2-13/13 Radiobiology lecture

Time, Dose and Fractionation in Radiotherapy

The introduction of Fractionation

FIGURE 23.1 Conventional multifraction radiotherapy was based on experiments performed in Paris in the 1920s and in the 1930s. Rams could not be sterilized with a single dose of x-rays without extensive skin damage, whereas if the radiation were delivered in daily fractions over a period of time, sterilization was possible without skin damage. The testes were regarded as a model of a growing tumor and skin as dose-limiting normal tissue.

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

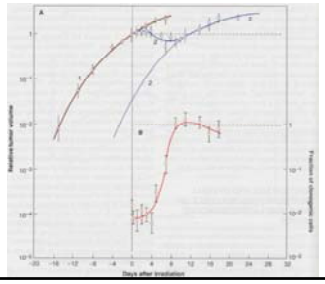
- Oxygen stabilizes free radicals
- Hypoxic cells require more radiation to kill
- Hypoxic tumors
  - Temporary vessel constriction
  - Outgrowth of blood supply and capillary collapse
- Tumor shrinkage reduces hypoxic areas
- Reinforces fractionated dosing

Redistribution

- Position in cell cycle at time of radiation determines sensitivity
- S phase is radioresistant
- G_2 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



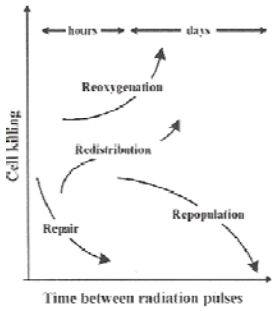
Basics of Fractionation

- 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

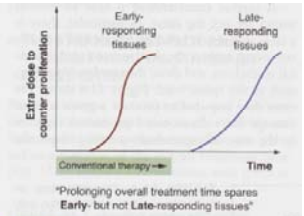
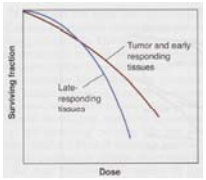


FIGURE 23.5 Highly speculative illustration attempting to extrapolate the experimental data for early- and late-responding tissue in rats and mice to principles that can be applied in clinical radiotherapy. The extra dose required to counter proliferation in early-responding tissues begins to increase after a few weeks into a fractionated regimen, certainly during the time course of conventional therapy. By contrast, conventional protocols are never sufficiently long to include the proliferation of 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

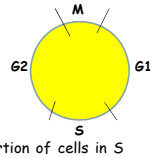
Dose Response for Early and Late Responsive Tissues



	α/β, Gy
Early	
Skin	9–12
Jejunum	9–10
Colon	10–11
Brain	12–13
Cartilage	9–10
Late	
Spinal cord	1.5–2.5
Kidney	1.5–2.5
Lung	2.5–4.5
Bladder	5.1–7

- 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, α/β is large
  - α dominates at low doses
  - Linear and quadratic components of cell killing are not equal until about 10 Gy
- For late effects, α/β is small
  - β 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 G_1
  - A slowly proliferating population may have many cells in early G_1 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

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

Radiation therapy fractionation schedule

Conventional Fractionation

Hyperfractionation

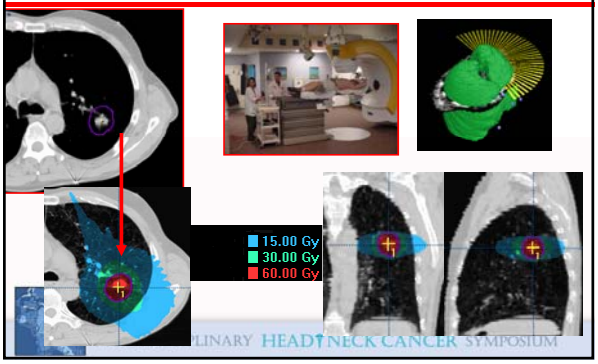
To further reduce late effects, same or slightly increased early effects
Achieve the same or better tumor control

Accelerated Treatment

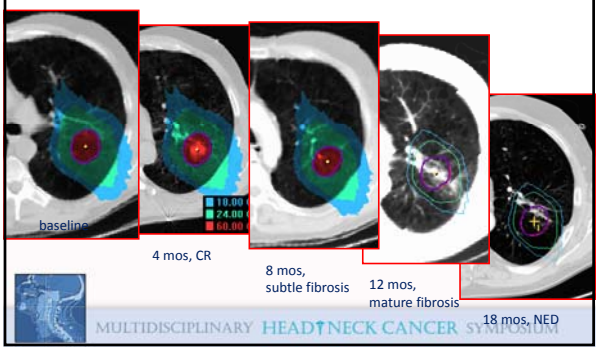
Continuous Hyperfractionated Accelerated Radiation Therapy (CHART)

Hypofractionation

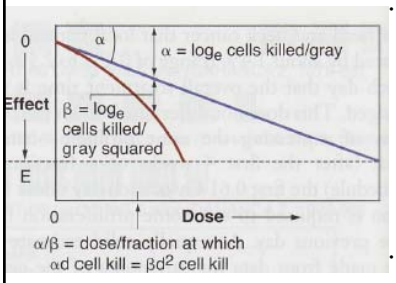
Treatment: 60 Gy/3 fractions



Characteristic radiographic findings

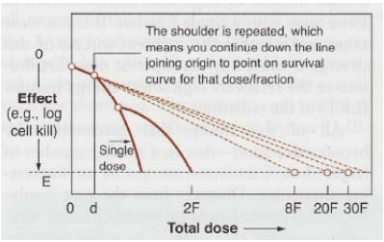


Review of Cell Survival Curves Following Radiation



- $S = e^{-\alpha D - \beta D^2}$
  - Where S is the fraction of cells surviving a dose D
  - α is the number of logs of cell kill per Gy from the linear portion of the curve
  - β is the number of logs of cell kill per Gy^2 from the quadratic portion of the curve
- Linear and quadratic components of cell kill are equal at D=α/β

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)

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

Using the linear-Quadrant concept to calculate BED

Conventional Treatment

- If we assume the α/β 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 and overall treatment times of 6 weeks:

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

Early effects $= 60\left(1+\frac{2}{10}\right)$

$= 72\ Gy_{10}$

Late Effects $= 60\left(1+\frac{2}{3}\right)$

$= 100\ Gy_{3}$

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: $= 80.5\left(1+\frac{1.15}{10}\right)$

$= 89.8\ Gy_{10}$

Late effects: $= 80.5\left(1+\frac{1.15}{3}\right)$

$= 111.4\ Gy_{3}$

i.e this treatment regime is more effective than the conventional 60 Gy for both early and late effects

Retreatment after Radiotherapy

The need for retreatment

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

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

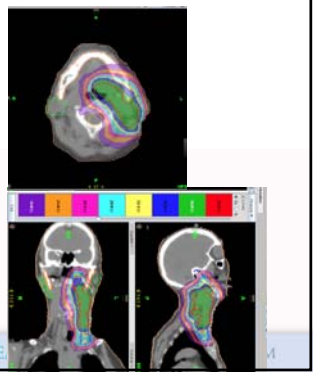
- early responding tissues recover well from initial radiation and will tolerate re-irradiation to almost full dose, such as skin reaction
- animal studies showed the late responding tissues such as spinal cord do recover from prior radiation, probably need longer time

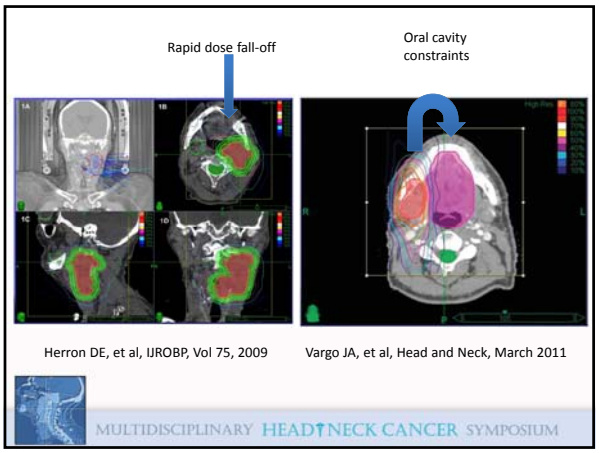
Clinical experiences

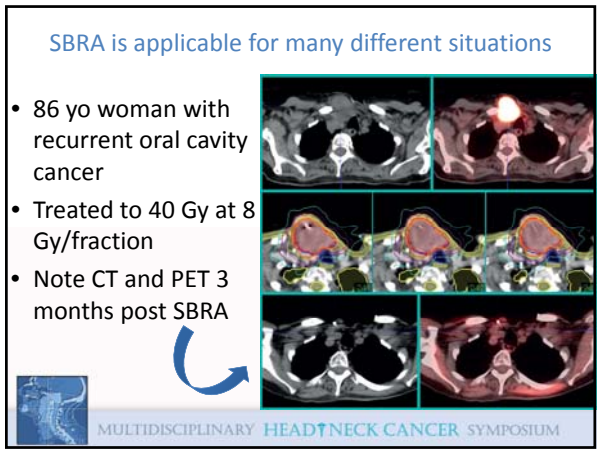
- Spinal cord
- Brain
- Head and neck
- Rectum
- Bone
- Breast
- lung

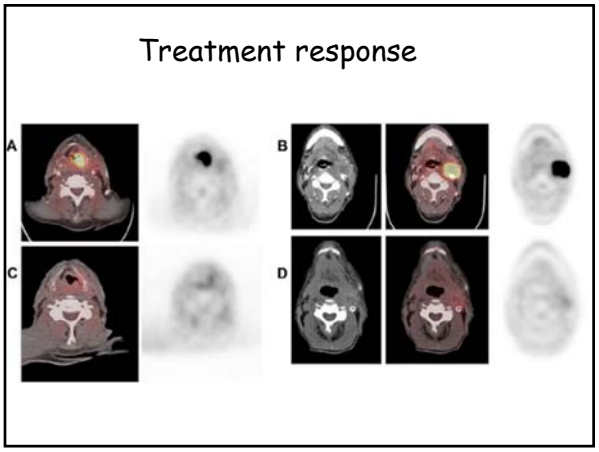
SBRA case in an 88 year old non-smoker, p16 + L Tonsil cancer recurred

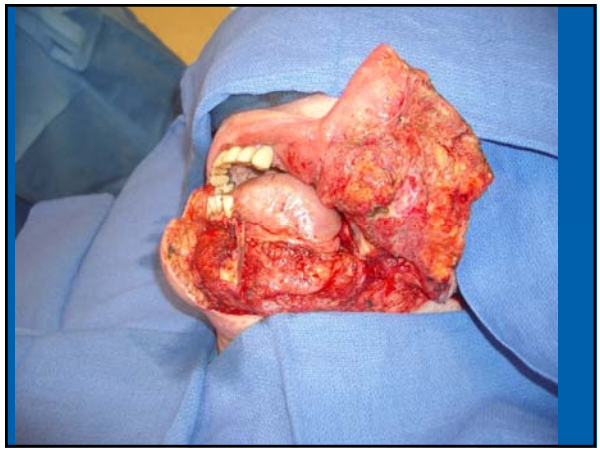
- 8 Gy/fraction x 5
- Treatment every 3rd day
- KPS 90%, no weight loss, no swallowing issues
- Ipsilateral tx only

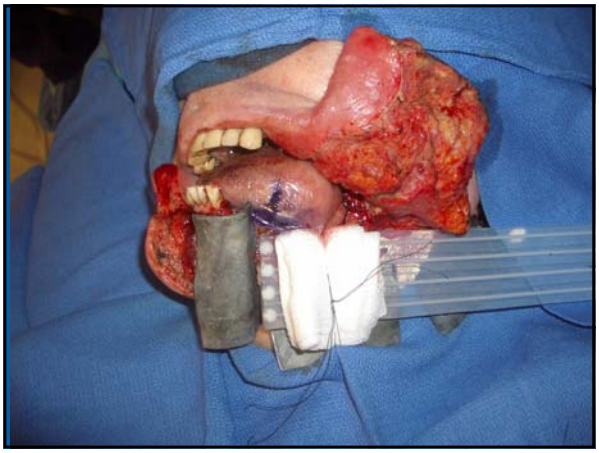


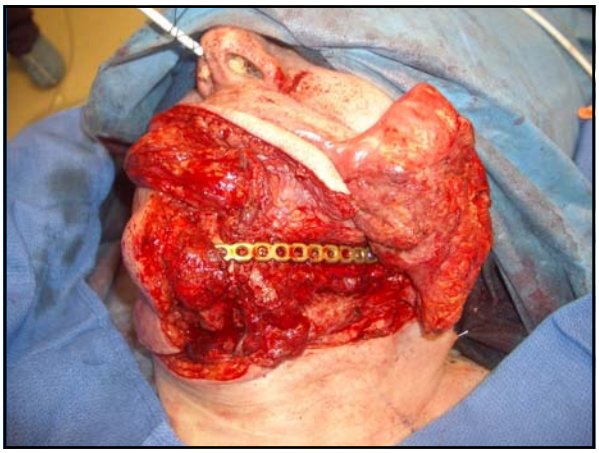

Rapid dose fall-off
Oral cavity constraints
Herron DE, et al, IJROBP, Vol 75, 2009
Vargo JA, et al, Head and Neck, March 2011
MULTIDISCIPLINARY HEAD&NECK CANCER SYMPOSIUM

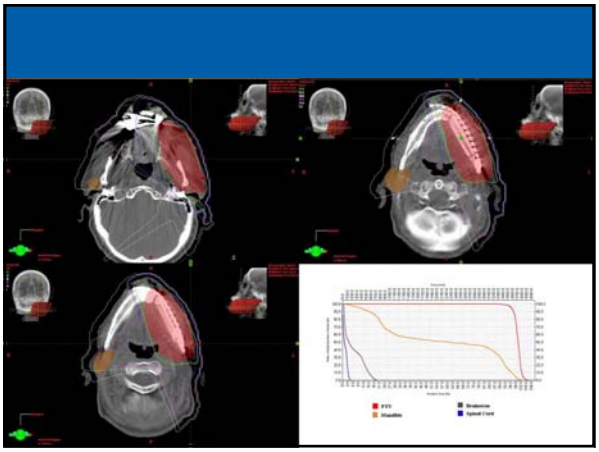

SBRA is applicable for many different situations
• 86 yo woman with recurrent oral cavity cancer
• Treated to 40 Gy at 8 Gy/fraction
• Note CT and PET 3 months post SBRA
MULTIDISCIPLINARY HEAD&NECK CANCER SYMPOSIUM


Treatment response
A
B
C
D









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 neurons

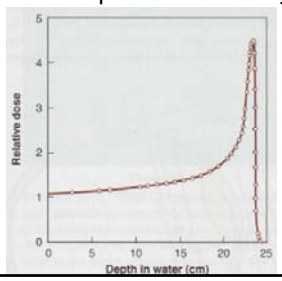
- Indirectly ionizing
- Giving up energy to producing recoil protons, a-particles and havier nuclear fragments
- Higher RBE, reduced OER, no sublethal damage repair, no variation of sensitivity through cell cycle
- Better local control in salivary gland tumor, but at the expense of normal tissue damage

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 a-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



Spread out of the Bragg Peak

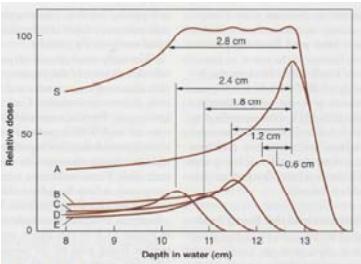


FIGURE 25.3 The way the Bragg peak for a proton beam can be spread out. Curve *A* is the depth-dose distribution for the primary beam of 160-MeV protons at the Harvard cyclotron, which has a half-width of only 0.6 cm. Beams of lower intensity and shorter range, as illustrated by curves *B*, *C*, *D*, and *E*, can be added to give a composite curve *S*, which results in a uniform dose of more than 2.8 cm. The broadening of the peak is achieved by passing the beam through a rotating wheel with sectors of varying thickness. (Adapted from Koehler AM, Preston WM. Protons in radiation therapy. Comparative dose distributions for protons, photons and electrons. Radiology 1972;104:191–195 with permission.)

Choroidal melanoma proton therapy

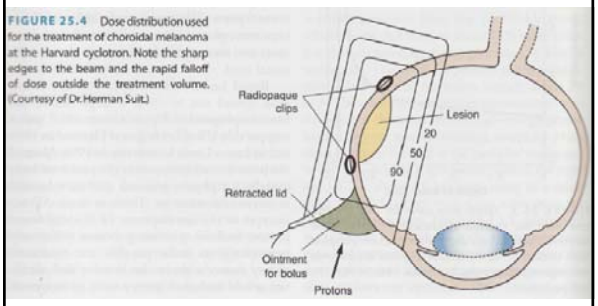


FIGURE 25.4 Dose distribution used for the treatment of choroidal melanoma at the Harvard cyclotron. Note the sharp edges to the beam and the rapid falloff of dose outside the treatment volume. (Courtesy of Dr. Herman Suit.)

IMRT and proton treatment plan comparison

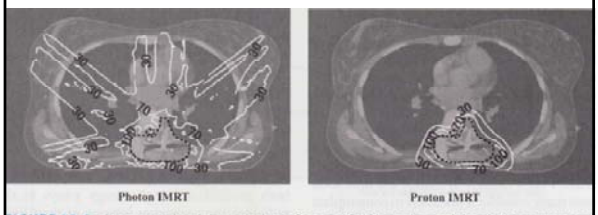
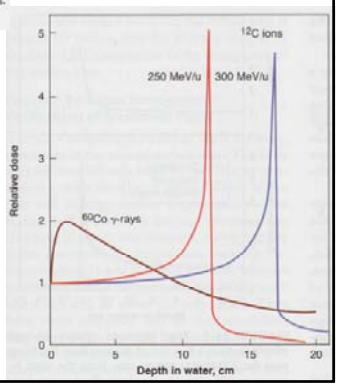


FIGURE 25.6 Treatment planning comparison of a seven-field intensity-modulated photon treatment plan **(left)** with an intensity-modulated proton (three scanned pencil beams) plan **(right)** for a patient with an epithelioid sarcoma involving the paravertebral tissues adjacent to the fifth through seventh vertebrae

Carbon ion radiotherapy

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

FIGURE 25.7 Comparison of the depth-dose profiles of carbon ions of two different energies with that of cobalt-60 γ-rays. (Adapted from Kraft G. Tumor therapy with heavy charged particles. *Prog Part Nucl Phys.* 2000;45:S473–S544.)



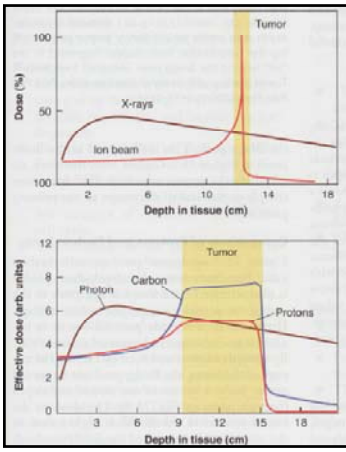


FIGURE 25.8 Illustrating the depth-dose profiles for protons and carbon ions compared with conventional high-energy photons. **Top panel:** Both protons and carbon ions are characterized by a sharp Bragg peak at the end of the particles' range, but it is too sharp and too narrow to encompass a tumor of realistic size. **Bottom panel:** By using a range shifter, or by varying the energy of the beam, the Bragg peak can be spread out to encompass a tumor of any size at any depth. For both protons and carbon ions, the dose to the tumor, located in the SOBP, is higher than in the normal tissue ahead of the SOBP, but the differential is greater for carbon ions because part of the radiation dose in the SOBP has a high LET and has a correspondingly higher RBE.

Increase in RBE toward the end of particle range