Chapter III.11

Radiation oncology: biology, physics and clinical applications

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Ionizing radiation is one of the main modalities used for cancer treatment and has been used in the clinic since the discovery of X-rays and radioactivity at the end of the 19th century. The development of linear accelerators (linacs) in the 1950s allowed treatment of deeply seated tumours and sparing of the skin. Further improvements in imaging, computer-assisted planning, dose-delivery techniques and globally treatment equipment, allowed vast improvements in curability and reduced toxicity; nowadays, over 50% of cancer patients receive radiotherapy. The majority of radiotherapy treatments globally are delivered with megavoltage electron linacs. Access to radiotherapy and improvement of available technology remain key issues of global health.

III.11.1 History of radiation oncology

Radiation therapy is the clinical modality dealing with the use of ionizing radiation in the treatment of patients with cancer, and occasionally benign diseases. Various sources can be used for ionizing radiation, such as photons, either delivered in the form of gamma rays emitted from the nucleus of a radioactive atom or X-rays generated by linear accelerators, as well as particle beams, such as protons, neutrons and electrons.

The history of radiation therapy starts soon after the discovery of X-rays by William Röntgen in 1895 while he was studying cathode rays in a gas-discharge tube. He observed that another type of radiation was produced that could be detected outside the tube, and that this radiation could penetrate opaque substances, produce fluorescence, blacken photographic plates, and ionize a gas. He named this new radiation "X-rays". He also noted that these X-rays could be used to image bones. The first known X-ray image produced was that of his wife Anna Bertha's left-hand. Röntgen characterized and validated his findings in a technical report within six weeks.

The first treatments of patients shortly followed this discovery. Two months later, Emil Grubbe, a medical student in Chicago, noted pealing of his hands on exposure to X-rays. He assembled his X-ray machine in 1896, and that same year used it to treat a woman with recurrent breast cancer. Around the same time, Victor Despeignes used X-rays to treat a patient who was suffering from stomach cancer in July 1896. He was the first physician to publish a paper on radiation therapy in 1896 dealing with that case. "Röntgenotherapy" was born, although it was still unclear how the X-rays acted. Initially, it was

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mostly used for hair removal, inflammatory skin diseases (eczema and acne), and skin cancers, as, at the time, the X-rays were of low energy and therefore of limited penetration in tissues. Despite these limitations, these works formed the basis for the development of external-beam radiation therapy, the most common form of radiation therapy used today.

Shortly afterwards, the discovery of radioactivity further promoted the use of radiation therapy. In early 1896, in the wave of excitement following Röntgen's discovery, Henri Becquerel thought that phosphorescent materials, such as some uranium salts, might emit penetrating X-ray-like radiation when illuminated by bright sunlight. By May 1896, after other experiments involving non-phosphorescent uranium salts, he concluded that the penetrating radiation came from the uranium itself, without any need for excitation by an external energy source. Becquerel's doctoral students Marie Skłodowska and her husband Pierre Curie showed that Becquerel rays could be measured using ionizing techniques, and radiation intensity was directly proportional to the amount of uranium in a substance. They then isolated the first known radioactive elements polonium and radium in 1898.

Radium was soon thought of as a way to treat disorders that were not affected enough by X-ray treatment, because it could be applied in a multitude of ways in which X-rays could not, at the time using glass applicators for radium emanation or tubes for applying radium salts. Today, the use of radiation therapy by a sealed radiation source placed inside or next to the area requiring treatment, is still ongoing and is called brachytherapy. Brachytherapy remains an effective treatment for cervical, endometrial, prostate, breast, oesophageal, and skin cancer, and can also be useful to treating tumours in a variety of other body sites.

To further improve the use of radiation therapy, several developments were necessary: from a clinical point of view, increasing curability and decreasing normal-tissue toxicity, what is called enhancing the therapeutic ratio, was un unmet clinical need. A large step was made with the introduction of the concept of fractionation in 1922, by Henri Coutard, a French radiologist working with the Institut Curie, who presented evidence that laryngeal cancer could be treated without disastrous side-effects, inspired by the observations of Claudius Regaud, who found that a single dose of X-rays sufficient enough to produce severe skin damage and tissue destruction in a rabbit, if administered in fractions, over a course of days, would sterilize the rabbit but have no effect on subcutaneous tissues. In 1935, hospitals everywhere began following his treatment plan, which was the first application of radiobiological principles in clinical practice.

From a technical point of view, the use of higher-energy photons was necessary to treat deeper tumours, as well as sparing the skin, to avoid burns and cutaneous toxicity. Ordinary X-ray tubes, which use voltages of 50–150 keV, can only treat superficial tumours. Beginning in the 1950s, cobalt-60, produced artificially in nuclear reactors, started to be widely used in external-beam radiotherapy machines, producing a beam of gamma rays at 1.17 and 1.33 MeV. Cobalt-60 is a high-intensity gamma-ray emitter with a relatively long half-life of 5.27 years. As a next step, linac-based radiation therapy for cancer treatment was introduced with the first patient treated in 1953 in London, UK, at the Hammersmith Hospital, using an 8 MV machine. A short while later in 1954, a 6 MV linac was installed in Stanford, USA, which began treatments in 1956. Currently, the vast majority of external-beam radiation therapy is delivered from linacs producing high-energy photons (6–20 MV) for deep-seated tumours, and electrons for superficial lesions.

III.11.2 Basics of radiation biology

Radiation biology is the study of the effects of ionizing radiation on living systems. Acute effects of radiation were first observed when Wilhelm Röntgen intentionally subjected his fingers to X-rays in 1895. He published his observations concerning the burns that developed and later healed. Henri Becquerel developed a skin burn as a result of carrying a glass tube containing radium salt in his vest pocket. Pierre Curie voluntarily exposed his arm to the action of radium during several hours. This resulted in a lesion resembling a burn that developed progressively and required several months to heal. Many of the initial scientists involved in the development and use of ionizing radiation suffered from burns and skin cancers. Emil Grubbe, for example, was operated over 90 times for cancerous burns from his own exposure to radiation.

Before people started to fear radioactivity, all they seemed to know about it was that it contained energy. Soon after its discovery, radioactive consumer products were available for sale, in the form of cosmetics, soaps, dairy products, and chocolate. Concerns of the dangers of radiation treatments were brought up before the US Senate in 1915. A wave of deaths of factory workers at radioluminescent watch factories was reported in the 1920s. These “radium girls” were female factory workers who contracted radiation poisoning from painting radium dials (watch dials and hands with self-luminous paint). They had been instructed to "point" their brushes on their lips in order to give them a fine tip, and ingested lethal amounts of radium. Also, cases sprung up of the development of carcinoma in patients who had used conventional radium therapy up to 40 years after the original treatments.

All these observations led to an increased attention to the interaction of radiation with tissues. Biological effects are due to the interaction of radiation with atoms, and results in an electron being emitted from the atom. Ions, generated in this way, are extremely unstable chemically, and generate indiscriminate chemical reactions. This can cause damage to cellular components such as DNA molecules. DNA damage can occur either directly or more commonly indirectly (by free radicals of water molecules reacting with DNA), leading to impaired reproduction of cells, cell death, or mutations. Whether and to what extent the radiation exposure leads to health damage depends on the radiation dose absorbed, the type of radiation, and the mainly affected organ or body tissue. All tissues have a tolerance level, or threshold, beyond which irreparable damage may occur. This is referred to as deterministic radiation damage. Deterministic effects are the result of massive cell killing and the subsequent loss of function of the affected organs or tissues. Particularly affected are the blood system, the skin, the hair, and the gastrointestinal system. Above this dose-threshold, the severity of the injury increases with dose and the damage appears earlier after higher doses. Radiation below the threshold dose causes no deterministic effects. However, a second type of radiation damage can occur, causing stochastic effects, due to random mutations in DNA, which can lead to the development of cancer.

Cancer is the term used for a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. It occurs as a result to altered cellular mechanisms usually resulting from DNA mutations. Both normal and cancer cells can be affected by radiation. Interestingly, dividing cells are more sensitive to radiation, due to the replication process of DNA. Cancer cells are more proliferative and generally have impaired ability to repair DNA damage, leading to cell death, thus being more sensitive to irradiation as compared to normal tissue cells. Therefore, the principle of radiation therapy consists of selectively eliminating cancer cells, while preserving normal cells. This process is facilitated by the concept of fractionation, mentioned above, being the delivery of the irradiation treatment in fractionated doses, in general with one session of radiation per day, for multiple sessions, 5 days a week. Fractionation spares normal tissue by permitting its repair and repopulation while increasing damage to tumour cells through their redistribution and reoxygenation.

Normal cells can selectively *repair* more sublethal damage between fractions thanks to their intact DNA repair mechanisms, as compared to tumor cells. Cells in the healthy tissue that die are removed and replaced through *repopulation*, i.e. regrowth of new cells between fractions. Tumour cells which are constantly dividing, will be redistributed into radiosensitive phases of the cell cycle in subsequent fractions (*redistribution*). Tumours can sometimes grow extremely fast leaving the central parts with inadequate oxygenation. Tissue oxygen is required for the formation of the water radicals necessary for indirect DNA damage. Thus, by destroying the oxygenated cancer cells that are then removed, *reoxygenation* of hypoxic cells can take place to make them more sensitive to radiation on the next fraction. Radiation therapy has a therapeutic window in which, at the doses used, the advantages of treatment, i.e. tumour control, are highly superior to the risk of complications (*therapeutic window*).

The dose of ionizing radiation used in therapy is expressed in grays (Gy), whereas 1 Gy represents the absorption of 1 J of radiation energy per kg of matter. The lethal dose 50% (dose that will kill half of the people exposed) is 4 Gy. This is if the entire body is exposed acutely. With the use of antibiotics and careful nursing, this dose increases to 7–8 Gy, and if a bone marrow transplantation is planned, the dose can be further increased up to 10 Gy. Acute doses above 10 Gy are uniformly fatal. To treat a prostate cancer, doses of 80 Gy are commonly used, however not all at once but spread out over 40 fractions of 2 Gy per day, five days a week, and only targeting the prostate and not the entire body.

III.11.3 Clinical applications

Radiation therapy is used to treat cancer patients, and more rarely for a limited number of benign diseases. Cancer is the second leading cause of death worldwide behind cardiovascular disease. The most common types of cancer are breast, lung, colon and rectum, and prostate, with the most common causes of cancer death being lung, colon and rectum, liver, stomach, and breast. Cancer can be treated by various modalities targeting the tumour on the local, locoregional (tumour and lymphatic drainage area), or systemic level (acting in most of the body). The modalities used are surgery, radiation therapy, classical chemotherapy, targeted therapy, and immunotherapy. Radiation therapy is used in over half of all cancer patients, most often as a combined modality. It can be used with a curative intent or with a palliative aim to reduce cancer-related symptoms.

The choice of which treatment modalities to use for treating a given cancer, as well as their sequencing and association, is based on years of patient treatments and the result of, when possible, large clinical trials. There are international guidelines suggesting what treatments should be offered, following evidence-based medicine, i.e. the use of the scientific method to organize and apply current data to improve healthcare decisions. Individual patient treatments are discussed and agreed upon, during multidisciplinary tumour boards, where radiologists, pathologists, surgeons, medical oncologists, radiation oncologists, and other specialists are present, before being offered to patients.

The delivery of external-beam radiation treatments is painless and usually scheduled five days a week for one to eight weeks. The effects of radiation therapy are cumulative with the most significant side effects occurring near the end or some weeks after the treatment course. Side effects usually resolve over the course of a few weeks. Side effects during and after treatment vary depending on site of the treatment and affected tissues in radiation field. Typical side effects include; in the breast area, swelling and skin redness; in the abdominal area, nausea, vomiting, and diarrhoea; in the chest area, cough, shortness of breath, and oesophageal irritation; in the head and neck area, taste alterations, dry mouth, mucositis, skin redness, hair loss; in the pelvic area, diarrhoea, cramping, urinary symptoms, vaginal irritation, impotence; moreover, fatigue is often seen when large areas are irradiated. Secondary cancer development is a rare and late complication (which can take over 20 years to develop) outweighed by the potential for curative treatment. Modern radiation therapy techniques have decreased these side effects significantly.

When radiotherapy is used for a curative intent, it can be delivered before surgery, instead of surgery, or after surgery. The reason to deliver *radiation therapy before surgery* is to decrease the risk for local or regional recurrence and to increase overall survival, and in some cases, where the tumour responds completely to the treatment, to avoid surgery altogether allowing organ preservation. Radiotherapy can be given before surgery alone as a sole modality, used for example in soft tissue sarcomas, or combined with a systemic therapy such as a radio-sensitizing chemotherapy in rectal cancer. Radiotherapy can in some cases completely replace surgery. It can be used as *the sole modality* in the treatment of vocal cord cancers that would require surgical removal otherwise, thus curing patients and preserving speech function. It can be given alone or in combination with hormone therapy to treat local or locoregional prostate cancer. There is however still no large trial directly comparing radiation to surgery in this setting. Another exciting development in the field is *stereotaxic radiotherapy*, i.e. the delivery of extremely high ablative doses, to a very small, well confined volume in very few fractions. This technique first developed for use in the brain and called radiosurgery in this setting, as a single fraction, is generally sufficient to completely destroy small brain tumours. It was subsequently developed for use in the rest of the body and is commonly used nowadays to treat early lung, prostate, liver and other cancers. Finally, radiation therapy used instead of surgery can also be combined with systemic therapy, for example in anal cancer where surgery would require amputation of the anus and a permanent colostomy pouch, or in inoperable but non metastatic lung or head and neck cancer. Finally, radiation can be given *after surgery* to decrease the risk of local and regional recurrence, and increase overall survival. A typical example is in breast cancer patients. Historically patients had major surgery where the entire breast and part of the chest wall was removed. Progressively, it was found that less surgery could be performed, and today, many early breast cancer patients only have the tumour removed (lumpectomy) followed by radiation to the remaining breast, which decreases the risk of recurrence to a similar level as a patient who had a mastectomy (removal of the entire breast).

Radiation is also used with a palliative intent in patients where a cure is not possible. The aim of irradiation in such settings is to improve symptoms rapidly and durably, with the fewest side effects possible, in the most comfortable and less cumbersome manner possible; therefore, palliative irradiation is delivered within a few fractions. Radiation to metastatic bone lesions permits effective alleviation of pain. Radiation to bone metastases will lead to the destruction of cancer cells but also to a consolidative reaction in the bone leading to a decreased risk of subsequent fractures. It can also be used in anticipation to prevent potential troublesome bone fractures. One site of bone metastasis of particular concern is the vertebra, where the tumour could lead to a compression of the spinal cord and thus paralysis. Time is of utmost importance in this setting, as after too much time the compression becomes irreversible. In another context, irradiation can help decrease the compression of various structures by the tumour, notably vascular structures where acute compressions can have life-threatening consequences. Finally, radiation can help stop bleeding of tumours that develop aberrant vasculature.

Over time, the treatment of metastatic cancer has improved tremendously, and numerous patients can live for many years with a good quality of life, thanks to the advent of effective systemic treatments. An increasing number of patients show no signs of disease years after initial treatment. An active field of research focuses on better understanding how to obtain these excellent results more predictably. The concept of oligometastatic disease (i.e. the condition of having only a few metastases) has emerged in recent years and many modern studies are testing the concept of treating these patients more radically, including stereotactic radiation to all or some of the visible cancer sites. This represents an emerging role of modern radiotherapy.

III.11.4 Technical evolutions and future developments

Currently in the world there are over 13 000 megavoltage radiation-therapy machines, of which the vast majority, over 11 000, are electron linacs. Hence most high-energy accelerators are used for medical purposes. Since the introduction and rapid proliferation of megavoltage radiation therapy machines in 1950s, treatment techniques have been vastly improved. Treatment fields were initially approximative, as treatment was delivered with two-dimensional techniques. The development, availability, and implementation into radiation oncology of CT scanners allowed the development of three-dimensional conformal treatment fields. Initially, treatment blocks to protect healthy organs needed to be designed individually for each patient and loaded onto the machine for each beam incidence. Nowadays, machines have multi-leaf collimators, a development that has vastly improved the process of precise dose delivery, as it allows more beam incidences during each treatment session. The use of computers to plan and deliver treatments has led to the development of techniques that have largely optimised the distribution of irradiation within the body. Such techniques consist of *intensity-modulated radiation therapy*, where multiple beam incidences are used with varying radiation intensity for each incidence and *volumetric arc therapy*, where radiation is delivered by a rotating gantry, whilst changing the speed and shape of the beam with a multi-leaf collimator and the dose rate of the medical linear accelerator. This improves the ability to conform the treatment volume to concave tumour shapes, for example when the tumor is wrapped around a vulnerable structure. Large efforts have been made to reduce the security margins of the target as much as possible, as even margins as small as 5 mm can lead to as much healthy tissue being in the target as the tumour itself. Various *immobilization techniques* are used such as thermoplastic castings of the head, neck or limbs. Treatment machines are equipped with imaging equipment, assuring of adequate setup, ranging from standard X-ray imagers, to CT scanner, and MRIs, allowing what is referred to *image-guided radiation therapy*. To better assess and master *organ respiratory motion*, four-dimensional planning CT scans are obtained. In any situation where motion control is important to reduce margins, breath holding techniques, tumour gating, or tracking are used and enable to safely avoid heathy tissue.

As previously said, the vast majority of machines used in radiation oncology are electron linacs, still an increasing number of centres have access to proton beam technology. Its advantage lies in the property of protons to depose the dose over a narrow range of depth (in a spread-out Bragg peak), with minimal entry, exit, or scattered radiation dose to healthy nearby tissues. Proton therapy is commonly used to treat childhood cancers, as growing patients are more at risk to develop long term complications and minimising scatter dose is of utmost importance. The advantages versus the disadvantages (higher cost, more complexity, risk of completely missing the target in a changing environment) are under study and have not been fully established. Other particles, such as carbon ions, which have a higher linear energy transfer and therefore create more double-strand DNA breaks, are being used and studied in a few selected centres in the world.

Radiation has traditionally been used for its local and regional effects on cancer cells. However, systemic effects of radiation, although first described in 1953, called the abscopal effect, being a systemic immune response of the host mediated by the interaction of irradiation with the immune system, did not gain full attention until recently, when the advent of immuno-oncology transformed the oncology landscape. Initially very rare, an increasing number of cases are observed since the introduction of immunotherapy, especially the wide use of immune-checkpoint inhibitors. Ongoing studies aim to better understand the mechanisms and potentially clinically explore the abscopal effect, but the concept is not yet ready for prime time.

In this same field of innovative perspectives of radiotherapy, another recent discovery, *flash radiation therapy*, i.e. the delivery of ultra-high dose rates of radiation (> 40 Gy/s), emerged as a modality of irradiation that enables tumour control to be maintained while reducing toxicity to surrounding non-malignant tissues, through a not yet fully understood radiobiologic phenomenon. Preclinical studies in various animal species have shown consistently that flash radiotherapy can substantially widen the therapeutic window and studies are ongoing in humans, delivering electrons and protons at these high dose rates. Appropriate technology is needed to successfully implement this modality into clinical practice, and projects are ongoing in this direction, aiming to develop very-high-energy electron or photon flash machines.

Future potential developments of radiotherapy include use of other particles and maybe someday even antimatter as potential tracks to be developed for cancer treatment. Access to radiotherapy for every patient around the world remains a pivotal challenge, and needs to come high in political healthcare agendas. Professional societies, such as ESTRO or ASTRO (the European and American societies of radiation oncology) are increasingly investing not only on innovation and research but also on equity and access to resources and education as important goals for improved cancer care. All these efforts underline the importance of radiation oncology as a sustainable pilar of cancer treatment and inspires respect for the early pivotal works of pioneers in the last century.

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Further reading

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