Clinical Radiobiology

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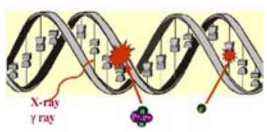
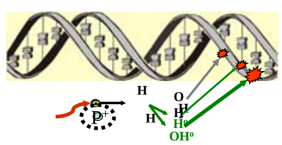
Interaction of Radiation with Tissue

- Energy deposited via:
  - ionization
  - excitation
  - thermal heating
- Radiation Interactions:
  - direct action (25%)
  - indirect action (75%)
  - Changes with radiation quality
    - Direction action % increases with higher LET





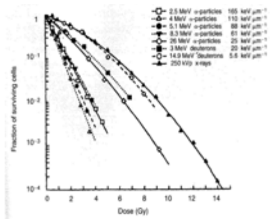
Linear Energy Transfer (LET)

- Linear Energy Transfer (LET): average energy (keV) given up by a charged particle traversing a distance (μm)
- ICRU (1962):

  L= *d*E/*d*l [keV/μm]
- Energy absorbed per unit path length
- Dependencies:
  - Charge of particle – greater the charge, the higher the LET
  - Mass of particle - greater the mass, the higher the LET
  - Energy of charge particle – the higher the energy, the lower the LET
- Different LET radiations result in different biological responses

Relative Biological Effectiveness

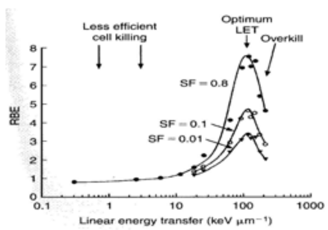
- Equal doses of different types of rad. do not produce same biologic effect
- Difference lies in pattern of energy deposition
- Standard needed to be set:



$$RBE = \frac{D_{250kvp}}{D_r} \Bigg|_{\text{specific endpoint*}}$$

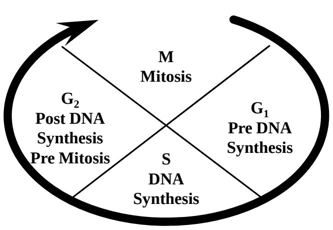
Relative Biological Effectiveness

- RBE depends on:
  - Biological endpoint
  - Biological system (type of cell)
  - Radiation quality—i.e. LET, high LET radiations have high RBE up to a point
  - Radiation dose – RBE at low doses are higher than high doses
  - Dose rate – lower the dose rate, higher RBE
  - Fractionation



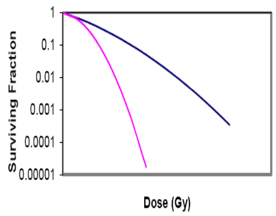
Mitotic Cell Cycle

- Mammalian cells divided into four phases
- Cell cycle times vary due to G1 time
- Cells most radiosensitive in M and late G_2
- Cells most resistant in late S phase



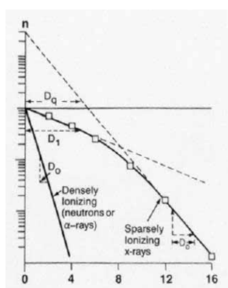
Cell Survival Curve

- Mammalian cell survival curves:
  - Curve characterizes the response of single cells to increasing single doses of radiation of different qualities delivered under various conditions and various dose rates
- Cell Death:
  - Proliferating Cell Systems
    - Loss of reproductive integrity
    - Tumors
  - Differentiated Cell Systems
    - Loss of specific metabolic functions



Curve Shape

- Shape:
  - Low dose region
  - High dose region
- Difference between high LET and low LET on same cells
- Various mathematical models used to fit the curve and explain the shape



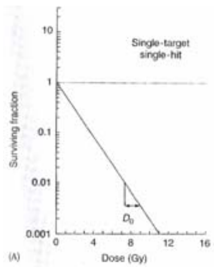
Target Theory: Single Hit

- Basic postulate that within each cell there is a critical site which must be hit once (or a number of times) to cause reproductive death of that cell
- During irradiation, large number of hits on cells but the probability of the next hit in a given cell is very small
  - Poisson statistics

$$P(\mu,x) = (\mu^x / x!) \exp(-\mu)$$

Single Hit, Single Target Model

- For each cell:
  P(survival) = P(0 hits) = exp (– D/D_o)
- D_o:
  - Dose that gives an average of one hit per target
  - Reduces SF from 1 to 0.37
- Describes response to:
  - Sensitive human cells
  - Cell response to high LET
- What about shoulder?



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Multi-Hit, Multiple Target Model

- Basic postulate that within each cell there are *n* critical sites which must be hit once (or a number of times) to cause reproductive death of that cell
- Again,

$$P(\text{0 hits on a specific target}) = \exp(-D/D_0)$$

$$P(\text{specific target inactivated}) = 1 - \exp(-D/D_0)$$

For n targets:

$$P(\text{all n targets inactivated}) = [1 - \exp(-D/D_0)]^n$$

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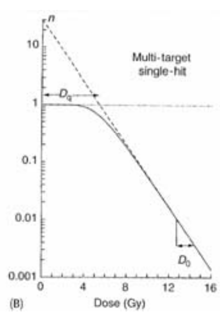
Target Theory: Multi-Hit

Thus,

$$P(\text{survival}) = 1 - [1 - \exp(-D/D_0)]^n$$

$$D_q = D_0 \log_e n$$

- Extrapolation number, n, measure of the width of shoulder
- Quasithreshold dose, D_q, is defined as the dose at which the straight portion of the survival curve cuts the dose axis through unity
- Models response well at high doses, off the shoulder



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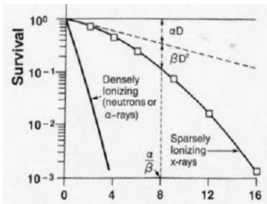
Linear-Quadratic Model

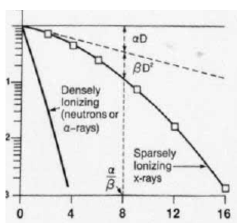
- Downward bending of curve fitted by second-order polynomial
- Model based on pure mathematics
- Better characterizes low dose region (0-3 Gy)
- Continuously bending with no straight portion



P(survival) = $\exp(-\alpha D-\beta D^2)$

Linear-Quadratic Model

- Assumes two components to cell killing
  - One proportional to dose
  - Second proportional to dose squared
- α is the probability of a single event causing damage, no repair
  - Steeper curve
- β is the probability of two separate events causing damage, chance of repair
  - Curvier curve



Linear-Quadratic Model

- α/β ratio is a dose at which linear and quadratic contributions to cell killing are equivalent
- α/β ratio single parameter which characterizes the shape of cell survival curve
- Tumors tend to display higher α/β ratios than normal cell due to lack of repair function
- Typical values of α/β ratio:
  - Tumors ~ 10Gy
  - Normal tissue ~ 3Gy (late effects) & 10Gy(early effects)

Radio sensitizers

- Hyperthermia
  - Radiation sensitivity increases when cells > 43°C
  - S-phase cells are sensitive to heat
  - Hypoxia does not protect cells from heat
  - Thermal Enhancement Ratio (TER): ratio of radiation dose with and without heat to produce same biological effect
- Drugs
  - Halogenated pyrimidines
    - Similar precursor to DNA thymidine
    - Incorporates into DNA and weakens chains
    - Requires tumor cells to be cycling faster than normal cells
- Oxygen
  - Oxygenation increases radiosensitivity

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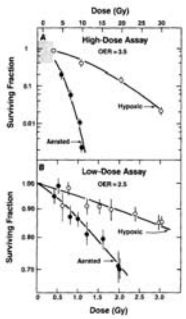
Oxygen Enhancement Ratio

- Oxygen Enhancement Ratio (OER):
  - Ratio of doses under hypoxic to aerated conditions for a given biological effect
- OER for x-rays:
  - High doses (2.5 to 3.5)
  - Low doses (~2.5)
    - Variation of OER with cell cycle (G1 lower OER than S phase)
- For effect, oxygen must be present *during or within microseconds after the irradiation*
- General agreement that oxygen acts at level of radical production
  - Indirect Action: radicals cause damage



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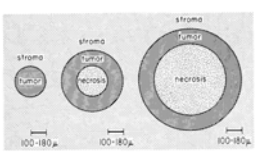
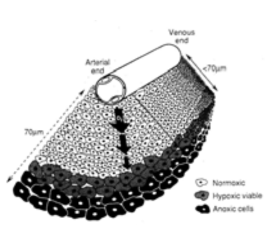
Chronic Hypoxia





- Found diffusion distance of oxygen ~70 μm
- Varies b/t arterial and venous end
- Tumors composed of oxygenated -> anoxic cells (spectrum)
- Hypoxic cell limit success of radiotherapy

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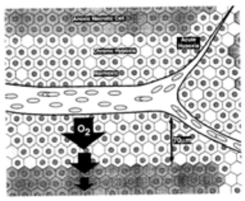
Acute Hypoxia

- Temporary closing of a tumor blood vessel
  - Malformed vasculature
- Evidence that blood vessels intermittently open/close
- Acutely hypoxic cells more likely to become oxygenated



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Sample Question

- Acutely hypoxic regions of a tumor:
  - a. are caused by temporary closing of blood vessels due to 'pinching' by the growing tumor
  - b. are often seen as "tumor cords" about 100 microns thick in histological sections
  - c. are caused by the limited diffusion distance of O_2 through tissue
  - d. are unimportant in practical radiotherapy

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Radio protectors

- Radio protectors are chemicals that reduce the biologic effects of radiation
- Sulfhydryl compounds which scavenge free radicals
  - Cysteine
  - Cysteamine
- Dose-reduction factor (DRF) is the ratio of radiation doses required to produce the same biologic effect in the absence and presence of the radio protector
- Effectiveness decreases with increasing LET
  - Why?

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Five "R's" of Radiobiology

- Reassortment
  - Return towards a more even cell-age distribution of a group of cells, following selective killing of cells in sensitive phases of cell cycle
- Repopulation
  - During extended course of radiotherapy, cells that survive an irradiation will repopulate
- Radiosensitivity
- Repair
- Reoxygenation

Sample Question

- Which of the following is not one of the 5Rs of radiobiology?
  - a. Reoxygenation
  - b. Repopulation
  - c. Resensitization
  - d. Repair

Radiosensitivity

- Bergonié and Tribondeau Law state that cells are radiosensitive if:
  - they are mitotically active
  - if they normally undergo many divisions
  - if they are morphologically and functionally undifferentiated.
- Various tissue types also possess an inherent apoptotic cell death pathway affinity

Repair

- Radiation damage to cells produce:
  - Lethal damage
    - Irreversible and irreparable
  - Potentially lethal damage (PLD)
  - Sublethal damage (SLD)
- Repair
  - PLDR
    - Radiation damage can be modified by post irradiation environment conditions
  - SLDR
    - Under normal conditions, if enough time (repairs in hours) is given

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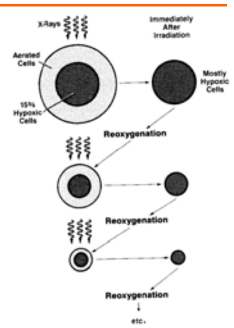
Reoxygenation

- Proportion of hypoxic cells in treated and untreated tumor similar
  - Hypoxic cells become oxygenated
- Oxygen status dynamic
- If occurring, hypoxic cells do not significantly affect outcome



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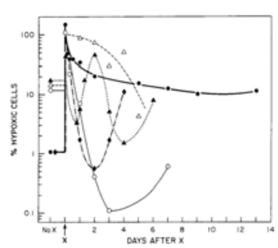
Time of Reoxygenation

- Reoxygenation rapidly after irradiation
- Reoxygenation time dependent on tumor histology
- Most showed rapid reoxygenation
- Proportion of hypoxic returning to pretreatment level



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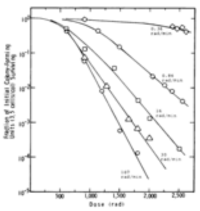
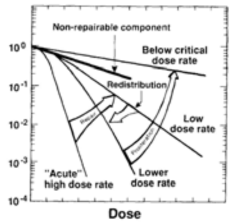
Dose Rate Effect





- ➢Repair of DNA DSBs
- ➢Decreased production of DSBs

- For x-rays, dose rate is one of the principal factors determining biological consequences of dose
- As dose rate lowered, biologic effect of a given dose generally is reduced

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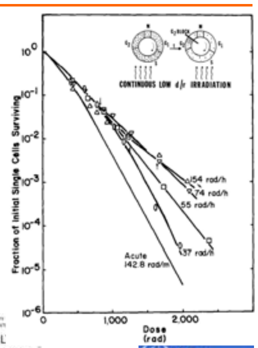
Inverse Dose-Rate Effect

- As dose-rate decreased, cell killing increases
- Low dose rate as damaging as acute exposure
- Why?
  - At low dose-rate, cells continue to progress through cell cycle and become arrested in G2 phase
  - At high dose-rates, cells are frozen in phase



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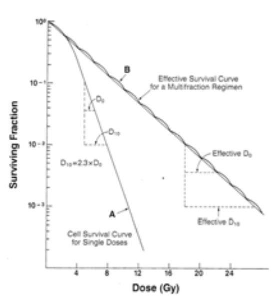
Fractionated Sur. Curve

- Fractionation changes shape of survival curve
- Time between fractions allows for sublethal damage repair
- Shoulder of curve becomes “effectively” an exponential function of dose
- Fractionation allows for reassortment and reoxygenation



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Fractionation Schedules

- Conventional
  - 2.0Gy per fraction
- Hyperfractionation
  - < 2.0Gy per fraction
  - Total number of fractions and dose increases
  - Treat BID
- Hypofractionation
  - >2.0Gy per fraction
  - Total dose decreases
- Accelerated
  - Decrease overall treatment time
  - >10Gy per week

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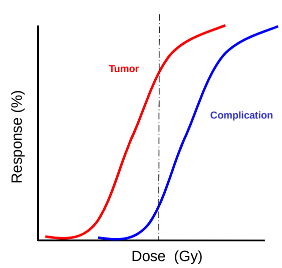
Dose-Response Relationship

- Response of tissue to radiation dose depends on:
  - Total dose
  - Time
  - Fractionation
  - Volume
- Sigmoid shape
  - Poisson Model
  - Logistic Model
  - Probit Model
- Therapeutic index



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Normal Tissue Effects

- Acute Effects:
  - Development in rapidly renewing tissues
  - Time of onset correlates w/ lifespan of differentiated functional cells
  - Ex. skin, gastrointestinal tract and haemopoietic system
  - High α/β ratios
  - Overall treatment time & fraction size dependent
- Late Effects:
  - Develop in slowly proliferating tissues
  - Ex. lung, kidney, heart, and liver
  - Low α/β ratios
  - Fraction size & total dose dependent

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Early (Acute) and Late Effects

	Early reactions	Late reactions
Latency	< 90 days, typically 3-9 weeks. No strong dependence on extent of damage, but greater damage may lead to slower healing of injury.	> 90 days, typically 0.5 -5 years. Greater damage leads to shorter latent period.
Fractional sensitivity	Low (α/β ~ 10 Gy)	High (α/β ~ 1 – 5 Gy)
Influence of overall treatment time	Shorter overall time leads to greater injury	No significant influence
Clinical course	Transient, but consequential late reactions may occur	Irreversible. Compensatory mechanisms or treatment for complications may relieve
Example	Reactions on epidermal layer of skin (mucositis dermatitis), hemapoietic system, Pneumonitis	Fibrosis, bone necrosis

From Bentzen and Overgaard, 1996

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Volume Effects

- Volume effects are dependent on the amount of volume an organ is irradiated
- Severity of volume effect depends:
  - Structural tissue tolerance
    - Parallel organization
    - Serial organization
  - Functional tolerance
- Tissues with parallel organization – pronounced volume effect (ex. Lung)
- Tissues with serial organization – little volume effect (ex. spinal cord)

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Tolerance Dose from Emami and Predictions of the 4-Parameter Model

	TD$_{5/5}$ (Gy) Volume			
ORGAN	**1/3**	**2/3**	**1**	**END POINT**
Bladder		80 / 80	65 / 65	**Symptomatic bladder contracture**
Brachial Plexus			60 / 60	Clinic. Apparent nerve damaged
Brain	60 / 60	50 / 50	45 / 45	Necrosis / infarction
Brain Stem	60 / 60	53 / 53	50 / 50	Necrosis / infarction
Cauda Equina			60 / 60	Clinic. Apparent nerve damaged
Colon	55 / 54		45 / 45	Obstruct/perforat/ulcerat/fistula
Ear (middle/external)	30 / 30	30 / 30	30 / 30	Acute serous otitis
Ear (middle/external)	55 / 55	55 / 55	55 / 55	Chronic serous otitis
Esophagus	60 / 60	58 / 57	55 / 56	Clinical structire/perforation
Femoral head & neck			52 / 52	Necrosis
Heart	60 / 59	45 / 46	40 / 40	Pericarditis
Kidney	50 / 50	30 / 31	23 / 23	Clinical nephritis
Larynx	79 / 79	70 / 73	70 / 70	Cartilage necrosis
Larynx	55 / 55	55 / 52	50 / 50	Laryngeal edema
Lens			10 / 10	Cataract requiring intervention

Tolerance Dose from Emami and Predictions of the 4-Parameter Model

ORGAN	TD5/5 (Gy) Volume 1/3	2/3	1	END POINT
Liver	50 / 43	35 / 34	30 / 30	Liver failure
Lung	45 / 45	30 / 25	17.5/17	Pneumonitis
Optic nerve			50 / 50	Blindness
Optic Chiasma			50 / 50	Blindness
Parotid		32 / 43	32 / 32	Xerostomia
Rectum			60 / 60	Severe proctitis/necrosis/stenosis
Retina			45 / 45	Blindness
Rib cage	50 / 50			Pathologic fracture
Skin (10, 30, 100 cm^2)	70 / 71	60 / 63	55 / 56	Necrosis / ulceration
Small intestine	50 / 48		40 / 40	Obstruction / perforation
Spinal cord(5, 10, 20 cm)	50 / 51	50 / 49	47 / 47	Myelitis / necrosis
Stomach	60 / 59	55 / 53	50 /50	Ulceration / perforation
Thyroid			45 /46	Clinical thyroiditis
TM joint & mandible	65 / 65	60 / 62	60 / 60	Marked limitation of joint function

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Acute Radiation Syndrome

- Hematopoietic Syndrome (~1 Gy)
  - 0.5 - 10 Gy (50 - 1000 rads)
  - $LD_{50/60}$ = 3 - 4 Gy (300 - 400 rads)
  - Bone Marrow damage
- Gastrointestinal Syndrome (~10 Gy)
  - 10 - 50 Gy
  - 100% lethal within 3 to 10 days (2 weeks with medical care)
  - Intestinal mucosa severely damaged
- Neurovascular Syndrome (~100 Gy)
  - 50+ Gy
  - Death in 2 to 3 days
  - Cardiovascular shock

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Radiation Effects *In Utero*

- Effects based on following factors:
  - Total dose
  - Dose rate
  - Radiation quality
  - Stage of development at time of exposure
- Classic effects are:
  - Lethal Effects
    - Irradiation during implantation, higher doses
    - Death occurs prenatal (1-2 weeks)
  - Malformations
    - Irradiation during the time of organogenesis (2-6 weeks)
    - Neonatal death possible
  - Growth disturbance without malformation
    - All stages, but particularly in latter part of pregnancy (6 weeks-term)

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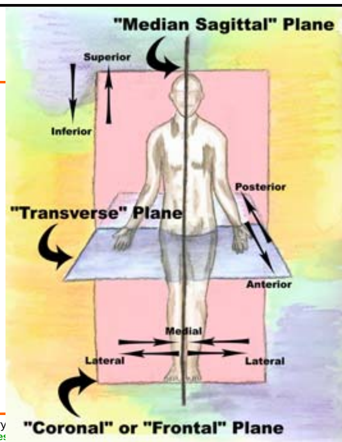
Fetal Irradiation

Stage	Growth Retardation	Death	General	Micro/Mental
Pre-Implant	-	embryonic	-	-
Organogenesis	temp	neonatal	risk	High risk
Fetal	permanent	LD_{50}	Low risk	risk

- Fetus most sensitive during 1st trimester
- Microcephaly/mental retardation – 2 & 3rd trimester



Anatomy

- H&N
  - Eyes
  - Lens
  - Optic Nerves
  - Optic Chiasm
  - Brainstem
  - Pituitary
  - Sinus Cavities
  - Parotid Glands
  - Mandible
  - Larynx
  - Trachea
  - Thyroid
  - Carotid Artery
- Thorax
  - Trachea
  - Esophagus
  - Lung
  - Spinal Cord
  - Heart (compartments)
  - Aorta
- Abdomen
  - Liver
  - Stomach
  - Spleen
  - Kidneys
  - Small bowel
  - Pancreas
- Pelvis
  - Prostate
  - Seminal Vesicles
  - Bladder
  - Rectum
  - Femur
  - Penile bulb
  - Ext/Int illiac
  - Large Intestine
  - Uterus

Example Question