Biological Models in Radiation Therapy: Normal Tissue Complication Probability

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High target dose for high local control rate

- Brainstem
- Parotid
- Cord
- Cochlea
- Temporal lobes
- Optic nerves, chiasm
- Tongue
- Mandible
- PTV to ~50 Gy
- PTV to 70 Gy

Avoid unacceptable complications
Normal Tissues below “Tolerance Dose”
Tolerance dose is a clinical choice

- Fatal complications (myelitis): complication rate $<0.1\%$
- Severe complications (Grade 3-4 pneumonitis): $<10-30\%$
- Q.O.L. complications (xerostomia, minor rectal bleeding): MD/patient ‘choice’: complication vs durable local control
Problem 1: Small Signal

- Clinical complication rates are low (by design)
- Most studies small (~ 100 pts), limited statistical power

\[ \gamma_{50} = \text{Normalized slope at TD50} \]

Slope (Gy\(^{-1}\)) = \(100 \gamma_{50}/\text{TD50} \) (Gy)

\[ \text{NTCP} = \text{Normal Tissue Complication Probability} \]

Assumed sigmoidal shape is rarely evidence-based

TD50: Dose for 50% complication probability
Problem 2: What complication?

• Different severities for single complication
  – Grade 0: No change
  – Grade 1: No impact on activities of daily life (ADL)
  – Grade 2: Mild ADL impact, outpatient management
  – Grade 3: Severe ADL impact; hospitalization
  – Grade 4: Life threatening
  – Grade 5: Lethal

• Different complications for single organ
  – Early/acute (<~ 120 days) vs chronic/late

• Different symptoms scored as one ‘complication’
  – Potentially different causes/different dose effects
Problem 2: Different Formal Scoring Systems

Radiation Pneumonitis Scoring

**CTCAE**


- 0  None
- 1  Radiographic changes (RC), asymptomatic
- 2  Symptomatic, not interfering with ADL
- 3  Symptoms interfere with ADL, O₂ use indicated
- 4  Ventilator support (AV) needed
- 5  Death

**RTOG**

http://www.rtog.org/members/toxicity/acute.html

- 0  None
- 1  Mild dry cough, dyspnea at exertion
- 2  Persistent cough, dyspnea at rest
- 3  Severe cough requiring steroids and/or intermittent oxygen
- 4  Severe respiratory insufficiency, continuous oxygen or AV
- 5  Death

CTCAE=common terminology criteria for adverse events
RTOG= Radiation Therapy Oncology Group
Problem 3: Defining the risk organ

Anat rectum: anal verge to sigmoid colon, solid

Rect_wall: outer contour minus lumen

Plan_rectum: 5 mm sup to 5 mm inf of PTV, solid

Studies use different organ definitions

• Solid or tube?
  • How thick is the tube?
• Length: standard anatomy or planner convenience
• Similar problems for other tubular or hollow organs

• Other problems if different parts of an organ have different functions (heart, brainstem)
Problem 4: What dose?
Inhomogeneity corrections used vs not used

INHOMOG_CORRECT: Dose distribution & MU with correction

EXPECTED: Dose distribution & MU with NO correction

NOT_CORRECTED: MU from “EXPECTED”; Dose distribution calculated with correction

“Biological” (LQ theory) corrections used vs not used
N=# fractions, D=total dose
Low $[\alpha/\beta]$: Sensitive to fractionation

$\alpha/\beta=3$ Gy

BED=D \((1+ [D/N]/[\alpha/\beta])\)

NTD=Normalized Total Dose, 2 Gy/ fx

NTD= BED/(1+2/[\alpha/\beta] )
Clinical NTCP estimates often based on the 1991 report by the NCI-collaborative working group on “Evaluation of treatment planning for external beam radiation therapy” Int Jnl of Radiat Oncol Biol Phys, Vol 21 #1 Emami et al, 9 authors – 7 MD’s, 2 PhD’s, over 1000 citations

At that time
• CT simulation: rare
• 3D CRT: new frontier
• DVHs: a new tool
• IMRT: theoretical

Parallel Opposed
The “Emami/Burman” Data

- **Emami et al** (IJROBP 21, 109-122, 1991)
- Reviewed literature up to 1991 for 28 dose-limiting complications
- Tabulated **TD50/5 and TD5/5**
  - NTCP 50% & 5% in 5 years, 1.8-2 Gy/Fx
- Tabulated volume dependences
  - **Partial irradiation** of volume fraction \( v \) of organ
    - TD50/5 and TD5/5 for \( v = 1, 2/3 \) and \( 1/3 \).
- Companion paper fit volume dependence to power law, NTCP to Lyman model (Burman, p 123-135)
  - Lyman Parameters \( TD50(1), n, m, V_{\text{reference}} \)

\[
\text{NTCP} = (2\pi)^{-0.5} \int \exp(-t^2/2) \, dt : \quad D_{\text{eff}} = (\sum_i v_i \, (D_i)^{1/n})^n
\]

\( \sum \) Is over DVH dose bins
Tolerance dose volume dependence: ‘Observed’

Partial organ irradiation

Zero dose
Volume fraction=1-v

Uniform Dose D
Volume fraction=v

TD5 vs irradiated volume fraction

• Iso-complication dose increases as irradiated volume fraction decreases

• Weak vs strong volume effects
Power Law Volume Dependence: ‘Fit’

Power law expresses inverse relationship between iso-complication dose and irradiated volume

\[ TDc(v) = \frac{TDc(1)}{v^n} \]

Phenomenological (no biology)

Small \( n \rightarrow \) weak volume dependency, \( D_{\text{max}} \) dominates

High \( n \rightarrow \) pneumonitis, xerostomia, RILD

Low \( n \rightarrow \) myelitis, brainstem necrosis

Mid \( n \rightarrow \) rectal bleeding, heart

Big \( n \rightarrow \) strong volume dependency (\( n=1 \): mean dose dependency)
Since 1991

Human genome data base established
• CT simulation replaces conventional sim
  – Increased awareness of setup error, physiological motion
  – Multimodality imaging (MRI, FDG-PET)
• Ever faster computers
  – Graphic displays, contouring, dose calculation
  – 4DCT, IGRT
• 3D-CRT the norm, IMRT explodes
  – Dose-volume oriented plan analysis
• Dose escalation and new fractions
  • SRS, SBRT
• Dose distributions less like partial irradiation
  – Steep dose gradients
  – Multiple beams – larger volumes at low doses
• 100’s of publications on normal tissue outcomes
Typical Use of DVHs for Plan Evaluation

- Substitute DVH for dose distribution
  - Spatial information lost

- Complications with a weak volume dependence
  - High-dose part of DVH important ($D_{\text{max}}$, $D_{05}$, $D_{1\text{cc}}$)
    - Values based on literature/clinical outcomes

- Complications with strong volume dependence
  - Mean dose and/or dose-volume points important
    - $V_D = \%$ or absolute Volume $\geq$ Dose D
    - Values based on literature/clinical outcomes

- Intermediate volume dependence
  - Selected $V_D$’s (Based on literature/clinical outcomes)

- NTCP Models (Lyman, relative seriality)
  - Process DVH through a formula
    - Parameters from literature/clinical outcomes
Time for consensus update to “Emami”

QUANTEC

- Quantitative Analysis of Normal Tissue Effects in Clinic
- Audience: MDs, physicists, dosimetrists
  - AAPM/ASTRO funding
- Writing groups for 16 critical organs
  - > 60 co-authors
- Literature review and new consensus guidelines
- Special IJROBP issue coming this year
  - Literature review/recommendations for critical organs
  - “Vision” papers: Future work
- Informal Steering Committee (alphabetical)

Soeren Bentzen, Louis Constine, Joseph Deasy, Avi Eisbruch, Andrew Jackson, Lawrence Marks, Randall Ten Haken, Ellen Yorke
QUANTEC Clinical Papers Format and Style

1. Clinical significance
2. Endpoints
3. Challenges in volume definition
4. Literature review of dose/volume data
5. Non-dosimetric risk factors
6. Models
7. Special situations
8. Consensus dose/volume guidance
9. Future toxicity studies
10. Future scoring improvements

Short papers, extensive references, many graphs
summary table of dose/volume guidance
• Task was harder than anticipated
  – Literature reports “noisy”, difficult to combine
• QUANTC guidelines are approximate
• Use with caution!
  – Do they make sense in your clinical context?

*Take with a grain of salt*

**QUANTEC recommendations DELIBERATELY not given here**
Synthesis by L. Marks and J. Nam for QUANTEC
Spinal Cord
Emami/Burman

• Myelitis/Necrosis (Late complication, long latency)
• Weak volume effect (n=0.05)
• Tolerance Dose: TD5=50 Gy; TD50=66.5 Gy

QUANTEC (Kirkpatrick, Van der Kogel, Schultheiss)
• Milder endpoint: CTCAE v3.0 ≥ Grade 2; Late, long latency
• Agree: Weak volume effect

• Tolerance Dose
  Conventional Fx

• Low $\alpha/\beta$
  • Sensitive to dose per fx
• Reirradiation: Partial recovery (~25%) by 6 months
• SBRT briefly discussed
Lung: Radiation Pneumonitis
Onset within < 6-10 months from tx start

Emami/Burman
– Total organ (v=1) is pair of lungs
– Most calculations not inhomogeneity corrected
– TD50(1)=24.5 Gy, TD5(1)=17.5 Gy, n=0.87

**QUANTEC (11 authors*)**

• Over 70 publications reviewed
  • Mostly lung cancer; TBI, SBRT also discussed
  • Confounding factors
    • Grading systems (RTOG vs SWOG, CTCAE)
    • Tumor response, heart radiation damage
• Meta-analysis Lyman Model: n=1 within 95% CI

* Marks, Bentzen, Deasy, Kong, Bradley, Vogelius, El Naqa, Hubbs, Timmerman, Martel, Jackson
Strong volume dependence: Mean Dose, $V_{dose}$

Logistic fit: $D_{50}=30.8 \text{ Gy}, \gamma_{50}=0.97$; No sharp thresholds seen

- Dose-volume guidelines for lung cancer, conventional Fx
  - Cautious on IMRT and 3DCRT
  - Avoid $\geq 80$ Gy for central airways
- Guidelines for TBI
- Suggested limits on mean dose, $V_{5}, V_{20}$
  - pts with mesothelioma and pneumonectomy
Late rectal complications
Occur within 3-4 yrs; 10-20% Grade 2 severity accepted, important complication for prostate treatment

**Emami/Burman**
- Endpoints: Severe proctitis/stenosis/necrosis/fistula
- $TD_{50}=80$ Gy, $TD_{5}=60$ Gy, $n=0.12$
  - Radioresistant, weak volume dependence
- Reference volume: “whole organ”

**QUANTEC** *
- Several endpoints: $\geq$ Grade 2 bleeding, stool symptoms
  - Should different endpoints be analyzed separately?
- Recommend whole organ (solid) as reference volume
- Meta-analysis of Lyman model parameters (4 studies) include Emami/Burman parameters within 95% CI
- Also recommends $V_D$ constraints for doses $\geq 50$ Gy
  - $\alpha/\beta \sim 3-6$ Gy

* Michalski, Gay, Jackson, Tucker, Marks, Deasy
• Rectum = Full length of anatomical rectum.
• Cooler colors: lower prescription doses
  • More volume exposed to medium doses if ‘hot spot’ dose is low
• Thicker lines: higher complication rate
Beyond QUANTEC

• **All:** Report/discuss applicability of QUANTEC guidelines to individual practices

• **Journals/Authors:** Improve reporting of new studies
  – Use formats that facilitate combination with other studies
    • Common contouring definitions for organs, endpoints
    • For fitted models, state parameters and their errors
    • Report complication rates vs planning constraints

• **MDs:** More precise definitions of clinical endpoints
  – Seek objective endpoints (imaging, physiological testing)
  – Validations of proposed models

• **All:** Devise/test “comprehensive reporting” methods
  – Facilitate inter-group data combination
  – Atlases, electronic data-sharing/data bases
References in handout