Initial Response

The first observed effects following radiotherapy are **vascular and inflammatory**.

The most commonly seen effect is **erythema (reddening) of the skin or mucous membranes.**

This is due to release of cytokines from irradiated cells, particularly endothelial cells and macrophages. These factors exert a paracrine effect on the area, leading to vascular dilatation and the resulting erythema and sensation of pain.

Acute radiation responses occur mainly in renewal tissues and have been related to death of critical cell populations such as the stem cells in the crypts of the small intestine, in the bone marrow, or in the basal layer of the skin. Responses in these tissues depend on the cell kinetics of the particular tissue but usually occur within **3 months of the start of radiotherapy.**

They are not usually limiting for fractionated radiotherapy because of the ability of the tissue to undergo rapid repopulation to regenerate the parenchymal cell population.

The time until healing takes place is dependent on total dose and fractionation schedule. **Higher doses**, or more intense fractionation may both lead to prolonged early effects due to increased stem cell depletion.

Generally these biological changes resolve within a few weeks after treatment and therefore are little cause for concern.

Early Skin Reactions

Initial Response (cont)

1. **Erythema (reddening)** occurs within hours of doses over 5 Gy to the skin; it is in response to release of inflammatory cytokines from the cells of the epidermis and dermis. With fractionated radiation, erythema may not become apparent for one - two weeks.

2. **Dry Desquamation** occurs after doses of 40 Gy, and is characterised by dry, itchy skin. The skin may appear pigmented or scaling. This situations is due to a loss of function of the merocrine sweat glands as well as complete dysfunction of the basal skin layer. Dry desquamation typically heals within 1 - 2 weeks after cessation of radiotherapy

3. **Moist desquamation** occurs when there is complete loss of the epidermis and exposure of the dermis. It is characterised by redness of the skin, with prominent ooze / slough. Infection is likely in this scenario as the protective epidermal layer has been completely lost. Moist desquamation usually requires doses in excess of 20 - 40 Gy. Doses over 60 Gy lead to a 50% risk of a non-healing **ulcer** of the skin.

The extent of these reactions and the length of time for recovery depend on the dose received and the volume (area) of skin irradiated, because early recovery depends on the number of surviving basal cells that are needed to repopulate the tissue.

Early Reactions of the Oral Mucosa

One of the most critical early responding tissues in the body.

Dysfunction of this mucosa can lead to reduced oral intake and severe pain, limiting the ability of the patient to continue with treatment.

Initial Response (cont)

Erythema (reddening) of the affected mucosa. This takes 5 - 10 days to develop with conventional fractionation, with doses over 20 Gy.

Mucousitis (Loss of the epithelium) becomes apparent between 10 - 15 days. This is initially patchy but gradually becomes confluent with increasing dose (usually 11 - 20 days to develop).

The **latency** in these effects is due to the gradual loss of dividing cells in the basal layer of the epithelium.

An important feature of the oral mucosa is the potential for **repopulation**. In response to loss of a significant part of the stem cell population, the surviving cells decrease their cell cycle time and tend to create more stem cells rather than differentiating cells. Repopulation begins after 1 week, and is fast enough to counter normal fractionation after two weeks.

Early Gut Reactions

The small and large intestines are frequently irradiated during abdominal or pelvic treatments. Areas of fixed bowel (eg. rectum or retroperitoneal parts), are particularly susceptible as they are unable to move significantly within the peritoneal cavity.

Stomach: the first response usually seen is **nausea.**

Small Intestine: death or disablement of the crypt stem cells from radiation leads to loss of the intestinal villi within several days. This leads to several problems: Poor absorption of gut contents, causing diarrhoea; Risk of sepsis; Nausea may also occur following radiation of the small intestine.

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Initial Response (cont)

Large Intestine: radiation causes changes in intestinal absorption, causing diarrhoea or constipation. Ulceration of the large bowel can also occur, with risks of sepsis

Rectum, which is often irradiated during pelvic treatments, often develops acute side effects. These include pain, urgency and rectal bleeding. Haemorrhoids are likely to recur or get worse in patients with a past history of this condition.

Early Eye Reactions The threshold dose for radiation-induced eye cataracts is now considered to be around 0.5 Gy for both acute and fractionated exposures. The eye lens seems to be the most sensitive organ to beta radiation, even in doses far below maximum permissible dose.

Fatigue And Radiotherapy Very common

Measurement of Early Toxicity

May be graded based on their severity or on their impact to quality of life

Endpoints are specific clinical situations which are seen following radiotherapy administration. They allow classification of radiotherapy reactions.

Grading Systems have been developed to grade radiation reactions.

For early effects, measurement needs to be taken regularly (at least weekly) as they may develop rapidly. The establishment of scoring systems allows clinicians and institutions to compare and contrast different treatment schedules. Most scoring systems are based on a 6 tier model:

Grade 0 – No effect

Grade 1 – Mild, reversible, and heal spontaneously without any intervention

Measurement of Early Toxicity (cont)

Grade 2 – Moderate side effects which require outpatient treatment and do not require cessation of radiotherapy

Grade 3 – Severe effects which usually necessitate hospital admission and intense supportive care. They may require cessation of radiotherapy or alteration of the treatment schedule.

Grade 4 – Life threatening effects which must be treated immediately to preserve life. Radiotherapy is permanently ceased.

Grade 5 – Lethal radiotherapy side effect.

Note: These grades are also used to measure late side effects.

Latency refers to the delay in side effects appearing after a dose sufficient to cause them has been delivered. The delay is due to the turnover time of the tissue. Although the stem cells have been killed, the transit cells may continue to divide and differentiate, maintaining the surface epithelium for a time. This may lead to side effects appearing after radiation has finished.

Subacute Radiation Effects

After treatment has completed but before 6 months have elapsed.

Lhermitte's sign is due to a transient demyelination (damage to the protective covering (myelin sheath)) within the spinal cord and occurs 1 - 3 months after radiation exposure (also seen in patients with multiple sclerosis).

Subacute Radiation Effects (cont)

It presents with pain radiation down the back from the neck to the sacrum. Lhermitte's sign is due to loss of oligodendrocytes, the myelinating cells of the central nervous system. They have a longer life span than epithelial cells but still require replacement from a proliferative compartment. The loss of proliferative ability only becomes apparent after several months, however Lhermitte's sign is usually reversible.

Radiation pneumonitis occurs 2 - 6 months following radiation treatment involving the lungs. It is a potentially fatal condition caused by inflammation of the lung in response to radiation. There is a broad spectrum of severity and corresponding symptoms. Mild cases may be asymptomatic or have a dry cough. Moderate cases may complain of a cough, fevers or mild breathlessness. Severe cases present with severe dyspnoea requiring admission for respiratory support.

Most cases respond without treatment, and more severe cases will usually respond to corticosteriods. Symptoms do not generally last beyond 6 months. Occasionally, pneumonitis may be progressive and fatal. Patients will nearly always develop radiation fibrosis in the affected area.

Late Responses of Tissue

Late responses usually limit the dose of radiation that can be delivered to a patient during radiotherapy.

Late effects occur in tissues that manifest early reactions, such as skin/subcutaneous tissue and intestine, but the nature of these reactions is quite different from the early reactions in these tissues.

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Late Responses of Tissue (cont)

Late effects occur due to processes that take significant time to develop, either because the tissue renews slowly, their relation to connective tissue cells, chronic inflammatory processes or genomic damage.

The nature and timing of late reactions depends on the tissue involved and can be expressed as diminished organ function.

Effects on Connective Tissue The connective tissues of an organ are a frequent cause of late effects. The endothelial cells and fibroblasts are the primary targets.

1. Endothelial Cells have a long life expectancy and divide rarely. If exposed to radiation, they may therefore die at a time distant to the exposure. Loss of endothelial cells leads to proliferation of the surviving cells. This can lead to:

Constriction of capillaries due to proliferating cells
Thrombosis (local coagulation or clotting of the blood) and **fibrosis (thickening and scarring of connective tissue)** due to bare areas of vessel walls

2. Fibroblasts - Genetic Damage: the DNA is the target of radiation, and sufficient damage leads to cell death. Cells may survive radiation exposure in one of two ways:

Repairing the damage
Not recognising the damage - if the damage is not fatal to the cell it may be 'missed' by repair pathways

Repair is not a process without faults and it is possible that surviving cells may carry mutations. If these mutations occur in sensitive parts of the DNA, there is potential for radiation carcinogenesis or hereditary effects (only if gametes are involved).

Late Skin Reactions

Telangiectasia: dilatation of the capillaries causing them to appear as small red or purple clusters

Oedema: Swelling

Fibrosis: the thickening and scarring of connective tissue. The latency for fibrosis is about 3 years, and once it occurs it may be progressive.

Chronic Ulceration / Necrosis (cell death)

Hair follicles epilation (loss of hair): occurs after very low doses - the threshold for this deterministic effect is about 4 Gy in a single dose. Permanent hair loss occurs with single doses of 10 Gy or more. Fractionated treatment spares hair follicles; hair growth may return eventually even after doses of 40 Gy.

Skin glands: the eccrine, apocrine and sebaeceous glands of the skin may all be rendered non-functional by radiation with tolerance doses of under 15 Gy. Recovery is possible but function may be permanently lost when doses climb over 30 - 40 Gy in fractionated schedules.

Late Central Nervous System Reactions

Consequential Late Effects

Consequential late effects occur when an early effect is so severe that healing cannot take place.

Consequential late effects are fundamentally different to other late effects as they: Are a continuation of an early effect; Are less dependent on the vascular and connective tissues seen with typical late effects

Examples:

Skin - non healing ulceration following severe moist desquamation

Consequential Late Effects (cont)

Oesophagus - healing of mucousitis can lead to formation of strictures when opposing surfaces stick together

Head and neck - mucosa may become permanently ulcerated if a large dose is administered before repopulation can occur

Dysfunction of salivary glands is often seen during the delivery of radiation, yet unlike most other 'early effects' it persists following treatment completion, and may never fully recover. Dry mouth syndrome is common, and usually persists after radiation is completed.

Survival Curves

The α/β ratio is relatively low for late-responding tissues.

The α/β ratio isrelatively high for early-responding tissues.

The dose-response relationship for late-responding tissues is more curved than that for early-responding tissues.

The overall response to multi-fraction radiation regimens can be illustrated by considering a tumour, an early-responding tissue and a late-responding tissue. The total dose delivered by multi-fraction treatment is the product of the number of fractions and the dose per fraction. A large number of small dose fractions will produce relatively less damage to late-responding than to early-responding tissues. This is because the cell survival fraction at low doses is higher for late-responding tissues. The tumour regresses and disappears. The early-responding tissues show a reaction but repopulate by rapid cell division. The late responding tissues show little damage.

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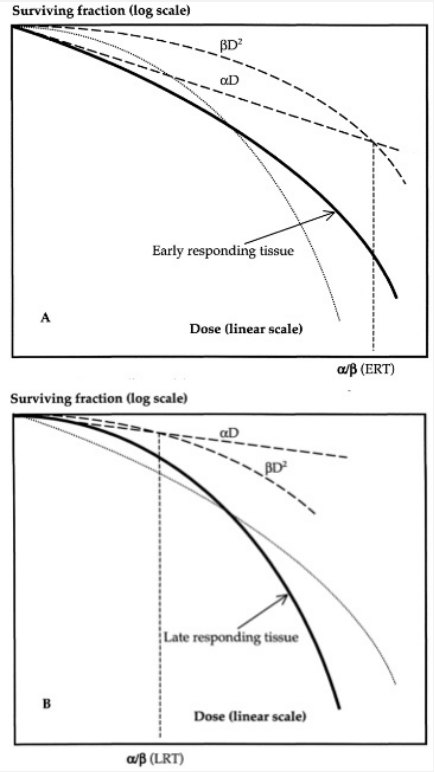
Survival Curves (cont)

In contrast, a small number of large dose fractions will produce relatively more damage to late-responding than to early--responding tissues. The tumour regresses and disappears, though there is evidence of a higher recurrence rate perhaps because there is less opportunity for reoxygenation to occur. The early-responding tissues show a reaction but repopulate by cell division, the same as for many small fractions. However, the late-responding tissues carry a large amount of latent damage, which is seen months or years later when the cells in these tissues begin to turn over.

Dose response curves



Effect of Time and Fractionation

Early responding tissues typically have a hierarchical organisation, with a population of stem cells that is constantly dividing to maintain population of differentiating cells.

The main implication of this is that early responding tissues continue proliferating, and if treatment takes place over a longer period of time they will be able to withstand the dose more easily.

The other factor affecting early responding tissues and total treatment time is that early tissues may begin **repopulation** after 1 - 2 weeks have elapsed of fractionated treatment.

This repopulation involves increasing the numbers of dividing cells as well as shortening the cell cycle time. These cells are capable of countering a standard fracti-onation dose; therefore healing may occur if hyperfractionation without acceleration occurs.

Total treatment time has a significant impact on the severity of early effects.

Fractionation, by itself, has little effect on the development of early effects.

It is the total dose delivered, rather than the fractionation of dose, that determines the development of effects.

Late effects show a significant dependence on the dose of individual fractions due to their quadratic cell survival curve.

Fraction size has a major impact on the occurrence of late effects.

This is because many of the cells which develop late effects have low α/β values - that is, they are able to resist radiation effectively at low doses but become overwhelmed rapidly at higher doses.

Effect of Time and Fractionation (cont)

This can be exploited by delivering the dose in small fractions that only deliver dose that the late tissues can tolerate. This feature is uncommon in early responding tissues or tumours, which have more dependence on total dose due to a high α/β ratio.

Volume Effects

Tissue tolerance describes the dose of radiation an organ can receive before it fails

It has expanded to include concepts such as serial/parallel functional sub units, volume effects and is one reason for using dose volume histograms. Tolerance values are usually quoted for conventional fracti-onation using photons or electrons.

The volume of a normal organ that is irradiated often plays a significant role in its sensitivity to irradiation. The effect of volume can be considered in the context of the functional subunits of an organ (e.g. in kidney, the tubules; in the lung, the alveoli) and whether the organ has a '**parallel**' functional structure (e.g. lung, kidney or liver), where the different function subunits perform the same function, or a '**serial**' functional structure (e.g. spinal cord) in which the functional subunits must work together in series for tissue function.

The identification of volume as an important concept in organs with parallel arrangement of FSUs allowed tolerance doses to be specified for partial irradiation of organs. In general, organs of this type (liver, lung, kidney) tolerate a higher dose if they are only partially irradiated.

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Volume Effects (cont)

Another way of giving a tolerance is the 'mean dose' to the entire organ. In organs with serial arrangement of FSUs, point doses are more important than volume irradiated. This is because loss of a single FSU leads to significant loss of function.

Modern radiotherapy using intensity modulation techniques (IMRT) can reduce the volume of normal tissue in the high dose volume, which can lead to reduced toxicity particularly in parallel organs but the improved high dose distribution is often gained at the expensive of giving a lower dose to a larger volume of normal tissue. The impact of this increased volume receiving a lower dose is currently unknown but has raised concerns about possible second malignancies.

Remembered Dose

Retreatment Tolerance

Previously irradiated tissues may have a reduced tolerance for subsequent radiation treatments, indicating the presence of residual injury

For **early responding** tissues there is almost complete recovery in a few months so that a second high dose of radiation can be tolerated.

For **late-responding** tissues the extent of residual injury depends on the level of the initial damage and is tissue dependent.

Remembered Dose refers to the 'memory' tissues retain of dose they have been exposed to in the past.

Remembered Dose (cont)

Remembered dose is an important concept when re-treating patients. Re-treatment may be necessary due to development of a second malignancy within the treatment field or in a nearby structure - for instance, rectal cancer following prostate radiotherapy. An important point is that for some reactions and in some tissues dose may be 'forgotten' over time, allowing a higher dose to be delivered safely.

Remembered Dose in Early Responding Tissues

Due to the nature of early reactions, it is likely that if full recovery from the effect has occurred tissues should be able to tolerate a similar dose with nearly identical pre-treatment tolerance.

This is mitigated somewhat by the late effects which can cause vascular insufficiency or fibrosis in the underlying submucosa.

Remembered dose is highly dependent on the initial treatment - if it is too toxic then there may be minimal recovery and minimal retreatment tolerance, whereas lower doses may allow significant repopulation of both tissue compartments.

Early responding tissues are able to recover their normal tolerance if:
-Their stem cell compartment is not completely depleted by large initial doses
-The supporting stroma is capable of supporting the regenerating tissue
-Sufficient time is left between the treatments

Remembered Dose in Late Responding Tissues

Late responding tissues typically have more 'memory' than their early counterparts and provide more of a barrier for retreatment.

Some tissues, in which there is progressive changes (such as lung fibrosis and the kidney) show worsening retreatment tolerance over time.

Remembered Dose (cont)

Others, such as spinal cord, show improved tolerance with time.

Therapeutic Ratio (or Index)

Ill-defined numerically but the concept is that of a comparison between tumour control and normal tissue complications.

Tumour-control curves tend to be shallower than those for normal tissue response because of heterogeneity.

The therapeutic ratio is often defined as the percentage of tumour cures that are obtained at a given level of normal tissue complications

i.e., by taking a vertical cut through the two curves at a dose that is clinically acceptable, e.g., at 5% complications after 5 years, to give the TD5/5 value

The dose leading to a 50% complication rate at 5 years is TD50/5

An approach more in keeping with the definition of other ratios, is to define the therapeutic ratio in terms of the ratio of radiation doses Dn/Dt required to produce a given percentage of complications and tumour control (usually 50%).

It is then a measure of the horizontal displacement between the two curves.

It remains imprecise, however, because it depends on the shape of the dose-response curves for tumour control and normal tissue complications.

Therapeutic Ratio

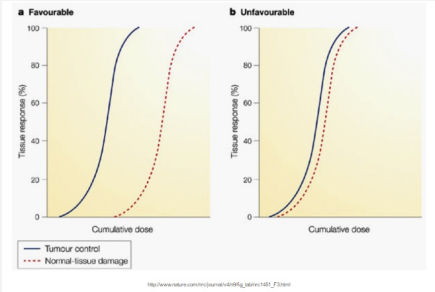

Figure 6.5 a) A favourable outcome would mean that the response of tumour tissue is greater than that of normal tissue to the same dose — the therapeutic index is large. b) An unfavourable outcome would mean that the response of tumour tissue and normal tissue is similar for the same dose — the therapeutic index is small.

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