Predicting Normal Tissue Injury in the Modern era: A Review of QUANTEC

Lawrence B. Marks, M.D.

University of North Carolina at Chapel Hill, NC
Disclosures

- Grants: NIH, Lance Armstrong
- Advisor: Impac (Mosaiq)
- UNC: Research grant-Siemens
- Recent:
  - Varian: grant, speaker
  - Dept of Defense: grant
Early summary table (Rubin, Cooper, Phillips)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Injury</th>
<th>TD5/5</th>
<th>TD50/5</th>
<th>Whole or Partial Organ (Field Size or Length)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>Aplasia, pancytopenia</td>
<td>250</td>
<td>450</td>
<td>Whole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3,000</td>
<td>4,000</td>
<td>Segmental</td>
</tr>
<tr>
<td>Liver</td>
<td>Acute and chronic hepatitis</td>
<td>2,500</td>
<td>4,000</td>
<td>Whole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,500</td>
<td>2,000</td>
<td>Whole (strip)</td>
</tr>
<tr>
<td>Stomach</td>
<td>Perforation, ulcer, hemorrhage</td>
<td>4,500</td>
<td>5,500</td>
<td>100 cm</td>
</tr>
<tr>
<td>Intestine</td>
<td>Ulcer, perforation, hemorrhage</td>
<td>4,500</td>
<td>5,500</td>
<td>400 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5,000</td>
<td>6,500</td>
<td>100 cm</td>
</tr>
<tr>
<td>Brain</td>
<td>Infarction, necrosis</td>
<td>5,000</td>
<td>6,000</td>
<td>Whole</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Infarction, necrosis</td>
<td>4,500</td>
<td>5,500</td>
<td>10 cm</td>
</tr>
<tr>
<td>Heart</td>
<td>Pericarditis, pancyarditis</td>
<td>4,500</td>
<td>5,500</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7,000</td>
<td>8,000</td>
<td>25%</td>
</tr>
<tr>
<td>Lung</td>
<td>Acute and chronic pneumonitis</td>
<td>3,000</td>
<td>3,500</td>
<td>100 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1,500</td>
<td>2,500</td>
<td>Whole</td>
</tr>
<tr>
<td>Kidney</td>
<td>Acute and chronic nephrosclerosis</td>
<td>1,500</td>
<td>2,000</td>
<td>Whole (strip)</td>
</tr>
<tr>
<td>Fetus</td>
<td>Death</td>
<td>200</td>
<td>400</td>
<td>Whole</td>
</tr>
</tbody>
</table>

**TD 5/5** = Max Tolerated Dose 5% rate at within 5 years.

**TD 50/5** = Max Tolerated Dose 50% rate within in 5 years.
Task force estimated normal tissue tolerance

TD 5/5, TD 50/5  (5% or 50% risk at 5 years)
for 1/3, 2/3 and whole organ, using

• Literature review
• Task force members’ “own experience”

... for 26 organs
<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 5/5 Volume</th>
<th></th>
<th>TD 50/5 Volume</th>
<th></th>
<th>Selected endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(1/3)</td>
<td>(2/3)</td>
<td>(2/3)</td>
<td>(1/3)</td>
<td></td>
</tr>
<tr>
<td>Kidney I</td>
<td>5000</td>
<td>3000*</td>
<td>2300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bladder</td>
<td>N/A</td>
<td>8000</td>
<td>6500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral Head I and II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-M joint mandible</td>
<td>6500</td>
<td>6000</td>
<td>6000</td>
<td>7700</td>
<td>7200</td>
</tr>
<tr>
<td>Rib cage</td>
<td>5000</td>
<td></td>
<td></td>
<td>6500</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>6000</td>
<td>5000</td>
<td>4500</td>
<td>7500</td>
<td>6500</td>
</tr>
<tr>
<td>Brain stem</td>
<td>6000</td>
<td>5300</td>
<td>5000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optic nerve I &amp; II</td>
<td>No partial volume</td>
<td>5000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiasma</td>
<td>No partial volume</td>
<td>5000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord</td>
<td>20 cm³</td>
<td>10 cm³</td>
<td>100 cm³</td>
<td>5000</td>
<td>6500</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>No volume effect</td>
<td>6000</td>
<td></td>
<td>No volume effect</td>
<td></td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>6200</td>
<td>6100</td>
<td>6000</td>
<td>7700</td>
<td>7600</td>
</tr>
<tr>
<td>Eye lens I and II</td>
<td>No partial volume</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye retina I and II</td>
<td>No partial volume</td>
<td>4500</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear mid/external</td>
<td>3000</td>
<td>3000</td>
<td>3000*</td>
<td>4000</td>
<td>4000</td>
</tr>
<tr>
<td>Ear mid/external</td>
<td>5500</td>
<td>5500</td>
<td>5500*</td>
<td>6500</td>
<td>6500</td>
</tr>
<tr>
<td>Parotid* I and II</td>
<td></td>
<td></td>
<td>3200*</td>
<td></td>
<td>4600*</td>
</tr>
<tr>
<td>Larynx</td>
<td>7900*</td>
<td>7000*</td>
<td>7000*</td>
<td>9000*</td>
<td>8000*</td>
</tr>
<tr>
<td>Lung I</td>
<td>4500</td>
<td>3000</td>
<td>1750</td>
<td></td>
<td>6500</td>
</tr>
<tr>
<td>Lung II</td>
<td>6000</td>
<td>4500</td>
<td>4000</td>
<td>7000</td>
<td>5500</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: TD 100/5 is 5000*
"3D Hope"

Dose/volume

Normal tissue outcome
"3D Hope"

Dose/volume

Normal tissue

outcome

"Reality"

Information overload.
Which parameters?
DVH limitations

Patient/tumor factors

Which endpoints?

Applicability? Evolving therapies, SRS, IMRT, Hypo fxn
Information overload. Revenge!
No wonder we crave models, figures of merit
QUANTITATIVE ANALYSES OF NORMAL TISSUE EFFECTS IN THE CLINIC

Guest Editors:
Lawrence B. Marks, M.D.  Randall K. Ten Haken, Ph.D.  Mary K. Martel, Ph.D.

Official Journal of
AMERICAN SOCIETY FOR RADIATION ONCOLOGY
PAEDIATRIC RADIATION ONCOLOGY SOCIETY
Affiliated with
LATIN AMERICAN ASSOCIATION OF THERAPEUTIC RADIATION AND ONCOLOGY
Organs Included

- Brain: Yaakov Lawrence
- Brainstem: Charles Mayo
- Optic Nerve: Charles Mayo
- Ear: Niranjan Bhandare
- Cord: John Kirkpatrick
- Salivary Glands: Joe Deasy
- Larynx/Pharynx: Avi Eisbruch
- Lung: Larry Marks
- Heart: Giovanna Gagliardi
- Esophagus: Maria Werner-Wasik
- Liver: Charlie Pan
- Kidney: Laura Dawson
- Bowel: Charlie Pan
- Rectum: Jeff Michalski
- Bladder: Akila Viswanathan
- Penile Bulb: Mack Roach
Objective: MDs, physicists, statistician
Clinically relevant: pneumonitis vs CT or PFT
Comparison of Emami vs QUANTEC

<table>
<thead>
<tr>
<th></th>
<th>Emami et al</th>
<th>QUANTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of organs</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>3D data available</td>
<td>Minimal</td>
<td>More/Moderate (18 year interval)</td>
</tr>
<tr>
<td>Format dose/volume limits</td>
<td>Uniform TD 5/5, 50/5 for 1/3, 2/3, 3/3</td>
<td>Non-uniform</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Specific</td>
<td>Specific</td>
</tr>
<tr>
<td>Expert Opinion</td>
<td>Moderate</td>
<td>Less</td>
</tr>
</tbody>
</table>
Examples from Quantec
Mean dose response of pneumonitis
(Andy Jackson and others)

• Patients treated for NSCLC
  • Data from 9 institutions, 10 separate studies
• 1,167 patients with 222 cases of pneumonitis
• ≥ Grade 3 RTOG ~ ≥ Grade 2 SWOG
  • (requiring steroids)
  • accepted ≥ grade 1 definition if few grade 1 cases
Pneumonitis, mean dose response - whole lung

Mean dose (Gy)

0 10 20 30

Probability of pneumonitis

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0

MSKCC (10/78)
Duke (39/201)
Michigan (17/109)
MD Anderson (~49?/223)
NKI (17/106)
WU (52/219)
Martel et al. (9/42)
Oeztel et al. (10/66)
Rancati et al. (7/55)
Kim et al. (12/68)

logistic fit

Objective data review: Jackson, Deasy, Martel, Bentzen

1,167 pts NSCLCa, 9 centers
Quantec Lung: Figure by Jessica Hubbs
Single Fraction Radiosurgery

Brain (1)

adverse events (%)

volume (cc)

Yaakov Lawrence

Chin2001/V10
Miyawaki1999/RxV
Korytko2006/V12
Nakamura2001/RxV
Varlotto2003/RxD
Voges1996/V10
Flickinger1997/V12/All
Flickinger1997/V12/Symp
Brain (2)

Long Term Side Effects

Standard fractionation (qd, d<2.5Gy)

α/β = 3Gy

Yaakov Lawrence
Brain (2)

Long Term Side Effects

Standard fractionation (qd, d<2.5Gy)

α/β = 3Gy

~36 x 2Gy qd

Yaakov Lawrence
Brain (3)
Big fractions (d≥2.5Gy)

Long Term Side Effects

Yaakov Lawrence
Brain (4)

BID (twice daily fractions)

- n<60
- n=160-120
- n>120

Long Term Side Effects

Yaakov Lawrence
Brain (4)

BID (twice daily fractions)

Long Term Side Effects

\[ \alpha/\beta = 3\text{Gy} \]

\(~50 \times 1.25\text{Gy bid}\)
Dose-volume limits
with LQ corrected doses (a/b = 3 Gy)

LQ equivalent dose in 2 Gy fractions (Gy)

70-75.6 Gy: 7%
75.6 Gy: 34%
70-78 Gy: 3% Grade 3

66 Gy: 33%
66 Gy: 14%
66.2-70.2 Gy: 11%
69 Gy: 25%
3 Gy / fr
75.6 Gy: 19%
70-76 Gy: 9%
70-78 Gy: 3% Grade 3

67.2-70.2 Gy: 11%
70-78 Gy: 23%
70-78 Gy: 3% Grade 3

Andy Jackson
LQ equivalent dose in 2 Gy fractions (Gy)
Dose-volume limits with LQ corrected doses (a/b = 3 Gy)

LQ equivalent dose in 2 Gy fractions (Gy)

10 20 30 40 50 60 70 80 90

% volume

0 20 40 60 80 100

Jackson 70.2
Jackson 75.6
Akimoto
Wachter
Koper
Cozarrino
Zapatero

70-75.6 Gy: 7%

Hartford

75.6 Gy: 34%

Grade 1

Fiorino
Boersma

66 Gy: 33%

66 Gy: 14%

66.2-70.2 Gy: 11%

75.6 Gy: 19%

70-76 Gy: 9%

70-78 Gy: 3% Grade 3

69 Gy: 25%

3 Gy/fr

70.2 Gy: 6%

70-78 Gy: 25%

74-78 Gy: 23%

Thicker Lines Higher Complication Rates
Dose-volume limits with LQ corrected doses (a/b = 3 Gy)

LQ equivalent dose in 2 Gy fractions (Gy)

10 20 30 40 50 60 70 80 90

% volume

Jackson 70.2
Jackson 75.6
Akimoto
Wachter
Koper
Cozarrino
Zapatero

70-75.6 Gy: 7%
Huang
Hartford
75.6 Gy: 34%
Grade 1

Fiorino
Boersma

66 Gy: 33%
66.2-70.2 Gy: 11%
75.6 Gy: 19%
70-76 Gy: 9%
74-78 Gy: 23%
70-78 Gy: 3% Grade 3
69 Gy: 25%
3 Gy/fr

Color: Prescription Doses

Andy Jackson  LQ equivalent dose in 2 Gy fractions (Gy)
Dose-volume limits with LQ corrected doses (a/b = 3 Gy)

LQ equivalent dose in 2 Gy fractions (Gy)

Jackson 70.2
Jackson 75.6
Akimoto
Wachter
Koper
Cozarrino
Zapatero
Huang
Hartford

70-75.6 Gy: 7%
75.6 Gy: 34%

Grade 1
Fiorino
Boersma

66.2-70.2 Gy: 11%
69 Gy: 25%
3 Gy/frac

Color: Prescription Doses

Rectum
Threshold DVHs

Thicker Lines Higher Complication Rates

Converge: High Dose Range

Andy Jackson LQ equivalent dose in 2 Gy fractions (Gy)
Bladder: Yorkee and Viswanathan
Penile Bulb (Roach, Nam)

Incidence of Severe ED (%)

Dose (Gy): Median/Mean (open symbols)
or D60 or 70 (solid symbols)
Tolerance of normal tissue • B. Emami et al.

Table 1. Normal tissue tolerance to therapeutic irradiation

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 5/5 Volume</th>
<th>TD 50/5 Volume</th>
<th>Selected endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1/3</td>
<td>2/3</td>
<td>3/3</td>
</tr>
<tr>
<td>Kidney I</td>
<td>5000</td>
<td>3000*</td>
<td>2300</td>
</tr>
<tr>
<td>Kidney II</td>
<td>N/A</td>
<td>8000</td>
<td>6500</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral Head I and II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-M joint mandible</td>
<td>6500</td>
<td>6000</td>
<td>6000</td>
</tr>
<tr>
<td>Rib cage</td>
<td>5000</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>10 cm²</td>
<td>30 cm²</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7000</td>
<td>6000</td>
<td>5500</td>
</tr>
<tr>
<td>Brain</td>
<td>6000</td>
<td>5000</td>
<td>4500</td>
</tr>
<tr>
<td>Brain stem</td>
<td>6000</td>
<td>5300</td>
<td>5000</td>
</tr>
<tr>
<td>Optic nerve I &amp; II</td>
<td>No partial volume</td>
<td>5000</td>
<td>5000</td>
</tr>
<tr>
<td>Chiasma</td>
<td>No partial volume</td>
<td>5000</td>
<td></td>
</tr>
<tr>
<td>Spinal cord</td>
<td>5 cm</td>
<td>10 cm</td>
<td>20 cm</td>
</tr>
<tr>
<td></td>
<td>5000</td>
<td>5000</td>
<td>4700</td>
</tr>
<tr>
<td>Cauda equina</td>
<td>No volume effect</td>
<td>6000</td>
<td></td>
</tr>
</tbody>
</table>
QUANTEC: Adult Focused

• Guidelines may apply
  lung
  heart
  bowel
  kidney
  liver

Missing
  growth
  neurocognitive
  endocrine
  cancer induction
Symptomatic Pneumonitis vs. Mean Lung Dose

Data in children from Matthew Krasin, St Jude
Quantec: Mostly conventional fractionation

Some hypo-fractionation

brain
lung
liver
Context/Limitations

- Data is NOT great!!!
- Incomplete (16 vs 26 organs); e.g. small bowel
- Clinically useful, MD’s
- MD’s want it made simple
- Be careful, recognize uncertainties
Discard spatial, anatomic, physiologic data

Extract unambiguous data
- Single Point: e.g. V20
- Global: e.g. mean dose

Compute model-based NTCP estimates

Cumulative DVH

% Volume at ≥ Dose x

20 Gy

V20
DVH-Based Models

- Exportability
- Applicability
  - IMRT vs. 3D
  - SRS
- Model limitations
- Fractionation
- Anatomy
Exportability?
Michigan (mets) vs. Fudan/Guangxi (primary liver tumors)

Xu et al. IJROBP 65:193, 2006; Fudan University, Shanghai, Cancer Hospital, Guangxi Medical University, Nanning, China

See letter to editor Nov 2006 from U Mich
Pneumonitis, mean dose response - whole lung

Mean dose (Gy)

- 0
- 10
- 20
- 30

Probability of pneumonitis

- 0.0
- 0.1
- 0.2
- 0.3
- 0.4
- 0.5
- 0.6
- 0.7
- 0.8
- 0.9
- 1.0

MSKCC (10/78)
Duke (39/201)
Michigan (17/109)
MD Anderson (~49?/223)
NKI (17/106)
WU (52/219)
Martel et al. (9/42)
Oeztel et al. (10/66)
Rancati et al. (7/55)
Kim et al. (12/68)

logistic fit

Low Risk Group:
70% of pts. x 15% risk RP = 10.5%

High Risk:
30% of pts. x 40% risks = 12%
17/109 with MLD >20
70% x 17 = 12 patients

92/109 with MLD < 20
10% x 92 = 9 patients

Kong, U Mich, IJROBP 2006
Ignores Anatomy/Physiology
Fig. 3. Schematic diagram illustrating the compression and tension stresses that exist in the normal femur. The diagram shows the anatomic gross section of the bone.

Fig. 4. Diagram illustrating the vascular supply of the proximal femur. The majority of blood to the femur is delivered via the medial circumflex artery. This artery passes medially and posterior to the neck as it supplies the neck and head. The secondary vessel is the lateral femoral circumflex artery. If radiation-induced damage to the femur occurs, knowledge of these vessels and their branches relative to the XRT beam is essential from [20].

1. Medial femoral circumflex a.
3. Lateral femoral circumflex a.
4. Ascending branch of internal nutrient a.
5. Muscular branch to quadiceps
6. Circumflex femoral branch
7. Anterior cervical branch
8. Superior branches of medial femoral circumflex a.
9. Artery of ligamentum teres
10. Inferior branches of medial femoral circumflex a.
Esophagus contours: variable area (volume)
Univariate and Multivariate Analyses

CT $\rightarrow$ esophageal contours $\rightarrow$ 3D metrics

Anatomic correction

“corrected” 3D metrics $\rightarrow$ Outcome

RTOG acute & late toxicity
Toxicity = f (Dosimetric Parameters)

<table>
<thead>
<tr>
<th></th>
<th>V 50 Uncorrected</th>
<th>V 50 Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ≥ grade 2</td>
<td>0.008</td>
<td>0.005</td>
</tr>
<tr>
<td>Acute ≥ grade 3</td>
<td>0.05</td>
<td>0.003</td>
</tr>
<tr>
<td>Late ≥ grade 1</td>
<td>0.14</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Adapted from Kahn et al. 2004 (Duke)
Organ interactions
Proton RT in Rats: 
Resp Rate = f (lung and heart RT)
Neighborhood Effects
Rat Proton Cord RT

ED 50 (Gy) to “shower”

No bath (control): 88 (dose in peak)

4 Gy bath, both sides 61

4 Gy bath, one side 69

18 Gy bath, both sides 31

Wide shower, 8 mm No bath effect

Serial vs. parallel

Less well defined
Migration of stem cells
Cytokine/neighborhood effects
Vascular

Bisl et al. IJROBP 64:1204-1210, 2006
What I really worry about

- Missing the tumor; Unrealistic fears
  - Blocking chiasm for GBM
- Large palliative fields work!! (fast, cheep)
  - Generation of fear, slaves to DVH’s
  - There was RT pre DVH’s
- Complication = death? Usually not
  - Grade 1 pneumonitis, rectal bleeding
- Don’t take data too seriously (models)
- Chemo, fraction size
Certainty of Gross Anatomy

Field Margins

Physically or biologically necessary margin

More conservative approach

Too fancy: marginal miss
# Prostate: Too Fancy?

<table>
<thead>
<tr>
<th>Method</th>
<th>Margins (mm)</th>
<th>Biochemical Disease Free Survival (5yrs)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implanted Seeds for Localization (N = 25)</td>
<td>3-5</td>
<td>58%</td>
<td>0.02</td>
</tr>
<tr>
<td>No Implanted Seeds (N = 213)</td>
<td>6-10</td>
<td>91%</td>
<td></td>
</tr>
</tbody>
</table>

Engels, IJROBP 74:388, 2009
# Too Fancy? Orbital Lymphoma

<table>
<thead>
<tr>
<th>Method</th>
<th>Local Control</th>
<th>Grade ≥2 Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV + Margin (12)</td>
<td>67%</td>
<td>25%</td>
</tr>
<tr>
<td>Whole Orbit (12)</td>
<td>100%</td>
<td>33%</td>
</tr>
</tbody>
</table>

From Pfeffer et al., IJROBP 2004
Used to lump them together: 1.5-2.0 cm margins routinely

Gross Tumor Volume (GTV) + Microscopic Spread + Internal Motion + Set-up Errors

Clinical Target Volume (CTV)

Internal Target Volume (ITV)

Planning Target Volume (PTV)- treated volume
Addressing physical uncertainties unmasked biological ignorance

**Imaging**
- CT, PET

**Gross Tumor Volume (GTV)**

**Microscopic Spread**

**Internal Motion**

**Set-up Errors**

**Respiratory gating**

**On board imaging**

---

**Clinical Target Volume (CTV)**

**Internal Target Volume (ITV)**

**Planning Target Volume (PTV) - treated volume**

---

**biologic uncertainties**
Old fashioned ways to reduce toxicity

• Positioning
  • Neck
  • Decubital
• Reducing skin folds
• Barium in bowel
• Careful team work
• Keep it simple!!, use time wisely

Applicable in Modern Era!
QUANTEC

- Each Organ-Specific Paper:
  - Needed research, challenges
- End of the issue: “Vision Papers”
  - True dose
  - Imaging
  - Biomarkers
  - Data Sharing
  - Lessons of Quantec

Research ideas
Summary

- Since Emami
  - More 3D dosimetry --> toxicity data
  - DVH-based predictions sub-optimal (physiology)
  - Quantec incomplete; Emami still relevant
- Is the prior data still applicable?
  - 3D beams --> IMRT
  - Chemo- moving target
  - BID RT
- Challenges for normal tissue injury studies
- Over-Reliance on technology to reduce morbidity (e.g. IMRT, OBI, CBCT)
Acknowledgments

• David Fried, Liyi Xie, Janet Bailey, Micheal Lawrence, Jessica Hubbs, Jiho Nam, Mert Saynack, John Kirkpatrick

• Quantec Steering Committee: Joe Deasy, Soren Bentzen, Randy Ten Haken, Ellen Yorke, Andy Jackson, Sandy Constine, Avi Eisbruch, David Morris

• Emami et al, Rubin, Cooper, Phillips, et al

• ASTRO, AAPM; Authors, Reviewers
Our quest for better dose distributions

• Complex solutions; e.g. IMRT
• Workload increased
• Safety concerns