Fractionation and its impact on the Management of Head & Neck Cancers

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FRACTIONATION

- *Refers to division of total dose into no. of separate fractions over total t/t conventionally given on daily basis , usually 5days a wk.*
- *Size of each dose # whether for cure or palliation depends on tumor dose as well as normal tissue tolerance .*
- *e.g. if 40Gy is to be delivered in 20# in a time of 4wks then daily dose is 2Gy.*

HISTORICAL REVIEW

- *X-ray were used for radiotherapy just 1 month after its discovery in a fractionated course because of the primitive X-ray machines available at that time & their low output*
- *To deliver a single dose to destroy a tumor would require several hours or even days.*
- *Single fraction radiotherapy became feasible only in 1914 with the advent of Coolidge hot cathode tube, with high output, adjustable tube currents & reproducible exposures.*

HISTORICAL REVIEW

- *Earlier some radiotherapists believed that fractionated treatment was inferior & single dose was necessary to cure cancer.*
- *While radiobiological experiments conducted in France favored fractionated regimen for radiotherapy which allows cancerocidal dose to be delivered without exceeding normal tissue tolerance*

RADIOBIOLOGICAL RATIONALE FOR FRACTIONATION

- *Delivery of tumorocidal dose in small dose fractions in conventional multifraction regimen is based on 4R's of radiobiology namely*
  - *Repair of SLD*
  - *Repopulation*
  - *Redistribution*
  - *Reoxygenation*
- *Radio sensitivity is considered by some authors to be 5th R of radiobiology.*

TIME DOSE MODELS

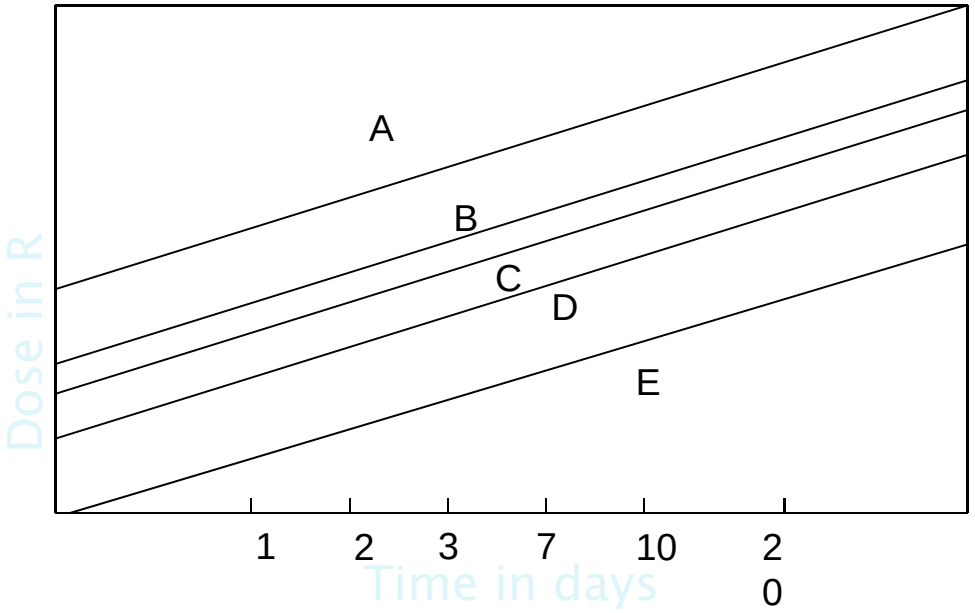
- *With introduction of various fractionation schemes in radiotherapy need for quantitative comparisons of treatments was felt in order to optimize treatment for particular tumor.*
- *Strandquist was 1st to device scientific approach for correlating dose to overall t/t to produce an equivalent biological isoeffect.*

CUBE ROOT MODEL

- *By Strandqvist (1944)*
- *He demonstrated that isoeffect curves (i.e. dose vs. no. of #s to produce equal biological effect) on log-log graph for skin reactions (erythema & skin tolerance) were st. lines with a slope of 0.33 i.e.*

$$D \propto T^{0.33}$$

- *As these plots were for fixed no. of #s N hence T was linear function of N & D was proportional to cube root of N also*



A – Skin necrosis C – moist desquamation

B – cure for skin carcinoma D – dry desquamation

E – skin erythema

Cohen's

- Cohen analyzed three diff. set of data of skin damage with end points as weak or strong erythema &skin tolerance.
- Cohen found an exponent of 0.33for skin erythema / skin tolerance & 0.22 for skin cancers.
- According to Cohen's results, relationship b/w total dose & overall treatment time for normal tissue tolerance & tumor can be written as

$$D_n = K_1 T^{0.33}$$

$$D_t = K_2 T^{0.22}$$

- Where K_1& K_2 are proportionality constants. D_n, D_t &T are normal tissue tolerance dose , tumor lethal dose & overall treatment time respectively
- The exponents ,0.33& 0.22 of time factor represents the repair capabilities of normal tissue & tumor cells respectively.

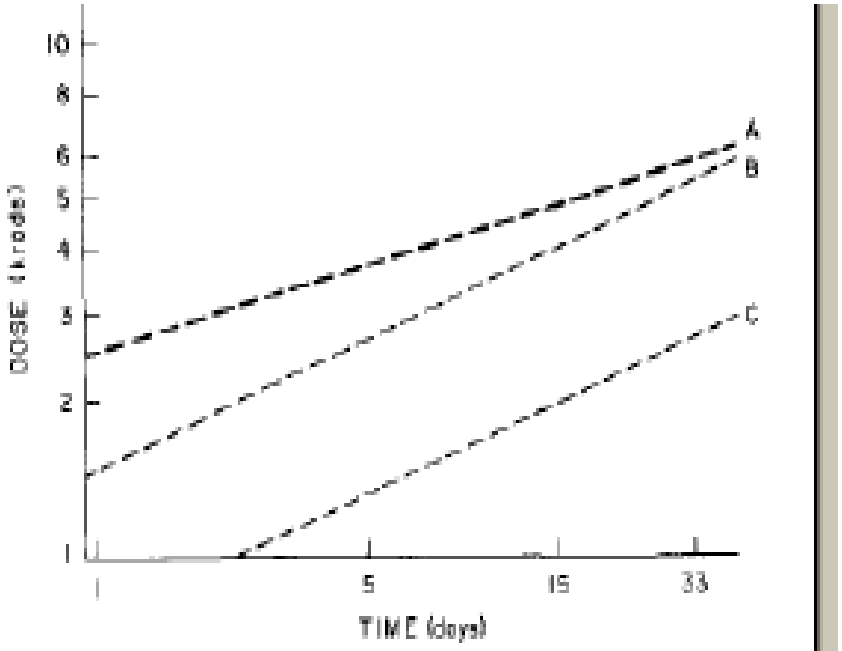


FIG. 1. Cohen's time–dose isoeffect model, shown on a log–log graph. Curve A = cure of squamous carcinoma of skin; Curve B = skin tolerance; Curve C = skin erythema.

Fowler

- Difference in exponents of time factor in Cohen's formulations indicate that repair capacity of normal tissue is larger than that of tumor
- Fowler carried experimental studies on pig skin showing normal tissue have two type of repair capabilities
  - Intracellular – having short repair half time of 0.5 to 3hrs & is complete within few hrs of irradiation. multiplicity of completion of recovery is equal to no. of #s.
  - Hence no. of #s are more important than overall t/t
  - Homeostatic recovery that takes longer time to complete
- This led Ellis to formulate NSD

NSD MODEL

- *According to Ellis 's NSD formula time factor was a composite of N (no. of #s) & T (overall treatment time)*
- *Exponents for intracellular & homeostatic recovery are 0.22 & 0.33-0.22=0.11 respectively*
- *Fractionation is twice as important as time according to clinical observations of Ellis.*
- *Hence dose is related to time & no. of #s as*

$$D = (NSD) \times T^{0.11} \times N^{0.24}$$

- *Where NSD (nominal stand. Dose) is proportionality constant for specific level of skin damage*

TDF

- Developed by Ortan & Ellis (1973)
- In a complex multi-phase treatment protocol, total effective partial tolerance:

  $PT = (PT)_a + (PT)_b + \ldots + (PT)_n$

  And to compare this protocol with another with partial tolerance PT'

  $(PT)_a + (PT)_b + \ldots + (PT)_n = (PT)'_a + (PT)'_b + \ldots + (PT)'_n$

Basic formula of NSD is

- $NSD = D \times T^{-0.11} \times N^{-0.24}$
- Replacing
  - $D = nd$ (where n – no. of #s & d – dose/#)
  - $T = T/N$ for fixed no. of #s

TDF contd.

- $NSD = Nd \times (T/N)^{-0.11} \times N^{-0.24}$
- $Or\ NSD = d \times T/N)^{-0.11} \times N^{0.65}$

- Raising both side of equation to power 1.538
  - $TDF = 10^{-3} \times NSD^{1.538} = Nd^{1.538} (T/N)^{-0.17} \times 10^{-3}$
- Where 10^{-3} is scaling factor
  - $TDF = 1.19\ Nd^{1.54} (T/N)^{-0.17}$
- Allowance must be made for repopulation during rest period or break
- According to Ellis, TDF before break should be reduced by decay factor to calculate TDF after break

  - $Decay\ factor = \left(\frac{T}{T+R} \right)^{0.11}$

- Where T days is time from beginning if course of radiotherapy to break & R days is length of rest period.

CRITICISMS OF NSD

- Do not take into account complex biological processes that take place during or after irradiation
- Values of exponent of N in NSD eq. are not same foe diff. tissue types.
- Validity of NSD w.r.t. different effects in same tissue is doubtful. For late effects in skin the influence of no. of #s may be considerably larger than for acute skin responses
- Uncertainty relates to no. of #s for which formula provides reasonable approximation of tolerance dose of a given tissue. For effects in skin approximation is obtained b/w 10 to 25 #s
- Another difficulty is with time factor $T^{0.11}$. this suggests an increase in dose ay approx.20% in 1^{st} week,10% in 2^{nd} week& 5% in 3^{rd} week. but for acute reactions in skin & mucosa accelerated repopulation starts only after 2-3wks after start of fractionated treatment while for late reacting tissue cell proliferation during the fractionated course(4-8 wks) is not expected to increase tolerance dose as predicted by NSD formula

TARGET THEORY

- To express relationship b/w no. of cells killed & dose delivered in mathematical terms Target theory was proposed by Crowther & expended by Lea.
- Curve representing relation b/w dose & surviving # after radiation delivery is called survival curve.

SIMPLE TARGET THEORY

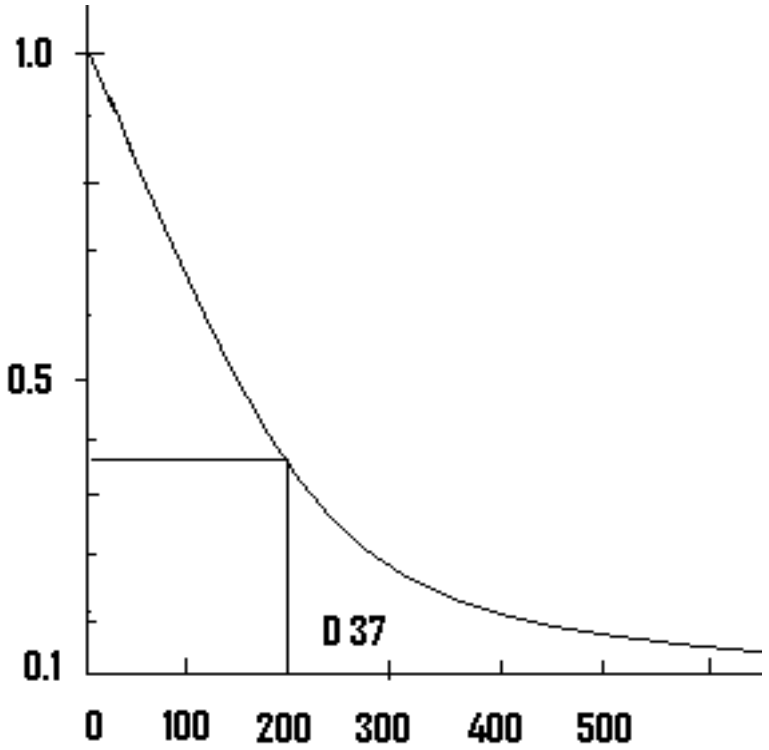
- Also called single hit single target theory.
- Single hit is sufficient to produce measured effect or to inactivate a cell
- The curve is exponential i.e. at low doses the relationship is linear as process continues larger doses are required to inactivate same no. of organisms.

$$S = e^{-p}$$

$$p \propto \frac{1}{D_o} D$$

- Where $1/D_o$ is constant of proportionality

$$S = e^{-\left(D/D_o\right)}$$

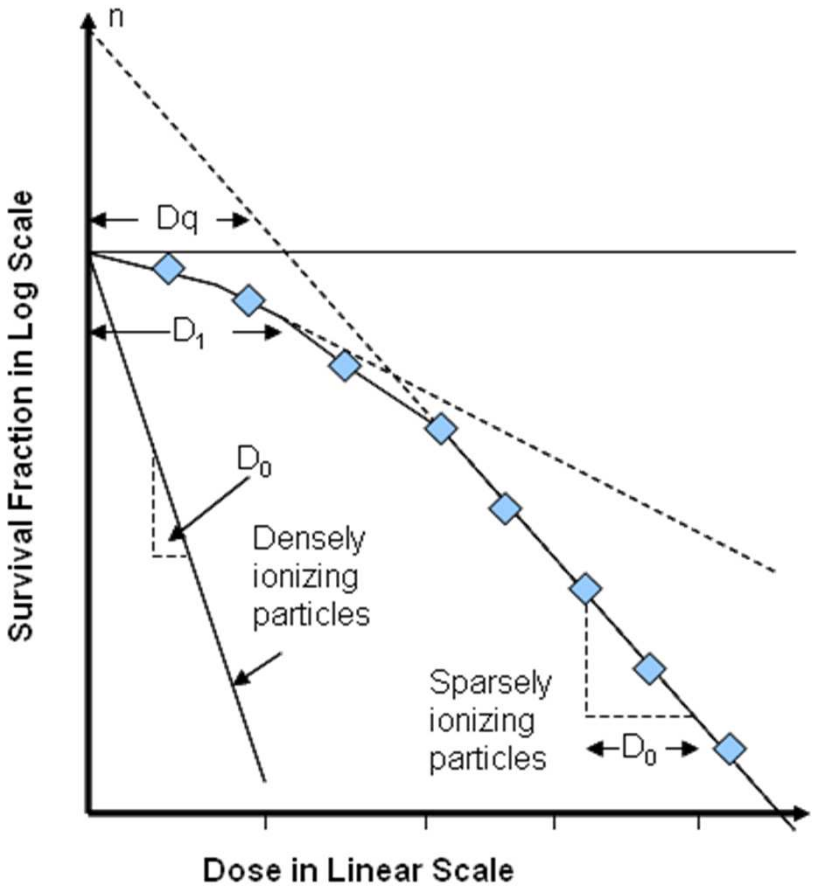


SIMPLE TARGET THEORY

- Where D_0 is the mean lethal dose that will produce avg. one hit per cell
- such log survival curve is linear showing D_0 as dose that reduce cell survival fraction to 37%
- Such curves are observed in mammalians cells only
- When cell are irradiated with high LET rad^n e.g. α - particles
- When cells irradiated are synchronized in most sensitive phases of cell cycle (lateG_2 or M)

MULTITARGET THEORY

- *According to this theory some organisms contain more than one target & to inactivate organism each target should receive one hit*
- *Survival curves corresponding to this theory start with less sensitive region at low doses & show exponential behavior at large doses i.e. curves show a shoulder region in the beginning.*
- *Such curves are observed when mammalian cells are irradiated with low LET radⁿ e.g. x-rays*
- *Shoulder represents cells in which fewer than n targets have been damaged after receiving a dose D i.e. cells have received SLD which can be repaired.*



LINEAR QUADRATIC MODEL

- *Basis of LQ theory is that cell is damaged when both strands of DNA are damaged.*
- *This can be produced either by single ionizing particle i.e.*

$$E \propto D \qquad E = \alpha D$$

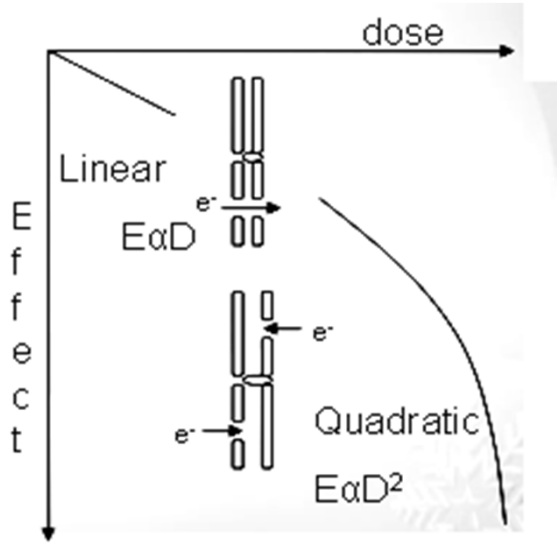
- *Where α is constant of proportionality*

$$S = e^{-\alpha D}$$

- *Or it can be accomplished by independent interaction by two separate ionizing particles such that*

$$E \propto D^2 \qquad E = \beta D^2$$

$$S = e^{-(\beta D)}$$

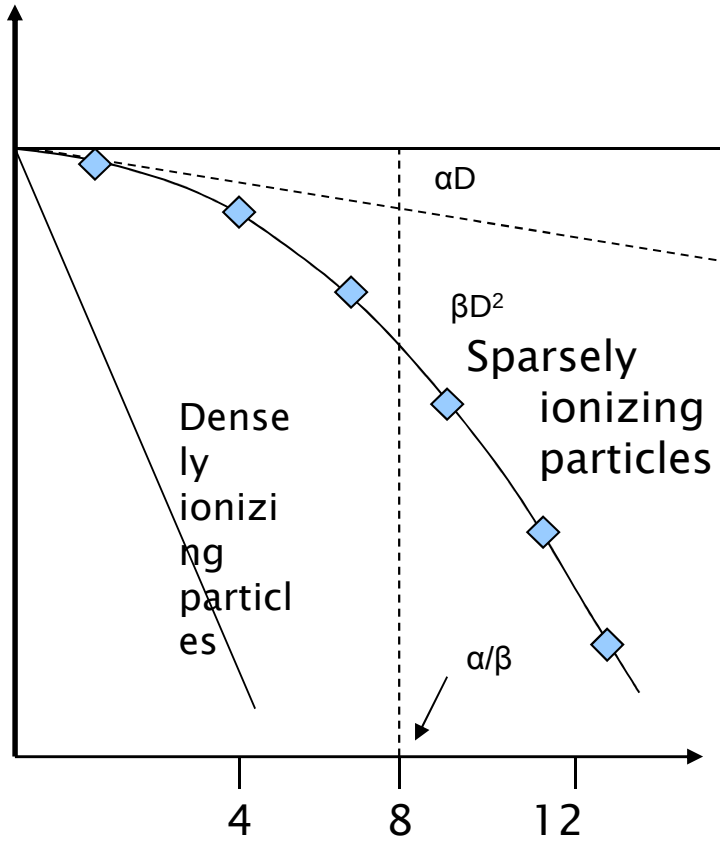


LINEAR QUADRATIC MODEL

- *Overall LQ eq. for cell survival is therefore*

$$S = e^{\left(-\alpha D - \beta D^2\right)}$$

- *This shows the two components to cell killing, α- damage (irreparable) & β- damage (reparable) combine to form cell survival curve.*
- *D= α / β is the dose at which log surviving # for α- damage equals that for β- damage.*
- *Parameter α / β represents curviness of cell survival curve.*
- *Higher the α / β, straighter is the curve & cells show little repair of SLD while low α / β indicates high capability of repair.*
- *Tumor usually have high α / β values in range of 5-20Gy (mean 10Gy) while late responding normal tissue have α / β in range 1-4Gy (mean 2.5Gy)*



LQ MODEL

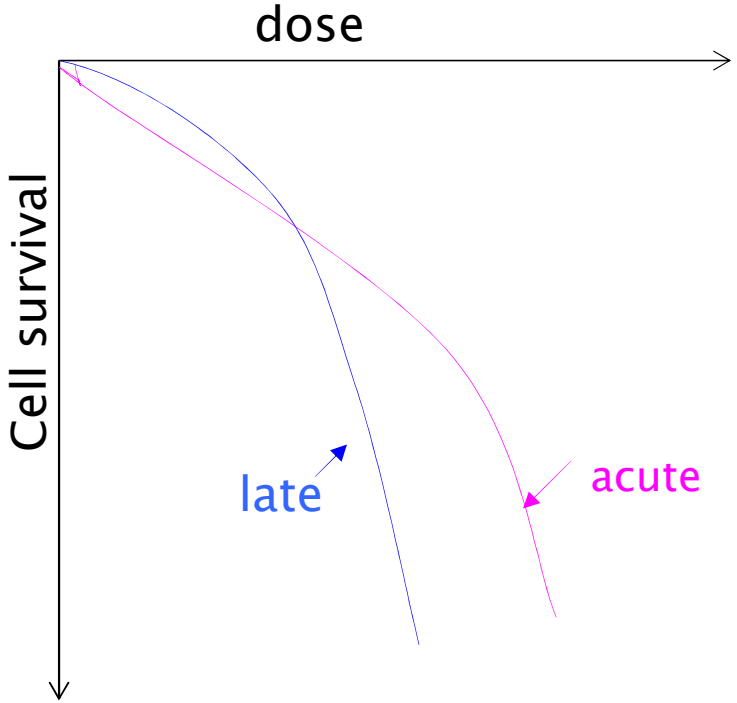
- *NSD & TDF models are empirical models while LQ model is derived from cell survival curves.*
- *LQ model is based on fundamental mechanism of interaction of radn with biological systems.*
- *Biologically effective dose is the quantity by which diff. fractionation regimens are intercom pared*
- *BED = total dose x relative effectiveness*

$$E/\alpha = nd \times \left(1 + \frac{d}{\alpha/\beta}\right)$$

- *Where*
- *n - no. of #s*
- *d - dose/#*

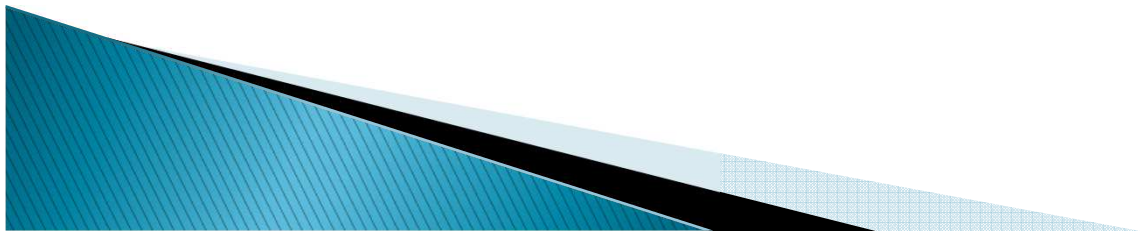
RADIATION RESPONSE

- *Survival curves of early & late responding cells have different shapes.*
- *Curves for late responding tissue are more curved because of difference in repair capacity of late & early responding tissues.*
- *In terms of linear quadratic relationship b/w effect & dose this translates into larger α/β ratio for early than late effects.*
- *If fewer & larger dose #s are given late reactions are more severe.*
- *It can be interpreted as diff. in repair capacity or shoulder shape of underlying dose – response curve.*



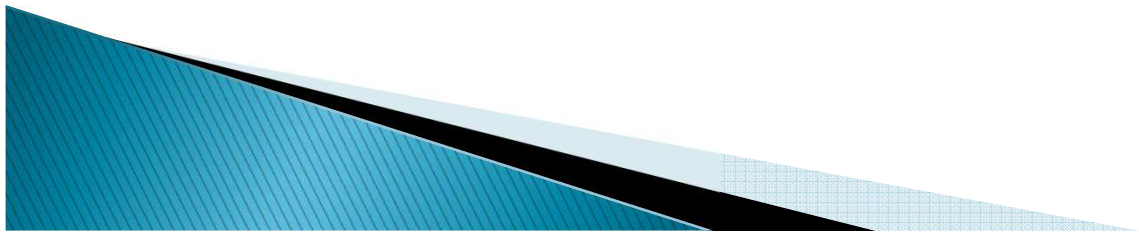
EXPLANATION FOR DIFF. IN SHAPE OF EARLY & LATE RESPONDING TISSUES

- *The radio sensitivity of a population of cells varies with the distribution of cells through the cycle .*
- *Two different cell populations may be radio resistant :-*
  1. *Population proliferating so fast that S phase occupies a major portion of cycle .*
  2. *Population proliferating so slowly that many cells are in early G_1 or not proliferating at all so that cells are in resting (G_0) phase.*



EXPLANATION FOR DIFF. IN SHAPE OF EARLY & LATE RESPONDING TISSUES

1. *Population proliferating so fast that S phase occupies a major portion of cycle .*
   - *Redistribution occurs through all phases of cell cycle in such population & is referred to as self sensitizing activity.*
   - *New cells produced by fast proliferating population offset cells killed by dose #s & thus offers resistance to effect of radiation in acutely responding tissues & tumors.*
   - *Thus proliferation occurring b/w dose #s help in repopulation of normal tissue (i.e. spares normal tissue) at the risk of tumor repopulation*

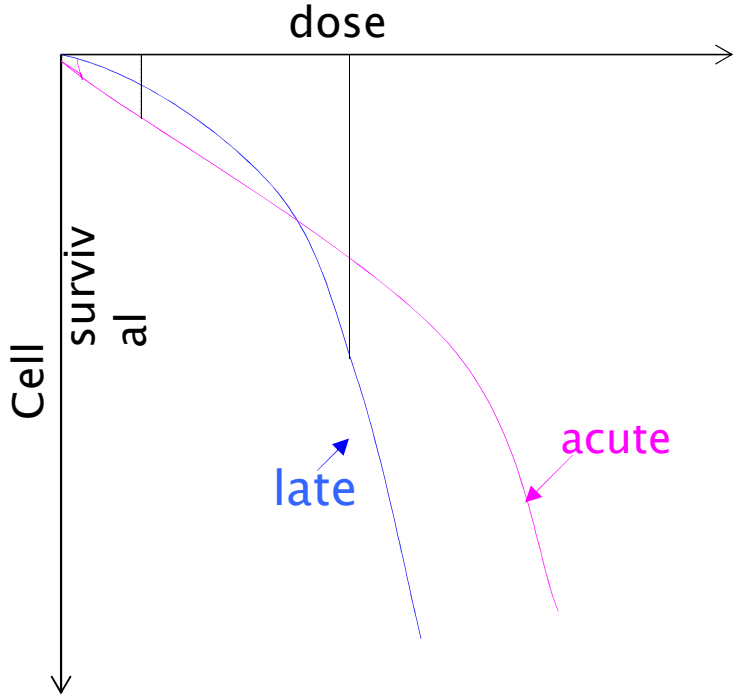


EXPLANATION FOR DIFF. IN SHAPE OF EARLY & LATE RESPONDING TISSUES

2. *Population proliferating so slowly that many cells are in early G_1 or not proliferating at all so that cells are in resting (G_0) phase.*
   - *Hence late responding normal tissue are resistant due to presence of many resting cells.*
   - *Such resistance disappears at high dose/#*

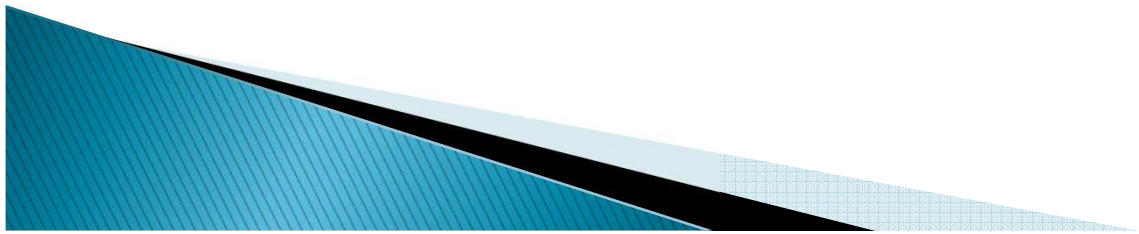
IMPLICATIONS

- *For early effects α/β is large, as a consequence α i.e. irreparable damage dominates at low doses & dose – response curve has marked initial slope & bends at higher doses.*
- *For late effects α/β is small ,i.e. β term (repairable damage) has an influence at low doses.*
- *Implications of diff. in shape of dose – response curves of early & late reacting tissues :-*
- *If fractionation regimen is changed from many small doses to few large dose fractions leads to severe late tissue toxicity.*
- *Late reacting tissues are more sensitive to changes in fractionation pattern than early responding tissue*



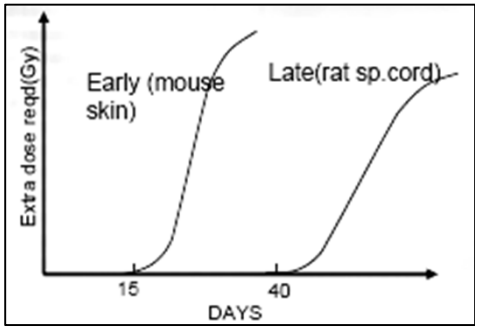
ADV. OF FRACTIONATION

- Acute effects of single dose of radiation can be decreased
- Pt.'s tolerance improves with fractionated RT
- Exploits diff. in recovery rate b/w normal tissues & tumors.
- Radⁿ induced redistribution & sensitization of rapidly proliferating cells.
- Reduction in hypoxic cells leads to –
  - Reoxygenation
  - Opening of compressed blood vessels
- Reduction in no. of tumor cells with each dose #



RADIATION RESPONSE

- Response of all normal tissues to rad^{n} is not same
- Depending on their response tissues are either
  - Early responding – constitute fast proliferating cells such as skin, mucosa, intestinal epithelium, colon, testis etc.
  - Late responding – have large no. of cells in the resting phase e.g. spinal cord, bladder, lung, kidneys etc.
- Early responding tissues are triggered to proliferate within 2-3wks after start of fractionated RT.
- Prolonging overall treatment time can reduce acute reactions without sparing late damage



VARIOUS FRACTIONATION SCHEDULES

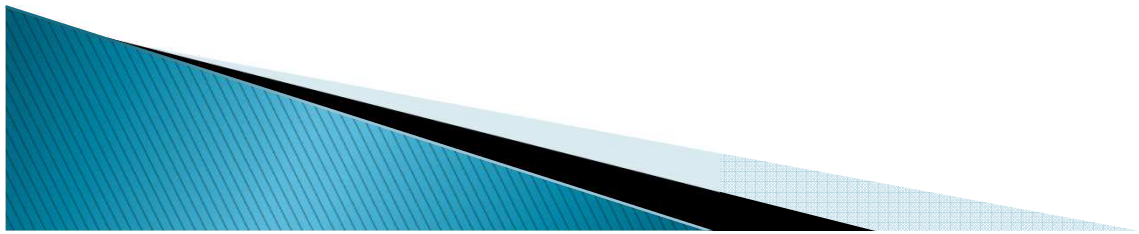
- *Fractionated radiation exploits difference in 4R's between tumors and normal tissue thereby improving therapeutic index*
- *Types*
  - *Conventional*
  - *Altered*
    - *Hyper fractionation*
    - *Accelerated fractionation*
    - *Split course*
    - *Hypofractionation*

Conventional fractionation

- Division of dose into multiple # spares normal tissue through repair of SLD b/w dose #s & repopulation of cells. The former is greater for late reacting tissues & the later for early reacting tissues.
- Concurrently , fractionation increases tumor damage through reoxygenation & redistribution of tumor cells.
- Hence a balance is achieved b/w the response of tumor & early & late reacting normal tissue.
- Most common fractionation for curative radiotherapy is 1.8 to 2.2Gy/#

CONVENTIONAL FRACTIONATION

- *Evolved as conventional regimen because it is*
  - *Convenient (no weekend treatment)*
  - *Efficient (treatment every weekday)*
  - *Effective (high doses can be delivered without exceeding either acute or chronic normal tissue tolerance)*
  - *Allows upkeep of machines.*
- *Rationale for using conventional fractionation*
  - *Most tried & trusted method*
  - *Both tumorocidal & tolerance doses are well documented*



HYPERFRACTIONATION

- *Rationale –*
  - *To take maximal adv. of diff. in repair capacity of late reacting normal tissue compared with tumors.*
  - *Radio sensitization through redistribution.*
- *Pure hyper fractionation – total dose & over all t/t same as conventional regimen but delivering dose in twice as many #s i.e. treating twice daily.*
- *Impure hyper fractionation - Since dose/# decreases hence total dose need to be increased.*

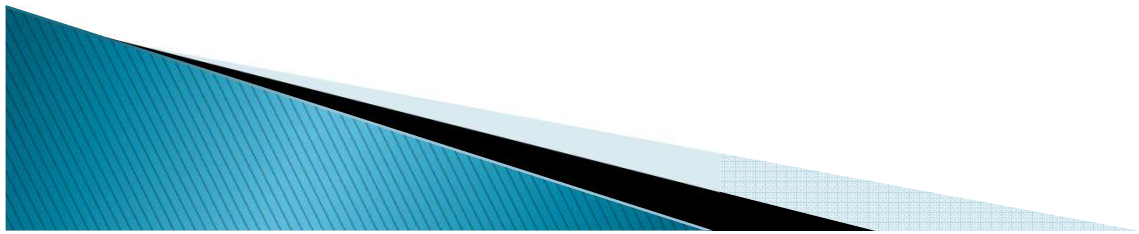
HYPERFRACTIONATION

- *A hyper fractionated schedule of 80.5Gy/70#(1.15Gy twice/day)/7wks compared with 70Gy/35#/7wks in head & neck cancer.*
- *Implications –*
  - *Increased local tumor control at 5yr from 40 to59%*
  - *Reflected in improved survival*
  - *No increase in side effects*

- **head and neck cancers and who are being treated with radiation therapy alone have improved local-regional control and no increase in late toxicity when radiation therapy is delivered twice a day in two smaller doses which we call hyperfractionation,”**
- **The results suggest that twice-daily radiation may improve cure and limit late side effects for patients. Twice-daily radiation might be worth considering in place of concurrent chemoradiotherapy for those patients who are at low risk for distant metastases and those patients who cannot tolerate systemic therapy.”**

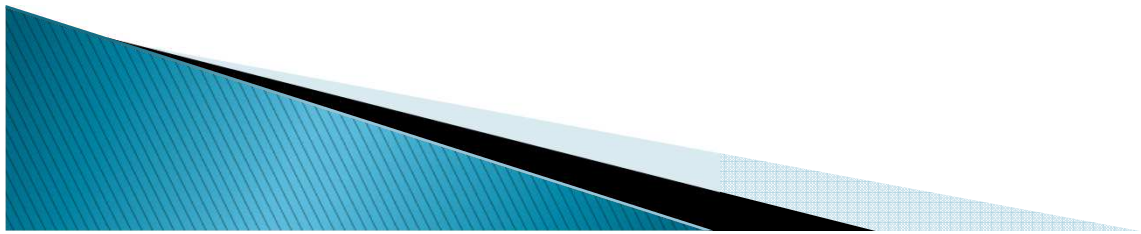
ACCELERATED TREATMENT

- *Alternative to hyper fractionation*
- *Rationale – To reduce repopulation in rapidly proliferating tumors by reducing overall treatment time.*
- *Pure accelerated treatment – same total dose delivered in half the overall time by giving 2or more #s/day. but it is not possible to achieve as acute effects become limiting factor.*
- *Impure accelerated treatment – dose is reduced or rest period is interposed in the middle of treatment.*



Types of accelerated fraction

- Multiple std # / day
- Comparison of head & neck cases accelerated regimen 72Gy/45# (1.6Gy,3#/day)/5wks with 70Gy/35#/7wks
- Implications –
  - 15% increase in loco regional control
  - No survival adv.
  - Increased acute effects
  - Unexpected increase in late complications



ACCELERATED TREATMENT

- Concomitant boost
  - Developed at M.D. Anderson cancer centre
  - Boost dose to a reduced volume given concomitantly , with t/t of initial layer volume
  - Conv 54Gy in 30 # over 6 wks & boost dose of 1.5 Gy per # in last 12 # with Inter # interval of 6 hr in last 12#
  - large field gets 54 Gy & boost field 72 Gy in 6 wks time
  - E.g. Head and Neck cancer

concomittant

- **2-year probability of local-regional disease control was 65% and of survival 55%. 14/53 patients sustained moderate to severe late complications:**

CHART

- Regimen conceived at Mount Vernon Hospital, London
- With CHART treatments 6hrs apart delivered 3times a day,7daya a wk. with dose # of 1.5Gy, total dose of 54Gy can be delivered in 36# over 12 consecutive days including weekends.
- This schedule was chosen to complete treatment before acute reactions start appearing i.e. 2wks
- Characteristics
  - Low dose /#
  - Short treatment time
  - No gap in treatment, 3#/day at 6hr interval
- Implications-
  - Better local tumor control
  - Acute reactions are brisk but peak after treatment is completed
  - Dose/# small hence late effects acceptable
  - Promising clinical results achieved with considerable trauma to pt.

CHART

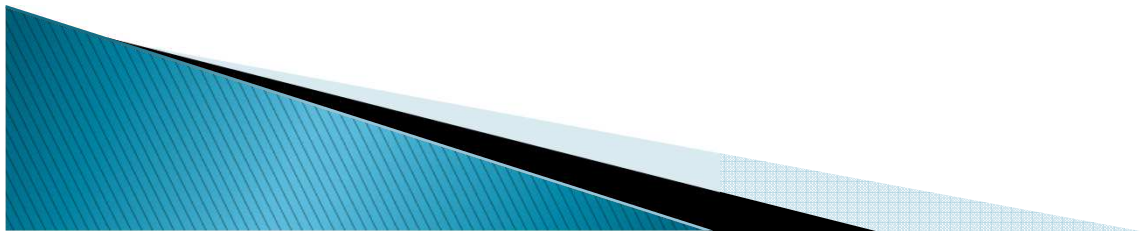
- **Similar local turnout control was achieved by CHART as compared with conventional radiotherapy despite the reduction in total dose from 66 to 54 Gy supporting the importance of repopulation as a cause of radiation failure. The effects seen in advanced laryngeal cancer and those related to histological differentiation need further study. Reduced late morbidity is a factor which together with patient preference should be considered in the decision as to the programme of radiotherapy to employ in the curative treatment of head and neck cancer.**

SPLIT-COURSE

- Total dose is delivered in two halves with a gap in b/w with interval of 4wks.
- Purpose of gap is
  - to allow elderly pts. to recover from acute reactions of treatment
  - to exclude pts. from further morbidity who have poorly tolerated 1st half or disease progressed despite treatment.
- Applied to elderly pts. in radical treatment of ca bladder & prostate & lung cancer.
- Disadv : impaired tumor control due to prolong T/T time that results in tumor cell repopulation

HYPOFRACTIONATION

- High dose is delivered in 2-3# / wk
- Rationale
  - Treatment completed in a shorter period of time.
  - Machine time well utilized for busy centers.
  - Higher dose /# gives better control for larger tumors.
  - Higher dose /# also useful for hypoxic fraction of large tumor.
- Disadv.
- Higher potential for late normal tissue complications.
- E.g. 50Gy/10#/5wks treating 2 days a wk in head & neck cancer.



5f/6f

- **Results : 5yrs LRC and DSS were 42% (6F) vs 30% (5F) (p=0.004) and 50% vs 40%(p=0.03). OS was trend to favor 6F/Wk but not statistical significant 35% vs 28%(p=0.07). No significant differences in late radiation side-effects**

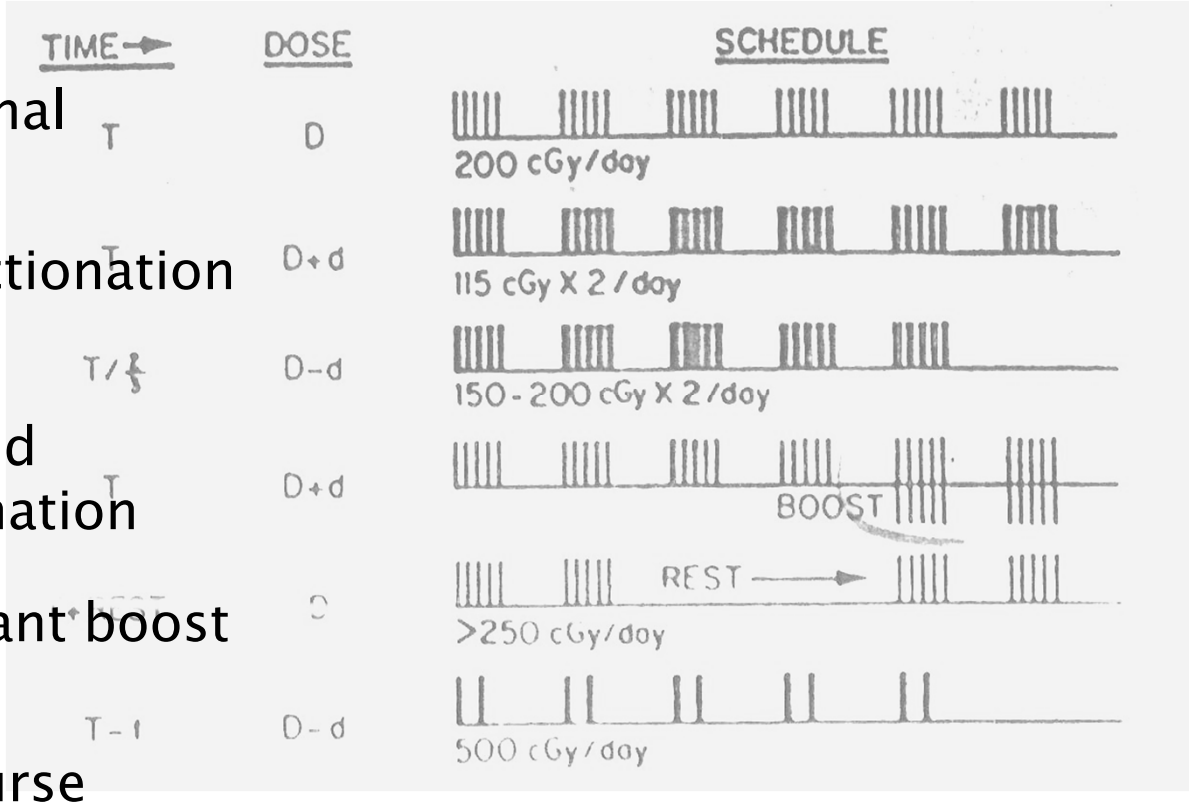
conventional

Hyper fractionation

Accelerated fractionation

Concomitant boost

Split – course



Hypo fractionation

THANK YOU