Biological Effects, Therapeutic Ratio and Hypofractionated RT

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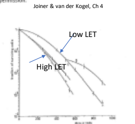
No Conflicts of Interest

- Jean St. Germain's career spanned a period of tremendous growth in radiation therapy. This owes much to the astounding development of computers and their applications to radiology and radiation therapy technology as well as an improved understanding of the radiobiology of radiotherapy.
- Although there is still much to learn (e.g. Session TH-BC-SAN1-0) the practical aspects of radiobiology developed during those 50 years have made a favorable **therapeutic ratio** - **durable tumor control** with **minimal complications-** standard of care for many cancers.
- The emergence of highly effective and safe hypofractionated treatments of primary tumors and metastases-SBRT (Stereotactic Body Radiotherapy, aka SABR- Stereotactic Ablative Radiotherapy) is an important development.
- The next slides follow the timeline of radiobiology and related radiotherapy developments. Jean's work in Radiation Safety is an integral foundation for this progress.

- Ionizing radiation causes DNA damage which, if not repaired by cellular mechanisms, will make the cell unable to proliferate at all or will prevent that cell's line after a few mitoses.
- Higher dose D-> more damage
- Simplest model is "probability of a 'death'=aD"
  - Poisson death distribution→surviving fraction=SF=exp(-aD)
- Sometimes it is simple, sometimes not. Depends on
  - Type of cell, type of radiation (low LET or high LET)
  - Dose rate, size of individual dose?
    - Low dose hypersensitivity?
    - High (> ~ 10 Gy) fraction doses?
    - Very high dose rate (FLASH)?
- In typical cell survival curves – logarithmic Y axis (SF), linear X axis (dose) - exp(-aD) would be a straight line
- For clinical x-rays and electrons (low LET), the cell survival curve is 'curvier' than linear

Figure 4.1 Pedigree of a clone of mouse L-cells irradiated with a dose of 200 R (i.e. röntgens) at the four-cell stage, illustrating the concept of surviving and non-surviving clonogenic cells. From Trott (1972), with permission.

Joiner & van der Kogel, Ch 4

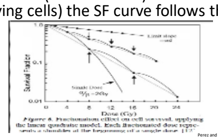


Thomas & Hogberg, Ch 3

Linear- Quadratic (LQ) Model

- For mammalian cells given a single fraction acute dose D of low LET radiation the SF is often well fit by
  SF=exp(-[αD+βD^2]) where α and β are independent of dose
- If **n** fractions of dose **d** are given with enough time (several hours) between (but not long enough for replication of surviving cells) the SF curve follows the vertical arrows in the figure:

  SF= exp(-n[αd+βd^2])



Perez and Brady, 1997

- This can be rewritten in many ways
  $SF = \exp(-\alpha(nd + nd^2/\frac{\alpha}{\beta}))$
  $SF = \exp(-\alpha D(1 + d/\frac{\alpha}{\beta}))$ where D=nd
- $\frac{\alpha}{\beta}$ determines dose per fraction dependence**;** α determines radiosensitivity
- The LQ model can be elaborated to account for low dose rate (brachy) and cell growth between fractions

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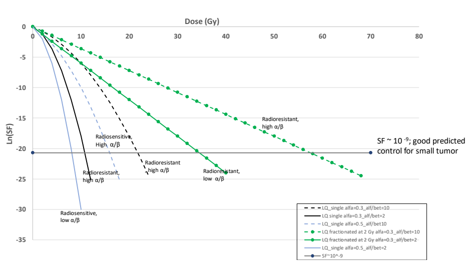
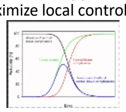
- Another way of writing the SF for the LQ model is $SF = exp(-\alpha \times BED)$ where **BED**=Biologically Effective Dose= $D(1 + d/\frac{\alpha}{\beta})$
- A word about dimensions: The exponent must be dimensionless. By convention, doses and BED are given in Gy, α in Gy^{-1}, β in Gy^{-2} and $\frac{\alpha}{\beta}$ in Gy
  - Often $\frac{\alpha}{\beta}$ is included in the BED expression: BED10 or BED_{10} ($\frac{\alpha}{\beta}$=10 Gy)
- Typical values of α for mammalian cells/low LET are in the range 0.1-1.5 Gy^{-1} (radioresistant to radiosensitive)
- Values of $\frac{\alpha}{\beta}$ run from ~1 Gy to ~ 20 Gy
- BED is often very large compared to the physical delivered doses
  - For 2 Gy/fx and Dose=60 Gy, if $\frac{\alpha}{\beta}$=2 Gy the BED_2 =120 Gy. For a typical single fraction cranial SRS treatment with prescription 21 Gy and $\frac{\alpha}{\beta}$=2 , BED_2 = 241.5 Gy !!!!
- For more comfortable numbers representing the same biological effect, we use the **Equivalent Dose in 2 Gy fractions** ($EQD2_{\alpha/\beta}$): $\mathbf{EQD2_{\alpha/\beta} = BED_{\alpha/\beta} / (1+2/\frac{\alpha}{\beta})}$
- For the 2 examples above, $EQD2_2$ is 60 Gy and 120.75 Gy (still big but less shocking)
- BED and EQD2 are used about equally often. **DON'T CONFUSE THEM!**

Variations on the LQ Theme



Radiation Effects

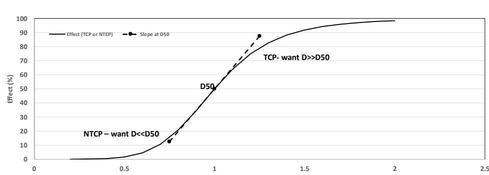
- **Tumor Control Probability** (TCP)
  - In a similarly treated population, **TCP** is the probability that the treated tumor will be locally controlled for the stated time
    - Often papers quote TCP at 5 years, 10 years, etc
- **Normal Tissue Complication Probability** (NTCP)
  - In a similarly treated population, **NTCP** is the probability that a particular normal tissue complication will be observed. A single organ can experience several different complications due to a single course of radiation
    - Severe esophagitis, esophageal ulcer; radiation pneumonitis, radiation lung fibrosis
- Radiation therapy aims for a high **Therapeutic Ratio**: a qualitative concept –maximize local control, minimize NTCPs *as well as possible*



- **Dose limiting complication**: Complication is so serious that MD will reduce prescription or reduce target coverage (reduce TCP) rather than risk it.
  - Prime examples: Radiation myelitis, pneumonitis

RT effects typically have a sigmoidal dependence on dose

- Two key parameters
  - Location of curve on dose or BED or EQD2 axis (50% effect=D50)
  - Slope of curve (usually at 50% point): ϒ50
- Many different functions are sigmoidal and are widely used



Isoeffective Regimens

- Isoeffective concept is more general than any model
- Let the effect of radiation damage to a specified tumor or other tissue or cells in vitro be given by a function f(D,d, {q})
  - {q} other factors; e.g. dose rate, type of radiation, extracellular environment,
- Two radiation regimens are **isoeffective** if they have the same effect for the same cellular system: f(D,d, {q})=f(D',d',{q'})
- For the simple LQ model, two fractionations (different doses and number of fractions) are isoeffective if $BED_{\alpha/\beta} = BED'_{\alpha/\beta}$ (or $EQD2_{\alpha/\beta} = EQD2'_{\alpha/\beta}$)
  - Example: if $\frac{\alpha}{\beta}$=2 Gy, 60 Gy in 30 fractions is isoeffective to a single 10 Gy fraction
- A surprising observation: The LQ model works pretty well for normal tissue complications!
  - Normal tissues are composed of many cell types and their complications are not necessarily due to obvious cell killing (and which cell??)

- **Early (acute)** complications: during or shortly after treatment course depend more weakly on dose per fraction (dpf); **higher** $\boldsymbol{\frac{\alpha}{\beta}}$
  - (e.g. skin erythema, mucosa, parotids, bone marrow-low blood counts)
- **Late** complications: months-years after treatment, depend strongly on dpf; **lower** $\boldsymbol{\frac{\alpha}{\beta}}$
  - (e.g. radiation myelitis, osteomyelitis, tubular organ strictures)
- Intermediate: during or shortly after course but strong dpf dependence
  - (e.g. radiation pneumonitis, $\frac{\alpha}{\beta} \sim 3-4$)

Graphs show isoeffective fractionations

Total dose=BED_{comp}/(1+dpf/$\frac{\alpha}{\beta}$)

- **Larger** $\boldsymbol{\frac{\alpha}{\beta}}$ **→ shallower slope**

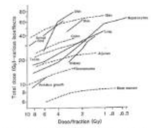
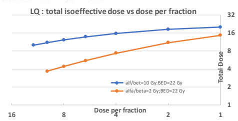


Figure 3.12. Increase in isoeffect dose with decreasing dose per fraction for various early-responding tissues and a tumour (dashed curves), and late-responding tissues (solid curves). Slopes are steeper for the late-responding tissues, which are more sensitive to change in fraction size and whose target-cell populations were correspondingly characterized by lower α/β ratios. Regeneration was minimal in the early-responding tissues surveyed but to the extent that this may have occurred the dashed isoeffect curves would be artificially steep; therefore when corrected for this effect the dashed curves would flatten and the disparity between slopes of dashed and solid lines would be even greater (Adapted from Thames et al. 1982 and Fisher and Hendry 1987).

(Thames + Hendry, Ch 3)



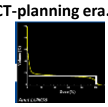
Volume Effects in Normal Tissues

- 1991: NCI contract in anticipation of 3D (CT-based) conformal RT
- The 'Emami paper': Consensus tolerance doses for 28 serious complications, based on literature and experience **prior to CT-planning era.**

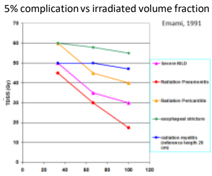
Zero dose Volume fraction=1-v	Uniform Dose D Volume fraction=v

Partial organ irradiation

Distribution similar to parallel opposed



5% complication vs irradiated volume fraction



- In general: Isocomplication dose increases as irradiated volume fraction decreases.
- Weak volume dependence: maximum dose dominates response
  - Radiation myelitis
- Strong volume dependence often approximated by dependence on mean organ dose
  - Radiation pneumonitis, xerostomia

Emami et al; IJROBP 21, 109-122

Google **1991- Early 2000's**

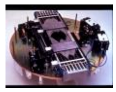
1991-early 2000's

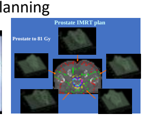
- Enormous increase in computer speed, capability
- CT scanners, CT simulation, computerized treatment planning

Three-dimensional conformal radiotherapy and dose escalation: where do we stand?
Zelefsky MJ, Leibel SA, **Kutcher GJ**, Fuks Z.
Semin Radiat Oncol. 1998 Apr;8(2):107-14. Review.
PMID: 9516591

- IMRT

Planning, delivery, and quality assurance of intensity-modulated radiotherapy using dynamic multileaf collimator: a strategy for large-scale implementation for the treatment of carcinoma of the prostate.
Burman C, Chui CS, Kutcher G, Leibel S, Zelefsky M, LoSasso T, Spirou S, Wu Q, Yang J, Stein J, Mohan R, **Fuks Z**, Ling CC.
Int J Radiat Oncol Biol Phys. 1997 Nov 1;39(4):863-73.





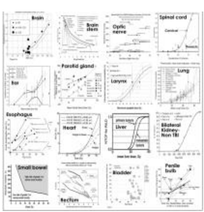
- Improved knowledge of dosimetric correlates of NTCP, TCP
  - Though not necessarily improved mechanistic explanation

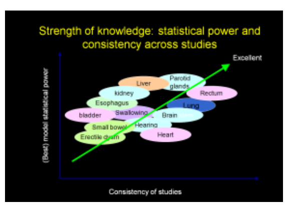
Logistic	Log Logistic	Lyman NTCP Model	TCP from SF (N=# cells)
For NTCP, reverse D and D_{50}			
$TCP(D) = \exp((D - D_{50})/k)/(1 + \exp((D - D_{50})/k))$	$TCP(D) = 1/(1 + (D_{50}/D)^k)$	$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx$ $t = \frac{EUD - TD_{50}}{m \cdot TD_{50}}$ $EUD = \left(\sum_{i=1}^{N} v_i D_i^{\frac{1}{n}}\right)^n$	$TCP = \exp(-N\,SF)$

QUANTEC

(Quantitative **A**nalysis of **N**ormal **T**issue **E**ffects in **C**linic**)**

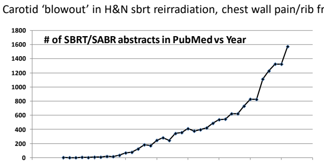
- Updated NTCP dose-volume dependence from **published outcomes** from the 3DCRT-early IMRT era
  - *IJROBP Vol 76, #3 Supplement, 2010*



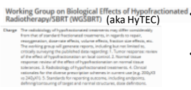


SBRT (SABR)……………………………The Next Frontier

- Greatly improved image guidance during treatment make it (relatively) safe to deliver large doses (>5 Gy) in a small # of fractions (1-10)
  - Stereotactic Body Radiation Therapy (or Stereotactic Ablative Radiation Therapy)
  - Used for increasingly many disease sites
  - Superior or at least equivalent TCP, much more convenient for patients
  - **Some unexpected complications** but with caution, these are not common
    - Carotid 'blowout' in H&N sbrt reirradiation, chest wall pain/rib fracture in lung sbrt



- Is SBRT's effectiveness due only to meticulous use of advanced technology or is there new radiobiology at high fraction doses?



(aka HyTEC)

- Summaries, models, recommendations for SBRT based on review of published outcomes literature
- At least 8 papers in press in IJROBP, another 8-10 in various stages of AAPM review

- No definitive answers yet but the simplicity of the LQ model make it widely used in clinic
  - (**one parameter**, $\frac{\alpha}{\beta}$, describing fractionation effects).
- New tools coming (protons, FLASH, MR linac, immunomodulatory drugs and effects)
- **STAY TUNED**

Additional References

- Fractionation in Radiotherapy: H D Thames and J H Hendry
- Basic Clinical Radiobiology: M C Joiner and A J van der Kogel
- Radiobiology for the Radiologist: E J Hall and H J Giacca