Time, Dose and Fractionation in Radiotherapy

The introduction of Fractionation

The Four Rs of Radiobiology

• Efficacy of fractionation based on the 4 Rs:
  - Repair of sublethal damage
  - Repopulation
  - Reassortment of cells within the cell cycle
  - Reoxygenation

Repair of Sublethal Damage

• Cells exposed to sparse radiation experience sublethal injury that can be repaired
• Cell killing requires a greater total dose when given in several fractions
• Most tissue repair occurs in about 3 hours and up to 24 hours post radiation
• Allows for repair of injured normal tissue and gives a potential therapeutic advantage over tumor cells

Reoxygenation

• Oxygen stabilizes free radicals
• Hypoxic cells require more radiation to kill
• Hypoxic tumors
  - Temporary vessel constriction
  - Outgrowth of blood supply and capillary collapse
• Tumor shrinkage reduces hypoxic areas
• Reinforces fractionated dosing

Redistribution

• Position in cell cycle at time of radiation determines sensitivity
• S phase is radiosensitive
• G₂ phase delay results in increased radiation resistance
• Fractionated RT redistributes cells
• Rapidly cycling cells like mucosa, skin are more sensitive
• Slower cyclers like connective tissue, brain are spared
Repopulation
• Increased regeneration of surviving fraction
• Rapidly proliferating tumors regenerate faster
• Determines the length and timing of therapy course
• Accelerated Repopulation

Basics of Fractionation
• Dividing a dose into several fractions spares normal tissues
  - Repair of sublethal damage between dose fractions
  - Repopulation of cells
• Dividing a dose into several fractions increases damage to the tumor
  - Reoxygenation of tumor environment
  - Reassortment of cells into radiosensitive phases of the cell cycle between dose fraction
• Prolongation of treatment reduces early reactions
• However, excessive prolongation allows surviving tumor cells to proliferate

Impact of the 4Rs
• Inherent radiosensitivity/repair capacity will make a tumor either sensitive or resistant to therapy, or a normal cell more or less prone to radiation-induced damage
• Reoxygenation of tumor during radiotherapy will have a net sensitizing effect
• Redistribution in the cell cycle is used to advantage in fractionated radiotherapy
• Repopulation
  - Has the net effect of making the tumor seem more resistant
  - Is a way for normal cells to recover from acute radiation reactions

The Time Scale of the 4 Rs
• Repair = fast
• Reoxygenation and redistribution = moderate
• Repopulation = slow

Early vs. Late Responding Tissues
• In normal tissue, there is a clear difference between tissues that are early responding and those that are late responding
• Early-responding tissues are triggered to proliferate within a few weeks of the start of fractionated radiation
• Prolongation of radiotherapy has little sparing effect on late responding tissues

Dose Response for Early and Late Responsive Tissues
• If fewer and larger dose fractions are given, late reactions are more severe
• Dose-response for late-responding tissues is more curved
• For early effects, \( \alpha/\beta \) is large
  - \( \alpha \) dominates at low doses
  - Linear and quadratic components of cell killing are not equal until about 10 Gy
• For late effects, \( \alpha/\beta \) is small
  - \( \beta \) term has an influence at low doses
  - Linear and quadratic components are equal at about 2 Gy
Early vs. Late Responding Tissues and Radiosensitivity

• Cells are most resistant in late S phase
  - Rapidly proliferating cells may have a major portion of cells in S phase
  - These cells are resistant because new cells offset those killed by dose fractions
• Slowly growing cells with a long cell cycle may have a second resistant phase in early G2
  - A slowly proliferating population may have many cells in early G2 or not proliferating at all (resting cells)
  - Many late-responding normal tissues are resistant because of the presence of many resting cells
• Applies to small doses per fraction and disappears at higher doses per fraction

Radiation therapy fractionation schedule

Conventional Fractionation

Hyperfractionation

To further reduce late effects, some or slightly increased early effects
Achieve the same or better tumor control

Accelerated Treatment
Continuous Hyperfractionated Accelerated Radiation Therapy (CHART)

Characteristic radiographic findings

Early vs. Late Responding Tissues and Radiosensitivity

• Fraction size is the dominant factor in determining late effects; overall treatment time has little influence.

• Fraction size and overall treatment time both determine the response of acutely responding tissue

Treatment: 60 Gy/3 fractions

Review of Cell Survival Curves Following Radiation

• For survival curve:
  - \( S = e^{-\alpha D - \beta D^2} \)
  - Where \( S \) is the fraction of cells surviving a dose \( D \)
  - \( \alpha \) is the number of logs of cell kill per Gy from the linear portion of the curve
  - \( \beta \) is the number of logs of cell kill per Gy² from the quadratic portion of the curve

• Linear and quadratic components of cell kill are equal at \( D = \alpha / \beta \)
Fractionated Radiation Survival Curves

- Shoulder of curve is repeated
- Effective dose-survival curve for multi-fractionation
  - an exponential function of dose
  - i.e. a straight line from the origin through a point on the single dose survival curve

Biologically Effective Dose (BED)

\[ \text{BED} = (nd)(1 + \frac{d}{\alpha/\beta}) \]

Using the linear-Quadrant concept to calculate BED

Conventional Treatment

- If we assume the \( \alpha/\beta \) is 3 Gy for late-responding tissue and 10 Gy for early-responding tissue, then:
- 30 fractions of 2 Gy given one fraction per day, 5 days per week for an overall treatment time of 6 weeks:
  \[ E = (nd) \left(1 + \frac{d}{\alpha/\beta}\right) \]
  Early effects: \( = 60 \left(1 + \frac{2}{10}\right) \)
  \( = 72 \text{ Gy} \)
  Late effects: \( = 60 \left(1 + \frac{2}{3}\right) \)
  \( = 100 \text{ Gy} \)

Example Calculation

Hyperfractionation

- 70 fractions of 1.15 Gy given twice daily, 6 hours apart, 5 days per week for an overall treatment time of 7 weeks:
  Early effects: \( = 80.5 \left(1 + \frac{1.15}{10}\right) \)
  \( = 99.8 \text{ Gy} \)
  Late effects: \( = 80.5 \left(1 + \frac{1.15}{3}\right) \)
  \( = 111.4 \text{ Gy} \)
  i.e. this treatment regime is more effective than the conventional 60 Gy for both early and late effects
Retreatment after Radiotherapy

Factors must be taken into account in retreatment

- Dose and volume treated in the past and the overlap with initial field
- Chemotherapy in the past
- The time interval
- Critical structures involved
- RT technique to be used in retreatment
- Any alternative

Recovery of early and late responding tissues

- early responding tissues recover well from initial radiation and will tolerate re-irradiation to almost full dose, such as skin reaction
- animal studies showed the late responding tissues such as spinal cord do recover from prior radiation, probably need longer time

Clinical experiences

- Spinal cord
- Brain
- Head and neck
- Rectum
- Bone
- Breast
- Lung

The need for retreatment

1. Tumor recurrence
2. Second tumor
   - bad lifestyle
   - genetic predisposition
   - treatment-induced

SBRA case in an 88 year old non-smoker, p16 + L Tonsil cancer recurred

- 8 Gy/fraction x 5
- Treatment every 3rd day
- KPS 90%, no weight loss, no swallowing issues
- Ipsilateral tx only
Rapid dose fall-off Oral cavity constraints


SBRA is applicable for many different situations

- 86 yo woman with recurrent oral cavity cancer
- Treated to 40 Gy at 8 Gy/fraction
- Note CT and PET 3 months post SBRA

Treatment response

A B C D

MULTIDISCIPLINARY HEAD\&NECK CANCER SYMPOSIUM
Alternative Radiation Modalities

- Fast neutrons
- Boron neutron capture
- Protons
- Carbon ion

Putative advantages of alternative radiation modalities

- Better physical dose distribution
- Advantageous radiobiologic properties
  - Higher LET
  - Higher RBE
  - Lower OER
  - Little sublethal damage repair
  - Less variation of sensitivity through the cell cycle

Fast neutrons

- Indirectly ionizing
- Giving up energy to producing recoil protons, a-particles and heavier nuclear fragments
- Higher RBE, reduced OER, no sublethal damage repair, no variation of sensitivity through cell cycle
- Better local control in salivary gland tumor, but at the expense of normal tissue damage
Boron neutron capture therapy

- To deliver a drug-containing boron that localizes only in the tumor, then treat with low-energy thermal neutrons that interact with boron to produce short-range, densely ionizing α-particles
- Where is the magic drug?
- Poor penetration with thermal neutrons

Protons

- RBE and OER of protons are not different from that of 250-kv x-rays
- Unique depth-dose patterns and Bragg peak

Carbon ion radiotherapy

- Similar depth-dose profile and Bragg peak as protons
- Higher LET
- Lower OER
- Loss of repair capacity
- Smaller variation in radiosensitivity through cell cycle
- Increase in RBE toward the end of particle range
- Target volume can be visualized by PET
Increase in RBE toward the end of particle range