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Historical essentials influencing the development of radiooncology in the past 100 years

S. Birkenhake and R. Sauer

Strahlentherapeutische Klinik der Friedrich Alexander Universität Erlangen-Nürnberg, Universitätsstr. 27, D-91054 Erlangen (Germany), Fax +49 9131 859 335

Abstract. An overview of the development in the recent 100 years is given. The work of the most important pioneers is described. Both technical preconditions and radiobiological fundamentals influencing advances in radiotherapy are lined out. It is shown that many modern techniques and therapeutical strategies have their origin in the beginning of radiotherapy and that this is the case for many unsolved problems as well.
Key words. Radiotherapy; history.

Introduction

The aim of this article is to point out some important basics of radiological history, which may have influenced modern radiooncology. This undertaking is, of course, subjective and is probably incomplete. However, there were a number of important developments in those times and they should be mentioned.

Pioneers of the early period

The idea of using the biological effects of radioactivity for treatment of proliferating, solid tumours is nearly as old as the discovery of X-rays. The effects of radiation on living tissues were known from the beginning. Some well known examples are Pierre Curie, who sustained burns to his hand after he had carried radium tubes, and his wife, Marie Curie, who died in 1934 at the age of 67 of aplastic anaemia, which was in all probability caused by her exposure to radium. Becquerel carried uranium, sent to him by the Curies, for several days near his body and noticed a skin reaction[15]. X-ray-related sequelae led regularly to amputation of fingers and hands of the pioneer technicians and physicians[1].
The first person to make use of X-rays for a therapeutical purpose was probably Leopold Freund in Austria[6]. His patient was a five-year-old girl, who suffered from *naevus pigmentosus*. She was treated in 1896 in Vienna. Schiff, who was the doctor responsible for the girl, published this case report in 1901; 70 years later Fuchs and Hofbauer described late effects and confirmed the cure of the patient[7]. The girl was born with a *naevus pigmentosus* originally covering her whole back. First the cranial and afterwards the caudal part were treated, in twelve treatments each. Acute dermatitis and hair-loss were noticed. In the following years several ulcers developed, but were treated successfully. At the age of 75 the woman was free of ulcer and showed no *naevus*.
Kümmell reported in 1898 on 16 patients who had been treated with X-rays because of lupus erythematosus. Gocht published in 1899 the 'Lehrbuch der Röntgen-Untersuchung,' and one chapter was concerned with the therapeutical applications of X-rays. He mentioned the pain-alleviating effect of radiation[18].
In 1899 in Stockholm Tage Sjögren and Tor Stenbeck treated patients with cancer[2,14]. Tor Stenbeck cured a patient suffering from basal cell carcinoma with X-rays. He photographed the man before and after 99 treatments applied over a period of several months. He remarked he 'had never seen an *ulcus rodens* treated in all its extensions so successfully and with such a small induration'. Sjögren treated a similar case and photographed his patient as well. He noticed that the cancer was healed except for the radiation border after 50 treatments. Therefore radiation was continued but a heavy reaction then occurred, which later disappeared. His comments are still important: 'I want only to mention that the correct dosage of roentgen ray is at present very difficult to determine. One has no safe method to measure the intensity of the active agent. One has therefore to work by intuition, if I may say so, only on the basis of the experience one has been able to collect.' Even nowadays dosage and treatment schemes are generally a result of experience. The only significant difference is that we have fortunately much more experience, profiting from both the successful and the partly disastrous experiences of several generations of radiotherapists (table 1).
The first successful treatment by brachytherapy was performed by Goldberg and London in 1903 in St. Petersburg[8]. They treated two patients with a basal cell carcinoma of the face. They, like Wickham and Degrais in Paris (1904), used radium. From 1908 to 1923 Wickham and Degrais documented several distinct responses of inoperable epithelioma treated by radium brachytherapy using superficial applicators. In contrast to these surface applications, Strebel in Munich was the first to use an interstitial technique[21]. He published a treatment involving interstitial afterloading brachytherapy in 1903. His idea was to avoid the skin lesions due

Table 1. Some 'pioneers' of radiotherapy (for details see text).

1896	Leopold Freund/Österreich: treatment of naevus pigmentosus
1898	Kümmel/Hamburg: treatment of lupus erythematosus
1898	Gocht: pain-alleviating effect of X-rays
1899	Sjögren/Stockholm: treatment of a squamous-cell carcinoma of the cheek
1899	Stenbock/Stockholm: treatment of a basal cell carcinoma of the nose
1903	Goldberg and London: treatment of two patients suffering from basal cell carcinoma of the face by radium-brachytherapy
1903	Strebel/München: first interstitial afterloading
1904	Beck/London: collimators/shielding

to external radium application by inserting an aluminium rod, which contained the radium, directly into the tumour. Beck in London in 1904 used collimators and shielding apparatus to protect healthy organs from X-ray-induced injury[1].

The central idea of radiology, to use a therapy which is relatively tumour-toxic on the one hand but on the other hand avoids unwanted effects on healthy organs, had its origin in the very early beginnings of radiotherapy.

Technical propositions

From the technical point of view two different kinds of X-ray application can be distinguished. Using radioactive sources, which work near the target volume is defined as brachytherapy. In contrast to this it is possible to use distant sources, for instance cobalt-60 or a generator. This is teletherapy. Both started very early and have evolved in parallel. Teletherapy is divided according to the X-ray generating voltage into orthovoltage (up to 300 kV) and megavoltage (above 1 MV).

Teletherapy

In teletherapy low energy means low penetration of the irradiated volume. Consequently the first successes were against superficial tumours. In the beginning gas tubes and later coolidge tubes were used. With these machines it was possible to perform orthovoltage therapy. At the time this was considered deep therapy, but today orthovoltage is only used for superficial treatment, because dose distribution in more extensive target volumes does not meet the necessary requirements of today's radiotherapy. However, in the 1920s the so-called Holfelder cannons were very common. In 1931 the Memorial Hospital in New York installed a 750 kV machine. One of the first supervoltage installations, dating from 1944, can be found in St. Bartholomew's Hospital, London[15]. Van de Graaf generators based on an electrostatic principle and using a rotating bell for producing high voltage, allowed treatment with energies up to 2 MV. One was installed in the Royal Marsden Hospital, London in 1961[15]. By the late 1940s the first radiotherapy linear accelerators became available. Their precursors were those used for research purposes in the late 1920s. With increasing energies, up to more than 40 MV, more homogeneous dose distributions were available and led to higher standards. However, no real advantage could be shown for energies above 20 MV, and the so-called betatrons, which were designed for clinical applications with energies up to 45 MV, did not become established.

Brachytherapy

The earliest brachytherapy treatments were superficial applications of radium. This was termed mould therapy. Intracavitary treatments of cancer of the cervix and vagina took place very soon. As already mentioned interstitial radiation was also introduced after a short time. So the three major types of brachytherapy existed from early on: interstitial (source within the tumour), intracavitary (source within a natural cavity, e.g. vagina), and mould therapy. The first two modalities are most popular today. Two further examples of interstitial regimens are given here: Cade from London described in 1922 the treatment of prostate cancer by placing radium needles into the tumour and leaving them in position for three weeks[4]. He also specified a method for interstitial implants for breast cancer, which was performed in the Westminster Hospital[4].

In those days, there was no dosimetry. The inability to calculate the applied dose can, because of the continuously decreasing activity of the sources, be disastrous. One of the first systems used for dosimetry of surface moulds was the Manchester system devised by Paterson and Parker in the 1930s, which allowed them to calculate the isodose distribution depending on the diameter of a circular radium source and the treatment distance of the mould[15,16]. Gradually radium was replaced by other sources like cobalt-60, caesium-136, gold-198, and in particular iridium-192, which is still used nowadays. All these systems had the disadvantage that they had to be handled manually. It was Henschke who developed the first remote-controlled brachytherapy after loading machine for treating gynecologic tumours[9]. He applied cobalt-60 at a low dose rate (dose rates are the emitted dose per time and are an important factor in brachytherapy). Two major types are distinguished: low dose rate (LDR) with 0.4–2 Gy/h and high dose rate (HDR) exceeding 2 Gy/min. Both methods are used today. HDR became available with the development of the Cathetron in 1963, which again used cobalt-60. Today brachytherapy plays an important role in the cure of solid cancers in both its intracavitary and interstitial modality. Remote-controlled systems are used and applied doses are calculated by computer.

So technical progress led to improvements in both quality of treatment and safety for therapists.

Influence of radiobiology

The effects of radiation on tissues have been classified into three categories: acute (first six months), subacute (up to six months), and late effects. Generally they depend on the radiation dose given, treatment time, and the tissue properties such as the speed of cell replacement.

Radiosensitivity of healthy organs limits the possibilities of radiotherapy. A compromise between tumour toxicity and damage to healthy tissue must always be made. In order to enlarge the therapeutic range various fractionation schedules have been used. Fractionation means dividing the required overall dose into multiple single doses. In general, fractionation lowers acute side effects because it allows for regeneration of healthy tissue, which itself accelerates during the first two weeks of treatment. However, a prolonged treatment time cannot prevent late sequelae and may lead to growth of tumour during therapy. To find the optimal combination of dose, treatment time and fractionation for each type of cancer is one of the central questions of radiooncology. Though radiobiology as a distinct scientific subject is pretty young, in 1923 Regaud had already analysed the correlation between the duration of radiation and its biological effects[17]. He could show that 28 days after radiation with 4.2 mCi, sterilization in rams was complete in contrast to rams after a 42 hours lasting exposure to 13 mCi. So he proved that a prolonged irradiation could be superior to a shorter one. Regaud himself and Coutard developed this idea and suggested the use of daily fractions, in contrast to the majority at that time who still used single-fraction schedules.

The most modern mathematical formulation was published by Fowler[5]. Making several assumptions he proposed the 'linear quadratic model' which is described by the equation:

$$S = e^{-(\alpha D + \beta D^2)}$$

with S = Survival, D = Dose, α = fraction of non-reparable component of cells killed and β = fraction of reparable component of cells killed.

The values for α and β must be determined in animal experiments for each tissue type in which cell death is observed in proportion to the applied dose. The model proposes that radiation-induced damage depends on the calculated α/β-ratio. Generally speaking, acutely-reacting tissues have a high α/β-ratio whereas tissues showing later damage have a low α/β-ratio (below 5 Gy). Based on the linear quadratic model Withers et al. published an equation which allows a comparison of two treatment regimens:

$$\frac{D_r}{D_x} = \frac{\alpha/\beta + d_x}{\alpha/\beta + d_r}$$

with D_r = known (reference) total dose necessary to achieve a certain biological effect, d_r = known single dose, D_x = new total dose, d_x = new single dose[23].

With a known, reliable radiation schedule this formula should allow the calculation of new combinations of overall and single doses. However, the model still does not reflect real biology, because it does not contain the important factor of time. Though it takes fractionation into account it does not consider whether the single fraction is given once or twice a day. Consequently, standard fractionation and total doses required to control a tumour are based on empirical approaches and experience.

Two important elements of modern radiotherapy: adjuvant radiation and radiochemotherapy

Modern oncological treatments always utilise both surgery and radiotherapy and chemotherapy, the proportions varying from tumour to tumour, depending on their stage and histology. Although the combination of surgery and X-ray beam has proven useful for many kinds of cancer, the indication for a pre- or postoperative radiation is still debated even today. This dialogue among oncologists, today very often influenced by political factors, was already taking place in the early years of this century.

An example for these discussions is given by Wintz from Erlangen in the 'Handbuch der gesamten Strahlenheilkunde', published by P. Lazarus in 1931. To his mind, small breast cancer needed surgery only, whereas advanced cases required postoperative radiation. He mentioned that 'an axilla-dissection is unnecessary, because radiotherapy is a reliable method, which avoids contractures'. He, as well as Holfelder from Frankfurt, preferred radiation of the axilla to lymphadenectomy. At present the number of lymph node metastases is regarded as one of the most important prognostic factors in breast cancer and influences adjuvant therapy. A simultaneous dissection of the ipsilateral axilla is usually carried out. If this is done adequately (a sufficient number of nodes are removed) it is possible not to have to irradiate the axilla. The discussion of those early years was strongly influenced by G. Jüngling from Tübingen. In 1913 he recognized a deterioration in patients who had been treated with postoperative radiation, and confirmed this in 1919[10]. In the above mentioned handbook by Lazarus, he emphasized that high toxicity is to be expected and refused to indicate adjuvant radiotherapy of breast cancer as a general treatment. To his mind, only incompletely removed tumours needed radiation[19].

Due to the putative failure of radiotherapy, in the following years many European centres rejected adjuvant radiotherapy of breast cancer, whereas in America it became standard therapy.

For this reason the metaanalysis of Hintze from Berlin, published in 1931, was based predominantly on data reported by American hospitals[10]. Hintze made great

Table 2. Results of adjuvant radiotherapy of breast cancer.

	n[1]	5 year[2]	10 year[2]
OP only	4952	28.4%	17.3%
OP + RT	2822	37.9%	22.1%

Metaanalyses by Hintze, 1931. [1]Number of patients involved, [2]'success' after five and ten years, respectively.
OP = operation, RT = radiotherapy.

Table 3. Patients treated with cervical radiation or neck dissection after resection of cancer of the oral cavity.

	RT[1]	Neck dissection[1]
Tongue	19/25 (67%)	6/15 (40%)
Sublingual reg.	7/10 (70%)	1/2 (50%)
Cheek	28/58 (35%)	0/4 (0%)

[1]Patients without symptoms after three years. Data published by Regaud 1928.

demands on the single publications which he used in his analysis. He requested at least 100 treated patients and a follow up of at least five years of 90% of all patients (conditions which are frequently not met in some recent publications). Hintze could show that patients treated with postoperative radiotherapy benefited (see table 2). He concluded: 'It is the duty of the attending physician to advise postoperative irradiation'.

Another example is the treatment of head and neck cancer. In the handbook by Lazarus Berven published data from patients with cancer of the oral cavity. In all patients the primary tumour was removed. Afterwards either a lymphadenectomy or a radiation of the cervical lymph nodes was performed. Although the number of patients is small, even in cases with metastatic lymph nodes radiotherapy was superior to neck dissection alone (see table 3)[3]. Berven cited Regaud, who confirmed this with 91 patients suffering from the same cancer.

In the above mentioned handbook of Lazarus the editor himself made some noteworthy remarks concerning differential indications of radiotherapy[13]. He distinguished between absolute, relative and co-operative indications. From his point of view an absolute indication for radiation was given by large, inoperable cancer, recurrence, counterindication against surgery (e.g. due to the age of patient), and for palliative therapy of advanced tumours. A relative indication would be given by tumours which could be treated with surgery and radiotherapy with similar results, for instance skin cancer. Co-operative indication covered all cases treated by pre-, intra- and postoperative radiation, for example breast cancer.

Nowadays, both definitive and adjuvant radiotherapy are performed regularly on many tumours. Concomitant chemotherapy is used to increase radiosensitivity and improve locoregional control. This method was already being tested in the 1920s. R. Werner from Heidelberg published in 1931 an overview of possible combinations with radiotherapy[21]. He mentioned hyperthermia, intratumoural injections, and systemically-given arsenic, and rejected iodine and silicates. He cited Opitz, who reported in 1926 a combination of radiation and olefins and achieved encouraging results. Werner himself experimented in 1921 with dextrose i.v. and radiation afterwards. He showed a glycolytic effect in the swelling cells of carcinomas and sarcomas, but no case of healing. He also used boracic choline for inoperable cancer. In 1926 he gave a lecture in which he mentioned survival rates of 14%, 8% and 4% after 3, 5 and 10 years, respectively. Though this investigation included 741 patients, the evaluation of these results is difficult because he did not distinguish between different tumour entities. Similar results were reported by Mayer (1926), who used 25% dextrose. Kahn added dextrose and bismuth and recognized a therapeutic response by previously refractive tumours[21].

Today, radiochemotherapy is still far from being standard therapy. This is certainly due to the fact that for many years no development took place. Chemotherapy was for a long time a domain of internal physicians and it was very difficult for a radiotherapist to treat patients not only by beam, but also with drugs. However, this is changing and nowadays many studies are examining the benefit of a combination of chemotherapy and radiation.

Conclusion

We pointed out some landmarks in the history of radio-oncology, landmarks which were, in our opinion, fundamental for the development of modern techniques and scientific approaches. Some of the problems encountered at the very beginning are not yet solved e.g. the question of the optimal duration of therapy. Even concrete indications are sometimes still in dispute, illustrated by the adjuvant therapy of breast cancer.

The example of the betatron shows that some investigations did not develop as they were supposed to. Progress in radiooncology depends on technical advancement more than almost any other branch of medicine. Consequently both physicians and doctors are responsible for the current state of radiotherapy. In the beginning they paid a high price for their research.

Whereas in the beginning the 'pioneers' were 'all-round-scientists', by and by special branches arose. On the one hand this certainly enabled in-depth research of detailed aspects. On the other it reduced the overview due to the lack of common information. One of the most important tasks of modern oncology may be to bring all information from the different special branches of medicine together.

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