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 5 days 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 4 wks 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.
Cohen’s

- Cohen analyzed three different sets of data of skin damage with endpoints as weak or strong erythema and skin tolerance.
- Cohen found an exponent of 0.33 for skin erythema and skin tolerance and 0.22 for skin cancers.
- According to Cohen’s results, the relationship between total dose, overall treatment time for normal tissue tolerance, and tumor can be written as

\[ D_n = K_1 T^{0.33} \]

\[ D_t = K_2 T^{0.22} \]

Where \( K_1 \) and \( K_2 \) are proportionality constants. \( D_n \), \( D_t \), and \( T \) are normal tissue tolerance dose, tumor lethal dose, and overall treatment time respectively.

The exponents 0.33 and 0.22 of time factor represent the repair capabilities of normal tissue and tumor cells respectively.
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 3 hrs & 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.
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 for different 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 by approx. 20% in 1st week, 10% in 2nd week, 5% in 3rd week, but for acute reactions in skin & mucosa accelerated repopulation starts only after 2-3 wks 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.

\[ p \propto \frac{1}{D_o} \]

- Where \( 1/D_o \) is constant of proportionality.

\[ S = e^{-\left(\frac{D}{D_o}\right)} \]
**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 mammals cells only
- When cells are irradiated with high LET rad e.g. $\alpha$ - particles
- When cells irradiated are synchronized in most sensitive phases of cell cycle (late $G_2$ or $M$)
MULTITARGET THEORY

- According to this theory, some organisms contain more than one target to inactivate the organism each target should receive one hit.

- Survival curves corresponding to this theory start with less sensitive region at low doses and 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 rad\(^n\) 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.
  \[ E \propto D \quad E = \alpha D \]
  - Where \( \alpha \) is constant of proportionality
- Or it can be accomplished by independent interaction by two separate ionizing particles such that
  \[ E \propto D^2 \quad E = \beta D^2 \]

\[ S = e^{-\alpha D} \]

\[ S = e^{-\beta D} \]
**LINEAR QUADRATIC MODEL**

- Overall LQ eq. for cell survival is therefore
  \[ S = e^{(-\alpha D - \beta D^2)} \]
- This shows the two components to cell killing, \(\alpha\)-damage (irreparable) & \(\beta\)-damage (reparable) combine to form cell survival curve.
- \(D = \alpha / \beta\) is the dose at which log surviving # for \(\alpha\)-damage equals that for \(\beta\)-damage.
- Parameter \(\alpha / \beta\) represents curviness of cell survival curve.
- Higher the \(\alpha / \beta\), straighter is the curve & cells show little repair of SLD while low \(\alpha / \beta\) indicates high capability of repair.
- Tumor usually have high \(\alpha / \beta\) values in range of 5-20Gy (mean 10Gy) while late responding normal tissue have \(\alpha / \beta\) 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 intercompared
- \[ \text{BED} = \text{total dose} \times \text{relative effectiveness} \]

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

- Where
- \( n \) - no. of #s
- \( d \) - dose/#
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 $h/w$ effect & dose this translates into larger $\alpha/\beta$ 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 G₁ or not proliferating at all so that cells are in resting (G₀) 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 $\alpha/\beta$ is large, as a consequence $\alpha$ i.e. irreparable damage dominates at low doses & dose – response curve has marked initial slope & bends at higher doses.
- For late effects $\alpha/\beta$ is small ,i.e. $\beta$ 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 tissues.
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.
- Rad 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 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 & overall 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 to 59%
    - 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 2 or 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:
Regimen conceived at Mount Vernon Hospital, London

With CHART treatments 6hrs apart delivered 3times a day, 7 day 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 statistically 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