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

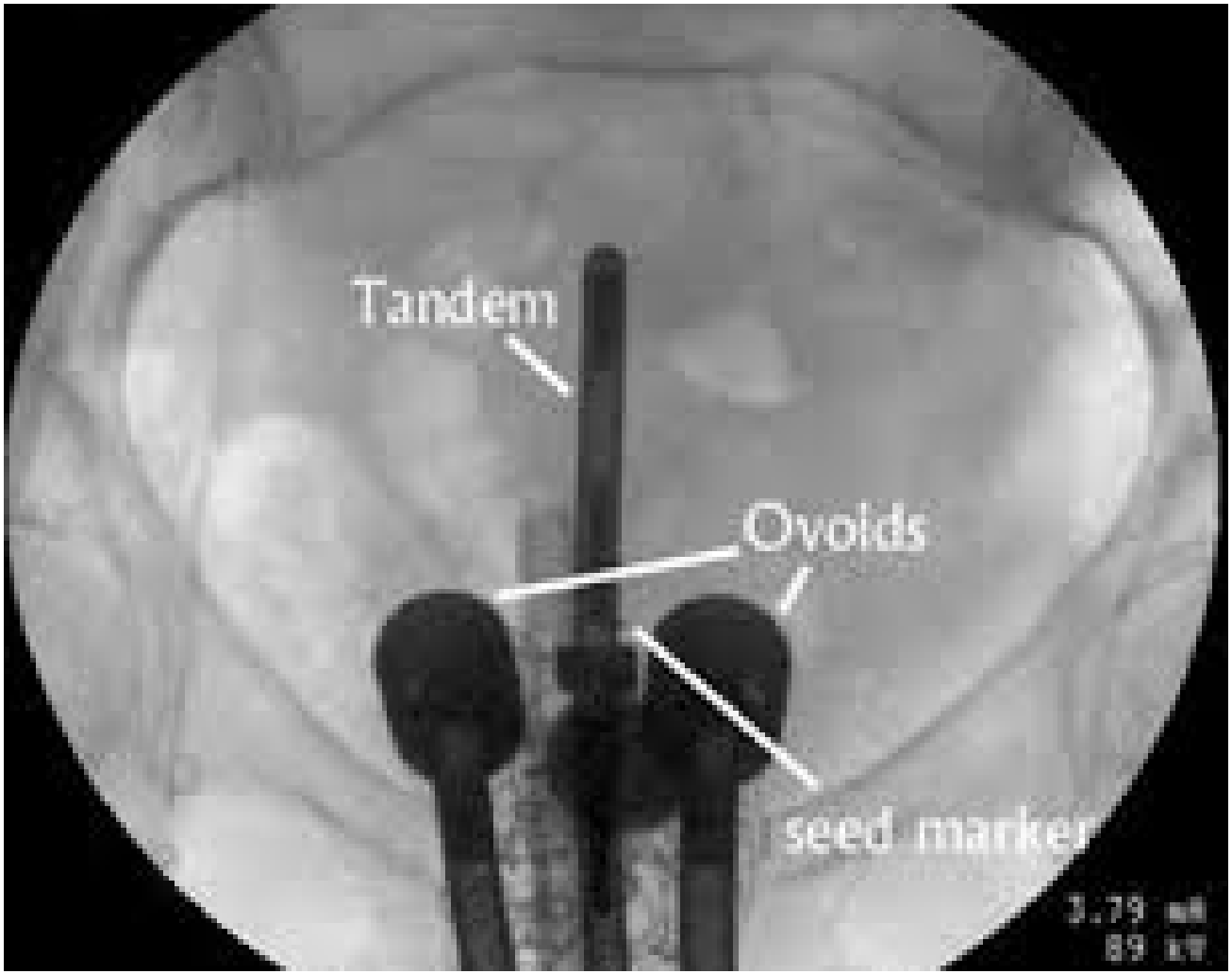
- **Use of dose rate instead of mg-hours**
- **Dose prescribed to a reference point corresponding to an area which is the main limiting factor for radiating the uterine cervix**
- **Applicator design and loading was such that dose rate remained constant regardless of combination of tube and ovoids**

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

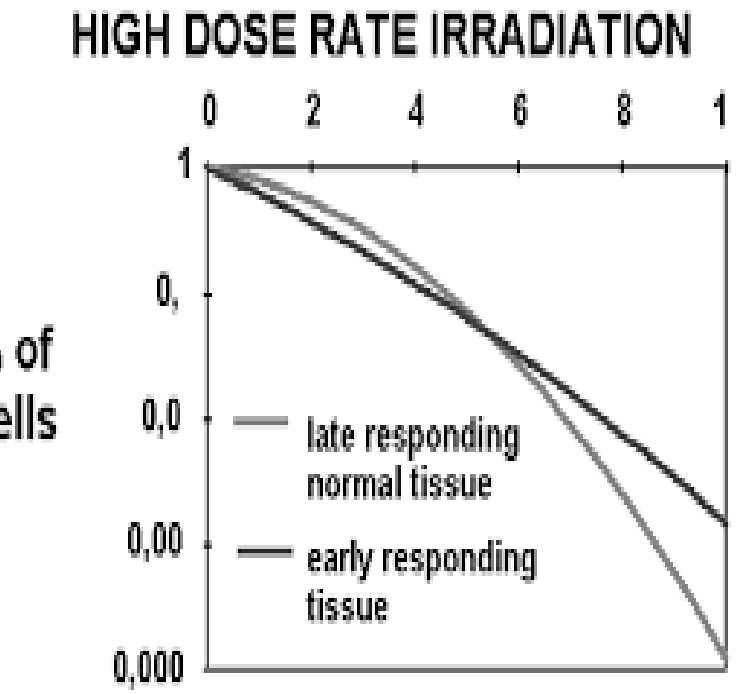
- **Based on principles of Manchester system**
- **Markedly reduced radiation exposure**
- **Remote controlled afterloading reduced further radiation exposure**
- **Availability of other radio-isotopes was another game-changer**



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

HDR: $ERD\text{-}Nd\left(1+\frac{d}{\alpha/\beta}\right)$ [1]

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

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 α/β (in Gy) and μ (in h^{-1}) are tissue-specific parameters.

GENESIS OF EVIDENCE

THE DOSE-RATE EFFECT

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

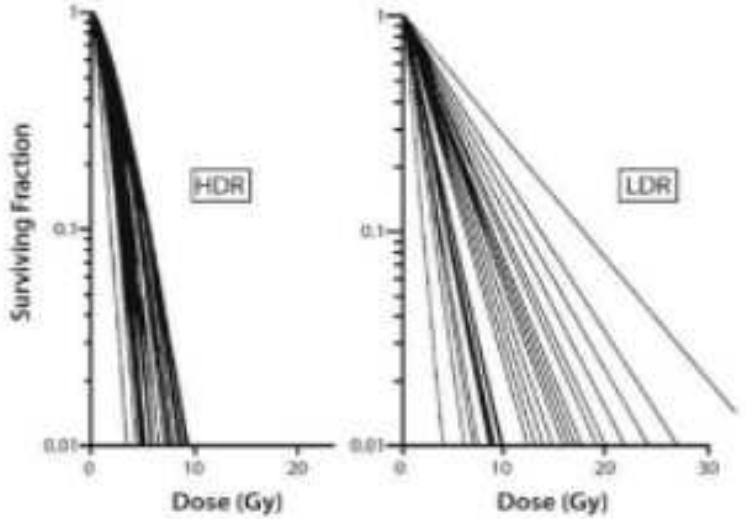
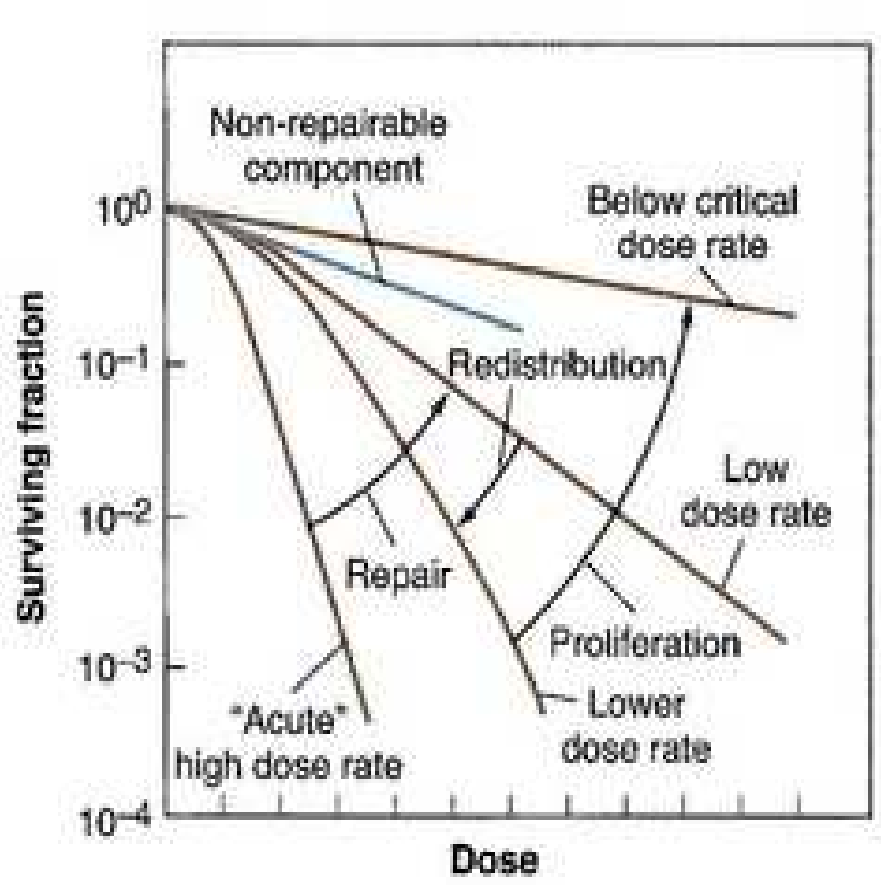


Fig. 13.11. Dose survival curves at high dose rate (*HDR*) and low dose rate (*LDR*) for a large number of cells of human origin cultured in vitro. Note that the survival curves fan out at low dose rate because, in addition to a range of inherent radiosensitivities (evident at *HDR*), there is also a 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