RADIOBIOLOGY OF HDR vs LDR BRACHYTHERAPY AND ITS RELEVANCE

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BRACHYTHERAPY FOR CARCINOMA CERVIX

• Intracavitary more common than interstitial brachytherapy
• Advantage of delivering radical dose of radiation in relatively short time
• Sparing of normal tissues and critical structures due to rapid “fall-off” of dose
• Applicable for small volume tumours only
• Pre-loaded applicators associated with risk of radiation exposure
• Classical Paris and Manchester systems qualify as LDR
CLASSICAL MANCHESTER SYSTEM

• Use of dose rate instead of mg-hours

• Dose prescribed to a reference point corresponding to an area which is the main limiting factor for radiating the uterine cervix

• Applicator design and loading was such that dose rate remained constant regardless of combination of tube and ovoids
DOSE RATE OF MANCHESTER I/C

- Prescription 8000R in 144 hours = 55.5R
- Standard insertions: 56.7 – 57.6R/hr
- Short tube with standard ovoids: 50R/hr (13% less)
- Ovoids in tandem: 53R/hr (7%) less
- Appropriate adjustments recommended with changing dose rate
AFTERLOADING

- Based on principles of Manchester system
- Markedly reduced radiation exposure
- Remote controlled afterloading reduced further radiation exposure
- Availability of other radio-isotopes was another game-changer
HDR – THE NEW KID ON THE BLOCK

- Remote-controlled after-loading with no radiation exposure to personnel
- Treatment delivered in very short time – can be OPD procedure
- Reduces the risks associated with prolonged immobilization
- Better maintenance of applicator geometry during short treatment time
- Optimisation of source loading possible
- Miniaturisation of source could reduce size of applicators
EARLY AND LATE EFFECTS

- Early responding normal tissues and tumour have lower sensitivity to dose/# compared to late responding tissue.
- Smaller dose/# is associated with lower risk of complications and better therapeutic ratio.
- Difference in # size sensitivity reflects difference in DNA repair capacity which is the basis of differential effect of fractionation.
LQ MODEL SIMPLIFIED

• Mechanistic radiobiological notion about how radiation kills cells
• Clear separation between early and late responding tissues
• Alpha component is dose rate independent
• Beta component approaches zero for LDR because there is scope of repair of sub-lethal damage from first hit before the second hit. In HDR, the exposure time is shorter than the half time for repair of sub-lethal damage
• When alpha component dominates, survival curves are straighter
EQUIVALENT PRESCRIPTIONS

• Extrapolated response dose (ERD) or BED assumed to be equal in the regimes being compared

• Tissue specific parameters are taken as average value from experimental data

• Dose ↓, no. of fractions ↑ to reduce late complications with HDR

\[ \text{HDR: } \text{ERD-Nd}(1+\frac{d}{\alpha/\beta}) \]  \[ \text{LDR: } \text{ERD-NRt}[1+\frac{2R}{\mu(\alpha/\beta)} (1-\frac{1-e^{-\mu t}}{\mu t})] \]

where:

\( N \) = number of fractions (for HDR or LDR);
\( d \) = dose/fraction (for HDR) in Gy;
\( R \) = dose rate (for LDR) in Gy/hour;
\( t \) = time for each fraction (for LDR) in hours;

and \( \alpha/\beta \) (in Gy) and \( \mu \) (in h^{-1}) are tissue-specific parameters.
THE DOSE-RATE EFFECT

survival curves for 40 different cell lines of human origin, cultured in vitro and irradiated at HDR and LDR

Fig. 13.11. Dose survival curves at high dose rate (HDR) and low dose rate (LDR) for a large number of cells of human origin cultured in vitro. Note that the survival curves fan out at low dose rate because, in addition to a range of inherent radiosensitivities (evident at HDR), there is also a range of repair times of sublethal damage. [Redrawn from Hall and Brenner (1992)]
WHO’S AFRAID OF HDR?

• Increased dose/# increases late toxicities
• To keep late toxicities comparable, total dose needs to be reduced
• With increasing dose/# of HDR, there is increased loss of therapeutic efficiency
RECOMMENDATIONS

• Dose corrections required when converting from LDR to HDR brachytherapy
• HDR brachytherapy needs to be fractionated to avoid unwanted late toxicities
• Various fractionation schedules have been calculated using iso-effect formulae and extrapolated response dose (ERD)
• Dose to critical organs can be reduced in I/C application for carcinoma cervix, so protocols may be designed by matching early effects
• If critical organs get same amount of dose as tumour, HDR will likely cause loss of therapeutic efficacy
PGIMER EXPERIENCE

• Patel et al (1994): comparable local control and 5 year survival in patients treated with LDR or HDR. Statistically significant decrease in overall incidence of rectal reactions in patients treated with HDR

• Patel et al (2005): fraction size of 9 Gy, 2- 4 fractions, along with external radiation to pelvis, was well tolerated with actuarial risk of developing Grade 3 or more toxicities at 3.31%

• Patel et al (1998): dose reduction is also required for LDR/MDR afterloading brachytherapy in order to decrease normal tissue toxicity of critical organs
CONCLUSIONS

• Essential difference between cell killing by LDR and HDR depends on the inherent radiosensitivity of tissues being irradiated and percentage of tumour clonogens

• The advantage of HDR intracavitary brachytherapy for carcinoma cervix comes from good radiobiology and good geometry of application

• When iso-effect formulae are used to convert from one dose rate to another, it is essential to clarify whether matching should be done for early or late responding tissues

• All mathematical models need to be validated by well-designed clinical studies