Fractionation, EQD2 and Re-Irradiation

2018 AAMD Annual Meeting Austin, Texas
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Disclosures

Upendra Parvathaneni, MD and Patricia Sponseller, CMD

Neither speaker has any disclosures for this presentation
Objectives

- Discuss the radiobiological concepts of fractionation
- Discuss the calculation of 2 Gy equivalent dose (EQD2) and its application during re-irradiation with a clinical case example
- Bonus round: review anatomy of brachial plexus

Fractionation in radiotherapy

- The 4 “R”s of radiobiology
  - **REPAIR** of sub lethal damage between fractions
  - **Reoxygenation** of hypoxic tumor cells
  - **Reassortment / Redistribution** of dividing cells within the cell cycle
  - **REPOPULATION** of tumor and normal cells
Effect of fractionation

Fractionation: extra dose reqd to cause same lethal effect

Fractionation improves tolerance to XRT

Late responding normal tissues - LRNT

- spinal cord, brain, bone necrosis, fibrosis
- Cells in these organs do not divide during a course of XRT
- Capable of accumulating and repairing damage between insults*
- *Inter fraction interval for near complete repair – 6 hrs
- Low a/b ratios (2-3)
- Fractionation is key to avoiding complications
Gd 3 fibrosis of neck several yrs after RT requiring airway support

RT temporal lobe necrosis at 18 months

RT caries after 6 months

Fractionation sensitivity of LRNT

Rod Withers, Cancer: 55, 2086-2095, 1985
Hyperfractionation

- HF = smaller dose per fraction (<1.8-2 Gy/fx) improves normal structure tolerance - LRNT

- Improved LRNT tolerance allows for dose escalation to tumor with greater tumor control

- conventional RT : 2Gy/# daily, TD: 70Gy
  HF : 1.15 – 1.2Gy/# b.i.d, TD: 77-82Gy

- Increased dose to tumor allowed by HF

Fractionation meta analysis:
Hyperfractionation improves loco regional control and survival

![Graph showing survival comparison between conventional RT and hyperfractionated RT](image-url)
Hyperfractionation

- HF = smaller dose per fraction
  (<1.8-2 Gy/fx) improves normal structure tolerance - LRNT

- Improved tolerance of LRNT for a given total dose may be exploited to increase the safety of re-irradiation

- conventional RT : 2Gy/# daily, TD: 70Gy
  HF for re-irradiation : 1.2 Gy/# b.i.d x 60fx, TD: 72 Gy

- Not treating tumor to a higher total dose, but using the increased repair capacity to make re-irradiation safer.

EQD2, BED, a/b ratios
Linear Quadratic equation, \(a/b\) ratios

- LQ equation is an attempt to mathematically explain the cell survival curve.
- Initial linear component (alpha) = exponential cell kill – not much repair, e.g., tumors, acute effects.
- “bendy” quadratic component (beta) = predominantly indirect cell kill: LRNT tend to accumulate & repair damage between fractions.
- \(a/b\) ratio (Gy) – when alpha kill = beta kill.
- LRNT have low \(a/b\) ratios (2-3) = low on alpha, high on beta (repair).
- ARNT and malignancies have high \(a/b\) ratios (10-25) = high on alpha (repopulation), low on beta (repair).

Biologically Equivalent Doses (BED)

- Effect (e.g., cell kill) = \(n (ad + bd^2)\)
- \(E/a = nd (1 + d/(a/b))\)
- \(E/a\) (biologically equivalent dose) is the dose in Gy required to produce a defined endpoint.
- BED – a useful concept to compare different fractionation regimens.
- However – we think of tolerance doses in 2Gy terms and not BED.
  Eg: spinal cord tolerance = 50 Gy/25#.
  i.e, cord tolerance BED = 50(1+2/3) = 50(5/3) = 250/3 Gy.

- How much is cord receiving with 50 Gy/10#?
  BED = 50(1+5/3) = 50(8/3) = 400/3 Gy.
  It is not intuitive to compare 400/3 Gy with 250/3 Gy.
- Simple solution – Rod Withers’ 2Gy iso-effective dose adaptation of BED (EQD2) – For 50 Gy in 10# cord is receiving 80 Gy.
**EQD2 (equivalent dose in 2 Gy/fx)**

- Calculating 2 Gy equivalent dose for LRNT based on LQ modal and a/b ratio of 3

\[
E = (\text{total dose}) \times (\text{relative effectiveness})
\]

\[
D_x = D_2 \times \frac{\alpha/\beta + 2}{\alpha/\beta + x}
\]

\[
\frac{D_2}{D_1} = \frac{d_1 + (\alpha/\beta)}{d_x + (\alpha/\beta)}
\]

**EQD2 = D (d+3)/5**

EQD2 for cord receiving 50 Gy/10# = 50(5+3)/5 = 80 Gy

*Acta Oncologica 27 (1988) Fasc. 2*

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**Re-irradiation**

- Application of principles of fractionation, hyperfractionation and EQD2 in re-irradiation
Case Study - History

- 63 year old male with 43 pack year history of smoking
- He received prior RT for T1N0 right tonsil and bilateral neck 3 years ago – 6825cGy in 35 fx
- Now presents with second primary SCC of left tonsil cT4bN2M0
- Tumor involves encases left carotid artery
- Not a surgical candidate

Re-irradiation in Head and Neck

- Irradiating a region that previously received high dose RT > 45-50 Gy
- ~ 40% of H&N cancer patients get re-irradiated
- It is fraught with serious and life threatening events ~ 30%  Sulman E et al. IJROBP 2009; 73 (2), 399
- However, cause of death in vast majority of cases is due to uncontrolled disease
- PFS is superior with immediate vs. delayed post op re-irradiation  Janot F et al. J Clin Oncol 2006; 24:18s
Case study - what we know

- Received outside Dosimetry for prior RT
- No DICOM data available
- Brain, brainstem and spinal cord contoured as one structure CNS
- Pdf file contained one multi-planar view and 2 DVH screen captures
- Plan contained only limited isodose lines
- Maximum dose reported on DVH for CNS structure = 42 Gy

Prior RT plan: SIB 35 fx
Prior RT Plan

Analyzing the prior RT plan:
spinal cord & brachial plexus dose

Cord dose < 45 Gy

Brachial Plexus dose ~ 60 Gy
EQD2 for spinal cord

- Spinal cord received 42 Gy in 35 fractions at 1.2 Gy/fx
- \[ \text{EQD2} = \frac{D(d+3)}{5} \quad 42(1.2+3)/5 = 35.3 \text{ Gy} \]
- "Forgotten dose" 10% per year x 3yrs:
  - \(3 \times 3.53 \text{ Gy} = 10.6 \text{ Gy}\)
- \(35.3 - 10.6 = 24.7 \text{ Gy}\) is the spinal cord's current "exposed dose" in 2 Gy per fx
- Available cord tolerance = 20-30 Gy

Planning objectives

- Treat patient BID 59 fx X 120 cGy
- PTV 70 and PTV 60 contoured
- Retreat left tonsil and neck
- Limit dose to spinal cord to Max 30 Gy
- Limit dose to left brachial plexus ALARA
- Limit dose to Larynx < 35 Gy
IMRT plan

Left brachial plexus max 40 Gy
Spinal cord max 30 Gy

Proton therapy
No EXIT DOSE
Carotid sparing irradiation
Proton RT vs. IMRT

Proton plan

IMRT plan

Brachial Plexus anatomy
Brachial plexus anatomy

- Upper limit – C4/5 neural foraminae
- Lower limit – T1/2 neural foraminae
- Roots - C5 – T1 ventral rami
- Trunks – between anterior and middle scalene muscles up to 1st rib
- Divisions and chords – distal to clavicle & 1st rib

Brachial plexus contouring tips

- Key = start with the great vessels of the neck to get oriented. Proceed to identify the anterior & middle scalene muscles - located posterior to great vessels
- Choose an axial slice where the scalenes clearly separate – forming the “cheese burger"
- This might be obvious only on a few slices – and sometimes, only on one side
- Once identified, use this landmark to contour on other slices

Brachial plexus contouring – the “cheese burger”

Great vessels
C = carotid art.
J = jugular vein

Buns
anterior & middle scalene muscles

Meat
brachial plexus
Brachial plexus contouring
– key = identify scalene muscles
Thank you!