A BRIEF HISTORY OF FRACTIONATION IN EXTERNAL-BEAM RADIOTHERAPY

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Contents

1. Introduction

Throughout the history of external beam radiotherapy, the practice of fractionation of treatments has gone through many phases, ranging from extreme hyperfractionation with about 100 fractions to extreme hypofractionation with just a single fraction. In this paper we will review how and why we have experienced these widely different practices and what we can expect in the future.

2. Early Experiences

Within a few months after Roentgen's discovery in 1895, x rays began to be used, rightly or wrongly, to treat a wide variety of medical ailments such as eczema, acne, varicose veins, leprosy, tuberculosis, keloids, neuralgia, migraine, epilepsy, hirsutism, and cancer. The most important, of course, has been the treatment of cancer. Although there is considerable controversy as to when the first cancer treatments began, it is claimed that the first attempt at this was on January 29, 1896, when Emile Grubbé, a medical student in Chicago, who had established a small business making x-ray tubes, initiated a course of treatment on a Mrs. Rose Lee, who had a breast cancer. He delivered a series of 18 one-hour treatments with the breast in contact with the x-ray tube. Treatments were terminated after the patient developed painful skin burning. It is not clear if the treatments provided any local control, however, since the patient died of systemic disease within one month. There is some considerable dispute as to whether this was the *first* application of x rays to treat cancer, however, since Grubbé did not document his claim until 1933(1). In contrast, Victor Depeignes, from Lyon, France did, immediately, document his treatment of a stomach cancer patient (his neighbor!) starting on July 4, 1896(2). He delivered 80 sessions of 15-30 minutes at two sessions per day and reported a reduction in pain and tumor size, but the patient died before the planned course of treatment could be completed. The first documented *successful* cancer treatment was for a patient treated by Tor Stenbeck, in Sweden, for a basal-cell carcinoma (see fig. 1), using a total of 99 fractions!(3).

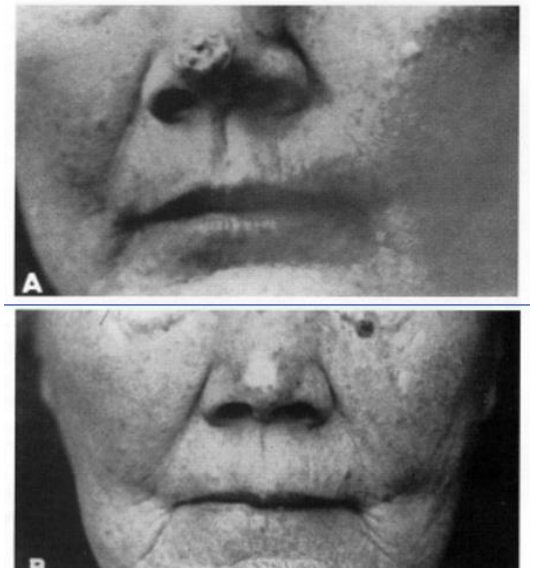
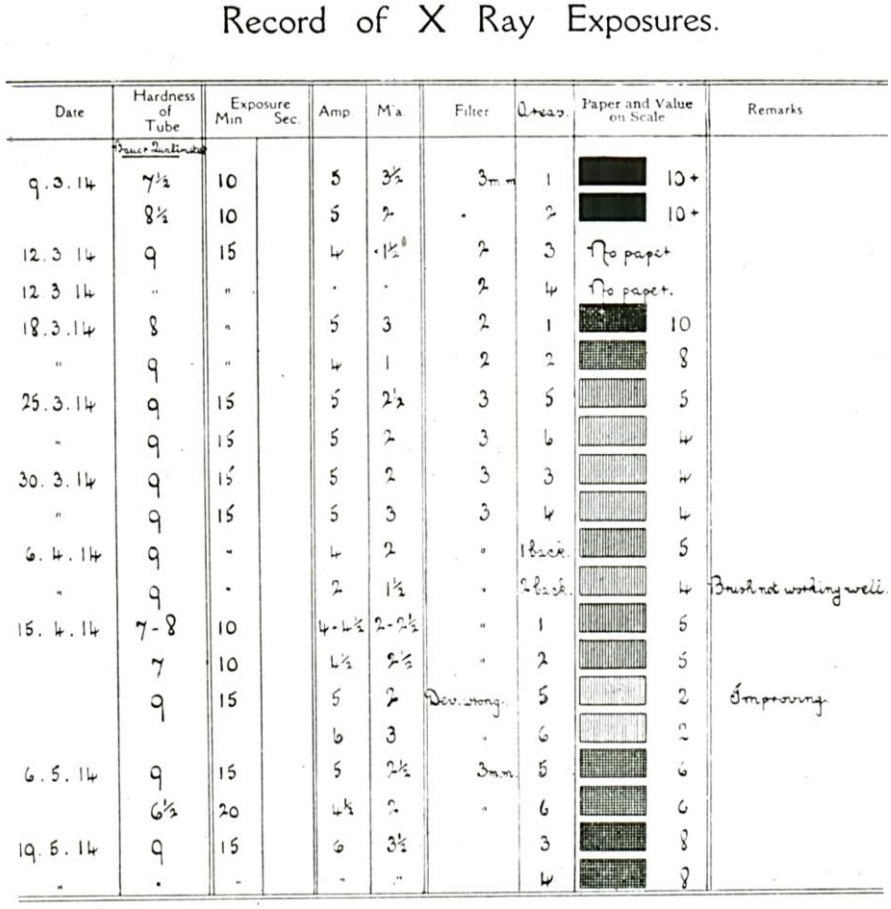


Fig. 1: Stenbeck's patient before treatment (A) and on follow up 30 years later (B).

Such extreme hyperfractionation was common in these early days of radiotherapy, not because it was believed that, *radiobiologically*, such fractionation was necessary, but because of *physical* constraints at the time. Firstly, the output from

early x-ray units was very low, and treatment sessions lasting many days would likely have been necessary to deliver enough dose to control the cancers. Secondly, it was because outputs of these primitive x-ray machines varied considerably from use to use, so exposures were highly unpredictable. It was only after completion of each treatment session that the "dose" delivered could be determined using, for example, the blackening of photographic paper strips placed on the skin of the patient to determine the exposure (see fig. 2).



Record of X Ray Exposures.

Date	Hardness of Tube (Spec. Radiator)	Exposure Min.	Exposure Sec.	Amp.	M'a.	Filter	Area.	Paper and Value on Scale	Remarks
9.3.14	7½	10		5	3½	3 m m	1	10+	
	8½	10		5	2	"	2	10+	
12.3.14	9	15		4	1½	2	3	No paper	
12.3.14	"	"		"	"	2	4	No paper.	
18.3.14	8	"		5	3	2	1	10	
"	9	"		4	1	2	2	8	
25.3.14	9	15		5	2½	3	5	5	
"	9	15		5	2	3	6	4	
30.3.14	9	15		5	2	3	3	4	
"	9	15		5	3	3	4	4	
6.4.14	9	"		4	2	"	Black.	5	
"	9	"		2	1½	"	Black.	4	Bush not working well.
15.4.14	7-8	10		4-4½	2-2½	"	1	6	
	7	10		4½	2½	"	2	5	
	9	15		5	2	Dev. wrong.	5	2	Improving.
				6	3	"	6	2	
6.5.14	9	15		5	2½	3 m m	5	6	
	6½	20		4½	2	"	6	6	
19.6.14	9	15		6	3½		3	8	
"	"	"		"	"		4	8	

Fig. 2. Typical treatment record of an early course of radiotherapy, showing that the exposure (as determined by the blackening of photographic paper strips) varied considerably from day-to-day.

It was not until 1914, with the development of the hot-cathode X-ray tube by William D. Coolidge, that high, predictable, exposures became possible. There followed several years of uncertainty regarding the best fractionation to use.

There were essentially two schools of thought about fractionation: the single-fraction, *Erlangen School*, headed by Hermann Wintz,(4), which believed that only with single fractions could you cure a cancer, and the multiple-fraction, *Paris School*, headed by Henri Coutard, which believed that only by fractionation could you cure cancers without exceeding normal tissue tolerance. According to the single-fraction school, fractionated treatments were inferior because they allowed cancer cells to proliferate during the course of treatment and, to overcome this, would have required doses to be delivered that were so high they would exceed the tolerance of surrounding normal tissues. They considered fractionated radiotherapy to be the "*primitive method*" and "*weak irradiation.*" The multi-fraction school, on the other hand, based their belief on the 1919 radiobiological experiments of Claude Regaud, in France, published in 1922 (5). He found that a ram could be sterilized by irradiation of its testes without exceeding the tolerance of the skin of the scrotum, only if the treatments were fractionated. They argued that the testes could be considered a good model of a proliferating tumor and that the skin represented normal tissues. Hence, only with fractionation could high enough doses be delivered to cure cancers without exceeding normal tissue tolerance. This controversy continued until 1932 when the radiotherapy world realized that fractionation was essential after Coutard, at the Institut Curie in Paris, published his excellent results with fractionated therapy (6).

Although Coutard's work demonstrated the importance of fractionation, it did not establish an appropriate fractionation technique, since he and his colleagues had used a wide variety of fractionation schedules. With regard to fractionation, the overall duration of their courses of therapy and the number of fractions was varied dependent upon the size of the tumor and ranged from as short as one week to as long as six or seven weeks, with appropriate dose/fraction, always treating seven

days/week and often at two fractions/day. Another important consideration was the dose rate they employed. All the patients were treated at low dose rate, not necessarily because Coutard and his colleagues believed that this would be superior to high dose rate, but because the relatively primitive equipment at that time available to them at the Institut Curie could only be operated at low dose rate. Treatment sessions typically lasted 30-60 minutes. It was not until François Baclesse took over from Coutard as head of the Institut Curie in 1937 using more modern equipment that a standard fractionation method was established of about 30 high dose rate fractions of about 2 Gy delivered over about six weeks, often referred to as the "*Paris*" technique (7). Many radiation oncologists visited the Institut Curie to learn from their expertise and this fractionation schedule became the standard of treatment in many countries for the next 50 years or more. One of the students of Baclesse was Gilbert Fletcher who, in 1948, introduced such a treatment regime when he was appointed to the M. D. Anderson Cancer Center in the USA, where it remained the most common fractionation for the next 60 years-or-so (7). We now know that there is a good *radiobiological* reason for the success of such a fractionation scheme, and this relates to the difference in the ability of late-reacting normal tissue cells and tumor cells to repair sublethal damage, as illustrated by the cell-survival curves in fig. 3 (8). This shows that, at low doses (and, therefore, low doses/fraction), the cells of late-reacting normal tissues exhibit a higher survival rate than those of typical cancers but this is reversed at high doses. There is a "window of opportunity" centered around about 2 Gy, where this advantage is most efficiently utilized.

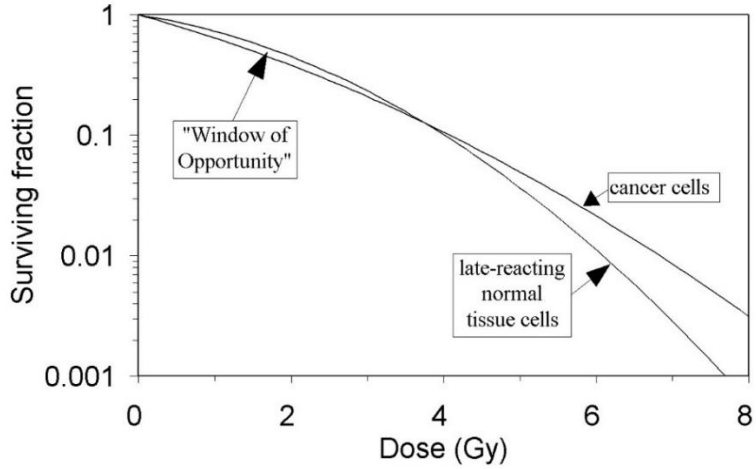


Fig. 3. Surviving fraction as a function of dose for late-reacting normal tissue and cancer cells, illustrating the "window of opportunity" centered about 2 Gy (8).

Just after World War II a somewhat different approach was more common in some countries, however, necessitated by the lack of sufficient treatment machines for each patient to have as many as 30 fractions. Most notable was the Ralston Paterson "*Manchester*" technique developed at the Christie Hospital, in which he delivered daily treatments of about 3-3.5 Gy over 3-4 weeks. After many years it was realized, however, that the *Manchester* technique was causing an unacceptable risk of late complications, and about 2 Gy fractions then became the standard (7). Because of many technical developments, however, this is not necessarily true today. So what has changed?

Almost all of the early clinical experience involved the use of relatively low-energy x rays in the range 80 – 300 kVp. With very poor depth-dose characteristics, this meant that the tumor often received a lower dose that the normal tissues surrounding it, especially the skin. Indeed, radiation therapy was often referred to as the "skin burning" treatment by potential patients and referring doctors. In that respect it did not have a good reputation and was often avoided in preference to much more debilitating surgery. It was not until the advent of skin-sparing Co-60 and linear accelerator radiotherapy in the mid-1950s that it became possible to consistently deliver higher doses to deep-seated tumors than to the intervening normal tissues. Although the vast majority of treatments continued with conventional fractionation at about 2 Gy/fraction, some new fractionation schemes began to emerge for specific applications.

3. Hypofractionataion

3.1. *Treatment of bone metastases*

With the availability of skin-sparing radiotherapy, it became possible to deliver single-field treatments to lesions not too deep below the surface without exceeding skin tolerance. Common among these was the treatment of painful bone metastases. Since these were usually not meant to be curative, just palliative, fractionation schemes were developed with fewer treatments at higher dose/fraction, which were more convenient for patients. Over the years, numerous clinical trials were developed to

study various fractionation schemes such as 10 fractions of 3 Gy, five fractions of 4 Gy, four fractions of 5 Gy, and even one fraction of 8 Gy. Indeed, an international survey published in 2009 found over 100 different hypofractionation schemes that had been used to treat bone metastases (9).

Such hypofractionation schemes were not confined to palliative therapy, however. By using stereotactic techniques radiation, with beams directed from multiple directions with the patient immobilized in order to minimize the dose to normal tissues and make the effective dose (e.g. the Equivalent Uniform Dose) (10) less for normal tissues than for tumors, it became possible to deliver treatments at high dose/fraction without exceeding tolerance. This is illustrated *radiobiologically* in fig. 4, which shows that the window of opportunity widens considerably due to the physical geometrical sparing of normal tissues inherent with stereotactic radiotherapy and represented here as the geometrical sparing factor, *f*, where:

$$f = \frac{effective\ dose\ to\ normal\ tissues}{effective\ dose\ to\ tumor}$$

Note that it was assumed in fig. 3 that the effective dose to normal tissues was the same as that for the tumor. This was a reasonable assumption in the early days of megavoltage radiotherapy but, with the advent of highly conformal techniques such as stereotactic radiosurgery and stereotactic body radiation therapy (SBRT), it became possible to keep the effective dose to normal tissues less than that to tumors. As shown in fig. 4, even a modest geometrical sparing factor of just 0.8 widens the window of opportunity to over 10 Gy, making hypofractionation possible.

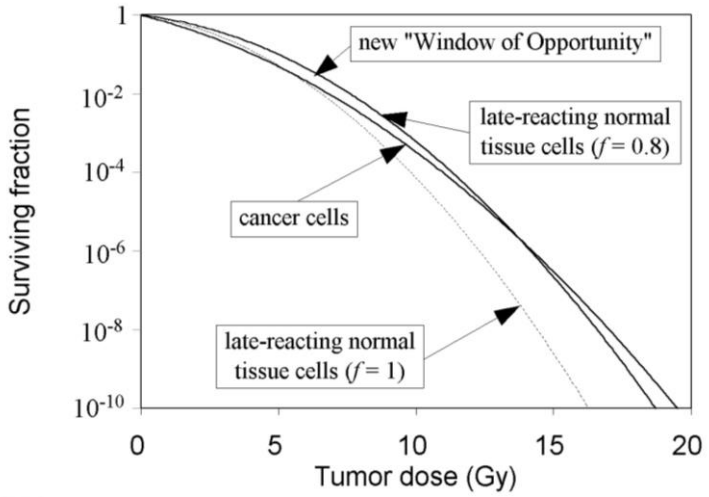


Fig. 4. Surviving fraction as a function of tumor dose for cancer cells and those late-reacting normal tissues, assuming a geometrical sparing factor of 0.8, illustrating that the "window of opportunity" widens to include doses over 10 Gy.

3.2 *Stereotactic radiosurgery*

In 1951, the Swedish neurosurgeon Lars Leksell introduced the concept of using single, very high doses of radiation employing multiple small beams directed at the lesion from multiple directions using stereotactic frame technology, for the treatment of small brain abnormalities, a technique now referred to as stereotactic radiosurgery (11). This led to his development of the gamma knife in the 1960s with which about 200 Co-60 sources, each with its own collimator, produced beams aimed at the lesion from different directions. Single doses as high as about 24 Gy (for very small lesions) were delivered. Due to the success of gamma knife radiosurgery, existing linear accelerators began to be modified to mimic the gamma knife treatments in the 1980s (12) and hypofractionation schemes began to be investigated ranging from 10 fractions of 4 Gy to 3 fractions of 12 Gy (13). The success of intracranial hypofractionated stereotactic radiosurgery with linear accelerators led to the development of hypofractionated stereotactic radiotherapy to other body sites.

3.3. *Stereotactic body radiation therapy*

The 1990s saw the development of stereotactic body frames which, along with advanced imaging and treatment planning technologies, made it possible to deliver high doses at high dose/fraction to extracranial targets without exceeding normal tissue tolerance known as Stereotactic Body Radiation Therapy (14). Since then, doses/fraction from about 6 – 30 Gy in 1 – 5 fractions have become standard practice for the treatment of many cancers, with dozens of clinical trials and hundreds of publications describing SBRT techniques and clinical results. In addition to the convenience and cost-saving aspects of such hypofractionation, there is a potential radiobiological benefit for cancers that contain cells that exhibit a high ability to repair

sublethal damage i.e. have a low α/β ratio. Two such examples are prostate and breast cancers. For other cancers, typically exhibiting a high α/β, however, more fractions rather than fewer should be radiobiologically superior, and this was the basis for numerous clinical trials of hyperfractionation.

4. Hyperfractionation

Hyperfractionated radiotherapy refers to the use of more than the typical 30 fractions used in conventional fractionation. This means use of doses/fraction considerably lower than 2.0 Gy. One problem with simply reducing the dose/fraction, is that the course of therapy lasts considerably longer than the normal 5 – 7 weeks, thus allowing cancer cells to repopulate during the course of therapy. This may work for very slow growing cancers but would be disadvantageous for others. This has usually been avoided by the use of 2 – 3 fractions per day. Typical doses/fraction for these studies ranged from 1 – 1.6 Gy. The outcome of numerous clinical trials of hyperfractionation in the 1970 – 2000 period has been that there is no consistent demonstration of any benefit relative to conventional fractionation (15). Since treatment of patients several times each day is both inconvenient and costly, it is not surprising that such treatment regimens are rarely used today.

5. Accelerated Fractionation

An approach for the treatment of rapidly growing cancers, is to use the dose/fraction of conventional fractionation (about 1.8 – 2.0 Gy) but to treat at two fractions/day to approximately the same total dose (7). Unfortunately, this has generally run into the problem of excessive acute reactions, which has led to having to give the patient a 2 – 3 week rest half way through the course of treatment, thus negating the advantage of giving the cancer cells less time to repopulate. The result is that such two fractions/day accelerated fractionation has never gained wide acceptance and is rarely used today (16).

6. Accelerated Hyperfractionation and Split-course Radiotherapy

In an attempt to take advantage of the radiobiological benefits of both hyperfractionation and accelerated fractionation, Wang developed accelerated hypofractionation consisting of 1.6 Gy per fraction, two fractions per day with a minimum of four hours between fractions, for 12 days, 5 days a week for the treatment of cancers in the oropharynx and supraglottis. After the first 24 fractions the patients were given a two-week rest to allow acute reactions to subside (17). Often referred to as split-course hyperfractionated radiotherapy, the insertion of a two-week rest part way through treatment allowed the cancer cells to repopulate and, like accelerated radiotherapy, this regimen was never widely adopted.

7. Continuous Hyperfractionated Accelerated Radiation Therapy

A potential way to treat rapidly growing cancers with accelerated hyperfractionation while avoiding the need to have a rest period part way through treatment has been to use relatively high doses/fraction three fractions/day. This was the basis for the Continuous Hyperfractionated Accelerated Radiation Therapy (CHART) trials initiated for the treatment of advanced head and neck and small-cell lung cancers at the Royal Marsden Hospital, London, in the 1990s (18). The fractionation was 1.5 Gy delivered three times/day over 12 successive days to a total dose of 54 Gy. The need to rest the patient part way through treatment was eliminated since the peak in acute reactions did not occur until *after* the course had been completed. With 54 Gy delivered in just 12 days, however, the patients suffered very extensive and painful acute reactions, requiring them to be hospitalized for observation and treatment. With some small modifications, such as weekend less treatments (CHARTWEL), this regimen was the basis of several clinical trials, which tended to show some benefit in terms of tumor control but which never gained wide use probably due to the excessive acute reactions, requiring hospitalization, and the inconvenience of treating patients at three fractions/day.

8. So Where Are We Today?

In the past decade, things have changed considerably due, primarily, to the development and exploitation of many advances in technology. Irradiation of normal tissues surrounding targets can be significantly reduced by employment of stereotactic techniques, image guidance, advanced planning, etc., such that avoidance of complications has become secondary to maximizing the probability of tumor control. No longer do we have to rely on fractionation to avoid late normal tissue complications and long courses of therapy to minimize excessive acute reactions. We can now keep these under control by avoiding the delivery of high doses to surrounding normal tissues. The result is an enormous increase in clinical trials of hypofractionated short courses of radiotherapy. This has the added benefit of reduced cost/patient for the institution and time and effort for staff. Increased convenience to the patient, as well. My prediction is that almost all patients will be treated with

5 – 10 fractions within the next decade, with courses as short as two weeks for rapidly growing cancers. And cure rates will improve!

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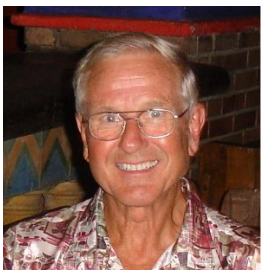
Colin Orton is a Past-President and Secretary-General of the IOMP and currently serves as President of the International Medical Physics Certification Board. He has a Ph.D. in Radiation Physics from the University of London and worked as chief medical physicist at New York University, Brown University, and Wayne State University. Throughout his career he taught medical physics and radiobiology to residents, technologists, and graduate students. His involvement in radiobiology began when he first moved from London to New York University in 1966 and was asked to teach the radiobiology course to radiology residents, there being nobody else on the faculty willing to teach it. It was then that he became interested in radiobiological principles of fractionated radiotherapy and developed the Time Dose Fractionation (TDF) mathematical model of radiotherapy that was used until it was replaced by the linear-quadratic model in the early 1980s. Since retiring in 2003 he has continued to teach classes in both medical physics and radiobiology.



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