Radiation therapy principles: clinical indications, outcome and applied radiobiology
Aims

To understand normal tissue and tumour related radiobiology
Specific Learning Objectives

• Describe the relationship between prescription of dose-volume and outcome.
• Distinguish the various aspects of radiotherapy that converge to justify the use of 3D-CRT and IMRT.
• Distinguish the various normal tissues and their reaction to radiation exposure.
• Apply dose equivalencies on a dose distribution.
Clinical indications and outcome

- Radiotherapy is a cancer treatment technique, on its own, or associated with other modalities (surgery, drug administration).
- It has the potential to deliver high energy to tissues with a disruptive effect on cancer cell DNA.
Clinical indications and outcome

- Cancer grows in organs that can still remain functional in their non-invaded (healthy) parts.
- Therefore, radiotherapy aims to eradicate cancer cells from the sick part and spare the healthy part of affected organs *simultaneously*.
- Radiotherapy is also expected to spare surrounding organs and structures that are not affected by cancer.
The tumour, in orange is located in the right lung. It does no longer participate in the gas exchanges. It is non-functional, but the lung tissue around that is still free of cancer and is functional. Irradiation of the tumour is required but, in order to reach the tumour, the radiation beams will pass through some of the healthy lung, destroying the capacity to exchange gas and reoxygenate the blood. If too much of the healthy lung is irradiated together with the tumour, the residual lung function might not be sufficient for normal life (it can even be lethal). In addition, the radiation dose needs to be limited at the level of other normal tissues like the spinal cord, the oesophagus, the heart, etc. Radiotherapy therefore faces the challenge of treating cancer efficiently without causing permanent damage to normal tissue that can impair quality of life.

An ideal radiotherapy treatment would have 100% efficacy and 0% permanent damage. This objective is seldom satisfied.
To discuss further about cell killing, we need to understand the concept of therapeutic ratio.

The response of normal tissues to radiation is a deterministic effect i.e. there is a threshold dose and the severity of response increases with dose. This response follows a sigmoidal shape as above.

The steep part of the slope marked A, indicates the region where small changes in dose may have a large change in toxicity.
The tumour control probability curve also follows a sigmoidal shape. At the steep part, small changes in dose may compromise tumour control.
The tumour control curve and normal tissue damage curve are close together. Radiotherapy is a compromise between cure and acceptable risk of complication.

Acceptable risk of complications depends on risk level, organ involved and severity on complications. The level of risk may differ between physician and patients.

At Dose Level 1 (D1), few patients are cured but no complications are seen. At D3, many patients are cured but with high rate of complications. At D2, there is moderate rate of cures with few complications. The dose level chosen for curative therapy may differ between physicians and centre but generally, a 5-10% rate of long term complication is expected and acceptable provided it is not too severe eg paralysis.
In this graph we can choose a dose point with 70% cure and 5% late complication or 90% cure and 20% late complications.
Acceptable complications depend strongly on the severity and consequence to the patient. “Inconsequential” complications such as 100% risk of skin telangiectasia may be acceptable for curative therapy but 5% risk of myelitis is usually unacceptable.
In most cancer it is hardly possible to obtain tumour control and long term survival without permanent damage (complications). An optimal situation is approached with breast cancer (surgery + radiotherapy), with high long term survival at very low complication cost (late cardiac death). Conversely, a high level of survival is obtained in prostate cancer but at the cost of high rate of permanent damage (impotence).

Lung cancer is the difficult case in which low survival levels at 5 years cannot be obtained without complication (20 % clinical pneumonitis). Cervix cancer shows an intermediate picture.

A more restrictive exposure, concentrated on the tumour and sparing normal tissue is the goal of 3D-CRT. Because tumours and organs in the body are better described by their volume and shape than by simple planar imaging, a volumetric approach to defining targets is of great help to tailor, in the 3 dimensions of space, the beams that will converge on the tumour. A volumetric approach will allow reduced volume of normal tissue irradiated and improved dosimetry to reduce the incidence of late effects.

Clinical indications and outcome

• Radiation delivery can be improved to allow for higher tumour dose at no additional cost for normal tissue.
• OR
• Radiation delivery can be improved to obtain a similar tumour control at a lower cost in normal tissue tolerance.
Successive reduction in volume receiving the curative prescribed dose (95% isodose) in prostate cancer, along with total dose increase.

The 2D (planar) technique meant a maximal tolerable dose of 60 Gy with about 10% of permanent rectal damage, because the irradiation technique was not able to avoid irradiating the entire circumference of the rectum with the prescribed cancer dose (deep blue 95% isodose). The introduction of 3D volume definition and dose calculation allowed to decrease the size of the fields because the position of the prostate was better defined and the radiation beams could be matched to the shape of the prostate (light blue 95% isodose). As a consequence, about half of the rectum could be shielded from the prescribed cancer dose and received less. A further consequence was that it became possible to deliver a higher cancer dose without damage to the rectum. Various techniques of segmentation of 3D CRT allowed for an even better shielding of the rectum (green 95% isodose) allowed a further increase of the cancer dose while the rectal dose was further decreased. In summary, the evolution from 2D to advanced 3D allowed simultaneously for a higher dose to the prostate and a lower irradiation of the rectum.
Radiotherapy kills cells proportionally with each fraction of treatment. The bigger the tumour, the higher the number of clonogens there are and therefore a higher dose of radiation is needed for gross tumour as opposed to microscopic disease.

Radiotherapy causes damage to both tumour and normal cells. If these cells are given time, some of this damage are repaired. Fractionation exploit the different repair capacities of normal tissue (better) compared to tumour tissues. Among the normal tissue, some organs are more sensitive to fraction size. These are called the late responding tissues. The volume of tissue irradiated also influence the their tolerance to radiation. This part depends on the architecture of the tissues.
The goal of radiotherapy is to deliver a high quantity of energy in the appropriate volume to cure cancer. Since there is a law of proportionality between the quantity of energy and the proportion of cancer cells that are sterilised (schematically described by the linear-quadratic model), the larger the number of cancer cells (i.e. the larger the tumour), the more dose is needed to kill up to the last surviving cancer cell. The example above shows what level of prostate cancer control can be obtained with various total dose levels [Viani, 2009, IJROBP]

Well oxygenated cells have a radiosensitivity three times higher than hypoxic cells.

As cancer develops anarchically, its vasculature is rather inefficient, with a chaotic perfusion and large unperfused or underperfused area. Regions that are deprived from blood supply die quickly (necrosis) and do not pose much of a problem for cure. Regions neighbouring necrosis only get limited oxygen supply, either permanently or in a transient manner. These cells are much less sensitive to ionising radiation because oxygen is required to “fix” radiation damage and make it efficient.

Fractionating the treatment in a large number of small fractions increases the probability that poorly perfused area on a given day receive another dose on a day where the perfusion is more efficient. In addition, the progressive reduction in size of the tumour during the treatment is likely to increase the oxygenation globally as less surviving cells are competing for the oxygen available.
This is a histological cross section of a tumour that has been stained with several markers in vivo, before a biopsy was processed to create this image. Blue chords represent endothelial cells from blood vessels. Pimonidazole (green) stains specifically regions with poor oxygen supply, at some distance from the blood vessels. Closer to the vessel there is abundant supply of oxygen and there is no specific staining. Zones marked “n” are necrotic, i.e. dead tumour tissue. The image clearly shows that hypoxic cells exist in the tumour, that are at a distance from the blood vessels. These cells are striving to survive in a poor environment and acquire new more aggressive characteristics; one of them is a low sensitivity to ionising radiation (radioresistance).
Tumours are “constructed” through the continuous proliferation of cancer cells, most often from a single progenitor that was transformed long ago. As radiotherapy treatment starts, the tumour continues to proliferate. Therefore, the actual number of cells that must be eventually destroyed is larger than the number of cells present at day 1. It can be schematically represented by the formula:

\[ N = N_0 + N_t \]

Where \( N \) is the total number of cells to be sterilised, \( N_0 \) is the number of cells present at day 1 of treatment and \( N_t \) is the number of new cells that will be produced by the tumour during treatment, before the last clonogen has been sterilised. This explains why the total dose needs to be adapted when the total treatment time is altered.
Estimate of the total dose required to cure 50% of head and neck cancer according to the total treatment time. For protocols delivering the total treatment in 30 days or less, there is not much need for altering the total dose. This indicates that the contribution of cell proliferation to the total number of cancer cells is minimal in such an interval. If, for any reason, the treatment is lengthened (interruption by long bank holiday, equipment breakdown, etc) beyond 30 day, then the contribution of cell proliferation becomes significant and an additional dose must be given to retain the same cure rate.

The dashed line indicates the expected tumour repopulation rate at about 2 months doubling rate. However, trials show that with prolongation of Overall Treatment Time (OTT), the dose needed for tumour control is more than predicted for normal tumour repopulation. This is due to accelerated repopulation of certain tumours, especially squamous cancers, beyond 30 days of starting radiotherapy. As a rule of thumb, it is estimated that 0.6 Gy must be added per day beyond 30 days of total treatment time. [ref to find in ESTRO radiobiology]

The Hazard Of Accelerated Tumor Clonogen Repopulation During Radiotherapy
H. R. Withersj.. M. G. Tayloarn D B. Maciejewski
*Acta Oncologica* 27 (1988) Fasc. 2
The existing radiotherapy regimens have been progressively developed as a trade-off solution between these contradictory requirements. However, this is only considering tumour effects of radiotherapy.

Normal tissues containing or surrounding the tumour are also exposed to significant radiation dose. They are actually limiting the ability to deliver the high doses required to sterilise all cancer cells.
Acute / early reactions are normal tissue damage that is expressed a few weeks to months after radiation exposure. It may happen during therapy and continue after treatment is completed. Late reaction are tissue damage expressed months or years after radiation exposure. By convention, acute reaction are those occurring <90 days after exposure and late reaction occur >90 days after exposure.

Acute reactions, provided that it is not too severe, usually heals over time and are not permanent. Late reactions on the other hand, tends to be progressive over time and are permanent. The late reacting tissues are usually considered as the dose limiting tissues in radiotherapy. Very severe acute damage may lead on to late damage known as Consequential Late Effect.

Two classes of normal tissue side effects:

- Acute reactions, observed during or short after the treatment in protective tissues that are constantly replaced (repopulation): skin, bowel mucosa, blood cells (white, red, platelets)...
- Late reactions observed long after treatment in structural tissues with very limited repopulation capacity (brain, kidney, bones...)

Applied normal tissue radiobiology
The skin is a typical example of an acute reacting tissue. Skin reddening (erythema) or skin breakdown (ulceration) can occur during treatment as a result of continuous progenitor kill by the radiation, at a rate exceeding the rate of progenitor replacement through the physiological process of skin homeostasis.

Skin has as function to offer a tight interface with the environment, against all external agents (mechanical, chemical, physical). This function progressively removes the superficial layers of keratocytes. This is compensated by continuous cell production by the basal layer (progenitors). In normal skin, there is a perfect equilibrium between cell production in the depth and cell desquamation at the surface. During radiotherapy, some progenitors are lost (DNA damage by radiation) and the pace of replacement of the skin accelerates. If the rate of progenitor kill exceeds the demand for superficial skin cells, the entire tissue will break down.

Therefore, treatment fractionation should be tailored to allow for sufficient progenitor replacement. This is the second reason why treatments need to be fractionated. It is to allow for sufficient replacement of normal cells in tissues that use cell repopulation for the maintenance of their structure. If this equilibrium is cared for, the epidermis can accumulate very high radiation dose.
Long term follow-up of patients treated with radiotherapy enables us to see late effects of treatment which comes many months or years later. Long term sequelae include neurological damage eg IQ drop (childhood CNS tumour) nerve damage/paralysis (eg breast cancer with radiotherapy to axilla/SCF), paralysis), skeletal deformities (childhood tumours) etc. Long term follow up of breast cancer patient shows increased risk of heart disease presumably due to radiation effects to the coronary arteries. (note that even with pelvic radiotherapy, there is an increase in IHD which is difficult to explain). Many of these complications come years after treatment and therefore long term follow-up is advised.
Histological section of the cervical spinal cord of a laboratory rat after experimental irradiation (exploring fractionation sensitivity). 9 months after irradiation, the animal developed hind leg paralysis, a typical late reaction of nervous tissue with extremely slow cell turnover. Two types of lesions are seen: demyelinisation, the typical nervous system damage, and telangectasia, a distinct late effect on blood small vasculature. Functional cells killed by radiation could not be replaced by repopulation as the nervous system has very limited repopulation capacity. The damage appeared only months after because the damaged cells experience delayed mitotic death (as opposed to apoptosis). This damage is irreversible.
Among the 2 most important determinants of tissue damage to both acute and late reacting tissue are the total dose and volume of organ exposed.
Organs like the liver, the lungs, the kidneys or the brain have each a particular architecture adapted to their function. Broadly, organs can be divided in two categories: serial and parallel organs. This architecture has a strong impact on their tolerance to radiotherapy.
On the left, a tissue with a parallel architecture, broken down in 6 functional subunits. If one subunit is damaged by radiation, the organ will lose 1/6 of its functional capacity. It is likely that, although the total function has been reduced, the remaining 5 subunits will be sufficient to ensure a satisfactory global function. Each organ will have a minimum volume to retain normal function.

On the right, a serial tissue with 3 subunits. The destruction of one subunit results in the complete breakdown of the global function of the organ. This could be in the spinal cord, for instance, or in the small bowels. Indeed, a short segment of bowel damaged by radiation is sufficient to cause occlusion, even if the majority of the bowel is still perfectly functional.
The kidney is an example of an organ with parallel architecture. The smallest subunit is the nephron which function independently of each other. Therefore damage to a subunit does not affect the function of the other subunits. The spinal cord is a classical example of an organ with serial architecture. The functions of the distal part of the spinal cord is dependant on the function of the sections proximal to it. Damage to even a section of the spinal cord will result in loss of function to the segments distal to it.
The kidney has a limited tolerance to radiation (in the order of 15-20 Gy), but to lose completely the renal function, both kidneys must be damaged. Many people live with one kidney only (congenital, accident, infection...). Therefore, if required by the cancer localisation, it might happen than a high dose needs to be delivered that will damage part of one (or both) kidney. As long as a sufficient volume of kidney is shielded from radiation, the patient will retain a renal function that is compatible with a normal (quality of) life.

On the contrary, the spinal cord tolerates higher doses than the kidney (up to 50 Gy on short segments). But, if the total dose exceeds tolerance, even on a short segment, the entire function distal to it will be lost. The maximal tolerable dose in this case can never be exceeded.
Both architectures, serial and parallel, are sometimes combined in the same organ, because different tissues cooperate to a common function. The lung, for example, has a parallel architecture at the level of parenchyma where gas exchanges take place. On the other hand, airways carrying air in and out of the alveoli have a serial arrangement.
Some normal tissues (in fact many) can experience both early and late effects of radiation, each within a typical time span. The lung for example has an early wave of reaction, in the first weeks or months after exposure, that very much resemble pneumonia (cough, haemoptysis, fever), but heals with time with little sequelae.

The late wave of reaction in the lung is septal fibrosis that obliterates the alveolar tissue and suppresses gas exchange permanently in the exposed area. It is irreversible.

Thus pneumonia has the attributes of an early reaction: it develops shortly after exposure and heals later on with little residual damage (if any). Lung fibrosis is a late reaction that develops over a long period and never recedes. On the contrary, it even tends to worsen as time passes.
Dose distribution in a breast irradiated with two tangential fields. The lung is sensitive to volume irradiated as a parallel organ structure. This example shows that only a small volume of lung is irradiated in breast irradiation and therefore late lung injury is not expected. In many cases, it is difficult to see the fibrosis on CT scan years later.
Every radiotherapy treatment is prescribed with a number of fraction, each fraction with a dose, both combining to define the total dose.

Dose per fraction + fraction number = total dose or \(d \times n = D\).

The daily fraction dose is often 2 Gy, and the total dose in the range of 60-70 Gy, i.e. 30 to 35 fractions of 2 Gy. (Of course large variation in fraction dose and fraction number exist, as required by particular clinical situations; a few large fractions is not uncommon in palliative radiotherapy, whereas longer treatments with small fraction dose are used for curative irradiations).

Biological factors that govern radiotherapy efficacy and toxicity depend on these two parameters: the total dose and the dose per fraction. A third parameter, the total treatment time, is also important but it is currently not captured in the mathematical linear quadratic model.

An important guide to radiotherapy is the knowledge of tolerance dose levels (and volume effects) of normal tissues. A “safe” prescription should take account of these tolerance levels, in order to avoid normal tissue damage. Tables of tolerance levels exist and will be presented in section 8 (prescribing for specific clinical sites). These tables correlate three parameters for each specific tissues: the volume of tissue that can receive a given total dose without risking permanent loss of function, plus the dose per fraction at which the total dose is expected to be delivered. Any change in the dose per fraction is going to affect the level of total dose that can be tolerated.
The benefit of dose fractionation has been discovered a long time ago. It has a strong protective effect on normal tissues (and less on tumour, or else radiotherapy would not exist). This is because some of the DNA radiation damage produced by a first fraction can be repaired before the second fraction, provided enough time is given for this repair to take place (6 to 24 hours, depending on the tissue under consideration).

This graph shows that the survival of cells is increased by giving 2 radiation fractions some time apart due the phenomenon of repair.
Different tissues have different fractionation sensitivity, related (in first approximation) to their capacity to repair DNA radiation damage. Early responding tissues have a limited DNA repair capacity (lower panel). As a consequence, fractionation has a modest sparing effect on the tissue tolerance. Conversely, late responding tissues have a large DNA repair capacity. They are exquisitely sensitive to fractionation (upper panel).

Thus the tolerance dose of early responding tissues is moderately affected by variation in fraction size (in the range 1.5 - 4 Gy). The tolerance dose of late responding tissues, on the other hand, varies greatly with the size of the fraction.

Graphically, this is illustrated by the shape of the survival curve. A broad shoulder is indicative of large repair capacity (upper panel) and a “flat” shoulder indicative of limited repair capacity (lower panel).

The number of cells repairing their DNA damage between consecutive fractions depends on the “repair capacity”
The shape of a survival curve can be modelled with a mathematical formula that establishes the equation between dose and cell survival. It is a negative bending curve as accumulating dose implies a decreasing survival. This equation is called the linear quadratic model; it states that the level of cell survival \( \ln(S) \) is a function of the dose \( \alpha \) and the square of the dose, affected by two radiosensitivity parameters: \( \alpha \) and \( \beta \). Both parameters are characteristic of a given cell population.

The full equation is:

\[ -\ln(S) = \alpha D + \beta D^2. \]

The target cell theory says that in each tissue, there is one target cell population that is affected by radiation and whose decreased survival explains the tissue reaction. In the example above, the epidermis shows 3 layers: (1) the skin progenitors or basal layer), (2) the layer of the keratocytes and (3) the layer of keratine. Irradiation of the epidermis only affects layer 1. Therefore, the skin reaction can be approximated to the reaction at the basal layer level, i.e. the number of progenitors surviving a radiation exposure. In other words, the entire epidermis reaction depends on the survival of one single cell population. The basal cell survival curve can be used to predict reactions of the epidermis. In turn, the linear quadratic model can then be applied to skin reaction and, by extension, to any tissue reaction.

\[ \text{Tissue effect} = f(\alpha D + \beta D^2). \]
Equivalencies between treatments with different fraction size can be calculated with the above formula. Two treatments with a different fraction size and a different total dose are isoeffective (i.e. have the same biological effect) if they satisfy the formula.

For example, it is possible to calculate a new treatment with a new total dose if the fraction size is changed:

Let say that a treatment delivering 60 Gy in 30 fractions of 2 Gy is to replaced by a new one with 3 Gy per fraction (in order to shorten it for example). The calculation will be:

$$\frac{60}{x} = \frac{3 + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}$$

$$x = \frac{60 (2 + \frac{\alpha}{\beta})}{3 + \frac{\alpha}{\beta}}$$

The equation can only be solved if a value for $a/b$ is selected. The values of $\alpha$ and $\beta$ individually are not known but the ratio $\frac{\alpha}{\beta}$ has been derived from numerous clinical series and is well known for most normal tissues in the body.

As a rule of thumb, it can be approximated that early reacting tissue have an $\alpha/\beta$ of 10 Gy and late reacting tissues an $\alpha/\beta$ of 2 to 3.

The equation has thus two solutions, depending on the tissue at risk in the particular treatment considered.

With $\alpha/\beta = 10$ Gy, the new total dose with 3 Gy per fraction will be $x = \frac{60 (2 + 10)}{3 + 10} = 55.4$ Gy. Thus the total dose is moderately altered by this change of the dose per fraction from 2 to 3 Gy.

With $\alpha/\beta = 3$ Gy, the new total dose with 3 Gy per fraction will be $x = \frac{60 (2 + 3)}{3 + 3} = 50$ Gy. The change in total dose is larger because the value of $\alpha/\beta$ is smaller, accounting
for the greater fractionation sensitivity of late responding tissues.

Therefore if we want to prescribe the equivalent dose of 60 Gy in 30 fractions, for early reacting tissues, it will be 55.4 Gy in 3 Gy fractions or for late reacting tissues, it is 50 Gy in 3 Gy fractions.
Calculations

- A radiotherapy plan for Head & Neck cancer gives 66 Gy in 33 fractions over 6.5 weeks.
- Due to holidays, the treatment has to be shorten to 66 Gy in 6 weeks.
- Calculate the new regime for early ($\alpha/\beta=10$) and late effects ($\alpha/\beta=3$)

Dose per fraction = 66 / 30 = 2.2 Gy

D (early) = 66 (2.2+ 10) / (2 + 10) = 67.1Gy

D (late) = 66 (2.2 + 3) / (2+3) = 68.6Gy
Some examples of tumours with low $\alpha/\beta$ values include prostate cancer and melanomas.
This is a simple treatment with AP/PA fields for a mediastinal lymphoma, delivered with a telecobalt unit with 80 cm SSD. The prescribed dose is 36Gy in 18 fractions of 2 Gy.

Because of the poor penetration of Cobalt60 gamma rays, some over-dosage at the surface of the patient (ventral and dorsal) is unavoidable. The spinal cord, for example, receives 120% of 40 Gy, i.e. 43.2 Gy. This is the first “trouble”

This is still in the region of low probability for spinal cord radiation damage.
As the spinal cord receives 120% of the prescribed total dose, i.e. 43.2 Gy, but also it receives daily a fraction size 120% of the nominal daily dose. In other words, the fractionation schedule that has been prescribed is 2 Gy per fraction, but the spinal cord receives 2.4 Gy per fraction (120% of 2 Gy). In that case, 43.2 Gy with 2.4 Gy per fraction is not quite the same as 43.2 Gy with 2 Gy per fraction.

So, both the total dose and the dose per fraction are higher than the target dose (36 Gy). This is what is called double trouble.

It must be remembered that the dose levels that the spinal cord can tolerate are defined for a fraction size of 2 Gy. If the actual dose per fraction in a given treatment, is superior to 2 Gy, then the tolerance dose must be adapted to this new fractions size.

The linear quadratic formula can be used. An $\alpha/\beta$ value of 2 Gy can be used (which is conservative but appropriate in the case of the spinal cord). It gives:

\[ X = \frac{43.2(2.4 + 2)}{(2 + 2)} = 47.5 \text{ Gy} \]

This is bad news! The biological dose delivered to the spinal cord is even higher than 43.2 Gy, it is actually 47.5 Gy or 132 % of the prescribed dose. This dose corrected for the dose per fraction is called a Biological Equivalent Dose or BED$_2$; the number 2 is added in subscript to inform on the value of $a/b$ that was used to solve the equation.
Treating on alternate days.

- Sometime not all fields are treated daily.
- If we treat the anterior field on one day and the posterior field the next day, then the problem of “double trouble” is compounded.
- If the spinal cord get 55% from the anterior field, then the dose per fraction is:
  \[(18\text{Gy} \times 55\%) / 9 = 1.1\text{ Gy}\]
- The dose to spinal cord from posterior field is:
  \[(36\text{Gy} \times 120\%) - 9.9\text{Gy} = 33.3\text{ Gy}\]
  or 3.7 Gy per fraction

A not uncommon situation in busy departments is that not all fields are treated every day. This can be modelled with the example above. If half of the treatment is delivered with an anterior field, say on even days, and half on uneven days with the posterior fields, the situation is even worse. BED’s should be calculated separately for the 9 anterior sessions and the 9 posterior sessions. This is because each session is separated from the other by 24h, i.e. full DNA repair has ample time to take place.

Anterior days are “good” days since the spinal cord lies on the beam exit and only receives 55% of the prescribed dose (1.1 Gy each day for 9 sessions = 9.9 Gy in total). Posterior days are “bad” days since the spinal cord lies on the entrance of the beam and receives 182% of the prescribed dose (3.7 Gy each day for the other 9 days = 33.3 Gy).
The anterior BED₂ becomes 7.67 Gy (smaller than 9.9 Gy because the dose per fraction is only 1.1 Gy, i.e. smaller than 2 Gy). The posterior BED₂ becomes 47.4 Gy because the dose per fraction is 3.7 Gy, much larger than the 2Gy prescribed at isocenter. At the end of treatment, these BED2 add up, so that the overall BED₂ becomes 7.67 + 47.4 Gy = 55.07 Gy.

This becomes a very dangerous dose, with a substantial probability of permanent spinal cord damage.
### Treating on alternate days.

<table>
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<th>Absorbed dose (Gy)</th>
<th>Dose per fraction (Gy)</th>
<th>BED (Gy\textsubscript{2})</th>
<th>Bisodose (%)</th>
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<td>55.07</td>
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</table>

This table summarizes the previous calculations.

The first line of the table gives the numbers calculated in the previous slide. The biological effective dose to the spinal cord is higher than the “physical” dose (or, more appropriately, absorbed dose). If the conversion is not properly done into a BED, then the actual biological damage is underestimated.

This becomes a very dangerous dose, with a substantial probability of permanent spinal cord damage.

The point is that this latent danger is not understood unless BED’s are calculated. Therefore, when evaluating a dose distribution, the various isodose levels should be understood for their real significance: they help to predict the biological effect of any treatment, both at the tumour level and at the level of the healthy tissues.
Summary

- The ability of radiotherapy to cure cancers is a trade-off between the probability of cure versus the probability of complications.
- Modern 3D radiotherapy and IMRT enables higher doses of radiation to be delivered to tumours while sparing more normal tissues.
- The risk of normal tissue complications is related to the total dose, dose per fraction and volume of tissue irradiated.
- When non-conventional fractionations are used, the equivalent dose must be calculated to avoid unexpected complications.
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