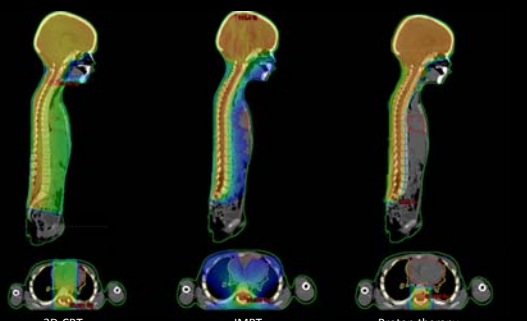
Methodology for literature review, data mining, modeling of dose-response in pediatric radiation oncology

Søren M Bentzen, Ph.D., D.M.Sc.
Division of Biostatistics and Bioinformatics, UMGCC Shared Biostatistics Service
University of Maryland Greenebaum Cancer Center, Baltimore, MD, USA
sbentzen@som.umaryland.edu

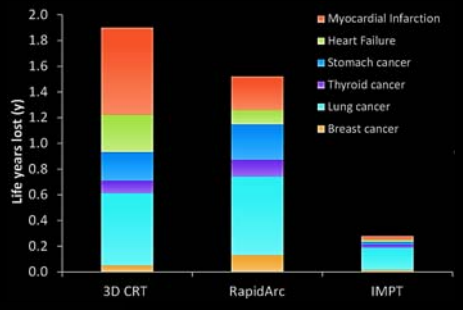
New RT techniques: childhood cancer



Patrik Brodin, ESTRO 2011

Rigshospitalet

Life Years Lost – radiation modalities



Brodin et al. *Cancer* 118: 5432 (2012)

/SMB 7/14

Performance of 'pediatric' search filters

- 82.5% of a sample of Cochrane systematic reviews had errors in the reported search strategy that could potentially bias the reviews' results

Sampson & McGowan *J Clin Epidemiol* 59: 1057 (2006)

- The Cochrane Childhood Cancer Group tested 7 published search filters for identifying pediatric studies in PubMed in a reference data set
- The sensitivity varied from 44.8% to 99.5%

Leclercq et al. *J Pediatr* 162: 629 (2013)

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14

Literature search (i): example of endpoint

- Cochrane style, systematic literature review
- Led by Cecile Ronckers and Leontine Kremer in collaboration with each site-specific review group
- EXAMPLE OF TOXICITY: **Hearing Loss**
  - Deafness OR hearing loss OR Loss, Hearing OR hearing disorder OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR heari* OR audiology OR audiologic OR audiometry OR audiometr* OR audiogram OR audiography OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacuses OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14

Literature search (ii):

- **Childhood cancer**
  - (((leukemia OR leukemi* OR leukaemi* OR ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia lymphocytic acute) OR (leukemia, lymphocytic, acute[mh])

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14

Literature search (iii)

- **Radiotherapy**
  - radiometry OR radiation dosage OR radiation dose OR radiation doses OR radiation dosis OR radiation dosage* OR radiation dosimetry OR radiation dosimetr* OR dose-response relationship, radiation OR radiometr* OR radiotherapy dosage OR radiotherapy[sh] OR radiotherapy/adverse effects OR irradiation dose OR radiotherapy dose OR dose calculation OR near beam dose OR in beam dose OR outside beam dose OR out of beam dose OR radiation/epidemiology OR Radiation monitoring OR Organs at risk OR radiation effects[sh] OR radiation injury OR radiation injuries OR radiation OR Radiotherapy/complications[Mesh] OR NCTP OR normal tissue complication probability OR DVH OR Dose Volume Histogram OR Radiotherapy Planning OR Conformal/adverse effects OR Dose Response Relationship, radiation OR Organs at Risk/Radiation Effects OR Radiation Injuries/Prevention and Control OR Chemoradiotherapy/Adverse Effects

Pubmed (Sept 23,2013): n=544 hits → title/abstract screening

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14

Radiation-induced hypothyroidism

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Vogelius et al. *Cancer* 117: 5250 (2011)

/SMB 7/14

Mining of 'big data' sets

- What data sets???
- …in pediatric radiation oncology?????
- 'Big data' are data sets in the terabyte to exabyte range
- Biomedical data sets are typically several orders of magnitude smaller than the above range… but some are relatively 'big'
- A number of attractive analytical techniques have been developed for data mining – supervised as well as unsupervised – and there is current interest in Natural Language Processing…
- …BUT…

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14

Two worlds colliding

RADIATION BIOLOGY

- Relative homogeneous population exposed
- Known exposure: Accurate estimate of dose to relevant target structure
- Specific clinico-biological endpoint
- Simple mathematical dose-response function characterized by two parameters

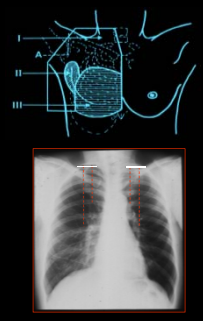
EPIDEMIOLOGY

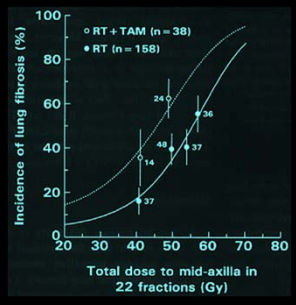
- Heterogeneous population exposed
- Poorly known exposure: Rough "guess-timate" of dose to relevant target structure
- Endpoint often NOT specific to radiation exposure
- Excess relative risk (ERR)/ Excess absolute risk (EAR)
  - ideally as a function of (some) dose

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14

Tamoxifen enhances XRT lung fibrosis



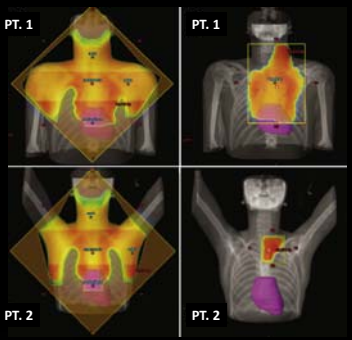


UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Bentzen et al. *JNCI* 88: 918 (1996)

/SMB 7/14

HD: Mantel field vs. Involved node RT

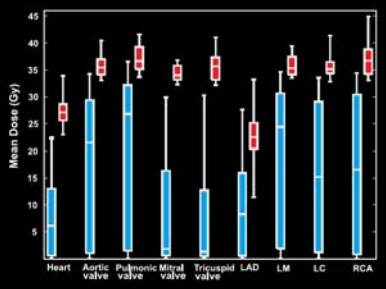


UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Maraldo et al. *IJROBP* 83: 1232 (2012)

/SMB 7/14

HD: Mantel field vs. Involved node RT

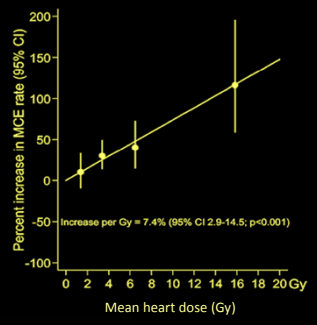


UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Maraldo et al. *IJROBP* 83: 1232 (2012)

/SMB 7/14

% increase in major coronary events v. dose



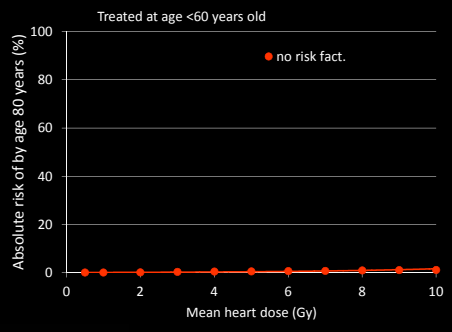
- Relative risk estimates are often more impressive than absolute risk estimates
- And may give rise to false impressions of e.g. risk vs. age
- The most relevant metric to a patient is ABSOLUTE RISK

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Darby et al. *NEJM* 368: 987 (2013)

/SMB 7/14

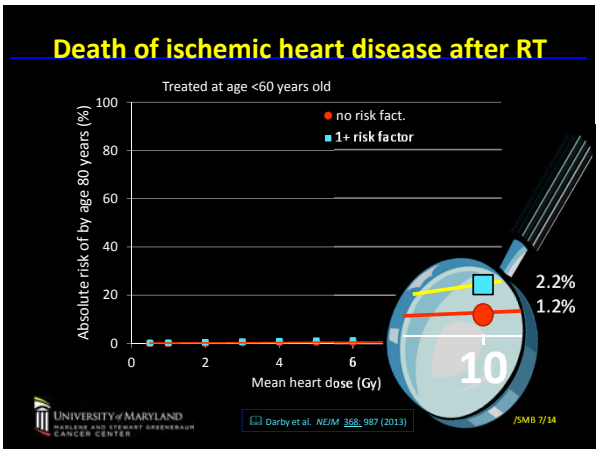
Death of ischemic heart disease after RT

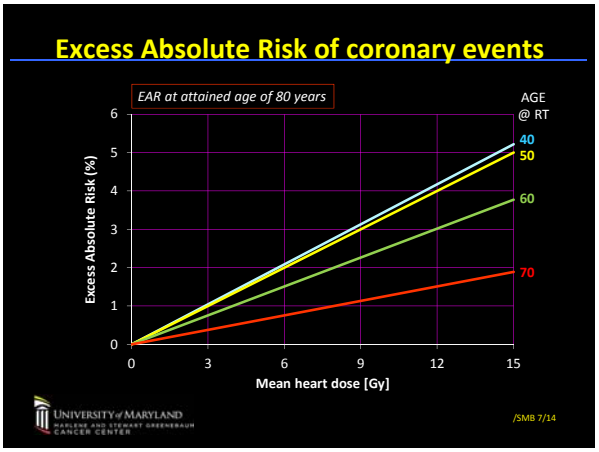


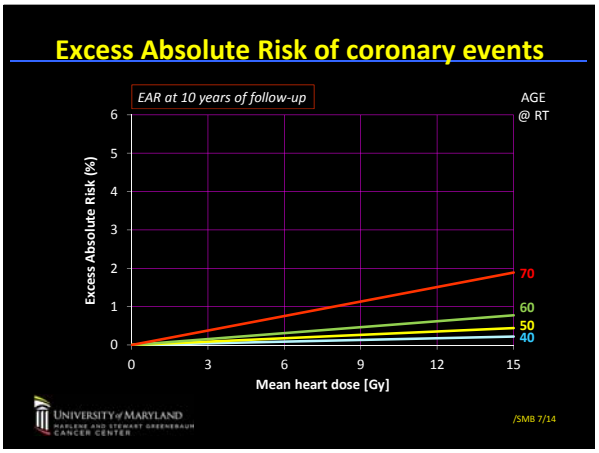
UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Darby et al. *NEJM* 368: 987 (2013)

/SMB 7/14


Death of ischemic heart disease after RT
Treated at age <60 years old
no risk fact.
1+ risk factor
Absolute risk of by age 80 years (%)
100
80
60
40
20
0
0
2
4
6
Mean heart dose (Gy)
2.2%
1.2%
10
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER
Darby et al. NEJM 368: 987 (2013)
/SMB 7/14


Excess Absolute Risk of coronary events
EAR at attained age of 80 years
AGE @ RT
40
50
60
70
Excess Absolute Risk (%)
6
5
4
3
2
1
0
0
3
6
9
12
15
Mean heart dose [Gy]
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER
/SMB 7/14


Excess Absolute Risk of coronary events
EAR at 10 years of follow-up
AGE @ RT
70
60
50
40
Excess Absolute Risk (%)
6
5
4
3
2
1
0
0
3
6
9
12
15
Mean heart dose [Gy]
UNIVERSITY of MARYLAND
MARLENE AND STEWART GREENEBAUM CANCER CENTER
/SMB 7/14

Radiation myelopathy after RT for NSCLC

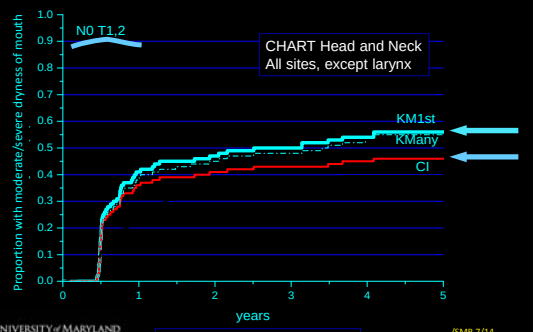
- Is it safe to give 3x6 Gy+5x4 Gy to the spinal cord?
- Linear quadratic model, assuming α/β = 2 Gy
  - This schedule has an EQD2 = 66 Gy
- Reported incidence of RM: 4±1%
- Actuarial estimate @ 3 years: 30±15%

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Hatlevoll et al. *IJROBP* 9: 41 (1983)

/SMB 7/14

Kaplan-Meier or cumulative incidence?

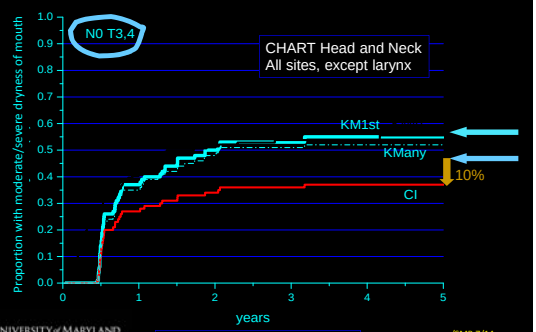


UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Ataman & Bentzen (unpublished)

/SMB 7/14

Kaplan-Meier or cumulative incidence?



UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

Ataman & Bentzen (unpublished)

/SMB 7/14

Late edema in the CHART trial

Incidence among 5-year survivors

	Pts with one or more incident (%)	K-M estimate @ 5 years
CHART	49/92 53.3%±5.2%	48.8%±2.7%
conv.	32/54 59.3%±6.2%	59.5%±3.4%
	2P=0.49	2P=0.02

UNIVERSITY of MARYLAND MARLENE AND STEWART GREENEBAUM CANCER CENTER

/SMB 7/14