Experiences at MD Anderson Cancer Center Normal Tissue Dose Reconstructions

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The Role of Physics in Long Term Epidemiological Studies of Pediatric Radiotherapy Patients ❖ 08-02-2017

Late Effects Studies

- Seek to identify the relationship between treatment exposures and late adverse effects (> 5 years) in cancer survivors.
- Important data for such studies are RT doses to the organs in which the outcomes are observed, but often not available in patients' RT record:
  - Historic RT used simple 2D planning.
  - Even with 3D planning, CT scans only include anatomy close to the treatment area; often only hard-copies of plans are available, which may include only selected views of the anatomy.

Organ doses must be "*reconstructed*" with available data from RT records!

Late Effects Group at MD Anderson

- Reconstruct doses to organs throughout the body from radiotherapy for large scale case-control and cohort studies. **500 to ~15,000 participants!**
- Provide organ doses for a wide spectrum of adverse late effects, e.g.,
  - **second cancers**
  - **heart disease**
  - visual impairment
  - infertility
  - premature menopause
  - cognitive impairment
  - Hearing loss
  - teeth damage

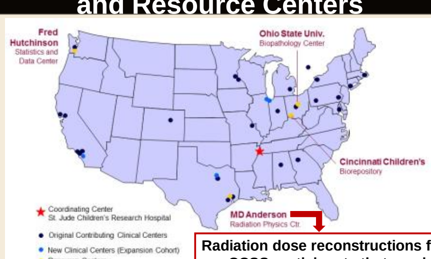
Current Cohort Collaborations

- Childhood Cancer Survivor Study (CCSS)
- St. Jude Life (SJL)
- Adult Life after Childhood Cancer in Scandinavia (ALiCCS)
- The Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (DCOG LATER)
- Kaiser Permanente Breast Cancer Cohort

CCSS General Overview

- Cohort of 24,368 childhood cancer survivors diagnosed between 1970 and 1999.
  - Two groups in "overall" cohort
    - Original cohort: 1970 – 1984
    - Expanded cohort: 1985- 1999
  - Derived from > 30 institutions
  - 8 different primary cancer diagnosis
    - Leukemia (ALL, AML, other), CNS (medulloblastoma, astrocytoma, PNET, other), Hodgkin lymphoma, non-Hodgkin lymphoma, kidney tumor (Wilm's), neuroblastoma, soft tissue sarcoma, bone cancer (Ewing sarcoma, osteosarcoma, other bone).
- Comparison group of siblings of survivors

Collaborating Institutions and Resource Centers

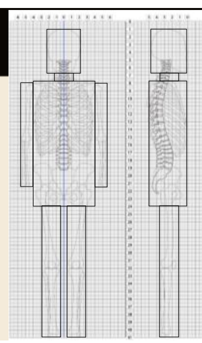


Radiation dose reconstructions for >13,000 CCSS participants that received RT.

Mathematical Phantom for Dose Reconstructions

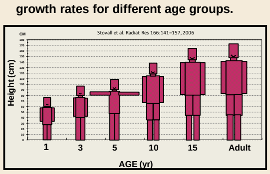
Master Phantom

- The phantom is divided into rectangular sections: head, neck, trunk, arms, and legs.
- Defined by a 3D grid of evenly spaced points (x, y, z).
- Grid system used
  - To define organs
  - To define/place field centers



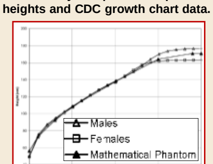
Age-Specific Phantom Scaling

- Master phantom scaled to age at RT.
  - use different scaling factors for the head, trunk and limbs to account for uneven growth rates for different age groups.



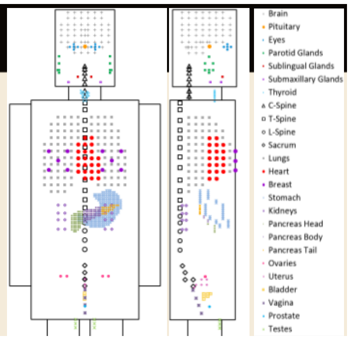
Note: Phantoms are scaled by age rather than BMI; height and weight are rarely in the historic RT records!

- Phantom "body sizes" based on body dimension study of > 4000 U.S. children (NSCSAE).
  - Validated by comparison of phantom heights and CDC growth chart data.



Phantom Organs

- Organs represented by a grid of points (x, y, z).
  - Grid can be moved.
  - Grid resolution can be ⇧ or ⇩.
- Organ positions
  - Defined using anatomy atlases based on bony anatomy, and proximity to other organs, etc.
  - Developed in collaboration with various study investigators.
- Organs can be divided into components, e.g.,
  - Pancreas: head, body, tail



Radiation Dose Reconstruction

"The Process"

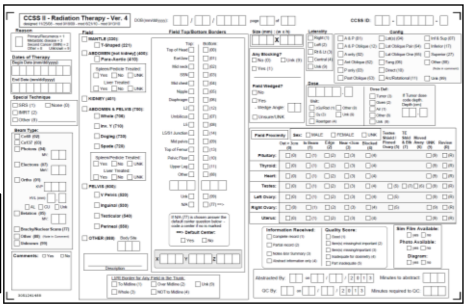
Radiation Dose Reconstruction

1. Abstract participants' RT (de-identified) record
2. Reconstruct RT fields on age-specific phantoms
3. Calculate dose to regions and organs of interest
4. Quality assurance of computed doses
5. Create output files and documentation
6. Provide data to FH Statistics Center for distribution of data to individual investigators.

Record Abstraction

- Pertinent data
  - Treatment Dates
  - Date of Birth
  - Prescription(s)
  - Field Data: orientation, energy, weighting, blocking, modifiers, borders etc.

- Record length varies
  - 1 to >250 pages
- Coding time varies
  - 20 min to 2 hrs
- No direct correlation between record length and quality.

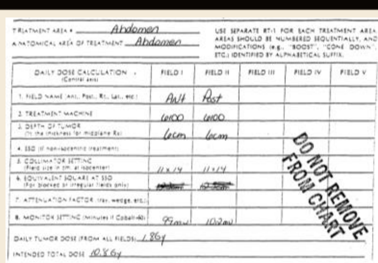

CCSS II - Radiation Therapy - Ver. 4

RT Record coding Must Look all "Clues"

- **Experienced Coders are ESSENTIAL**
- **Details, details, details**
- **Diagrams, photos, and films are not always consistent with each other**
- **Daily logs are useful**
  - **Lots of plans, which treated, was entire treatment delivered, etc.**
  - **Blocks get added but not shown in plan, e.g., heart block at 20 Gy.**
- **Some summaries can be as useful as a record**
  - **May give Rx, energy, location, borders, etc.**

Example Record

- **38 page record**


TREATMENT AREA # Abdomen
ANATOMICAL AREA OF TREATMENT Abdomen

USE SEPARATE RT-1 FOR EACH TREATMENT AREA. AREAS SHOULD BE NUMBERED SEQUENTIALLY, AND MODIFICATIONS (e.g., "BOOST", "CONE DOWN", ETC.) IDENTIFIED BY ALPHABETICAL SUFFIX.

DAILY DOSE CALCULATION (Central axis)	FIELD I	FIELD II	FIELD III	FIELD IV	FIELD V
1. FIELD NAME (Ant., Post., Rt., Lat., etc.)	Ant	Post			
2. TREATMENT MACHINE	6100	6100			
3. DEPTH OF TUMOR (Or the thickness for midplane Rx)	6cm	6cm			
4. SSD (if non-isocentric treatment)					
5. COLLIMATOR SETTING (Field size in cm. at isocenter)	11x14	11x14			
6. EQUIVALENT SQUARE AT SSD (For blocked or irregular fields only)	[illegible]	[illegible]			
7. ATTENUATION FACTOR (tray, wedge, etc.)					
8. MONITOR SETTING (Minutes if Cobalt-60)	99mu	102mu			

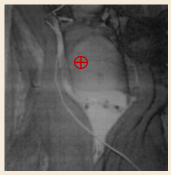
DAILY TUMOR DOSE (FROM ALL FIELDS) 1.8Gy
INTENDED TOTAL DOSE 10.8Gy

DO NOT REMOVE FROM CHART

Example Record

- Photographs are sometimes in the charts and can be useful for determining field borders or isocenter.

Not a useful photo!



Useful: Field isocenter is visible

Example Record

- Diagrams provide useful information for field placement on the mathematical phantom for dose reconstruction.
- Some uncertainty in field position relative to midline
  - AP drawn to midline
  - PA not quite to midline

These sorts of discrepancies can sometimes be sorted out based on a photo or the physicians' notes.

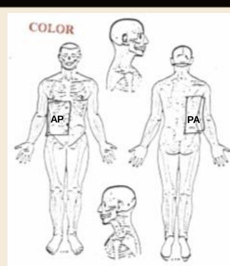
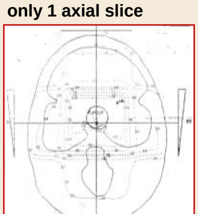


Diagram Examples

- CT Data, not very useful, only 1 axial slice



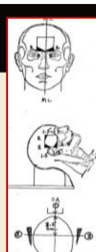
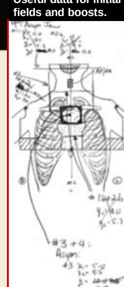


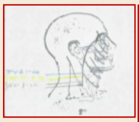
Diagram more informative → field center and borders

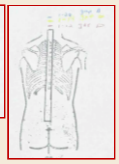
Useful data for initial fields and boosts.



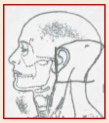
Field Placement
Cranial Spinal Record Example

- Initial Fields (6 MV)
  - Right and left lateral brain fields top of head to C6
  - Posterior spine field C6 to L5/S1 junction



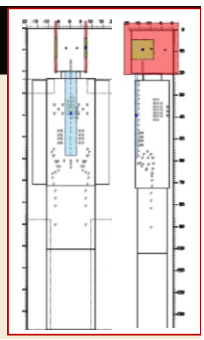


- Boost (6 MV)
  - Right and left lateral posterior fossa fields



Field Placement
CSI Record Example

- Coded fields are placed on an age-specific mathematical phantom based on abstracted data.
  - Note “eye and face” blocking not shown in the rendering, but included for dosimetry calculations.
- Dose calculated for each field and can be determined for any point within phantom’s 3D grid.

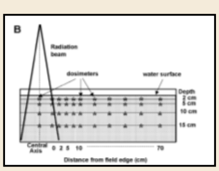


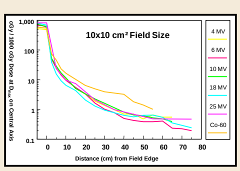
Dose Calculations
In-field and Out-of-field

In-beam

- Open
  - BJR-17
- Blocked
  - 10% of in-beam
- Edge
  - 50% of in-beam

- Out-of-beam: analytical models based on measured data for different beam energies, field sizes, depths





Levels of Radiation Dosimetry

Different Levels of Radiation Dosimetry

Study Specific Dosimetry Tiers

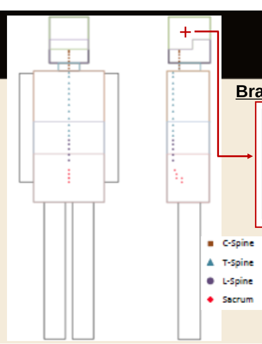
- Y/N RT (per FH stats/data center)
- Y/N for specific types of RT, e.g., CSI, TBI, etc.
- Body region maximum tumor dose (maxTD)
- Organ specific doses, e.g., heart, thyroid, gonads, pancreas, etc.
  - Average dose (most common parameter)
  - Average dose to organ parts, e.g., pancreas head, body, tail
  - Percent volume that received ≥ X Gy, e.g., PV_5, PV_{10}, PV_{20}

M
D
A

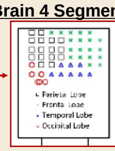
Body Region Dosimetry

Body Regions

- brain
- other head
- neck
- chest
- abdomen
- pelvis
- extremities



Brain 4 Segments



Yes/No

- **Brain**
- **Spine**
- **TBI**

Body Region Dosimetry

- **In-beam Region**
  - **Maximum treatment dose (MaxTD) to specific body regions taking into account only direct in-beam contributions to that region.**

- **Out-of-beam Regions (2)**
  - **based on distance from in-beam region**

Stray High (SH) Region
- Adjacent to in-beam region
- Doses are 1% to 10% of maxTD

Stray Low (SL) Region
- Not Adjacent to in-beam region
- Doses <1% of maxTD

Body Region Dosimetry Calculation Example

Research

JAMA | Original Investigation

Temporal Trends in Treatment and Subsequent Neoplasm Risk Among 5-Year Survivors of Childhood Cancer, 1970-2015

Lucie M. Turcotte, MD, MPH, MS; Qi Liu, MS; Yutaka Yasui, PhD; Michael A. Arnold, MD, PhD; Sue Hammond, MD; Rebecca M. Howell, PhD; Susan A. Smith, MPH; Rita E. Weathers, MS; Tara O. Henderson, MD; Todd M. Gibson, PhD; Wendy Leisenring, ScD; Gregory T. Armstrong, MD, MSCE; Leslie L. Robison, PhD; Joseph P. Neglia, MD, MPH

JAMA. 2017;317(8):814-824.

CONCLUSIONS AND RELEVANCE Among survivors of childhood cancer, the risk of subsequent malignancies at 15 years after initial cancer diagnosis remained increased for those diagnosed in the 1990s, although the risk was lower compared with those diagnosed in the 1970s. This lower risk was associated with reduction in therapeutic radiation dose.

Relative Rates of Subsequent Neoplasm, Overall and by Subtypes, According to Multivariable Analysis

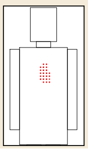
Table 2. Relative Rates of Subsequent Neoplasm, Overall and by Subtypes, According to Multivariable Analysis[a]

	Subsequent Neoplasm		Subsequent Malignant Neoplasm		Meningioma		Nonmelanoma Skin Cancer	
Variable	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value	RR (95% CI)	P Value
Maximum radiation treatment dose to any body region, Gy								
None	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
0.1-10	4.55 (2.51-8.24)	<.001	2.94 (1.48-5.86)	.002	24.39 (4.42-134.44)	<.001	6.55 (2.45-17.47)	<.001
10.1-20	3.16 (2.32-4.31)	<.001	1.67 (1.23-2.27)	.001	14.77 (5.89-37.03)	<.001	5.75 (3.16-10.45)	<.001
20.1-30	3.32 (2.55-4.33)	<.001	1.96 (1.49-2.58)	<.001	23.44 (9.85-55.79)	<.001	4.82 (2.79-8.34)	<.001
30.1-40	4.32 (3.13-5.97)	<.001	2.63 (1.98-3.50)	<.001	10.91 (3.60-33.05)	<.001	6.98 (3.81-12.79)	<.001
40.1-50	5.19 (3.75-7.18)	<.001	2.82 (2.15-3.71)	<.001	23.80 (9.32-60.80)	<.001	8.57 (4.61-15.93)	<.001
≥50.1	3.81 (2.84-5.10)	<.001	2.36 (1.73-3.21)	<.001	34.93 (14.20-85.93)	<.001	4.93 (2.69-9.04)	<.001

Organ Dosimetry
Average Dose

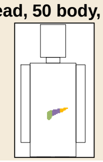
- Mathematical average of dose to all points in the organ.
- Average Organ dose can be computed for:

<u>Entire Organ: Heart (55 points)</u>



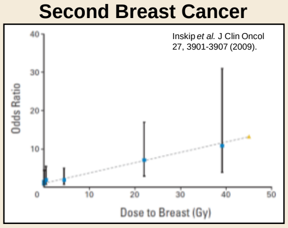
<u>Organ Parts: Pancreas (129 points)</u>

54 head, 50 body, 25 tail

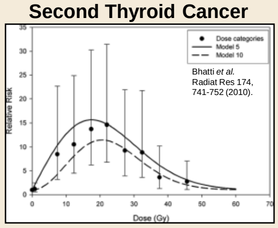


Example Studies
Average Organ Dose

Second Breast Cancer

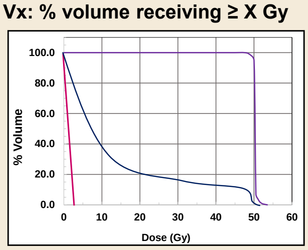


Second Thyroid Cancer



Organ Dosimetry
Dose Volume Metrics

- Vx: % volume receiving ≥ X Gy



- % of points in an organ that receive ≥ “x” dose can be used to represent Vx.
  - dose is calculated for each point within an organ.
  - points within organs are evenly spaced.

We recently calculated Vx data for heart and pancreas for overall cohort (13649 patients).

Example Study
Dose Volume Metric

- Bates *et al.* Age-associated vulnerability to treatment-related late cardiotoxicity: A report from the Childhood Cancer Survivor Study (CCSS), ASCO Annual Meeting, Chicago, IL, 6/2017
- Bates *et al.* Volumetric dose-effect analysis of late cardiotoxicity: a report from the childhood cancer survivor study (CCSS), ASTRO 59th Annual Meeting, San Diego, CA, 9/2017

Manuscript drafted (in-review by co-authors)

Radiation Dose Reconstruction

"Record Quality and Uncertainty"

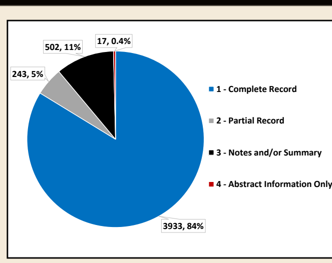
Record Quality Scores

Record "Completeness"

- Did we receive all RT data that were available?

Information Received:

- ☐ Complete record (1)
- ☐ Partial record (2)
- ☐ Notes &/or Summary (3)
- ☐ Abstract information only (4)



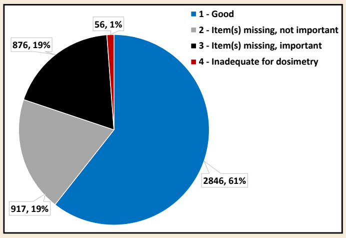
Record Quality Score

Dosimetric "Adequacy"

- Does the missing information matter?

Quality Score:

- ☐ Good (1)
- ☐ Item(s) missing/not important (2)
- ☐ Item(s) missing/important (3)
- ☐ Inadequate for dosimetry (4)



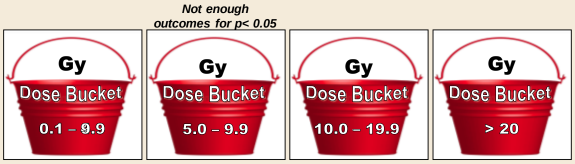
Dosimetric Uncertainty

- Adequate for Dosimetry?
  - The answer is "location dependent"
    - Near Organ: data may be insufficient for organ dosimetry, but acceptable for body-region dosimetry.
    - Data which are insufficient for "near organ" dosimetry may be acceptable for "far organ"
- Adequate for Dosimetry?
  - The answer is "dose bucket dependent"

Dosimetric Uncertainty

- Must be considered in the context of the study dose bins!

Not enough outcomes for p< 0.05



Completed Organ Doses *to Date* for the CCSS Cohort

Organ/Region	Data Reported	Cohort
Body Regions + brain 4 seg	MaxTD, SH, SL	Overall
Eyes/lenses	Average Dose	Original
Heart	Average dose, V_5, V_{10}, V_{15}, V_{20}	Overall
Lungs	Average dose	Overall (*12,846 patients)
Ovaries	Average dose	Overall (female)
Uterus	Average dose	Overall (female)
Pancreas	Average dose for whole, head, body, tail, V_{20} and V_{30} for whole pancreas	Overall
Pituitary	Average dose	Original, Expansion (est. 6/17)
Salivary Glands	Average dose	Original
Spleen (Abdomen LUQ)	Average dose	Overall
Testes	Average dose	Original
Thyroid	Average dose	Original
Teeth	Average dose	Original

Summary and Conclusions

- Radiation dose reconstructions are an essential component of late effects studies.
- The level of dosimetry that can be done for a study is dependent on the quality of data in the records.
- Important questions can be answered with body-region dosimetry.
- Organ-specific doses are important for establishing dose response models, but the dosimetry for individual studies should be considered in the context of other sources of uncertainty.

Acknowledgements

Funding
- Federally Funded Subcontracts
  - Childhood Survivor Cancer Study
  - NCI Radiation Epidemiology Branch
- Research service agreements
  - St. Jude Children's Research Hospital
  - Helsinki Children's Hospital
  - Danish Cancer Society Research Center

Marilyn Stovall, PhD

- Medical Physicist at MDA for 65 years (1951 – 2016).
- Late Effects Group Founder
- > 300 publications; h=85

Our Team Today

- Susan Smith
- Jacob Palmer
- Irene Harris
- Rita Weathers
- Tera Jones
- Samantha Murray
- Debbie Tanner

End

Thank you.

THE UNIVERSITY OF TEXAS
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