A Review Of QUANTEC Normal Tissue Tolerances

QUANTEC = QUantitative Analysis of Normal Tissue Effects in the Clinic

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Learning Objectives

• Understand:
  – What increased knowledge the **QUANTEC** effort provides over the 1991 **Emami** normal tissue tolerance tables
  – New/revised QUANTEC **dose constraints** for various organs
  – How to **incorporate new information** into treatment planning
  – New **biologically-based treatment planning** trials
Normal Tissue Tolerance

• “The Emami paper” (1991)
  – Committee of experts to review known data, provide guidelines
    • Some clinical data to suggest tissue tolerance
      – Comparatively poor ability to deliver dose
      – Poor ability to measure dose actually delivered
    • Some laboratory data (cell cultures, etc)
    • Some data “made up” based upon best-guess principles

Emami “Out of Date?”

- Move from 2D to 3D treatment planning
- Higher energy beams/better penetration
- Improved ability to measure dose
- Increased use combined chemoradiotherapy
- Numerous additional studies of tissue tolerance subsequently published
QUANTEC

- **Quantitative Analysis of Normal Tissue Effects in the Clinic**
  - Large committee of experts (n=57)
  - Convened by ASTRO / AAPM
  - Updated guidelines published in Red Journal supplement (vol 76, No. 3)
  - 16 organ-specific papers
  - Several “general principle” papers
QUANTEC-General Theme

- Importance of gathering prospective toxicity data on patients
- Standardized scale:
  - NCI Common Terminology for Criteria for Adverse Events (CTCAE) v4.0
  - LENT-SOMA
  - IIEF
  - etc
Brain – Data Summary

(a) Standard Fractionation (Daily, d<2.5 Gy)

(b) Larger Fractions (Daily, d ≥ 2.5 Gy)

(c) Twice-Daily Fractionation
Brain – Proposed Constraints

- 5% risk radiation necrosis @ BED 120 Gy (72 Gy/2 Gy)
  - Emami: “overly conservative”
- 10% risk @ 150 Gy (90 Gy/2Gy)
- Increased risk with hypofractionation/BID
- 18 Gy WBRT: cognitive changes in children
- SRS: Increased risk if >5-10 cm³ exposed to >12 Gy (proposed reporting)
Brainstem

- Entire brainstem can get 54 Gy (?)
- Smaller portions to 59 Gy (?)
- SRS: 12.5 Gy = low (<5%) risk
Spinal Cord

- 50 Gy = 0.2% risk
- 60 Gy = 6% risk
- ~69 Gy = 50% risk
- SBRT: D_{max} 13 Gy (1 fx) or 20 Gy (3 fx)
- Reirradiation: 25% of dose “forgotten” at 6 months
- Cervical cord more sensitive than thoracic cord?
Optic Nerves/Chiasm

- Fraction size important
- Greater age → increased risk
- Threshold Dmax ~55-60 Gy

- SRS: Dmax <8 Gy appears safe
Cochlea
Cochlea

• Other factors
  – Cisplatinum (adjuvant or concurrent)
  – Increasing patient age
  – Better hearing → increased hearing loss
  – Post-RT otitis media

• Recommendations
  – MCD ≤ 45 Gy (more conservative: 35 Gy)
  – SRS: Limit dose to 12-14 Gy
Salivary Gland

- Much data re: parotid gland sparing
- Some data re: submandibular gland sparing
- Sparing 1 parotid eliminates xerostomia (mean dose < 20 Gy)
- Mean dose both glands < 25 Gy
- Sparing 1 submandibular gland reduces xerostomia
Larynx/Pharynx - Guidelines

- Vocal Dysfunction

  Table 2. Larynx toxicity: summary of dose–volume relationship and constraints above which toxicity is significantly increased

<table>
<thead>
<tr>
<th>Investigator/patients (n)</th>
<th>Critical organs</th>
<th>Predictive dose–volume parameter</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dornfeld et al. (7)/27 patients</td>
<td>Aryepiglottic folds, pre-epiglottic space, false vocal cords, lateral pharyngeal walls</td>
<td>Point dose &lt;68 Gy</td>
<td>Vocal function</td>
</tr>
<tr>
<td>Sanguineti et al. (8)/66 patients†</td>
<td>Larynx</td>
<td>$V_{30} &lt; 27%$: mean dose &lt;43.5 Gy</td>
<td>Laryngeal edema (fiberoptic examination)</td>
</tr>
<tr>
<td>Ranceti et al. (10)/38 patients ‡</td>
<td>Larynx</td>
<td>EUD &lt;30-35 Gy ($n = 0.45$)</td>
<td>Laryngeal edema (fiberoptic examination)</td>
</tr>
</tbody>
</table>

Abbreviation: EUD = equivalent uniform dose.
* Twenty-two of 27 patients who received chemotherapy plus radiotherapy.
† Twelve of 66 patients received chemotherapy plus radiotherapy.
‡ Seven of 38 patients received chemotherapy plus radiotherapy.

- Dysphagia: reduce volume of pharyngeal constrictors/larynx $\leq 60$ Gy (preferably $\leq 50$ Gy)
- (Is that safe to do, clinically? “Beyond the scope of this report.”)
- Importance of subjective evaluation (stroboscopy, NPL exam, swallow study)
Summary
H&N: Rx = 7000cGy/35fx

<table>
<thead>
<tr>
<th>Organ</th>
<th>Presently</th>
<th>QUANTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>Mean &lt; 4500 cGy &amp; 5000 max (0.3cc)</td>
<td>No change</td>
</tr>
<tr>
<td>Brain Stem</td>
<td>Mean &lt; 5400 cGy &amp; 6000 max (0.3cc)</td>
<td>No change</td>
</tr>
<tr>
<td>Chiasm</td>
<td>Mean &lt; 5000 cGy &amp; 5400 max (0.3cc)</td>
<td>~ up to max of 5500-6000cGy if needed</td>
</tr>
<tr>
<td>Optic Nerves</td>
<td>Mean &lt; 5400 cGy &amp; 6000 max (0.3cc)</td>
<td>No change</td>
</tr>
<tr>
<td>Oral Cav</td>
<td>Mean &lt; 4500 cGy</td>
<td>No Q data</td>
</tr>
<tr>
<td>Larynx</td>
<td>Mean &lt; 4000 cGy</td>
<td>~ up to mean of &lt;5000 if needed</td>
</tr>
<tr>
<td>Trachea</td>
<td>Mean &lt; 3000 cGy</td>
<td>No Q data</td>
</tr>
<tr>
<td>Parotids</td>
<td>TBD for each patient one Mean &lt; 1500 &amp; combo Mean &lt; 2600</td>
<td>One Mean &lt; 2000 &amp; combo mean &lt; 2500</td>
</tr>
</tbody>
</table>
Lung

(a) Symptomatic Pneumonitis vs. Mean Lung Dose

(b) Incidence of Pneumonitis (%)

Graphs showing the relationship between lung dose and pneumonitis incidence.
Lung

- Factors impacting on side effects
  - Current smoking is protective
  - Chemotherapy increases risk

- General guidelines
  - Limit V20 ≤ 30-35%
  - Limit MLD ≤ 20-23 Gy
  - Limit central airways <80 Gy (stenosis)
  - Mesothelioma: V5 <50%, V20 < 4-10%, MLD <8 Gy

- Recommend LENT-SOMA scoring
Heart

- Mostly breast/lymphoma data (high cure rate/long survival)
- Patient factors an issue
  - Age
  - Gender
  - Diabetes Mellitus (Hemoglobin A1c)
  - Smoking
  - HTN
  - Cholesterol
  - Parental history of early MI
Heart

- Breast patients: ALARA!
- V25 <10% (2 Gy fractions)
- Whole heart to 30 Gy ok without chemo (old lymphoma data)
- Whole heart to 15 Gy with Adriamycin
- Pericarditis: Mean pericardium dose <26 Gy, V30 <46%
- LENT-SOMA to rate cardiac effects
Esophagus

- Various metrics used in publications
  - Esophageal length receiving full circumference dose
  - Length with $\geq 70$ Gy to 75% circumference
  - Mean esophageal dose
  - V20, V35, Dmax
Esophagus

- "Not possible to identify single best threshold volumetric parameter"
- Mean esophageal dose < 34 Gy
- Record V60
- Minimize hot spots
- Use CTCAE criteria to log toxicity
### Summary

**Lung: Rx = 7000cGy/35fx**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Presently</th>
<th>QUANTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>Max: 5200cGy</td>
<td>No change</td>
</tr>
<tr>
<td></td>
<td>1cc ≤ 5000cGy</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>V20 &lt; 35% (chemo)</td>
<td>V20 &lt; 30%</td>
</tr>
<tr>
<td></td>
<td>V20 ≤ 40%</td>
<td>Mean &lt; 2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Airway &lt; 8000</td>
</tr>
<tr>
<td>Heart</td>
<td>&lt;6000 to 33%</td>
<td>V25 &lt; 10%</td>
</tr>
<tr>
<td></td>
<td>&lt;4500 to 66%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;3000 to 100%</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>&lt;6500 to 33%</td>
<td>Mean &lt; 34%</td>
</tr>
<tr>
<td></td>
<td>&lt;5500 to 66%</td>
<td>Record V60</td>
</tr>
<tr>
<td></td>
<td>&lt;4500 to 100%</td>
<td>No HotSpots</td>
</tr>
</tbody>
</table>
Liver

- Patients (and livers) vary:
  - Primary HCC vs mets (healthy vs unhealthy liver)
  - Hepatitis B/C
  - Portal vein thrombosis
  - Prior arterial chemoembolization
  - Concurrent chemo
  - Tumor stage
  - Male sex
  - Child-Pugh score
Liver – Conventional Fractionation

• Whole liver
  – Mets:
    • $\leq 30$ Gy (2 Gy)
    • $\leq 21$ Gy (3 Gy)
  – Primary Liver:
    • $\leq 28$ Gy (2 Gy)
    • $\leq 21$ Gy (3 Gy)

• Partial Liver
  – MLD $< 28$ Gy (2 Gy): HCC
  – MLD $< 32$ Gy (2 Gy): mets
Liver - SBRT

- HCC
  - MLD < 13 Gy (3 fx), <18 Gy (6 fx)
- Mets
  - MLD < 15 Gy (3 fx), <20 Gy (6 fx)
- Other guidelines
  - MLD <6 Gy for HCC, Child-Pugh B, in 4-6 Gy fx’s
  - 15 Gy to ≤ 700 mL normal liver (3-5 fx)
Kidney

- Long latency period → toxicity underreported?
- Acute toxicity subclinical
Kidney

- Recommendations

Table 5. Suggested dose–volume constraints for estimated risk of <5%

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dose–volume metric</th>
<th>Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral kidney irradiation TBI</td>
<td>Mean kidney dose &lt;10 Gy</td>
<td>Cheng et al. (8)</td>
</tr>
<tr>
<td>Non-TBI</td>
<td>Mean kidney dose &lt;18 Gy</td>
<td>Cassady (10)</td>
</tr>
<tr>
<td>Partial kidney irradiation Bilateral kidneys</td>
<td>Mean kidney dose &lt;18 Gy</td>
<td>Nevinnay-Stickel et al. (34)</td>
</tr>
<tr>
<td>Bilateral kidneys</td>
<td>( V_{20Gy} &lt; 20% )</td>
<td>Nevinnay-Stickel et al. (34)</td>
</tr>
<tr>
<td>Bilateral kidneys</td>
<td>( V_{23Gy} &lt; 30% )</td>
<td>Nevinnay-Stickel et al. (34)</td>
</tr>
<tr>
<td>Bilateral kidneys</td>
<td>( V_{20Gy} &lt; 32% )</td>
<td>Jansen et al. (15)</td>
</tr>
<tr>
<td>Bilateral kidneys</td>
<td>( V_{12Gy} &lt; 55% )</td>
<td>Welz et al. (13)*</td>
</tr>
<tr>
<td>If mean kidney dose to 1 kidney &gt;18 Gy</td>
<td>( V_{6Gy} ) (remaining kidney) &lt;30%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: \( V_{xGy} \) = volume of bilateral kidneys receiving >\( x \) Gy; TBI = total body irradiation.

* Estimated from Welz et al. (13); 62.5% reduced to 55% because 62.5% was functional volume.
Stomach/Small Bowel

• How to contour small bowel (individual loops vs one large region in peritoneum)?

• Stomach/(most sections of) small bowel move day to day
Stomach/Small Bowel

- **Stomach Guidelines**
  - 45 Gy whole stomach → 5-7% risk
  - Maximum point dose predictive?
  - SBRT: V22.5 <4% (or 5cc)
  - SBRT: Dmax <30 Gy (3 fx)

- **Small Bowel**
  - V15 Gy <120 cc
    (contouring individual bowel loops)
  - V45 Gy <195 cc
    (contour peritoneal space)
  - Single-Fx BRT V12.5 <30 cc
    (avoid circumferential dose)
  - SBRT Dmax <30 Gy (3-5 fx)
Summary
Esophagus: Rx = 5600cGy/28fx

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<thead>
<tr>
<th>Organ</th>
<th>Presently</th>
<th>QUANTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>33% &lt; 3000cGy</td>
<td>Mean &lt; 28%</td>
</tr>
<tr>
<td>Rt Kidney</td>
<td>Mean &lt; 1300</td>
<td>Mean &lt; 1500</td>
</tr>
<tr>
<td>Lt Kidney</td>
<td>Mean &lt; 1300</td>
<td>V12&lt;55%, V20&lt;32%</td>
</tr>
<tr>
<td>Bowel</td>
<td>Max 5800</td>
<td>V23&lt;30%, V28&lt;20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>V45 Gy &lt;195 cc</td>
</tr>
</tbody>
</table>
Bladder

• Poor data re: partial volume XRT (bladder motion not accounted for)

• Confounding factors
  – Pre-RT GU toxicity
  – Smoking history, obesity, black race
  – (Age, DM, HTN, PID not correlative)

• Recommendations
  – Whole bladder V80 <15%, V75 <25%, V70 < 35%, V65 < 50%
Penile Bulb

- Dose to penile bulb correlates to risk of erectile dysfunction (?)
- Difficult to define structure anatomically
Penile Bulb (PB)

- “Prudent to keep mean dose to 95% of volume to <50 Gy”
- “May be prudent to limit PB D70 and D90 to 70 Gy and 50 Gy, respectively”
- “PB may not be critical component of erectile apparatus, but seems to be a surrogate for yet to be determined structure(s) critical for erectile function”
- Recommend pre- and post-RT IIEF
Rectum

- TD50 = 76.9 Gy
- Guidelines: V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, V75 < 15%
# QUANTEC Summary of SRS / SBRT normal tissue constraints

<table>
<thead>
<tr>
<th>Organ</th>
<th>QUANTEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>10 cc &lt; 12 Gy</td>
</tr>
<tr>
<td>Brainstem</td>
<td>≤ 12.5 Gy</td>
</tr>
<tr>
<td>Spinal Cord (5fx) &lt; 10</td>
<td>Max &lt; 13 Gy (1 fx)</td>
</tr>
<tr>
<td></td>
<td>Max &lt; 20 Gy (3 fx)</td>
</tr>
<tr>
<td>Chiasm / Optic Nerves</td>
<td>Max &lt; 8 Gy</td>
</tr>
<tr>
<td>Cochlea</td>
<td>Max &lt; 14 Gy</td>
</tr>
</tbody>
</table>
## QUANTEC Summary of SRS / SBRT normal tissue constraints

<table>
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<tr>
<th>Organ</th>
<th>QUANTEC</th>
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</thead>
<tbody>
<tr>
<td>Liver (HCC)</td>
<td>Mean &lt; 13 Gy (3 fx), &lt;18 Gy (6 fx)</td>
</tr>
<tr>
<td>Liver (Mets)</td>
<td>Mean &lt; 15 Gy (3 fx), &lt;20 Gy (6 fx)</td>
</tr>
<tr>
<td>Stomach</td>
<td>V22.5 &lt; 4%</td>
</tr>
<tr>
<td></td>
<td>Max &lt; 30 Gy (3 fx)</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>Max &lt; 30 Gy (3-5 fx)</td>
</tr>
</tbody>
</table>
Lessons from QUANTEC

• Need for peer-reviewed central repository of dose-volume constraint standards
  – Atlases
  – Contouring standards
  – Toxicity grading schemas
  – Endpoint definitions
  – Toxicity data/rates
Lessons from QUANTEC

3D dose distribution

Discard spatial, anatomic, physiologic data

% Volume at $\geq$ Dose $\times$

Cumulative DVH

20 Gy

V20

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

Compute model-based NTCP estimates
Normal Tissue Complication Probabilities (NTCP)
NTCP

- To improve results, need to share data
- Central repository of dosimetric and clinical factors
- Build collective model into treatment planning software (TPS)
- Then, from TPS, directly calculate risks of toxicity for individual patient
NTCP – Treatment Planning

- Models we have are incomplete, but some TPS allow one to estimate risks
TCP (Tumor Control Probability)

• Based on cell cultures in large part
• Scanty clinical data
NTCP, TCP & P+

It not only tells us the risk to normal tissues, it also gives a Tumor Control Probability.
Biologically Effective Dose

• BED useful to compare the effect of different fractionation schedules

• Need to know a/b ratio of the tissues concerned.

• a/b ratio lower for normal tissues than for tumor.

• BED = nd \((1 + \frac{d}{a/b})\) with n number of fractions, d dose per fraction and a/b the alpha/beta ratio
There’s An App For That!
Really there’s 2 apps for that!

<table>
<thead>
<tr>
<th>Tissue</th>
<th>α/β</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>3</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>2</td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
</tr>
<tr>
<td>Kidney</td>
<td>3</td>
</tr>
<tr>
<td>Parotid gland</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System</td>
<td>3</td>
</tr>
<tr>
<td>Testicle</td>
<td>1</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
</tr>
<tr>
<td>Eye</td>
<td>1</td>
</tr>
<tr>
<td>Bone</td>
<td>3</td>
</tr>
<tr>
<td>Cartilage</td>
<td>1</td>
</tr>
<tr>
<td>Rectum</td>
<td>5</td>
</tr>
<tr>
<td>Bladder</td>
<td>2</td>
</tr>
</tbody>
</table>
Alternative Tx Approach

• Selectively dose-escalate patients, up to some threshold for normal tissue complication

• Example (MAASTRO):
  Deliver 2 Gy fx’s to lung tumor, up to MLD = 18 Gy
  – Disadvantage: Bigger tumor → lower dose

• Alternative: cone-down part-way through
Conedown/Boost

- Lung Cancer:
  - Repeat PET/CT at 45-50 Gy
  - Adaptive replan to smaller volume
  - Permits safe, meaningful dose escalation and/or reduced NTCP

Multi-Institutional Trial

• RTOG 1106 (stage IIIB-IIIIB NSCLC)
Biology-Based Tx Planning Objective & Trial Objective
Biology-Based Tx Planning
Start with a plan to 7400
Biology-Based Tx Planning
5000cGy: 8 IMRT Beams
Biology-Based Tx Planning
5000cGy Plan Objectives
Biology-Based Tx Planning
5000cGy Plan: DVH(base)
Biology-Based Tx Planning 3600cGy Boost: Objectives
Biology-Based Tx Planning Composite Plan: 5000 & 3600
Biology-Based Tx Planning
Tumor Control Probability
Biology-Based Tx Planning Contouring Normal Tissues
Contouring Normal Tissues

Heart: start at inf aspect of aortic arch
Esophagus Contour Variants
Use mediastinal windows

Feng-Ming (Spring) Kong, M.D., PhD, et al. “Consideration Of Dose Limits For Organs At Risk of Thoracic Radiotherapy: Atlas For Lung, Proximal Bronchial Tree, Esophagus, Spinal Cord, Ribs and Brachial Plexus"
Lung Contour Variants

- Use pulmonary windows
- Contour collapsed lung
- Do not include trachea or bronchus
- Delete GTV from Total Lung volume for V20 / Mean

Standardize contouring
Thank You!

• Questions?
• MaryLou.DeMarco@moffitt.org