Acta Oncologica Vol. 34, No. 8, pp. 995–1003, 1995

DEVELOPMENT OF CLINICAL RADIOTHERAPY SINCE 1896

LARS R. HOLSTI

From the discovery of x-rays in November 1895 and the first publication in December 1895 it did not take long for the first x-ray therapy of cancer in January 1896. The first 25 years in the history of radiotherapy was not a very flattering period for the discipline. During the following 25 years, however, important developments in clinical radiotherapy occurred and in some countries the speciality of radiotherapy was established in the 1930s. In the last 50 years gradual changes have taken place and now modern radiotherapy is an established curative method in the treatment of cancer. The scientific background of radiotherapy is solid, and the understanding of cancer biology and radiobiology has improved drastically. The radiotherapists of today are cancer specialists, oncologists. The technical development has been enormous. The future of radiation oncology looks very promising, with local cancer treatment being shown to be most effective.

The first report on the new rays was heralded by W.C. Röntgen in November 1895 and his first written report was published at the end of December 1985. Within a few days the publicity in the German press reached London on January 6, 1896 and from there was cabled to newspapers all over the world (1). Just three weeks later, on January 29, 1896, E.H. Grubbé a vacuum tube manufacturer in Chicago used the new rays therapeutically for the first time, at the suggestion of Dr. Ludlam. The patient had breast cancer and was exposed to single treatment for about 1 h (1, 2). In Austria, the dermatologist Leopold Freund had among others observed epilation after exposure to x-rays. In 1896 he treated a patient with hairy nevus (3) daily over 2 weeks and was the first to give fractionated radiotherapy. The first cases of basal cell carcinoma of the skin and squamous cell carcinoma of the skin were cured in Stockholm in 1900 by T. Stenbeck and T. Sjögren (4), who used the same technique as Freund. These patients with cured skin cancer were followed up by Gösta Forssel for 28 years. In Finland, the first cancer patient was treated in 1903 by Ali Krogius, professor of surgery, in Helsinki. The patient was a 40-year-old man with recurrent multiple periostal round cell sarcoma of the skull. Daily he received treatment of 2–10 min duration. After 2 weeks the tumors had almost completely disappeared. Additional treatment was given but no longer every day. The tumors had disappeared completely 4 months after the treatment (5). No skin reaction was observed, but there was hair loss.

Accepted 8 September 1995.
From the Department of Radiotherapy and Oncology, Helsinki, University Central Hospital, Helsinki, Finland.
Correspondence to: Emeritus Prof. Lars R. Holsti, Department of Radiotherapy and Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, SF 00250 Helsinki, Finland.

Central Europe

Despeignes was the first to apply roentgen therapy in France. In July 1896 he treated a case of gastric carcinoma with 80 sessions lasting between 15 and 30 min daily. He reported improvement and pain relief. Treatment was given twice daily (1). In 1903, Nicolas Senn treated the first leukemia by irradiating the spleen and believing that he had cured the disease (6). In 1929 the Swiss dermatologist Miescher described the first dose–response relationship for human tumor, primarily basal cell carcinoma of the skin (7). In 1936 Holthusen graphically illustrated the relationships between tumor control and complications (8).

The first advance toward a method of roentgen dosimetry was suggested by the Austrian radiology pioneer Guido Holzknecht in 1902. In his chromoradiometer a mixture of

 ISSN 0284-186X

salts would change from yellow to green when exposed to x-rays. This change in proportion to dose was compared with a colorimetric scale demarcated in Holzknecht or H units (4). The ionization chamber was proposed as a dosimeter a few years later and the first physical unit of dose, the roentgen, was adopted at the first International Radiology Congress in Stockholm in 1928. The history of dosimetry has been reviewed by Quimby (9).

The early radiotherapists initially adopted treatment techniques involving a single massive dose aimed at the eradication of tumors comparable to extirpation of tumors by surgery. Wintz in Erlangen was an advocate of this technique proposed by Perthes in 1904 (4). In 1914 the Austrian radiologist Gottwald Schwarz suggested that multiple doses would be more effective because the time of greater radiosensitivity was the time of mitosis (10). In 1918 Kroening and Friedrich showed that the dose necessary to produce the same skin reaction had to be increased when multiple fractions were used rather than just one (4). However, throughout the 1920s there were supporters in Germany, primarily in Erlangen of single dose treatment. The single massive dose treatment resulted in major complications, and the controversy between single dose and fractionated treatments continued, into the 1920s.

Clinical radiotherapy is considered to have started in 1922. Claude Regaud had his classic series of experiments and had demonstrated that spermatogens and the ram testis could be permanently eradicated by successive daily doses of fractionated radiotherapy, whereas single massive doses failed to elicit the same biologic effect and often caused intolerable injury to the scrotal skin (11). Henri Coutard soon applied these techniques of fractionated radiotherapy to the treatment of patients with cancer of the head and neck. At the International Congress of Otology in Paris in 1922 Regaud, Coutard and Hautant presented 6 patients with advanced carcinoma of the larynx treated by radiation therapy and now free of disease (12). This was the first time radiation therapy was shown to be an independent speciality practised not by surgeons but by radiation therapists (6). Beginning in 1919 Coutard treated incurable head and neck tumors with fractionated low dose roentgenotherapy. His methods were designed to mimic the low dosage radium technique of Regaud. Both Regaud in Paris and Forssell in Stockholm used radium not only for uterine carcinoma but also for head and neck carcinomas, generally tonsils and oral cavity (4). Coutard reported cures but also described reactions of the skin and mucosa showing that they depended for specific doses on the total duration of treatment (13). In the beginning he gave large daily doses to small tumors at a low dose-rate. When the daily dose was reduced for large tumors low dose-rate was no longer necessary, which led to the technique of small fraction sizes at a relatively high dose-rate, called simple fractionation. This method was accepted in many centers by leading radiotherapists, including Schinz in Zürich and Holzknecht in Vienna. The technique of fractionation around 1930 has been reviewed by Schinz (14).

Coutard experimented with several different fractionation regimens, including over-fractionation, progressive daily doses, interrupted courses of treatment, intensive short treatments. Later developments in fractionation of radiotherapy have shown that Coutard was a pioneer in many respects. In the early 1930s Coutard and his collegues started to report 5-year results of cancer treatments (13, 15). Coutard kept his patients under careful clinical control, examining them daily, and taking care to immobilize them properly at each treatment (16).

At about the same time as the great individualist Coutard was working in Paris, the great organizer Paterson had started using radical small field x-ray treatment in Manchester. In most cases treatment was given 5 days a week over 5 weeks with all fields treated each day (17). The daily dose was higher than in Paris. After 1944 shorter 3-week treatments were used in Manchester.

Nordic countries

Thor Stenbeck taught Gösta Forssell (1876–1950), who was the real pioneer in Scandinavia with great influence on the development of diagnostic radiology and radiotherapy in all the Nordic countries. He was very keen on the care of cancer patients. Radiumhemmet in Stockholm was founded in 1910 with Forssell as its first head of institute. He was very well known internationally, presenting the early results of radiotherapy in Sweden in London in 1929 (18). From the beginning, practically all patients treated at Radiumhemmet were followed up. Elis Berven was the first professor of radiotherapy in Sweden; nominated in 1936 and he succeeded Forssell as head of Radiumhemmet. Forssell preferred the chair of radiodiagnosis. The discovery of radium by Pierre and Marie Curie in 1898 added a new source of radiation to cancer treatment and by the early 1900s three techniques of treatment were being practised in Paris, in Stockholm and later in Manchester.

The Finsen Institute in Copenhagen, is equally established as Radiumhemmet. Primarily a cancer research laboratory, it expanded towards therapy. The Danish Cancer Society founded three radium stations in Denmark, with Jens Nielsen (1900–1964) as the head of the radium station in Copenhagen and professor of radiotherapy. He is well known for his studies on radiotherapy of the larynx carcinoma (19). In 1953 he proposed the creation of an international club of radiotherapists. A chair in radiology was founded in Aarhus with Karl Crebs as its first professor.

The Radium Hospital in Oslo has been a center for radiotherapy for decades with its former head Rolf Bull Engelstad publishing a textbook in radiotherapy in Norwegian in 1946 (20). Later, Professor Erik Poppe became the leading authority in Norway. It is noteworthy that most of the leading departments in the field were Radium Institutes or Radium Hospitals, not Radiotherapy Departments.

In Finland the first radiotherapy was given in 1903 by Ali Krogius (5), professor of surgery. In 1904 A. Clopatt, the first radiologist in Finland, treated a mediastinal tumor and in 1909 Hugo Holsti, professor of internal medicine, treated a leukemia patient (21). G.A. Wetterstrand was the leading radiologist in the 1920s and reported results of roentgenotherapy of breast cancer. In the 1930s and 1940s the most important person in radiology was Gösta Jansson, who was also interested in radiobiology. In 1942 Jansson published a review paper on the importance of the time factor in radiotherapy (22). Sakari Mustakallio (1899–1989) was the pioneer and grand old man in radiotherapy in Finland (23). He was the first head of the Department of Radiotherapy in Helsinki, founded in 1936, and also the first professor of radiology in Finland (1950–1967). He adopted many of the treatment techniques of Elis Berven in Stockholm. Mustakallio also created the new department, a separate building for radiotherapy and other cancer therapy. The building, opened in 1962, housed a radiotherapy department, units of surgery, pathology, radiodiagnostics and nuclear medicine. A chemotherapy unit was established a few years later. Mustakallio was one of the first advocates of conservative treatment of breast cancer (24). He very quickly came to the conclusion that distant metastases did not spread postoperatively but rather before or during the operation. Radical operation seemed unnecessary in cases in which the primary tumor could be extirpated and in which there were no axillary metastases. In such situations extirpation of the tumor, sparing the breast, and radiation treatment is a satisfactory method. The radiation doses were modest, 3.5 Gy per day, one field per day, totalling 21–28 Gy per field. The results were the equal of those achieved by radical surgery and roentgenotherapy. Mustakallio later updated his results in a material of about 400 patients (25, 26). He also carefully analysed the material of carcinoma of the larynx and hypopharynx that he had treated (27). During the Second World War he irradiated some of the head and neck patients twice a day. Sakari Mustakallio was also one of the first to use intraoperative roentgenotherapy for carcinoma of the bladder and pancreas.

North America

Development in the United States has been described in review papers by Case (1), Buschke (6), Fletcher (28) and Kaplan (29). It has to be remembered that the first radiotherapy ever was given in the United States.

The great leaders in clinical radiotherapy

Henri Coutard (1876—1950) was the first great leader to influence the whole radiotherapy community and the praxis of clinical radiotherapy in Europe and in North America.

After Henri Coutard the principals were Francoise Baclesse in Paris and Ralston Paterson in Manchester influencing the 1940s through to the 1960s, followed by Gilbert H. Fletcher, whose carrier in Houston lasted over a period of 30 years. Paris and Manchester have maintained to keep the traditions and many important and influential departments have been created in North America. Several important personalities have of course been leaders in specific fields of radiation oncology and influenced the development of radiotherapy.

Francoise Baclesse (1896–1967), born in Luxemburg, succeeded Coutard at the Institute du Radium in Paris 1937. He developed a radiotherapy technique aimed at avoiding acute reactions of the mucosa and of the skin. Another basic principle of the Baclesse technique was the shrinking field technique. Baclesse protracted the overall treatment time up to 12–16 weeks (30) and increased the dose as the time increased. Cures were obtained in advanced cancers of the larynx. Baclesse also explored the use of external irradiation in the curative treatment of primary breast cancer. Just as Coutard before him, he had several foreign visitors in his department. The Baclesse technique was brought to the United States by his many students, including Gilbert Fletcher and Maurice Lenz.

Ralston Paterson (1897–1981) was the predominant figure in England from 1931 when he was appointed director of the Holt Radium Institute in Manchester. Within 5 years he had developed it into a leading radiotherapy center in the world along with Paris. In 1936 Paterson stated (17) that radical x-ray therapy was essentially a treatment for early cases, that is had to be radical and that it was essential that treatment be taken to the absolute limits of tolerance. The next step in the Manchester concepts was the evolution standarized field arrangements. The standardized techniques for particular tumors were planned to include the primary tumor and the potential tumor zone in one block, which was irradiated as homogeneously as possible (31). The optimum dosage in relation to the volume irradiated interested Paterson very much (32). The greater the volume irradiated, the lower the dose which could be given without exceeding the tolerance limit.

By the Second World War marked changes in radiotherapy practice had come about in Manchester. Radical small field x-ray treatment was started in 1935. For head and neck cancer between 55 and 60 Gy was recommended, later 50 Gy in 3 weeks. The fraction dose was more than 0.02 Gy whereas Baclesse in Paris used 0.02 Gy. The success of these Manchester treatments with multiple field arrangements made this the standard schedule for radical treatment that lasted over a long time. In the 1930s radiotherapy changed from a mainly palliative procedure into a major curative method in the treatment of cancer, and radiotherapy became an established medical science. Accurate radiation dosimetry was one of Paterson's interests. Along with Parker he developed the well-known Radium Dosage System. Paterson understood well the need to integrate physics into the everyday practice of radiotherapy (32). His textbook, first published in 1948 was reprinted several times, and the second edition (1963) was the main source of information on radiotherapy for a long period, documenting his philosophy (33). Although Paterson was dedicated to science he always thought the best of his patients. Once in the early 1980s in Austria, I mentioned to Gilbert Fletcher in a lighter moment that he was the pope of radiotherapy, prompting the response that Ralston Paterson was then the archbishop. This episode showed how highly Fletcher esteemed Paterson.

Gilbert H. Fletcher (1911–1992) was trained by Baclesse in Paris. In 1948 he was appointed to the Department of Radiotherapy at the University of Texas M.D. Anderson Cancer Center, a department he had founded and chaired until his retirement 1981. He was undoubtedly the greatest leader in the history of radiotherapy. An epoch in the history of radiotherapy ended when Gilbert Fletcher died (34). He established a school of radiotherapy which is followed practically everywhere in the radiotherapy community. He developed reproducible treatment strategies and techniques for cancer of the head and neck, breast, cervix and endometrium. His obervations of the dose response for control of human tumors of different sizes led in the early 1960s to the concept of subclinical disease which could be destroyed effectively with lower doses of radiation than required for bigger tumors (31, 35, 36). Fletcher advocated the shrinking field technique. He also realized early the great importance of radiobiological research in clinical radiotherapy. The laboratory of experimental radiotherapy has been one of the leading radiobiological research units. The most important of Fletcher's contributions to clinical research might be the systematic analysis of causes of failure and complications in patients treated in a consequent way. His philosophy led to continuous refinement of techniques and practices. The scientific production of Gilbert Fletcher including his classic 'Textbook of Radiotherapy' in three editions (1966, 1973, 1980) will remain a treasure for scientific knowledge methodology (37). Probably the whole international radiotherapy community visited the 'Mecca' of radiotherapy in Houston. Fletcher was a strong personality, but also a warm friend to those who knew him well. The scientist Fletcher always had the quality of life of the patients in mind.

Time–dose models

The relationship between dose, fractionation and total overall time has interested radiotherapists for many years. Skin reactions were the first recognized biological effects of x-rays and radium treatment. Since 1909 correlations with doses have been made for various degrees of skin reactions, from light erythema, epilation, pigmentation and dry desquamation to moist desquamation. The best known experiments on skin reaction recovery were done in 1933 by Reisner (38) and in 1936 by McComb & Quimby (39). Magnus Strandqvist carried out a thorough review of the literature on fractionation and found that its significance was not well understood (40). He carried out a study of 183 cases of basal cell carcinoma of the skin, 74 cases of squamous cell carcinoma of the skin and 23 of the lower lip treated by a single massive dose or by daily irradiations over 2 weeks, in a few cases extending over 6 weeks. Strandqvist plotted in graphic coordinates the total doses given against the total number of days in which they were administered. Successfully treated cases followed a curve above which most of the necrotic effects and below which most recurrences were found. A straight line drawn on log-log paper approximated this curve satisfactorily. He extrapolated the curve to 0.35 day for a single treatment. The slope of the curves 0.22 was the same for the curative dose for squamous cell carcinoma and for various degrees of skin reactions. This slope was in accordance with previous observations of Quimby and Reisner. Strandqvist came to the conclusion that within certain limits the effects depended only on total dose and overall time. Similar time–dose formulae were applied to different sets of clinical data by Andrews & Moody (41), duSault (42) and Finnish born von Essen (43).

The Strandqvist curve was used for the next 20 years to vary treatment schemes. Hypofractionation, 2 or 3 fractions per week, sometimes caused severe complications (44, 45). Botstein (46), however, reported encouraging results. Tumor response was in fact quite good, but normal tissue reactions were too great. Other variants of conventional fractionation were tried by many institutions. Interrupted treatment was used by Coutard when strong reactions forced a break in the treatment (13). Preplanned interruption, split-course, was used by many departments around the world in the 1960s and 1970s (47–49). Split-course is a method of decreasing acute reactions and of increasing total dose. The break was not always compensated by increasing the total dose however, which quite naturally led to worse local control and survival than conventional fractionation (50). A 10% increase in total dose resulted in the same local control and survival as continuous treatment, but not better (51). It was felt that shrinkage of the tumor during the rest period would increase reoxygenation (47, 49).

The next development was the NSD isoeffect formula of Ellis (52). This took into consideration not only the overall time but also the number of fractions. Previously, Fowler et al. (53) had demonstrated in animal experiments that for skin reactions the number of fractions was of greater importance in determining isoeffect doses than time, at least up to 28 days. The NSD equation has had a significant impact on clinical practice. The most important reason is that it established a method for giving fewer than 5 fractions per week (4). However, it was found that 2 fractions per week caused more damage to normal tissues than would be expected from the NSD formula (54). The TDF and CRE are mathematical derivations from the NSD formula. Generalizations of these formulas were developed to account for split-course and continuous treatments (55). Critique of the formula has been presented in the literature (4, 56).

The latest development in fractionation shows that the number of fractions is less important than earlier believed. The important parameter is the size of the fraction. In 1976 Douglas & Fowler (57) employed the so-called linear-quadratic LQ model. It has been shown that the fractionation sensitivity of tissues may be classified according to the alpha/beta ratio (58). There is now clear evidence of a separation between acute and late response with changes in dose per fraction (57–59). It is a well-known fact that radiation changes will progress with time (60). Much higher doses can now be achieved by giving small individual doses. Hyperfractionated and accelerated fractionated schedules have been developed and clinically tested, as well as the concomitant boost technique (62) and the continuous hyperactionated accelerated treatment (CHART) (63). Small-dose fractionation, i.e. hyperfractionation has been shown to beneficial in bladder cancer (64) and in head and neck tumors (65, 66).

Clinical studies support the view that repopulation during prolonged courses of radiotherapy is a cause of failure in patients with head and neck cancer (67). Accelerated repopulation has been shown by Withers et al. (68) in head and neck cancer during the course of radiotherapy. The time for the change in tumor kinetics is not well known, varying between 2 and 4 weeks (69). Prolongation of radiotherapy results in loss of local control in head and neck cancer (70). In slowly proliferating tumors like prostatic carcinoma, however, prolongation seems not to affect local control (71, 72, 73).

Split-course irradiation with a planned break of 2–3 weeks in the treatment was used in the 1960s and 1970s to minimize acute reactions. Split-course allows an increase in total dose in step with the prolongation of overall time. If the total dose remains the same as in the corresponding continuous treatment, the local control and survival are inferior (50). When a break is compensated by increasing total dose, the results are equal to conventional fractionation but not better (50). The split-course technique has been used in accelerated fractionation schemes (74).

Recently, a new method designed to counteract proliferation in squamous cell carcinomas has been presented, the dose per fraction escalating roughly in step with proliferation (75, 76). Total doses of 74 to 76 Gy can safely be given for 5 to 5 1/2 weeks. Local control is excellent and the normal tissue reactions tolerable.

Of the new fractionation schemes in which multiple small fractions are used hyperfractionation is used increasingly. By purer accelerated fractionation the results have not yet been in accordance with the theoretical calculations and expectations.

Radiobiology

With the exception of the studies on fractionation the fundamental radiobiologic foundation of radiotherapy started in the early 1950s, when DNA as a target and the cell cycle were discovered. In 1956, Puck & Marcus (77) published their fundamental experiment on survival fractions of clonogenic mammalian cells. The famous survival curve is exponential. For the first time a quantitative analysis of radiation dose–cell survival relationship was permitted. The survival curve thinking in radiotherapy started.

The studies by H. Gray and his colleagues drew attention to the possible relevance for the outcome of clinical radiotherapy of the existence of hypoxic foci in tumors. Thomlinson & Gray established that there were areas of hypoxia in human lung carcinomas at a distance from capillaries where necrotic foci occur (78). This discovery initiated the use of hyperbaric tank therapy (79) and later the use of high LET radiation and the search for hypoxic cell sensitizers. The sensitizers in clinical use have so far been disappointing (80). Because of limited progress in chemotherapy of solid tumors, with the exception of breast cancer, interest in radiotherapy has continued to increase. The spectrum of radiotherapy research presented by Peckham (81) has been actively carried out. Radiotherapy has advanced many aspects of our understanding of the biological responses that underlie radiation responses (82). These include the mechanisms of radiation injury, the four Rs of radiotherapy and dose and tumor control and predictive assays. Radiobiology has developed from conventional radiobiology in the early 1980s to molecular biology in 1990s (83).

Curative radiotherapy

Based on early experiences during the first two decades of the century, radiotherapy had the unfortunate reputation of being a useful palliative treatment without curative potential. As early as the 1920s, however, radiotherapists could report achievements with x-ray treatment. It took another decade nevertheless before radiotherapy was recognized as a discipline which could present permanent curative results. The introduction of megavoltage equipment changed the picture definitively and the scope of curative radiotherapy extended to tumors that for technical reasons could not be effectively treated with low energy equipment. This was, however, only one of the events in the curative radiotherapy. The concept of radiosensitivity and radio-responsiveness changed. Adenocarcinomas were no longer radioresistant. The size of the carcinoma mass was shown to be more important than the histological type (28).

Surgery had been the only curative method of cancer treatment. Today surgery is effective provided the tumor is resectable. Gross cancer can be removed but the diffuse microscopic disease around the mass is left behind irrespective of how radical the surgical procedure has been. Realization of this fact led to the concept of conservative surgery combined with radiotherapy. Radical neck dissection and radical mastectomy were not necessary. The removal of gross tumor was enough in itself. The concept of organ preservation developed. Subclinical and microscopic disease was effectively eradicated by radiotherapy (31).

The most dramatic example of improvement was seen in Hodgkin's disease. With improving staging and development of total lymphoid radiotherapy the 5-year survival exceeded 80%. Aggressive systematic radiotherapy transformed this incurable disease to a curable one (84, 85). Combination chemotherapy has further improved the curative rates. This success with a goal-minded radiotherapy was a stimulus by which improvement of treatment results was achieved in many other malignancies, e.g. many childhood cancers, testicular seminomas. Dose–response relationships were discovered and in many cases dose escalation was the consequence.

Five-year survival rates have improved for cancer of the cervix, prostate, nasopharynx, bladder, ovary, tonsil with megavoltage therapy. In many other tumors improved treatment techniques and strategy have led to improved survival for example in carcinoma of the rectum, soft tissue sarcomas and even carcinoma of the breast. In many cancers early stages are now curable with radiotherapy, e.g. cancer of the larynx, other head and neck cancers, cancer of the thyroid, cervix, breast, testicular seminoma. Remarkable results have been reported (86). These include cancers of the head and neck, oral cavity, oropharynx, larynx, breast, endometrium, bladder and prostate. In most cases irradiation has been used for primary tumors, in some cases as an adjunct to surgical procedures and of elective irradiation of regional lymph nodes. Altered fractionation schemes have been introduced with promising early results.

For a long period the practice was to report survival rates only. However, local control has been shown to be equally important (87), but even more important is the trend to report failure analysis and causes of death. The quality of life patients must also be taken into consideration.

The response to radiotherapy depends on factors such as, hypoxia, tumor cell kinetics, inherent radiosensitivity, fractionation of treatment. Greater tumor control and reduced morbidity of treatment have been stressed (88).

Meta-analysis used for many years in summarizing the results of separate but simular studies comes into its own when a controversy exists concerning the real effect of a given treatment (89). In revealing more detail than is available from separate radiotherapy studies meta-analysis is advantageous when analysing curative radiotherapy data.

Palliative treatment is valuable for many patients for its strong relief of symptoms.

From therapist on oncologist

In the early 1970s there was a need internationally to reorganize cancer care (90). In the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) radiotherapy has long been a clinical discipline with its own ward accomodations and responsibility for the following up of patients. Radiotherapists in these countries have also adopted and evaluated all kinds of drug therapy. The situation has at least partly been the same in Great Britain. Radiotherapy is a clinical discipline in which almost all activities deal with cancerous diseases, their treatment and complete responsibility of a great proportion of cancer patients.

Although not all radiotherapists in all countries use chemotherapy, the trend to create a clinical discipline, clinical radiation oncology or clinical oncology has been the same. Radiation oncologists are broadly considered as clinical cancer specialists. Detailed studies of the pattern of spread of carcinomas, sarcomas and lymphomas arising at various sites, as well as description of radiation reactions in various organs have contributed to the image of a comprehensive cancer doctor. Besides practical training, radiation oncologists today take theoretical courses in radiation physics, radiation biology, tumor pathology and biology and cell kinetics. They are also educated in chemotherapy, hormonal therapy and basic immunotherapy. New developments in molecular biology will add new aspects to the training of modern radiation oncologists.

Franz Busche (91) defined radiotherapists as clinicians who treat cancer patients with radiotherapy and take full and exclusive responsibility for the patients under their care. Twenty years later Raymond Bush reinforced and amplified these concepts to cover the oncologist (92).

Technical development

The construction of megavoltage apparatus was an important step in the development of curative radiotherapy. Progress in imaging techniques, especially computed tomography and magnetic resonance imaging have resulted in improvement of tumor localization. Advances in the quality and penetrating power of radiotherapy equipment have resulted in well localized radiation beams that can be delivered with homogeneous energy deposition across the tumors. Tumor volume, target volume and treatment volume have been clearly defined. Radiation fields can be shaped by means of shielding blocks.

The development of precise 3-dimensional imaging and of computer control of many treatment machine parameters allows much more complex target volumes than cubes. Conformal radiotherapy is likely to cause fever side effects in patients. Three dimensional radiotherapy planning permits localization and treatment of irregularly shaped tumors while excluding most of the normal tissue (93–95). It is possible to conform the spatial distribution of high radiation dose to the shape of the tumor contour and concomitantly to decrease the volume of the surrounding normal tissue receiving high radiation dose.

Besides high LET therapy, new developments in radiotherapy, like radiosurgery, boron neutron capture therapy, photodynamic therapy and radio-immunotherapy, may contribute to the outcome of therapy in the future.

REFERENCES

1. Case JT. History of radiation therapy. In: Buschke F. ed. Progress in radiation therapy. New York, London: Grune & Stratton, 1958: 13–41.
2. Lederman M. The early history of radiotherapy: 1895–1939. Int J Radiat Oncol Biol Phys 1981; 7: 639–48.
3. Freund L. Ein mit X-Strahlen behandelten Fall von Naevus pigmentosus piliferus. Wien Med Wochenschr 1987; 47: 428–34.
4. Thames HD. Early fractionation methods and the origin of the NSD-concept. Acta Oncol 1988; 27: 89–103.
5. Krogius A. Über einen mit Röntgenstrahlen behandelten Fall von Schädelsarkom. Acta Klin Chir 1903; 71: 97–110.
6. Buschke F. Radiation therapy: the past, the present, the future. Am J Roentgenol Radiat Ther Nucl Med 1970; 108: 236–46.
7. Miescher G. Zur Roentgentherapie der Hautcarcinome. Schweiz Med Wochenschr 1929; 2: 1225.
8. Holthusen H. Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden. Strahlentherapie 1936; 57: 254–69.
9. Quimby EH. The history of dosimetry in roentgen therapy. Am J Roentgenol 1945; 54: 688–703.
10. Kogelnik HD. Gottwald Schwarz. In: Ellegast HH, Kogelnik HD, Strasser E. eds. Hundert Jahre Medizinsche Radiologie in Österreich. Wien, München, Bern: Verlag Wilhelm Maudrich, 1995; 65–71.
11. Regaud C. Influence de la durée d'irradiation sur les effects déterminés dans le testicule par le radium. Compt Rend Soc Biol Paris 1922; 86: 787–95.
12. Regaud C, Coutard H, Hautant A. Contribution au traitement des cancers endolaryngés par les rayons—X. X Internat Congr d'Otol 1922: 19–22.
13. Coutard H. Roentgen therapy of epitheliomas of the tonsillar region hypopharynx and larynx from 1920 to 1926. Am J Roentgenol 1932; 28: 313–31.
14. Schinz HR. Gegenwärtige Methoden des Krebsbestrahlung und ihre Erfolge II. Verteilte Dosis. Strahlentherapie 1930; 37: 31–49.
15. Coutard H. Principles of x-ray therapy of malignant disease. Lancet 1934; July 7: 1–8.
16. del Regato JA, History and Heritage. Henri Coutard. Int J Radial Oncol Biol Phys 1987; 13: 433–43.
17. Paterson R. The radical x-ray treatment of the carcinomata. Br J Radiol 1936; 9: 671–9.
18. Forssell G. Radiotherapy of malignant tumours in Sweden. Br J Radiol 1930; 3: 198–234.
19. Nielsen J. Fundamental results and permanent cure following roentgentherapy of intralaryngeal carcinoma. Clin Radiol 1951; 2: 29–38.
20. Engelstad RB. Stråleterapi. Johan Grundt Tanum, Oslo 1946. (In Norwegian)
21. von Bonsdorff B. The history of medicine in Finland 1828–1918. vol 3. In: The history of learning and science in Finland. Soc Scient Fenn, Helsinki, 1975.
22. Jansson G. Tidsfaktorns betydelse vid röntgenbehandling. Nord Med 1942; 13: 731–4.
23. Holsti LR. How radiation oncology emerged as a speciality in Finland. Int J Radiat Oncol Biol Phys 1995. (in press)
24. Mustakallio S. Über die Möglichkeiten der Röntgentherapie bei der behandlung des Brustkrebses. Acta Radiol 1945; 26: 503–52.
25. Mustakallio S. Treatment of breast cancer by tumour extirpation and roentgentherapy instead of radical operation. J Fac Radiol 1954; 6: 23–6.
26. Mustakallio S. Conservative treatment of breast carcinoma – review of 25 year follow-up. Clin Radiol 1972; 23: 110–6.
27. Mustakallio S. Über das Larynx-und Hypopharynxkarzinom, ihre Röntgenbehandlung und die Ergebnisse der Therapie. Acta Radiol 1944; 25: 13–32.
28. Fletcher GH. The evolution of the basic concepts undelying the practice of radiotherapy from 1949 to 1977. Radiology 1978; 127: 3–19.
29. Kaplan HS. Historic milestones in radiobiology and radiation therapy. Semin Oncol 1979; 6: 479–89.
30. Baclesse F. Clinical experience with ultra-fractionated roentgen therapy. In: Buschke F, ed. Progress in radiation therapy. New York, London, 1958: 128–43.
31. Fletcher GH. Regaud lecture perspectives on the history of radiotherapy. Radiother Oncol 1988; 12: 253–71.
32. Paterson R. Studies in optimum dosage. Br J Radiol 1952; 15: 505–16.
33. Meredith WJ. Obituary. Ralston Paterson. Br J Radiol 1981; 54: 1122–3.
34. Peters LJ. In Memoriam Gilbert Hungerford Fletcher. Int J Radiat Oncol Biol Phys 1992; 23: 245–6.
35. Fletcher GH. Clinical dose-response curves of human malignant epithelial tumours. Br J Radiol 1973; 46: 1–12.
36. Fletcher GH. Keynote address: The scientific basis of the present and future practice of clinical radiotherapy. Int J Radiol Oncol Biol Phys 1983; 9: 1073–82.
37. Horiot JC. Obituary: Gilbert Hungerford Fletcher. Radiother Oncol 1992; 23: V.
38. Reisner A. Hauterythem und Röntgenbestrahlung. Ergeb Med Strahlenforsch 1933; 6: 1–60.
39. MacComb WS, Quimby EH. The rate of recovery of human skin from the effect of hard and soft roentgen rays or gamma rays. Radiology 1936; 27: 196–204.
40. Strandqvist M. Studien über die Kumulative Wirkung der Röntgenstrahlen bei Fraktionierung. Acta Radiol 1944; (Suppl 155).
41. Andrews JR, Moody JM. The dose-time relationships in radiotherapy Am J Roentgenol 1956; 75: 590–6.
42. duSault LA. Time-dose relationships in radiotherapy. In: Buschke F, ed. Progress in radiation therapy. New York, London: Grune & Stratton, 1958: 100–14.

43. von Essen CF. Roentgen therapy of skin and lip carcinoma. Factors influencing success and failure. Am J Roentgenol 1960; 83: 556–70.
44. Montague ED. Experience with altered fractionation in radiotherapy of breast cancer. Radiology 1968; 90: 962–6.
45. Holsti LR. An introduction to unconventional fractionation. Clinical experiences and future indications (excluding MFD). Proc Varians Fourth Europ Clinac Users Meeting, Malta May 25–26 1984, Zug, Switzerland 1984: 51–6.
46. Botstein C. Reduced fractionation in radiation therapy. Am J Roentgenol 1964; 91: 46–9.
47. Sambrook DK. Split-course radiotherapy in malignant tumors. Am J Roentgenol 1964; 91: 37–45.
48. Scanlon PW. Initial experience with split-dose periodic radiation therapy. Am J Roentgenol 1960; 84: 632–44.
49. Holsti LR. Clinical experience with split-course radiotherapy. A randomized trial. Radiology 1969; 92: 591–7.
50. Parsons JT, Thar TL, Bova FJ, Million RR. A re-evaluation of split-course technique for squamous cell carcinoma of head and neck. Int J Radiat Oncol Biol Phys 1980; 6: 1645–52.
51. Holsti LR, Mäntylä M. Split-course versus continuous radiotherapy. Analysis of a randomized trial from 1964 to 1967. Acta Oncol 1988; 27: 153–61.
52. Ellis F. Dose, time and fractionation: A clinical hypothesis. Clin Radiol 1969; 20: 1–7.
53. Fowler JF, Morgan MA, Silvester JA, Bewley DK. Experiments with fractionated x-ray treatment of the skin of pigs. I Fractionation up to 28 days. Br J Radiol 1963; 36: 188–96.
54. Bates TD, Peters LJ. Dangers of the clinical use of NSD formula for small fraction numbers. Br J Radiol 1975; 48: 793.
55. Orton CG, Ellis F. A simplification in the use of the NSD concept in practical radiotherapy (TDF). Br J Radiol 1973; 46: 529–37.
56. Fletcher GH, Barkley HT, Shukovsky LJ. Present status of the time factor in clinical radiotherapy. Part II. The nominal standard dose formula. J Radiol Electrol 1974; 55: 745–51.
57. Douglas BG, Fowler JF. The effect of multiple small doses fo x-rays on skin reactions in the mouse and a basic interpretation. Radiat Res 1976; 66: 401–26.
58. Thames HD, Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation. Implications for dose-survival relationships. Int J Radiat Oncol Biol Phys 1982; 8: 219–26.
59. Withers HR, Thames HD, Peters LJ. Differences in the fractionation response of acutely and late responding tissues. In: Kärcher KH, Kogelnik HD, Reinartz G, eds. Progress in radio-oncology II. New York: Raven Press, 1982: 287–96.
60. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships for normal tissue response. Int J Radiat Oncol Biol Phys 1982; 8: 1981–97.
61. Turesson I, Thames HD. Repair capacity and kinetics of human skin during fractionated radiotherapy: erythema, desquamation and teleangiectasia after and 5 year follow-up. Radiother Oncol 1989: 169–88.
62. Ang KK, Peters LJ. Concomitant boost radiotherapy in the treatment of head and neck cancers. Semin Radiat Oncol 1992; 2: 31–3.
63. Saunders MI, Dische S. Continuous hyperfractionated, accelerated radiotherapy. Semin Radiat Oncol 1992; 2: 41–4.
64. Edsmyr F, Andersson L, Esposti PL, Littbrand B, Nilsson B. Irradiation therapy with multiple small fractions per day in urinary bladder cancer. Radiother Oncol 1985; 4: 197–203.
65. Horiot JC, LeFur R, Schraub S, et al. Status of the experience of the EORTC cooperative group of radiotherapy with hyperfractionated and accelerated radiotherapy regimes. Semin Radiat Oncol 1992; 2: 34–7.
66. Parson JT. Hyperfractionation for head and neck cancer. Int J Radiat Oncol Biol Phys 1988; 14: 649–58. 1992; 2: 31–33.?
67. Maciejewski B, Preuss-Bayer G, Trott KR. The infleunce of the number of fractions and of the overall treatment time on local control and the late complication rate in squamous cell carcinoma of the I larynx. Int J Radiat Oncol Phys 1983; 9: 321–8.
68. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27: 131–46.
69. Fowler JF. Brief summary of radiobiological principles in fractionated radiotherapy. Semin Oncol 1992; 2: 16–21.
70. Fowler JF, Lindstrom MJ. Loss of local control with prolongation in radiotherapy. Int J Radiat Oncol Biol Phys 1992; 23: 457–67.
71. Fowler JF. The effect of overall treatment time in radiotherapy for localized prostate carcinoma. Int J Radiat Oncol Biol Phys 1991; 21: 1097–8.
72. Kajanti M, Holsti LR, Holsti P, Möykkynen K. Effect of split-course radiotherapy on survival and local control in advanced localized prostatic carcinoma. Int J Radiat Oncol Biol Phys 1993; 26: 211–6.
73. Tubiana M. Repopulation in human tumors. A biological background for fractionated radiotherapy. Acta Oncol 1988; 27: 83–8.
74. van der Schueren E, van den Bogaert W, Vanytsel L, van Limbergen E. Radiotherapy by multiple fractions per day (MFD) in head and neck cancer: acute reactions of skin and mucosa. Int J Radiat Oncol Biol Phys 1990; 19: 301–11.
75. Harari PM. Adding dose escalation to accelerated hyperfractionation for head and neck cancer: 76 Gy in 5 weeks. Semin Radiat Oncol 1992; 2: 58–61.
76. Holsti LR, Kajanti M, Blomqvist C, Lehtonen H, Wiklund T. Dose escalation in accelerated hyperfractionation for advanced head and neck cancer. In: Kogelnik HD, ed. 5th International Meeting on Progression in Radio-Oncology. Salzburg: Monduzzi Editore, Bologna, 1995: 175–9.
77. Puck TT, Marcus PI. Action of x-rays on mammalian cells. J Exp Med 1956; 103: 653–66.
78. Thomlinson RH, Gray LH. The histological structure of some human lung cancers and the possible implication for radiotherapy. Br J Cancer 1955; 9: 539–49.
79. Churchill-Davidson I, Sanger C, Thomlinson RH. High-pressure oxygen and radiotherapy. Lancet 1955; 2: 1091–5.
80. Dische S. A review of hypoxic cell sensitization. Int J Radiat Oncol Biol Phys 1991; 20: 147–52.
81. Peckham MJ. The scope of radiotherapy research. In: Steel GG, Adams GE, Peckham MJ, eds. The biological basis of radiotherapy. Amsterdam, New York, Oxford: Elsevier, 1983: 1–12.
82. Withers HR. Biological basis of radiation therapy for cancer. Lancet 1992; 339: 156–9.
83. Hall EJ. Molecular biology in radiation therapy: The potential impact of recombinant technology on clinical practice. Int J Radiat Oncol Biol Phys 1994; 30: 1019–28.
84. Kaplan HS. The radical radiotherapy of regionally localized Hodgkin's disease. Radiology 1962; 78: 553–61.
85. Kaplan HS. Prognostic significance of the relapse-free interval after radiotherapy in Hodgkin's disease. Cancer 1968; 22: 1131–6.
86. du V Tapley N. Results of conventional radiation therapy. In: Fletcher GH, Nervi C, Withers HR, eds. Biological Bases and Clinical implications of Tumor Radioresistance, New York, Paris, Barcelona, Milan: Masson Publ Inc USA; 1983: 281–90.

87. Tubiana M. The role of local treatment in the cure of cancer. Eur J Cancer 1992; 28A: 2061–9.
88. Dische S. Radiotherapy in the nineties. Increase in cure, decrease in morbidity. Acta Oncol 1992; 31: 501–11.
89. Gelber RD, Goldhirsch A. Meta-analysis: The fashion of summing-up evidence. Part I. Rationale and conduct. Ann Oncol 1991; 2: 461–8.
90. Einhorn J, Thorén M. The place of radiation therapy in the reorganization of cancer care: An international study. Int J Radiat Oncol Biol Phys 1975; 1: 77–84.
91. Buschke F. What is a radiotherapist? Radiology 1962; 79: 319–21.
92. Bush RS. The complete oncologist. Int J Radiat Oncol Biol Phys 1982; 8: 1019–28.
93. Horwich A. Radiotherapy update. Br Med J 1991; 304: 1554–7.
94. Tobias JS. Clinical practice of radiotherapy. Lancet 1992; 339: 159–63.
95. Leibel SA. The biologic basis for conformal three-dimensional radiation therapy. Int J Radiat Oncol Biol Phys 1991; 21: 805–11.