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

  - Two groups in “overall” cohort
    - Expanded cohort: 1995-1999
  - 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 (Wilms'), 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.
- 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.

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

- Organs represented by a grid of points (x, y, z).
  - Grid can be moved.
  - Grid resolution can be $6 \times 8$ or $8 \times 3$.

- 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"

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.

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**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.

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**Example Record**

- 38 page record
Example Record

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

![Not a useful photo!](image1)

![Useful: Field isocenter is visible](image2)

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.*

Example Record

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

![Diagram more informative field center and borders](image3)
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

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_{10}, PV_{20}

Different Levels of Radiation Dosimetry

Body Region Dosimetry

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

Relative Rates of Subsequent Neoplasm, Overall and by Subtypes, According to Multivariable Analysis
Organ Dosimetry
Average Dose

• Mathematical average of dose to all points in the organ.
• Average Organ dose can be computed for:
  
  **Entire Organ: Heart (55 points)**
  
  **Organ Parts: Pancreas (129 points)**

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

- Did we receive all RT data that were available?

<table>
<thead>
<tr>
<th>Information Received:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete record (1)</td>
</tr>
<tr>
<td>Partial record (2)</td>
</tr>
<tr>
<td>Notes &amp;/or Summary (3)</td>
</tr>
<tr>
<td>Abstract information only (4)</td>
</tr>
</tbody>
</table>

- 582, 11.5%
- 22, 4.9%
- 3, 0.5%
- 4, 0.8%
- 243, 5%
- 502, 11%
- 17, 0.4%

1 - Complete Record
2 - Partial Record
3 - Notes and/or Summary
4 - Abstract Information Only
Record Quality Score

Dosimetric “Adequacy”
- Does the missing information matter?

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”

Dosimetric Uncertainty
- 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

<table>
<thead>
<tr>
<th>Organ/Region</th>
<th>Data Reported</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Regions + Brain 4 seg</td>
<td>MaxTD, SH, SL</td>
<td>Overall</td>
</tr>
<tr>
<td>Eyes/Irradiance</td>
<td>Average dose</td>
<td>Original</td>
</tr>
<tr>
<td>Heart</td>
<td>Average dose, V5, V10, V15</td>
<td>Overall</td>
</tr>
<tr>
<td>Lungs</td>
<td>Average dose</td>
<td>Overall</td>
</tr>
<tr>
<td>Ovaries</td>
<td>Average dose</td>
<td>Overall (female)</td>
</tr>
<tr>
<td>Uterus</td>
<td>Average dose</td>
<td>Overall (female)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Average dose for whole, head, body,</td>
<td>Overall</td>
</tr>
<tr>
<td></td>
<td>tail, V20 and V30 for whole pancreas</td>
<td></td>
</tr>
<tr>
<td>Pituitary</td>
<td>Average dose</td>
<td>Original, Expansion (est. 6/17)</td>
</tr>
<tr>
<td>Salivary Glands</td>
<td>Average dose</td>
<td>Original</td>
</tr>
<tr>
<td>Spleen (Abdomen LUQ)</td>
<td>Average dose</td>
<td>Overall</td>
</tr>
<tr>
<td>Testes</td>
<td>Average dose</td>
<td>Original</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Average dose</td>
<td>Original</td>
</tr>
<tr>
<td>Teeth</td>
<td>Average dose</td>
<td>Original</td>
</tr>
</tbody>
</table>

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.

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End

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