Radiobiology in Brachytherapy

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Radiobiology

- For changing the fractionation schedules
- Change of dose rate systems (LDR/HDR)
- Gap correction
- Combining EBRT with Brachytherapy
- Choosing the right isotope
- Comparison of data between centres
Experimental- Ram testis

- Stranquist Curves 1944
- NSD –Ellis 1969
- Orton TDF Brachytherapy 1974
- Elkind kind of repair
  - Inter Fr time, Dose/Fr, Dose Rate
- Cummulative Response Dose(CRE)
  - Kirk et al
- Tumor Significant Dose (TSD)
- It does not take all complex biological process
- Doubts on validity of NSD relation with tissue type
- Doubts on validity of NSD relation with different effect in same tissue type
- Range of number of fractions. The formula is provided
- Concern on the time factor taken.
Radiobiology (RB)

- Dose Rate
- Fractionation
- Overall treatment time
- Biology Of Tumor (Radiosensitivity)
- Biology of Normal Tissue (sensitivity and repair mechanisms)
Biological Models

- Linear Quadratic Model
  - Lea & Catcheside
- Various modifications of LQ model
- BED : Biological Equivalent dose
- EUD : Equivalent Uniform Dose
L Q model

- It quantitatively predicts the dose/fraction dependence. The principal determinants are $\alpha$ & $\beta$
- $\alpha$ – Linear portion in Cell Survival Curve.
  - Occurs along a single ionizing tract
  - Tumor cells (rapid proliferation rates & short duration for repair)
- $\beta$ - Quadratic portion in Cell Survival Curve
  - Occurs along a two different ionizing tracts
  - Normal cells (coordinated repair & hence requiring double hit)
- $\alpha/\beta$ ratio
  - Dose where there is proportionate of cell death due to linear & quadratic portions
Interpretation of $\alpha/\beta$

- High $\alpha/\beta$ ratio
  For a particular dose of radiation either the
  - $\alpha$ DNA injury is higher
  - $\beta$ DNA injury is lower

- Low $\alpha/\beta$ ratio
  For a particular dose of radiation either the
  - $\alpha$ DNA injury is lower
  - $\beta$ DNA injury is higher
Pros & Cons

Low $\alpha/\beta$ means

↓ in dose/fraction
less injury to normal tissue

High $\alpha/\beta$ means

↑ in dose/fraction
More injury to normal tissue

Limitations
Fractionated Rx delivered @ regular interval period (once in 24hrs) & 5Fr/Wk.
Gap in Rx in pt NOT considered
Biological Effective Dose (BED)

- Concept used to compare the effectiveness of cell killing by different fractionation regimen by using LQ Model
- Use
  - Intercomparison of various RT schedules
  - Intercomparison of different types of radiotherapy
- Formula
  \[ = \text{Total Physical dose} \ [D] \times \text{Relative effectiveness} \ [RE] \]
Factors considered in BED

- **Physical**
  - Dose
  - Dose/fr
  - Inter fraction interval

- **Radiobiology**
  - $\alpha/\beta$
  - Repair rate
  - T pot
  - Repopulation & Redistribution
  - Overall treatment time
BED differs for different normal tissue & also for different tumor biology.

BED is represented as numerical value of dose with suffix indicating the α/β value.

Eg: 100 BED$_3$, 65 BED$_{10}$

Relative Effective factor
  = Phy Factor + RB Factor
Repopulation

- RE for repopulation when taken into consideration uses subtractive repopulation correction factor w.r.t repopulation rate and Rx time.
- BED = D X RE – RCF (repopulation correction factor)

- RCF = K (T-\(T_{\text{delay}}\))
- \(T_{\text{delay}}\) is delay time after beginning of treatment before the repopulation rate becomes significant.

Eg: 28 days for HNSCC
Differences

**EBRT**
- Large Volume
- Homogeneous
- -5% to +7% acceptable
- Small dose, protracted time (weeks)
- Full repair

**Brachytherapy**
- Isodose encircling a small target volume
- Very heterogeneous
- High dose, short treatment (hours to days)
- Short interval (HDR), Continuosly (LDR)
LDR vs HDR

- Several Trials comparing LDR Vs HDR
  - Historical data
- Most cases similar results
- HDR beneficial with equivalent normal tissue tolerance & the tumoricidal doses
- Severe Complications
  - 3.44% (>7 Gy) & 1.28% (<7 Gy)
Volume, Anatomical site

- The Dose reqd increases with size of tumor
- As Dose increases tolerance of late responding normal tissues decreases.
Tumor shrinkage

- Combining HDR with EBRT
  - Eg: Ca Cervix
- Important in permanent implants. Outcome depends on shrinkage which is difficult to predict.
Reirradiation

- High doses can be delivered to previously irradiated area
- Can be tolerated if delivered to a limited volume. recovery seems to be less in some like CNS
- No clarity regarding minimal interval between two irradiations.
Combined with EBRT

- Because BEDs are additive the determination of biological effects associated with combined modality treatments is straightforward.

- Total BED

\[ \text{Total BED} = \text{BED}_{(\text{EBRT})} + \text{BED}_{(\text{Brachy})} - \text{RCF} \]

RCF (repopulation correction factor) is reqd only for tumor calculations and should be calculated using the overall treatment time of the combined treatments.

- In Brachytherapy calculation allowance for dose gradient effect. Should also be considered.
The radiobiological models helps in:

- Quantification of CLDR & FHDR
- Quantification of dose rate effect
- Quantification Permanent implants
- Quantification of PDR Brachytherapy
- Treatment intercomparison
- Designing new Fr & Rx schedules
- Calculating dose equivalence used with different isodose
Future

- Commercially TPS incorporating biological models
  - Bioplan
  - Orbit
  - LQ Survivor
Dose correction

- Recommended when dose rate >1Gyhr

- At 1.5-2Gyhr little differential effect is expected but fractionation (2-3Fr) compensates to some extent

- RB interpretation of clinical data should therefore combine dose rate & dose fractionation parameters.
Dose conversion CLDR to FHDR

- **BED** = Total Dose $\times [1 + \frac{2R}{\mu} (\alpha/\beta \text{ ratio})]$
- **R** = dose rate, $\mu = \text{Constant} \ 0.5$
- **Eg 40 Gy in 48 Hrs, BED10 (Tumor) 3 (Late normal tissue) HDR**

\[ \text{CLDR}_{\text{tumor}} = 40 \times [1 + 2(40 \text{Gy}/48\text{hr})/ 0.5 \times 10] \]
\[ = 53.3 \text{Gy}_{10} \]

\[ \text{CLDR}_{\text{normal}} = 40 \times [1 + 2(40 \text{Gy}/48\text{hr})/ 0.5 \times 3] \]
\[ = 84.4 \text{Gy}_{3} \]
\[ \text{BED}_{10} = 6 \quad \text{FHDR} = 53.3 \text{ Gy} \]
\[ 6d \times [1 + d/10] = 53.3 \text{ Gy}, \quad d = 5.67 \text{ Gy} \]

\[ \text{HDR}_{\text{normal}} = 34.02 \times [1 + 2(5.67/10)] \]
\[ = 98.3 \text{ Gy}_{\text{HDR}} \]

Compared to 84.4 Gy\(_{\text{LD}}\)

in order to achieve 10% less dose to normal tissue, equivalent to LDR then

\[ \text{HDR}_{\text{normal}} = 34.02 \times [1 + 2(5.67-10\%)/10)] \]
\[ = 82.7 \text{ Gy} \]
In other words in order to achieve the same tumor control the dose as per HDR should be 5.67Fr.

Dose to be reduced from 40 Gy > 34.02 Gy

Also in order to achieve the same normal tissue toxicity the dose as per HDR should be 5.1Gy/Fr instead of 5.67Fr without compromising on the tumor control