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Competing interests statement
The authors declare no competing financial interests.

🌐 **Online links**

DATABASES
The following terms in this article are linked online to:
Cancer.gov: http://cancer.gov/
breast cancer | lung cancer
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TIMELINE

Radiation oncology: a century of achievements

Jacques Bernier, Eric J. Hall and Amato Giaccia

Abstract | Over the twentieth century the discipline of radiation oncology has developed from an experimental application of X-rays to a highly sophisticated treatment of cancer. Experts from many disciplines — chiefly clinicians, physicists and biologists — have contributed to these advances. Whereas the emphasis in the past was on refining techniques to ensure the accurate delivery of radiation, the future of radiation oncology lies in exploiting the genetics or the microenvironment of the tumour to turn cancer from an acute disease to a chronic disease that can be treated effectively with radiation.

In the early days of development of radiation as an anticancer therapy, physics had the biggest contribution — the focus was on increasing the quality and quantity of radiation that could be delivered to a tumour. Radiobiology was a field split between understanding fundamental changes in irradiated cells and understanding the responses of normal tissue versus tumours to radiation. The early studies in experimental radiation oncology evolved from using large single doses to using small doses of radiation to kill tumour cells and spare normal tissues.

Radiation oncology emerged as a discipline when health and science professionals from numerous disciplines (from nurses to radiographers, from radiologists to pathologists, from surgeons to medical oncologists, from biologists and physicists to radiation oncologists) began to interact in their common search for more effective anticancer treatments. Collaboration between scientists and clinicians in radiation oncology has always been two-way: discoveries in radiation physics, chemistry and biology have stimulated the interest of clinicians to start implementing a novel technique, agent or strategy as soon as possible ('bench to bedside'), and the results in the clinic have guided scientific research and the development of new technologies.

We are now at a turning point in radiation oncology — techniques have been refined to allow accurate delivery and we now need the insight of molecular biology and genetics to further refine targeting. We need to know what the most important targets are that will increase cytotoxicity towards tumour cells and spare normal tissue. The development of new approaches and their implementation in clinical practice will again require an integrated effort between clinicians, physicists and biologists.

Scientific breakthroughs are rare and great advances in health care are even rarer. In the twentieth century, important discoveries and advances were made both in Europe and the United States. Recognition of the importance of radiation oncology by governments and societies also played a big part in these advances in many countries. There were four main schools of radiation oncology in the twentieth century (BOX 1): the German school (1900 to ~1920), the French school (1920 to ~1940), the British school (1940 to ~1960) and the United States then European Union school (1970 to date).

The discovery of X-rays, in 1895, by Wilhelm Conrad Röntgen in Germany (FIG. 1) and of natural radioactivity a few months later, by the French physicist Henry Becquerel, were two such breakthroughs that paved the way for a new era in science. Although the mechanisms of X-ray action were far from understood, the speed with which the pioneers worked together to develop and implement the first successful X-ray therapies is amazing (TIMELINE 1). Less than 60 days after the discovery of X-rays, clinical radiotherapy was born — Emil Grubbé treated an advanced ulcerated breast cancer with X-rays[1] in January 1896 in Chicago. Over the next century, discoveries in radiation physics, chemistry and biology informed approaches in the clinic to develop an increasingly more accurate, more efficient and less harmful anticancer therapy.

Radiation physics 1896–1945

X-rays. Röntgen discovered X-rays while he was experimenting with a Hittorf–Crookes cathode-ray tube[2]. This consisted of a pear-shaped glass chamber from which almost all the air had been evacuated, and into which two electrodes were sealed at opposite ends of the tube — the cathode (negative) and the anode (positive). When these electrodes were connected to a high-voltage source, ions in the residual gas were accelerated to high speeds. The cathode repelled the negative electrons, which then struck the opposite end of the glass tube with considerable energy — the impact of these fast electrons on the glass produced photon energy called X-rays. With these tubes, both the quality and the quantity of the rays depended on the internal gas pressure, which changed as the air was ionized and used up. Such equipment was difficult to control.

In 1913, the American William Coolidge produced a 'hot-cathode tube'[3], in which the electron source was a tungsten filament heated by a low-voltage circuit; electrons were freely released from the hot metal (thermionic effect). It was now possible to control the quality and quantity (dose) of radiation independently — the development of these tubes revolutionized radiology.

Throughout the first four decades of the twentieth century, technical developments were essentially based on improving X-ray generator and tube output, and led to the routine clinical application of low-energy

X-rays (with a wavelength longer than 0.1 nm, ranging from 10–50 kV) at short treatment distances for superficial tumours. Throughout the first half of the twentieth century, radiation oncologists could only use X-rays with an energy of 200–500 kV (called ortho-voltage X-rays) to irradiate deep-seated tumours. There were various setbacks to this radiotherapy: first, an already low penetration power (about 4–6 cm in soft tissues) due to tissue attenuation was further reduced by short treatment times, which were necessary to prevent overheating of the X-ray tube; second, rather than high doses of radiation being delivered to the tumour, a high proportion of the dose was absorbed in the surface layer of healthy tissue, causing both severe acute reactions and late skin damage; third, a high proportion of the dose was attenuated in the bone, leading to an inhomogeneous dose distribution in soft tissue and significant bone-fracture risk.

On top of that, treatment planning in the early 1900s was very rudimentary. The first methods for measuring which parts of anatomical body sections received the same dose levels — called isodose distribution diagrams — only became available in the 1920s[4,5].

γ-rays. Following Henry Becquerel's discovery of natural radioactivity and the discovery of radium in 1898 by the French physicist Marie Curie as a natural source of high-energy photons or γ-rays, radium was the only source of γ-rays for the treatment of cancer for 20 years. The use of high-energy photons[6] for treatment of deep-seated tumours was important in early radiation-physics research. In Paris in 1901, Danlos and Bloch performed the first local application of a sealed radium source to treat a patient with the non-malignant skin condition lupus erythematous[7]. The first histologically confirmed cancers were successfully treated using this approach in St. Petersburg in 1903. In the early 1920s, leaded containers of radium needles and tubes were applied to the patient, with a source–skin distance of few centimetres[8,9].

This technique was the precursor to the 'tele-radium therapy' designed later in the United States, France and Belgium[9,10]. The term teletherapy is used to describe the external treatment of tumours in which the source of radiation is distant from the target. As teleradium units contained limited amounts of radium (3–10 grams), short source–skin distances were required and treatment often lasted several hours. Importantly, the build-up effect of this beam quality allowed, for the first time, a clinically significant skin sparing, particularly during treatment of head and neck or breast tumours[11].

The surface application of radium in moulds or other applicators was used until the 1970s[12]. One breakthrough was the development of techniques for the γ-irradiation of tumours through body cavities — called brachytherapy — where the radiation source is placed in or near the target tumour. Cervical cancer and endometrial cancer were ideal indications for intracavity brachytherapy, and many techniques were developed both in the United States and Europe to treat these cancers. Implantation of radium tubes directly into sarcomas and carcinomas was first used in 1910, by Abbe in the United States[13]. Implants of radium needles lasted from a few hours to several days. In 1936, Heyman developed the 'packing technique'[14], a method for filling a body cavity — such as the uterus in patients with cancer of the corpus — with capsules containing radium sources.

Box 1 | The four schools of radiation oncology

It is, of course, always an oversimplification to separate any subject into a limited number of divisions, but it helps to understand the evolution of radiation oncology and its international nature to think in terms of four eras.

1900 to ~1920: the German school
Although radiotherapy was being developed in many places during the early part of the twentieth century, German research dominated. The German approach was characterized by the use of a few large 'caustic' doses of radiation. Such treatments frequently led to impressive responses, but few long-term 'cures', for reasons of biology that we now understand, but that were not appreciated at the time. The start of this period might date from the report of Freund in 1903 of the disappearance of a hairy mole after treatment with X-rays[87].

1920 to ~1940: the French school
The greatest single contribution during the French era was the realization that protracted radiation treatment over a period of time both improved tumour control and exploited a differential between sterilization of the tumour and unwanted damage to adjacent normal tissue. This change of philosophy and of strategy was based on observations in animal experiments. If radiation was delivered in small daily fractions over a few weeks, rams could be sterilized without causing skin necrosis — the testis is a model of a growing cancer, whereas the skin represents a dose-limiting normal tissue. In this way, fractionated protracted radiation therapy was born[20].

Numerous individuals who were trained in France at this time were to have an enormous impact much later in other countries, most notably in the United States.

1940–1960: the British school
During this era, the field became highly quantitative, and the fact that so many of the advances came from the United Kingdom reflects the strong development of medical physics, with the founding of the Hospital Physicist's Association in 1945. Another factor of importance was that radiation oncology was not a division of the much larger field of radiology, as it was (for example) in the United States until the 1970s. Accurate dosimetry, more sophisticated beam direction and treatment planning all contributed to a rapid development of radiation oncology with medical physics as an (almost) equal partner. Radiation oncology in Britain was also to benefit from the fact that the British were the first to recognize the need for carefully controlled randomized clinical trials.

1970 to date: the United States then European Union school
Although there were always pockets of excellence in the United States, radiation oncology in general was slow off the mark compared with the United Kingdom, France and the Scandinavian countries. This was based historically on the fact that most individuals trained in general radiology, and radiotherapy was often the poor relation in the basement.

All of this changed in the 1970s. President Nixon's 'war on cancer' supplied huge amounts funding for research in physics, biology and clinical oncology, and at the same time the American Society of Therapeutic radiology and oncology was founded. Research groups and training programmes were set up as radiation oncology became a separate discipline, and the standard of clinical practice improved. This was the beginning of evidence-based medicine in radiation oncology, with the proliferation of clinical trials to match the new and improved treatment machines, and the revolution in medical physics and computer-controlled technology.

The European Society of Therapeutic Radiology and Oncology (ESTRO) was founded in the early eighties, and the clinical trials organized by the European Organisation for Research and Treatment of Cancer have certainly matched, in number and in quality, those performed in the United States. Another outstanding feature of ESTRO is that they have placed much greater emphasis than their American counterparts on aiding the advance of radiation oncology in developing countries.

Figure 1 | **Wilhelm Conrad Röntgen (1845–1923).** He received the Nobel Prize in Physics in 1901 for the discovery of X-rays. For further information on Wilhelm Conrad Röntgen, see REF. 2. © Photo courtesy of Science Photo Library.

Early clinical results

Efficacy. Between 1896 and the early 1920s, radiologists targeted a large number of non-malignant conditions (for example, pain, chronic inflammation and tuberculosis) and cancers. Dermatological lesions were the first clinical model that radiologists investigated, because they were readily accessible by direct inspection, and were the only conditions accessible to the rather primitive X-ray tubes available. At first, radiologists claimed that patients with skin infections benefited from the bactericidal effects of X-rays — a concept flawed because of the fact that bacteria require doses that are 100 times greater than doses needed to kill mammalian cells. Viennese scientists were the first to systematically study the effects of radiation on both skin tumours and non-malignant conditions such as tuberculosis and lupus. And in 1900 in Stockholm, a patient with skin cancer was cured by Thor Stenbeck, using small doses given each day[15] —this technique would later be called fractionated radiotherapy (see below). In 1903, the first case of cancer of the cervix cured by X-rays was reported by Cleaves[16].

Side effects and fractionation. Patients and doctors also experienced the first complications during these early years of radiotherapy. For instance, Henry Becquerel noted a skin ulceration on his lower abdomen and then realized that it was next to the pocket in

which he had kept a tube of radium salts. By 1900, the first five cases of radiation-induced leukaemia were reported, as well as lost fingers and malignant skin changes. In 1903, Heineke noted the radiosensitivity of lymphoid cells[17]. The first case of lung fibrosis as a complication after treatment of breast cancer was described in 1922 and this led to the use of tangential beams of radiation to irradiate the chest wall and breast, considerably reducing the late effects seen in the lung. In Germany, X-ray treatments were mostly given as single doses until the mid-1920s, so attempts to treat deep-seated tumours caused severe skin complications.

It is at this point that biological experiments began to have an important impact on the future of radiotherapy. Scientists, led by Claude Regaud in 1927 in France, found that it was not possible to sterilize a ram testis with a single dose of radiation without causing necrosis of the skin of the scrotum, whereas if radiation was delivered in small daily fractions over a period of weeks, the animal could be sterilized with a minimal skin reaction over the scrotum[18]. (As the urgency to publish results was not as acute in the 1920s as it is now, there is some confusion about whether this experiment was actually first shown in rabbits by another group — however, the observations made were the same.) The implication was that the testis, a self-renewing tissue with a proliferating stem-cell compartment, was a model of a growing cancer, whereas the overlying skin represented the dose-limiting normal tissue. In this way, fractionated radiation therapy was born. The principle was applied to external beam therapy with X-rays, where several daily treatments were given, and to treatment with implanted radium sources, where the dose-rates were sufficiently low that treatment lasted for a week or more[18].

In the 1930s, a consensus finally emerged in favour of fractionated treatments. Pioneering what would later be the time–dose factor concept, Coutard showed, in Paris in 1934, that, in patients with cancers of the pharynx and larynx, both skin and mucosal reactions depended on the dose, the treatment time (FIG. 2) and the number of treatment sessions[19]. He paved the way for Baclesse, who, again in Paris, showed clearly that, by reducing the dose per fraction, it was possible to delay the time to normal tissue reactions and to deliver higher doses to the tumour over longer times. Baclesse was also the first radiologist to use radiotherapy alone in the treatment of breast cancer — he used high doses, given
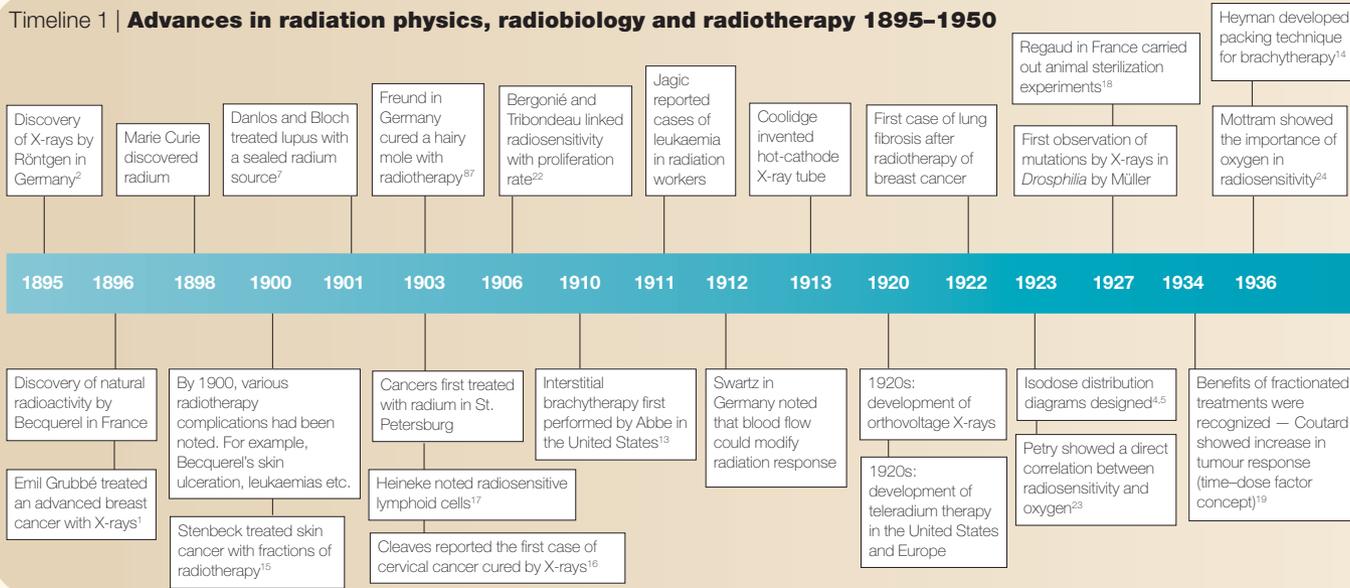
over a long time and with volume reduction during the course of treatment. While Coutard had been a pioneer of the time–dose factor concept, Baclesse's work undoubtedly led to new strategies exploiting dose–volume relationships[20]. In fact, in the 1960s Ellis and colleagues hypothesized that the total dose that a tissue could tolerate without loss of function is related both to the number of fractions and overall time over which the fractions are administered[21]. We now know that in addition to time–dose considerations, irradiation damage to normal tissues is also dependent on the volume of normal tissue irradiated.

Early concepts of radiobiology

One of the oldest rules in radiobiology — developed in 1906 by two French radiobiologists, Bergonié and Tribondeau — offered a prediction about the relative sensitivity of different types of cells to radiation. The so-called 'Law of Bergonié and Tribondeau' concluded that cells tend to be radiosensitive if they have three properties: a high division rate, a long dividing future, and an unspecialized phenotype[22]. This law paved the way for several radiobiology rules that were discovered a few years later by German and British radiation scientists from *in vitro* experiments.

Realizing the importance of oxygen. In 1912 in Germany, Swartz observed that skin reactions were less severe if the radiation source was pressed tight to the skin — this indicated that blood flow could modify radiation response. In Germany in 1923, Petry used vegetable seeds — a simple model in which to study radiation effects — to show that radiation inhibited germination or altered protein levels in these seeds only in conditions of normal oxygen levels, and that there was a direct correlation between radiosensitivity and oxygen[23]. In the 1930s in England, the importance of oxygen for tumour-cell radiosensitivity was championed by Mottram[24], and was further highlighted by the quantitative studies on the effect of oxygen on radiation-induced growth inhibition of the broad bean *Vicia faba* by Gray in 1953 (REF. 25). The landmark study that proved this point was performed in 1955 by Thomlinson and Gray when they proposed that oxygen levels decreased in a respiring tumour mass through each successive cell layer distal to the lumen of the capillary[26] (TIMELINE 2). As solid-tumour vasculature is often distorted and tortuous, there are frequently regions of low oxygen or hypoxia. Cells at a distance of ~10–12

Timeline 1 | **Advances in radiation physics, radiobiology and radiotherapy 1895–1950**

Discovery of X-rays by Röntgen in Germany[2]

Marie Curie discovered radium

Danlos and Bloch treated lupus with a sealed radium source[7]

Freund in Germany cured a hairy mole with radiotherapy[87]

Bergonié and Tribondeau linked radiosensitivity with proliferation rate[22]

Jagic reported cases of leukaemia in radiation workers

Coolidge invented hot-cathode X-ray tube

First case of lung fibrosis after radiotherapy of breast cancer

Regaud in France carried out animal sterilization experiments[18]

First observation of mutations by X-rays in *Drosphilia* by Müller

Heyman developed packing technique for brachytherapy[14]

Mottram showed the importance of oxygen in radiosensitivity[24]

| 1895 | 1896 | 1898 | 1900 | 1901 | 1903 | 1906 | 1910 | 1911 | 1912 | 1913 | 1920 | 1922 | 1923 | 1927 | 1934 | 1936 |

Discovery of natural radioactivity by Becquerel in France

Emil Grubbé treated an advanced breast cancer with X-rays[1]

By 1900, various radiotherapy complications had been noted. For example, Becquerel's skin ulceration, leukaemias etc.

Stenbeck treated skin cancer with fractions of radiotherapy[15]

Cancers first treated with radium in St. Petersburg

Heineke noted radiosensitive lymphoid cells[17]

Cleaves reported the first case of cervical cancer cured by X-rays[16]

Interstitial brachytherapy first performed by Abbe in the United States[13]

Swartz in Germany noted that blood flow could modify radiation response

1920s: development of orthovoltage X-rays

1920s: development of teleradium therapy in the United States and Europe

Isodose distribution diagrams designed[4,5]

Petry showed a direct correlation between radiosensitivity and oxygen[23]

Benefits of fractionated treatments were recognized — Coutard showed increase in tumour response (time–dose factor concept)[19]

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cell diameters from a capillary are still viable, but are radioresistant. If these cells re-oxygenate after radiation therapy, the tumours might re-grow. Several clinics such as St. Thomas Hospital, London, therefore started giving irradiation under hyperbaric oxygen conditions to try and force more oxygen into the blood and into the tumour, paving the way for the manipulation of the oxygen effect to increase radiosensitivity of hypoxic cells. The effects of radiation are modified by the fraction of the tumour that is hypoxic, so the oxygen effect was particularly important in experimental radiobiology. In addition, Thomlinson and Gray's findings established the foundation for research into tumour angiogenesis — the recruitment of new blood vessels to tumours.

Radiation physics after 1945

Electron therapy. The physical properties and possible advantages of high-energy electron beams had actually been reported in the 1930s. A reduced dose at the surface, a maximal dose to a relatively broad thickness of tissue and a rapid fall off of dose at a depth corresponding to the electron energy indicated future applications in dermatology. In fact, electrons in the very low mega electron volt (MeV) range (1–3 MeV) have been used for whole-body irradiation of patients with mycosis fungoides[27].

Microwave technology was developed, mostly in England, before and during the Second World War, for radar for use in the detection of aircraft[28,29]. The principle of a 'travelling wave' linear accelerator machine is that an electromagnetic wave travels down an evacuated tube of 1–2 metres in length, with electrons trapped in the electric and magnetic fields. The electron is accelerated in much the same way as a surfer is carried up the beach on a wave and has higher energy and greater penetration power than X-rays. The first electron linear accelerator designed for radiotherapy was developed by D.W. Fry and co-workers in 1948 (REF. 29) and was installed at Hammersmith Hospital, London. It operated at 8,000 kV, compared with orthovoltage X-rays, which have a range of only 10–50 kV. Meanwhile, work by W. W. Hansen and others at the Stanford Microwave Laboratory led to the development of a 6-MV accelerator, which was installed at Stanford University Hospital, California, in 1956.

Betatrons were invented in the late 1940s by an American, Donald Kurst; these are circular electron accelerators that produce electrons with an energy up to several tens of MeV. However, the beam current is typically less than in linear accelerators and the useful radiation field is typically smaller. In the 1960s, electrons of high energy produced by betatron machines were used to irradiate deep-seated tumours in the lungs and the pelvic region[30].

Today, the linear accelerator, or Linac, is the most widely used treatment device in the Western world. Lead shields — collimators — were designed to reduce X-rays or γ-ray leakage in the machines and to shape irradiation beams for more accurate delivery. These shields are positioned statically over crucial regions such as the heart and spine to protect them from irradiation.

Cobalt 60. The advent of artificial radionuclides such as cobalt 60 in the 1950s[31–33] offered new treatment opportunities The use of high-activity cobalt-60 sources paved the way for the era of high-energy teletherapy, with the first telegamma units working at source–skin distances ranging from 60–80 cm[34,35]. Treatment time was reduced from hours to minutes.

Various drawbacks motivated the progressive disappearance of cobalt-60 units, such as the need to regularly replace the radiation sources. The availability of linear accelerators — which provide higher energy, more penetrating beams with a smaller penumbra — also led to the decline in use of cobalt-60 units. However, because these units are simple mechanical devices that need little servicing, many are still in use in the developing world.

Brachytherapy. It was not until the 1960s that the interest in radioactive 'non-permanent' implants — brachytherapy — was rekindled because of the advent of new artificial radionuclides such as caesium-137 and iridium-192. Iridium-192 is produced in thin wires and can be inserted into a tumour through removable flexible plastic tubes or stiff guiding metal tubes. This is called after-loading. Pierquin showed impressive results in treatment of tumours in the oral cavity and also for breast tumours[36]. Based on this, Pierquin and Dutreix proposed a new dosimetry system for brachytherapy in 1966 (REF. 37).

Twenty years after the advent of remote after-loading techniques in the 1960s, high-dose-rate units were introduced. These allowed a type of endocavity or interstitial brachytherapy in which the radium source is
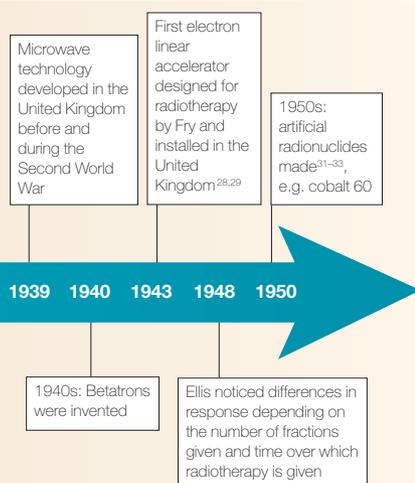
removed between treatments, making short sessions of irradiation possible. These developments mean that brachytherapy can be delivered on an outpatient basis, without any risk of undue irradiation to the patient, medical or paramedical staff.

Many tumours can now be treated by interstitial or endocavity brachytherapy, either as a definitive treatment or as a booster dose after external radiotherapy. Since the 1970s, numerous technical improvements such as better imaging and three-dimensional dosimetry reconstruction have allowed an optimized delivery of high doses to the target volume and a substantial sparing of surrounding normal tissues.

Radiobiology 1950s–1970s

The ability to quantitate cell killing. One of the most important contributions of radiobiology to radiation oncology in the twentieth century was the development of assays to quantitate cell killing *in vitro* and *in vivo* for both normal and tumour tissue. In 1956, the cell-survival assay was developed by Puck and Marcus[38], which allowed researchers to investigate the intrinsic sensitivity of cells to genotoxic damage. This technique is based on the fact that one reproductively viable cultured cell can generate a large colony of cells. The underlying theory was that cultured cells die by mitotic death after radiation treatment and, therefore, reproductive viability — assessed by colony-forming ability — was an appropriate end point. Puck and Marcus found that radiation reduces survival and colony formation in a dose-dependent manner.
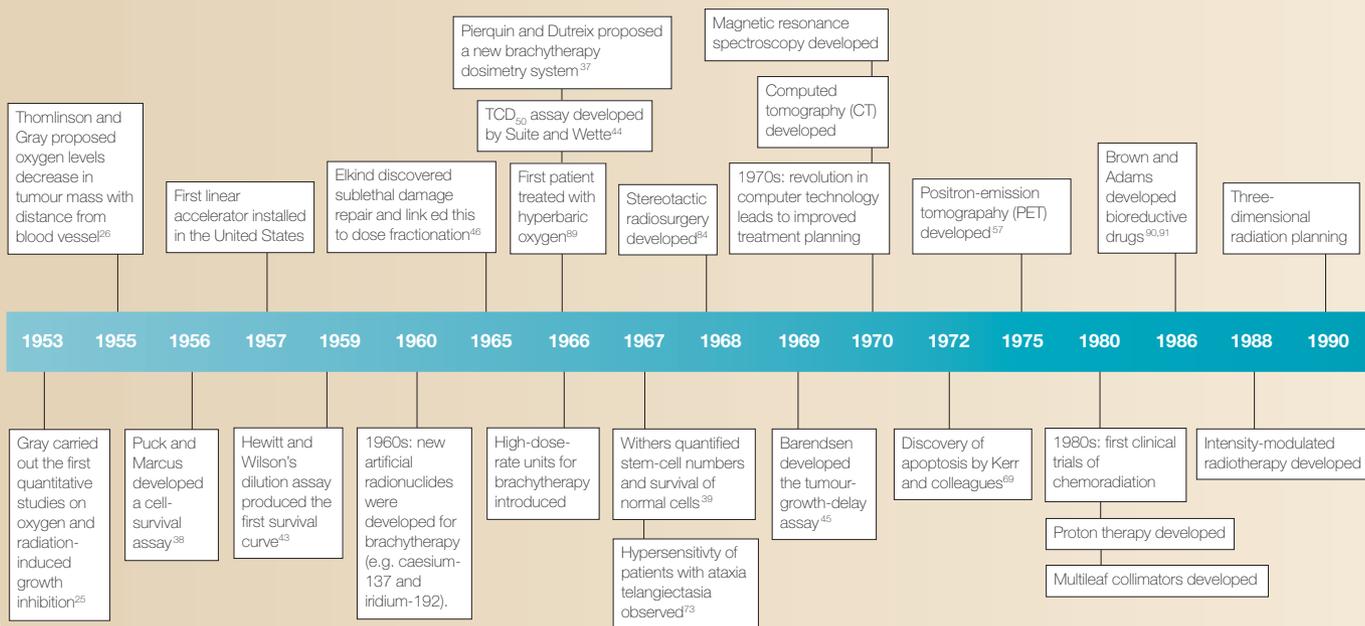
Although this technique provided an important tool to quantitate radiation effects, it relied heavily on established tumour cell lines and could not be used to assess effects of radiation in normal tissues because normal cells were difficult to grow in cell culture. The development of assays to assess cell killing of stem cells that are found in normal tissues led to the development of clinically important dose-response models for normal tissues, such as the skin and intestine. In 1967, Withers demonstrated that stem-cell number could be assesed by irradiating small patches of isolated skin and that skin nodule formation was directly proportional to the number of stem cells that survived radiation[39]. He then showed that the survival of intestinal-crypt cells can be quantified by counting the number of regenerating crypts after radiation that are not typically found in the unirradiated small intestine[40]. Although these techniques were limited in the range of doses that could be used, they showed over 50 years ago that normal tissues respond to irradiation by regeneration through their stem cells — the field of stem-cell research for cancer was launched.

Much attention was focused on understanding the variation in the intrinsic radiosensitivity of tumour cells, but it was clear that the response of tumours of the same histology and mass was heterogeneous both in spontaneous and transplanted tumour models[41,42]. This heterogeneity could only be explained by alterations in the microenvironment of tumour cells. Developing techniques to measure the effects of radiation on tumours was more straightforward than assessing the viability of normal tissues. In 1959, Hewitt and Wilson developed the dilution-assay technique[43], which was used to produce the first *in vivo* survival curve. The basic concept is that by injecting known numbers of tumour cells into healthy mice and knowing the lowest number of cells required to produce that tumour, one can then calculate the survival of irradiated tumour cells that are transplanted.

The TCD_{50} assay developed by Suit and colleagues in 1966 was based on irradiating many animals with tumours of similar size with defined doses and observing the mice for tumour recurrence[44]. By plotting the proportion of tumours that are locally
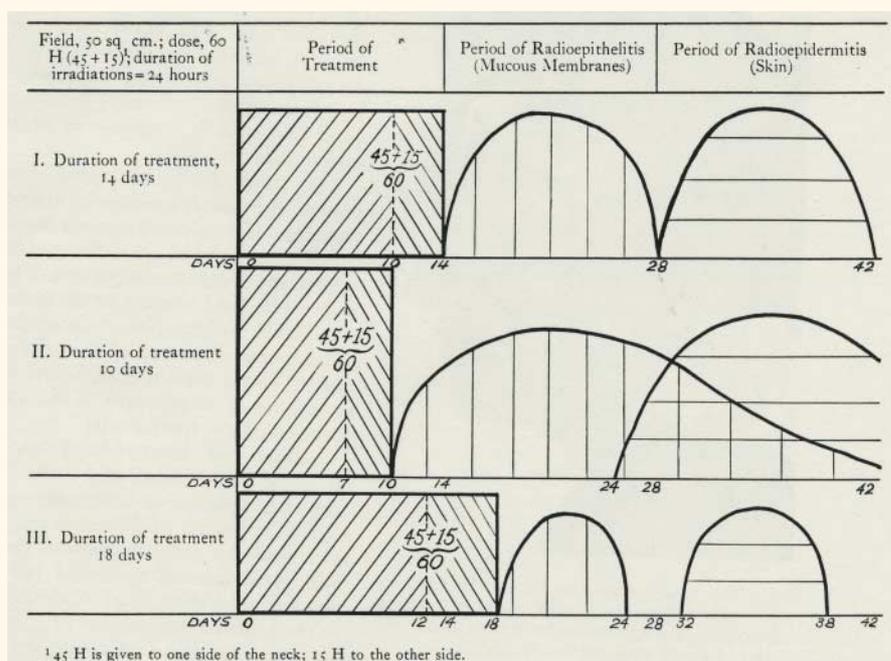
Figure 2 | **The first illustration of the effect of the duration of Röntgen therapy (now called X-rays) on normal tissues.** Patients with squamous epitheliomas of the hypopharynx and larynx were treated with radiotherapy over 10, 14 or 18 days. This study by Coutard concentrated on normal-tissue reactions — the efficacy of each regimen was not reported. However, we know that patients treated with protracted treatments did not respond as well as those receiving shorter treatments. The accelerated treatment over 10 days caused more acute and chronic reactions to the mucous membranes (radioepithelitis) and skin (radioepidermitis) than when given over 14 or 18 days. We now know that this is because the mucosa and skin cells have less time to repair. When the radiation was spread over 18 days, acute reactions were less and lasted for a shorter time. The *y* axis shows the grade of acute reaction intensity. H, Holzknecht units (equivalent to 1 Gy). Reproduced from REF. 88

Timeline 2 | **Advances in radiation physics, radiobiology and radiotherapy: 1950 to date**

Pierquin and Dutreix proposed a new brachytherapy dosimetry system[37]

Magnetic resonance spectroscopy developed

Thomlinson and Gray proposed oxygen levels decrease in tumour mass with distance from blood vessel[26]

TCD$_{50}$ assay developed by Suite and Wette[44]

Computed tomography (CT) developed

First linear accelerator installed in the United States

Elkind discovered sublethal damage repair and link ed this to dose fractionation[46]

First patient treated with hyperbaric oxygen[89]

Stereotactic radiosurgery developed[84]

1970s: revolution in computer technology leads to improved treatment planning

Positron-emission tomograpahy (PET) developed[57]

Brown and Adams developed bioreductive drugs[90,91]

Three-dimensional radiation planning

1953 1955 1956 1957 1959 1960 1965 1966 1967 1968 1969 1970 1972 1975 1980 1986 1988 1990

Gray carried out the first quantitative studies on oxygen and radiation-induced growth inhibition[25]

Puck and Marcus developed a cell-survival assay[38]

Hewitt and Wilson's dilution assay produced the first survival curve[43]

1960s: new artificial radionuclides were developed for brachytherapy (e.g. caesium-137 and iridium-192).

High-dose-rate units for brachytherapy introduced

Withers quantified stem-cell numbers and survival of normal cells[39]

Barendsen developed the tumour-growth-delay assay[45]

Discovery of apoptosis by Kerr and colleagues[69]

1980s: first clinical trials of chemoradiation

Intensity-modulated radiotherapy developed

Hypersensitivty of patients with ataxia telangiectasia observed[73]

Proton therapy developed

Multileaf collimators developed

controlled as a function of dose, the dose at which 50% of the tumours are locally controlled (TCD$_{50}$) can be determined. This assay can be used for any type of tumour, but requires many mice. In 1969, Barendsen and colleagues measured volume changes in tumours after irradiation with different doses of radiation[45]. They showed that the effects of radiation could be quantified by changes in tumour volume as a function of time (for example, growth delay). Both the TCD$_{50}$ and tumour-growth-delay assays are still widely used today.

Principles that explain the benefits of fractionation. In the 1960s, Elkind explained that if a given dose of ionizing radiation was divided into fractions and given at different time intervals (split dose) rather than in one single dose[46], the increase of patient survival seen was defined largely by sublethal damage repair of radiation damage in normal tissues. Fractionated radiation could be beneficial for many normal tissues, which proliferate relatively slowly and therefore have time to repair damage before replication, and deleterious for tumour tissue that is rapidly proliferating, where the unrepaired damage can be lethal. In addition to rapid repair, the increased efficacy seen using split-dose radiation was also recognized to be because of differences in progression of cells through the cell cycle (redistribution), reoxygenation of tissues and cell division (repopulation). These are the fundamental

principles of radiobiology — repair, redistribution, reoxygenation and repopulation — and are known as the 'four Rs'[47]. Cells are most resistant to radiation damage when they are in the S phase of the cell cycle. Therefore, after a large dose of radiation most of the surviving cells will be those that were in S phase. So, a second dose of radiation to these cells will be less effective unless time is allowed for the cells to redistribute throughout the cell cycle before the second dose is given. Accelerated repopulation of tumour cells occurs after a dose of irradiation, so the second dose must not be delayed for too long. Finally, reoxygenation will increase the radiation effectiveness by increasing radiosensitivity, but only for hypoxic tumour cells and not for normal tissues.

Fractionation of radiation doses to spare normal tissue toxicity and kill tumour tissue led to the concept of the therapeutic index (FIG. 3). Fractionation is beneficial when the response of the tumour occurs at a total cumulative dose that does not result in severe normal-tissue complications; it is detrimental when there is no separation between the total cumulative doses required to control the tumour and induce normal-tissue complications.

Technological advances: 1970s to date
Imaging and treatment planning. Throughout the past four decades, technological improvements have led to a significant improvement of the local control rates of

many tumours, even in patients with locally advanced tumours. Treatment planning in radiation oncology has benefited enormously from the revolution in computer technology. This technology has enabled the size and location of the tumour to be determined, and the beams of radiation to be aimed in such a way as to maximize the tumour dose and minimize the dose to healthy normal tissue[48,49].

The imaging of tumours became a reality with the introduction of computed tomography (CT) in the early 1970s and magnetic-resonance imaging (MRI) in the late 1970s[50,51]. The use of CT scanning to plan the treatment area is shown in FIG. 4. To achieve this advantageous dose distribution, intensity-modulated radiotherapy (IMRT) was used using several treatment beams. In the early 1980s, IMRT was developed by several labs, enabling radiation oncologists to deliver therapy shaped to the contours of the tumour with a high dose volume surrounding the target, even in the case of complex geometry or invagination. The delivery and impact of IMRT is now under investigation in clinical trials of patients with head and neck, prostate, brain, breast and lung cancers. In the 1980s, multileaf collimators were also developed; these travel on movable carriages and move independently to allow modulation of the photon-beam intensity, therefore providing a more homogeneous irradiation of the tumour and protection of normal tissues. The leaves of the multileaf collimator can also be
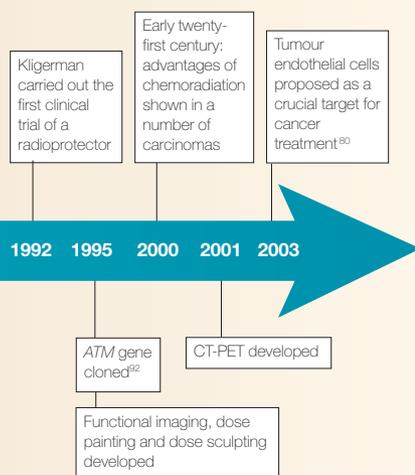
controlled accurately using computers (FIG. 4). Furthermore, by modulating the intensity of a large number of small beamlets — typically 10 × 10 mm — within a larger open field, an intensity variation within that field is created that will generate, under computer control, a complex three-dimensional plan that conforms to the anatomy of the patient[52–55]. This allows the delivery of much higher doses to the tumour without increasing the adverse effects on adjacent normal tissue.

Biological imaging and dose painting. In the past, radiological images were largely anatomical; that is, they could show the position of the cancer relative to normal structures. Over the past two decades, new types of images can provide biological data about the tumour — this is referred to as functional imaging[56]. The role of functional imaging is likely to have a key role in the clinician's search for a more accurate definition of irradiation target volumes in the near future.

There are two imaging modalities that are important in this context: positron-emission tomography (PET) and magnetic resonance spectroscopy (MRS). PET imaging is a technique in which the scanner detects the collinear pairs of 0.511-MeV photons emitted when a positron emitted from a radionuclide annihilates after colliding with an electron. A positron is a particle with the same mass as an electron, except that the charge is positive. Radionuclides that emit positrons have an excess of protons in their nuclei and

are produced by bombarding stable elements in a machine called a cyclotron. The development of PET began in the 1950s at the Massachusetts General Hospital, but the first practical clinical scanner was built by Michael Ter-Pogossian in St. Louis in the 1970s[57].

Second, there is MRS, which differs from MRS in that it shows details of physiology, metabolism and biochemistry as well as anatomy. MRI was developed by several individuals on both sides of Atlantic, notably Lauterbeur and Mansfield who shared the 2003 Nobel Prize[50,51]. MRS was also the result of many contributions in the late 1970s; the Swiss chemist Kurt Wuthrich shared the 2002 Nobel Prize for chemistry for his part in the development[58].

Using this advanced imaging technology, information can be obtained about four main properties of a tumour: proliferation, metabolism, oxygenation and vascularization, and specific disease markers[59]. For instance, the increased glucose metabolism of cancer cells compared with normal tissues results in an increased uptake of 2-deoxy-2-fluoro-D-glucose(FDG) in malignant tissue. FDG can be labelled with the isotope ^{18}F, which can be detected with PET[60–62]. Areas of rapid proliferation in a tumour might be identified by administering a DNA precursor, such as thymidine or deoxyuridine labelled with radioactive ^{11}C or [124]I and imaged with PET[63,64]. Hypoxic cells, which are intransigent to killing by X-rays, can be identified by the use of a nitroimidazole labelled with ^{18}F and imaged with PET[65]. In the prostate, an

increased level of choline (resulting from the increased phospholipid-cell-membrane turnover associated with tumour proliferation, increased cellularity and growth) might be an indicator of an active tumour[66,67].

None of these processes can be unequivocally linked to tumour aggressiveness or curability, but it is an attractive hypothesis that increasing the dose to those areas of the tumour that are hypoxic, most rapidly proliferating or most malignant will have beneficial effects.

The prevailing philosophy of the past 50 years was to aim for a uniform or homogeneous dose across the target volume, which includes the gross tumour plus a safety margin. Deliberately planning to give a non-uniform dose to the target volume has been termed 'dose painting' when planned in two dimensions, and 'dose sculpting' in three dimensions. These terms were coined by scientists at the Memorial Sloan–Kettering Cancer Center in New York, including Clifton Ling, Steven Leibel and Zvi Fuks. The advent of IMRT (see above) makes it possible to give such a non-homogenous dose, with extra doses to the biological target[68]. At present, we do not know which biological target is most important, but this is a fruitful area of research.

Molecular targets: 1970s to date
Cellular radiosensitivity is influenced by intrinsic factors such as phase of the cell cycle, activation of apoptotic programmes, DNA strand break repair proficiency and accumulation of genetic mutations in
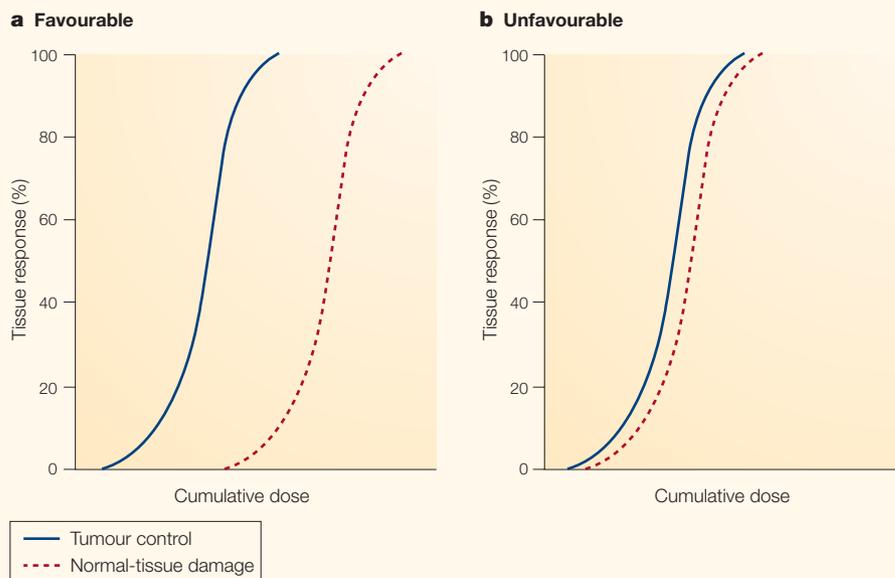

Figure 3 | **Graph to show the therapeutic index with respect to cumulative dose. a** | A favourable outcome would mean that the response of tumour tissue is greater than that of normal tissue to the same dose — the therapeutic index is large. **b** | An unfavourable outcome would mean that the response of tumour tissue and normal tissue is similar for the same dose — the therapeutic index is small.

a   b   c
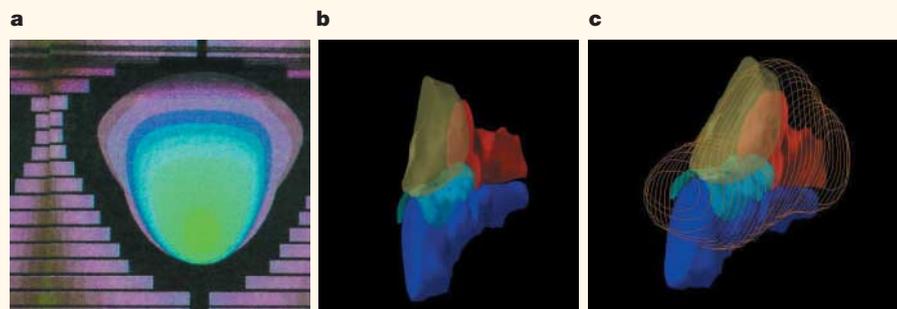
Figure 4 | **Imaging and treatment planning a** | The X-ray beam to be given to a tumour is 'shaped' by a multileaf collimator in a linear accelerator. Each leaf — made of lead, which completely absorbs photons — can be moved independently under computer control so any irregular field size can be produced. This allows homogeneous irradiation of the tumour and protection of normal tissues. **b** | Three-dimensional representation of the anatomy of a patient with prostate cancer reconstructed from computed tomography images. The organs are close together and even intertwined. This illustrates the complication of trying to treat the prostate (red) and seminal vesicles (light blue) — which might also be cancerous — with a high dose of radiation, while sparing as much as possible the normal bladder (yellow) and rectum (dark blue). **c** | The anatomy is the same as in **b**. The red lines represent the volume that can be treated to a high dose — this encompasses the prostate and seminal vesicles where the tumour is. The plan is designed to give maximum dose to the prostate and seminal vesicles, with a safety margin to allow for movement of the prostate and microscopic extensions of disease, while minimizing the dose to the bladder and prostate. To administer the radiation accurately to this patient, intensity-modulated radiotherapy was used with six treatment beams. Figure courtesy of C. S. Wuu.

oncogenes and tumour-suppressor genes. In addition, extrinsic factors such as oxygen, nutrients and metabolic-waste elimination can also influence the response of tumour cells to ionizing radiation. Our increased understanding of both intrinsic and extrinsic factors of radiosensitivity has identified molecular targets that could be manipulated pharmacologically to increase tumour-cell killing and minimize normal-tissue toxicity.

Apoptosis. As described above, various assays have been developed to assess normal-tissue and tumour-tissue sensitivity to radiotherapy. As most of these assays are based on determining reproductive viability, it has taken several decades for the importance of interphase or apoptotic cell death (first described in 1972 by Kerr and colleagues[69]) in the response of radiosensitive tissues to ionizing radiation to be recognized. Although few argue that activating the apoptotic machinery will increase the ability of tumours to be controlled by radiotherapy, especially when this radiotherapy is fractionated, there has been debate since the 1990s as to the extent of the contribution of apoptosis to the control of human tumours by radiotherapy and whether resistant clones can be selected by the tumour microenvironment[70]. Early in their evolution, tumour cells undergo oncogenic activation that increases their sensitivity to apoptotic stimuli, principally

because aberrant oncogene expression triggers activation of the tumour suppressor p53 (REF. 71). In fact, the reinstatement of rapid p53-signalled apoptosis following ionizing radiation, which is normally lost during the malignant progression of solid tumors, is now a key goal of developing effective anticancer therapies. The protection of normal tissue through the inhibition of pathways that lead to normal tissue toxicity or selectively sensitize tumour tissue by engaging the apoptotic programme of a cell will result in the increased effectiveness of radiotherapy.

Repair. Although most solid-tumour cells possess diminished apoptotic programmes, they rarely possess alterations in their DNA strand break repair mechanisms. The molecular mechanisms involved in signalling and enzymatically restoring broken DNA and chromosomes in tumours have elegantly been elucidated and represent future targets for intervention that can enhance radiotherapy. A good example of this comes from the study of the rare disease ataxia telangiectasia, which was first described by Syllaba and Henner in 1926 (REF. 72). Patients with ataxia telangiectasia showed hypersensitive reactions to radiotherapy[73], and cell lines derived from these patients are hypersensitive to killing by ionizing radiation[74]. The *ATM* gene was cloned in 1995; this gene is mutated in patients who have ataxia telangiectasia, encodes a protein kinase that has an important role in the

normal response of cells to ionizing radiation and is activated by DNA-strand breaks[75]. Tumour-selective inhibition of the kinase activity of ATM would be a powerful approach to sensitize tumour cells; this could be achieved by combining an ATM inhibitor with IMRT.

Hypoxia. Thomlinson and Gray's model showing that hypoxia occurred with increasing distance from blood vessels[26] led to use of hyperbaric oxygen (see above) to radiosensitize hypoxic cells, but these techniques were not very successful. In the 1990s, compounds were developed to mimic oxygen and thereby sensitize these cells (hypoxic-cell sensitizers). Clinical trial data have shown some benefit of such an approach, but the overall increase in local control or survival is only incremental[76]. In 1979, Brown suggested that the malformed vasculature found in tumours was subjected to changes in blood flow that could result in transient opening and closing of blood vessels that would result in transient hypoxia[77]. An understanding of the physiological mechanisms by which tumours become hypoxic has led to a change in thinking on how to deal with this problem — rather than developing hypoxic-cell sensitizers, the focus is now on developing hypoxic-cell cytotoxins. The next decade will see a greater effort in the development of new hypoxic-cell cytotoxins based on key regulatory molecules that are necessary for cells to survive or adapt to hypoxic conditions, such as the hypoxia-inducible factor 1 (HIF1) transcription factor[78]. Although inhibition of HIF substantially impedes tumour growth, tumours will adapt to loss of HIF and regrow. Therefore, future strategies should be focused on developing compounds that kill cells that possess increased levels of HIF, so that they will not have the chance to adapt to surviving without HIF.

Tumour vasculature. Until very recently, it was assumed that the target of radiotherapy was the tumour cell itself. Opinions are now changing. Over 30 years ago, tumour angiogenesis was recognized by Judah Folkman as a potential target of therapy[79]. Until the past decade, agents that effectively inhibited blood-vessel formation or destroyed existing vasculature did not exist. The combination of anti-angiogenic agents or anti-vasculature agents with radiotherapy represents a future direction that has great promise. It was only in 2003 that people began to investigate whether it is the tumour cells or the endothelial cells that line blood vessels that are the main target of radiotherapy. Richard Kolesnick and Zvi Fuks demonstrated that by

making endothelial cells refractory to radiation without changing the sensitivity of tumour cells, they could alter the radiosensitivity of transplanted tumours to single-dose radiotherapy[80]. These studies should lead to the development of compounds that exploit the abnormal histology of the tumour vasculature to specifically sensitize tumour endothelial cells to radiation therapy.

Fractionation and combinations

Altered fractionation. Conventional radiotherapy regimens deliver 1.8–2.0 Gy in one session per day, up to a weekly dose of 9.0–10 Gy. However, most locally advanced diseases can not be satisfactorily controlled by these regimens. New schedules are derived from laboratory and clinical observations made in the 1970s and 1980s. First, these studies showed that giving smaller doses per fraction — hyperfractionation — allows an increase in total dose and, therefore, in tumour-cell killing without causing significant undue morbidity in normal tissues. Second, the fast cell proliferation that is found in a significant number of tumours justifies shorter schedules — accelerated fractionation — to compensate for repopulation. Both approaches require at least two radiotherapy sessions per day, with a minimum 6-hour interval between dose fractions to allow sufficient repair in normal tissues. Various clinical trials on altered fractionation were recently completed, demonstrating a significant gain in local and regional control rates, which might be increased by 15% compared with those observed after conventional regimens of radiotherapy[81,82].

Radiotherapy and surgery. Although there was often strong competition between surgeons and radiotherapists throughout the first half of the twentieth century, the combination of radiotherapy with surgery progressively gained ground with the advent of the megavoltage era in the mid-1950s, as continuing education and better results from radiation–surgery combinations, either in a pre- or post-operative setting, indicated that such approaches could be efficacious. Malignant tumours of the brain, head and neck, lung, large parts of the gastro-intestinal or genito-urinary tracts, and bone or soft tissues are among the most well known indications for radiosurgical approaches[83]. Improved local and regional control can often be achieved using radiosurgery. Once the gross disease is resected, radiotherapy can be used to kill residual tumour cells. Preoperative radiotherapy can make an unresectable tumour amenable to surgery.

Stereotactic radiosurgery was introduced by Leksell to allow high-dose radiation to be delivered to small targets in the brain that were not amenable to conventional surgery[84]. In 1974, Larsson *et al.* installed an irradiation unit with a large number of small beams converging towards an isocentre[85]; the coordinates of the target are accurately determined by means of a special frame placed around the patient's head. The technique can also be applied with a linear accelerator supplied with proper auxiliary equipment. Stereotactic radiotherapy is now used not only to treat brain tumours and tumours at the base of the skull, but also tumours located close to crucial organs such as the spinal cord in the trunk.

Radiotherapy and chemotherapy. Although some clinical experiments on the concurrent use of cytostatic agents and radiation were performed in the early 1960s, the addition of chemotherapy to radiotherapy during the course of irradiation was not investigated prospectively and on a solid biological basis until the 1970s. The rationale for this switch from a sequential to a concurrent delivery of the two therapeutic modalities was not only to increase tumour-cell killing, but also to achieve a synergistic effect of chemo- and radiosensitization, mainly through increased inhibition of DNA-repair mechanisms.

Throughout the past two decades, combinations of radiotherapy with chemotherapy have yielded encouraging results in patients with locally advanced diseases and for whom the prognosis remains dismal in terms of local control and distant metastasis. Both radiosensitizing effects for low doses of drugs like cisplatin, 5-fluorouracil and mitomycin C, and supra-additive effects for full doses of these agents are observed when they are given concurrently with radiotherapy. Since the 1980s, significant gains in local control and survival following chemoradiation regimens have been observed in patients with malignant epithelial tumours, especially head and neck[86], lung and gastrointestinal-tract tumours (for example, oesophageal and rectal tumours). Similarly, patients with high-risk prostate cancer benefit from the concurrent delivery of hormones with radiotherapy. Other compounds, both cytotoxic (such as gemcitabine and the taxanes) and non-cytotoxic (such as anti-angiogenic factors, receptor-blockading agents, and bioreductive drugs targeting or exploiting hypoxic compartments), are under investigation and could pave the way for treatment strategies based on new therapeutic targets.

In future studies, molecularly targeted therapies need to be mixed and matched with the type of radiation given. Topical application of radiation sensitizers with brachytherapy might be quite effective in increasing tumour control and preventing normal-tissue complications, but systemic administration of radiosensitizers with external beam radiation could lead to increased normal-tissue complications, especially when the investigated compound discriminates poorly between normal and tumour cells. There could also be a role for material scientists to design polymers that will release active drugs on exposure to low doses of radiation or for chemists to develop radiation-activated prodrugs.

Conclusions

From the questions addressed by radiation science before and after the advent of the megavoltage era in the 1950s to the opportunities now offered by the development of advanced techniques, multidisciplinary approaches and translational research, radiation oncology has always required a strong commitment from all individuals involved in research and treatment in our laboratories and hospitals.

The key to the future of radiobiology will be to meld the information we have obtained on the molecular profiles of tumour cells and their microenvironment to develop new radiotherapy approaches. Translational studies are needed, for example, to determine how anti-angiogenic or anti-vascular therapy, which cause transient tumour hypoxia, should be combined with radiotherapy. How can inhibition of growth-factor-receptor signalling by the new small-molecule inhibitors and antibodies be optimally combined with radiotherapy? Most importantly, will it ever be possible to selectively sensitize tumour cells to radiation through the use of DNA-repair inhibitors or to develop selective normal-tissue radioprotectors?

Moreover, recent translational research on cell-signalling pathways and an increased understanding of the human genome are bound to boost the role of radiation science in oncology.

The goal of radiation oncology for the future is to turn cancer from an acute disease to a chronic disease that can be treated with radiation. One thing is for sure, radiation oncology will continue to be a key modality in the treatment and management of cancer during the next century, as it is a non-invasive and indiscriminant killing force that can be focused and enhanced with pharmacological agents.

PERSPECTIVES

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