Presented at the
Armed Forces Radiobiology Research Institute
Scientific Medical Effects of Ionizing Radiation Course
July 28 through August 1, 2008
Bethesda, Maryland

Distributed via the AFRRI Web site
http://www.afrri.usuhs.mil

The Scientific Medical Effects of Ionizing Radiation Course, conducted once a year, focuses on the latest research about the medical effects of ionizing radiation to help clinicians, health physicists, and medical planners preserve troop health in the face of radiological/nuclear terrorism or warfare.

For additional information about AFRRI training opportunities, contact AFRRI Military Medical Operations at 301-295-9150 or press the “Request info about: MEIR courses” button on this web page. To view more AFRRI information products, go to this web page.

For questions or more information about the content of this presentation, contact the presentation author.

Uniformed Services University
of the Health Sciences
Armed Forces Radiobiology Research Institute

Report Documentation Page

Form Approved
OMB No. 0704-0188

Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
JUL 2008		**00-00-2008 to 00-00-2008**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Fundamentals of Radiation Biology	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **Uniformed Services University of the Health Sciences,Armed Forces Radiobiology Research Institute (AFRRI),8901 Wisconsin Avenue BG 42,Bethesda,MD,20889-5603**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**Same as Report (SAR)**	**27**	

Fundamentals of Radiation Biology

Scientific MEIR
AFRRI – July 2008
Col Mark S. Smyczynski

Uniformed Services University of the Health Sciences
Armed Forces Radiobiology Research Institute

Objectives

- **Describe chemistry of radiation absorption**
- **Describe cell survival curves and assay systems**
- **Describe interaction of ionizing radiation at cellular, tissue, and entire organism level**
- **Describe effect of dose rate**
- **Describe effect of time, dose, and fractionation**
- **Describe early and late reacting tissue response**
- **Describe acute effects of whole body radiation**
- **Describe oncogenic transformation 2° to radiation**

Radiochemical reactions

incident photon	
↓	
fast electron	10^{-15} sec
↓	
ion radical	10^{-10} sec
↓	
free radical	10^{-5} sec
↓	
breakage of chemical bonds	< 1 sec ≥
↓	
biological effects	hours to years

Direct & Indirect Action of Radiation

- Direct action:

  Direct ionization of target

  Secondary e^- directly ionizes target
- Indirect action:

  Secondary e^- produces ion radicals that ionize target

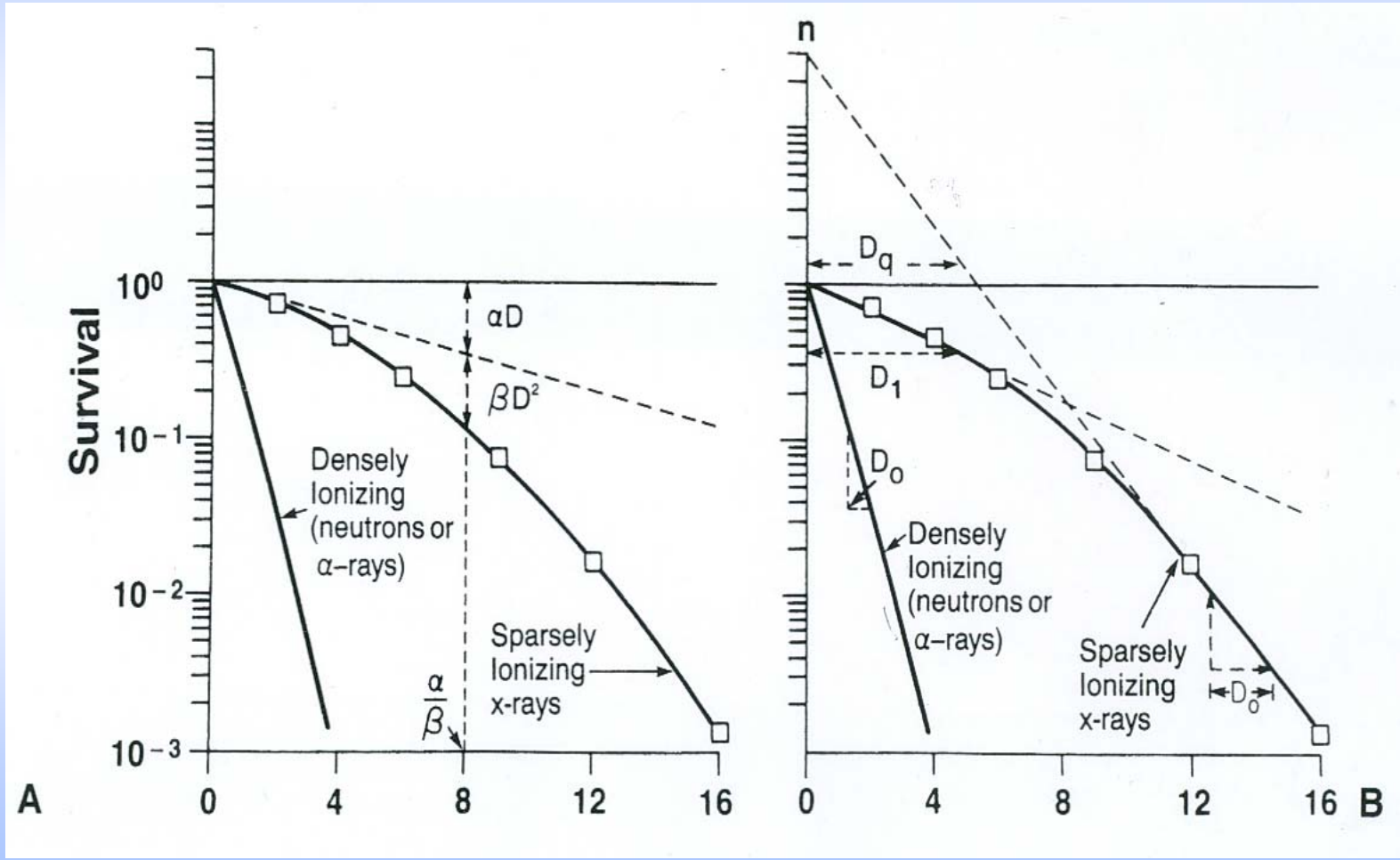
  Ion radicals produce free radicals that ionize target
- Indirect action predominates at ≈ 2:1
- Water commonly ionized as cell is 80% water
- Evidence supports DNA as the critical target
- More recent evidence demonstrates “bystander effect”

  Likely related to release of cytotoxic agents, presence of gap-junctions, and membrane damage

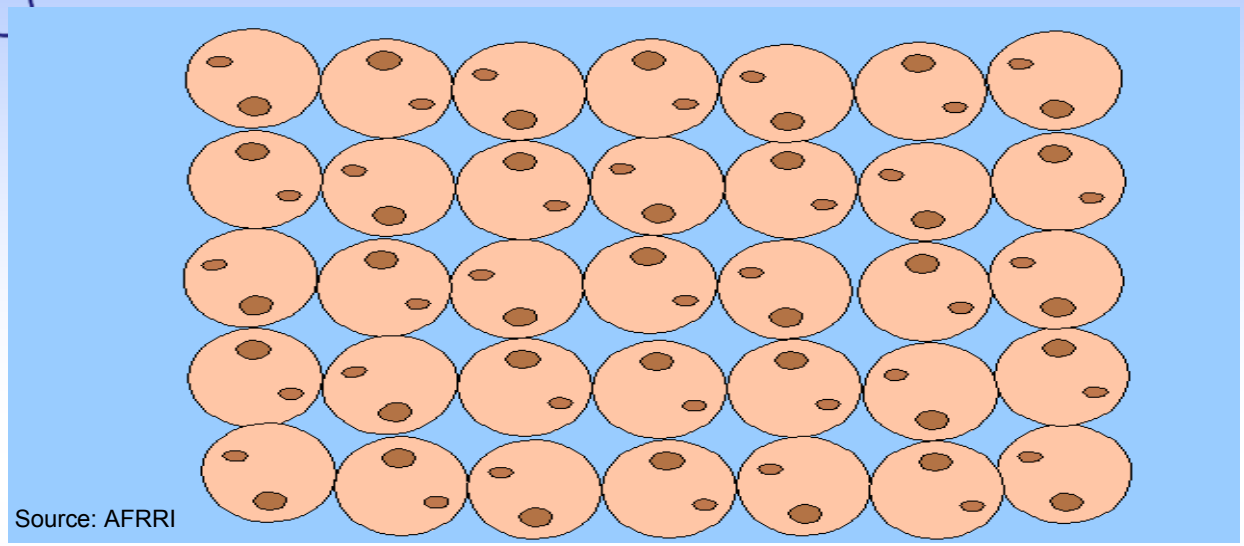
Radiolysis of Water (Saline)

- $H_2O \rightarrow H_2O^+ + e^-$ (solvated electron)
- $H_2O^+ + H_2O \rightarrow H_3O^+ + OH\cdot$ (hydroxyl radical)
- $2\ OH\cdot \rightarrow H_2O_2$ (hydrogen peroxide)
- $e^- + O_2 \rightarrow O_2^-$ (dioxygen radical anion)
- $OH\cdot$ + alkyl (R) $\rightarrow$ $ROH\cdot$ (alkyl free radical)
- $OH\cdot + Cl^- \rightarrow ClO^-$ (hypochlorite anion)

Cell Survival Curves



Linear Energy Transfer

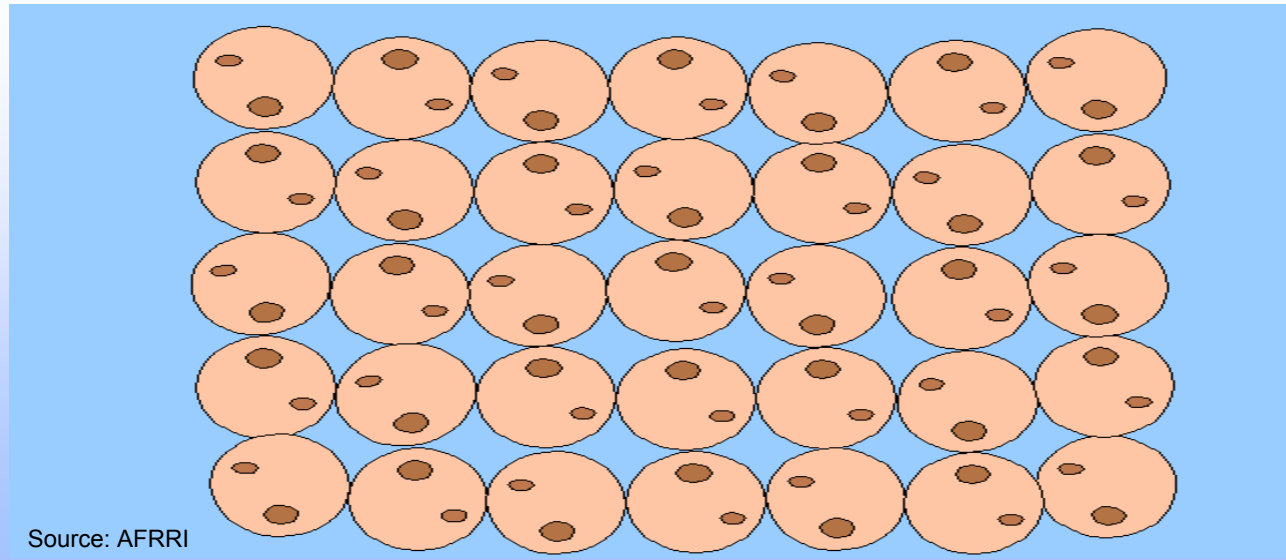


Low LET

(photons)

High LET

(alpha particles)



Cell Survival Curves

- Refer to article (p 260-261) for more complete review
- Surviving fraction per linear-quadratic model

$$S/S_0 = e^{-\alpha D-\beta D^2}$$

$$S/S_0 = e^{-\alpha/\beta D-D^2}$$

$$S/S_0 = e^{-(\alpha/\beta D+D^2)}$$

- Significance of the α/β ratio covered subsequently

Radiobiology Assay Systems

- Cell survival curves represent *in vitro* conditions

  S/S_0 = colonies counted/(cells seeded)(PE/100)

  where PE is defined as the plating efficiency

  PE = cells seeded/cells that grow into colonies

- Clonogenic end point assays determined by observing a clone of regenerating cells *in situ*

  → murine skin colony assay

  → murine jujunal crypt cell assay

  → murine testes stem cell assay

  → murine kidney tubule assay

Radiobiology Assay Systems

- Clonogenic assays from donor animals

  eg: bone marrow stem cell assay

  (sometimes called spleen colony assay)

  step 1: lethally irradiate recipient mouse

  step 2: radiate donor mouse to test dose

  step 3: harvest bone marrow cells from donor mouse, form cell suspension, and inject into recipient mouse

  step 4: harvest spleen from recipient mouse 10 days later and count colonies

S/S_0 = colonies counted/cells inoculated x PE

Radiobiology Tumor System Assays

- Growth delay assay

  Radiate tumor and measure the time for regrowth to size at time of radiation or time to specified size

- TCD_{50} assay (TDC = tumor control dose)

  Radiate tumors of uniform size at graded doses in series of animals, measure proportion controlled, and score dose achieving 50% local control

- Lung colony assay

  Radiate tumor to test dose, excise tumor, form cell suspension, inject into recipient mouse, harvest lungs 21 days later and count lung colonies

Radiosensitivity in the Mitotic Cycle

- Cell cycle: G1 → S → G2→ M → G1 etc.
  Recall cells can enter in to and out of G0 from G1
- Time for M almost universally at 1 hour
- Time for G2 quite consistent at 3 to 4 hours
- Time for S usually 6 to 8 hours and not > 15 hours
- Time for G1 highly variable from 1 to > 12 hours
- Mitotic harvest technique
- Synchronized cells obtained by block at end of G1
  Cells accumulate at block using hydroxyurea then progress through cell cycle when drug removed
- Refer to article (p 261) regarding cell survival curves

Classification of Radiation Damage

- Lethal damage

  Occurs subsequent to cytocidal radiation dose

  Damage irreversible and irreparable

  Most cells die in association with mitosis*

  Cell death usually occurs in subsequent mitosis

  Cells that die mitotic death may require up to 5 mitoses

  Some cells die from activated apoptotic pathways

  Many cell populations die both mitotic and apoptotic

  Radiosensitive cells tend to die from apoptosis

  *Lymphocytes and oocytes die an interphase death

Classification of Radiation Damage

- Potentially lethal damage (PLD)

  Cytocidal under normal growth conditions

  Cell survival enhanced by modifying the post-irradiation cellular environment

  Suboptimal growth conditions inhibit cell cycle progression and complex process of mitosis

  Evidence indicates that PLD equates to DNA repair

Classification of Radiation Damage

- Sublethal damage (SLD)

  Cell survival enhanced if total dose is divided in time

  Two different patterns of repair demonstrated

  Two fraction split dose experiments at 24°C & 37°C

  One pattern of SLD repair demonstrated at 24°C

  when cells do not progress through the cell cycle

  More complex pattern of SLD repair shown at 37°C

  →Prompt repair of SLD seen in first few hours

  →Surviving fraction decreases reaching low at 5 hours

  →Surviving fraction then increases again

Four R's of Radiobiology

- Pattern of SLD repair based on mitotic cycle
- Three simultaneous processes account for pattern

  Prompt repair of SLD occurs initially

  In asynchronous population most sensitive cells die

  Surviving population of becomes partly synchronized

  Radioresistant S-phase cells progress through cycle

  Cell cycle progression often termed reassortment

  Cell division of surviving fraction causes repopulation

  First three "R's" = repair - reassortment - repopulation

  Fourth "R" = reoxygenation represents separate topic

Dose Rate Effect

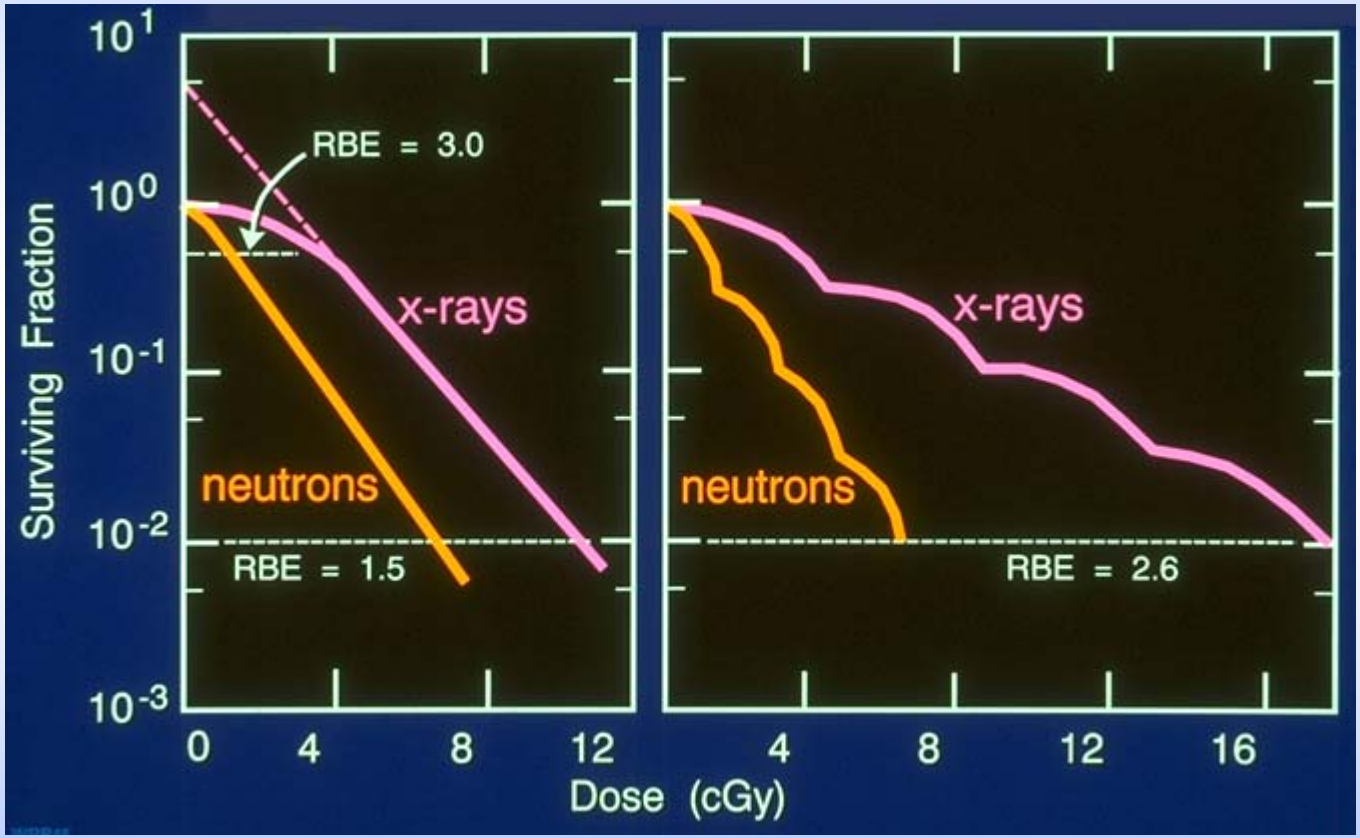
- Effect of dose rate extremely important
- Biologic effects strongly dependent on dose rate
- Dose rate effect essentially due to SLD repair
- Effect of dose rate separate from fractionation
- Refer to single page handout

Time - Dose - Fractionation (TDF)

- Time, dose, & fractionation important in radiotherapy
- Time refers to the total time in days radiation delivered
- Dose refers to the total dose delivered
- Fractionation refers to the dose delivered per fraction
- Conventional fractionation = 1.8 to 2.0 Gy/day
- For a dose known to control a given burden of tumor at conventional fractionation, that dose must be increased when the standard treatment time exceeded

  eg: 60 Gy over six weeks (thirty 2Gy/day fractions) does not have the same biological endpoint as 60 Gy over ten weeks while 80 Gy over ten weeks might

Fractionated Cell Survival Curves



RBE and OER

- Relative biological effectiveness = $D_{250kV_P}/D_{Test\ Radiation}$ required for equivalent biological effect
- 250 kV_P x-rays "traditional" historic standard
- Numerical value of RBE dependent on isoeffect endpoint and can vary based on the TDF
- Oxygen enhancement ratio = $D_{Hypoxic}/D_{Aerated}$ required for equivalent biological effect
- Numerical value of OER dependent on isoeffect endpoint and can vary based on the TDF
- OER and reoxygenation only pertinent to radiotherapy

Early & Late Reacting Tissues

- At least two different tissue types recognized
- Early reacting tissues: actively mitotic

  egs: skin & mucosa (buccal, intestinal, bladder)
- Late reacting tissues: post-mitotic

  egs: connective tissue, bone, muscle, & nerve
- In linear-quadratic model, components of cell killing proportional to dose and $(dose)^2$ are equal when $\alpha D = \beta D^2$ or $D = \alpha/\beta$
- The α/β ratio defines the type of tissue response
- Early reacting: $\alpha/\beta \approx 10$ Gy; late reacting: $\alpha/\beta \approx 2$ Gy
- Shape of cell survival curve differ (refer to figure)
- Volume of tissue irradiated <u>extremely</u> important

Acute Effects of Whole Body Radiation

- Exposure interval (time), dose, fractionation, and dose rate critically important determining clinical endpoint
- Effects of whole body radiation significantly different compared to partial body or localized radiation
- “Classic” acute radiation syndromes (ARS) based on single fraction whole body exposure at high dose rates
- Syndromes follow three phases referred to as the prodromal phase, latent phase, and manifest illness
- Duration of each phase and interval between phases varies depending primarily on total dose and dose rate
- Mixed photon/neutron beams may worsen prognosis

Acute Effects of Whole Body Radiation

- Traditional ARS includes cerebrovascular syndrome gastrointestinal syndrome & hematopoietic syndrome
- Recent approaches to the classification of ARS have shifted to five tiers of predicted clinical severity

Mild	Moderate	Severe	Very Severe	Lethal
1-2 Gy	2-4 Gy	4-6 Gy	6-8 Gy	> 8 Gy

- Predicted onset of symptoms, clinical manifestations, and laboratory findings developed for each category
- Overall prognosis and treatment recommendations provided for each of the five classifications
- Refer to single page handout

Radiation Induced Oncogenic Transformation

- Radiation capable of producing genetic changes
- Genetic alterations shown to be the cause of cancer
- Cancer development to two contributing processes
- Conversion of proto-oncogenes to oncogenes represents the gain of oncogenic potential
- Loss of tumor suppressor genes (emerogenes) represents the loss of anti-oncogenic potential
- Emergence of radiation induced oncogenic phenotype secondary to “balance” of transformation & cell killing
- Refer to single page handout

Thank you for your attention

- Questions
- Comments
- Discussion


MEIR