Dose-Response Relationships for Model Normal Tissues

Chapter 19

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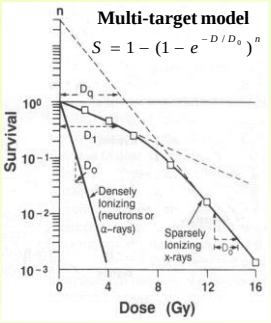
Radiobiology for the Radiologist

Introduction

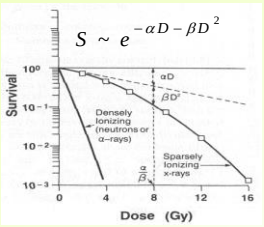
- Dose-response relationships are important for prescribing a proper therapy course
- Response is quantified as either increase of radiation effects in severity, or frequency (% incidence), or both
- In *vitro* vs. in *vivo* experiments
- Different cells have different response based on their reproduction rate (acute vs. late effects)

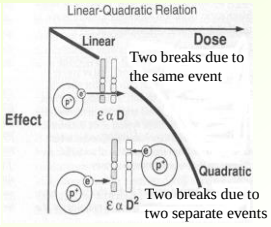
Cell survival curve parameters



- D_1 – initial slope (the dose required to reduce the fraction of surviving cells to 37% of its previous value); D_0 – final slope
- D_q – quasi-threshold, the dose at which the straight portion of the survival curve, extrapolated backward, cuts the dose axis drawn through a survival fraction of unity
- n – extrapolation number
- Radiosensitive cells are characterized by curves with steep slope D_0 and/or small shoulder (low n)

Survival curves and LQ model





- Linear-quadratic model assumes there are two components to cell killing, only two parameters
- An adequate representation of the data up to doses used as daily fractions in clinical radiotherapy

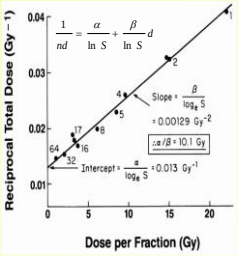
α/β ratios

- If the dose-response relationship is adequately represented by LQ-model:

$$S \sim e^{-\alpha D - \beta D^2}$$

- The dose at which $\alpha D = \beta D^2$, or $D = \alpha/\beta$
- The α/β ratios can be inferred from multi-fraction experiments, assuming :
  - each dose in fractionated regime produces the same effect
  - there is full repair of sub-lethal damage between fractions
  - there is no cell proliferation between fractions

α/β ratios



- For the total dose D divided in *n* equal fractions of dose *d*

$$S = (e^{-\alpha d - \beta d^2})^n \Rightarrow$$

$$-\ln S / nd = \alpha + \beta d$$

- If the reciprocal dose $1/nd$ is plotted against the dose per fraction *d*, the ratio of the intercept/slope gives α/β

α/β ratios

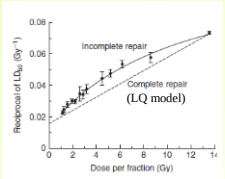


Figure 8.9 Reciprocal dose plot (compare Fig. 8.5a) of data for pneumonitis in mice produced by fractionated irradiation; the points derive from experiments with different dose per fraction (and therefore different fraction numbers), always with 3 hours between doses. The upward bend in the data illustrates lack of sparing because of incomplete repair. From Thames *et al.* (1984), with permission.

- LQ approach is used for iso-effect calculations (equivalent fractionation schemes)
- Has its limitations, for example, when continuous radiation is used (>5cGy/h dose rate), not allowing for complete repair of SLD

α/β ratios

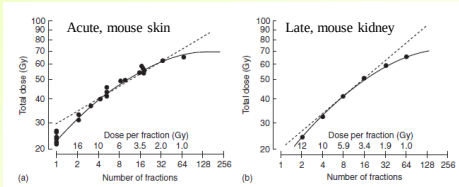


Figure 8.2 Relationship between total dose to achieve an isoeffect and number of fractions. (a) Acute reactions in mouse skin (Douglas and Fowler, 1976), with permission. (b) Late injury in mouse kidney (Stewart *et al.*, 1984), with permission. Note that the relationship for kidney is steeper than that for skin. The broken lines are nominal standard dose (NSD) formulae fitted to the central part of each dataset. The solid lines show the linear-quadratic (LQ) model, from which the guide to the dose per fraction has been calculated.

Slopes are different

α/β ratios

TABLE 1-6 Summary of the Linear-Quadratic Isoeffect Model Parameters and Concepts

Tissue Type	α/β Ratio*	Dose-Response Curve Shape†	Isoeffect Curve Shape‡
Early-responding normal tissues and most tumors	High (6-30 Gy)	Steep initial slope (α is large)	Shallow
Late-responding normal tissues	Low (1-6 Gy)	Shallow initial slope (α is small)	Steep

*Determined from the reciprocal dose plot technique of Douglas BG, Fowler JF: The effect of multiple small doses of x-rays on skin reactions in the mouse and a basic interpretation, Radiat Res 66:401-426, 1976.

†Based on the assumption that differences in the calculated α/β ratio are usually caused by differences in α rather than β.

‡Using the Thames and colleagues isoeffect curve plot. Thames HD, Withers HR, Peters LJ, et al: Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships, Int J Radiat Oncol Biol Phys 8:219-226, 1982. (See also Fig. 1-28).

Table from Gunderson & Tepper, Clinical radiation oncology, 3rd edition

Tumors should follow α/β for early-responding tissues …

α/β ratios

TABLE 1-5 Representative α/β Ratios for Human Normal Tissues and Tumors

Tissue Type (and Endpoint)	α/β Ratio (±95% Confidence Interval)
Early-Responding Normal Tissues	
Skin	
Erythema	10.6 (1.8; 22.8) Gy
Desquamation	11.2 (8.5; 17.6) Gy
Lung: pneumonitis ≤90 days after radiotherapy	>8.8 Gy
Oral mucosa: mucositis	8-15 Gy
Late-Responding Normal Tissues	
Skin	
Telangiectasia	~2.7 (~0.1; 8.1) Gy
Fibrosis	1.7 (0.6; 3.0) Gy
Breast	
Cosmesis	3.4 (2.3; 4.5) Gy
Fibrosis	3.1 (1.8; 4.4) Gy
Lung	
Pneumonitis >90 days after radiotherapy	4.0 (2.2; 5.8) Gy
Fibrosis	3.1 (~0.2; 8.5) Gy
Bowel	
Perforation/stricture	3.9 (2.5; 5.3) Gy
Various other	4.3 (2.2; 9.6) Gy
Spinal cord: myelopathy	<3.3 Gy
Muscle, vasculature, or cartilage: impaired movement	3.5 (0.7; 6.2) Gy
Nerve	
Brachial plexopathy	2.0-3.5 Gy
Optic neuropathy	1.6 (~7; 10) Gy
Head and neck: Various	3.5-4 Gy
Tumors	
Head and neck: nasopharynx	16 (~11; 43) Gy
Vocal cord	~13 Gy
Buccal mucosa	~6.6 (2.9; ∞) Gy
Tonsil	7.2 (3.6; ∞) Gy
Larynx	14.5 (4.9; 24) Gy
Lung: squamous cell carcinoma	~50-90 Gy
Cervix: squamous cell carcinoma	>13.9 Gy
Skin	
Squamous cell carcinoma	8.5 (4.5; 11.3) Gy
Melanoma	0.6 (~1.1; 2.5) Gy
Prostate	1.1 (~3.3; 5.6) Gy
Breast (early-stage invasive ductal, lobular, and mixed)	4.6 (1.1; 8.1) Gy
Esophagus	4.9 (1.5; 17) Gy
Liposarcoma	0.4 (~1.4; 5.4) Gy

Data from Joiner M, van der Kogel A, editors: Basic clinical radiobiology, ed 4, London, 2009, Hodder Arnold.

Table from Gunderson & Tepper, Clinical radiation oncology, 3rd edition

…but they do not always do

Dose-response relationships

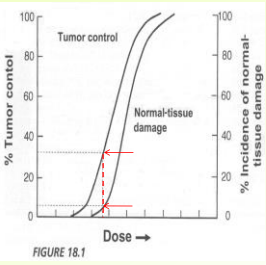


FIGURE 18.1

- Curves are typically sigmoid (S)-shaped for both tumor and normal cells (y-axis is "flipped" compared to cell survival curves)
- Therapeutic ratio (index) TR: tumor response for a fixed level of a normal tissue damage

Therapeutic ratio

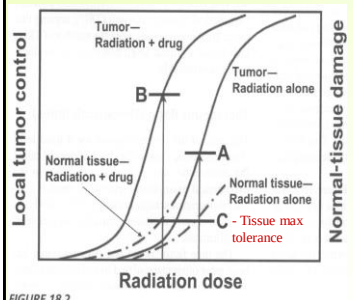


FIGURE 18.2

- The time factor is often employed to manipulate the TR (hyperfractionation for sparing of late-responding normal tissues)
- Addition of a drug, a chemotherapy agent, or a radiosensitizer may improve the TR

Mechanisms of cell death after irradiation

- The main target of radiation is cell's DNA; single breaks are often reparable, double breaks lethal
- Mitotic death – cells die attempting to divide, primarily due to asymmetric chromosome aberrations; most common mechanism
- Apoptosis – programmed cell death; characterized by a predefined sequence of events resulting in cell separation in apoptotic bodies
  - Cell shrinks, chromatin condenses, cell breaks into fragments, no inflammation

Mechanisms of cell death after irradiation

- Additional mechanisms under investigation:
  - Autophagic: cell degradation of unnecessary or dysfunctional cellular components through lysosomes
  - Necrotic: cell swells, leakage of membrane, inflammation
  - Entosis: cell death by invasion
- Bystander (abscopal) effect – cells directly affected by radiation release cytotoxic molecules inducing death in neighboring cells

Assays for dose-response relationships

- Clonogenic end points
  - Depend directly on reproductive integrity of individual cells (cell survival)
  - Cell re-growth *in situ* and by transplantation into another site
- Functional end points
  - Reflect the minimum number of functional cells remaining in a tissue or organ
  - Dose-response can be inferred from multifraction experiments
  - More pertinent to radiation therapy

Early and late responding tissues

- Observation: cells of different tissues demonstrate different response rates to the same radiation dose
- Rapidly dividing self-renewing tissues respond early to the effects of radiation; examples: skin, intestinal epithelium, bone-marrow
- Late-responding tissues: spinal cord, lung, kidney
- Early or late radiation response reflects different cell turnover rates

Clonogenic end points: Skin clones

to sterilize the area (skin cells can migrate)

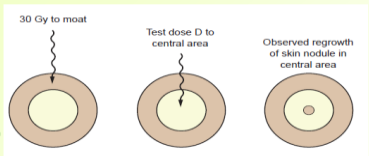
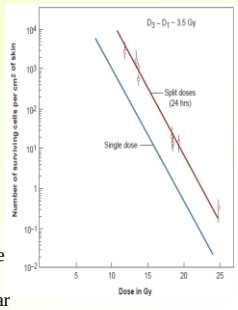


FIGURE 19.3 Technique used to isolate an area of skin for experimental irradiation. A superficial (30 kV) x-ray machine is used to irradiate an annulus of skin to a massive dose of about 30 Gy. An isolated island of intact skin in the center of this "moat" is protected from the radiation by a metal sphere. The intact skin is then given a test dose (D) and observed for nodules of regrowing skin. (Adapted from Withers HR. The dose–survival relationship for irradiation of epithelial cells of mouse skin. *Br J Radiol.* 1967;40:187–194, with permission.)

- Survival curve for mouse skin cells
- Central area is given a test dose and monitored for cell re-growth

Clonogenic end points: Skin clones

FIGURE 19.5 Single-dose and two-dose survival curves for epithelial cells of mouse skin exposed to 29 KVp x-rays. The 37% dose slope (D_0) is 1.35 Gy. The ordinate is not the surviving fraction, as in the survival curves for cells cultured *in vitro*, but is the number of surviving cells per square centimeter of skin. In the two-dose survival curve, the interval between dose fractions was always 24 hours. The curves are parallel, their horizontal separation being equal to about 3.5 Gy; this corresponds to D_q. From a knowledge of D_q and the slope of the survival curve, D_0, the extrapolation number, n, may be calculated. (Adapted from Withers HR. Recovery and repopulation in vivo by mouse skin epithelial cells during fractionated irradiation. *Radiat Res.* 1967;32:227–239; and Withers HR. The dose–survival relationship for irradiation of epithelial cells of mouse skin. *Br J Radiol.* 1967;40:187–194, with permission.)



- There are practical limits to the range of doses
- Determine D_0 =1.35 Gy from the single dose curve
- Determine D_q =3.4 Gy from the curve separation
- Values for D_0 and D_q are similar to those obtained *in vitro*

Clonogenic end points: Crypt cells of the mouse jejunum

FIGURE 19.6 Scanning electron micrograph that allows three-dimensional visualization of the jejunal villi from the hamster. (Magnification × 175.) (From Taylor AB, Anderson JH. Scanning electron microscope observations of mammalian intestinal villi, intervillus floor and crypt tubules. *Micron*. 1972;3:430–453, with permission.)

- Intestinal epithelium is a classic example of a self-renewing system
- Crypt cells divide rapidly and replenish cells on the top of villi
- Mice are given total body irradiation and are sacrificed after 3.5 days
- Radiation effect is assessed based on the number of regenerating crypts per circumference of the sectioned jejunum

Clonogenic end points: Crypt cells of the mouse jejunum

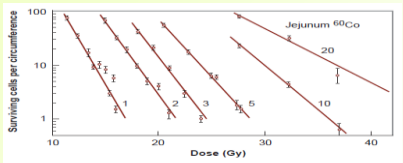


FIGURE 19.8 Survival curves for crypt cells in the mouse jejunum exposed to single or multiple doses of γ-rays (1–20 fractions). The score of radiation damage is the number of surviving cells per circumference (i.e., the number of regenerating crypts per circumference of the sectioned jejunum) counted from sections such as those shown in Figure 19.7. This quantity is plotted on a logarithmic scale against radiation dose on a linear scale. The D_0 for the single-dose survival curve is about 1.3 Gy. The shoulder of the survival curve is very large. The separation between the single-dose survival and two-dose survival curves indicates that the D_q is 4 to 4.5 Gy. (Adapted from Withers HR,

Have to use high minimal dose of 10 Gy to produce enough damage

Clonogenic end points: Crypt cells of the mouse jejunum

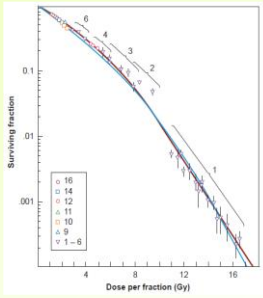


FIGURE 19.9 Effective single-dose survival curve reconstructed from multifraction experiments for clonogenic cells of the jejunal crypts of mice. The numbers on the curve refer to the number of fractions used to reconstruct that part of the curve. The initial and final slopes are about 3.57 and 1.43 Gy, respectively. The quasi-threshold dose is 4.3 Gy. The data are equally well fitted by the linear-quadratic formulation. (Adapted from Thames HD, Withers HR, Mason K, et al. Dose survival characteristics of mouse jejunal crypt cells. *Int J Radiat Oncol Biol Phys*. 1981;7:1591–1597, with permission.)

- To obtain the data for doses below 10Gy - use multiple fractions of smaller dose
- The data are fitted equally by multi-target and LQ models

Clonogenic end points: Kidney tubules

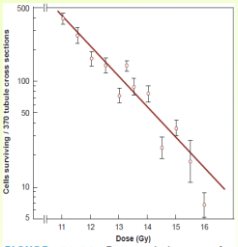


FIGURE 19.14 Dose-survival curve for tubule-regenerating cells. The D_0 is 1.53 Gy. (Adapted from Withers HR, Mason K, Thames HD Jr. Late radiation response of kidney assayed by tubule cell survival. *Br J Radiol*. 1986;59:587–595.)

- Late responding tissue
- One kidney per mouse is irradiated and examined 60 weeks later
- Summary of **response rates** as time required for depletion of the epithelium after a single dose of 14Gy:
  - 3 days in jejunum
  - 12 to 24 days in the skin
  - 30 days in the seminiferous tubules of the testes
  - 300 days in the kidney tubules

Clonogenic end points: donor-recipient approach

- Systems in which cell survival is assessed by transplantation into another site: bone-marrow stem cells, thyroid and mammary gland cells
- Un-irradiated cells are transplanted into recipient animals irradiated supralethally
- Irradiated cells are injected into white fat pads of healthy recipient animals to produce a growing unit

Clonogenic end points: donor-recipient

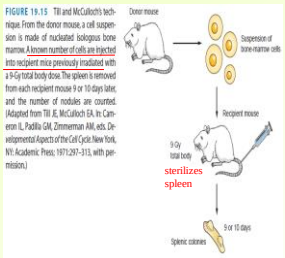
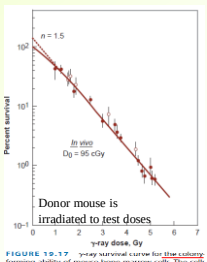


FIGURE 19.15 Till and McCulloch's technique. From the donor mouse, a cell suspension is made of nucleated isologous bone marrow. A known number of cells are injected into recipient mice previously irradiated with a 9-Gy total body dose. The spleen is removed from each recipient mouse 9 or 10 days later, and the number of nodules are counted. (Adapted from Till JE, McCulloch EA. In: Cameron IL, Padilla GM, Zimmerman AM, eds. Developmental Aspects of the Cell Cycle. New York, NY: Academic Press; 1971:297–313, with permission.)



Donor mouse is irradiated to test doses

FIGURE 19.17 γ-ray survival curve for the colony-forming ability of mouse bone marrow cells. The cells are irradiated in vivo in the donor animal and grow into colonies in the spleens of supralethally irradiated recipient animals. (Adapted from McCulloch EA, Till JE

Normal tissue clonogenic assays summary

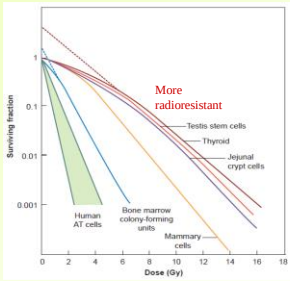


FIGURE 19.20 Summary of survival curves for clonogenic assays of cells from normal tissues. The human AT cells are included because they are the most sensitive mammalian cells. The bone marrow colony-forming units, together with the mammary and thyroid cells, represent systems in which cells are irradiated and assayed by transplantation into a different tissue in recipient animals. The jejunal crypt and testis stem cells are examples of systems in which cells are assayed for regrowth *in situ* after irradiation.

- Radiosensitivity of a cell line is determined by the curve shoulder (D_q parameter)
- Significant variability observed

Human AT - most radiosensitive mammalian cells (for comparison)

Dose-response curves for functional end points

- Can be obtained on pig and rodent skin by assessing skin reaction
- For mouse lung system based on breathing rate, assess early and late response
- Spinal cords of rats by observing myelopathy after local irradiation
  - complex system
  - various syndromes are similar to those described in humans

Myelopathy - functional disturbance or pathological change in the spinal cord

Spinal cord system

- Assess late damage caused by local irradiation of the spinal cords of rats
- First symptoms develop after 4 to 12 months
- Delayed injuries peak at 1 to 2 years postirradiation
- The regimen of dose delivery has a strong effect on the resultant effect such as the extend of necrosis, loss of functionality, etc.
- Obtain the information on the tolerance to radiation

Spinal cord system

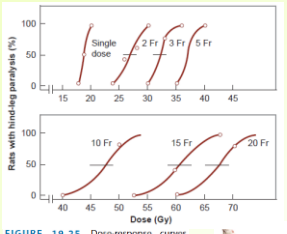


FIGURE 19.25 Dose-response curves for the induction of hind leg paralysis in rats following irradiation of a section of the spinal cord (L2–L5). Note how the dose necessary to produce paralysis increases rapidly with increasing numbers of fractions. (Adapted from van der Kogel AJ. *Late Effects of Radiation on*

- Dose-response relationship is steep
- Fractionation demonstrates dramatic sparing (lower graph)
- Latency decreases with increase in dose
- Variation with the region of cord irradiated

Spinal cord system

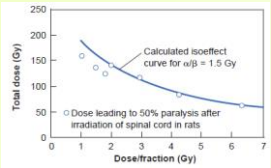


FIGURE 19.26 The data points show total dose, as a function of dose per fraction, to produce paralysis in 50% of rats after irradiation of the spinal cord. The curve is an isoeffect relationship based on the linear-quadratic equation with an α/β value of 1.5 Gy. The experimental data suggest that the linear-quadratic model overestimates tolerance for dose-per-fraction values less than 2 Gy. This may be a result of incomplete repair because the interfraction interval was only 4 hours. (Adapted from van der Kogel AJ. Central ner-

- Total dose vs. dose per fraction
- Data fitted with LQ model for α/β=1.5 Gy
- LQ model overestimates the tolerance for small doses per fraction
  - Could be the result of too short repair time between the fractions

Spinal cord system

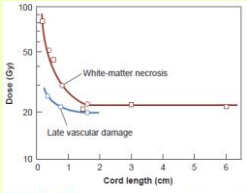


FIGURE 19.27 The dependence of spinal cord tolerance on the length of cord irradiated in the rat. For short lengths of cord, shorter than about 1 cm, tolerance for white matter necrosis shows a marked dependence on the length of cord irradiated. Late vascular injury shows less dependence on cord length. Beyond a few centimeters, the tolerance dose is virtually independent of the length of cord irradiated. (Adapted from van der Kogel AJ. Central nervous system radiation injury in

- The total volume of irradiated tissue has to have an effect on the resultant injury
- Functional subunits (FSUs) in a spinal cord are arranged in linear fashion therefore above a certain length of ~1cm the dependence is very weak

Clinical Response of Normal Tissues

Chapter 20

Eric J. Hall., Amato Giaccia,
Radiobiology for the Radiologist

Normal tissues in radiation therapy

- The target volume in radiotherapy necessarily includes normal tissues
  - Malignant cells infiltrate into normal structures, which must be included as a tumor margin
  - Normal tissues within the tumor (soft tissue and blood vessels) are exposed to the full tumor dose
  - Normal structures in the entrance and exit areas of the radiation beam may be exposed to clinically relevant doses

Tissue response to radiation damage

- Cells of normal tissues are not independent
- For a tissue to function properly its organization and the number of cells have to be at a certain level
- Typically there is no effect after small doses
- The response to radiation damage is governed by:
  - The inherent cellular radiosensitivity
  - The kinetics of the tissue
  - The way cells are organized in that tissue

Effects beyond cell killing

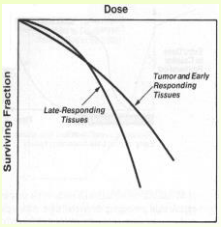
Mediated by inflammatory cytokines

- Nausea or vomiting that may occur a few hours after irradiation of the abdomen
- Fatigue felt by patients receiving irradiation to a large volume, especially within the abdomen
- Somnolence that may develop several hours after cranial irradiation
- Acute edema or erythema that results from radiation-induced acute inflammation and associated vascular leakage

Response to radiation damage

- In tissues with a rapid turnover rate, damage becomes evident quickly
- In tissues in which cells divide rarely, radiation damage to cells may remain latent for a long period of time and be expressed very slowly
- Radiation damage to cells that are already on the path to differentiation (and would not have divided many times anyway) is of little consequence - they appear more *radioresistant*
- Stem cells appear more *radiosensitive* since loss of their reproductive integrity results in loss of their potential descendants
- At a cell level survival curves may be identical, but tissue *radioresponse* may be very different

α/β ratios



- The value of the α/β ratio tends to be
  - larger (~10 Gy) for early-responding tissues and tumors
  - lower (~2 Gy) for late-responding tissues
- There are exceptions
  - prostate cancer ~3 (or less)
  - breast cancer ~4

Early and late effects

- *Early* (*acute*) effects result from death of a large number cells and occur within a few days or weeks of irradiation in tissues with a rapid rate of turnover
- Examples: the epidermal layer of the skin, gastrointestinal epithelium, and hematopoietic system
- The time of onset of early reactions correlates with the relatively short life span of the mature functional cells
- Acute damage is repaired rapidly and may be completely reversible

Early and late effects

- *Late* effects occur predominantly in slow-proliferating tissues, and appear after a delay of months or years from irradiation
- Examples: tissues of the lung, kidney, heart, liver, and central nervous system
- The late reactions are very sensitive to dose fractionation
- Late damage may improve but is never completely repaired (could have a vascular component and loss of parenchymal cells)

Early and late effects

- *Consequential late effect* - a late effect consequent to, or evolving out of, a persistent severe early effect; an early reaction in a rapidly proliferating tissue may persist as a chronic injury
- Occurs upon depletion of the stem-cell population below levels needed for tissue restoration
- The earlier damage is most often attributable to an overlying acutely responding epithelial surface. Example: fibrosis or necrosis of skin consequent to desquamation (skin shedding) and acute ulceration

Functional subunits in normal tissues

- The relationship between the survival of clonogenic cells and organ function or failure depends on the structural organization of the tissue: tissues may be thought of as consisting of **functional sub-units (FSUs)**
- In some tissues the FSUs are discrete, anatomically delineated structures; examples: the nephron in the kidney, the lobule in the liver
- In other tissues, the FSUs have no clear anatomic demarcation; examples: the skin, the mucosa, and the spinal cord
- The response to radiation of these two types of tissue is quite different

Functional subunits in normal tissues

- The survival of **structurally defined** FSUs depend on the survival of one or more clonogenic cells within them, which are easily depleted by low doses
- Surviving clonogens cannot migrate from one unit to another
- Tissue survival in turn depends on the number and radiosensitivity of these clonogens
- Examples: the lung, liver, and exocrine organs (salivary glands, sweat glands, etc.)

Functional subunits in normal tissues

- In **structurally undefined** FSUs the clonogenic cells that can re-populate after the depletion by radiation are not confined to one particular FSU
- Clonogenic cells can migrate from one FSU to another and allow repopulation of a depleted FSU
- Examples: reepithelialization of a denuded area of skin can occur either from surviving clonogens within the denuded area or by migration from adjacent areas.

Tissue rescue unit

- To link the survival of clonogenic cells and functional survival, introduce a concept of the **tissue rescue unit**: the minimum number of FSUs required to maintain tissue function. Model assumptions:
  - The number of tissue rescue units in a tissue is proportional to the number of clonogenic cells
  - FSUs contain a constant number of clonogens
  - FSUs can be repopulated from a single surviving clonogen
- Not all tissue fit the classification by this model

The volume effect in radiotherapy

- Generally, the total dose that can be tolerated depends on the volume of irradiated tissue
- However, the spatial arrangement of FSUs in the tissue is critical
  - FSUs are arranged in a series. Elimination of any unit is critical to the organ function
  - FSUs are arranged in parallel. Elimination of a single unit is not critical to the organ function

The volume effect in radiotherapy

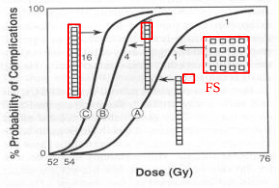


FIGURE 19.1 Relationship between dose and probability of complications for different types of normal tissues. Curve A relates to a normal tissue in which the functional subunits are not arranged serially regardless of whether one or all subunits are exposed (i.e., regardless of field size). It also applies to a normal tissue in which functional subunits are arranged serially if only one subunit is exposed (i.e., if the field is small). Note that the curve is relatively shallow (i.e., the probability of a complication rises relatively slowly with dose). Curves B and C refer to a tissue with serially arranged functional subunits; the complication curve gets steeper and moves to lower doses as the treatment field size increases. For example, curves B and C, respectively, relate to 4 or 16 functional subunits exposed. (Note that

- In tissue with FSUs arranged serially, the radiation effect is binary with a threshold (spinal cord)
- In tissue with FSUs arranged in parallel, there is a large reserve capacity, the radiation effect is gradual (kidney and lung)
- In tissue with no well-defined FSUs the effect is similar to the parallel arrangement tissue

Casarett's classification of tissue radiosensitivity

- Based on histological observations of early cell death
- All parenchymal cells are divided into four major categories I (most sensitive) through IV; supporting structure cells are placed between groups II and III
- The general trend: sensitivity decreases for highly differentiated cells, that do not divide regularly, and have a longer life span
- Exception: small lymphocytes – do not divide, but are very radiosensitive

Casarett's classification of tissue radiosensitivity

TABLE 20.1 Categories of Mammalian Cell Sensitivity

Cell Type	Properties	Examples	Sensitivity[a]
I. Vegetative intermitotic cells	Divide regularly; no differentiation	Erythroblasts Intestinal crypt cells Germinal cells of epidermis	High
II. Differentiating intermitotic cells	Divide regularly; some differentiation between divisions	Myelocytes	
Connective tissue cells[b]			
III. Reverting postmitotic cells	Do not divide regularly; variably differentiated	Liver	
IV. Fixed postmitotic cells	Do not divide; highly differentiated	Nerve cells Muscle cells	Low

[a]Sensitivity decreases for each successive group.
[b]Intermediate in sensitivity between groups II and III.
Based on Rubin P, Casarett GW. *Clinical Radiation Pathology*. Vol 1. Philadelphia, PA: WB Saunders; 1968, with permission.

Michalowski's classification

- Tissues are following either "hierarchical" or "flexible" model, many tissues are hybrids of these two extremes
- Hierarchical model tissue consists of cells of three distinct categories (bone marrow, intestinal epithelium, epidermis)
  - Stem cells, capable of unlimited proliferation
  - Functional cells: fully differentiated, incapable of divisions, die after a finite lifespan
  - Maturing partially differentiated cells: descendants of stem cells, still multiplying
- Flexible model tissue consists of cells that rarely divide under normal conditions, no strict hierarchy (liver, thyroid, dermis)

Growth factors

- Growth factors are proteins that bind to receptors on the cell surface, with the primary result of activating cellular proliferation and/or differentiation. Many growth factors are quite versatile, acting on numerous different cell types, while others are specific to a particular cell type
- The response of a tissue to radiation is influenced greatly by a host of growth factors:
  - Interleukin-1 acts as radioprotectant of hematopoetic cells
  - Basic fibroblast growth factor induces endothelial cell growth, inhibits radiation-induced apoptosis, and therefore protects against microvascular damage
  - Platelet-derived growth factor β increases damage to vascular tissue
  - Transforming growth factor β (TGF–β), induces a strong inflammatory response
  - Tumor necrosis factor (TNF) induces proliferation of inflammatory cells, and endothelial cells and so is associated with complications. TNF protects hematopoietic cells and sensitizes tumor cells to radiation.

Radiosensitivity of specific tissues and organs

- Compilation of data (1968) in Table 20.2, pp.334-5
- Tolerance for each organ and for a partial organ irradiation (volume fraction)
  - TD5/5, Gy: dose for complication probability 5% in 5 years
  - TD50/5 dose for complication probability of 50% in 5 years
- Organs are classified as:
  - Class I - fatal or severe morbidity
  - Class II - moderate to mild morbidity
  - Class III - low morbidity

Radiosensitivity of specific tissues and organs

- QUANTEC data compilation Table 20.3, pp.345-9 (published in "red journal", Int. J. Radiation Oncology Biol. Phys., Vol. 76, Issue 3, Supplement, S1-S160, 2010)
- Our clinic uses compilation of "Timmerman's" dose constraints (hypo-fractionation, 2012)

Skin

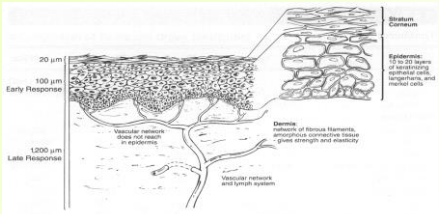


FIGURE 19.2 ● The skin from the perspective of a radiation biologist. The epidermis has a thickness of about 100 μm, though it varies with body site (30–300 μm). It consists of 10 to 20 layers of keratinizing epithelial cells. This is a self-renewing tissue. The stem-cell compartment forms part of the basal layer and has an unlimited capacity for proliferation. Cells produced in the basal layer migrate to the surface, differentiating as they do so, but retaining some proliferative potential. Cells in the surface layer are fully differentiated and keratinized and gradually are sloughed off and lost. The transit time for an epidermal cell to pass from the basal layer to the surface is 12 to 48 days, depending on skin thickness. The dermis is about 1,200 μm thick (1,000–3,000 μm) and consists of a dense network of fibrous filaments and connective tissue. The vascular network, capillaries, and lymph system are in the dermis. The vascular network does not extend into the epidermis. Two distinct waves of reactions are observed in the skin following irradiation. An early, or acute, reaction is observed about 10 days after a single dose and results from damage to the epidermis. Late reactions occur months later, mediated through damage to the dermis, principally to the vasculature. In clinical radiation therapy, late damage is now the dose-limiting reaction, because the buildup associated with megavoltage beams spares the epidermis.

Hematopoetic system

- Tissues are located primarily in the bone marrow
- In the normal healthy adult, the liver and spleen have no hematopoietic activity, but they can become active after partial-body irradiation
- The hematopoetic system is very sensitive to radiation, especially the stem cells
- There is little sparing from either fractioning the dose or lowering the dose rate

Hematopoetic system

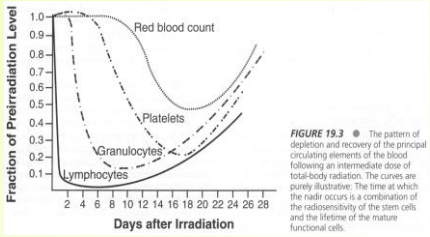


FIGURE 19.3 ● The pattern of depletion and recovery of the principal circulating elements of the blood following an intermediate dose of total-body radiation. The curves are purely illustrative. The time at which the nadir occurs is a combination of the radiosensitivity of the stem cells and the lifetime of the mature functional cells.

•The complex changes seen in peripheral blood count after irradiation reflect differences in transit time from stem cell to functioning cell for the various circulatory blood elements

Lymphoid tissue and the immune system

- The lymphoid tissues (e.g., nodes, spleen) are very radiosensitive and get depleted by small radiation doses
- The effect of irradiation on the immune function is complex, depending on the volume irradiated and the number of surviving cells
- A total-body dose of 3.5 to 4.5 Gy inhibits the immune response against a new antigen
- Partial-body irradiation, characteristic of ordinary radiation therapy, has only a limited effect on the immune response, and whether it influences metastatic dissemination is controversial

Other organs

- The **lung** is an intermediate- to late-responding tissue. Two waves of damage can be identified, an acute pneumonitis and a later fibrosis. The lung is among the most sensitive late-responding organs.
- Together with the lung, the **kidney** is among the more radiosensitive late-responding critical organs. Dose of 30 Gy in 2-Gy fractions to both kidneys results in nephropathy
- In terms of radiosensitivity, the **liver** ranks immediately below kidney and lung. FSUs are in parallel, so that much larger doses are tolerated if only part of the organ is exposed. Fatal hepatitis may result from 35 Gy (conventional fractionation) to the whole organ
- The **nervous system** is less sensitive to radiation than other late-responding organs

Radiosensitivity of tissues and organs

High Radiosensitivity
Lymphoid organs, bone marrow, blood, testes, ovaries, intestines
Fairly High Radiosensitivity
Skin and other organs with epithelial cell lining (cornea, oral cavity, esophagus, rectum, bladder, vagina, uterine cervix, ureters)
Moderate Radiosensitivity
Optic lens, stomach, growing cartilage, fine vasculature, growing bone
Fairly Low Radiosensitivity
Mature cartilage or bones, salivary glands, respiratory organs, kidneys, liver, pancreas, thyroid, adrenal and pituitary glands
Low Radiosensitivity
Muscle, brain, spinal cord

Reference: Rubin, P. and Casarett. G. W.: Clinical Radiation Pathology (Philadelphia: W. B. Saunders. 1968).

Scoring systems for tissue injury: LENT and SOMA

- The European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) formed working groups to produce systems for assessing the late effects of treatment on normal tissues
- Two acronyms introduce the new scoring system for late effects toxicity and the key elements forming the scales:
  LENT = Late Effects Normal Tissues (grades 1 – minor through 4 - irreversible functional damage)
  SOMA = Subjective, Objective, Management, and Analytic (descriptors of toxicity)

LENT and SOMA example

TABLE 20.5 Central Nervous System SOMA

Subjective	Objective	Management	Analytic
Headache	Neurologic deficit	Anticonvulsives	MRI
Somnolence	Cognitive function	Steroids	CT
Intellectual deficit	Mood and personality changes	Sedation	MRS
			PET
Functional competence	Seizures		Magnetic mapping
Memory			Serum
			Cerebrospinal fluid

Based on Late Effects of Normal Tissues Consensus Conference, San Francisco, CA, August 26–28, 1992. Rubin P, Constine LS, Fajardo LF, Phillips TL, Wasserman TH, eds. Published as a special issue of *Int J Radiat Oncol Biol Phys.* 1995;31:1049–1081.

- There is a number of anatomical sites for which LENT and SOMA are scored

Summary

- Dose-response relationships based on cell assays
  - Clonogenic end points
  - Functional end points
- Clinical response of normal tissues
  - Functional subunits
  - Other complicating factors
  - Tissue tolerance