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Progress in Physics (36)

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Introduction

Besides cardiovascular diseases cancer has become the major cause of death in the developed world. Between the ages of 45 and 84 years cancer actually is the number one cause of death in Switzerland. There are 37'000 new cancers diagnosed each year in Switzerland and 15'000 patients die of the disease. Statistically this equals about 63'000 potential life years lost for these patients (Bundesamt für Statistik; *www.bfs.admin.ch*). Because cancer is generally a disease of older people its importance will further increase in the next decades because of increasing life expectancy.

The main pillars of cancer treatment are surgery, radiotherapy and chemotherapy. Today patients usually receive multimodal treatments that include at least two or all three modalities. During the course of their disease 50-60% of all cancer patients will be treated with radiotherapy at least once, which underlines the importance of the discipline. Modern radiation oncology looks back on more than a century of developments. The beginning lies in the late 19th century when within a couple of years several ground breaking discoveries were made such as x-rays (Röntgen 1895), natural radioactivity (Becquerel 1896) and the first radioactive element radium (Curie 1898). Almost immediately the biological effects of the novel rays were recognized and no later than 1896 the Viennese physician Leopold Freund published a paper about the successful treatment of a skin cancer with x-rays. In the early days as well as today, both, x-rays as well as g-rays, are used in medical treatments. More recently also charged particles, mostly protons but also heavier particles such as carbon ions, have been used for patient treatments. Two principle methods exist to deliver the dose to the patient: In brachytherapy (=radiation from short distance) the radiation source is placed inside the body of the patient in close proximity to the tumor or even within the tumor whereas in external beam radiotherapy (EBRT) the radiation is pointed on a specific part of the body from outside. The following article is focusing on EBRT. Medically applied x-rays today are usually produced by linear accelerators (see information box) and protons or other charged particles are produced by cyclotrons or synchrotrons.

Physical, chemical and biological effects of high energy x-rays and charged particles

The physical effects of high energy x-rays as well as charged particles in matter (e.g. human tissue) are indirect and direct ionizations of atoms. X-rays are mainly indirectly ionizing by producing high energy electrons, when they interact with matter. The three main interaction processes are: Photoelectric Effect, Compton Effect and Pair Production. In the MeV - range that is most commonly used in radiation-oncology the Compton Effect is predominant. The high energy electrons have enough energy to produce a large number of ionizations by collisions. Charged particles on the other side are directly ionizing.

As the beam enters the matter (patient) the absorbed dose varies with depth. For photons in the MeV - range the largest dose is absorbed approximately 1.4 - 2 cm below the surface, then it falls off continuously (blue curve in Figure 1). The absorbed dose of the charged ions is relatively low between the surface and the point where they stop. The velocity of the heavy particles decreases continuously up to the end of their range, where they stop moving and generate a dose peak, the Bragg peak. After the Bragg peak the dose falls to close to zero within a few millimeters (red curve in Figure 1).

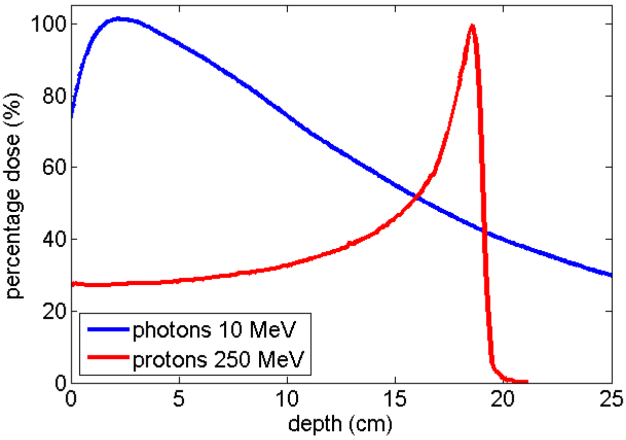

Figure 1: Dose distribution of high energetic photons and protons in water.

The major biological effect of ionizing radiation (IR) is DNA damage, e.g. when a secondary electron or a charged particle ionizes directly DNA molecules or indirectly by hydroxyl radicals (OH^-) that interact with DNA. Hydroxyl radicals are produced as a result of the ionization and chemical reaction of water molecules. By giving 1-2 Gy to a tumor more than 1000 single strand breaks and approximately 40 double strand breaks of the DNA double helix are induced per cancer cell. This damage could theoretically be repaired by the cellular DNA damage repair system. Because cancer cells are in many ways altered and abnormal, e.g. they divide more often and therefore are more vulnerable and they often have defective repair systems due to mutations, they are much more sensitive to radiation than normal cells. The knowledge about the biological effects of IR at molecular level has increased dramatically in recent years and today it is known that IR not only induces DNA damage but in addition a multitude of responses on the cellular level and the level of the tumor microenvironment. For example IR can activate cell membrane receptors that mediate survival signals into the cell in order to protect the cells from radiation damage. Another mechanism is that radiation can induce secretion of proteins from the cell that stimulate production of blood vessels in order to maintain the tumor cells' supply

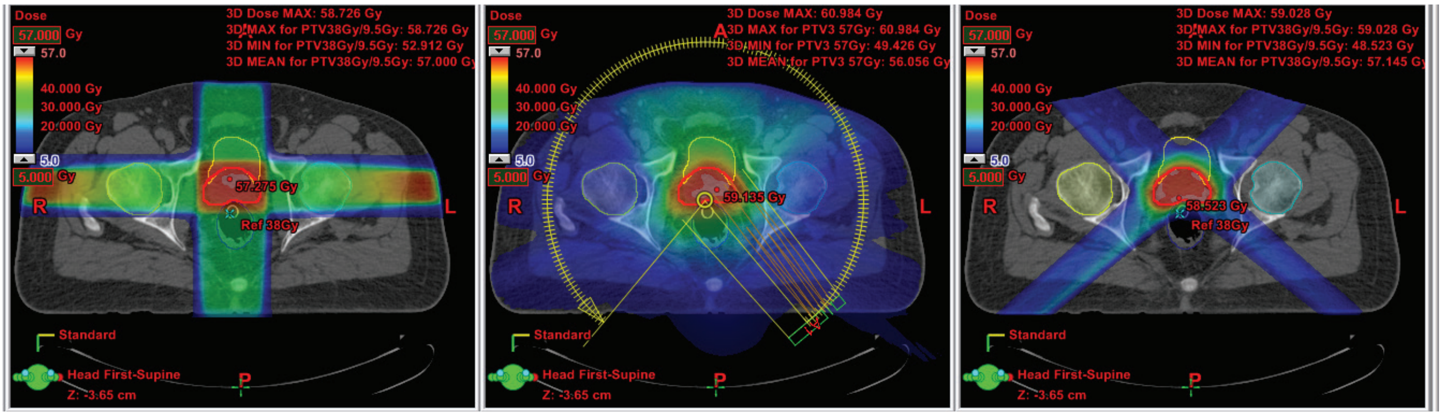

Figure 2: Comparison of treatment plans in a patient with prostate cancer. Shown is a typical slice of the planning CT in the pelvis with different radiation plans calculated: Left image: Conventional 4-field 3D-conformal plan; middle image: intensity modulated volumetric arc plan, right image: 4 field proton plan. The arrows show the target contour (prostate, red), the rectum (black with inflated rectum balloon) and the hips. Red volume signifies high dose, green volume intermediate dose and blue volume low dose. The rectum is the major organ that has to be spared from radiation in the case of prostate cancer. In order to protect the rectum an endorectal balloon is inserted before every radiation fraction and inflated with air. The rectum balloon serves to move major parts of the rectal wall away from the prostate and the high dose volume. The volumetric arc plan spares the rectum much better and conforms the dose better to the prostate than the 3D Plan. In comparison the proton plan shows equal target coverage as the VMAT plan but much less dose to the surrounding tissue, especially the rectum and both hip bones.

with oxygen and nutrients. In the clinical setting radiotherapy is often combined with classic chemotherapeutics in order to increase DNA damage (e.g. combination of IR and cisplatin that also induces DNA damage). A novel approach that is currently investigated in clinical and preclinical research is the combination of IR and molecular therapeutics, i.e. molecules or antibodies that counteract specific cellular or microenvironmental responses of the tumor (DNA repair, cell survival, angiogenesis = formation of tumor blood vessels etc.).

Elements of Modern Radiotherapy

The major elements of modern radiotherapy are diagnostic imaging, computer based treatment planning, treatment delivery (usually with a modern linear accelerator), and last but not least specialized personnel: doctors referred to as "radiation oncologists", medical physicists who are responsible for all physical aspects of treatment planning, treatment delivery, quality assurance and maintenance of treatment machines and radiation therapists, who usually are trained in treatment planning, practical aspects of quality assurance and to operate the treatment machines during patient treatment.

Treatment Planning

In the early days of radiation oncology only 2D treatment planning was possible. Based on anatomical landmarks and/or simple x-ray films the physicist calculated a 2D dose distribution in one slice plane of the patient. This treatment was not very conformal, i.e. the healthy tissue around the tumor could only minimally be spared. With the progress in information technology (hard- and software) and the invention of computed tomography (CT) modern 3D-conformal radiotherapy (3D-CRT) became possible and has been widely adopted since the 1980s. In the case of 3D-CRT a treatment plan is created on CT images using dedicated software that allows conforming the dose around the tumor and sparing the adjacent tissue. Before treatment planning the radiation oncologist defines the volume to be treated by drawing the target volume (GTV, gross tumor volume) on each CT slice. Usually a geometrical volume (PTV, planning target volume) is drawn around the GTV to compensate for positioning uncertainty of the patient and tumor. In addition the normal structures, that should be spared are drawn on the CT slices. Thereafter the radiotherapist prepares the treatment plan in close collaboration with the physicist. For 3D-CRT usually 2 to 5 beams from different angles and with different beam shaping profiles are used. Treatment planning became much more complex since the 1990's, when "intensity modulated radiotherapy" (IMRT) became available. In the case of IMRT the radiation beam is modulated at every time point by use of up to 120 dynamic and computer guided metal leafs introduced into the beam aperture. Intensity modulation allows improved conformity around the tumor and better sparing of surrounding normal structures. However it leads to an increase in the so-called "low dose bath", because of the increased scatter from the metal leafs, which might lead to an increase in secondary cancer. IMRT plans usually use multiple beams. Today most patients are treated with intensity modulated techniques. A variant of IMRT is volumetric modulated arc therapy (VMAT) where the LINAC rotates around the patient thereby applying hundreds of fields, by changing the shape of the metal leaf collimators and the dose per minute at each control point (depending on the vendor the control points are spaced between 2° and 5°). Figure 2 shows a comparison between a 3D-CRT plan and a VMAT plan in a patient with prostate cancer. Additionally the dose distribution, which can be achieved with protons is shown. As explained earlier protons (as other heavy ions) have the advantage that they deposit most of their energy in the Bragg peak. By adjusting the energy of the protons, in a way that the Bragg peak is in the tumor the healthy tissue can be better spared.

Treatment machines

The first linear accelerator was constructed in the 1950s and was basically a byproduct from Second World War radar technology. Later on, i.e. approximately in the 1970s, also particle therapy came up. Particle therapy uses immense installations to generate particle beams (usually protons but also heavier particles such as carbon ions) that, due to their physical properties, are able to deliver even more conformal radiotherapy than IMRT in selected cases. Switzerland with its proton facility at the Paul Scherrer Institute in Villigen has been pioneering proton therapy. Because the logistics of proton therapy are still immense with huge and expensive facilities it is still limited to specific indications such as pediatric cancers. In recent years several proton facilities opened all over the world and proton therapy has become more broadly available. Because proton therapy is still much more expensive than photon therapy and only few studies exist in patients its optimal use is still under debate. In Switzerland the construction of an additional proton facility is currently under discussion. In comparison, at least 55 linear accelerators are installed in 25 radiation centers.

Modern linear accelerators (box, figure 4) as well as proton treatment machines can deliver radiation therapy with sub-millimeter accuracy. Additionally they have integrated imaging systems such as computed tomography or MV image detectors introduced into the beam path allowing to identify the target in 3D shortly before and during treatment. This allows for very small safety margins between the actual tumor volume and the irradiated volume and ensures maximum sparing of healthy tissue.

Current Fields of Physical Research

As mentioned modern accelerators achieve sub-millimeter accuracy. However not all tumors are stable during the treatment session. Tumors in the lung can move up to 16 mm, in the liver up to 34 mm and the thoracic wall moves up to 14 mm due to respiratory motion. Prostate tumors move up to 9 mm mainly due to bowel motion and bladder filling. Tumor motion management to irradiate the tumor while sparing the healthy tissue is needed. There are different methods to manage tumor motion already in use and/or in development. First a motion encompassing treatment can be performed in which all tumor positions within the breathing cycle serve as target (Figure 3). Second treatment can be delivered gated, i.e. that the tumor is only treated in inspiration or expiration. Third the tumor is tracked which means that the beam follows the tumor. Tumor motion management is an important research topic for proton as well as photon therapy. However the interplay effect between the modulating beam and the moving organ is larger in proton therapy, leading to larger deviations between the planned and the delivered dose distribution. Therefore most protons centers currently don't treat moving tumors.

Tumor motion today can be imaged by 4-dimensional computed tomography (4D CT). Briefly, the respiratory curve of the patient is recorded during CT acquisition by means of an in-room installed infrared camera and a corresponding marker block put on the patient's chest. By use of a dedicated software the CT images are then sorted according to the respiratory phase and a 4D CT data set is generated. The development and clinical implementation of 4D magnetic resonance imaging similar to 4D computer tomography is another research topic currently under investigation.

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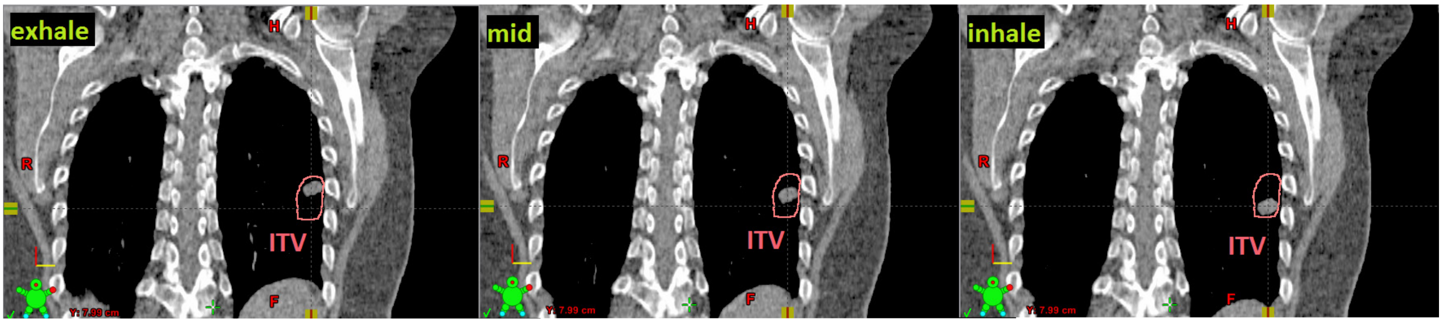
Stephanie Lang is Medical Physicist at the Department of Radiation Oncology of the University Hospital Zurich. Her clinical focuses are linear accelerator technology, dosimetry, quality assurance and stereotactic radiotherapy. Her main research interests are image-guided radiotherapy and motion management.



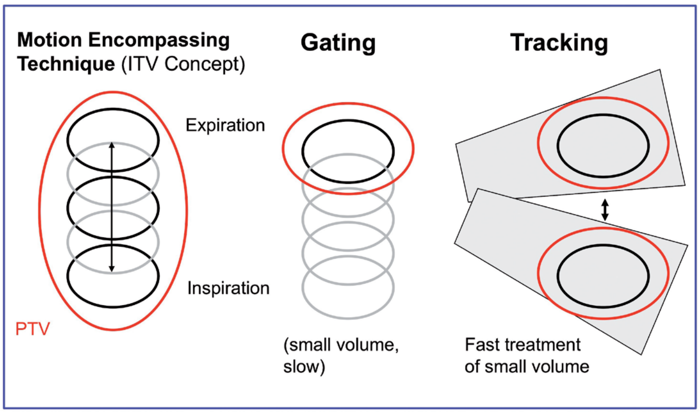


Figure 3a (top row): Coronal 4D CT slices of a patient with lung cancer. Shown are slices in expiration (left), mid ventilation (middle) and inspiration (right). The target volume (ITV = internal target volume) comprises all positions of the tumor within the breathing cycle.
Figure 3b: Methods of Motion Management: Left: Motion encompassing techniques (includes ITV as target volume). Middle: Gating: The tumor is only treated in deep inspiration or expiration. Right: Tumor tracking: The beam follows the movement of the tumor. With gating the treated volume is much smaller with less side effects but overall treatment time is prolonged because only a small part of the breathing cycle can be used for treatment (beam switches on and off).

A linear accelerator consists of 5 main parts:

- The modulator serves as a power supply for the linear accelerator.
- The stand is the non-rotating part that contains the cooling water supply and the klystron.
- The gantry is the rotating part of the linear accelerator. All beam generating and collimating parts are inside the gantry.
- The imaging system: Today most systems are equipped with high resolution imaging systems to correct the patient's position and orientation with respect to CT data, taken during planning phase.
- The treatment couch is used for positioning of the patient.

Figure 4 is a schematic drawing of a high energy linear accelerator, as it is installed at the University Hospital in Zürich. The electrons, emitted from a heated cathode and extracted by the anode field are properly focused by lens elements for injection into the accelerator tube. In the tube a standing high frequency wave (330 MHz) further accelerates the electrons to a maximum energy between 4 MeV and 20 MeV. The energy switch determines the length of the standing accelerating wave and therefore the energy of the electrons. After the energy switch the wave is phase shifted and cancels out so that it no longer accelerates the electrons. The klystron inside the stand produces the high frequency wave.
After leaving the waveguide, the electrons are bended by 270° and energy selected by one or multiple deflecting magnets. After hitting a tungsten target, high intensity Bremsstrahlung is produced. The beam intensity profile is anisotropic due to the forward scattering process and must be homogenized. First a primary collimator cuts out the central part of the beam, then a flattening filter, i.e. a metal cone with stronger absorption in the beam center than at the side lopes flattens the profile. The shape and flatness of the beam are monitored by two ionization chambers.
In order to radiate only the tumor and not the healthy tissue the beam profile needs to be shaped patient specifically. Several beam profile shaping devices are available. The jaws are used for the basic collimation of the beam, only square fields can be achieved using the jaws. The 120 metal multi leaf collimators are used to achieve more complex shapes.

The authors in front of the linear accelerator at the University Hospital in Zürich.