thyroid autoimmune</td>
<td>No data</td>
<td>Weak</td>
</tr>
<tr>
<td>Kidney</td>
<td>same</td>
<td>weak</td>
</tr>
<tr>
<td>Bladder</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder capacity reduced</td>
</tr>
<tr>
<td>Testes</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most severe during puberty</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Less</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less sensitive to radiation at younger age</td>
</tr>
<tr>
<td>Uterus</td>
<td>More</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine vasculature impaired</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>More</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoplasia, deformity, osteochondroma</td>
</tr>
<tr>
<td>Immune</td>
<td>No data</td>
<td>Weak</td>
</tr>
<tr>
<td>Marrow whole body</td>
<td>Less</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Less available marrow when older</td>
</tr>
</tbody>
</table>

UN Scientific Committee: Constine, Mettler 2013
Risk-Based Survivor Care

- Host Factors
  - Age
  - Gender
  - Race

- Premorbid conditions

- Genetic
  - BRCA, ATM, p53 polymorphisms

- Tumor Factors
  - Histology
  - Site
  - Biology

- Treatment Factors
  - Surgery
  - Chemotherapy
  - Radiation therapy

- Treatment Events
- Aging
- Health Behaviors
  - Tobacco
  - Diet
  - Alcohol
  - Exercise
  - Sun
Technical issues increasing risk

- Children are little
- Things are packed in tight
- Even small RT fields treat a lot of organs
Smaller distances
Smaller distances
<table>
<thead>
<tr>
<th></th>
<th>Pre-RT</th>
<th>During-RT</th>
<th>Post-RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kids</strong></td>
<td>All CNS, Rhabdo, Neuroblastoma</td>
<td>All Rhabdo, Ewings, Wilms, Medullo</td>
<td>All Rhabdo, Ewings, Wilms</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td>Some Breast</td>
<td>Most ENT, Lung, GI, Gyn</td>
<td>GI</td>
</tr>
</tbody>
</table>

*Kids: most get chemo, adults, some don’t: e.g. Prostate, sarcoma, many breast, etc.*
## Broad Issues

<table>
<thead>
<tr>
<th>Kids</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Growth and development</td>
<td>Comorbid diseases</td>
</tr>
<tr>
<td>Smaller size</td>
<td>Less reserve</td>
</tr>
<tr>
<td>Long horizon</td>
<td>Larger size</td>
</tr>
<tr>
<td></td>
<td>Variable horizon</td>
</tr>
</tbody>
</table>
Tissues at Risk for Late Toxicity

- Bone/soft tissues
- Cardiovascular
- Dental
- Endocrine
- Gastrointestinal
- Hepatic
- Hematological
- Immune system
- Nervous system
- Neuropsychological
- Ophthalmologic
- Pulmonary
- Renal
- Reproductive
Growth Impairment

Risk factors

- Younger age (prepubertal)
- Higher dose (> 20 Gy)
- Higher daily fraction (≥ 2 Gy)
- Larger treatment field
- Epiphysis in treatment field
Radiation Treatment Sequelae with Limb-shortening and Muscle Hypoplasia
Man Treated With High-Dose Mantle RT for Hodgkin’s Lymphoma

12 yrs post RT
2 yr old girl treated with high dose RT to hemi-abdomen for Wilms

2 yrs post RT  
(age 4 yrs)

4 yrs post RT  
(age 6 yrs)

9 yrs post RT  
(age 11 yrs)

9 yrs post RT  
(age 11 yrs)
Scoliosis in Neuroblastoma

Paulino et al. IJROBP. Volume 61, Number 3, 2005
Height loss as function of age/dose after RT to lumbar spine for Wilms tumor

Hogeboom CJ et al. Medical and Pediatric Oncology 2001;36:295-304
Wilm’s Tumor
Bone Growth

CLINICAL MODELING

POLARITY
RADIOGRAPHIC SITES

SHOULDERS

RIBS

LUMBAR SPINE

PELVIS

WRISTS

PHALANGES

AMPLIFICATION

2–12 YRS.
CM. + % INCREASE

+19 CM.
(400%) HUMERUS

+14 CM.
(350%) RADIUS

+16 CM.
(300%) ULNA

+31 CM.
(500%) FEMUR

+25 CM.
(500%) FIBULA

+25 CM.
(450%) TIBIA
9-year-old Girl Treated With Implants and EBRT For Synovial Cell Sarcoma of Knee

3 yr post RT

Dosimetry
Cardiac Risks after Childhood Cancer: Childhood Cancer Survivor Study (CCSS)

- Stroke: 9.3 X
- Coronary Artery Dz: 10.4 X
- Heart Failure (CHF): 15.1 X

**Anthracycline Cardiac Injury**

- **Cardiac myocyte injury**
- **Reduced LV wall thickness**
- **Elevated LV afterload**
- **Depressed LV performance**

**Risk Factors**
- Younger age (< 5 y)
- Female sex
- African American
- Higher dose (> 250/m2)
- Use of chest radiation
- Longer time from Rx

**Manifestations**
- Cardiomyopathy
- Congestive heart failure
- Arrhythmia
- Sudden death

**Cardiomyopathy**
Anthracycline-Induced CHF
830 survivors; 8.5 yrs mean follow-up

Anthracyclines and risk of cardiomyopathy, stratified by patients’ CBR3 genotype status

Anthracyclines and risk of cardiomyopathy, stratified by patients’ CBR3 genotype status

No safe dose for patients homozygous for the CBR3 V244M G allele

Radiation Cardiac Injury

Manifestations
- Restrictive cardiomyopathy
- Premature CAD
- Myocardial infarction
- Valvular disease
- Autonomic dysfunction
- Conduction defects

Risk Factors
- Younger age (< 5 y)
- Higher dose (> 35 Gy)
- Higher daily fraction (≥ 2 Gy)
- Larger volume of heart in field
- Anteriorly weighted field
- Subcarinal shielding
- Longer time from RT
- Use of cardiotoxic chemoRx

Mantle Field
Incidence of CVD vs RT Dose to Heart (Childhood Cancer Survivors)

Adapted from Mulrooney, BMJ 2009
Pulmonary Dysfunction

- Paramediastinal fibrosis
- Pulmonary fibrosis
- Restrictive lung disease
- Pneumothorax
Symptomatic Pneumonitis vs. Mean Lung Dose

- MSKCC (10/78)
- Duke (39/201)
- Michigan-1 (17/109)
- MD Anderson (~49?/223)
- NKI (17/106)
- WU (52/219)
- Michigan-2 (9/42)
- Heidelberg (10/66)
- Milan (7/55)
- Gyeonggi (12/68)

logistic fit
68% CI

Probability of Pneumonitis vs. Mean Lung Dose (Gy)

Krasin, Constine, Friedman, Marks. Sem Rad Onc 20:21, 2010
Dental Abnormalities After RT

- Tooth/root agenesis
- Adontia
- Microdontia
- Root thinning or shortening
- Enamel dysplasia

Dose thresholds are age/endpoint dependent: 10-20 Gy
Dental Abnormalities After Radiation

- Salivary gland dysfunction
- Xerostomia
- Dental caries
- Periodontal disease

Dose thresholds relate to salivary gland dysfunction: 20-40 Gy dependent on volume, bilateral vs unilateral
Hypothyroidism

Risk Factors

- Female sex
- Older age (> 15 y)
- Higher radiation dose
  - 30% if 35-44 Gy
  - 50% if > 45 Gy
- Time < 5 y from Dx

Sklar et al, JCEM 2000
Peak Growth Hormone according to hypothalamic mean dose and time from irradiation

Merchant et al, JCO 29:4776, 2111
Relative Proportions and Overlap Among Anterior Pituitary Deficiencies Following Cranial Radiotherapy

ACTHD, adrenocorticotropic hormone deficiency
GHD, growth hormone deficiency
LH/FSHD, luteinizing hormone/follicle-stimulating hormone deficiency
TSHD, thyroid-stimulating hormone deficiency
Female Gonadal Dysfunction

Manifestations:
- Delayed/arrested puberty
- Infertility/early menopause

Risk factors:
- Older age
- High doses of alkylators
- > 6-10 Gy radiation to pelvis (permanent if > 20 Gy)
- Gonadal radiation combined with alkylators

Age & Risk of Ovarian Failure
# Effect of Fractionated Testicular Radiation on Sperm Count

<table>
<thead>
<tr>
<th>Rounded Dose (Gy)</th>
<th>Effect post-RT</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 – 0.3</td>
<td>Temporary oligospermia</td>
<td></td>
</tr>
<tr>
<td>0.3 – 0.5</td>
<td>Temporary aspermia at 4-12 months</td>
<td>Full recovery by 48 months</td>
</tr>
<tr>
<td>0.5 – 1.0</td>
<td>100% temporary aspermia from 3 – 17 months</td>
<td>Recovery begins at 8–38 months</td>
</tr>
<tr>
<td>1.0 – 2.0</td>
<td>100% temporary aspermia from 2 – 15 months</td>
<td>Recovery begins at 9–20 months</td>
</tr>
<tr>
<td>2.0 – 3.0</td>
<td>100% temporary aspermia beginning at 1-2 months</td>
<td>Recovery begins in some cases at 12–14 years</td>
</tr>
<tr>
<td></td>
<td>(a certain percentage will suffer permanent aspermia)—large daily fractions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100% aspermia beginning at about 2 months —small daily fractions</td>
<td>No recovery observed up to 40 months</td>
</tr>
</tbody>
</table>

Ash P; Brit J Radiol; 53:271; 1980
Abnormal Testosterone Value vs Radiation Dose to Testicles

Abnormal testosterone (percent of patients) vs Dose (cGy)

Izard M, Rad & Onc; 34:1 (1995)
Bilateral Whole Kidney RT – non TBI

Correlation of Dose with Symptomatic Radiation Nephropathy

- Thompson, et al.
- Luxton
- Dewit, et al.
- LeBourgeois; Dewit; Kim
- Avioli, et al.
- Kim, et al.

% Incidence vs. Dose (cGy)
Bladder Complications

- Hemorrhagic cystitis
- Bladder fibrosis
- Dysfunctional voiding
- Urinary incontinence
- Bladder carcinoma
Neuroimaging Abnormalities

- Brain atrophy
- Encephalomalacia
- Cerebral lacunes
- Dystrophic calcification
- Leukoencephalopathy
- Necrosis/gliosis
IQ After Conformal RT for Low Grade Glioma

$n = 78$

54 Gy

10mm margin

Merchant TE, J Clin Oncol 2009; 27:3691
Hearing loss

- 78 children, 155 ears after RT for BT: 14% hearing loss at 3-5 yrs

Table 1. Incidence of hearing loss for 155 ears of 78 pediatric patients with brain tumor

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Mean cochlear dose (Gy)</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>50</th>
<th>55</th>
<th>60*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (6,000 and 8,000 Hz)</td>
<td>1.0</td>
<td>2.0</td>
<td>4.0</td>
<td>5.0</td>
<td>11.0</td>
<td>24.0</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>Intermediate (2,000, 3,000, and 4,000 Hz)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>5.0</td>
<td>13.0</td>
<td></td>
</tr>
<tr>
<td>Low (250, 500, and 1,000 Hz)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.5</td>
<td>10.0</td>
<td>16.0</td>
<td></td>
</tr>
</tbody>
</table>

Incidence of hearing loss expressed as percent.
* Linearly extrapolated to 60 Gy.

HUA et al. IJROBP 72:892, 2008

Fig. 5. Histogram of hearing loss onset. RT = radiotherapy.
Subsequent Neoplasms

- Overall risk of 5%-12% by 25 years
- Higher risk in specific subgroups
- Determinants of risk:
  - Presence of cancer gene mutation
  - Cancer treatment exposures
  - Environmental factors
  - Lifestyle practices
Secondary Acute Myeloid Leukemia

- Brief latency: 3 to 10 years
- Risk related to chemotherapy
  - Alkylating agents
  - Epipodophyllotoxins
- No additional risk after radiation
Second Solid Tumors

- Long latency period (> 10 years)
- Primarily associated with radiation
- Risk for specific histologies can be enhanced by chemotherapy
- Adult tumor histologies predominate
- Higher risk with cancer gene mutations
Incidence: Second Malignancies

Neglia, 2001
Cumulative Proportion of Second Malignancies After Hodgkin Lymphoma According to Gender

The dashed lines represent standard errors.

P<.0001
Children’s Oncology Group

Mammogram and breast MRI annually, starting at the age of 25 or 8 yrs after chest radiation

International Meeting for Harmonization of Health Screening and Surveillance Guidelines for Childhood Cancer Survivors

Secondary Breast Cancer

Amsterdam, the Netherlands
Secondary Thyroid Malignancy After RT

Ronckers et al, Rad Res, 166:618, 2006
Dose-response Relations Between RT Dose and Relative Risk (RR) of Second Neoplasms

A  
- Observed RR Meningioma  
- Fitted Line Meningioma  
- Observed RR Glioma  
- Fitted Line Glioma

B  
- Linear  
- Linear exponential  
- Recorded ORs

Copyright American Society of Clinical Oncology
Solid Tumors After Radiation
Conclusions About Late Effects

- Risk depends on tissues and age of patient
- Late effects are dose and modality specific
- Most late effects may be anticipated
- Combined therapy may have additive effects
Make everything as simple as possible, but not simpler.

Or

Make everything as simple as possible, if not simpler.

» Albert Einstein
Curing Children with Cancer, But At What Cost? 
PENTEC: Pediatric Normal Tissue Effects in the Clinic, An International Collaboration

Louis S. Constine, MD, FASTRO 
Philip Rubin Professor of Radiation Oncology and Pediatrics 
Director, Judy DiMarzo Cancer Survivorship Program 
Vice Chair, Department of Radiation Oncology

No conflicts of interest
What is PENTEC?

Physicians (radiation and pediatric oncologists, subspecialists), physicists (clinical and modelers), and epidemiologists critically synthesizing existing data to:

- Develop quantitative evidence-based dose/volume guidelines, as impacted by developmental status, to inform RT planning and improve outcomes
- Describe relevant physics issues specific to pediatric radiotherapy
- Propose dose-volume-outcome reporting standards to inform future RT guidelines
What PENTEC will include
Introductory Reports

• Introduction to scientific issues
• Summary of Pediatrics NTCP data and models
• Pediatric bio-developmental considerations
• Pediatric physics aspects
• Epidemiologic considerations
• Improving NTCP and modeling in pediatrics
• Contrasting Pediatrics vs. Adult QUANTEC
<table>
<thead>
<tr>
<th>Specialty</th>
<th>Working Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial/Brain Stem</td>
<td>A. Mahajan</td>
</tr>
<tr>
<td>Head/Neck</td>
<td>A. Paulino</td>
</tr>
<tr>
<td>Stroke</td>
<td>S. MacDonald</td>
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<tr>
<td>Endocrine</td>
<td>G. Wheeler</td>
</tr>
<tr>
<td>Hearing</td>
<td>T. Yock</td>
</tr>
<tr>
<td>Eye</td>
<td>J. Buchsbaum</td>
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<tr>
<td>Thyroid</td>
<td>M. Milano</td>
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<tr>
<td>Pulmonary</td>
<td>MF. McAleer</td>
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<tr>
<td>Breast</td>
<td>K. Marcus</td>
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<tr>
<td>Cardiac</td>
<td>D. Hodgson</td>
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<tr>
<td>Gastrointestinal tract</td>
<td>J. Bradley</td>
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<tr>
<td>Kidney/bladder</td>
<td>A. Liu</td>
</tr>
<tr>
<td>Testes/male fertility</td>
<td>B. Hoppe</td>
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<tr>
<td>Female Genital</td>
<td>C. Hill</td>
</tr>
<tr>
<td>Muscle/Skin/Bone</td>
<td>N. Esiashvili</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>N. Laack</td>
</tr>
<tr>
<td>SMN</td>
<td>K. Roberts</td>
</tr>
<tr>
<td>TBI</td>
<td>K. Dusenbery</td>
</tr>
</tbody>
</table>
Visionary Reports

• Methodology for accurate data acquisition on radiation dose distribution
• Biomarkers and surrogate endpoints
• Pediatric imaging issues
• Secondary malignancy as impacted by evolution of technology
• Recommendations for reporting and gathering data—to cooperative groups
• Future directions
Content of organ-specific reports

- Required sections:
  - Anatomy & developmental dynamics
  - Clinical significance
  - Endpoints & Toxicity Scoring
  - Challenges defining volumes: pediatric image issues
  - Review of Dose Volume Response data/risk factors
  - Recommended dose volume (Dose per fraction)
  - Toxicity scoring recommendations
  - Contrast Pediatric & Adult NTCP data
  - Future Investigations
PENTEC
Methodology
Overview
1. Identify and select evidence
2. Uniform data extraction
3. Quantitative and descriptive synthesis
4. Expert opinion Consensus
5. Conclusions and recommendations
Identify and Select Evidence

PICO
P  Childhood Cancer Patients
I  Radiotherapy
C  Internal control group (no RT) or general population
O  Musculoskeletal development

Research question
What is the association between radiation dose/volume and the risk impairment of ___”endpoint”___?

Search filters
RT pentec AND skeletal problems AND children; Limits: Humans

Search results, PubMed, date 2014.09.08
1. Identify and select evidence

2. Uniform data extraction

Quantitative and descriptive synthesis

Expert opinion Consensus
Synthesis

Heterogeneity
- Radiation exposure assessment
  - Radiation technique
  - Prescribed vs. absorbed (measured) dose
  - Volume, fractionation
- Covariates
  - Age at RT / attained age
  - Chemotherapy/Surgery/SCT/other treatments
- Follow-up
  - Duration
  - Completeness
- Outcome
  - Definition of endpoints
  - Methodology for assessment
Anticipated Hurdles and Potential Solutions for Modeling

Ideal dataset: associates dose/volume for an organ with a specific endpoint, impacted by age at RT and interval to endpoint.

Anticipated problems:

1. Reports containing dose/volume data are limited and may not have adequate spread for reliable curve fitting
2. Definitions of endpoints across institutions may vary (e.g. hearing loss thresholds; various cognitive and behavioral outcome measures)
3. Data only reports age range and median (or mean), or lumps all patients into one group, or arbitrarily divides into different groups (e.g. young vs. old)
Anticipated Hurdles and Potential Solutions for Modeling (continued)

4. Dose-fractionation schemes or dose rates vary
5. Extent of irradiation or dose distribution varies (whole lungs vs. partial lungs; proton vs. photon)
6. Many organs were exposed, or no organ-specific dose data were reported (e.g. TBI)
7. Chemo regimens and surgical techniques evolved (confounding factors)
3. Conclusions and recommendations
Conclusions

• What we know
• And what we don’t know yet

Recommendations

• Constraints
• Impact of covariates
• Outcome definitions
• Research priorities to answer clinical questions
PENTEC Steering Committee

- Louis S Constine *Chair* (University of Rochester)
- Søren Bentzen: (University of Maryland)
- Cécile Ronckers: (Emma Children’s Hospital)
- Sughosh Dhakal: (University of Rochester)
- Chia-Ho Hua: (St. Jude)
- David Hodgson: (University of Toronto)
- Melissa Hudson: (St. Jude)
- Andrew Jackson: (MSK Cancer Center)
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- Jackie Williams: (University of Rochester)
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- Yorkee@mskcc.org
We are working hard:

» To cure children with cancer
» To minimize late effects

And we are making progress!