Biological Effects of Ionizing Radiation in Tissues – A Review

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Abstract: The biologic effects of diagnostic and therapeutic radiation, with special emphasis on maxillofacial tissue effects. It describes stochastic and deterministic effects of radiation and the clinical relevance of these effects.

Key Words: Cell damage, radiation-induced cancer, stochastic radiation effects; deterministic radiation effects, osteoradionecrosis

1 Introduction

Radiobiology is the study of effects of ionizing radiation on living systems. The initial interaction between ionizing radiation and matter occurs at the level of the electron within the first 10^{-13} seconds after exposure. These changes result in modification of biologic molecules within the ensuing seconds to hours. In turn, the molecular changes may lead to alterations in cells and organisms that persist for hours, decades, and possibly even generations. These changes may result in injury or death

2 Radiation Chemistry

Radiation acts on living systems through direct and indirect effects. Both direct and indirect effects yield unstable free radicals. Free radicals are extremely reactive and short lives.

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In **direct effects**, biologic molecules absorb energy from ionizing radiation and form unstable free radicals. Free radicals play a dominant role in producing molecular changes in biologic molecules. Approximately one third of the biologic effects of x-ray exposure result from direct effects.

In **indirect effects** the initial interaction of a photon occurs with water molecules. Radiolysis of water refers to complex series of chemical reaction when ionizing radiation interacts with water. The initial interaction of X-ray photon with water produces hydrogen and hydroxyl free radicals that interact with biologic macromolecules. About two thirds of radiation-induced biologic damage results from indirect effects.

Both direct and indirect effects are completed within 10^{-5} second. The resulting damage may take hours to decades to become evident.

3 Deterministic and Stochastic

Radiation injury to organisms results from either killing of large numbers of cells (deterministic effects) or sub lethal damage to individual cells that results in cancer formation or heritable mutation (stochastic effects).

Changes in Deoxyribonucleic Acid

Damage to a cells deoxyribonucleic acid (DNA)(Fig.1) is the primary cause of radiation-induced cell death, heritable (genetic) mutations, and cancer formation (carcinogenesis). The sensitive site in the nucleus is the DNA within chromosomes. Chromosomes serve as useful markers for radiation injury. The type of damage that may be observed, depends on the stage of the cell in the cell cycle (Fig. 2) at the time of irradiation. If radiation exposure occurs after DNA synthesis (i.e., in G_2 or mid and late S), only one arm of the affected chromosome is broken (chromatid aberration) (Fig.3). However, if the radiation-induced break occurs before the DNA has replicated (i.e., in G_1 or early S), the damage manifests as a break in both arms (chromosome aberration) at the next mitosis

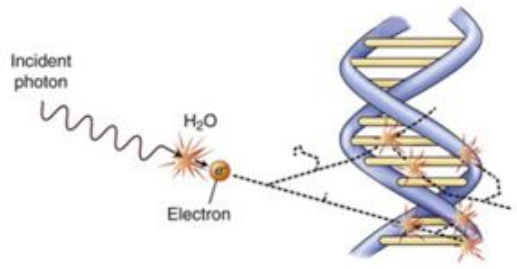

Figure 1: An incident photon causes ionization of a water molecule, and the recoil electron causes a cluster of damage to multiple sites in a DNA molecule. Such cluster damage is responsible for most radiation cell killing, carcinogenesis, and heritable effects.

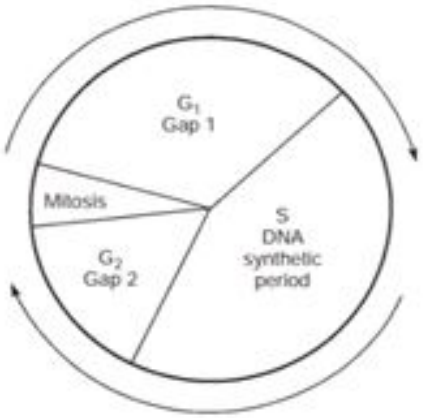

Figure 2: Cell cycle

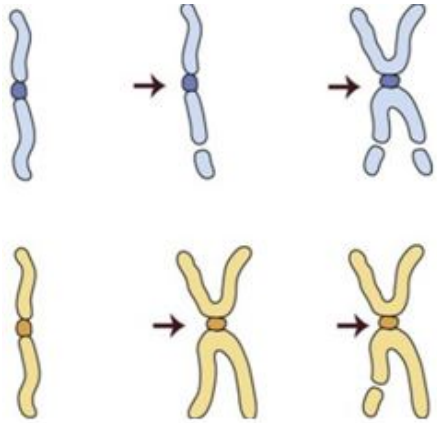

Figure 3. Chromosome aberrations. (A) Irradiation before deoxyribonucleicacid (DNA) synthesis results in a double-arm (chromosome) aberration because the damage is replicated in the next S phase and becomes visible in the next mitosis phase. (B) Irradiation of a cell after DNA synthesis results in a single-arm (chromatid) aberration.

Cell cycle

A proliferating cell moves in the cycle from mitosis to gap 1 (G_1) to the period of DNA synthesis (S) to gap 2 (G_2) to the next mitosis.

The three mechanisms of reproductive death are

- DNA damage,
- Bystander effect,
- Apoptosis

Deoxyribonucleic Acid Damage

When a population of slowly dividing cells is irradiated, larger doses and longer time intervals are required for induction of deterministic effects than when a rapidly dividing cell system is involved.

Bystander Effect

Cells that are damaged by radiation, release into their immediate environment molecules that kill nearby cells. This bystander effect has been demonstrated for both particles and x rays and causes chromosome aberrations, cell killing, gene mutations, and carcinogenesis.

Apoptosis

Apoptosis, also known as programmed cell death, occurs during normal embryogenesis. Cells round up, draw away from their neighbors, and condense nuclear chromatin. This characteristic pattern, different from necrosis, can be induced by radiation in both normal tissue and in some tumors. Apoptosis is particularly common in hemopoietic and lymphoid tissues.

Recovery

Cell recovery from DNA damage and the bystander effect involves enzymatic repair of single-strand breaks of DNA. Because of this repair, a higher total dose is required to achieve a given degree of cell killing when multiple fractions are used (e.g., in radiation therapy) than when the same total dose is given in a single brief exposure. Damage to both strands of DNA at the same site is usually lethal to the cell.

Radiosensitivity and Cell Type

The most radiosensitive cells have the following characteristics:

- A high mitotic rate
- Undergo many future mitoses
- Are most primitive in differentiation

Relative Radio sensitivity of Various Organs

High	Intermediate	Low
Lymphoid organs Bone marrow Testes Intestines Mucous membrane	Fine vasculature Growing cartilage Growing bone Salivary glands Lungs Kidney Liver	Optic lens Muscle

4 Deterministic Effects –Acute Radiation Syndrome

Dose (GY)	Manifestations	
1 to 2	Prodromal symptoms	Within few minutes to hours after radiation Anorexia, nausea, vomiting, diarrhea, weakness, and fatigue.
2 to 4	Mild Hematopoietic Syndrome	Highly radiosensitive cells Reduction in no of proliferating leukocytes, redblood cells and platelets
4 to 7	Severe Hematopoietic syndrome	Severe reduction in bone marrow cells. Signs include infection, hemorrhage, anemia
7 to 15	Gastrointestinal Syndrome	Injury to the rapidly proliferating basal epithelial cells of the intestinal villi Loss of plasma and electrolytes, loss of efficient intestinal absorption, and ulceration of the mucosal lining with hemorrhaging into the intestines. Diarrhea, dehydration, and loss of weight.
50	Cardiovascular and Central Nervous System Syndrome	Circulatory collapse& fall in blood pressure Death within 2 to 3 days

Management of Acute Radiation Syndrome

Antibiotics are indicated when the granulocyte count falls. Fluid and electrolyte replacement is used as necessary. Whole blood transfusions are used to treat anemia, and platelets may be administered to arrest thrombocytopenia. Bone marrow grafts are indicated between identical twins because there is no risk for graft-versus-host disease.

Radiation Effects on Embryos and Fetuses

Embryos and fetuses are considerably more radiosensitive than adults because most embryonic cells are relatively undifferentiated and rapidly mitotic. Exposures in the

range of 2 to 3 Gy during the first few days after conception are thought to cause undetectable death of the embryo.

Late Effects

Growth and Development

Children exposed in the bombings showed impairment of growth and development. They have reduced height, weight, and skeletal development. The younger the individual was at the time of exposure, the more pronounced the effects.

Cataracts

The threshold for induction of cataracts (opacities in the lens of the eye) ranges from about 0.6 Gy when the dose is received in a single exposure to more than 5 Gy when the dose is received in multiple exposures over a period of weeks.

Life Span Shortening

The survivors of the atomic bombings show a clear decrease in median life expectancy with increasing radiation dose. Survivors demonstrate increased frequency of heart disease, stroke, and diseases of the digestive, respiratory, and hematopoietic systems.

5 Stochastic Effects

Stochastic effects result from sublethal changes in the DNA of individual cells. The most important consequence of such damage is carcinogenesis.

Carcinogenesis

Radiation causes cancer by modifying DNA. The most likely mechanism is radiation-induced gene mutation. Gene mutations may also involve a loss of function in the case of tumor suppressor genes. Radiation-induced cancers are not distinguishable from cancers produced by other causes.

Leukemia

For individuals exposed under age 30 years, the risk for development of leukemia ceases after about 30 years. For individuals exposed as adults, the risk persists throughout life. Persons younger than 20 years are more at risk than adults.

Thyroid Cancer

Susceptibility to radiation-induced thyroid cancer is greater early in childhood than at any time later in life, and children are more susceptible than adults. Females are two to three times more susceptible than males to radiogenic and spontaneous thyroid cancers.

Brain and Nervous System Cancers

Patients exposed to diagnostic x-ray examinations in utero and to therapeutic doses in childhood or as adults (average midbrain dose of about 1 Gy) show excess numbers of malignant and benign brain tumors.

Salivary Gland Cancer

The incidence of salivary gland tumors is increased. An association between tumors of the salivary glands and dental radiography has been shown, the risk being highest in persons receiving full-mouth examinations before the age of 20 years in patients treated with irradiation for diseases of the head and neck. An estimated cumulative parotid dose of 0.5 Gy or more showed a significant correlation between dental radiography and salivary gland tumors.

6 Heritable Effects

The knowledge of heritable effects of radiation on humans comes largely from the atomic bomb survivors. To date, no such radiation related genetic damage has been demonstrated. No increase has occurred in adverse pregnancy outcome, leukemia or other cancers, or impairment of growth and development in the children of atomic bomb survivors. Similarly, studies of the children of patients who received radiotherapy show no detectable increase in the frequency of genetic diseases.

Radiotherapy in the oral cavity

Radiation therapy for malignant lesions in the oral cavity is usually indicated when the lesion is radiosensitive, advanced, or deeply invasive and cannot be approached surgically. Combined surgical and radio therapeutic treatment often provides optimal treatment. Fractionation of the total x-ray dose into multiple small doses provides greater tumor destruction than is possible with a large single dose.

Typically, 2 Gy is delivered daily for a weekly exposure of 10 Gy. This continues typically for 6 to 7 weeks until a total of 64 to 70 Gy is administered. Cobalt is often the source of γ radiation; however, on occasion small implants containing radon or iodine 125 are placed directly in a tumor mass. Such implants deliver a high dose of radiation to a relatively small volume of tissue in a short time. Recently a three-dimensional technique called intensity-modulated radiotherapy (IMRT) has been used to control the dose distribution with high accuracy.

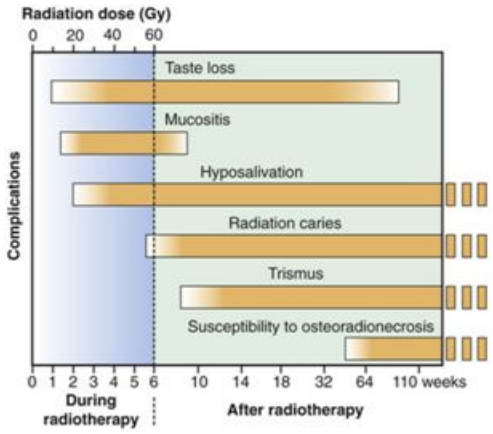

Figure 4: Oral complications. Typical time course of complications seen during and after a course of radiation therapy to the head and neck. Shaded area in first 6 weeks represents accumulated dose Shading within bars indicates severity of complication.

Oral Mucous Membrane

The oral mucous membrane contains a basal layer composed of rapidly dividing, radiosensitive stem cells. Near the end of the second week of therapy, the mucous membrane begins to show areas of redness and inflammation (mucositis). As the therapy continues, the irradiated mucous membrane begins to separate from the underlying connective tissue, with the formation of a white to yellow pseudomembrane (the desquamated epithelial layer). (Fig.5a). At the end of therapy, the mucositis is usually most severe, discomfort is at a maximum, and food intake is difficult. Good oral hygiene minimizes infection. Topical anesthetics may be required at mealtimes. Secondary yeast infection by Candida albicans is a common complication and may require treatment.

After irradiation is completed, the mucosa will begin to heal and complete by about 2 months. Later the mucous membrane tends to become atrophic, thin, and relatively avascular. These atrophic changes complicate denture wearing because they may cause oral ulcerations of the compromised tissue.

Taste Buds

Taste buds are sensitive to radiation. Patients often notice a loss of taste acuity during the second or third week of radiotherapy. Bitter and acid flavors are more severely affected when the posterior two thirds of the tongue are irradiated and salt and sweet when the anterior third of the tongue is irradiated. Alterations in the saliva may partly account for this reduction, which may proceed to a state of virtual insensitivity. Taste loss is reversible, and recovery takes 60 to 120 days.

Salivary Glands

The major salivary glands are at times unavoidably exposed to 20 to 30 Gy during radiotherapy for cancer in the oral cavity or oropharynx. A marked and progressive loss of salivary secretion (hyposalivation) is usually seen in the first few weeks after initiation of radiotherapy. The extent of reduced flow is dose dependent. The mouth becomes dry (xerostomia) and tender, and swallowing is difficult and painful. Patients with irradiation of both parotid glands are more likely to complain of dry mouth and difficulty with chewing and swallowing than are those with unilateral irradiation. Various saliva substitutes are available to help restore function. Use of IMRT has helped to spare the contralateral salivary glands and thus minimize the loss of salivary function. serous cells are more radiosensitive than mucous cells, the residual saliva is more viscous than usual. Further, the small volume of viscous saliva that is secreted usually has a pH value 1 unit below normal (i.e., an average of 5.5 in irradiated patients compared with 6.5 in unexposed individuals). In addition, the buffering capacity of saliva falls during radiation therapy. If some portions of the major salivary glands are spared, dryness of the mouth usually subsides in 6 to 12 months because of compensatory hypertrophy of residual salivary gland tissue. Reduced salivary flow that persists beyond a year is unlikely to show significant recovery.

Teeth

Children receiving radiation therapy to the jaws may show defects in the permanent dentition such as retarded root development, dwarfed teeth, or failure to form one or more teeth. Adult teeth are resistant to the direct effects of radiation exposure. Pulpal tissue demonstrates long-term fibro atrophy after irradiation. Radiation has no discernible effect on the crystalline structure of enamel, dentin, or cementum, and radiation does not increase their solubility.

Radiation Caries

Radiation caries is a rampant form of dental decay that may occur in individuals who receive a course of radiotherapy that includes exposure of the salivary glands. Patients receiving radiation therapy to oral structures have increases in Streptococcus mutans, Lactobacillus, and Candida. Caries results from changes in the salivary glands and saliva, including reduced flow, decreased pH, reduced buffering capacity, increased viscosity, and altered flora. The residual saliva in individuals with xerostomia also has a low concentration of Ca^{+2}. Clinically, three types of radiation caries exist. The most common is widespread superficial lesions attacking buccal, occlusal, incisal, and palatal surfaces (Fig.5b). Another type involves primarily the cementum and dentin in the cervical region.The best method of reducing radiation caries is daily application for 5 minutes of a viscous topical 1% neutral sodium fluoride gel in custom-made applicator trays.

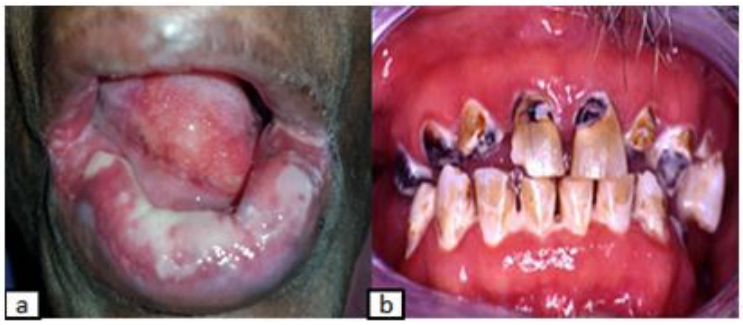

Figure 5: a. Radiation induced mucositis, b. Radiation caries

Bone

The primary damage to mature bone results from radiation-induced damage to the vasculature of the periosteum and cortical bone, which are normally already sparse. Radiation also acts by destroying osteoblasts and, to a lesser extent,osteoclasts. Osteoradionecrosis is the most serious clinical complication that occurs in bone after irradiation. The decreased vascularity of the mandible renders it easily infected by microorganisms from the oral cavity. This bone infection may result from radiation-induced breakdown of the oral mucous membrane, by mechanical damage to the weakened oral mucous membrane such as from a denture sore or tooth extraction, through a periodontal lesion, or from radiation caries. It is more common in the mandible than in the maxilla, probably because of the richer vascular supply to the maxilla and the fact that the mandible is more frequently irradiated. Whenever possible, it is desirable to avoid taking radiographs during the first 6 months after completion of radiotherapy, however, to allow time for the mucous membrane to heal. Radiation caries can be minimized by restoring all carious lesions before radiation therapy and initiating preventive techniques of good oral hygiene and daily topical fluoride. The risk for osteoradionecrosis and infection can be minimized by removing all teeth with extensive caries or with poor periodontal support (allowing sufficient time for the extraction wounds to heal before beginning radiation therapy) and adjusting dentures to minimize the risk of denture sores. Removal of teeth after irradiation should be avoided when possible.

Musculature

Radiation may cause inflammation and fibrosis of muscles of mastication resulting in trismus. Masster and pterygoid muscles are commonly involved. Restriction in mouth opening usually starts about 2 months after radiotherapy is completed and progresses thereafter. An exercise program may be helpful in increasing opening distance.

7 Conclusion

Hence the proper justification should be made for diagnostic and therapeutic use of radiation to minimize the complications.

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