

What is the correct dose for radiation treatment?

By Johnny T. Ottesen & Morten Andersen, Roskilde University.

Only 5-10 years after the discovery of the x-ray in 1895 by Røntgen several scientists were speculating if this form of radiation could be used for treatment of cancer. The idea rested on experiments which showed that the fast growing cancer cells were much more sensitive to x-ray than normal cells. After the discovery of the DNA and the mechanism of DNA replication this could be explained with two main relations. The damage radiation causes in the structure of DNA has a larger probability of creating breakage in chromosomes in the fast growing cancer cells compared to normal cells. There is simply shorter time between DNA replications to repair the damage. Furthermore, the radiation produces so-called free radicals within the cells - for instance hydrogen atoms with an extra electron. These free radicals which are hyper reactive attack DNA during the replication phase and can thereby cause breaks in DNA strings which once again can become chromosome breakage by the replication. Cancer cells are much more sensitive to such chemical attack on DNA because they replicate their DNA much more often than normal cells. This difference in sensitivity to ionizing radiation makes it possible to treat cancerous tumors using radiation known as radio therapy. However, normal cell tissue is also damaged by the ionizing radiation but to a somehow less degree. Thus, each series of radio therapy needs careful preparation. The dose and frequency of treatment should be chosen such that the tumor shrinks while the normal cells mass should not be reduced too much. In the end the tumor cells mass should become eradicated or become so small a mass that it is no longer a problem to the health of the patient. The tumor, which of course grows larger in between treatments, must under no circumstances grow so large that there is a risk that it will send metastases out into the blood circulation. On the other hand, the treatment should not have serious side effects on the surrounding normal cell tissue. The preparation of radio therapy of cancer tumors is then a problem of optimization. The optimization of radio therapy has in fact developed into a separate discipline of mathematical modeling, see for instance¹.

The models rest on the assumption that the cell demolishing effect of the radiation is due to a chain of events. The first model we look at describes radiation therapy by assuming that the cell demolishing effect is caused by two events; at first the radiation causes a break in one of the strings of a DNA molecule and secondly this break leads to a breakage of the chromosome after the next replication and then the cell is assumed to die. This situation can be described in a so-called compartment diagram with three compartments. The first compartment (L) keeps account of the number of fully functional cancer cells, $L(t)$, the second compartment (B) of the damaged cancer cells, $B(t)$, and the third compartment (D) of the dead cancer cells, $D(t)$, as functions of time t . During a radiation treatment the flow from L to B and from B to D will of course depend on the intensity of the radiation, p measured in [rad/min]. We may assume that the flow from L to B and B to D is proportional to the intensity of radiation. But the cancer cells in L and in B are not equally receptive to the radiation. Here we assume that the probability of damaging a functional cell is higher than the probability of killing a damaged cell. There are simply a larger number of events that can bring a cell

¹ Swan, G.W. (1981) *Optimization of Human Cancer Radiotherapy*, Springer-Verlag, New York

from L to B. Therefore, we introduce two sensitivity parameters, q and w with the unit $[\text{rad}^{-1}]$, such that the flow from L to B can be described with an expression of the form $q \cdot p \cdot L$, and that the flow from B to D can be described with $w \cdot p \cdot B$.

Exercise 1. Set up an illustration of the compartments and the flows between these for the model of radio therapy which is described in the text. Then set up the system of differential equations based on the compartment diagram. (A compartment is drawn as a box and represents a conservation equation like a bank account, money goes in and out and the balance of the account is computed instantly)

Exercise 2. Solve the system of differential equations. You may use the parameter values: $p=5$ $[\text{rad}/\text{min}]$, $q=4 \cdot 10^{-3}$ $[\text{rad}^{-1}]$ og $w=0.5 \cdot q$. Instead of calculating an absolute number of cells you can set $L(0)=1$ and then calculate the progress of the relative number of cells in the three compartments during a radiation treatment. Draw the solution curves for the three state variables $L(t)$, $B(t)$, and $D(t)$ as function of time t . Make a graph that shows the progress in the share of surviving cancer cells.

Exercise 3. For how long do you need to expose a tumor to radiation to reduce the share of fully functional tumor cells with 25%? How long do you need if you want to reduce the share of surviving tumor cells with 25%?

Exercise 4. For normal healthy cells q can be set to $4 \cdot 10^{-4}$ $[\text{rad}^{-1}]$. What is the difference in sensitivity between healthy cells and cancer cells measured in the share of surviving cells after 30 minutes of treatment assuming both cell types follow the model depicted in your compartment diagram (exercise 1) without coupling to each other?

Exercise 5. Both healthy cells and cancer cells can repair DNA damage caused by ionizing radiation. The rate of reparation for healthy cells can be set to $r = 0.03 \text{ min}^{-1}$, while the rate for cancer cells can be assumed to be substantially smaller, e.g. one third of r . Expand the model so that it includes the possibility to repair damaged cells. Solve the expanded model for both cancer cells and healthy cells and draw suitable graphs for the solutions. What is the difference in sensitivity in the expanded model measured in the share of surviving cells after 30 minutes of treatment?

A cancer tumor of course grows in between treatments. A lot of different mathematical models have been proposed to describe the growth of different types of cancer tumors. Here we assume that the growth follows a logistic model, i.e. assume that a tumor grows according to the model $y' = k \cdot y \cdot (1-y)$, where prime denotes the time derivative.

Exercise 6. Make a schedule of treatment that makes sure that the tumor will be reduced to 1% of its initial size. It can be assumed that the tumor grows logistic with a growth rate $k = 10$ per week (letting the carrying capacity be $m=1$). The size of the tumor at the start of the treatment can for instance be set to $y_0 = 0.95$. The total dose at each treatment must never exceed 25 rad per day and the patient can only be subject to 200 rad per week. Make a simulation of the series of treatments. How long

time does it take to reduce the tumor to 1% of its initial size using your designed schedule? Calculate the total cell mass $L(t)+B(t)+D(t)$ and comment on your result.

Exercise 7. A patient was exposed to 25 rad per minutes for 20 minutes daily except at weekend days for a period of time. Some parameters depend on the tumor and on the specific patient, e.g. the sensitivity parameters q and w . Estimate the sensitivity parameters q and w for the specific tumor in the specific patient having the normalized data (the equipment cannot measure below 1%) using data from the table.

Measurements of cancer and damaged cancer cells ($L(t)+B(t)$):

Day	1	2	2	3	3	4	4	5	5	weekend	8	8	9	9
Time	9am	7am	9pm	7am	9pm	7am	9pm	7am	9am	-	7am	9am	7am	9am
Cancer cells	0.95	0.96	0.61	0.65	0.27	0.30	0.16	0.13	0.06	-	0.07	0.03	0.03	0.00

You may define your clock to be zero at 9am the first day, i.e. at the first measurement.

Treatments:

Day	1	2	3	4	5	weekend	8	9
Time	-	8am	8am	8am	8am	-	8am	8am
Duration (min)	-	20	20	20	20	-	20	20
Intensity p	0	25	25	25	25	0	25	25

For the data shown calculate the share of fully functional cancer cells based on your patient specific estimate for q and $w=q$ (you may assume $w=0.5q$).



Want to know more?

[Mathematics at RUC: ruc.dk/en/bachelor/mathematics-int](http://ruc.dk/en/bachelor/mathematics-int)

[The Cancitis Research-group: dirac.ruc.dk/cancitis](http://dirac.ruc.dk/cancitis)