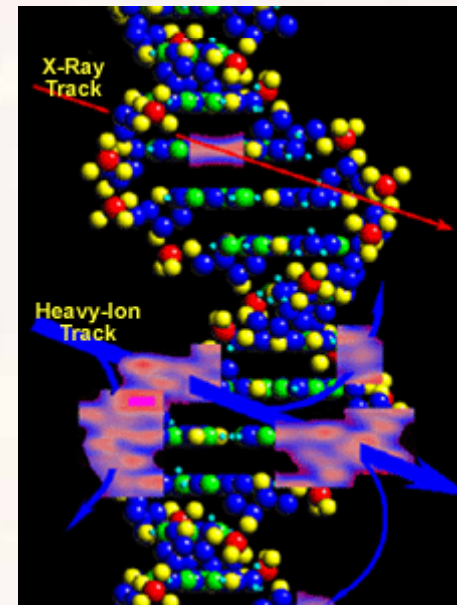
The background of the slide is an abstract, artistic composition. It features a dense network of thin, glowing orange and yellow lines that intersect and curve across the frame. Interspersed among these lines are numerous circular shapes, some of which are brightly lit, creating a bokeh effect. The overall color palette is warm, dominated by shades of orange, amber, and golden yellow, with some darker, almost black, areas that provide contrast. The lighting is soft and diffused, giving the impression of a complex, interconnected system or perhaps a microscopic view of a biological or chemical process.

PRINCIPLES OF RADIOBIOLOGY

I Principles of Radiobiology

1. Introduction - Effects of irradiation on Cells

Radiobiology is the scientific study of the effect of ionizing radiation on cells and tissues (a "young science") dating from the 1950s.



I Principles of Radiobiology

Dose and fractionation schedules were determined empirically, before radiobiology.

I Principles of Radiobiology



LOUIS HAROLD GRAY
1905 -1965

**Oxygen Effect (Gray, 1953)
has not resulted in increased
cure rates.**

I Principles of Radiobiology

1. Effects of Irradiation on Cells

A. Biologic target is the cell (results of irradiation of cells)

1. Cell death

2. Loss of reproductive capacity.

B. DNA - the target molecule with two spiral threads in a "double helix" orientation.



I Principles of Radiobiology

2. Effects of Ionizing Radiation on DNA

A. Radiation may produce double-or-single strand breaks in DNA

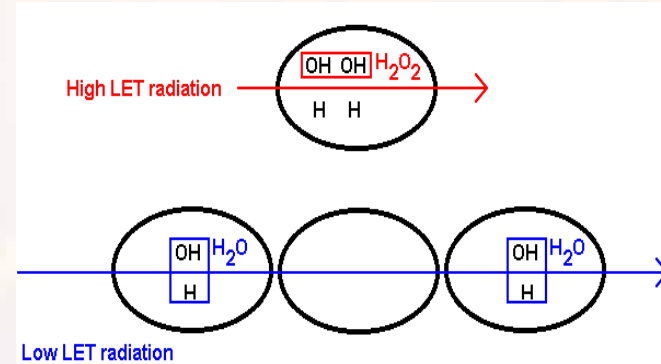
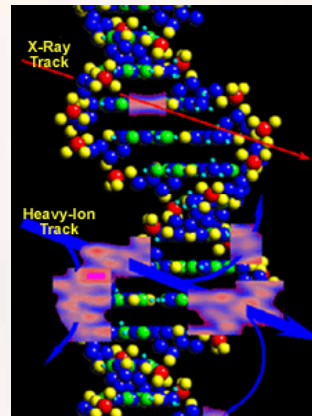
1. Single- strand breaks may be repaired
2. Double- strand breaks may not be easily repaired and can irreversibly damage the cell



I Principles of Radiobiology

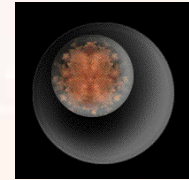
2. Effects of Ionizing Radiation on DNA

B. The quality of radiation -- Linear Energy Transfer (LET) -- amount of ionization per unit length (micron)

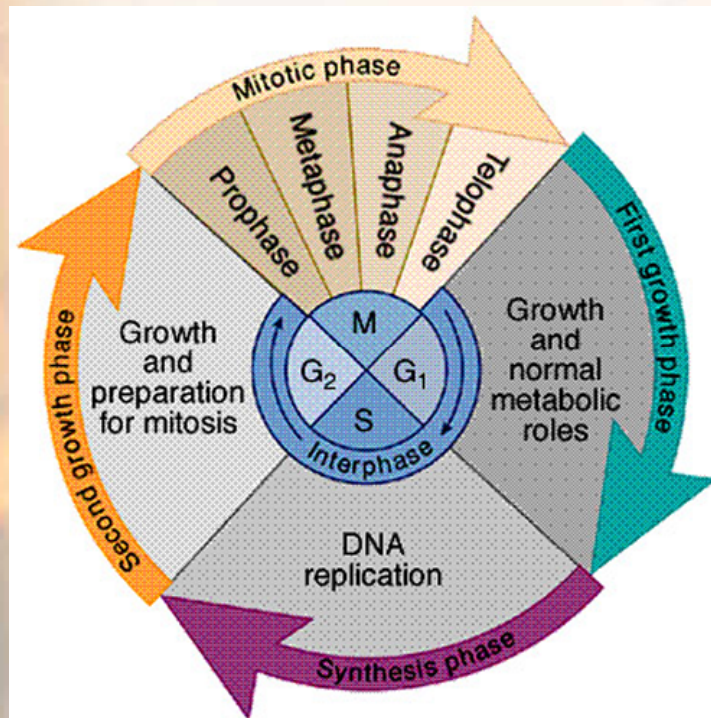


1. High LET -- Alpha particles, fast neutrons and "soft" x-rays (greater biologic effect).
2. Low LET -- Gamma rays, high energy x-rays (smaller biologic effect).

I Principles of Radiobiology



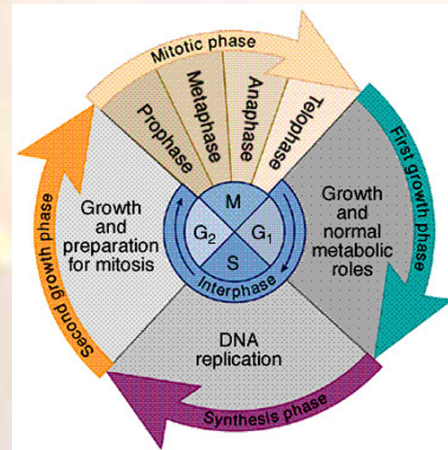
3. Radiation and the Cell Cycle



- A. S - DNA synthesis
- B. G₁ - gaps
- C. G₂
- D. M- mitosis (cell division) - Radiation is particularly lethal

I Principles of Radiobiology

4. Radiosensitivity in the cell cycle

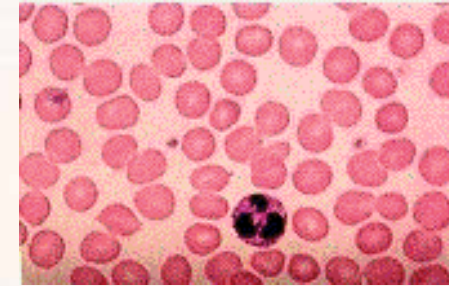


- A. M phase - most sensitive
- B. Late S phase - most resistant

There is no difference in the radiosensitivity of normal and malignant cell survival. However, small differences in cell survival (due to differing ability between normal and malignant cell for repair of damage) for a given dose are "amplified" by fractionation.

I Principles of Radiobiology

5. Growth Fraction



1. Proliferating cells in the cell cycle

- a) The portion of the total cell population that is proliferating
- b) The growth fraction varies widely from normal tissue to tumors and within tumor types (1-100%)

2. Differentiation - Maturity of the cell

- a) Immature cell = undifferentiated cell = anaplastic cell - the more anaplastic (undifferentiated) the tumor, the higher the growth fraction
- b) The higher the growth fraction, the more cells killed.

I Principles of Radiobiology

6. Direct & Indirect damage by ionizing radiation

A. Radiation can cause both direct and indirect effects on the molecular level.

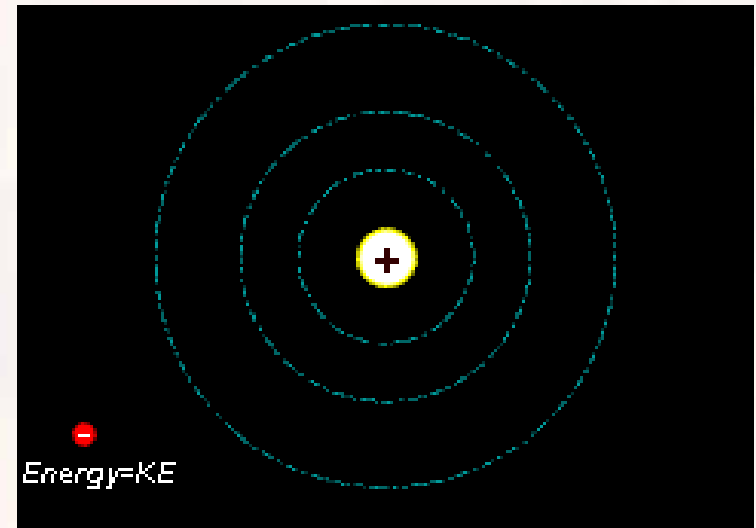
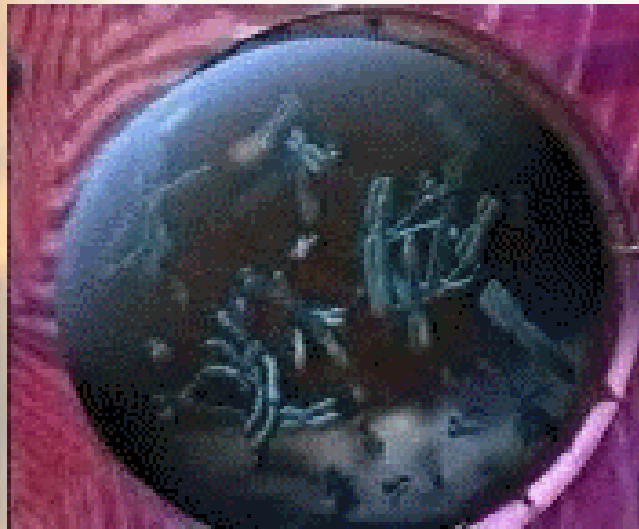
- 1. Direct action - ionization of the atoms of the nucleus**
- 2. Indirect action - X-rays interact with water producing a "free radical", which is highly reactive and causes damage to the cell nucleus.**



I Principles of Radiobiology

6. Direct & Indirect damage by ionizing radiation

B. Immediate cell death may result after massive radiation doses. At lower doses the chromosomal damage is not revealed until the cell attempts to divide.



II Biological Factors Influencing Radiosensitivity

1. Intrinsic radiosensitivity

- A. Tumor cells = normal tissue; however, different types of tumors vary in their radiosensitivity.**
- B. Different responses (due to repair)**

Four R's of Radiobiology

- 1. Repair of cellular damage**
- 2. Repopulation of tumor cells**
- 3. Reoxygenation during the course of irradiation**
- 4. Reassortment or Redistribution of the cells in the cell cycle**

B.1. Repair of cellular damage

a. Damage of repair will vary; slowly responding tissues have a greater capacity for repair than tumors.

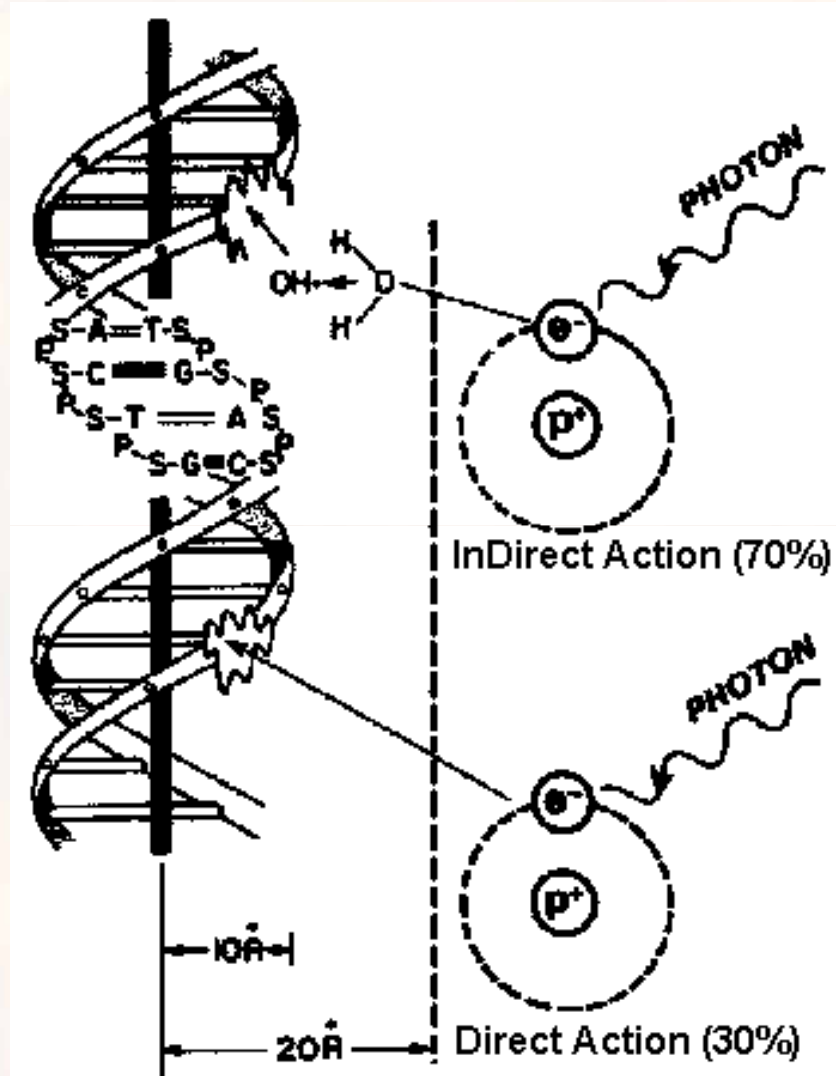
b. Sublethal damage

1. Occurs in proliferating cell

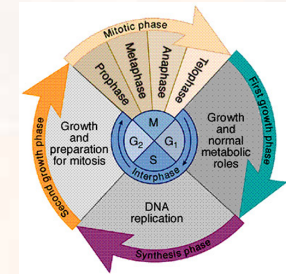
2. Repair depends upon oxygenation of cells during and after irradiation (lower O₂ concentrations, smaller repair)



RADIATION ABSORPTION



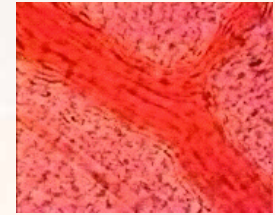
II Biological Factors Influencing Radiosensitivity



Repopulation of tumor cells

- a. Normal and malignant cells are replaced by recruitment of resting cells (G₀)
- b. Allows acutely responding tissues (mucosa) to tolerate higher fractionated doses (no similar relationship between responding tissues)
 1. Occurs in proliferating cells
 2. Repair depends upon oxygenation of cells during and after irradiation
 3. Treatment may accelerate tumor growth with high growth fractions (blood supply may be increased as tumor shrinks)
 4. Multiple daily fractions (irradiation 2X per day) may overcome repopulation

II Biological Factors Influencing Radiosensitivity



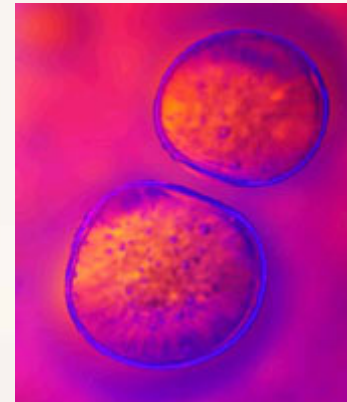
Reoxygenation during the course of irradiation

- a. Tumor growth often outstrips the blood supply - hypoxic tumor cells are 2-3 times more radioresistant**
- b. Even a small hypoxic cell population can prevent cure**
- c. Once the radiosensitive population has been eliminated the hypoxic cells are closer to the blood supply better oxygenated**
- d. Multiple fractions may enable the radiosensitive population to be removed several times a day**

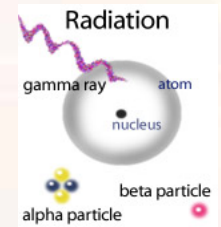
II Biological Factors Influencing Radiosensitivity

Reassortment or Redistribution of cells in the cell cycle

- a. The residual cell population is synchronous in radioresistant phases of the cell cycle (after radiosensitive cells have been removed)**
- b. The population of residual cells grow at differing rates and soon radiosensitivity of the residual cell population is greater than the population following the last dose**
- c. Redistribution has a neutral effect in late responding tissues**

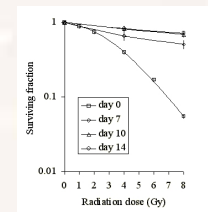


II Biological Factors Influencing Radiosensitivity



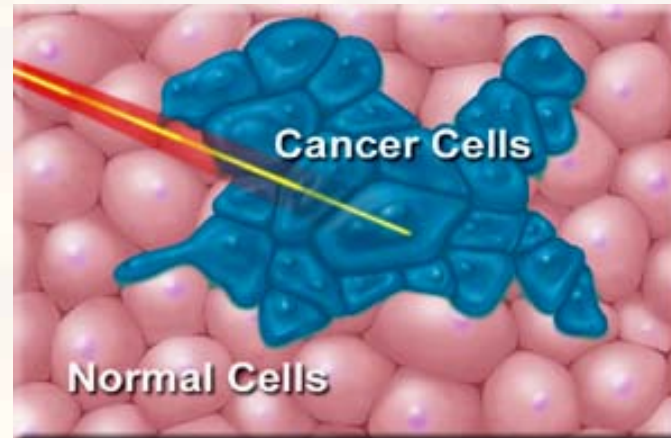
Cell survival following irradiation

- a. **Plating efficiency** - the number of cells that develop in colonies
- b. **Used to measure the capacity of surviving cells to proliferate**
- c. **Cell survival curves** - the relationship between the number of cells surviving and the dose of radiation delivered
 1. **Linear plot = exponential curve**
 2. **Logarithmic plot = a straight line**



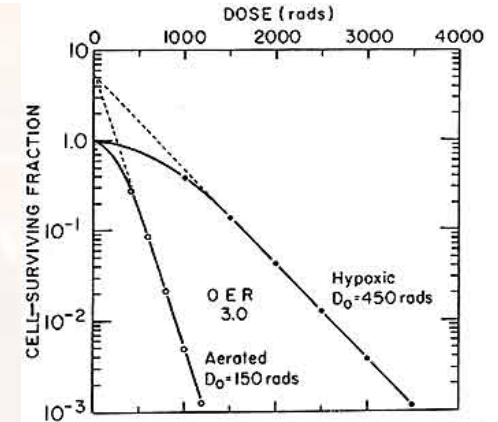
III The Oxygen Effect

1. The presence of oxygen enhances the reaction in tissues following exposure to ionizing radiation
2. This is due to the formation of free radicals
3. Tissues irradiated in the presence of oxygen are 3 times more sensitive than hypoxic tissues
4. The outermost portions of the tumor are well oxygenated, while the center of the tumor contains cells that are relatively hypoxic



III The Oxygen Effect

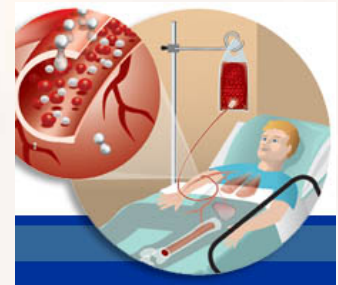
Oxygen Enhancement Ratio



- The ratio of the doses necessary to achieve the same biological effect in the presence or absence of oxygen
- A larger dose is required to produce the same effect in hypoxic tissue
- The percentage of hypoxic cells in human tumors is unknown (10-20% of tumors are hypoxic in lab animals)
- Hypoxic cells are located at the limit that oxygen can diffuse in tissue
- The center of tumors is hypoxic or areas of tumor may have transient hypoxia

IV Methods of Overcoming Tumor Hypoxia

1. **Anemia** - may cause a lower cure rate due to hypoxia, hemoglobin should be monitored, and a transfusion may be necessary.
2. **Hyperbaric Oxygen** - Oxygen at 3 times normal atmospheric pressure breathed by patients in special "tanks"
 - a. **Better local control in head and neck tumors + cervical cancer**
 - b. **Problems with hyperbaric oxygen**
 1. **Gains in local control not significant**
 2. **Irradiation technique difficult, time consuming**
 3. **Patient claustrophobia**



IV Methods of Overcoming Tumor Hypoxia

3. Hypoxic cell sensitizers - compounds that mimic the sensitizing effect of oxygen

a. results disappointing (these compounds may be useful with fast neutrons)

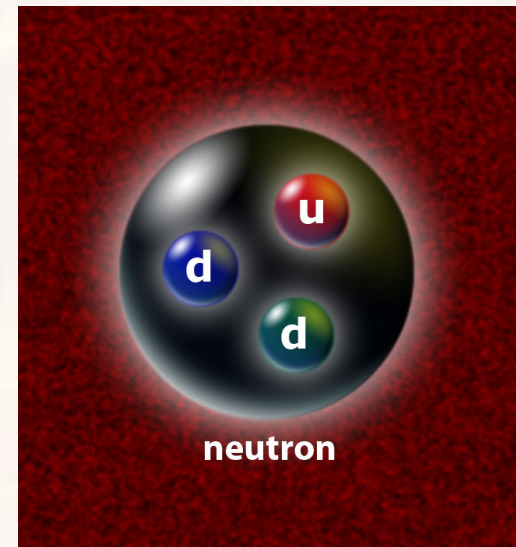
b. Examples: Misonidazole - halogenated pyrimidines

c. Attempts to increase the concentrations of these compounds is limited by toxicity of these compounds

IV Methods of Overcoming Tumor Hypoxia

4. Fast Neutrons

- a. OER of fast neutrons = 1.6, lower than X-rays and gamma rays (almost the same amount of damage to normal tissue as to tumor tissue)
- b. Higher RBE and LET than X-rays and gamma rays



V. Therapeutic Ratio and Therapeutic Gain

1. Therapeutic Ratio

- a. Goal of curative radiotherapy: to eradicate a tumor with minimal damage to normal tissue**
- b. Failure of local control (dose too low) late normal tissue injury (dose too high)**
- c. Therapeutic Ratio, expresses the likelihood of local control, introduced by Patterson**

Therapeutic Ratio = $NTTD/TLD$

Where: $NTTD$ = Normal Tissue Tolerance Dose

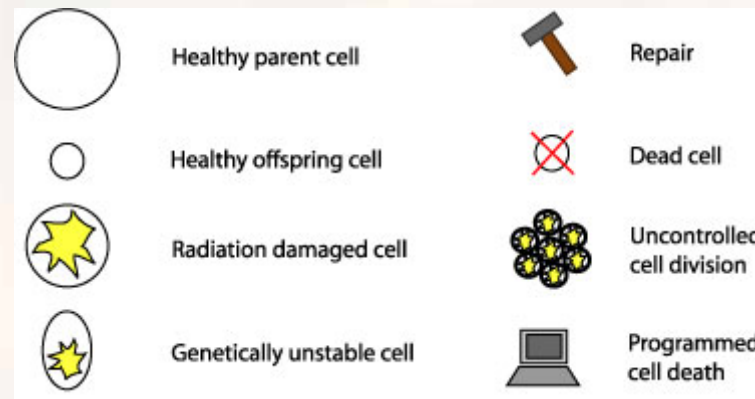
TLD = Tumor Lethal Dose

V. Therapeutic Ratio and Therapeutic Gain

2. Therapeutic Gain

a. The ratio of the RBE of radiation of any form on tumor and normal tissue

b. An improvement in therapeutic gain can only be achieved by increasing RBE of the tumor relative to RBE of the normal tissue



THERAPEUTIC RATIO

The therapeutic ratio was proposed by Patterson in 1948. The ratio was between the normal tolerance dose (NTD) and the tumor lethal dose (TLD). When the ratio is greater than one there is a favorable outcome. When the ratio is less than one, the outcome is unfavorable. It should be noted that the outcome is defined in terms of local destruction of the tumor.

EXAMPLES:

$$\frac{\text{NTD}}{\text{TLD}} \quad 2000/6000 = 1/3 \quad < 1 \text{ poor outcome}$$

$$\frac{\text{NTD}}{\text{TLD}} \quad 6000/3600 = 1.6 \quad > 1 \text{ good outcome}$$

CLASS I ORGANS: FATAL/SEVERE MORBIDITY

| Organ | Injury | TD 5/5* | TD 50/5** | Whole or Partial Organ (field size or length) |
|-------------|--------------------------------------|------------|--------------|---|
| Bone Marrow | Aplasia pancytopenia | 250 | 450 | Whole |
| | | 3,000 | 4,000 | Segmental |
| Liver | Acute and chronic hepatitis | 2,500 | 4,000 | Whole |
| | | 1,500 | 2,000 | Whole(strip) |
| Stomach | Perforation, ulcer hemorrhage | 4,500 | 5,500 | 100 cm |
| Intestine | Ulcer, perforation, hemorrhage | 4,500 | 5,500 | 400 cm |
| | | 5,000 | 6,500 | 100cm |
| Brain | Infarction, necrosis | 5,000 | 6,000 | Whole |
| | | 4,500 | 5,500 | 10 cm |

TD
5/5*

Minimal tolerance dose. The dose to which a given population of patients is exposed under a standard set of treatment conditions resulting in no more than a 5% severe complication rate within 5 years.

TD
50/5**

The maximal tolerance dose is defined as the dose to which a given population of patients is exposed under a standard set of treatment conditions resulting in a 50% severe complication rate within 5 years.

CLASS I ORGANS: FATAL/SEVERE MORBIDITY

| Organ | Injury | TD 5/5* | TD 50/5** | Whole or Partial Organ (field size or length) |
|-------------|-----------------------------------|----------------|----------------|---|
| Spinal Cord | Infarction, Necrosis | 4,500 | 5,500 | 10 cm |
| Heart | Pericarditis, Pneumonitis | 4,500 7,000 | 5,500 8,000 | 60% 25% |
| Lung | Acute and chronic pneumonia | 3,000 1,500 | 3,500 2,500 | 100 cm Whole |

TD
5/5* Minimal tolerance dose. The dose to which a given population of patients is exposed under a standard set of treatment conditions resulting in no more than a 5% severe complication rate within 5 years.

TD
50/5** The maximal tolerance dose is defined as the dose to which a given population of patients is exposed under a standard set of treatment conditions resulting in a 50% severe complication rate within 5 years.

CLASS I ORGANS: FATAL/SEVERE MORBIDITY

| Organ | Injury | TD 5/5* | TD 50/5** | Whole or Partial Organ (field size or length) |
|--------|--------------------------------|----------------|----------------|---|
| Kidney | Acute and chronic hepatitis | 1,500 2,000 | 2,000 2,500 | Whole (strip) Whole |
| Fetus | Death | 200 | 400 | Whole |

**TD
5/5*** Minimal tolerance dose. The dose to which a given population of patients is exposed under a standard set of treatment conditions resulting in no more than a 5% severe complication rate within 5 years.

**TD
50/5**** The maximal tolerance dose is defined as the dose to which a given population of patients is exposed under a standard set of treatment conditions resulting in a 50% severe complication rate within 5 years.