Aspects on the Development of Radiation Therapy and Radiation Biology Since the Early Work of Rolf Wideröe

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At one of my very first scientific meetings—the International Meeting on the Medical Application of High-Energy Electrons, held in Berlin in May 1974—I had the pleasure of meeting Rolf Wideröe for the first time. This was in the early days of modern electron therapy. The first symposia held in Montreux (1) and New York (2) a few years earlier had just been published and many of the European pioneers behind the technical development of electron therapy equipment were present. Besides Rolf Wideröe, the Berlin meeting also included Rudolf Schittenhelm, Benno Markus, Dietrich Harder and Wolfgang Pohlit. I was there together with Hans Svensson to present betatron data and preliminary data on the first clinical microtron accelerator. I still remember that I was very impressed by the way Dr Wideröe combined his basic technical and physical knowledge with a great interest in basic radiation biology of therapeutic electron beams. Since then, I had the privilege to meet him a few times at different conferences during the 1970s and 80s, most often in Germany and Switzerland.

Dr Wideröe conceived his first ideas on a 'ray transformer' or betatron with an external electron injector as early as the fall of 1922, probably unaware that in the spring of the same year Joseph Slepian had filed a patent on a transformer-based x-ray tube, not granted until 1927. However, as far as I know, to date nobody had ever succeeded in making an operating betatron with an external electron gun. It was not until 1940 that Donald Kerst, using an internal electron gun, succeeded in putting the first 2.3 MeV betatron into operation, making use of the magnetic field condition previously derived by Wideröe. It is a strange coincidence that Rolf Wideröe, instead, was the first to make an operational linear accelerator (1926) with which he could accelerate potassium ions to 50 keV using an alternating voltage of about half that value. The first conception of a linear accelerator was probably proposed by the Swedish physicist Gustav Ising a few years earlier.

After Kerst's success with the internal electron gun, several groups sought to develop practical betatrons for electron and photon therapy and radiography during the 1940s. Donald Kerst, with his, by now, well-known group of scientists Gail Adams, Larry Lanzl, John Laughlin and Lester Skags in Chicago, developed a 21 MeV machine which became the prototype for the Alice-Chalmers 24 MeV betatron. In Erlangen, Gund and Schittenhelm worked for Siemens also on the development of radiotherapy and radiography betatrons, first a 6 MeV betatron and later 18 and 42 MeV machines. Rolf Wideröe joined the Swiss Brown Boveri Co. to develop 31, 35 and 45 MeV betatrons for radiation therapy. The first patient treatments with these early betatrons were not started until the end of the 1940s.

DEVELOPMENT OF CLINICAL ELECTRON ACCELERATORS

During the 1950s and early 1960s Dr Wideröe was extensively involved in the clinical development of betatrons and he had a large number of patents on their technical development. One example is the difficult task of collimating high-energy electrons, where he fully understood the complex problem of electron edge scatter (3). Wideröe modified the collimator edge by combining high and low atomic number materials. More than 15 years later the electron collimator was further optimized quantitatively using a high atomic number lining of the collimator edge (4) and a few years later by multiple solid tungsten collimator leaves (5), giving maximum flexibility and ease of

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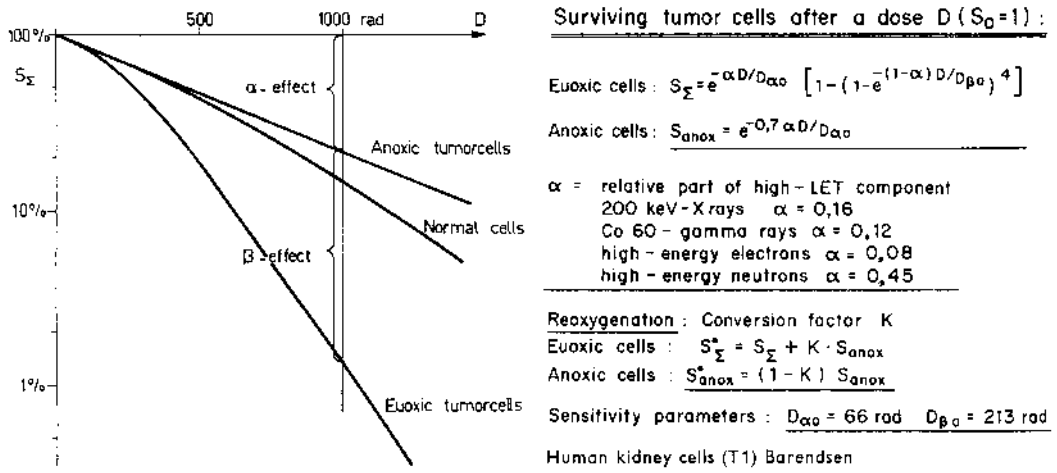

Fig. 1. Illustration of the cell survival curve model of Wideröe and its ability to be adopted to different radiation modalities.

collimation all the way up to 50 MeV electrons. More recently, it has been shown that a continuously increasing atomic number in an electron stopper actually produces the highest possible forward bremsstrahlung yield (6). However, as Wideröe already pointed out (3), the area irradiated is generally so small that the bremsstrahlung produced is no real threat to the patient.

Another very interesting observation made by Wideröe was that the fringing field of the betatron magnet had the power to remove photon-produced secondary electrons and positrons from the lower part of the target and the beam-flattening filter (7). In modern high-energy scanning photon beam machines, such as the racetrack accelerator, these secondary electrons and positrons are removed by a dedicated purging magnet (5) to prevent the downstream end of the target or the filter from functioning like a bolus placed at the patient surface. Owing to the high secondary electron production and the low scattering power of the high-energy electrons, the surface dose of the photon beams would otherwise be raised substantially. It is fascinating that the technical development of scanned beams in order to achieve high-quality, high-energy electron and photon beams from the racetrack (7) had a spin-off in starting the development of modern intensity-modulated, conformal radiation therapy techniques (8).

In a similar way the technical development of the betatron opened up the field of very high-energy electron and photon therapy and showed the considerable clinical advantages of the high-energy beams. More recently, the development of the multileaf collimator (MLC), not least when combined with scanning electron and photon beam techniques, indicated how modern conformal and biologically optimized radiation therapy could be realized. Even if new developments sometimes can be foreseen early on, it is obvious that new technical solutions often result in new developments that could not otherwise have been foreseen and the new developments may be more important than the initial problems that they were first intended to solve. For example, was the first high-resolution MLC for the racetrack accelerator designed to avoid the otherwise enormously heavy electron applicators that would be needed to collimate 50 MeV electrons (5). Similarly, the scanning system was designed primarily to improve the quality of the high-energy electron and photon beams and to avoid beam deterioration in flattening filters and scattering foils (5) and not to allow efficient intensity modulation.

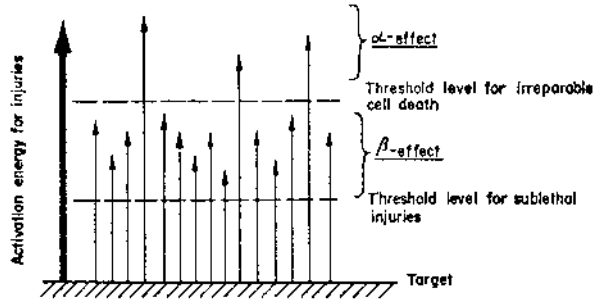

Fig. 2. Schematic view of the energy levels for producing irreparable (α) and potentially lethal (β) damage according to Wideröe.

DEVELOPMENT OF RADIOBIOLOGICAL MODELS FOR TREATMENT PLANNING

In the mid-1960s Dr Wideröe (9) took a great interest in radiation biology, seeking to model the therapeutic properties and to better understand how to make the best use of radiation therapy beams. In this modeling of the cell survival curve he frequently made use of Barendsen's extensive in vitro data set for human kidney cells (10). During his work with these models, he was awarded the Gold Medal by the International Radiological Society during the XIIIth Congress of Radiology in Madrid in 1973.

His survival curve model had two important advantages over the presently dominating linear quadratic model.

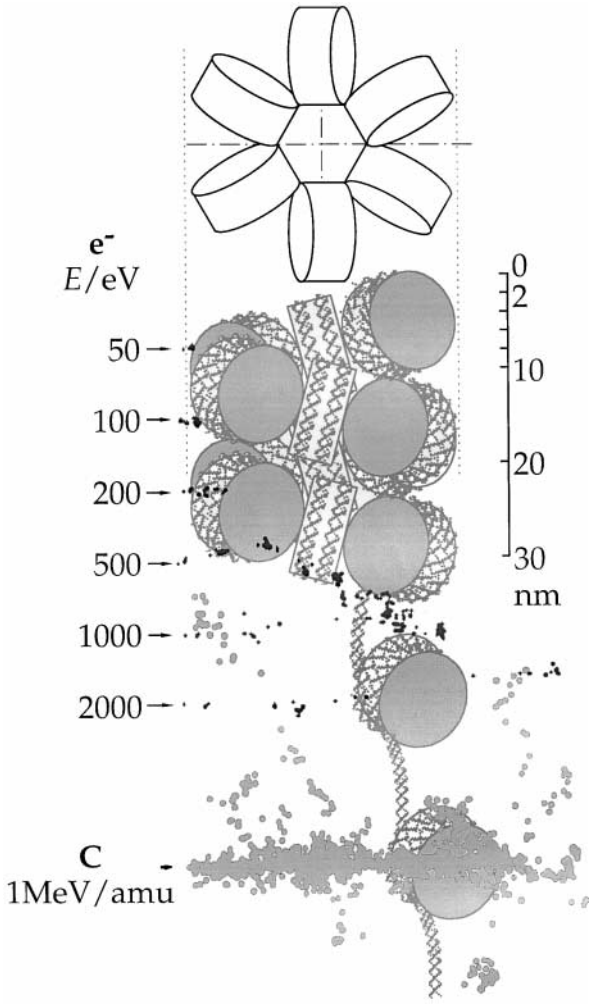

Fig. 3. More or less randomly placed low-energy electron tracks covering the energy range from 50 to 2000 eV superimposed over the 30, 11 and 2 nm DNA fibers.

First of all, it had a parameter α which took into account the relative dose fraction delivered with a high LET (the Linear Energy Transfer is related to the ionization density along the particle tracks). Thus he could model the shape of the cell survival curve for beams of increasing ionization density from electrons and photons through light ions to heavy ions and neutrons. His high LET component therefore corresponds approximately to the α term in the linear quadratic model (the linear quadratic α is equal to $\alpha/D_{\alpha 0}$ in Wideröe's notation) (10).

To be more precise, the α term describes the more severe part of the DNA damage that could not be repaired by the cell, as illustrated in Figs. 1 and 2. The β part, on the other hand, is sublethal and repairable, as illustrated further in Fig. 2. From this point of view the two models are similar, since the β term in the linear quadratic model also corresponds to repairable sublethal damage which depends on the post-irradiation conditions and may be repaired by the cells if they are allowed to rest after the irradiation. Wideröe's model (Fig. 2) agrees well with the modern view of cell inactivation where we know that simple single- and double strand breaks are often repairable with rather similar kinetics. There is one fast component with a half time of repair of about 20 min and a slow component that may need about 3 h.

The more severe type of damage, which is irreparable or more difficult for the cell to handle, is, instead, in the form of multiply damaged sites (11). The most common form of multiply damaged sites is probably the dual double strand breaks that can be induced on the periphery of a nucleosome by an energetic δ-electron (cf. Fig. 3 and (12)). Low-energy electrons in the energy range from about 100 eV up to about 1.0 to 1.5 keV produce very dense ionization clusters, the size of which can be several nanometers. When such a cluster is located anywhere on the periphery of a nucleosome, both of the double-stranded DNA fibers wound around the histone core of the nucleosome may be broken by the same event. Thus, when the histones are removed to allow repair of the damage, four generally blunt DNA ends are located close together and there is a high risk of either loss of one DNA turn around the nucleosome or misrepair. The fact that dual double strand breaks are quite a common occurrence is shown in the DNA segment histogram after x-ray exposure in Fig. 4. The prominent peak is seen for a DNA segment length of around 70 base pairs closely corresponding to the nucleosomal circumference (12). Obviously, the energetic δ-electrons, when correctly aligned, can also produce two spatially correlated double-strand breaks along a single DNA fiber. Unfortunately, such an event would result in segments of about 20 base pairs or shorter which is below the resolution in Fig. 4.

Secondly, the high-dose behavior of Wideröe's formalism is more linear and thus more realistic than the common linear quadratic model which produces a continuously steeper bending survival curve at high doses when the β value is finite. Wideröe, instead, uses a multitarget expression (often with 4 targets per cell) which is curved at low doses but approaches pure exponential survival at very high doses, as most high-dose experiments indicate. Obviously, his model also has some disadvantages, perhaps the greatest being that the mathematical formulation is more complex and may not always describe the shape of the shoulder as well as the linear quadratic relation generally does. However, today we know that even the linear quadratic relation may need corrections, particularly at low doses up to about 0.5 Gy, since the initial part of the survival curve seems generally to be associated with an initial steep portion (13).

The steepness of this initial portion is very close to the α part of high LET beams such as neutrons and heavy ions. The real reason for this very steep initial portion of the survival curve is not known even though it seems to indicate that there is some heterogeneity in the sensitivity

as is often the case when non-convex dose-response relations are seen. Michael Joiner's preferred explanation is that a certain amount of damage needs to be accumulated in the cell before the cell is fully aware that it has been seriously damaged and the DNA repair machinery is turned on at full speed. Some DNA repair enzyme systems are certainly continuously active as a lot of particularly milder forms of DNA damage are continuously being induced and repaired, such as the base damage handled by the excision repair system. More unusual and severe forms of DNA damage, for example those induced by ionizing radiations, will require more labor-intensive repair mechanisms such as sister chromatid exchange, and they may have more of a threshold or checkpoint-like response.

However, 0.5 Gy is a fairly large dose which does produce a lot of damage in the cells, so it is strange that such a threshold has not been observed earlier. Another possibility could be that there is a small proportion of more sensitive cells such as mitotic or potentially apoptotic cells. As has happened many times before in the history of science when more and more information about a phenomenon has been collected, there will finally be a point where the models have to be revised in order to incorporate the new knowledge. It would therefore not surprise me very much if such a revision were also to include some of the advantages of Dr Wideröe's form of the $\alpha-\beta$ model and, in a way, Joiner's new model does just that (13).

RECENT DEVELOPMENTS OF INVERSE TREATMENT PLANNING THERAPY AND OPTIMIZATION

Since the advent of betatrons and the first three generations of external beam radiotherapy equipment (5), a new era in radiation therapy is gradually emerging with new powerful methods for optimization of radiation dose delivery and therapy planning. In many ways the rapid development in treatment techniques and planning methods we are witnessing today is in parallel with the rapid development in medical imaging technology that has taken place during the past two decades. Computed tomography (CT), magnetic resonance imaging (MRI), single photon and positron emission tomography (SPECT) are rapidly maturing as universal diagnostic tools for clinical use. Obviously, the development of modern 3-dimensional (3D) imaging techniques has been an important prerequisite for the development of improved accuracy in diagnostic procedures and the work-up of the cancer patient.

Both the diagnostic and therapeutic technologies also allow a true 3D approach through the whole therapeutic chain from diagnostic imaging to the delivery of the therapeutic effect by accurately shaped radiation beams incident on the tumor. But there are also deeper parallels between the two disciplines, because the mathematical methods used in tomographic image reconstruction are similar to the mathematical techniques used in some of the new radiation therapy optimization methods. This is more clearly seen from the analogy between the non-uniform dose delivery required by most advanced radiation therapy optimization methods and the back projection of filtered transmission or emission profiles used in many image reconstruction algorithms (14–17).

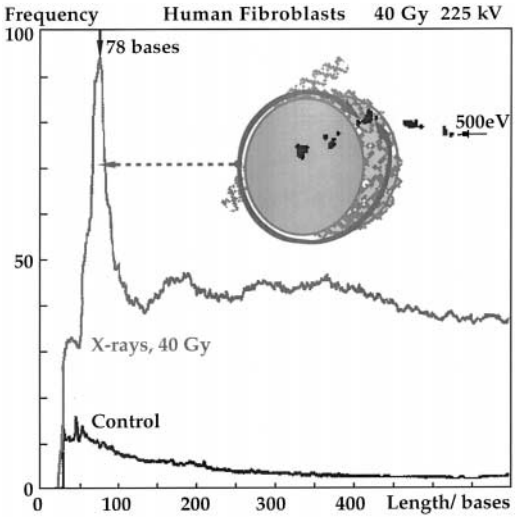

Fig. 4. DNA segment distribution from the irradiation of normal human fibroblasts to 40 Gy. Fragments from two single strand breaks on the same strand, or from a single- and a double-strand break are all recorded by the post-irradiation end labeling. Note in this case the very strong peak systematically falling at 78 base pairs. It is most likely that this peak is due to a single strong energy deposition event by a δ-electron somewhere on the periphery of the nucleosome.

Owing to the existence of nuclide uptake, a distribution of photon attenuation properties, or a proton density distribution for SPECT, CT or MRI respectively, these imaging modalities have the advantage that there exists a true solution of the reconstruction problem (at least if all physical interaction processes such as absorption, scatter and detection noise are taken into account). The problem of radiation therapy optimization is much more difficult because in general most desired dose distributions can, due to the laws of nature, never be exactly reproduced either by internal brachytherapy or by external radiation therapy sources (17). It would, for example, be ideal to have a high tumor dose and zero dose everywhere else in the body, which is clearly impossible to deliver. From this point of view radiation therapy optimization is therefore a much more complex problem than that of image reconstruction.

INVERSE RADIATION THERAPY PLANNING

Mathematically speaking, classical radiation therapy planning is essentially a forward process, as it tries to answer the question: how will the absorbed dose in the target

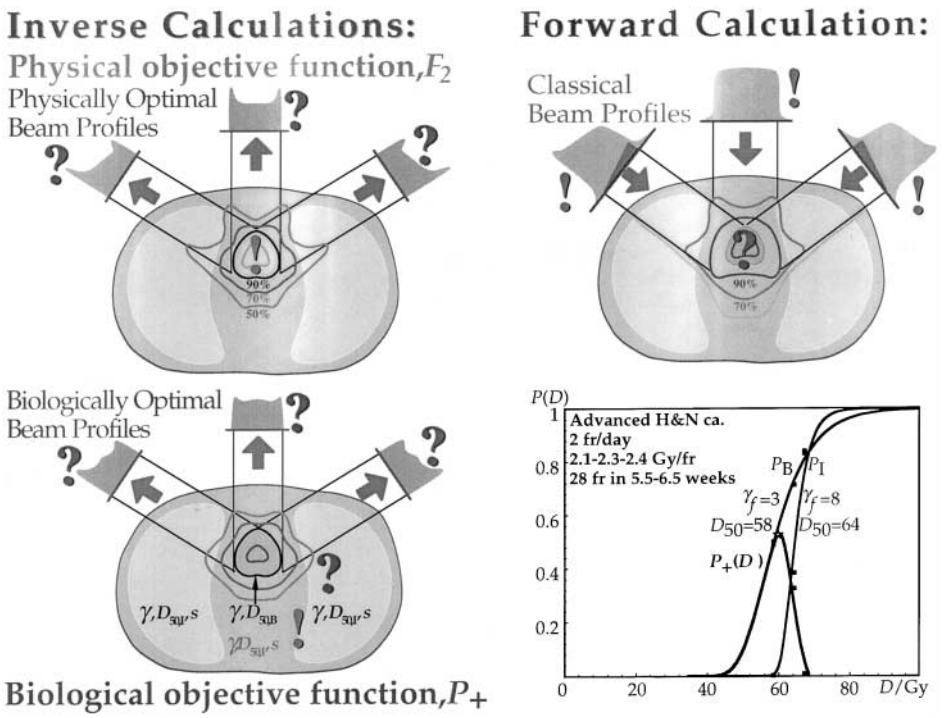

Fig. 5. Schematic illustration of the difference between conventional forward radiation therapy planning and inverse planning. Dose optimization using forward planning is generally a trial and error process (upper right panel), whereas inverse planning directly results in optimal beam profiles (upper left with physical objective function) and isodose distributions (lower left with biological objective functions).

volume and surrounding normal tissues be distributed for a given target volume, associated patient geometry and suggested configuration of the incident beams? This is schematically illustrated in the upper panel of Fig. 5. Classical-radiation-therapy optimization is therefore generally a trial and error process, where gradually improved dose plans can be found by trying an increasing number of configurations of the incident beams (18).

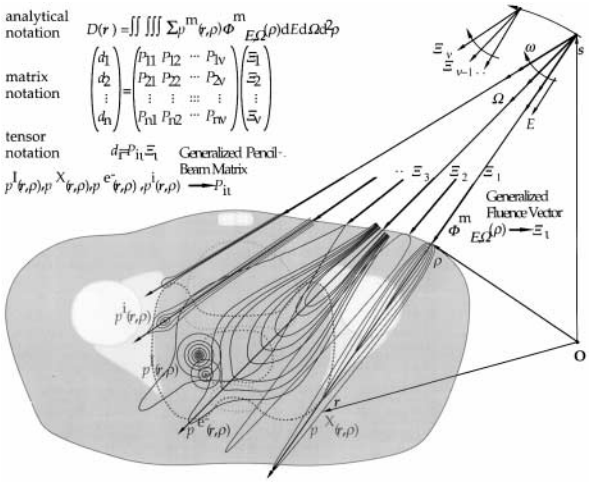

Fig. 6. Illustration of irradiation geometry used in the optimization of the total dose distribution in the patient delivered by the fluence $\Phi_{E,\Omega}$ of pencil beams p. Through the use of accurately calculated pencil beams, even taking patient inhomogeneities into account, a very strict optimization is possible considering all major constraints on the dose delivery.

By contrast, true radiation therapy optimization is fundamentally an inverse problem, because what we really want is to find the best combination of incident beams for a given target volume. More exactly, the planning process should answer the question: which configuration and shape of the incident beams is best suited for controlling the tumor growth, with the minimum of damage to normal tissues? This question is illustrated in the lower half of Fig. 5. At least under the assumption that the desired dose to the target volume (upper left panel) or the geometrical and radiobiological properties of the tumor and normal tissues of the patient are known (lower panels), it should be possible to find the optimal irradiation technique (19, 20).

This conceptual difference between the classical forward calculation and the inverse approach is further clarified by comparing the three panels in Fig. 5. In each case the exclamation marks indicate the known quantities, whereas the question marks indicate the principal unknown quantity to be calculated, such as the optimal isodose distribution in the patient or the optimal incident beam profiles. Interestingly, the best possible absorbed dose distribution in the patient from a radiobiological point of view is also obtained by the inverse calculation, either by an ordinary forward calculation or by the inversion method itself

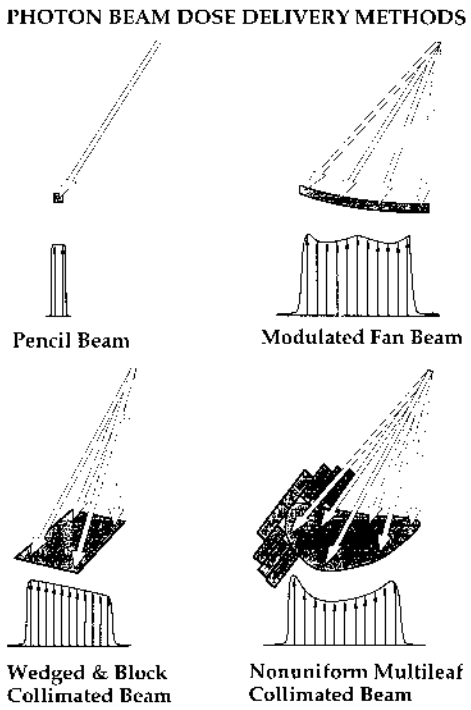

Fig. 7. The four major groups of dose delivery methods for external beam radiation therapy. The most differential are the pencil beam methods using either electromagnetically scanned beams or mechanically moved beams. The Peacock device and the tomotherapy method belong to the fan beam group. Classical external beam therapy mainly employs uniform rectangular block collimated beams, sometimes with a wedge filter. Fully non-uniform beams can be delivered with any of the methods in Fig. 8 and the associated treatment technique is generally the fastest and simplest one to verify.

(lower left panel and (16, 20, 21)). From Fig. 5 it is clear that there are similarities between the inverse problem of radiation therapy and the problem of image reconstruction from a limited number of angles in diagnostic radiology.

BIOLOGICALLY OPTIMIZED TREATMENT

It has recently been shown that for the most difficult clinical situations where the organ at risk is close to the tumor, it is essential to use an optimization method that takes the true radiation responses of the tumor and normal tissues into account as accurately as possible. The pencil-beam method (Fig. 6) with realistic radiobiological dose-response data for the tumor and surrounding normal tissue (cf. Fig. 5, lower right panel) provides the highest accuracy, since it allows a direct optimization of the probability of curing the patient without inducing severe damage to normal tissue. Optimization algorithms based on pencil beams are today undergoing rapid development and they have the potential to improve the outcome of treatment by at least 10%–20%, especially for advanced tumors that have spread locally in a complex pattern (17, 19, 22–25).

MODERN DOSE DELIVERY METHODS

As illustrated in Fig. 7, there are essentially four methods for increasing the flexibility of dose delivery in external beam radiation therapy. These methods are based on using 1) narrow pencil beams, 2) elongated, intensity-modulated fan beams, 3) classical block-collimated beams with a wedge filter, and 4) generalized non-uniform beams of irregular cross-section generated, for example, by dynamic multileaf collimation or scanned beams. We will begin by describing the methods that are available today for non-uniform dose delivery before describing the more 'differential' pencil beam approaches.

The principal methods for non-uniform dose delivery are summarized in Fig. 8. It can be seen that if full dynamic flexibility and reasonable treatment times are required, when applied in the clinic, the best methods for non-uniform dose delivery are dynamic multileaf collimation (25) and scanned elementary beams (21).

The dual dynamic jaw collimation method (Fig. 8) also allows, in principle, full modulation of the incident beam but at the cost of substantially extended treatment times. Furthermore, this method requires that both the upper and lower jaw pairs are fully asymmetric so that a narrow rectangular beam spot can be scanned arbitrarily across the entire target volume. If very high dose rates were available and the speed of motion of the collimator jaws was very fast, the time required could be reduced but this is not a very realistic method with presently available accelerator systems.

The classical filter and transmission block techniques also have the flexibility but they are fairly time-consuming, so they are probably impractical for more than three treatment beams per patient. They could, for example, work with the few field techniques indicated in the lower panels of Fig. 5, either by manual change or with a filter revolver on the front end of the treatment head carrying 3–5 filters. In recent years several compensator-based optimization techniques have been developed (26, 27) which are quite useful in handling few field techniques, provided suitable beam directions can be identified. In reality, the optimal choice of beam direction is one of the most difficult problems of treatment optimization since it involves a restriction on the phase space of feasible beam combinations. This cannot be achieved without having located all beam combinations corresponding to local optima, which in practice is equal to a global optimization (24). It also accentuates a difficult radiobiological problem, in a way the Scylla and Charybdis of radiation therapy: with a single beam the small volumes of normal tissue in the entrance region receive a rather high local dose, whereas at the other extreme, with a continuum of arc beams, large volumes receive rather low doses (28). To allow a strict optimization, realistic radiobiological objective functions capable of distinguishing between these ex-

tremes are needed. During recent years considerable development of such biological objective functions has been initiated and this will form the basis for modern treatment optimization algorithms (10, 13, 17, 29, 30). Unfortunately, the accuracy of the biological models has not yet reached the level that they can differentiate between Scylla and Charybdis. However, they are accurate enough to introduce substantial improvements by intensity modulation (17, 18, 35, 40)

FAN- AND PENCIL-BEAM THERAPIES

There are a great many projects centered around the use of uniform or non-uniform fan beams (cf. Fig. 7). The earliest was probably in the computer-controlled therapy in Boston, where the length of a narrow elongated slit beam through the isocenter (the fan beam) was varied as the gantry rotated and the patient was slowly moved through the beam (31). The treatment time was often long, of the order of 20 min, and the setup time was also considerable. This problem is shared with all small-volume irradiation techniques, unless the dose rate and speed of rotation are increased by about one order of magnitude.

More recently, a special modulated fan-beam collimator has been developed (Peacock: (32)). This device allows temporal modulation of the treatment time along the fan beam and this allows non-uniform dose delivery.

The latest development has been suggested by the group in Madison (33). Their idea is to use a fan-beam modulating collimator for 'spiral irradiation' with a longitudinally moving patient, much in the same way as used in spiral CT. Unless the accelerator output is very high, all the fan-beam approaches described here are unfortunately prone to fairly long treatment times.

At the cost of a further increase in treatment time, it is possible to use a moving narrowly collimated beam (pencil beam) to deliver non-uniform dose distributions. The pioneering work for uniform beam delivery was done in Chicago using a mechanically moving bending magnet in a rotary gantry (34). Since the dose rate in the electron beam was quite high, the treatment time was not too greatly increased.

More recently, a robot-mounted linear accelerator has been developed. This device has the advantage of a high degree of freedom since the computer-controlled dynamic dose delivery is performed by a robot. However, for large target volumes, this device requires even longer irradiation times since the beam is narrow (< 4 cm) and the dose rate is normal (a few Gy/min). An ideal algorithm for planning and optimization of pencil-beam and also more general types of treatment techniques has recently been developed (23, 35, 36).

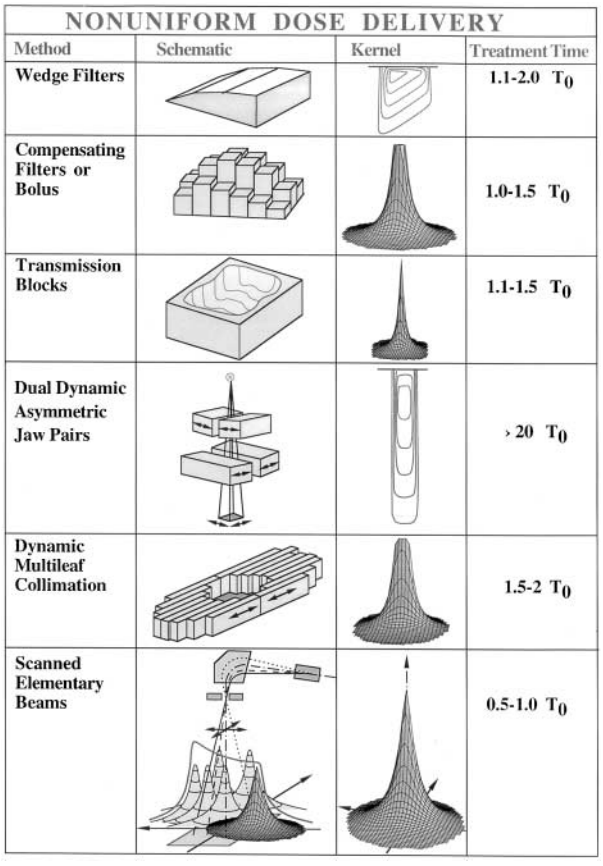

Fig. 8. Comparison of six different methods available for delivering of non-uniform therapeutic beams. T_0 is the standard treatment time of about 1 min for uniform dose delivery to the target volume. Only the lower three methods allow dynamic beam shaping but at greatly varying treatment times.

SCANNING BEAM THERAPY

Radiation therapy is traditionally performed with stationary bremsstrahlung beams and flattening filters to render the beam uniform. Today, the fastest and probably safest way to deliver non-uniform beams in real time is by moving a small elementary electron, photon or proton beam over the patient, similar to the electron beam in a TV monitor. Such beams have been available for almost 10 years on a 5–50 MeV racetrack accelerator (5, 37). Because the elementary essentially Guassian electron beams and the bremsstrahlung beams have fairly wide half widths (≥ 12 and ≥ 30 mm respectively at the isocenter) the MLC may be needed for spatial modulation when a higher geometric precision is required. Despite this shortcoming, the scanned beams are very useful and often sufficient, at least for beam compensation. In combination with dynamic multileaf collimation, a very rapid and flexible dose delivery is possible and ideal for few field, non-uniform, generalized conformal therapy with treatment times of the order of a few minutes in most cases.

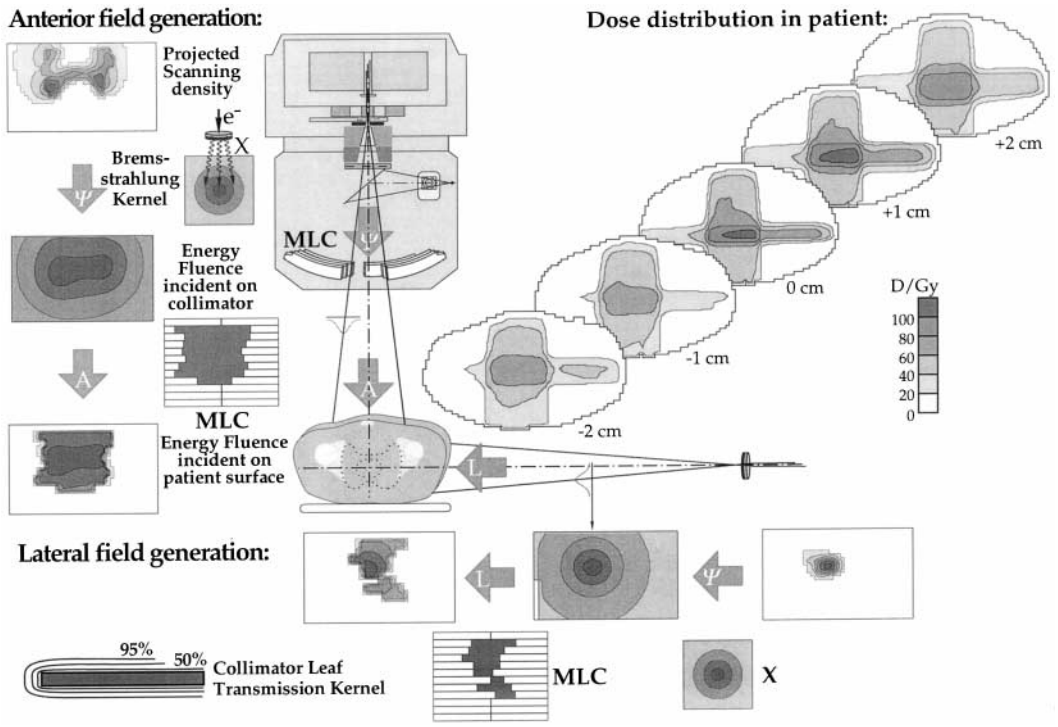

Fig. 9. Production of the energy fluence on the patient surface for two fields, one anterior and one right lateral field, using scanned photon beams and multileaf collimation. The optimized scanning pattern incident on the bremsstrahlung target is convolved with the bremsstrahlung kernel and the energy fluence incident on the multileaf collimator is obtained. The transmission function of the multileaf collimator (MLC) is multiplied by the incident energy fluence to get the energy fluence on the patient surface. Also illustrated is the resultant dose distribution in the most important slices around the cervix uteri.

The most modern electron and photon beam scanning system is based on the beam optical property of the last bending magnet in the treatment head of the accelerator such that the first scanning magnet deflects the beam in the bending plane of the rotary gantry and the second magnet deflects the beam in and out of the bending plane, as illustrated in the cross-sectional view in Fig. 8. The rotary gantry may also be equipped with a cadmiumtungstate (CWO) detector array for transmission imaging of the patient, allowing full comparison of diagnostic and radiotherapeutic CT images for accurate patient setup (38). The energy fluence of the bremsstrahlung beam is obtained by convolving the scanning density with the elementary bremsstrahlung beam kernel, as illustrated in Fig. 9. The therapeutic beam is then formed by collimation using MLC. On this cervix cancer patient with the rectum and bladder as main organs at risk, one anterior and one lateral beam were employed with the resultant isodose distributions shown to the right (21, 23). By this technique the treatment outcome can be improved by some 20%, making full use of the tolerance of the patient by shaping the high-dose region to conform with the target volume.

Dynamically scanned proton beams will probably be the ultimate radiation therapy modality when high geometrical precision is required, since the pencil-beam penumbra is so narrow that additional collimation is not required (39) and the finite proton range protects tissues also beyond the tumor volume. The role of the higher LET ions still have to be demonstrated clinically, because of their very high microscopic dose heterogeneity (39).

DISCUSSION AND CONCLUSIONS

It is clear that radiation therapy today, as in the early days of Wideröe, has to develop through a close collaboration between the research areas of radiation therapy equipment and technology, with radiation biology as the bridge between absorbed dose and clinical effects, and, finally, oncology and molecular biology. All the degrees of freedom in dose delivery must be explored—not just the physical-intensity-modulated dose distribution, the radiation modality (electrons, photons or protons, etc.) but also the time–dose fractionation and the possibility of making a predictive assay of radiation sensitivity for both the tumor and the dose-limiting normal tissues. It is becoming increasingly clear that the treatment outcome can be improved if the total treatment time is reduced and sometimes if the dose is delivered in many small fractions. Even if the general decision criteria are not accurately established, we will need new treatment units that are accurate and fast in setup, not least when intensity modulation and many dose fractions per day are being used (40, 41).

For these reasons improved optical setup devices based on lasers and physical fixation devices are needed. A new type of adaptive control algorithm has recently been developed, where setup errors in previous treatments can be completely eliminated with regard to their influence on the dose distribution in the target volume (40). With such state-of-the-art techniques it is also possible to achieve an accuracy in dose delivery to complex target volumes of the order of a few percent. Modern intensity-modulated radiation therapy is therefore by far the most accurate medical procedure known to date, being able to deliver arbitrary dose distributions in three dimensions to almost any target in the body with percent accuracy. The accuracy of more conventional uniform beam radiation therapy techniques is generally in the order of 5% (1σ) largely due to the uncertainty in beam flattening filter alignment etc.

Finally, it is interesting to observe how the many new biological models, despite their shortcomings with regard to the absolute accuracy of the underlying data, still describe the clinical response accurately enough to introduce substantial improvement in our treatment techniques. This should not come as a great surprise, since the first 100 years of radiation therapy have been mainly focused on uniform dose delivery to the target. In conclusion, it is also interesting to note that many of Rolf Wideröe's early publications contain the precursors of the rapid development of radiobiologically optimized treatment planning techniques that we are witnessing today.

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