FRACTIONATION IN RADIOTHERAPY

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What is Fractionation in radiotherapy?

- When the total dose of radiation is divided into several, smaller doses over a period of several days,
Why Should we Fractionate?

Fractionation improves the therapeutic ratio, whereby complications are reduced and tumor kill is increased.
Let's take a crude Analogy to understand the importance of fractionation.
A trip by a fair skinned Pacific North westerner to Hawaii

Spent the entire first ten hour day snorkeling and surfing

Limited sun exposure to 30 minutes per day

Dividing Sun exposure into small amounts over a briefly extended period, instead of a large single exposure, can result in a more favorable outcome.
History Of Fractionation

Marie Curie

The discovery of radioactivity by Becquerel led to in 1898 the isolation of polonium, rare material found in the country of Marie's birth. Curie developed methods of isolating and refining radium from radioactivity samples, and was able to produce sufficient quantities for research. She later discovered the properties of radium, which she called radium, in particular.

Antoine Henri Becquerel

In 1896, decided to investigate whether there was a connection between X-rays and naturally occurring phosphorescence. He had inherited from his father a supply of uranium salts, which phosphoresce on exposure to light. When the salts were placed near to a photographic plate covered with opaque paper, the plate was discovered to be fogged.

Emil Grubbe

Medical Student in Chicago

March 29, 1896 in an X-ray Tube factory in Chicago he began to bombard rose Lee an elderly woman with recurrent breast cancer and had the first documented response to radiation.

(15 December 1852 – 25 August 1906) was a French physicist, Nobel laureate, and the discoverer of radioactivity along with Marie Sklodowska Curie and Pierre Curie, for which all three won the 1903 Nobel Prize in Physics.
History of Fractionation

- 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.
2 schools of thought about Fractionation

☐ ERLANGEN

Single dose was only necessary to cure cancer
   Fractionated treatments are inferior

☐ PARIS

He showed that a ram's testis could not be sterilized by a single fraction without causing significant skin reaction.

But sterilization was possible with fractionated RT without damage to scrotal skin.

   The reasoning was wrong. But conclusion stood valid.
Henry Coutard published his excellent results with fractionated RT in 1932.

- **The testes** --- model of a tumor. (many rapidly proliferating cells, like a cancer)
- **Surrounding skin** -- model for adjacent normal healthy tissue.

**Single dose:**
- Sterilization

**Skin damage**

**Multiple smaller:**
- Sterilization

**No skin damage**

**Fractionation of radiation produced better tumor control for a given level of normal tissue toxicity than a single large dose.**
Today’s Topics

- Rationale behind Radiation Fractionation
- Early vs Late responding tissues
- 4Rs of Radiotherapy and their implication in Fractionation
- Survival curve and a/b ratio
- Types of Fractionation
Rationale behind fractionation

- **GOAL**— Maximum Tumor Kill
  - Minimum Normal Tissue damage.

- There are differences in cell kinetics between Tumor cells and Normal cells.

- Hence, the effect of radiation is different in Tumor cells and Normal Cells.
Radiation Action

- Critical target in a biological system – DNA

- **Direct action** –
  Radiation interacts with critical target.
  Atoms of target get ionized & lead to biological damage

- **Indirect action** –
  Secondary e- interacts with e.g. water molecule to produce free radicals which damage DNA & produce biological changes.
Linear Quadratic Model

Single target, single hit (linear model)

- Only one target has to be inactivated.
- This target is considered to be two strands of DNA.
- Effect $\propto D$

$$S = e^{-D/D_0} = e^{-\alpha D}$$

- The $\alpha$ term represents the probability of inactivating a target directly by single hit, meaning two strands of DNA are hit by single exposure.

Single target, two hits (quadratic model)

- The term represents the inactivation of two strands of DNA by two different radiation events, each strand inactivation represents sublethal damage, interaction of which result into cell death. The sublethal damage may be repaired called Elkind's Recovery.

$$S = e^{-\beta D^2}$$

- Effect $\propto D^2$

S.F.

- Viable cells (no lesions)
- Lesions produced by irradiation
- Correct repair $\epsilon_L$
- Potentially lethal (i.e. repairable) lesions
- Binary misrepair $\epsilon_{SPL}$
- Lethal lesions (cell death)

The sum of the two processes of cell killing (linear and quadratic) will decide the final survival fraction.
Linear-Quadratic Model

- There are two components to cell killing by radiation
  1. proportional to dose (Linear)
  2. proportional to the square of the dose (Quadratic)

- \( S \) is the fraction of cells surviving a dose \( (D) \)

- \( \alpha \) and \( \beta \) are constants.

- The ‘Curviness’ is determined by \( \alpha/\beta \) ratio

- Better in the low dose–high survival region
Radiation Damages and REPAIR

- There are three types of damage that ionising radiation can cause to cells:
  - **Lethal Damage**: Irreversible and irreparable and leads irrevocably to cell death
  - **Potentially Lethal Damage (PLD)**: Can be modified by post irradiation environmental conditions
  - **Sublethal Damage (SLD)**: Under normal circumstances can be repaired in hours unless additional sublethal damage is added

Repair is the one of the primary reasons to fractionate radiotherapy.
Summery --- Rational of Fractionation

- There are differences in cell kinetics between Tumor and Normal cells.
- Hence, the effect of radiation is different in Tumor cells and Normal Cells.
- The goal is to achieve maximum tumor kill and minimum Normal Tissue damage.
- There are two components to cell killing by radiation:
  1. Proportional to dose (Linear)
  2. Proportional to the square of the dose (Quadratic)
- Repair of normal cells is the primary reason to fractionate radiotherapy.
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Early And Late Responding Tissues

- Responses to all the normal Tissues to radiation are not the same

- **Early responding** – constitute fast proliferating cells
  
  e.g. 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

Rapidly Proliferating—within 2 to 3 weeks of starting Fractionated radiotherapy

• May have a major portion of cells in S phase
  These cells are resistant because new cells offset those killed by dose fractions

Late Responding Tissues—

Slowly Proliferating Tissues

• Have large number of cells in Resting Phase, and are resistant G1
• Slowly growing cells with a long cell cycle may have a second resistant phase in early G1

Tumour Tissues—
Behave Like Early Responding Tissues
Spared by low dose per Fraction
Spared if overall Time is too Long
Dose Response Difference in Early and Late Responding Tissues

**Early Responding Tissues**

- Dose-response is Less curved
- **α/β is large**
  - α dominates at low doses
  - Linear and quadratic components of cell killing are not equal until about 10 Gy

**Late Responding Tissues**

- Dose-response is more curved
- **α/β is Small**
  - β term has an influence at low doses
  - Linear and quadratic components are equal at about 2 Gy

*Fraction size and overall treatment time* both affect acutely responding tissue as they Repopulate

Early reactions Reduced by
- Lengthening Over all time
- Fractionating with 5 to 6 Hrs between

**Fraction size is the dominant** in determining late effects;
**Overall treatment time** has little influence

If fewer and larger dose fractions are given, late reactions are more severe

Late Reactions Reduced by
- Reducing Dose Per Fraction
Effect of dose change in Early and Late Responding Tissues

- As Dose/# Increases from D1 to D2, SF reduces more in Late reacting tissues.
- More cell killing seen in Late reacting tissues than Early reacting Tissues.
- Changes in dose/# damages the late responding tissues more than Early responding Tissues.
Tissues respond differently to changes in fractionation.

Late-responding normal tissues are more sensitive to changes in fractionation (small $\alpha/\beta$) than are early-responding tissues such as tumors (large $\alpha/\beta$).
Summery – Early vs Late Responding Tissues

- **Early Responding Tissues** are Rapidly Proliferating and Late Responding are slow proliferating.
- Tumor Tissues behave like early responding Tissues.
- Dose response is less curved in ERT than LRT.
- a/b large in ERT and small in LRT – Low a/b → high capability of SLD repair.
- Changes in dose/# damages the LRT more than ERT.
- Fraction size and overall treatment time both affect ERT as they Repopulate.
- Fraction size is the dominant and Overall treatment time has little influence in LRT.

- Early reactions Reduced by Lengthening Overall time.
- Late Reactions Reduced by Reducing Dose Per Fraction.
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4 Rs Of Radiotherapy

- Repair of sublethal damage by Normal Cells
- Repopulation of normal Healthy Cells
- Redistribution of Tumor Cells in More Radiosensitive phases the cell cycle
- Re oxygenation Of Tumor Cells

These are radiobiological mechanisms that impact the response to a fractionated course of radiation therapy
4Rs OF DOSE FRACTIONATION

1. Repair of sublethal DNA damage by normal cells. Normal cells have better DNA repair. Fractionation allows normal cells to repair sublethal DNA damage.

- spares late responding normal tissue preferentially

2. Repopulation of normal healthy cells. Fractions allows normal cells to grow, divide, and continue normal function.

spares acute responding normal tissue, no effect on late effects,
- danger of tumor repopulation

3. Redistribution of tumor cells into more radiosensitive phases of the cell cycle. Between treatments, some proportion of cancer cells enter into a more sensitive phase, rendering them more susceptible to radiation damage.

increases acute and tumor damage, no effect on late responding normal tissue

4. Reoxygenation of tumor cells. Radiation damage to the DNA of cancer cells occurs through free radical, that is enhanced by oxygen. Fractions allows oxygenation of hypoxic areas of tumor, leading to an enhanced effect of radiation in the tumor.

increases tumor damage, no effect in normal tissues
**4^th R – Re-oxygenation**

- O2 – most powerful radiation sensitizer.
- Hypoxic cells relatively radio resistant
- Increase in dose- would exceed Normal tissue tolerance.

When time given between exposures

- decrease in the no of hypoxic cells

- can be handled by a dose without exceeding tolerance.
Summery--Basics of Fractionation

- Dividing a dose into several fractions *spares normal tissues*
  - Repair of sublethal damage between dose fractions
  - Repopulation of normal cells

- Dividing a dose into several fractions *increases damage to the tumor*
  - Redistribution of cells into radiosensitive phases of the cell cycle between dose fraction
  - Reoxygenation of tumor environment

- Prolongation of treatment reduces early reactions

- However, excessive prolongation allows surviving tumor cells to proliferate
Answering The Question---- Why Should We Fractionate?

- Must fractionate treatment
  * to overcome hypoxia
  * for differential response with late effects

- Must prolong treatment
  * to limit early sequelae

- Would like to shorten treatment
  * to prevent accelerated tumour cell repopulation
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Survival curve and a/b
The dose at which contribution in cell kill by Both Single Hit and Double Hit are equal

Represents the point beyond which the curve becomes a straight line And predominantly Double Hit Take place

Indicates capability of tissue to repair SLD

Low $a/b$ → high capability of repair

Small $a/b$ means a curvy, narrow shoulder (late responding Tissue)

Large $a/b$ means less curvy, Broad shoulder (Early Responding tissues)
- **Tumor cell** (High a/b) --> straighter curve.
- **Late reacting Normal tissue** (low a/b) --> curvier
- 2 curves for normal tissue and tumor cross at 2 to 5 Gy.
- Below the **cross over dose** normal cells have increased survival. Above --> the tumour.

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**Normal Tissues—Low a/b—curvier survival curve—Higher SLD Repair**

**Tumour Cells—High a/b—straight survival curve—Low SLD Repair**
If the dose for each # is below the cross over value, there is increased tumor cell damage and death with each fraction. Hence the curves separate from each other.

The optimal dose/# is that which produces max separation of the 2 curves.

This occurs at around 50% of the cross over dose.

So optimal dose/# is 1 to 2.5 Gy.
Survival Curve

- But doses >5 Gy is required for tumor cell kill
- And, delivery of dose >5 Gy is destructive to Normal tissue than tumor cells.

- 2 ways:
  1. To deliver high doses to tumor alone and avoiding the normal tissues by techniques like SRS.
  2. To fractionate....
• With fractionated RT, if sufficient time is allowed between fractions, all SLD cells would be repaired before next exposure.

• So surviving fraction (SF) for each successive treatment would be identical.

• Hence the shape of the Survival Curve would repeat for each fraction.

• The effective dose-survival curve becomes an exponential function of dose.

• Very low Dose /#, repair takes place during radiotherapy and reduces cell death due to SLD and show reduced effectiveness.
Summery-

- **a/b- Dose at which Both Single Hit and Double Hit are equa**
  
  - **a/b Indicates capability of tissue to repair SLD**
  
- **LRT-** Small a/b — curvy, narrow shoulder — High capability of SLD Repair

- **ERT-** Large a/b – less curvy, Broad shoulder -- Low capability of SLD Repair

- 2 curves for normal tissue and tumor cross at **2 to 5 Gy**

- Below this dose, there is increased tumor cell damage and increased Normal cell survival— WINDOW OF OPPORTUNITY— CURVES SEPARATE MAXIMUM

- **This is achieved by fractionation/SRS**

- With fractionated RT, if sufficient time is allowed between fractions, all SLD cells would be repaired before next exposure
Summery

- The repopulation principle dictates that a course of RT should not be overly prolonged.
- Acutely responding normal tissues need to repopulate during RT to avoid acute toxicity.
- It should not allow tumor repopulation,
- The reduction of fraction size is to protect normal late responding tissues, but the fraction number is increased.
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FRACTIONATION TYPES

Fractionation exploits difference in 4R’s between tumors and normal tissue thereby improving therapeutic index

- Conventional

- Altered
  - Hyper fractionation
  - Accelerated fractionation
  - Split course
  - Hypo fractionation
Conventional Fractionation

- Division of dose into multiple Fractionation.
- Spares normal tissue through repair of SLD & repopulation of cells.
- Concurrently, fractionation increases tumor damage through reoxygenation & redistribution of tumor cells.
- Hence a balance is achieved the response of tumor & early & late reacting normal tissue.
- Most common fractionation for curative radiotherapy is 1.8 to 2.0 Gy per fraction
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 tumoricidal & tolerance doses are well documented
HYPOFRACTIONATION

- Fraction Size – Increased > 2 Gy/per fraction.
- Fraction Number – Decreased
- Total treatment Time - Decreased

**Rationale**

Treatment completed in a shorter time.
Higher dose/# gives better control for larger tumors.
Higher dose/# also useful for hypoxic fraction of large tumor.

**Disadvantage**-

Higher potential for late normal tissue complications.

**Palliative**-

Total dose is lower than curative dose. Eg. 3 Gy x 10 Fx.

**Curative**

Stereotactic Radiosurgery: single dose
HYPERFRACTIONATION

- Fraction Size—**Decreased**  < 1.8 Gy/fraction, usually 1.15-1.6 Gy
- Fraction number—**Increased**
  
  Usually treat more than 1 fraction/per day.
- Total treatment Time—**same**
- Rationale : - Since smaller fraction size.

  - Spare normal tissue (late complication tissue)
  - Tumor control probability is expected to increase but same possibility of late complications.

Hyperfractionation

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<tr>
<th>Hyperfractionation</th>
<th>115 cGy X 2 per day; 5 days a week.</th>
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Hyper-fractionation

- **Pure hyper fractionation** – total dose & over all treatment time same as conventional but dose delivered in twice as many fractions i.e. treating twice daily.

- **Impure hyper fractionation** - Since dose/# decreases hence total dose need to be increased.

  - 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
ACCELERATED FRACTIONATION

- **Fraction size**— *Same* 1.8 – 2 Gy
- **Fraction number**— *Same*
- **Total treatment time**— *Short*
  - Eg. twice per day, or > 5 fractions/per week
- **Rationale**: *reduce tumor repopulation during RT.*
- **Disadvantage**: *Severe acute reaction.*
- **Pure accelerated treatment** – same total dose delivered in half the overall time by giving 2 or more fractions/day. *Severe acute effects are limiting factor.*
- **Impure accelerated treatment** – dose is reduced or rest period is interposed in the middle of treatment.
Accelerated fractionation-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
CHART (Continuous hyperfractionated, accelerated radiotherapy)

- Fraction Size—**Decreased** 150 cGy/Fx. 3 fx./day, W1-7, total dose = 54 Gy.
- Fraction Number—**Increased**
- Total treatment time: **Decreased**, No Gap in treatment. 12 days.
- Rationale—Reduce repopulation
  - Acute reactions are brisk but peak after treatment is completed
  - Dose/Fraction is small hence late effects acceptable

- Results:
  - Increased acute toxicity.
  - Late complications: not increased except spinal cord.
  - Similar or slightly better local control for different types of tumor.
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
  - further morbidity who have poorly tolerated or disease progressed despite treatment.
- Applied to elderly pts. in radical treatment of ca bladder & prostate & lung cancer.
The parameters that determine the N tissue tolerance are:

- Overall Treatment Time
- Total Dose
- Dose per fraction
- Frequency of fractionation

**IMPORTANCE**

1. To calculate new total dose required to keep biological effectiveness when conventional fractionation is altered.
2. To compare different treatment fractionation schedules
3. To strive for optimal fractionation regimen.
Advantages Of Fractionation

- Acute effects of single dose of radiation can be decreased
- Tolerance improves with fractionated RT
- Exploits difference in
  - Recovery rate between normal tissues & tumors.
  - Radiation 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 #
THANK YOU