Chapter 10

Radiation used for therapy – radiation therapy

In this chapter we shall discuss the use of radiation for cancer therapy. For this purpose the radiation source is usually outside the body – and a number of large therapy sources have been developed. Furthermore, radium and other radioactive isotopes have been used both in the form of external sources as well as sources placed inside the body.

Let us however, start with the three strategies available for fighting cancer, namely;

1. Surgery
2. Radiation
3 Chemotherapy

Surgery is by far the strategy with the best long-lasting results, but radiation seems to be a good number two. Radiation may be used as the prime treatment of the cancer as well as in connection with other treatment strategies like surgery. Radiation is often used for palliative treatment – that is to release pain and improve the quality of life for the cancer patient..

It is interesting to see the improvements of radiation therapy from the first fumbling experiments more than 100 years ago. The improvements are mainly based on the developments of radiation sources as well as the diagnostic improvements that gives us the opportunity to give large doses to the tumor with a smaller damage to the surrounding healthy tissue.

The early history

Shortly after the discovery of X-rays and radioactivity in 1895 and 1896, some deleterious biological effects like hair loss and skin damage were observed. This resulted in the idea that the radiation may be used to treat superficial skin diseases and unwanted hair. The first fumbling experiments in radiation therapy started with simple instruments (sources) and with no dosimetry system developed. Let us briefly mention some of the highlights from that period.

1896 Emil Grubbe

A young medical student in Chicago, named Emil Grubbe, obtained in 1896 an x-ray tube. He observed that the radiation resulted in skin reddening (like sunburn). As a consequence of this he convinced one of his professors to allow him to irradiate a cancer patient suffering from locally advanced breast cancer. The patient benefited from this treatment, demonstrating the potential value of radiation for therapy. By doing so, Grubbe became the world's first radiation oncologist

Emil Grubbe
(1875 – 1960)

1899 Cancer is successfully treated in Sweden

The first proven successful x-ray treatment of histologically verified cancer was reported at the Swedish Society of Medicine meeting in December 1899 by Thor Stenbeck and Tage Sjögren.
The Stenbeck case was a basal cell carcinoma of the nose, and the Sjögren case was a squamous cell carcinoma of the cheek; both cases were documented by photographs. It can be mentioned that the patient with treatment of the nose was healthy 30 years later.

In Sweden Tage Sjögren opened the first private x-ray institute already in 1899. In 1910 Radiumhemmet in Stockholm was opened. They started the treatment based on 120 mg Ra – i.e. $4.44 \cdot 10^9$ Bq.
One of the Swedish pioneers was Gösta Forssell.

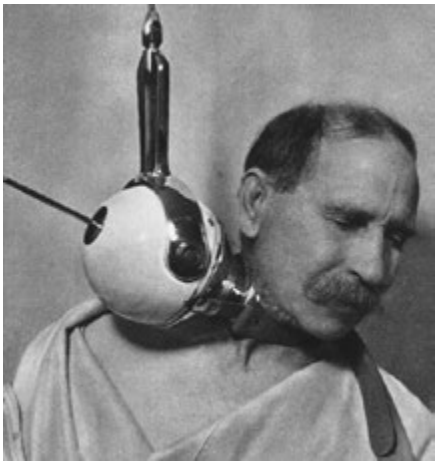
Gösta Forssell
(1876 – 1950)

1901 – 1904 Radium was introduced as the radiation source

The first clinical use of radium was reported by Henri Danlos in 1901, who successfully treated a few cases of lupus with a mixture of radium and barium chloride. Also other investigators explored the use of radium in chronic inflammatory skin diseases.

When radium is used the treatment is based on the γ-radiation. Radium has during the years been used both for "*teletherapy*" as well as for "*brachytherapy*".

The picture shows an example of teletherapy from about 1930. The source is 2 gram and the distance to the skin about 3 cm.



Radium teletherapy

It all started in the 1920s with radium in a lead container and with an opening to let out the radiation. The γ-radiation from radium and its decay products consists of 49 γ-lines with energies ranging from 0.184 to 2.45 MeV. The average energy is 0.83 MeV. This is much higher than the x-ray sources available at that time (up to about 200 kV with maximum energy of 200 keV). Consequently, the radiation from radium was more suited for tumors below the skin (we shall discuss depth-dose curves later on).

We also have to mention the disadvantage of using radium and other radioactive sources. The radiation ***can not be stopped*** – and this consequently implies problems with regard to storage. Furthermore, the personnel treating the patients will be exposed more or less when positioning the patients.

Radium sources and dosimetry

The sources consisted of about 1 to 5 gram of the isotope Ra - 226. This implies that the strength of the source, measured in becquerel, is in the range;
30 – 200 GBq (1 Gbq = 10^9 Bq)

Comments on dosimetry

A radium source of 1 gram yield a dose of $8.4 \cdot 10^{-3}$ Gy per hour at a distance of 1 meter. Consequently, if we take the distance into consideration (inverse square law) and use a source – skin distance of 3 cm the skin dose would be:

$$D = 8.4 \cdot 10^{-3} \cdot (100/3)^2 \text{ Gyh}^{-1} = 0.16 \text{ Gy per minute}$$

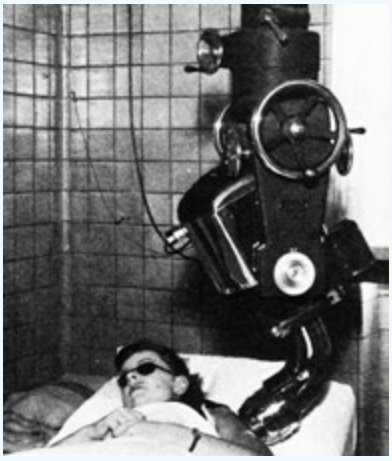
Today we usually give a treatment in fractions of 2 Gy per day. This would imply a treatment time of approximately 10 minutes and upwards with the old teletherapy machines. The source skin distance is the most important parameter.

We must point out that in those years none or very simple dosimetry systems were available (see chapter 5 and in particular page 58).

Teletherapy in Norway

On page 55 (also to the right) you can see a picture of the teletherapy unit that was used at The Norwegian Radium Hospital from about 1932. The source consisted of 3 gram radium; that is 3 Ci or 111 GBq. The source skin distance was about 10 cm. Using the above information, it is easy to calculate that the dose per minute was 0.042 Gy.

The treatment time for a dose of 2 Gy would be 47 minutes.



Radium brachytherapy

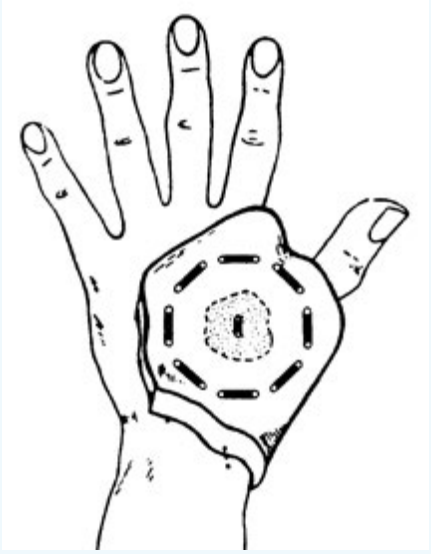
Brachytherapy ("brachios" is a Greek word, meaning "short-distance") is a form of radiotherapy where the source is placed on the skin or inside the body. It is often used for treatment of cervical, prostate, breast and skin cancer.

The first successful brachytherapy application for malignancy was carried out at St. Petersburg in 1903 for basal cell carcinoma of the facial skin.

About 1904 the intercavitary use started for uterine and cervical cancers. This opened a broad field of applications in brachytherapy. In the next few decades it was a continuous refinements in applicator design and dosimetry methods.

In 1903, Alexander Graham Bell wrote;

"There is no reason why a tiny fragment of radium sealed in a fine glass tube should not be inserted into the very heart of the cancer, thus acting directly upon the disease material. Would it not be worthwhile making experiments along this line ?



The needles are filled with Radium and a non-radioactive substance to obtain a uniform radioactivity

The needles were about 1 cm long and 1 mm in diameter and contained radium in the form of radium sulfate or radium chloride. The content of radium in the needles was a few milligram (see page 54). One of the problems with the radium needles was leakage of the decay product radon, which is a noble gas.

Fractionation therapy

Claude Rigaud
(1870 – 1941)

Claude Regaud at the Radium Institute in Paris recognized in the 1920s that treatment may be better tolerated and more effective if delivered more slowly with modest doses per day over several weeks.
This approach, known as *fractionation*, is one of the most important underlying principles in radiation therapy.

Today, fractionation lies at the heart of many treatment programs currently used in radiation oncology. The total dose is fractionated (spread out over time) for several important reasons:

1. Fractionation allows normal cells time to recover, while tumor cells are generally less efficient in repair between fractions.

2. Fractionation allows tumor cells that were in a relatively resistant phase of the cell cycle during one treatment to cycle into a sensitive phase before the next fraction is given.

3. Tumor cells that were chronically or acutely hypoxic (and therefore more radioresistant) may reoxygenate between fractions. This would improve the tumor cell kill.

The fractionation regimes are quite equal around the world – and the typical fractionation schedule for adults is about 2 Gy per day, five days a week.

1950s and high energy radiation therapy machines

With the ordinary x-ray equipment the upper limit in energy was about 250 kV. With the Ra-sources the energy was up to about 1 MeV. However, in order to treat tumors inside the body, without too much burning of the skin, it was important to attain radiation with higher energy. This high energy radiation equipment came into use in the 1950s with the first betatrons and in 1960s with linear accelerators.
In order to understand the advantages with high energy photons let us explore the depth dose curves. We discussed this slightly on page 77 and showed examples of depthdose curves for soft tissue.

Depthdose curves

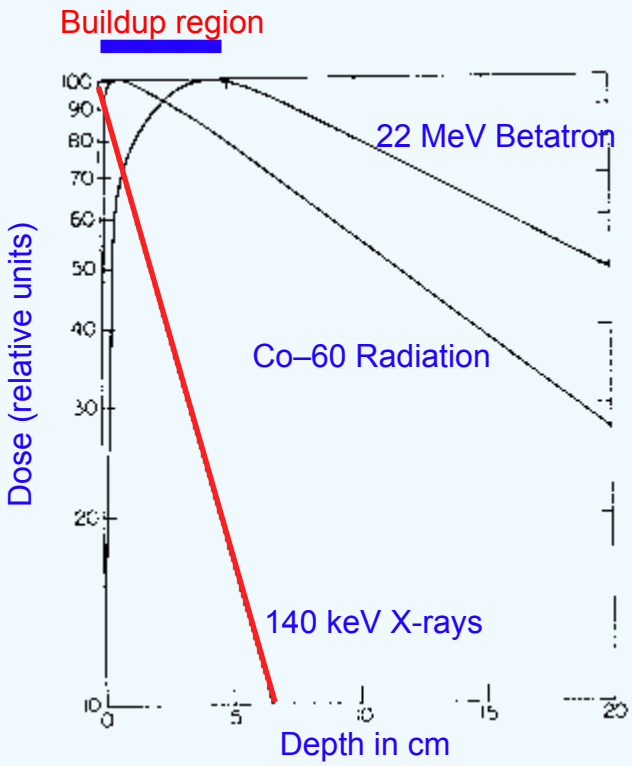
X– and γ-radiation is absorbed by the three processes; photoelectric effect, Compton-scattering and pair production. In all these processes secondary electrons are formed – that, in turn, give off energy in ionization and excitation processes when they are slowed down and stopped.

The radiation dose is defined as energy absorbed. Both the primary ionizations, as well as the energy given off by the secondary electrons, contribute.
The number of secondary electrons ***increases*** from the surface of the skin and down to the range of the most energetic secondary electrons for the radiation in question. Thus the range of electrons with a start energy of 1 MeV is approximately 0.5 cm in tissue. Electrons with a start energy of 10 MeV will have a range of about 5 cm.

As a result of this – we observe a region under the skin where the energy absorption, or rather the dose, increases and reach a maximum before it starts to go down. This is the socalled "***build up region***"

For ordinary X-rays (up to 250 kV) the buildup region is less than one mm. For the radiation from Ra and Co-60 it is about 5 mm.

In order to give maximum doses to tumors inside the body the therapist would like to have radiation with higher energy and thus be able to extend the "build up region" to 3 – 10 cm inside the skin. Such a requirement calls for high energy radiation accelerators.



The figure shows the depthdose curves for different types of x and γ-radiation in tissue. The depth in tissue is given in cm and the dose in relative units. Note that the vertical axis is logarithmic.
All curves become straight lines in this figure after a build up region. The straight lines implies that the absorption of radiation is exponential.

High energy accelerators – Betatrons and Linear accelerators

The first high energy therapy units were betatrons and linear accelerators. For both types electrons are accelerated to an energy of from about 10 MeV to 35 MeV. When the electrons reach the maximum energy they smash into a metal target and "***bremssthralung"*** with maximum energy like the maximum electron energy is formed. The radiation spectrum is equal to that for x-rays – but includes much higher energies. In the pictures on page 77 and on the page above you can see the resulting depthdose curve for radiation from a 22 MeV betatron.

Let us see in some more details into the physics behind the betatrons and linear accelerators.

Betatron

The first ideas with regard to particle accelerators was put forward in the 1920ties by the young Norwegian Rolf Widerøe. He came to Germany as a teenager and started his studies. Already in 1923 he proposed the principle for the betatron. He called it the "Strahlentransformator". However, he was not able at that time to construct the accelerator itself.

The first workable betatron was made in 1940 by Donald Kerst in USA. In April 1941 he submitted his famous paper on the operation of the 2.3 MeV-betatron to Physical Review.

Donald William Kerst
(1911 – 1993)

In a betatron electrons are accelerated in a toroidal vacuum chamber (a doughnut) by a magnetic field. The electrons are kept within the torus by the magnetic field (see illustration).
The relation between the accelerating field and the field that keep the electron in place is given by the "*betatron condition*" (also called the *Wideröe-relation* for betatrons):

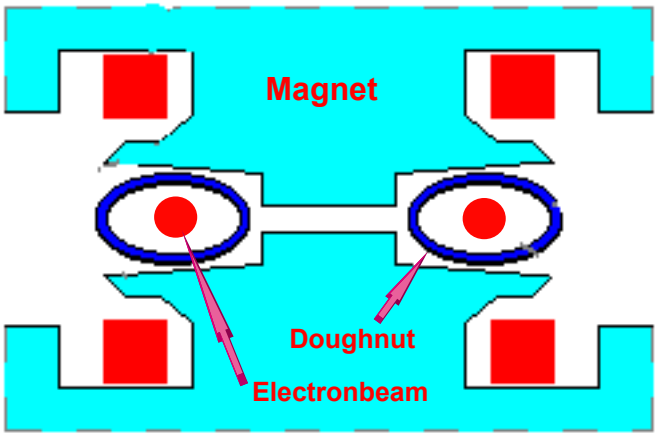
$$B_1 = 1/2\ B_2$$

i.e. the steering field is half the acceleration field.

The first betatron for radiation therapy was the 15-MeV Hamburg-betatron in 1944.

In 1946 Rolf Widerøe started to work on a 31 MeV-betatron for the Swiss company BBC (Brown Boveri and Cie). The betatron was designed for radiation therapy and the first one was installed at the Kanton hospital Zurich and used for the first patient in April 1951.

The next BBC betatron was delivered in the summer of 1952 to the Norwegian Radium hospital.



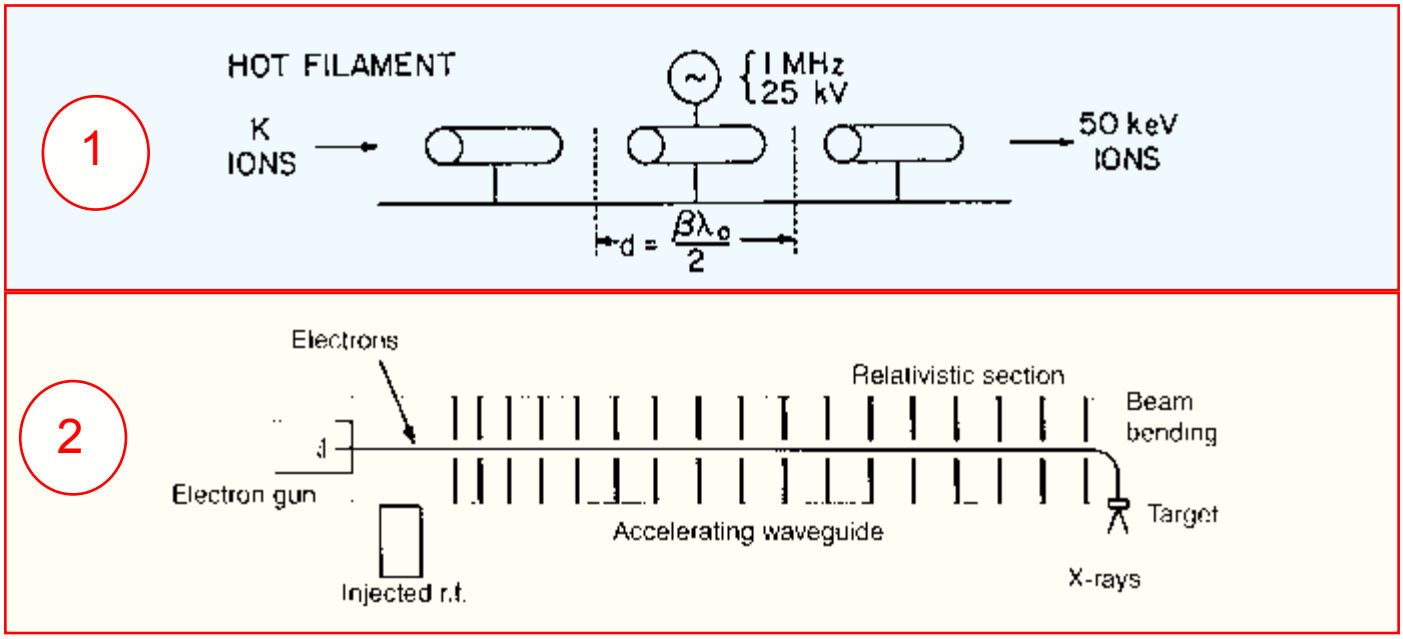
An illustration of the main parts of a betatron. Electrons are accelerated and kept in a torus (blue) by a magnetic field.

Linear accelerator

The use of betatrons for radiation therapy lasted some years – before the cheaper and simpler linear accelerators took over. Again Rolf Widerøe played a significant role in the development of the linear accelerators. It started already in 1927 when Widerøe built a small linear accelerator where he could accelerate potassium ions to 50,000 volts, having only 25,000 volts at his disposal. In the figure below we have shown the experimental setup. The ions pass successively through three drift tubes: the first and last are grounded, the center one is attached to a 1 MHz oscillator with a voltage of 25 kV. The distance d between gaps is adjusted so that it is:

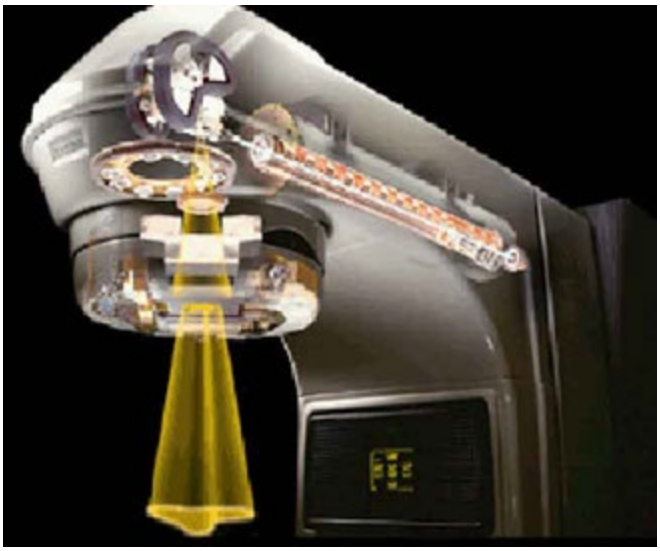
$$d = \frac{\beta\lambda_0}{2}$$

β = v/c and λ_0 = free space wavelength

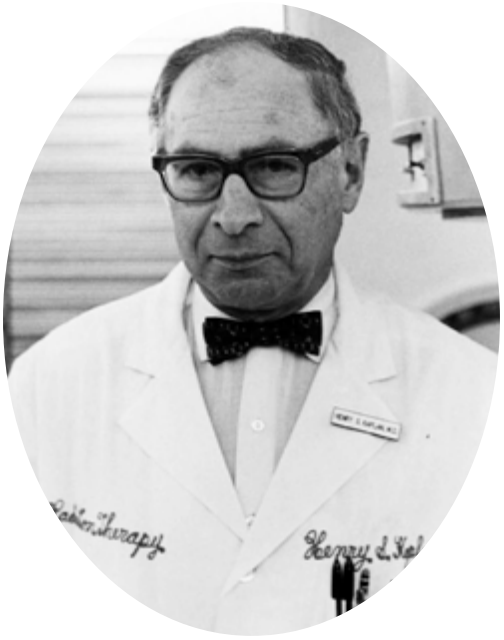


Figures that give the principle for the linear accelerator. Above is the simple Widerøe`s linear accelerator. The potassium ions travelled from one gap to the next in 1/2 radiofrequency period. The ions attained an energy of 50 keV.
In the lower figure electrons are accelerated by interacting with a synchronised RF- field. The accelerating waveguide is a long cylindrical tube with a series of cylindrical baffles. Electrons are generated in bunches in the gun and these electrons are riding or surfing on the microwave radiation to en energy of 6 MeV or above. They can be used directly or they may hit a high atomic number target and the kinetic energy is converted to heat and X-rays (bremsstrahlung).

In the illustration to the right you can see the interior of a linear accelerator. You see the acceleration tube where the electrons reach the high energy. When the electrons hit the target a part of the energy is converted to x-rays. This beam is colored yellow.



Henry Kaplan was the first one to use a linear accelerator at Stanford Hospital in San Francisco in 1957. The patient was a boy (Gordon Isaacs) that was suffering from a tumor in his eye (retinoblastoma). The treatment saved the child's sight and he lived the rest of his life with his vision intact.
Below is a picture taken during the treatment.



Henry Kaplan
(1918 – 1984)

Fifty years and about 50 million patients later, medical linear accelerators have become the backbone of radiation therapy for cancer worldwide. Roughly half of all cancer patients receive radiation therapy, primarily from the rays generated by a linear accelerator.

Guidelines for treatment

The goal for radiation treatment is to kill the cancer cells. This can be achieved by giving a dose of radiation that is large enough for killing. However, you will always irradiate healthy tissue near the tumor. You are faced with a situation where you should kill the cancer cells and at the same time give the healthy tissue the smallest available radiation dose. This is a "*balance on a knifes edge*" situation.

The advancement in radiation therapy is due to the use of higher energy of the x-rays which has given more suitable depth-dose curves (see page 219). In recent years ions with high energy have been introduced. They all have depth-dose curve which ends with a Bragg-peak (see pages 29 and 77). The goal is to position the Bragg-peak in the center of the tumor – and thus optimize the radiation.

The improvements in radiation quality have been followed by improvements and new methods in doseplanning. Thus both MR and CT and even PET is used to plan and follow up the treatment.

The goal is to kill the cancer cells and at the same time let the healthy cells survive.

You balance on "the knifes edge" to reach the goal!

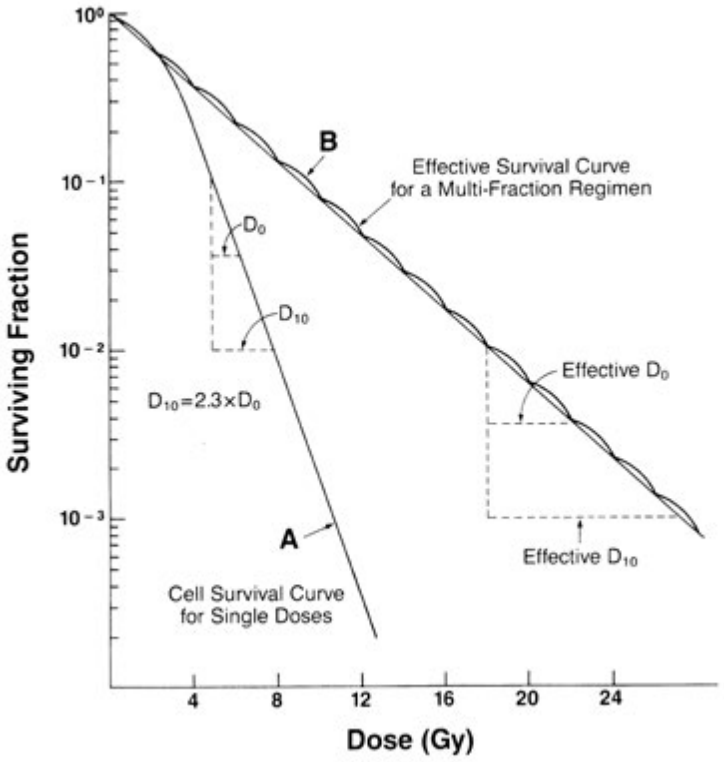
The radiation dose

The goal is to give the tumor a dose that kill the cancer cells, and at the same time let the surrounding healthy tissue survive. Information on therapy doses can be obtained from experiments on single mammalian cells.

The figure to the right can be used to arrive at the dose region which can be used in therapy. The curves demonstrate the results of radiation on single cells.
Since it is impossible to observe dead cells, you observe those that survive. The survival curves are usually described by a linear-quadratic equation.

In clinical therapy the total dose is given by a number of smaller doses (each 2 Gy) 5 or 6 days per week. The effective survival curve is like that marked B in the figure. The curve is almost a straight line in this semi logarithmic plot. The sensitivity, defined as the dose that reduce the survival to 37 %, is called D_0 and the dose necessary to kill 90 % is called D_{10}.

For human cells D_0 is of the order 3 Gy. Since the survival curve is a straight line in this semi logarithmic plot we have;
$D_{10} = 2.3 \bullet 3 = 6.9$ Gy.



Here is given an example of a survival curve (A). The dose axis is linear and the survival is plotted on a logarithmic scale. The curve can be described by a linear-quadratic equation. After a shoulder it is a straight line in this plot. In curve B the total dose is given by a serious of fractions – similar to a radiation treatment protocol.

We can use the above data to arrive at a dose that can kill the cancer. A tumor consists of 10^9 to 10^{10} cells. In order to kill these cells – that is reduce the survival by 10 decades the required dose wold be about 69 Gy.

The amount of radiation used in therapy varies depending on the type and stage of the cancer. The typical dose for a solid epithelial tumor ranges from 60 to 80 Gy, while lymphomas are treated with 20 to 40 Gy.
A number of factors are considered in the dose planning, such as the use of chemotherapy and of course surgery.

Today the treatment is planned on computers and the purpose is to give a high dose to the cancer cells and at the same time to minimize the dose to the surrounding healthy tissue.

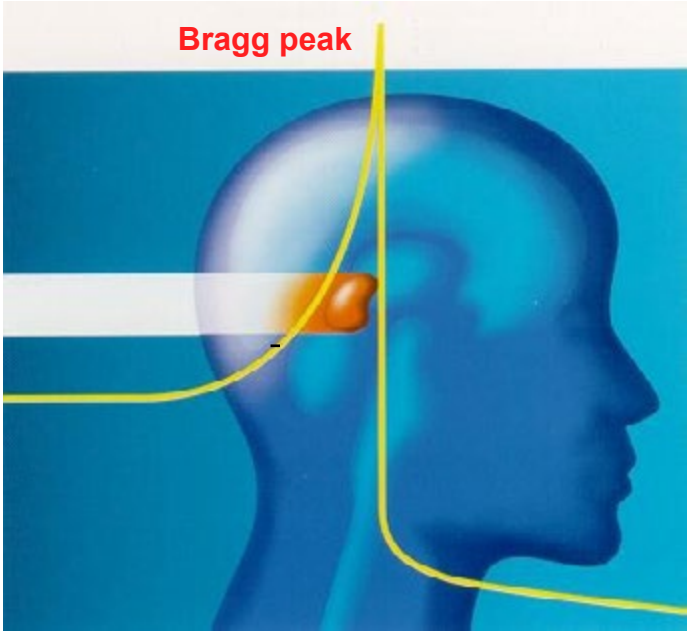
In order to optimize radiation therapy we can mention two lines; A). To improve the diagnostic side. B). To use radiation that gives the best possible dose distribution (for example protons and carbon ions).

THE GOAL FOR RADIATION THERAPY

A large dose to the tumor and a small dose to the healthy tissue.

Radiation quality and heavy ion therapy

Most tumors are inside the body – which implies that several centimeters of healthy tissue has to be irradiated on the way to the tumor. The guidelines for treatment are connected to the depthdose curves for the different types of radiation. We have presented depthdose curves on page 219 for x- and γ-rays and on page 29 for α-particles and other charged ions. On page 77 we also present a depthdose curve for carbon ions (stripped for all 6 electrons).



When you switch from x-rays (or bremssthralung) to ions (nuclei stripped for electrons) you get a completely new depthdose curve which is outlined in the illustrationf to the right. The energy deposition along the track (dE/dx) can be described by the Bethe-Bloch equation. In a simple form it can be given as;

$$\frac{dE}{dx} \approx k\frac{z^2}{v^2}$$

Here z is the particle charge (for protons z = 1, for α-particles z = 2 and for carbon ions z = 6). The speed of the particle is given by v. You can easily see that when the particle slows down (v goes to zero) the energy deposition (or rather the dose) goes up. The result is the famous ***Bragg-peak***. The Bragg peak can be very sharp – down to millimeter size. It is sharper for carbon ions compared to protons. The depth in the body for the Bragg peak is determined by the energy of the particles. The technology with proton and heavy ion therapy is excellent to fulfil the requirement of maximum dose to the cancer and minimum dose to the healthy tissue. In the beginning there was a lack of diagnostic methods to position the patient and the tumor in order to attain maximum effect of the Bragg peak. Furthermore, we could not follow the results of the treatment. Today we have techniques like CT and PET which has brought the radiation therapy to a new level. With this type of therapy it is possible to spare healthy tissue—for instance, the eye, the base of the skull, the prostate, and tumors very close to sensitive organs. Ion therapy is especially good with large tumors that wrap around critical structures.

History

The history of heavy ion therapy is surprisingly old. It dates from 1946 when Robert Wilson proposed the use of protons and heavier ions for therapy. The pioneering experimental work of Cornelius Tobias and the Lawrence brothers at Berkeley confirmed Wilson's predictions. Between 1954 and 1957, 30 patients were treated on the 184 inch cyclotron at Berkeley.

Cornelius Tobias
(1918 – 2000)

Proton therapy continued in the USA (Harvard University) and also in other countries like Russia (Dubna) in 1967, Japan (Chiba) in 1979.
In 1990, a facility for proton therapy was set up in the hospital of Loma Linda University in California. They have treated a large number of patients during the years. In 2013, there were a total of 37 proton therapy centers and 6 carbon centers in Canada, China, England, France, Germany, Italy, Japan, Korea, Russia, South Africa, Sweden, Switzerland, and USA. More than 108 000 patients had been treated. A number of new heavy ion therapy centers are planned and under constructions.

A strange experiment with heavy ions

In the picture to the right Cornelius Tobias is performing a strange experiment at the Berkeley cyclotron in 1970. The purpose was to explain the mystery behind the peculiar flashes and streaks of light reported by Edwin Aldrin and the other Apollo-11 astronauts after their 1969 moon mission.
With a special black hood to prevent light from the outside, Tobias exposed his own eyes to a variety of low-dose beams of α-particles. He saw the same display of lights and they subsequently identified the source of the lights, witnessed by the astronauts, as cosmic rays, a phenomenon that Tobias had predicted nearly 20 years earlier. In the picture John Lyman is lining up the beam.
Picture to the left exhibits the entrance of the Lawrence Radiation Laboratory with the 184 inch cyclotron in the background.

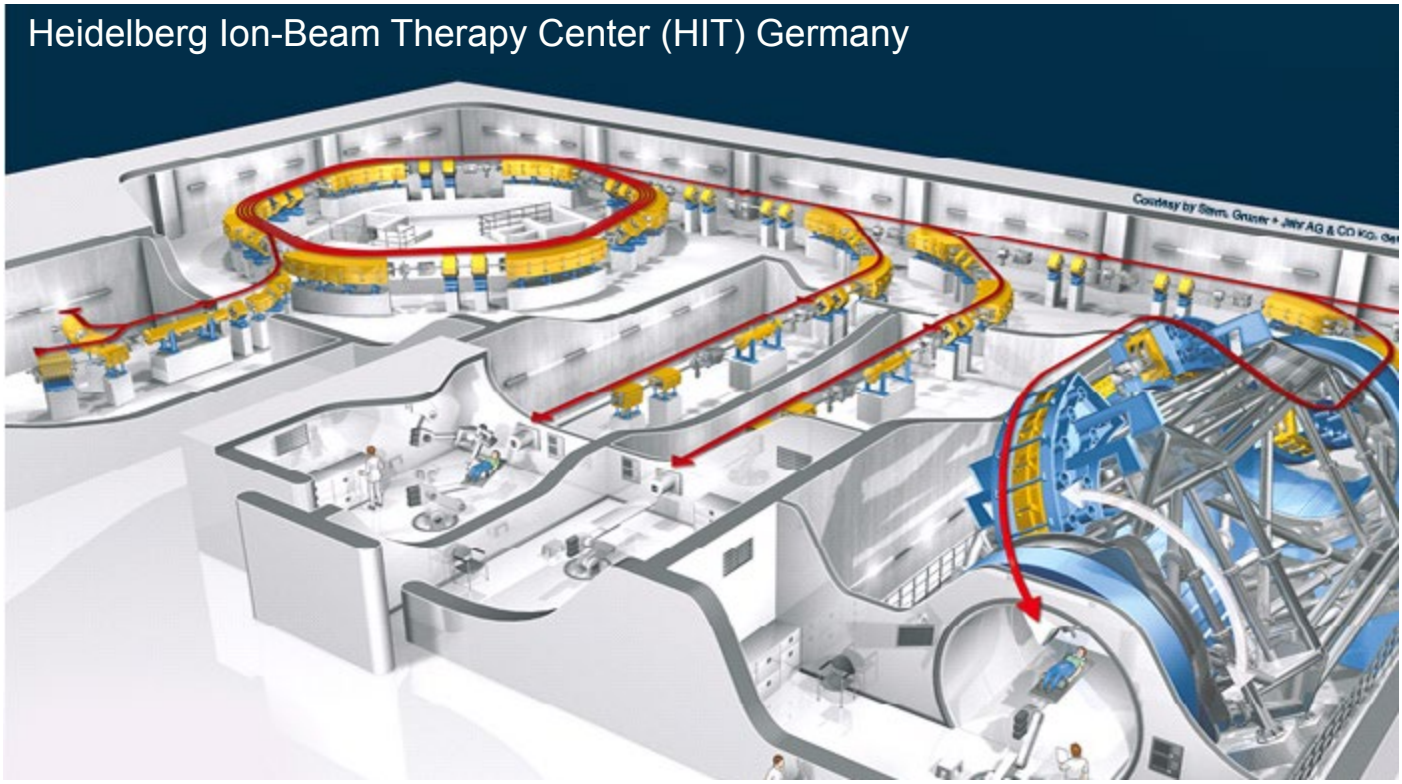
Radiation therapy for the future

If we look into the physics for radiation therapy we easily recognize the great possibilities we have if we could use the full capabilities of the Bragg-peak. With a beam focussed to a diameter of about a millimeter hitting the tumor with its Bragg peak would be a dream. With modern diagnostic methods and new accelerators this goal will be reached.

In November 2009 a therapy center in Heidelberg, Germany was opened. In the picture next page you see an outline of this center. The building is half-buried in the ground to minimize radiation exposure for the environment. You can follow the beam which is outlined by a red curve. We start from the left with the ion source and a linear accelerator. The beam enter the synchrotron with a circumference of 65 metres, which can accelerate protons, alpha particles, or nuclei of carbon and oxygen to final energies of 50 to 430 MeV/nucleon.

This implies that protons can be accelerated to energies from 50 to 430 MeV. However, for carbon ions with 12 nucleons, the energy is in the range from 600 MeV to 5.16 GeV.

The heavy-ion beam, which is focussed to a diameter of about a millimeter, is steered by magnets to one of two treatment places, or into a big installation of bending magnets, the so-called "*gantry*". The gantry allows the beam to be directed from any direction of a vertical plane into one point.



Modern brachytherapy

On page 218 we described the beginning of brachytherapy. Radium was used and the treatment time was usually a few days which included a number of problems with regard to safety for the people around the patient.

Now all use of radium is over and a number of new isotopes have been introduced. The sources are sometimes formed as seeds (0.8 mm in diameter and 4 – 5 mm in length). The treatment can be divided into; a) High dose rate (HDR), b) Low dose rate (LDR) and c) Permanent implants. In the table below an overview of different isotopes, radiation and half lives is given.

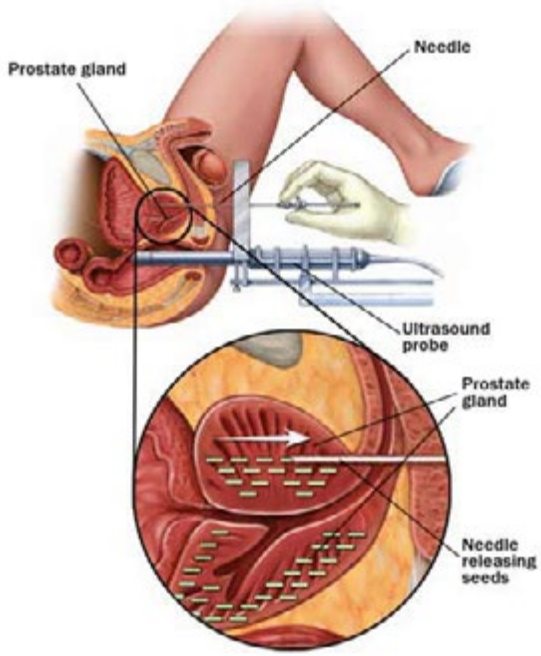
Isotope	Radiation	Half life $T_{1/2}$
Ra-226	Average 0.83 MeV	1620 years
Co-60	1.17 and 1.31 MeV	5.26 years
Cs-137	0.66 MeV	30 years
Au-198	0.42 MeV	2.7 days
Ir-192	0.38 MeV	73.8 days
I-125	28 keV EC. γ + x-rays	60 days
Pd-103	21 keV EC. x-rays	17 days
Cs-131	29 keV EC. x-rays	9.7 days

For all these isotopes it is the γ-radiation that is used. It can be noted that the isotopes I-125, Pd-103 and Cs-131 decay via electron capture (EC) and that the emitted radiation is a combination of γ-radiation and characteristic x-rays – because one of the orbital electrons is captured by the nucleus and leaves a hole that is filled with other electrons.

Brachytherapy is used to treat several types of cancer like cervical, prostate, breast, and skin cancer. Brachytherapy can be used alone or in combination with other therapies such as surgery.

Let us give a couple of examples.

Prostate cancer



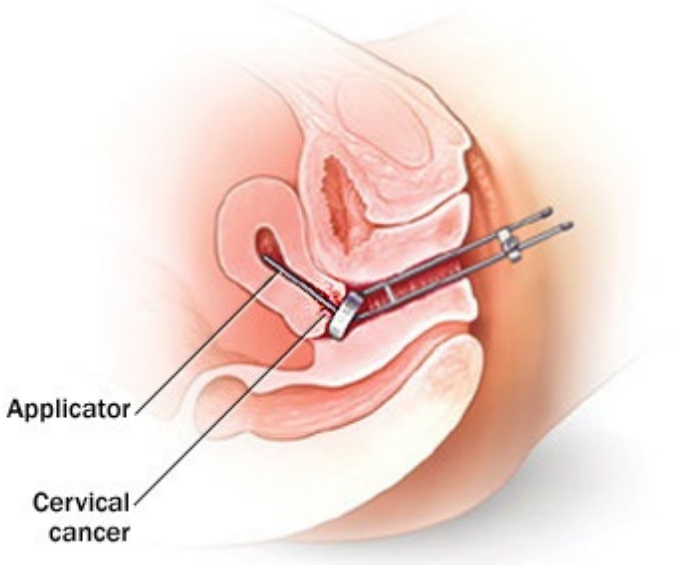
Prostate cancer can be treated in several ways. One possibility is to use brachytherapy. In the case of LDR I–125 or Pd–103 in the form of small seeds are placed directly into the prostate as shown in the figure to the right. The seeds are guided by a ultrasound probe in rectum. The seeds are permanently in the prostate and the radiation is given mainly during the first half life of the isotope.

Another method is HDR radiation using Ir–192 in the form of an iridium wire. A much stronger source is placed into the prostate and taken out again.

We have also to mention that prostate cancer can be treated with proton therapy. The Loma Linda center in California have used this technique with success for a number of patients.

Cervical cancer

Three methods can be used to treat cervical cancer: surgery, chemotherapy, and radiation therapy. In the case of brachytherapy the isotope Ir-192 can be used with a dose-rate (HDR) of the order 12 Gy per hour.



Conclusion

The table above demonstrate the development within brachytherapy. In the beginning only radium was available. This source has γ-radiation with an average energy of 830 keV. The advantage of brachytherapy is that the source is close to the tumor, – and due to the inverse square law this treatment would give a good dose picture.

With sources such as I-125, Pd-103 and Cs-131 the photon energy is down to 20 – 30 keV. This radiation has a much shorter range in tissue and the requirements for therapy – maximum dose to the tumor and a small dose to the healthy tissue – is far better. Furthermore, the half lives are of the order days and the radioactive seeds remain in the body.