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A Multidisciplinary Approach

Edited by
Manjit Dosanjh
Jacques Bernier
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At a time when radiotherapy is undergoing profound changes considerable efforts have been made to give hadron therapy the place it deserves in the battle against cancer. For too many years and in many countries, numerous particle therapy programmes have remained at the level of discussion only: indeed, uncertainties surrounding their real therapeutic indices and fears about a low cost/benefit ratio have led many national health authorities to remain careful about investing in these technologies. However, recent, significant developments in both the diagnostic and therapeutic spheres, linked to hadrons in a direct or indirect manner, have propelled major institutions and laboratories involved in translational and clinical research to intensify their R&D programmes on particle therapy.

To be effective, this evolution requires an intense and continuous exchange of information and educational programmes among the various scientific communities. The main objective of this textbook is to be part of this effort both by strengthening the knowledge of readers in their own field of expertise (e.g., biology, physics and clinics) and by increasing their familiarity with the know-how developed in the other domains of hadron therapy with which they are called to interact and collaborate.

Towards this aim, the first part of this textbook places hadrons in their historical, biological and technological contexts. In the second part, particular emphasis has been given to the interactions between imaging and particle therapy, as well as to the advantages that can be expected from multi-disciplinary collaborative network in this domain. The most recent developments in clinical practice have been described in depth, with special attention paid to various examples of hadron therapy indications, also in consideration of the expected risks of complications in normal tissues and to issues related to health economics.

The final section is dedicated to various future projections, and revisits a number of fundamental aspects in precision medicine and future technologies. We hope the exhaustive review of the most burning challenges in radiotherapy that concludes the textbook will help increase understanding of the real dimension and place of radiation sciences in this era of globalisation.
The editors express our gratitude to the scientists and clinicians who accepted our invitation to contribute: they are all preeminent in their area of expertise and should be commended for their commitment to promoting modernity and making the dream of curing cancer with particles an option available to many more patients.

Manjit Dosanjh and Jacques Bernier
Manjit Dosanjh went to the Massachusetts Institute of Technology (MIT) in Boston as a postdoctoral fellow after obtaining her degree in biochemistry/chemistry at the University of Leeds and PhD in biochemical engineering from the University of Birmingham, England. She has held positions as a senior scientist at LBNL Berkeley, BEST professor at Jackson State University and visiting professor at University of Padua and University of Cagliari, Italy.

She joined CERN, Geneva, in 2000 and is actively involved in applying particle physics-derived technologies in the field of life sciences and is currently Senior Advisor for Medical Applications. In 2002, she was key in launching the European Network for Light Ion Hadron Therapy (ENLIGHT), a multi-disciplinary platform that strives for a coordinated effort towards particle therapy research in Europe. In 2006, she was appointed Coordinator of ENLIGHT (www.cern.ch/enlight).

Dosanjh also co-chairs with Professor Jacques Bernier the International Conference on Translational Research in Radio-Oncology and Physics for Health – ICTR–PHE, organised every two years in Switzerland.

Dosanjh is actively involved in helping non-profit science, education and gender-related organisations in Geneva and is the UN representative for GWI (International Federation of University Women).
Jacques Bernier completed his training at the MD Anderson Cancer Center, Houston (Texas), and the Curie Institute, Paris, after obtaining his degree in radio-oncology at the University of Liege, Belgium. In 1988, he moved to Switzerland, where he was appointed Chair of the Radio-Oncology Division, Tessin Cantonal Hospital. In 1995, he received a Privat-Docent Chair from the Geneva University. In the early 2000s, he founded the Oncology Institute of Southern Switzerland (IOSI) in Bellinzona. In 2006, he joined the Swiss Genolier Medical Network, where he has since chaired the Radio-Oncology Department. Throughout most of his career, Bernier has been heavily involved with translational and clinical research. In 1993, he received the Yalow-Berson Award, in St Louis, Missouri, for his laboratory work on interferons and interleukins. In 2010, Bernier was awarded the ‘Claudius Regaud Medal’ by the European Society of Therapeutic Radiology and Oncology (ESTRO).

A course director since 1990, and now member of the Core Faculty at the European School of Oncology, Bernier also co-chairs the International ICTR-PHE Conferences, organised every other year in Geneva. In 2009, he pioneered the application of breast cancer intra-operative electron-therapy (IORT), as innovative approach in Switzerland. In 2014, he created the Genolier Swiss Oncology Network (GSON), and in 2016, he received the accreditation from the Swiss Cancer Network as member of the core team of the GSON. Since 2013, he is member of the Board of the Genolier Breast Unit, accredited by the Swiss Society of Senology. In July 2016, he was elected President of the Euro–Asian Society of Mastology – EURAMA, in Milan, Italy. He is currently President of the Genolier Cancer Centre in Switzerland.
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From Röntgen Rays to Carbon Ion Therapy

The Evolution of Modern Radiation Oncology

K. Seidensaal and J. Debus

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DISCOVERY OF X-RAYS AND BIRTH OF RADIATION ONCOLOGY

The association of radiation and medicine began after an experiment by Wilhelm Conrad Röntgen, a professor at Würzburg University, who accidentally discovered in 1895 a new type of rays which have the capability of visualising what is hidden inside the organism. He called them X-rays in tribute to their mystery. Just days later, the very first and most famous X-ray image of his wife’s hand wearing a ring was created in a 20-minutes exposure to a Crooks tube, an experimental electrical device. Röntgen published his famous paper ‘Über eine neue Art von Strahlung’ (‘On a New Type of Ray’) in 1896 and was invited to present his results to the German Emperor Wilhelm I just two weeks later. Because the potential of his discovery was easily understood by the public, the application of X-rays spread faster than any scientific discovery previously known. Within a short period of time, radiographs were being used for diagnosis of wounded soldiers in military hospitals.

Just months after the discovery, the first attempt to treat a breast cancer patient by X-rays was performed by Emil Grubbe, a student at the University of Chicago. His work was followed by the attempt of Lyon physician Victor Despeignes to treat a patient with stomach...
cancer. The origins of radiation oncology, however, are commonly assigned to Leopold Freund, who successfully treated a five-year-old patient with *Naevus pigmentosus piliferus* in Vienna just months after the discovery of X-rays by Röntgen. Freund concentrated on dermatology because he was convinced that the penetration depth of X-rays was insignificant beyond the skin; he was the first one to apply scientific methods to the development of treatment protocols.

**MADAME CURIE AND FRENCH CONTRIBUTIONS TO RADIobiology AND RADIATION ONCOLOGY**

The discovery of X-rays was followed by the discovery of radium in 1898 by Marie and Pierre Curie; it yielded them the Nobel Prize in 1903. After the tragic death of her husband and the outbreak of First World War, Marie Curie devoted herself to a new task. Using her celebrity and influence, she initiated the construction of portable X-ray machines to assist surgeons treating the wounded at the battlefield. She often undertook long journeys, driving the X-ray unit herself to teach doctors and nurses the handling of equipment, thereby saving the lives of many French soldiers with the use of approximately 200 stationary and 20 mobile X-ray units.

The radiobiological knowledge that made modern radiation oncology possible was acquired in France at the Institute Curie after the end of the First World War. At this time in Lyon, the law of Bergonié and Tribondeau was discovered. This law describes the correlation of greater reproductive activity and sensitivity to radiation during the M-phase of the cell cycle. Claudius Regaud, a physician and biologist, postulated long before the discovery of DNA that chromatin is the target within the cell. Additionally, Regaud observed in animal experiments that subdividing the dose in subsets that were applied subsequently resulted in different, less harmful effects on healthy tissue than applying the entire dose at once. The continuously proliferating spermatozoa, his model tumour cells, were destroyed nonetheless, leaving the model animal infertile. Inspired by these findings, by 1934, the radiologist Henri Coutard developed a fractionation concept using 30 sessions for treatment of laryngeal carcinoma; this formed the basis of modern radiation oncology. Furthermore, Regaud started treating different types of tumours with radium sources which he placed close to the tumour – for example, by utilising interstitial needles – and thus initiated the development of brachytherapy.

**TECHNICAL ADVANCES IN HIGH-ENERGETIC PHOTON THERAPY**

Coolidge tubes, the successor of X-ray emitting Crooks tubes, were developed in 1913 and named after the inventor; these were the standard source for cancer treatment until the 1950s. Unfortunately, due to still quite low energy levels, deep-seated tumours could not be treated because most of the dose was applied to the skin. Post World War II, a substantial advance in radiation oncology occurred after the introduction of ‘Cobalt bombs’; the radioactive isotope Cobalt-60 was placed in a lead shielding which could be opened by a shutter, thus allowing treatment by photons with an energy of 1.2 megaelectron volts. Although obsolete in relation to current standards, those units are currently still operating in several Third World countries. The Cobalt bomb was succeeded by the 10 megaelectron
volts betatron and the electron linear accelerator, which was developed by William Webster Hansen together with the two brothers Sigurd and Russel Varian. Nowadays, Varian is a manufacturer and provider of radiotherapeutic equipment.

Radiation oncologists next started to use shielding blocks to shape the radiation field and reduce the dose delivered to normal tissues and critical organs. This was followed by the invention of the multileaf collimator (MLC) which consists of movable leaves arranged in pairs that allow the shaping of individual conformal fields simply and without time- and cost-consuming preparation of shielding blocks. Subsequently with the invention of computer tomography (CT), more powerful computers and advanced dose-calculation algorithms, two-dimensional (2D) planning was replaced by three-dimensional (3D) conformal treatment planning which allowed dose escalation trials. The first inverse treatment planning algorithm was developed by Steve Webb in 1989. It permitted radiation oncologists to define dose constraints to certain organs at risk and prescribe dose to the treated target volume (tumour), and then a planner would issue importance factors and an optimisation algorithm would calculate a plan which best met all the necessary criteria. A seminal paper published in 1988 by Anders Brahme of Karolinska Institutet is generally considered as the starting point of the field of intensity-modulated radiotherapy (IMRT). The principle of static (step and shoot) IMRT was developed next; modulation of the fields yielded improvement in dose coverage of the tumour and reduced the dose to neighbouring organs at risk. One of the first IMRT programs in Europe originated at the German Cancer Research Center and included a significant contribution by Thomas Bortfeld, currently the Chief of the Physics Division at the Massachusetts General Hospital. Gradually, target volume definition became more accurate thanks to modern imaging modalities such as magnetic resonance (MR) and positron-emission tomography (PET)-CT imaging. The first helical IMRT was developed in Wisconsin in 1993 and became commercial in 2002; it introduced modern image-guided radiotherapy. Volumetric-modulated arc therapy (VMAT) with dynamic MLCs provided an additional technique to perform IMRT using reduced treatment time. The first proposal that optimal delivery of IMRT might be achieved by a short-length linac mounted on a robotic arm arose in 1999 and was accomplished with the Cyberknife of Accuray which was developed at Stanford University and is used for modern radiosurgery. Recently, the combination of (MRI) and a linear accelerator promises to put image-guided radiotherapy at new level, thereby providing real-time imaging as well as target volume and plan adaptation; these machines are already beginning to operate in different institutions around the world. In summary, it took more than 100 years to develop conformal radiotherapy with photons. Currently, scientists are working closely at the physical limits of this technology.

CYCLOTRON, SYNCHROCYCLOTRON AND SYNCHROTRON – THE BEGINNINGS OF PARTICLE THERAPY

The golden age of physics started in the 1920s and continued for the next five decades. Extensive research in general and physics in particular was conducted; never before had scientific developments influenced the history of civilisation to this extent. Ernest Rutherford, one of the greatest experimentalists who managed to prove the existence of
the nucleus in 1911 and theorise about the existence of neutrons, requested that physicists provide a ‘copious supply’ of higher energetic particles than those from natural radioactivity. At this time, Ernest Lawrence, an associate professor at Berkeley University and later a Nobel prize laureate as well as a member of the Manhattan Project, learned about linear acceleration by switching potentials. He was scanning illustrations of a publication by the Norwegian Rolf Widerøe in a German journal on electrical engineering, a language he did not understand. His idea to adapt this type of acceleration by bending the path of charged particles into circular trajectories and circulate them many times laid the groundwork for the construction of the cyclotron in 1930. His new accelerator which he generously shared provided synthetic radionuclides for nuclear medicine and radiation oncology.

The phase stability principle was discovered by the Russian scientist Wladimir Iossifowitsch Weksler and the American scientist Edwin Mattison McMillan, who shared the Atoms for Peace Award in 1963. This principle describes that gradually and continuously increasing the oscillation period of particles with the number of turns in the accelerator leads to formation of a stable and tight bundle of accelerated particles. Subsequently, Lawrence adapted this principle in the development of the synchrocyclotron, which began operating in 1946 and allowed acceleration of protons to 55% of the speed of light (200 megaelectron volts). For the first time, the particle energy was sufficient to provide for protons which could penetrate the patients’ relevant depth, and here also was the basis for application to treated tumour target volumes. The spiral form of orbits in the synchrocyclotron makes a large uniform magnetic field necessary in contrast with a synchrotron which requires several smaller magnets that are placed around a hollow doughnut-shaped circular accelerator. The first synchrotrons were constructed by the two discoverers of the phase stability principle; until 1957, energies up to 10 giga electron volts were reached. The advantage of these among others is that the weight of the magnets is lower, so beams of much higher energy can be created. Discovery of the model of strong focusing finally lead to the birth of the European Organization for Nuclear Research (CERN) in Europe.

PROTON THERAPY

The idea to use high-energy protons for therapy is older than one might assume; it was proposed first by the physicist Robert R. Wilson, the founder of Fermi National Accelerator Laboratory (Fermilab) and member of the Manhattan Project, in his 1946 publication ‘Radiological Use of Fast Protons’ in Radiology during his work on the design of the Harvard Cyclotron Laboratory. He postulated that maximum irradiation dose could be placed within the tumour, thus sparing healthy tissue based on the ‘Bragg Peak’ phenomenon which was first described by William Bragg for alpha particles. This was followed by extensive research which managed to confirm Wilson’s predictions. The first patients were subsequently treated in 1954 at Lawrence Berkeley National Laboratory (LBL) and in 1957 in Uppsala, Sweden. Initially, treatment was performed in and restricted to research facilities using particle accelerators conducted for physics research.

With progressing technical advances in imaging, computers, accelerators and treatment-delivery techniques, proton therapy became more accessible to the routine medical
treatment of cancer patients in the 1970s and was approved as a therapy option for certain tumours by the Federal Drug Administration (FDA) in 1988. The first hospital-based oncological particle centre that opened in 1989 was Clatterbridge Centre for Oncology in the United Kingdom, followed in 1990 by the Loma Linda University Medical Center (LLUMC) in the United States. Currently, over 60 centres worldwide offer proton therapy to cancer patients and more than 30 additional proton centres are in the planning phase or under construction. The use of protons enables radiotherapy to be more precise by decreasing the severity of acute and late side effects, thus making it favourable, for example, in the treatment of paediatric cancer patients; however, because the relative biological effectiveness (RBE) of protons is similar to that of photons, scientific attention turned to heavier ions in hopes of increasing biological impact due to higher linear energetic transfer (LET).

CARBON ION-TREATMENT

John H. Lawrence, the brother of Nobel-prize winner and cyclotron inventor Ernest Lawrence, was an American physicist and physician who pioneered the field of nuclear medicine as well as particle therapy. Between 1935 and 1938, he conducted the first biomedical studies and demonstrated the greater biological effect by dense tissue ionisation of heavy particles in normal and cancerous tissue. In the following years, he demonstrated the therapeutic advantages of heavy-charged particles with higher energy together with Cornelius A. Tobias, a nuclear physicist and member of LBL best known for his radio-biological studies and application of the high LET. Since 1952, the very first patients were treated with argon-, neon-, silicon- and helium-particle beams until carbon ion was found to have the ideal radiobiological characteristics. The Bevalac, a 1974-onward combination of the Super Heavy Ion Linear Accelerator (SuperHILAC) linac and the Bevatron, a proton accelerator, enabled clinical trials with heavy ions of more than 1,400 cancer patients at what is now LBL before it was decommissioned in 1993.

The foundation for fast-neutron therapy was also laid at LBL in 1938. After a break during the Second World War when the cyclotron was used for the war effort, research continued in the 1960s. It was the first high LET radiation therapy which was applied clinically with maximum use in the 1970s and 1980s. Effectiveness and favourable local control were shown for different tumour entities, but tremendous late reactions resulted in stopping the use in almost all the centres in Europe, Japan and the United States.

In Japan in 1984, the government began constructing the first heavy-ion facility for routine medical use called the National Institute of Radiological Sciences (NIRS) which employed many of the LBL and Bevalac scientists. The Heavy Ion Medical Accelerator in Chiba (HIMAC) was established in 1994, and provided, similarly as the Bevalac, passive beam irradiation (passive scattering) with protons and carbon ions. It was unique until 1997. Further advances included the installation of a pencil beam raster scanning (PBS) facility and markerless respiration-gated PBS, the carrying out of nearly 70 treatment protocols with treatment of approximately 1,000 patients per year. The Microdosimetric Kinetic Model (MKM) was developed, updated (MKM2010) and implemented within Japan; efforts were made to provide for dose translations to the European local effect model (LEM). The Japan Carbon-ion Radiation Oncology Study Group (J-CROS) is today
composed of five carbon-ion therapy centres with horizontal and vertical fixed beams and one gantry offering PBS as well as passive scattering. NIRS is a pioneer which has performed major breakthroughs and paradigm changes in radiation oncology with more than 20 years of experience in carbon-ion irradiation.

The ‘Helmholz Gesellschaft für Schwerionenforschung’ (GSI) was founded in 1969 in Western Germany; the era of particle treatment started when Gerhard Kraft, a trained nuclear physicist and radiobiologist and a fellow of Cornelius Tobias at LBL, introduced ion therapy in Europe after his return from the United States. During the following years, Germany achieved a pioneering position in proton and carbon-ion therapy. At GSI, the innovative pencil beam, active raster scanning technique was developed using magnetic fields to deflect the beam in horizontal and vertical direction and conform it over the targeted volume, thus performing intensity modulation and more flexible therapy treatment planning compared to the previously implemented passive scattering. Furthermore, optimisation of inverse treatment planning for biological parameters due to the quantitative calculation of the RBE in carbon-ion treatment with the theoretical LEM, which is today widespread throughout Europe, was created there. After promising basic research results, translation to clinical practice allowed treatment of more than 400 patients from 1997 to 2009. The research and experience of GSI were implemented in the Heidelberg Ion-Beam Therapy Center (HIT) which was developed and built by the University Hospital Heidelberg, the German Cancer Research Center (DKFZ), the Helmholtz-Zentrum Dresden-Rossendorf (HZDR), and the company SIEMENS from 2003 to 2009. Currently, more than 4,400 patients have been treated at HIT with excellent results using carbon-ion and proton-beam irradiation by concentrating on rare radioresistant malignancies such as nonsquamous cell tumours of the head and neck – especially adenoidcystic carcinoma; chordoma; chondrosarcomas of the skull base and pelvis as well as more common entities such as glioma; skull base meningioma; and prostate cancer. Several clinical phase I–III studies are investigating the safety and efficacy of particle therapy in combined boost-concepts or alone, such as PROMETHEUS for inoperable hepatocellular carcinoma; MARCIE for anaplastic meningioma; Cinderella for recurrent glioma; ISAC for pelvine chordoma; and OSCAR for inoperable osteosarcoma which is the first carbon-ion treated paediatric study cohort worldwide. Pre-clinical studies investigate the use of additional heavy ions such as helium and oxygen for cancer treatment. Complementing two treatment locations with horizontal beam position, the first worldwide rotating proton- and carbon-ion gantry was created using astronomy telescope technology and implemented in the year 2012; it weighed over 600 tons and allowing a 360-degree rotation of the beam. A similar second proton-and carbon-ion centre with three horizontal treatment places and one 45-degree place started treating patients in 2015 in Marburg and is operated partially by HIT. Further centres treating cancer patients with carbon-ion irradiation are MedAustron in Austria and CNAO in Italy as well as two additional centres located in China.

In summary, together hadron therapy and high precision X-ray therapy costimulated their own development over the last century. The new technologies allow conformal radiotherapy with submillimetre accuracy. The big challenge of radiation oncology remains the biological optimisation and selection of the treatment regarding dose, volume and time.
REFERENCES


Particle therapy co-operative group; a non-profit organisation for those interested in proton, light ion and heavy charged particle radiotherapy. https://www.ptcog.ch/index.php.


Yarris, L. 1930s: The rad lab—From a small wooden building to a national laboratory. http://history.lbl.gov/1930s/.
REFERENCES


Dosanjh, M., Cirilli, M., Myers, S., and Navin, S. Medical applications at CERN and the ENLIGHT network. Front Oncol. 6 (2016): 9.


Derenchuk, V. Particle beam technology and delivery. 55th Annual AAPM Meeting, Proton Symposium, Indiana, 2013.


Johnson R P, Bashkirov V, Giacometti V, Hurley R F, Piersimoni P, Plautz T E, Sadrozinski H F W et al. 2014. Results from a pre-clinical head scanner for proton CT. *2014 IEEE Nuclear Science Symposium and Medical Imaging Conference (Nss/Mic).*


Jongen Y and Stichelbaut F. 2003. Verification of the proton beam position in the patient by the detection of prompt gamma-rays emission. *Presentation at the 39th Particle Therapy Co-Operative Group (PTCOG).*


ENLIGHT Annual Meeting 2015, Kraków, Poland: http://indico.cern.ch/event/392790/.


Combs, S.E. et al., Intensity modulated radiotherapy (IMRT) and fractionated stereotactic radiotherapy (FSRT) for children with head-and-neck-rhabdomyosarcoma. *BMC Cancer*, 2007. 7: 177.


Glimelius B, Montelius A. Proton beam therapy—Do we need the randomized trials and can we do them? *Radiother Oncol*. 2007;83(2):105–109.


The ICRU and IAEA/ICRU report on ion beam. 2018, in press.


Proton beam therapy, ASTRO model policy, ASTRO 2014. [www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ASTRO PBT Model Policy FINAL.pdf](http://www.astro.org/uploadedFiles/Main_Site/Practice_Management/Reimbursement/ASTRO PBT Model Policy FINAL.pdf)


Amaldi, U., The Italian hadrontherapy project, in *Hadrontherapy in Oncology*, U. Amaldi and B. Larsson (Eds.), Amsterdam, the Netherlands, Elsevier, 1994, pp. 45–58.


Apsimon, R., G. Burt, S. Pitman and H. Owen, ProBE proton boosting extension for imaging and therapy, in *Proceedings of International Particle Accelerator Conference*, Busan, South Korea, IPAC16, 2016.


Degiovanni, A. et al., A linac booster for high energy proton therapy and i’maging, 2018.


Hardt, W., Ultraslow extraction out of LEAR, CERN, PS/DL/LEAR Note 81-6, Geneva, Switzerland, 1981.


Reimoser, S. T., M. Pavlovic and M. Regler, Status of the riesenrad ion gantry design, Proceedings of the EPAC, 2000, Vienna, Austria.


Vretenar, M., Opportunities for ion accelerators in medicine and industry, Workshop on Ions for Cancer Therapy, Space Research and Material Science, 26–30 August 2017, Athens, Greece.


