Basic Radiobiology

Why do we treatment cancer tumours with ionising radiation? What is the aim? The simplest answer is that we are trying to induce cell death or at least reproductive death.

The Therapeutic Ratio

The aim of radiotherapy is to deliver a sufficient quantity of ionising radiation to a cancerous tumour to destroy it whilst minimising irradiation to normal tissue. The two sigmoid curves (figure 1) represent tumour control probability (TCP) (curve A) and normal tissue complication probability (NTCP) (curve B).
The optimum choice of irradiation technique should be such that it maximizes the TCP and simultaneously minimizes the NTCP. Typically TCP ≥ 0.5 and NTCP ≤ 0.05. The further curve B (NTCP) is to the right of curve A (TCP), the easier it is to achieve the radiotherapeutic goal, the larger is the therapeutic ratio and the less likely will it be that the treatment causes complications. The therapeutic ratio generally refers to the ratio of the TCP and NTCP at a specified level of response (usually 0.05) for normal tissue.

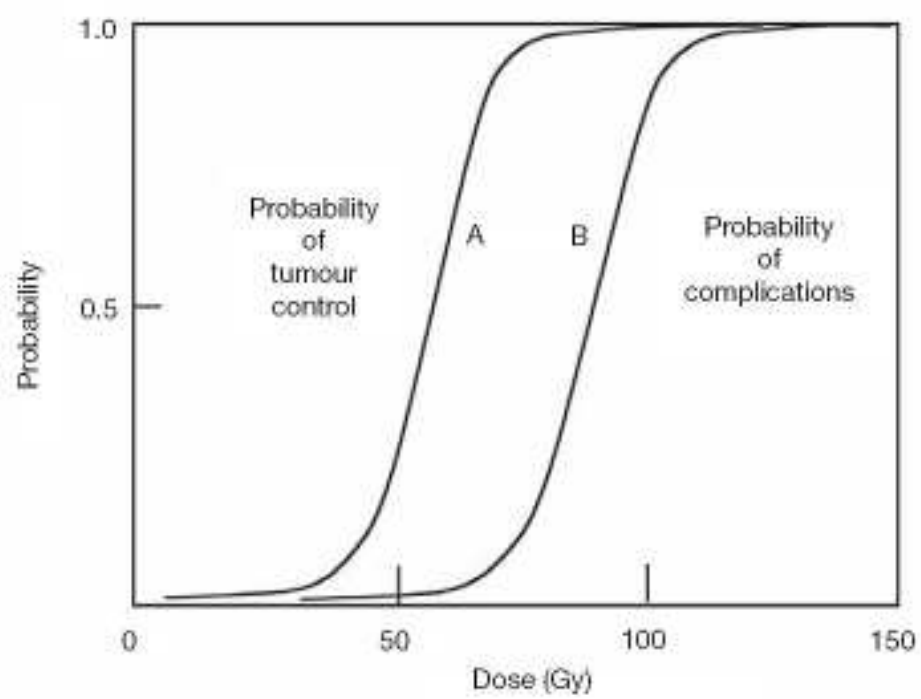

Figure 1: The principle of therapeutic ratio. Curve A represents the TCP, curve B the probability of complications. The total clinical dose is usually delivered in 2 Gy fractions.

For differentiated cells that do not proliferate such as nerve and muscle, cell death can be defined as the loss of specific function. For proliferating cells such as stem cells in the intestinal epithelium, cell death equates to the loss of reproductive integrity (reproductive death). So after radiation treatment a particular cell may retain the ability to make proteins or synthesis DNA but if it had lost the ability to reproduce, it is effectively dead. The cells are destroyed via mitotic death or apoptosis. This is what we trying to achieve with radiotherapy.

Survival curves for mammalian cells can be represented as shown in figure 2.

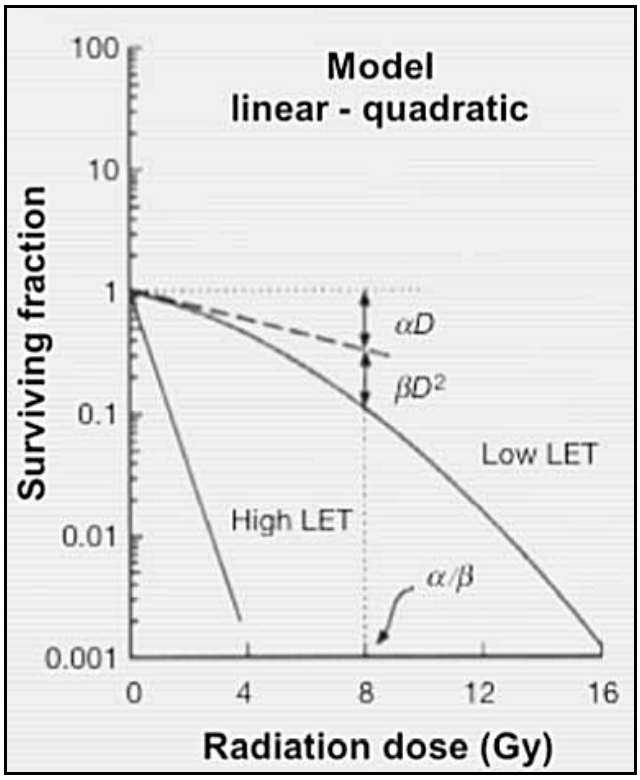

Figure 2: Linear Quadratic Model of Cell Survival

At low doses for sparsely ionising (low LET) radiation such as x-rays, the survival curve begins straight on the log-linear plot. This means that the surviving fraction is an exponential function of dose. At higher doses the curve bends. This curved region extends over a dose range of a few Gray. At very high doses, the survival curve tends to become linear again.
For densely ionising (high LET) radiation such as α-particles of low energy neutrons, the cell survival curve is linear from the origin. That is, survival approximates to an exponential function of the dose.
The Linear Quadratic Model assumes that there are two components to cell destruction by radiation. One is proportional to the dose and the other to the square of the dose. The notion of a component of cell inactivation that varies with the square of the dose introduces the concept of dual-radiation action.

The expression for cell survival can be represented as:

$$S = e^{-\alpha D - \beta D2}$$

Where **S** is the fraction of cells surviving a dose **D** and **α** and **β** are constants. The components of cell killing that are proportional to dose and to the square of the dose are equal if:

$$\alpha D = \beta D^2$$

or

$$D = \alpha/\beta$$

The linear and quadratic contributions to cell death are equal at a dose that is equal to the ratio of α and β.

The cell survival curves for late responding tissues are more curved than those for early responding tissues. For early effects the ratio **α/β** is large and **α** dominates at low doses. For late effects **α/β** is small and **β** has an influence at doses lower than for early responding tissues. The **α** and **β** components of mammalian cell killing are equal at approximately **α/β** = 10 Gy and **α/β** = 3 Gy for early and late effects, respectively.

Mechanisms of Cell Destruction

DNA Target – cells are killed by radioactive tritiated thymidine incorporated into the DNA. The radiation dose results from short-range α-particles and is very localised. Also certain structural analogues of thymidine are incorporated selectively into DNA in place of thymidine if substituted in cell culture growth medium. This substitution dramatically increases the radiosensitivity of mammalian cells.

The Bystander Effect – this is defined as the induction of biologic effects in cells that are not directly traversed by a charged particle. Experiments have shown that up to 30% of cells show biological damage even though less than 1% were calculated to have undergone nuclear traversal. This observation has been extended by the use of single-particle microbeams. Further, there is evidence that medium transferred from irradiated cells induce a biologic effect when added to non-irradiated cells. This suggests that irradiated cells secrete a molecule into the medium capable of killing cells.

Apoptotic and Mitotic Death – apoptosis or programmed cell death is characterised by a sequence of morphologic events. The cells first ceases to communicate with neighbouring cells, it rounds up and detaches from them. Condensation of the chromatin at the nuclear membrane and fragmentation of the nucleus then occurs. There is cell shrinkage due to cytoplasmic condensation and eventually the cell separates into a number of membrane-bound fragments called apoptotic bodies. The most common form of cell death from radiation is mitotic death. Cells die due to damages chromosomes while attempting to divide.

Relative Biological Effectiveness (RBE)

As the LET of radiation increases, the ability of the radiation to produce biological damage also increases. The relative biological effectiveness (RBE) compares the dose of test radiation to the dose of standard radiation to produce the same biological effect. The standard radiation has been taken as 250 kVp X-rays for historical reasons, but is now recommended to be ^{60}Co γ-rays. The RBE is defined by the following ratio:

$$\text{RBE} = \frac{\text{Dose from standard radiation to produce a given biological effect}}{\text{Dose from test radiation to produce the same biological effect}}$$

The RBE is a complex quantity and varies with radiation quantity (LET), radiation dose, number of fractions, dose rate and biologic system or end-point. In general, the RBE increases with the LET to reach a maximum RBE of 3–8 (depending on the level of cell kill) at LET ~ 200 keV/m and then decreases because of energy overkill. An increase in the RBE in itself offers no therapeutic advantage unless there is a differential effect making the RBE for normal tissue smaller than that for the tumour, increasing the relative level of tumour cell killing and the therapeutic ratio.

Dose Rate and Fractionation

For the same dose, radiation delivered at a lower dose rate may produce less cell killing than radiation delivered at a higher dose rate, because sublethal damage repair occurs during the protracted exposure. As the dose rate is reduced, the slope of the survival curve becomes shallower and the shoulder tends to disappear, since in the linear quadratic model a does not change significantly; however, $\beta \rightarrow 0$.

The typical dose rates used in radiotherapy are of the order of:

- 1 Gy/min in standard radiotherapy and high dose rate (HDR) brachytherapy
- 0.1 Gy/min in TBI
- 0.01 Gy/min in low dose rate (LDR) brachytherapy.

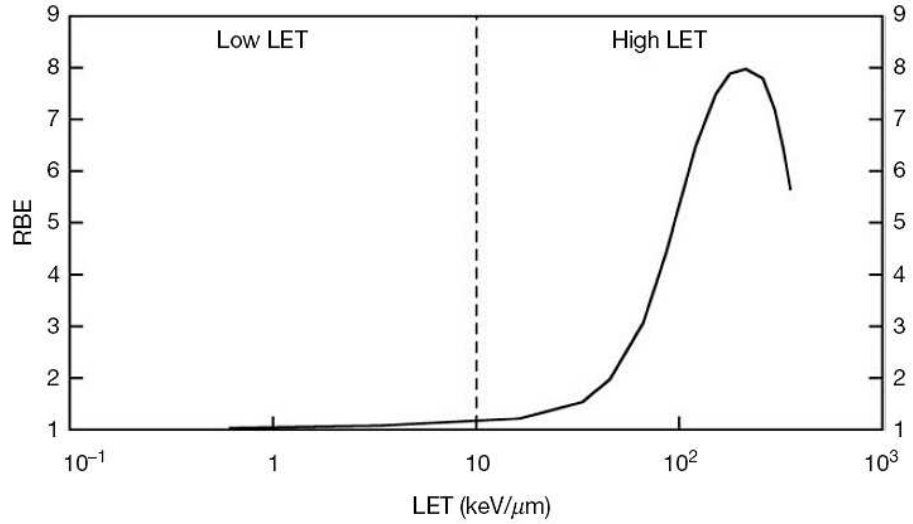

Figure 3: RBE v LET

In figure 3 the vertical dashed line separates the low LET region, where RBE ~ 1, from the high LET region, where the RBE first rises with the LET, reaches a peak of about 8 for LET ~ 200 keV/mm, and then drops with a further increase in the LET.

Fractionation of radiation treatment so that it is given over a period of weeks rather than in a single session results in a better therapeutic ratio. However, to achieve the desired level of biological damage the total dose in a fractionated treatment must be much larger than that in a single treatment.

The basis of fractionation is rooted in five primary biological factors called the five Rs of radiotherapy:

Radiosensitivity - mammalian cells have different radiosensitivities.

Repair - mammalian cells can repair radiation damage. This is a complex process that involves repair of sublethal damage by a variety of repair enzymes and pathways.

Repopulation - cells repopulate while receiving fractionated doses of radiation.

Redistribution in proliferating cell populations throughout the cell cycle phases increases the cell kill from a fractionated treatment relative to a single session treatment.

Reoxygenation of hypoxic cells occurs during a fractionated course of treatment, making them more radiosensitive to subsequent doses of radiation. Reoxygenation is the process by which cells that are hypoxic at the time of irradiation become oxygenated afterward. The extent of reoxygenation and the rapidity with which it occurs varies widely. If it is rapid and complete, hypoxic cells have little influence on the outcome of a fractionated radiation schedule.

Conventional fractionation is explained as follows: division of dose into multiple fractions spares normal tissues through repair of sublethal damage between dose fractions and repopulation of cells. The former is greater for late reacting tissues and the latter for early reacting tissues. Concurrently, fractionation increases tumour damage through reoxygenation and redistribution of tumour cells. A balance is achieved between the response of tumour and early and late reacting normal tissues, so that small doses per fraction spare late reactions preferentially, and a reasonable schedule duration allows regeneration of early reacting tissues and tumour reoxygenation to likely occur. The current standard fractionation is based on five daily treatments per week and a total treatment time of several weeks. This regimen reflects the practical aspects of dose delivery to a patient, successful outcome of patient treatments and convenience to the staff delivering the treatment.
Other fractionation schemes are being studied with the aim of improving the therapeutic ratio. Some of these are hyperfractionation, accelerated fractionation and CHART:

1. Hyperfractionation uses more than one fraction per day with a smaller dose per fraction (<1.8 Gy) to reduce long term complications and to allow delivery of higher total tumour dose.
2. Accelerated fractionation reduces the overall treatment time, minimizing tumour cell repopulation during the course of treatment.
3. CHART (continuous hyperfractionated accelerated radiation therapy) is an experimental programme used with three fractions per day for 12 continuous days.

Radiation Damage Repair and Dose Rate Effect

DNA Repair Pathways

Ionising radiation induces base damage, single-strand breaks, double-strand breaks and DNA protein cross-links. Cells have evolved an intricate series of sensors and pathways to respond to each type of radiation-induced damage. DNA double-strand breaks, the most lethal form of radiation damage, is repaired by nonhomologous recombination in the G_1 phase of the cell cycle and homologous recombination in the S/G_2 phase of the cell cycle.

Hereditary Syndromes Affecting Radiosensitivity

Ataxia-telangiectasia (AT) is an autosomal recessive disorder that is due to a defect in the ATM kinase. AT cells fail to activate checkpoints in response to DNA damage, exhibit increased genomic instability at the chromosome level and have an increased risk of lymphomas. AT cells and individuals are hypersensitive to ionising radiation.
Severe Combined Immunodefficiency Syndrome (SCID) humans are immune deficient and radiosensitive owing to a mutation in Artemis. Cells defective in Artemis are defective in nonhomologous recombination and are radiosensitive.
Nijmegen Breakage Syndrome (NBS) is a very rare disorder that results in increased cancer incidence. Cells defective in NBS lack an S phase checkpoint and are radiosensitive.

Potentially Lethal Damage Repair

The component of radiation damage that can be modified by manipulation of the post-irradiation conditions is known as potentially lethal damage (PLD). PLD repair can occur if cells are prevented from dividing for 6 hours or more after irradiation. This is manifest as an increase in survival. PLD repair is significant for x-rays but does not occur after neutron irradiation.

Sublethal Damage Repair

Sublethal damage (SLD) repair describes the increase in survival if a dose of radiation is split into two fractions separated in time. The half-time of SLD repair in mammalian cells is about 1 hour. The repair of sublethal damage reflects the repair of DNA breaks before they can interact to form lethal chromosome aberrations. SLD repair is significant for x-rays but almost non-existent for neutrons.

Dose Rate Effect

If the radiation dose rate is reduced from about 1 Gy/min to 0.3 Gy/h, there is a reduction in the cell killing from a given dose because SLD repair occurs during the protracted exposure. As the dose rate is reduced, the slope of the survival curve becomes shallower and the shoulder tends to disappear.

The Nature of the Oxygen Effect

The presence or absence of molecular oxygen dramatically influences the biologic effect of x-rays. The ratio of doses administered under hypoxic to aerated conditions needed to achieve the same biological effect is called the oxygen enhancement ratio (OER). For sparsely ionising radiations such as x-rays and γ-rays, the OER at high doses has a value of between 2.5 and 3.5.
The OER decreases as LET increases and approaches unity (no effect) for α-particles. For neutrons, the OER has an intermediate value of about 1.6. Molecular oxygen must be present during irradiation and it makes permanent the damage produced by free radicals. Only a small quantity of oxygen is required for radiosensitisation (0.5% O_2). There are two forms of hypoxia, chronic and acute. Chronic hypoxia results from the limited diffusion range of oxygen through respiring tissue. Acute hypoxia is a result of the temporary closing of tumour blood vessels and is transient.

Radiation Carcinogenesis

If cellular damage occurs as a result of radiation and it is not adequately repaired, it may prevent the cell from surviving or reproducing or it may result in a viable cell that has been modified. Meaning the cell has suffered a change or mutation that it retains as a legacy of the radiation exposure.
Most tissues of the human body are unaffected by the loss of a few cells but if the number of affected cells is sufficiently large, then there is observable harm. The probability of such harm is zero at small radiation doses but above a threshold dose, the probability increases rapidly with dose to 100%. This results in **deterministic effects** for example radiation radiation-induced cataracts.
The outcome is very different if the irradiated cell is viable but modified. Radiation carcinogenesis and hereditary effects fall into this category and are called random or **stochastic effects**. The probability of an effect increases with dose, with no dose threshold but the severity of the effect is not dose related.

Latency is the time interval between irradiation and the appearance of a malignancy. The shortest latency is for leukaemia with a peak of 5-7 years. For solid tumours, the latency may extend to 60 years or more. Regardless of the age at exposure, radiation-induced malignancies tend to appear at the same age as spontaneous malignancies of the same type.
There are two main risk models, the absolute and the relative models. The absolute risk model assumes that radiation produces a discrete crop of cancers over and above normal levels. The relative risk model assumes that radiation increases the spontaneous incidence by some factor. Because the natural cancer incidence increases with age, this model predicts a large number of excess cancers appearing late in life after irradiation.
The ICRP suggests a risk estimate of excess cancer mortality in a working population of 10 x 10^{-2} per sievert for high dose rates and 5 x 10^{-2} per sievert for low dose rates. The ICRP estimates that on average, 13 to 15 years are lost over a life expectancy of 68 to 70 years.
There is clear evidence of induced second cancers subsequent to radiotherapy, both in heavily irradiated tissue and remote organs. This has been shown for prostate and cervical cancer and Hodgkin's lymphoma. Irradiation *in utero* by diagnostic x-rays appears to increase the spontaneous incidence of childhood cancers by a factor of about 1.4.

Hereditary Effects of Radiation

In males, radiation dose as low as 0.15 Gy result in a diminished sperm count (oligospermia) after a latent period of about 6 weeks. Doses above 0.5 Gy result in the absence of living spermatozoa (azoospermia) and the recovery time depends on the dose. Permanent sterility ensues after a single dose greater than 6 Gy and fractionated doses causes more gonadal damage than a single dose in males.
In females, excess radiation induces permanent ovarian failure with a marked age dependence on the dose required. Permanent sterility in females ensues from a dose of 12 Gy pre-pubertal to about 2 Gy pre-menopausal.
Hereditary diseases are either: Mendelian, chromosomal or multifactorial. Radiation does not produce new, unique mutations but increases the incidence of the same mutations that occur spontaneously. Not more than 1 to 6% of spontaneous mutations in humans may be ascribed to background radiation. The ICRP estimates that the hereditary risk of radiation is about 0.2%/Sv for the general population and about 0.1%/Sv for the working population.
In terms of detriment, expressed in years of life lost or impaired, congenital anomalies are much more important than hereditary disorders.

Effects of Radiation on the Embryo and Foetus

Moderate doses of ionising radiation can produce detrimental effects on the developing embryo and foetus. The effects depend on the stage of gestation, the dose and the dose rate. Gestation is divided into pre-implantation (0 - 9 days), organogenesis (10 days – 6 weeks) and the foetal period (6 weeks to term). The principal effects of radiation on the developing embryo and foetus are cancer, embryonic, foetal or neonatal death, congenital malformations, growth retardation and functional impairment. Irradiation during pre-implantation leads to potential embryonic death.
Until a pregnancy is declared, no special limits apply to women other than those applicable to any radiation worker. Once a pregnancy is confirmed, the maximum permissible dose to the foetus is 0.5 mSv per month. A dose of 0.1 Gy to the embryo during the sensitive period of gestation (10 days – 25 weeks) is often taken to be the cut-off point above which a therapeutic abortion may be considered.

Radiation Cataractogenesis

A cataract is an opacification of the normally transparent lens of the eye. Dividing cells are limited to the pre-equatorial region of the epithelium. The failure of these cells to differentiate correctly leads to a cataract. A radiation induced cataract is a deterministic late effect. A feature of the lens is that there is no mechanism for the removal of dead or damaged cells. The minimum dose required to produce a progressive cataract is about 2 Gy in a single exposure; larger doses are necessary in a fractionated course. The latent period between irradiation and the appearance of lens opacity is dose related. The latency is about 8 years post-exposure to a dose range of 2.5 to 6.5 Gy.

Time, Dose and Fractionation in Radiotherapy

Conventional fractionation involves dividing a dose into a number of fractions to spare normal tissues by enabling the repair of sublethal damage between dose fractions. Fractionation also increases tumour damage because of reoxygenation and reassortment. Prolonging overall time within the normal radiotherapy range has little sparing effect on late reactions but a large sparing effect on early reactions. Fraction size is the dominant factor in determining late effects; overall treatment time has little influence. By contrast, fraction size and overall treatment time both determine the response of acutely responding tissues.

Accelerated repopulation refers to the triggering of surviving cells (clonogens) to divide more rapidly as a tumour shrinks after irradiation or treatment with any cytotoxic agent. Accelerated repopulation starts in head and neck cancer in humans about 4 weeks after initiation of fractionated radiotherapy. About 0.6 Gy per day is required to compensate for this repopulation. This phenomenon necessitates that treatment be completed as soon as practical once it has started; it may be better to delay the start than to introduce interruptions during the course of treatment.

The basic aim of hyperfractionation is to further separate early and late effects. The overall treatment time remains conventional at 6 to 8 weeks. However, because two fractions per day are used, the total number of fractions is 60 to 80. The dose must be increased because the dose per fraction is decreased. Early reactions may be increased slightly, tumour control improved and late effects greatly reduced.

In accelerated treatment, to reduce repopulation in rapidly proliferating tumours, conventional doses and number of fractions are used. But because two doses per day are administered, the overall treatment time is halved. In practice, the dose must be reduced or a rest interval allowed because acute effects become the limiting factor.

The EORTC trial of 72 Gy in 45 fractions (3 per day) over 5 weeks showed an increase in local tumour control but no increase in survival. There was also an unexpected increase in late effects some of which were lethal. Incomplete repair between fractions may have been a problem because the time interval between fractions was too short.

Continuous hyperfractionated accelerated radiation therapy (CHART) consists of 36 fractions over 12 days (3 per day) to a total dose of 50.4 to 54 Gy. Tumour control was maintained; late effects were not increased and acute effects were severe but their peak occurred after completion of treatment.

ARCON involves accelerated treatment to overcome tumour cell proliferation, hyperfractionation to spare late-responding normal tissues, carbogen breathing to overcome chronic hypoxia and nicotinamide to overcome acute hypoxia.

Overall treatment time is a very important factor for fast growing tumours. In head and neck cancer, local tumour control is decreased by about 1.4% for each day that the overall treatment time is prolonged. For carcinoma of the cervix this figure is about 0.5%. Such rapid proliferation has not been observed in breast or prostate cancer.

Early (Acute) and Late Effects

Radiation effects are commonly divided into two categories, early and late. Both show quite different patterns of response to fractionation, their dose-response relations are characterised by different α/β ratios. Late effects are much more sensitive to changes in fractionation than early effects.
Early effects result from the death of a large number of cells and occur within a few days or weeks of irradiation in tissues with a rapid rate turnover. Examples include effects in the epidermal layer of the skin, gastrointestinal epithelium and haematopoietic system, in which the response is determined by hierarchical cell lineage composed of stem cells and their differentiating offspring.
Late effects appear after a delay of months or years and occur predominantly in slowly proliferating tissues such as tissues of the lung, kidney, heart, liver and CNS. The difference between the two types of lesions lies in their progression. Acute damage is repaired rapidly because of the rapid proliferation of stem cells and may be completely reversible. By contrast, late damage may improve but is never completely repaired. A late effect may result from a combination of vascular damage and loss of parenchymal cells.

The Volume Effect: Tissue Architecture

The generally accepted rule is that the total dose depends on the volume of tissue to be irradiated. Tolerance dose has been defined as the dose that produces an acceptable probability of a treatment complication. This definition includes objective criteria, such as the radiobiology involved and subjective factors such as socio-economic, medico-legal or psychological.
The spatial arrangement of the functional subunits (FSU) in the tissue is critical. In the case of tissues in which the FSUs are arranged in a series, like links in a chain, the integrity of each is critical to organ function and elimination of any one FSU results in a measurable probability of a complication. With the spinal cord for example, specific functions are controlled by specific segments arranged linearly or serially. Because impulses must pass along the cord, death of critical cells in any one segment results in complete failure of the organ. Radiation damage to such tissues is expected to show a binary response with a threshold below which there is normal function and above which there is loss of function.
Clinical tolerance also depends strongly on the volume irradiated in the kidney and lung. Both of these organs are very sensitive to irradiation of their entire volume but small volumes can be treated to much higher doses. This is because there is considerable functional reserve capacity with only about 30% of the organ required to maintain adequate function under normal physiologic conditions. The large reserve capacity and increased tolerance to partial-volume irradiation are due to the parallel organisation of functional nephrons and alveolar subunits. Functional damage will not occur until a critical number of FSUs are inactivated by irradiation. Above this threshold damage is usually exhibited as a graded response rather than a binary one.

Normal Tissue Tolerance doses

Organ	TD5/5(1/3)+/- 95% CI	TD5/5(2/3)+/- 95% CI	TD5/5(3/3)+/- 95% CI	TD50/5(1/3)+/- 95% CI	TD50/5(2/3)+/- 95% CI	TD50/5(3/3)+/- 95% CI
Kidney	43.92 (41.31–46.54)	27.02 (24.40-29.63)	17.12 (14.51-19.74)	59.14 (56.53-61.76)	42.23 (39.62-44.85)	32.34 (29.73-34.95)
Brain	58.56 (55.34–61.78)	51.42 (48.21-54.64)	47.25 (44.03-50.46)	80 (76.78-83.21)	72.86 (69.64-76.07)	68.68 (65.47-71.90)
Brain stem	59.20 (56.10–62.31)	55.15 (52.05-58.26)	52.78 (49.67-55.89)	72.99 (69.88-76.09)	68.93 (65.83-72.04)	66.56 (63.46-69.67)
Ear(Mid/Ext)	29.99 (29.99-30)	29.99 (29.99-30)	29.99 (29.99-30)	39.99 (39.99-40)	39.99 (39.99-40)	39.99 (39.99-40)
Ear(Mid/Ext)	57.30 (54.74-59.86)	56.41 (53.85-58.98)	55.9 (53.33-58.46)	68.66 (66.06-71.22)	67.77 (65.21-70.33)	67.25 (64.69-69.81)
Esophagus	59.10 (57.34-60.87)	57.82 (56.05-59.58)	57.07 (55.3-58.83)	74.1 (72.34-75.87)	72.82 (71.05-74.58)	72.07 (70.30-73.83)
Heart	59.91 (58.25-61.56)	44.53 (42.88-46.19)	35.54 (33.88-37.20)	72.54 (70.89-74.20)	57.17 (55.51-58.83)	48.18 (46.52-49.84)
Bladder	59.40 (54.71-64.09)	57.1 (52.41-61.79)	55.75 (51.06-60.44)	90.14 (85.45-94.83)	87.84 (83.15-92.53)	86.49 (81.80-91.18)
Larynx (Cartilage necrosis)	77.90 (76.52-79.26)	71.57 (70.19-72.96)	67.88 (66.49-69.26)	89.24 (87.85-90.62)	82.91 (81.53-84.29)	79.21 (77.83-80.60)
Larynx (Edema)	41.05 (37.14-44.96)	55.69 (51.78-59.60)	64.25 (60.34-68.17)	64.92 (61.01-68.84)	79.56 (75.65-83.48)	88.13 (84.21-92.04)
Liver	44.73 (42.51-46.94)	34.15 (31.94-36.37)	27.96 (25.75-30.18)	58.66 (56.45-60.88)	48.09 (45.87-50.30)	41.9 (39.69-44.12)
Lung	29.93 (21.51-38.34)	14.69 (6.269-23.10)	5.771 (-2.65-14.19)	61.18 (52.76-69.60)	45.94 (37.52-54.35)	37.02 (28.6-45.44)
Skin->						
Necrosis:	60.84 (58.48-63.20)	55.97 (53.61-58.33)	53.12 (50.76-55.48)	77.92 (75.57-80.28)	73.06 (70.70-75.42)	70.21 (67.85-72.57)
Telangiectasia:	48.54 (47.51-49.58)	48.54 (47.51-49.58)	48.54 (47.51-49.58)	65.09 (64.06-66.13)	65.09 (64.06-66.13)	65.09 (64.06-66.13)
Small intestine	48.17 (45.77-50.56)	45.75 (43.36-48.14)	44.33 (41.94-46.73)	61.83 (59.44-64.23)	59.41 (57.02-61.81)	58 (55.61-60.39)
Colon	55.00 (0.0-0.0)	48.69 (0.0-0.0)	45 (0.0-0.0)	65 (0.0-0.0)	58.69 (0.0-0.0)	55 (0.0-0.0)
Spinal cord	46.89 (43.58-50.19)	47.44 (44.13-50.75)	47.76 (44.45-51.07)	70.74 (67.44-74.05)	71.30 (67.99-74.61)	71.62 (68.31-74.93)
Stomach	58.33 (56.10-60.55)	51.04 (48.81-53.26)	46.77 (44.55-49.00)	73.45 (71.22-75.67)	66.16 (63.93-68.39)	61.9 (59.67-64.12)
Temporo-mandibular joint & mandible	60.51 (57.75-63.27)	60.32 (57.56-63.08)	60.2 (57.44-62.96)	78.90 (76.14-81.66)	78.7 (75.94-81.46)	78.58 (75.82-81.35)
Cauda equina	58.65 (47.06-70.25)	58.65 (47.06-70.25)	58.65 (47.06-70.25)	75.19 (63.60-86.79)	75.19 (63.60-86.79)	75.19 (63.60-86.79)
Brachial plexus	61.09 (59.70-62.48)	58.67 (57.27-60.06)	57.25 (55.86-58.64)	78.67 (77.28-80.06)	76.25 (74.86-77.64)	74.83 (73.44-76.23)
Femoral head & neck	51.61 (41.56-61.66)	51.61 (41.56-61.66)	51.61 (41.56-61.66)	63.70 (53.65-73.74)	63.7 (53.65-73.74)	63.7 (53.65-73.74)
Eye lens	6.762 (4.29-9.23)	6.762 (4.294-9.229)	6.762 (4.294-9.229)	16.86 (14.39-19.32)	16.86 (14.39-19.32)	16.86 (14.39-19.32)
Optic nerve	49.34 (46.06-52.62)	49.34 (46.06-52.62)	49.34 (46.06-52.62)	67.02 (63.74-70.31)	67.02 (63.74-70.31)	67.02 (63.74-70.31)
Optic chiasma	49.54 (37.54-61.54)	49.54 (37.54-61.54)	49.54 (37.54-61.54)	84.57 (72.57-96.57)	84.57 (72.57-96.57)	84.57 (72.57-96.57)
Retina	44.67 (43.04-46.29)	44.67 (43.04-46.29)	44.67 (43.04-46.29)	61.58 (59.95-63.20)	61.58 (59.95-63.20)	61.58 (59.95-63.20)

Rectum	58.56 (55.15-61.97)	55.73 (52.32-59.14)	54.08 (50.66-57.49)	88.42 (85.00-91.83)	85.59 (82.17-89.00)	83.93 (80.52-87.35)
Rib cage	52.23 (49.78-54.69)	52.23 (49.78-54.69)	52.23 (49.78-54.69)	67.74 (65.29-70.19)	67.74 (65.29-70.19)	67.74 (65.29-70.19)
Parotid	26.38 (9.74-43.02)	26.14 (9.501-42.78)	26 (9.364-42.65)	52.09 (35.45-68.73)	51.86 (35.22-68.50)	51.72 (35.08-68.36)
Thyroid	27.50 (-2.21-57.20)	27.5 (-2.2-57.2)	27.5 (-2.2-57.20)	132.5 (102.8-162.2))	132.5 (102.8-162.2)	132.5 (102.8-162.2)

Table 1: Normal Tissue Tolerance doses with 95% confidence interval (Gy)