Normal Tissue and Tumor Response in Clinical Fractionation Protocols

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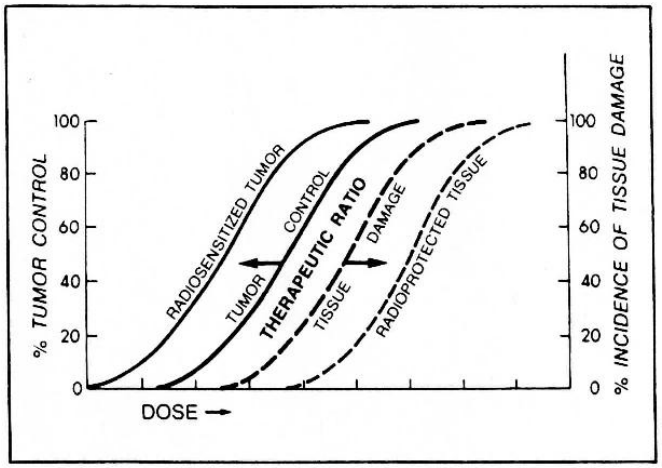
A. Therapeutic ratio



The therapeutic ratio is determined by selecting a level of normal tissue response and then identifying the associated tumor response. For example, at 5% normal tissue response, tumor control is ~25%. With a radioprotector in the mix, at 5% normal tissue response, tumor control is ~90% (therapeutic gain results).

B. Factors that influence tissue tolerance
   1. Inherent cellular radiosensitivity (D_0 and D_q, or α-slope and β-slope)
   2. Regenerative characteristics (turnover rate; related to life span of mature cells)
   3. Structural organization of tissues (special arrangement of FSUs; serial/parallel)
   4. Cytokines and growth factors (responsiveness of cells to these factors)

C. Systemic Radiation Damage

Response of tissues and organs is dependent upon **inherent cellular radiosensitivity** and the **kinetics (turnover rate) of the population as a whole**. The sensitivity of cells to radiation is determined to some degree by its state of maturity and its functional role. Generally speaking, **immature cells are considerably more sensitive to radiation** (as mitotic activity increases, sensitivity also increases). One exception is the lymphocyte.

The time interval between irradiation and expression of damage in late reacting tissues depends on the life-span of the mature functional cells and total dose.

The time interval between irradiation of early reacting tissues and its expression as tissue damage depends on the life-span of the mature functional cells <u>but not the total dose</u>.

Two systems have been used to correlate sensitivity and proliferative ability:

1. Casarett's classification of tissue radiosensitivity:

Cell Type	Characteristics	Systems	Sensitivity
I. Vegetative intermitotic	divide regularly	erythroblasts	high
II. Differentiating intermitotic	partially differentiated	Crypt cells	
III. Reverting postmitotic	do not divide regularly	Liver	
IV. Fixed postmitotic	do not divide	nerve, muscle	low

2. Michalowski's H-type, F-type Classification:
   a. Hierarchal-type tissues (H-type): **Rapid division to replenish cells with a short mature life**. Homeostasis maintains cell numbers at a constant level. **Expression time for damage is dependent on the life span of the mature cells (but not the dose). Time to express is not a good indicator of radiosensitivity.** Cell types include epithelial lining of the G.I. tract, stem cells in bone marrow, skin, and mucosa.
   b. Loss of tissue function is due to the inability of damaged stem cells to replace the depleted functional cells.
   c. Increased severity of damage may be caused by increased dose which results in increased numbers of damaged stem cells and a longer regeneration time.
   d. Flexible-type tissues (F-type): Includes liver, kidney, bladder, lung, spinal cord, brain. Most of the cells in these tissues are not in the cell cycle because they are **cells performing a function and their life span is long and therefore active proliferation of vast numbers of cells is not required**. Stem cells are not programmed for proliferation and because of the long life span of the mature functioning cells; response is delayed (late reacting tissue). Compensatory proliferation will occur when stem cells are recruited into the cell cycle.

      As dose increases (↑), the time interval between irradiation and complications decreases (↓).

      Repair occurs during the latency period. Complications are seen as failed repair and are functional failures rather than clonogenic (kidney is the exception because damage to the glomerulus or tubules is possible and tubules can regenerate from a single cell).
3. Repopulation after exposure
   a. Because the life span of mature early reacting tissues is short (high cell loss), repopulation of damaged cells is rapid (occurs during most therapy schedules). Examples: Jejunal mucosa lag time before the compensatory response is less than 24 h and the colon and stomach is a little longer than 24 h. Prior stimulation (exposure to growth factors, physical manipulation, chemical irritants) or early in the lag phase can shorten the response time.

Large doses may shorten the lag time if given early in the treatment (but has little effect if given late in treatment).

b. Tumors
Tumors behave in a manner similar to early reacting tissues because there is a relatively large growth fraction (ave of 30%) so the 4 Rs are working).

c. Late responding tissues
Cells with a long mature life span are not depleted rapidly after irradiation and therefore the compensatory response (repopulation) and expression of damage to cells of the proliferative compartment is slow. Example: Renal tubule cell depletion takes several months (up to 12 months in some animal models). While acutely responding tissues benefit from extended treatment because of repopulation, late responding tissues do not. The therapeutic gain from extending treatment as a means to increase acute tissue tolerance (assuming repopulation is more rapid in acute tissues compared to tumor tissue) will have no effect on late responding tissue tolerance.

D. Normal Tissue Effects

Target cells for radiation-induced tissue injury.

1. Damage to the vascular bed may be the mediator of the late response and/or it may be depletion of parenchymal/stromal cells. Large differences in doses required for late injury points to parenchymal/stromal cells as the culprits for late effects. However, vascular lesions leading to impaired vascularity occurs after therapeutic doses is well known.
2. The concept of Functional Subunits (FSU) may help to explain the variation in tissue/organ late effect radiosensitivities (including the volume effect).
   a. Functional Subunits (FSU): FSUs are structurally distinct and self-contained units (examples: nephrons in the kidney liver lobule in the liver, and the pulmonary lobule in the lung). Some organs have undefined FSUs where cells can migrate into the irradiated area and repopulate depleted areas (example: skin). For an FSU to survive irradiation, at least 1 clonogen must survive. **Radiation sensitivity depends on intrinsic cellular radiosensitivity (D_0, D_q or α, β) and the number of target cells in a subunit.** There are many FSUs in an organ. If an individual FSU has a small number of cells, low doses of radiation can destroy sufficient numbers of cells to compromise the unit. Variation in total numbers of cells in each subunit appears to correlate with tolerance doses of some organs. Hair depigmentation occurs at a lower dose than skin because hair follicles have fewer melanocytes. For example, hair loss occurs at lower doses than skin for the same reason (fewer clonogenic cells in a subunit).

Type	Organs	Radiosensitivity	Volume
Series	spinal cord, nerves	Little or no reserve cells High dose volumes compromise organ	**Weaker volume effect than parallel FSUs** **Low dose** to a **large volume** may **not** produce any complications. **High dose** to a **small volume may produce** tissue complications (a radiation-induced loss of one FSU results in expression of injury even though the other FSUs in the series are healthy).
Parallel	Kidney, lung, liver	Much larger doses are tolerated with partial organ irradiation	**Strong volume effect** **Reserve cells determine volume effect** Effect is related to the number of FSUs that are NOT irradiated. **Low dose** to a **large volume may produce** serious tissue complications. **High doses** to a **small volume** may **not** produce complications (because of large functional reserve capacity).

Tissues like skin have poorly defined FSUs (respond in a way similar to parallel FSU tissues). Migration of cells from outside the irradiated field can assist with recovery. Therefore, the larger the field, the less likely skin will recover from exposure.

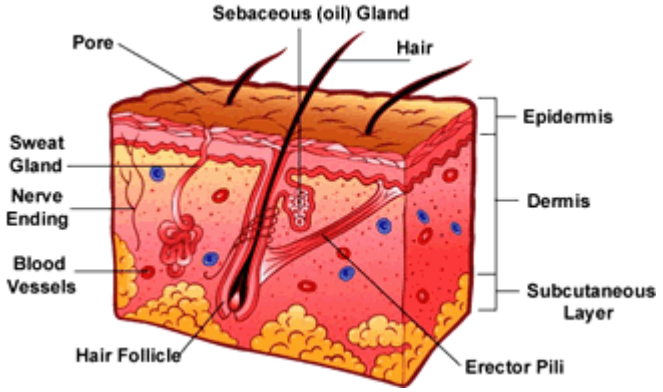
E. Radiation-induced release of factors

1. Interleukin-1 (IL-1) & IL-6 are inflammatory cytokines
   Radiation induces IL-1 (& IL-6) in macrophages. **Radioprotector of hematopoietic cells** by increasing shoulder and D_o. IL-1 and TNF may work together to affect normal tissue and tumor cells.
2. Basic fibroblast growth factor (bFGF) is involved in angiogenesis and induces endothelial cell growth and protects against microvascular damage. It is a **radioprotector of endothelial cells (reduces late effects).** Cells exposed to bFGF respond well to stress (heat, shock, hypoxia, chemicals, and radiation). Microvascular protection is observed more in branching midsize capillaries than non-branching capillaries. In slowly proliferating normal tissues, damage to vessels is responsible for radiation-induced late effects. Radiation tolerance is better in areas of larger vessels in organs (corresponds to high levels of factors) and are low near non-branching capillaries. **bFGF prevents apoptosis**. Also, vascular endothelial growth factor (VEGF) and TNF-α are involved in angiogenesis.
3. Platelet derived growth factor-beta ($PDGF_\beta$) increases damage to vascular tissue and therefore increases late effects.
4. Transforming growth factor-beta (TGF_β) is a fibrotic cytokine and is produced by inflammatory cells and induces a strong inflammatory response (for example, causes pneumonitis). It stimulates growth of connective tissue. It tends to inhibit epithelial cell growth. **Fibrosis and vascular changes are associated with late radiation effects** due to this factor. For example, when there are high levels in the liver, late damage to liver is apparent. Also, increases damage to hematopoietic system. It may down regulate IL-1 and TNF.

5. Tumor necrosis factor (TNF-α): Produced by monocytes and tumor cells. It binds to cell surface receptors which initiate signal transduction pathways. TNF induces proliferation of fibroblasts, inflammatory cells and endothelial cells and so is associated with complications. It causes microvascular obliteration. In clinical trials, administration of TNF causes fatigue, anorexia, weight loss, transient leukopenia. **It is a radioprotector of hematopoietic cells while sensitizing tumor cells to radiation**. Serum concentration of TNF correlates with severity of interstitial pneumonitis, hepatic dysfunction, renal insufficiency, and demyelination. TNF may contribute to the pathophysiology of radiation central nervous symptoms. TNF expression is regulated following radiation at the transcriptional level and involves the protein kinase C (PKC) dependent pathway.
6. Colony stimulating factors (CSF): G-CSF, GM CSF, IL GSF, IL-3, EPO, SCF are also released and assists with regeneration of cells in damaged tissues.

F. Early reacting tissues.

1. Skin
   a. Epidermis: Site of early reactions.
      Epidermis is thick and contains a proliferative basal cell layer, a senescent layer, and a malpighian layer. 100% of basal cells are dividing (2.25×10^6 cells/cm^2). It takes ~13 days for cells to migrate from the basal layer to the Malpighian layer.
   b. Dermis: Site of late reactions.
      The dermis is ~1-3 mm thick with the upper layer (papillary) housing microvessels to supply the epidermis. The remaining dermis (rete dermis) has collagen bundles, fibroblasts, and skin appendages. (i) Fibroblasts and vascular endothelial cells are slowly proliferating but become active after injury. (ii) Dermal fibrosis, telangiectasia and late dermal necrosis are the main late effects.

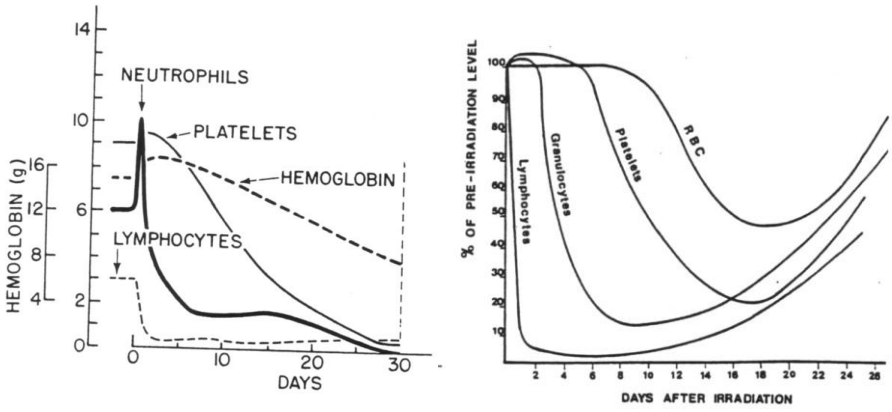


   c. Skin Appendages: Within 1-3 days after irradiation, the death of germinal cells leads to hair dysplasia (short thin hair). Epilation occurs during the third week and regrowth may occur after 1-3 months. Sebaceous glands are as sensitive as hair but sweat glands are less radiosensitive. Regenerated skin may be dry and hairless.

d. Non-Epidermal Elements: Because melanoblasts are slowly dividing, injury leads to depigmentation as a late effect. Hyperpigmentation may occur near the boundary zone.
e. Functional subunit of the skin: The death of two adjacent endothelial cells (of about 10 to 20 total cells per tuft) may lead to collapse of the tuft and eventually the FSU. Atrophy and fibrosis results from loss of fibrocytes and collagen. Fibrosis is a response to growth factors (TGFβ) released during injury in response to necrotic foci.

   Manifestation of normal tissue damage can be complex. In skin, acute erythema can occur in 1-2 days after 2-6 Gy; erythema and epilation can occur 2-3 weeks after 5-10 Gy; desquamation can occur 2-3 weeks after 15-20 Gy; re-epithelialization can take place after 6-8 weeks; late effects are atrophy, fibrosis, necrosis, telangiectasia.

2. Hematopoietic tissue.
   a. Radiosensitive bone marrow is located in the pelvis and vertebrae (60%) with the remainder in the ribs, sternum, skull, scapulae and proximal sections of the femur and humerus. Stem cells are also located in the spleen and circulation.
   b. Killing of stem cells and early committed precursors leads to a decline in the number of mature cells. The reduction of these cells in the peripheral blood is related to their pre-irradiation life span.



3. Lymphoid tissue and the immune system.
   a. Lymphocytes are susceptible to both mitotic death (severe chromosomal aberrations including acentric fragments) and intermitotic death (apoptosis) and therefore strongly influence the immune response to radiation exposure.
   b. B cells are more radiosensitive than T cells but recover quickly.

4. The digestive tract.
   a. Oral cavity

      Acute radiation mucositis (50-60 Gy in 180-200 cGy fractions)

      Desquamation of the oral cavity around day 12 with recovery in 2-3 weeks. Soft palate desquamation is first; then the hypopharynx, vallecula, FOM, cheeks, epiglottis, base of tongue, vocal cords, dorsum of the tongue.

      1st week: Asymptomatic to slight focal hyperemia and edema (because of dilatation of capillaries) in sensitive patients.

      2nd week: Increasing pain and loss of desire to eat. Sense of taste is altered. Bitter and acid flavors are most changed (less change with salty and sweet tastes). Erythema and edema increases and early desquamative mucositis seen. Mucositis is patchy.

      3rd week: Mucositis and swelling with depletion of gland secretions (difficulty in swallowing). Mucositis is confluent

      4th week: Progression of signs. Confluent mucositis sloughs resulting in denuded lamina propria. Mucosa becomes covered by fibrin and polymorphonuclear leukocytes.

      5th week: Maximum radiation damage. Extreme sensitivity to touch, temperature, grainy food. Recovery of epithelial layer may begin during therapy.

      Post therapy: Basal cells migrate into the area and proliferate. In 2-4 weeks, complete resolution is observed.

      The serous acinar cells of the parotid and submaxillary salivary glands undergo interphase death so salivary dysfunction appears early after irradiation, with no threshold dose and little sparing by fractionation. Xerostomia is the main clinical effect that can interfere with nutrition, deteriorate oral hygiene, and predispose a patient to dental problems. Impairment of taste acuity occurs during the third week.

   b. Esophagus

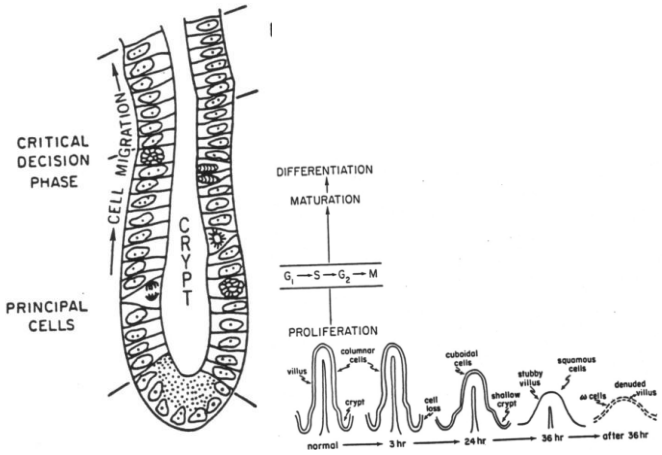
      Mucosa of rapidly dividing cells after radiation displays acute mucosal response of esophagitis and increased thickness of the squamous layer. Symptoms of substernal burning with pain on swallowing about 10-12 days after the start of therapy (return to normal within a week post therapy).

   c. Stomach

      Nausea and often vomiting immediately after radiation occurs. The precursor cells of the gastric glands give rise to mucin-secreting surface columnar cells with short life spans (~3-4 days) and to acid-secreting parietal and pepsinogen-secreting chief cells that have long life spans (hundreds of days).

   d. Small and large intestines

      In the small intestine, stem cells are located towards the bottom of the crypts of Lieberkuhn. Atrophy of the villus occurs after 2-4 days post irradiation (clinical signs appear in about 2 weeks). A regenerative response appears rapidly and within 2-4 days micro- and macro-colonies are detectable. The surviving crypts have the same radiosensitivity to re-irradiation as the un-irradiated crypts (minimal dose memory).



5. The testes.
   a. Stem cells develop into spermatozoa in about 67 days.
   b. Spermatogonial cells are more sensitive than spermatocytes or spermatids.
   c. After a single dose of about 3 Gy oligospermia or azospermia develops in two months (4-8 Gy in 2 Gy fractions). The time to appear is dose dependent (because of direct killing of spermatocytes and spermatids). A dose of 6-8 Gy given in a single dose produces azospermia.
   d. Recovery is very slow and gets slower as dose increases (more than 6 months after 1 Gy). Recovery is delayed for 2 or more years after 6 Gy.
   e. **Fractionated irradiation is more effective than single dose exposures** principally because a large proportion of normally radiosensitive stem cells are in the radioresistant G_o growth compartment at any one time.
   f. Both Leydig and Sertoli cells are sensitive in man. This may explain the severe damage following testicular irradiation during childhood which often requires the administration of replacement therapy in order to achieve normal development.
   g. 0.1 – 0.15 Gy can cause temporary sterility.
6. Radiation effects on the female reproductive system
   a. Vulva
      1. Skin is normal but because of moisture and friction its radiation tolerance dose of 50-70 Gy (given 1.6 to 1.8 Gy per day) at times will be on the high side.
   b. Vagina
      1. Acute effects include erythema, moist desquamation and a confluent mucositis leading to loss of vaginal epithelium that persists for 3-6 months.
      2. Gross abnormalities in the vagina include pale color with a thin atrophic mucosa, inflammation and tissue necrosis with ulceration that can progress to fistula (tolerance dose of 90 Gy before ulceration is likely and more than 100 Gy for fistulas.
   c. Cervix/Uterus
      1. The tolerance dose may reach 200 Gy. Ulcerations may be seen when atrophy of endometrial glands and stroma progresses.

d. Ovary/Reproduction/Endocrine
    1. After irradiation, oocytes die in interphase. A dose of 4-18 Gy induces sterility, depending on age, followed by reduced fertility, increased risk of miscarriage, and genetic mutations.
    2. Ovarian damage is not affected by fractionation apparently due to the very poor repair capacity of oocytes.
    3. Germ cell and endocrine ovarian functions are closely linked. Sterility is hence associated with manifestations of artificial menopause. Premenopausal patients given external pelvic exposure may experience hot flashes. After therapy, the effects of ovarian endocrine insufficiency include vasomotor instability (hot flashes), atrophia, vulvitis and vaginitis, body fat changes, changes of the breast.

G. Late reacting tissues.
1. Lung.
    a. Target cells for radiation damage
        1. Type I pneumocytes are the major structural component of the alveolus and are **fixed post-mitotic cells**. Type II cells produce pulmonary surfactant and are **reverting post-mitotic** cells. The turn-over rate is about 3-5 weeks. In response to injury, stem cell numbers increase and progress towards differentiation into type I and II cells.
        2. Pulmonary endothelial cells (capillary)
        Cells are self-renewal with an estimated doubling time of 8 weeks. Bronchial endothelial cells have an estimated turn over time of 1-3 weeks (shorter when inflammation is present).
    b. Initial pneumonitis (early response) and radiation fibrosis (late response). Pulmonary injury may be clinically manifested 10-16 weeks after the start of radiotherapy (acute radiation pneumonitis which is characterized by dyspnea, cough and fever; and accompanied by radiographic signs of radiation-induced pneumonitis). Early pneumonitis and late lung fibrosis have distinct histologic features but present with similar symptoms (labored breathing and shortness of breath). Pneumonitis is linked to the increase in type II pneumocyte cells (changes in the surfactant levels). Lung damage is strongly dependent on the dose per fraction.
    c. The FSU of the lung is the pulmonary lobule, consisting of the terminal bronchiole and respiratory parenchyma that it serves. The lung is a parallel-type critical organ in that large numbers of bronchi and alveoli are working together such that volume as well as dose are important.
2. The urinary tract.
    Kidney, urinary bladder, urethra, and ureter
    Whether the initial lesion responsible for the genesis of radiation nephropathy is parenchymal (tubular) or endothelial or both is a controversial issue. However, the ultimate pathology involves both tubular and glomerular damage. FSUs (the nephron consisting of the glomerulus with its capillary network and the proximal and distal convoluted tubule arrangements) are arranged in parallel. Although each FSU has cells in series, the parallel nature of the units allows for significant accumulation of damage. The

functional subunit of the bladder is the mucosa, muscularis, vessels, and nerves. Risk of late effects increases with the length of the ureter irradiated.

3. Liver.

   Two main lesions are responsible for radiation-induced liver damage: (i) damage of the endothelium of the central lobular vein, and (ii) direct hepatocellular damage which is expressed only upon attempt at division.

4. Central nervous system.

   a. Late radiation necrosis occurs three months to a few years after exposure. Progressive neurological deficit is seen. Pallor of white matter and diffuse cerebral edema and demylination in addition to vascular thickening perivascular fibrosis, calcium deposition, fibrin deposition, fibrin exudate, petechiae, and chronic inflammatory cell infiltrate. Fine vasculature damage and proliferation of glial cells (oligodendrogliocytes which produce myelin) may be the cause of late effects. Oligodendrocytes and endothelial cells contribute to damage depending on dose. As oligodendrocytes (slowly proliferating) stop dividing because of inherent damage as well as damage to blood vessels, and glial cells, late effects are observed.

      Three main cell categories are found in the CNS: neurons, vascular endothelial cells and glial cells. Neurons are nonproliferating cells in the adult. Glial cells have a slow turnover rate with a small precursor (stem-cell) compartment (1.0%). Endothelial cells also have a slow turnover rate but proliferate rapidly after injury. Myelination of the nerve axon is accomplished by the oligodendrocytes in the CNS and by Schwann cells in peripheral nerves.

   b. Retreatment: Data suggests that after two years, the majority of initial damage is repaired. The extent of repair is dependent on the initial total dose. The brain stem is more sensitive than the cerebrum. It contains a high concentration of white matter and therefore a 10% reduction in total dose is recommended during retreatments. Necrosis is the main complication. Blindness is the endpoint of evaluation. Fraction size is important.

5. Ear

   Irradiation of the external/middle ear can result in acute serious otitis external/media. Painful fullness in the ear (because of otitis media) is common for head and neck irradiations.

6. Eye

   The lens of the eye has a TD 5/5 of 10 Gy (TD 50/5 of 18 Gy) when given in fractions. Radiation retinopathy has microaneurysms, exudates, hemorrhages and new vessel formation. Radiation can result in microvascular damage as well as retinal artery thrombosis.

7. Heart.

   a. Pericardial disease appears as either acute or chronic pericarditis.

      1. Acute pericarditis seldom occurs during treatment or in the first year post therapy and involves viral infection. It varies in severity from transient pericarditis to dense sclerosis with cardiac constriction.

Anterior chest pain, shortness of breath and low-grade fever is observed. Fibrotic tissue replaces the adipose tissue in less than a year. Dense fibrous tissue has spotty hemorrhage, irregular sinusoids and capillaries. Fibrin is characteristic with a shaggy "bread and butter" exudate.

2. Chronic pericarditis appears several years post treatment (40 Gy). The pericardium is thickened and constricted that impedes filling of the heart and reduces cardiac output.

b. Myocardial disease is induced by vascular endothelial damage as well as diffuse fibrosis (threshold dose of 45 Gy). Myocarditis is a slowly evolving lesion with a long latency period which may amount to several years.

c. Coronary artery disease
Small arteries and arterioles are at risk of accelerated atherosclerotic disease as a late consequence of treatment.

d. The heart possesses a high repair capacity with a low α/β ratio (approximately 1.0). Fractionation results in substantial cardiac sparing.

e. Pacemaker failure
1. Early pacemakers were sensitive to microwaves. Linear accelerators use microwaves that cause pacer disruption.
2. Disruption now is seen in the programmable units containing metal oxide semi-conductors (avoidable by keeping modern pacing unit out of the direct beam).

8. Bone
Humeral and femoral heads develop necrosis and femoral neck fracture.

9. Muscle
The clinical endpoint after irradiation is myositis.

10. Rib cage
Pathologic fracture is seen after exposure.

11. Blood vessels (late effects)
The endothelial cells of the vessels are moderately radiosensitive. Irradiation can cause permeability, blebs resulting in occlusions of small vessels, detachment of the endothelial cells from the basement membrane, cell pyknosis, thrombosis, and rupture of the capillary wall. Reduction in the microvascular network leading to ischemia is the most serious problem. Regrowth as telangiectasia can be seen.

Response of arterioles and small arteries (smaller than 100 μm): muscle layer protects vessels from rupture. Delayed reaction includes subendothelial or adventitial fibrosis, hyalinization of the media (dense, acellular, acidophillic infiltrate), accumulation of lipid-laden macrophages in the intima, thrombosis and fibrinoid necrosis.

Response of medium-sized arteries (100-500 μm): Late reaction includes intimal fibrosis with deposition of collagen and fibroblasts, foam cells (lipid-laden macrophages accumulate in the intima and can lead to occlusion), fibrin deposition leading to thrombosis, and foam cell plaques that can lead to atherosclerosis of large vessels. Vasculitis and obliterative end-arteritis (cellular inflammation) is seen.

Response of large arteries: Occlusions and stenotic atheromatous reactions are seen.
Response of veins: Veins are less sensitive to radiation than arteries. In small veins especially in the mesentery intimal and medial fibrosis is seen. Very little effect seen in large veins (some transmural scars that may be healed from tumor invasion rather than radiation-induced invasion of cells). A unique venous response to radiation is seen in the centrolbular veins and the terminal portion of their afferent sinusoids of the liver. Endothelial injury results in delicate fibrin strands in the lumina followed by collagen deposition and subsequent centrolubular necrosis.

A combination of Rubin and Casarett and Emami et al, IJROBP 21:109, 1991

Class I organs	Injury	$TD_{5/5}$ (Gy)	$TD_{50/5}$ (Gy)	Field Size
bone marrow	aplasia, pancytopenia	2.5 30	4.5 40	whole segment
liver	acute and chronic hepatitis	30 50	40 55	whole 1/3
intestine	obstruction, perforation, fistula	40 50	55 65	whole 1/3 or 1/2
stomach	perforation, ulcer, hemorrhage	50 60	65 70	whole 1/3
brain	infarction, necrosis	45 60	60 75	whole 1/3
spinal cord	infarction, necrosis	47 50	- 70	20 cm 5 or 10 cm
heart	pericarditis and pancarditis	40 60	50 70	whole 1/3
lung	acute and chronic pneumonitis	17.5 45	24.5 65	whole 1/3
kidney	acute and chronic nephrosclerosis	23 50	28 45	whole 1/3 or 1/2

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Class II organs	Injury	$TD_{5/5}$ (Gy)	$TD_{50/5}$ (Gy)	Field Size
oral cavity and pharynx	ulceration, mucositis	60	75	50 cm^2
skin	acute and chronic dermatitis, telangiectasia	55	65	100 cm^2
esophagus	esophagitis, ulceration	55 60	65 70	whole 1/3
rectum	ulcer, stenosis, fistula	60	80	no vol effect
salivary glands	xerostomia	32	46	1/3 or 1/2
bladder	contracture	65 80	80 85	2/3 1/3
ureters	stricture	70	100	5-10 cm length
testes	sterilization	1	2	whole
ovary	sterilization	2-3	6-12	whole (age depend.)
growing cartilage, child bone	growth arrest dwarfing	10	30	whole
mature cartilage, adult bone	necrosis fracture, sclerosis	60 60	100 100	whole 10 cm^2
Eye a) retina b) cornea c) lens	blindness cataract	45 50 10	65 60 18	whole whole whole
Endocrine a) thyroid b) adrenal c) pituitary	hypothyroidism hypoadrenalism hypopituitarism	45 60 45	150 200	whole whole whole
peripheral nerves	neuritis	60	100	
a) middle ear b) vestibular ear	serous otitis Meniere's syndrome	30 60	40 70	no vol. eff.

Class III organs	injury	$TD_{5/5}$ (Gy)	$TD_{50/5}$ (Gy)	Field Size
muscle (child)	atrophy	20	40	whole
muscle (adult)	fibrosis	60	80	whole
lymph nodes and lymphatics	atrophy, sclerosis	50	70	whole node
large arteries and veins	sclerosis	80	100	10 cm^2
articular cartilage	none	500	5000	whole
uterus	necrosis, perforation	100	200	whole
vagina	ulcer, fistula	90	100	whole
breast (child)	no development	10	15	whole
breast (adult)	atrophy, necrosis	50	100	whole