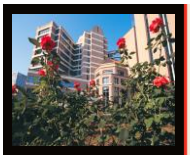

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Multi-Institutional Data Pooling

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Learning Objective

- *Discuss technical and process issues related to pooling data among institutions in the context of collaborative studies among the presenting institutions.*
- In particular, I will be discussing an on-going data pooling project between my institution and the Mayo Clinic.
  - Focusing on rationale for data pooling, challenges in data collection, understanding results, and long-term goals.

Interest in RT-related cardiac effects grew almost exponentially after a publication in NEJM by Darby *et al.* in 2013.

The NEW ENGLAND JOURNAL of MEDICINE

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Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

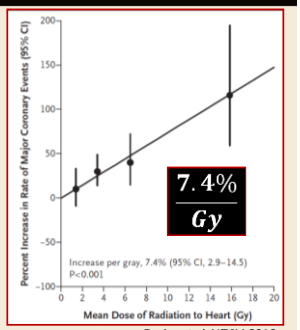
Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

Linear Dose Response Model

- Rate of major coronary events according to mean radiation dose to the heart compared with the rate with no radiation exposure to the heart.

But how were mean heart doses determined?

Based on patients' individual RT records, but were retrospectively reconstruted treatment plans using CT scan of a "representative" patient.



Darby *et al.* NEJM 2013

Many More Unanswered Questions

- Only mean heart dose was considered.

Risk associated with partial volume effects remains unknown…..

- Considered *historic* type BRT and reported a mean heart dose for the population ≈ 6 Gy

Are those data relevant in the context of modern BRT?

Motivation for Data Pooling in BRT

- Currently no large database exists that reports standard dose metrics of modern BRT for the heart and lungs.
- Normal tissue complications after BRT have been widely published, including cardiac and pulmonary toxicities.
  - However, these are based on early treatment trials or population studies and with no normal tissue doses or dose estimations only.

Objectives

- Primary objectives of our study were
  1. To establish a bi-institutional database in order to ascertain baseline values for typical heart and lung doses for modern BRT.
  2. To evaluate the effect of various treatment techniques on those doses.

Basic Requirements for Study

- Consensus on what data to collect
- How many patients to include from each institution
- DVH data extraction from TPS

How many patients?

- How many could we reasonably accrue in about 6 months?
  - Institutions 1 and 2 treat approximately 1000 and 350 breast patients with EBRT each year, respectively.
- Agreed to collect data for 100 right and 100 left BRT patients from each institution.
- Data were collected using consecutive sampling and included patients who received definitive EBRT for a primary breast cancer and who completed RT.

How did we decide what data to collect?

- We wanted to of course collect DVH metrics that we thought may be related to normal tissue toxicities, but also….

  Needed to collect sufficient additional details about the patients, the prescriptions, and treatment beams so that we could interpret any differences that we might observe in data from collected at different institutions.

Data Collected for Each Patient

Treatment Technique
- Right, Left, Bilateral
- For Left: FB or DIBH
- Breast or CW
- Prescription Dose(s)
- Field type: T, SC, IMC (upper/lower/supp),
- Field Energies

Demographics
- DOB
- Gender
- Age at RT
- Race/Ethnicity
- BMI

DVH Data

Heart	Lungs
Max[Gy]	Max[Gy]
Min[Gy]	Min[Gy]
Mean[Gy]	Mean[Gy]
V4Gy[%]	V5Gy[%]
V25Gy[%]	V13Gy[%]
V30Gy[%]	V20Gy[%]
V50Gy[%]	

DVH Data Extraction

- DVH data extraction generally includes the tasks of manually retrieving the treatment plan from storage, navigating its contents, and transcribing plan information into the analysis software.
- This process can be **time-consuming and error-prone**, especially when information needs to be extracted from a large number of treatment plans for clinical studies.

Methods

- **How were DVH data extracted in our study?**
  - In-house developed *system*, PlanDB, that can store, organize, and present radiation treatment plan data.
  - In use at our institution since 2008.

ME Kantor, G Starkschall, and P Balter. Relational Database of Treatment Planning System Information. J Radiat Oncol Inform 2013;5:1:1-10)

PlanDB Components and Implementation

- Components
  - Data source: Pinnacle[3] (Philips Medical Systems, Milpitas, CA)
  - Database: open-source, relational database (PostgreSQL, PostgreSQL Global Development Group, http://www.postgresql.org).
- Implementation
  - The system was implemented through a combination of the internal scripting language in the TPS and 3 externally executed codes.

Kantor, Starkschall, and Balter, J Radiat Oncol Inform 2013;5:1:1-10

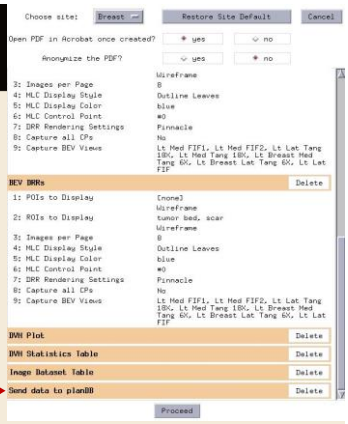
PlanDB Code Details

- The internal scripting language in the TPS is used to access and output the DVH data.
- 3 additional externally executed codes are used to parse ASCII data and interact with a networked database server:
  1. File parser capable of converting structured TPS files into hierarchical objects (Python).
  2. Abstraction function to take these raw objects as input and convert them to processed objects more suited for database input (MATLAB).
  3. General function that accepts processed objects as input and queries the database (Python).

Kantor, Starkschall, and Balter, J Radiat Oncol Inform 2013;5:1:1-10

DVH Data Exported to Database

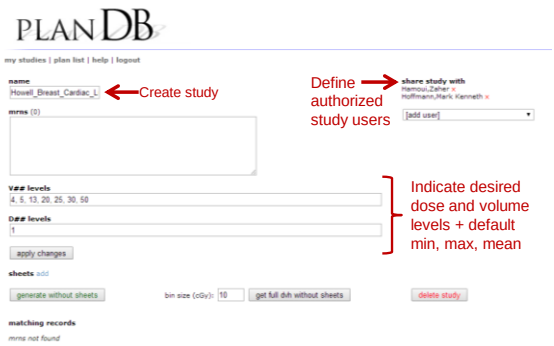
- Pinnacle hot script "Darkroom" create pdf, also includes option to send DVH data to PlanDB.
- Script is run for every approved plan that is sent to Mosaic.



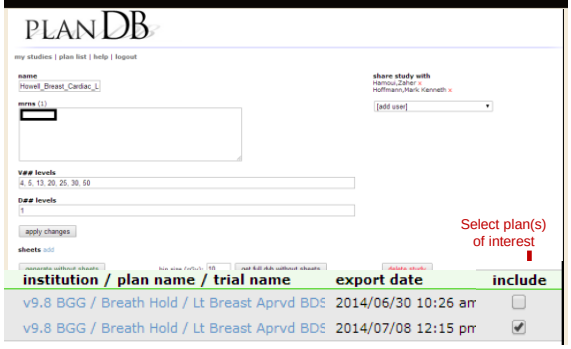
PLANDB Web-based Interface

- Easily accessible from our physics intranet.

Customizable Database Queries



Customizable Database Queries



Customizable Database Queries

- Selected data parameters sent via email to user (based on login) as .xml file
- Example of output data

mrn	name	plan	trial	roi	volume	dose min	dose mean	dose max	V5	V13	V20	D1
123456	Doe, Jane	DIBH	Lt Breast	Total Lung	3766.94	0.02	1.88	39.35	8.13	4.52	3.36	33.12
123456	Doe, Jane	DIBH	Lt Breast	Lt Lung	1704.20	0.09	4.01	39.35	17.96	10.00	7.42	34.99
123456	Doe, Jane	DIBH	Lt Breast	tumor bed	4.44	39.72	40.66	41.12	100.00	100.00	100.00	41.06
123456	Doe, Jane	DIBH	Lt Breast	Rt Lung	2062.48	0.02	0.12	1.01	0.00	0.00	0.00	0.40
123456	Doe, Jane	DIBH	Lt Breast	Heart	577.70	0.15	0.51	10.34	0.27	0.00	0.00	3.36

Data is sorted by roi name

Standardized roi nomenclature is beneficial

Now the non-automated part

- Limitations of current method
  - Format of PlanDB data not ideal for our data pooling study.
    - For pilot study, we manually sorted data to best format
    - Next steps, automate this process.
  - In our pilot study, we only used PlanDB to extract DVH data.
    - Patients' demographics and prescription information were abstracted from electronic medical records and Mosaic.

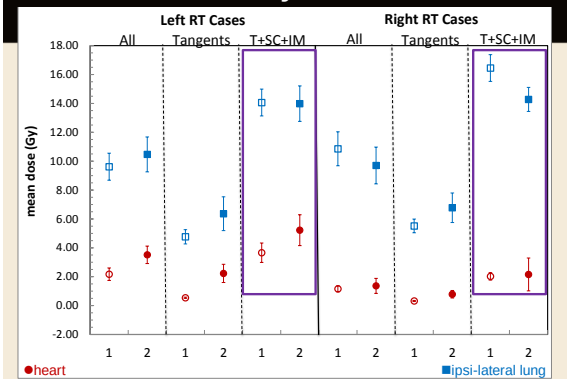
Results

- Between our the 2 participating institutions, we pooled data for 350 BRT patients:
  - 200 with left-sided cancers (74% treated with DIBH) and
  - 150 with right-sided cancers

Results - Pooled Data

Organ	Dose Metric	Tangent (T) Left (N=93)	Tangent (T) Right (N=77)	T + SCN Left (N=10)	T + SCN Right (N=8)	T + SCN + IMN Left (N=89)	T + SCN + IMN Right (N=64)
Heart	Mean[Gy]	1.1±1.2	0.5±0.5	2.9±1.6	1.7±2.8	4.0±2.8	2.1±1.2
	V4Gy[%]	3.6+6.7	0.8±2.5	14.4±9.2	7.4±18.9	27.2±14.5	14.3±13.2
	V25Gy[%]	0.5±1.7	0.0±0.0	2.0±2.3	1.3±3.4	2.0±5.0	0.3±0.8
	V30Gy[%]	0.5±1.5	0.0±0.0	1.5±1.7	1.2±3.1	1.3±3.3	0.2±0.5
	V50Gy[%]	0.0±0.1	0.0±0.0	0.0±0.1	0.0±0.0	0.1±0.2	0.0±0.0
Lungs	Mean[Gy]	2.6±1.4	3.4±1.3	6.0±1.7	7.9±3.4	7.0±2.0	9.3±2.0
	V5Gy[%]	10.7±5.7	13.7±4.9	23.1±6.3	31.8±13.6	27.4±9.5	35.8±7.3
	V13Gy[%]	5.8±3.4	7.4±2.9	14.1±5.1	18.2±10.0	17.2±5.5	23.1±5.9
	V20Gy[%]	4.4±2.5	5.7±2.5	10.9±3.7	14.1±6.9	13.0±4.0	18.0±4.7
Ipsi-lateral Lungs	Mean[Gy]	5.2±2.5	6.0±2.2	12.7±3.7	12.7±3.5	14.0±3.6	16.0±3.1
	V5Gy[%]	21.8±9.2	24.7±8.4	50.2±13.9	49.3±10.3	55.9±12.7	62.7±11.4
	V13Gy[%]	11.9±5.8	13.3±5.0	31.0±11.8	27.6±7.4	35.8±10.3	40.7±9.4
	V20Gy[%]	9.0±4.8	10.3±4.4	24.1±8.7	22.9±7.7	27.5±8.1	31.8±7.5

Results – by Institution



Understanding the Differences in Data between Institutions

- It is important not to jump to conclusions about differences in the data between the institutions, but ……

  rather to try to understand differences in treatment techniques and data collection processes that may be the underlying source(s) of the differences.

Differences

- Potential sources of differences in dose metrics between our two institutions include the following:
  - Initial plan versus composite plan DVH data.
  - Different percent of left BRT treated with DIBH and FB.
  - May be using different target definition
  - Different patient populations and breast cancer staging.

Future Implications of Cooperative Prospective Data Pooling for BRT

- Define standard dose metrics.
- Correlation of actual lung and heart doses with long-term outcomes.
- Establishment of more accurate NTC dose-response models based on:
  - actual patient doses, and
  - dose volume effects not simply mean dose.
- Evaluation of treatment techniques across multiple institutions for quality comparisons.

Acknowledgements

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- Robert W. Mutter, MD

Thank you

Extra Slides

Evidence of Radiation Related Cardiac Effects

- Until recently, there was a general belief that radiation related cardiac effects were only associated with high doses, *i.e.,* >30 Gy.
- More recently, evidence is emerging that cardiac toxicity can occur at much lower doses.
  - A bomb survivors (*Preston et al.* 2003)
  - Patients treated for peptic ulcers (*Carr et al.* 2005)
  - Childhood cancer survivors (*Mulroony et al.* 2009, Tukenova et al 2010)
  - Breast cancer survivors (*Taylor et al.* 2007, EBCTCG, 2005, Darby et al. 2010).

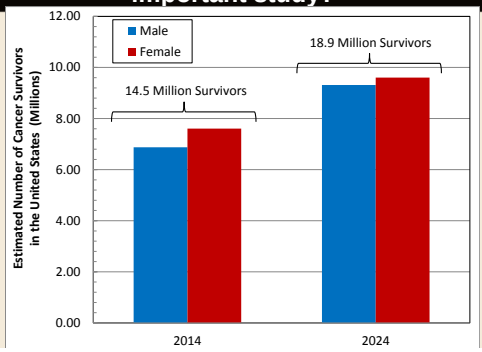
Absolute Risk of a RT-Related Major Coronary Event

- For a 50 year old woman with no preexisting heart disease, the absolute risk of death from ischemic heard disease would increase from 1.9% to **2.4 %** and **3.4 %**, respectively for mean heart doses of **3 Gy** and **10 Gy**, respectively:

Absolute increase in risk is relatively small, between 0.5 and 1.5%.

Darby *et al.* NEJM 2013

Why was the Darby *et al.* study such an important study?



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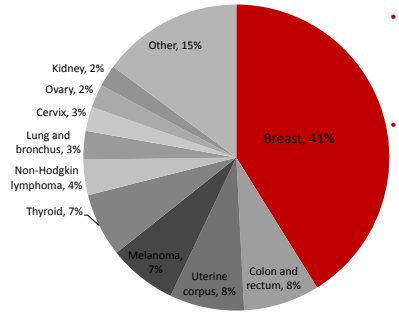

- By 2024, it's estimated that there will be > 3.9 x10^6 breast cancer survivors.
- Assuming 50% receive RT, radiation may be related to 10,000 to 30,000 deaths from major coronary events for mean heart doses between 3 and 10 Gy.