The development of conformal radiation therapy

Benedick A. Fraass
Department of Radiation Oncology, University of Michigan Medical Center, Ann Arbor, Michigan 48105

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The development and clinical use of conformal radiation therapy, and the application of modern computer-controlled radiation therapy treatment techniques to the delivery of conformal therapy, has been a major research area in the field of radiation oncology in recent years. The introduction of three-dimensional (3-D) patient imaging, 3-D treatment planning systems, computer-controlled treatment machines equipped with multileaf collimators, and the continuing increase in computer power and software sophistication has finally allowed the clinical implementation of the kinds of conformal treatment planning and delivery that were envisioned decades ago. The use of 3-D treatment planning in conjunction with conformal treatments and the analysis of clinical normal tissue complications has also begun to give the field the clinical complication (and eventually tumor control) probability data which can be used to truly optimize radiation treatments. At this centennial anniversary of the discovery of the x ray, it is appropriate to look back at the contributions which have led to the current developments in conformal therapy. Few if any of the "new developments" associated with modern computer-controlled conformal therapy (CCRT) are actually new. However, modern technology has finally progressed to the point that we can integrate all of the features that are necessary to really make the concepts work in the clinic. This paper traces some of the developments which have led to the current interest and progress in CCRT treatments. A brief summary of the current status of conformal therapy and the work still to be done is also included.

Key words: conformal therapy, treatment planning, 3-D, computer-control, multileaf collimator

I. INTRODUCTION

The discovery of the x ray by Roentgen, reported in late 1895,[1] was followed almost immediately by the treatment of a patient with x rays.[2] This immediate application of a totally new and not-understood physical phenomenon to patient treatment certainly would not be repeated in our current environment. It is clear, however, that the development of the fields of radiation therapy and radiation oncology have continually progressed in the one hundred years which have passed since the first application of this new treatment modality.

Now, in 1995, one of the most exciting current fields of interest in radiation therapy is the development, use, and evaluation of conformal radiation treatment technology, in particular computer-controlled conformal radiation therapy ("CCRT"). There are numerous ways to define conformal therapy. In this work we define conformal therapy as radiation treatment in which the high dose region conforms closely to the shape of the target volume, in three dimensions, while minimizing the dose to normal tissues outside the target volume. CCRT, which is described in more detail elsewhere,[3] makes use of sophisticated 3-D treatment plans, multileaf collimators (MLCs), and computer-controlled treatment machines in order to deliver highly conformal treatments. The interest in CCRT is developing quite rapidly, and it shows great potential for improving treatment outcome and or treatment delivery efficiency.[3–5] Recent improvements in treatment planning and treatment delivery technology have allowed the pursuit of formal studies aimed at understanding tumor control and normal tissue complications as a function of dose, volume, and other factors.[6] In fact, one can argue that now, perhaps for the first time in the history of radiation therapy, we can pursue well-defined and quantitative studies to acquire the data and understanding which are necessary if we are to optimize the therapeutic ratio for our patients. The ideas and techniques which are currently being implemented, however, trace their roots nearly to the beginning of radiation therapy.

In this paper, the history of the development of radiation therapy technology is briefly reviewed, in the context of the current interest in conformal therapy treatment. Study of the work of earlier decades can be quite instructive as we continue to try to improve the quality, sophistication, and clinical results associated with radiation treatments. Virtually all of the current exciting topics in improved treatment technology, including CCRT delivery techniques, have been visualized and attempted decades ago. The main difference between then and now is the phenomenal increase in computer power, the related advances in imaging, software, and computer graphics, and in improved treatment machine designs. This improved technology has finally allowed the realistic development and clinical implementation of the treatment techniques envisioned by the early pioneers. This paper attempts to illustrate the historical precedents and their relationships to today's work in conformal therapy.

II. EARLY RADIATION THERAPY

The first x-ray therapy began less than two months after the first report of the x ray by Roentgen in 1895. The first patient treatment is credited to Emil Grubbe in Chicago on January 29, 1895, for an advanced breast cancer.[7] During the year of 1896, there were reports of treatments of nasopharyngeal carcinoma, carcinomas of the stomach and skin, and nonmalignant problems like inflammation and tuberculosis.[2]

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Very little was known about the properties of these new rays, and clinical application of the modality was totally empirical. While x-ray use grew, other sources of radiation were also developed: the Curies discovered radium in 1898, and by 1904 it was used to treat a patient with cervix cancer.[2] By 1920, 200-kV x-ray machines[2] and radium teletherapy machines[8] were both available.

One of the important features of current conformal therapy is the analysis of and minimization of the probability of normal tissue complications. This is a critical issue in radiation therapy, and has been important from the early days of radiation therapy. For example, fibrosis of the lung resulting from breast cancer treatment was recognized as early as 1922.[2] The use of tangential fields for breast cancer in order to minimize lung dose was described in 1925 by Finzi.[9] In fact, the first radiotherapy treatment performed by Grubbe actually included the use of lead sheet to protect the healthy tissues around the lesion.[7,10] However, the ability to quantitatively analyze the relationship between complications, dose, and volume of tissue irradiated was not available until the 1980s, after the CT scanner and 3-D treatment planning were developed.

A generally empirical approach to the field of radiation therapy persisted for nearly 30 years. A major advance came in the late 1920s with the First (1925) and Second (1928) International Congresses of Radiology, which resulted in the establishment of the Roentgen as the unit of radiation exposure.[11] The acceptance of a single unit for the first time allowed one of the most important aspects of treatment delivery, the amount of radiation delivered to the patient, to be reported, compared, and used clinically.[11]

The improved radiation physics associated with the definition of the Roentgen, and its use to start a truly scientific approach to the application of radiation therapy, led to substantial developments in treatment delivery during the 1930s and 1940s. As described by Paterson:[12] "radiation ceased to be purely palliative, and gradually entered more effectively into the curative field of malignant disease." With the relatively high energy orthovoltage units which became available in the 1930s (700–800 kV in 1931[7]), it was possible to treat tumors with multiple fields, crossfiring on the tumor in order to achieve a higher dose at the tumor, while spreading the dose out over the normal tissues. This principle is still at the heart of much of the sophisticated CCRT which is contemplated today. The multiple field technique led quickly to arc therapy, and many different types of beam-patient combinations were investigated. As early as 1906 Kohl described mechanisms for moving x-ray tubes over arcs so that the x-rays continued to point at one point,[13] as shown in Fig. 1(a). This kind of device was a precursor for a number of early treatment schemes, for example the "Conical–Rotation Therapy" described by Knox and Caulfield in 1933.[14,15] These kinds of treatments are quite similar to current conformal therapy techniques like the segmental cone[16] [shown in Fig. 1(b)] which can be delivered today using a computer-controlled machine.

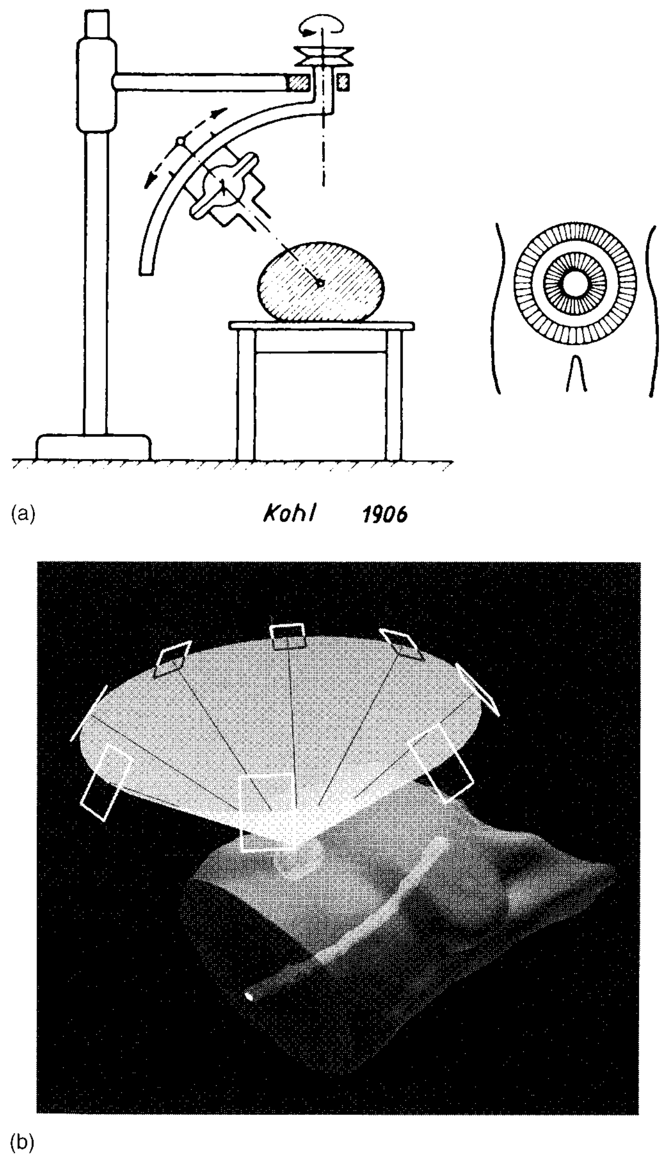

FIG. 1. (a) An apparatus designed to allow the use of "Conical rotation therapy" originally described by Kohl in 1906. Figure reproduced from Ref. 35. (b) Modern day treatment planning for the delivery of a "segmental cone," in which the beam aperture is shaped with a MLC for each segment, and the entire set of segments is delivered automatically with a computer-controlled machine. This image shows the patient external surface, the target volume, and the spinal cord.

III. DOSIMETRY AND MANUAL TREATMENT PLANNING

One of the keys to improved treatment technology is improvement in the measurement and prediction of the dose distribution with which patients are treated. Although the basic concept of the "depth dose" was apparently published as early as 1906,[11] the modern depth dose curve did not appear until the early 1930s.[17,18] The earliest "isointensity curves" (measured with film) were described about 1921,[11] while measuring isodose curves in a water phantom with an ion chamber was described by Mayneord in 1929.[19] It was not until 1946 that an automatic plotter for isodose curves was reported.[20] Characterization of the radiation fields used to treat patients is clearly a precursor to any kind of detailed modeling or prediction of the expected dose distributions.

The decade of the 1940s saw many developments critical to the evolution of modern treatment planning.[11] Clarkson developed the basic method for handling irregular fields,[21] and this basic method is still widely used. Meredith and Neary first used empirical formulas to calculate radiation dose distributions,[22] while Day described the equivalent square,[23] a concept which is still central to many clinical dose calculation methods today. The tissue–air-ratio (TAR) method of dose calculation was not introduced until 1953,[24] leading to a long line of improvements and extensions of the basic concept.[25–27] With the development of these methodologies for measurement and calculation of the dose delivered by various treatment techniques, simple manual methods of "treatment planning" became possible, and this hand planning was used for several decades.

IV. INTRODUCTION OF MEGAVOLTAGE MACHINES AND ASSOCIATED TREATMENT TECHNIQUES

The next major improvement in treatment delivery techniques came with the achievement of megavoltage acceleration of electrons and other charged particles. Although the appropriate acceleration energies for diagnostic x rays had been feasible almost from Roentgen's time, insulation problems had blocked the use of the higher energies desirable for radiation treatment. It was not until Kerst[28] developed the betatron, which could accelerate electrons to any desired energy with no voltage in excess of 60 kV, that high-energy x-ray and electron treatment became feasible. At this point, the cyclotron for heavy charged particles had already been invented (and the linear accelerator was not developed until later, after World War II).

Kerst developed the betatron in 1940, and within several years the first high-energy treatments were performed using a betatron.[28] This initial treatment with photons created from a 22-MeV electron beam from the betatron consisted of treatment of a brain tumor with a highly conformal 25 field noncoplanar treatment.[29] Within a year or two of this first treatment with a betatron, a number of clinical betatron treatment units had been installed in hospitals.[28,30] High-energy electron treatment with betatron electrons was initiated in 1951.[31] Eventually, linear accelerators (with their higher output) superseded betatrons, but the basic clinical physics pioneered with the betatrons continued to be of great value.

With the growth of nuclear physics research reactors after the end of World War II, ^{60}Co sources became available, and the first cobalt machines were introduced by Johns and coworkers in Canada in 1951.[30] In 1953, 4- and 8-MV linear accelerators were introduced into clinical use in England[28,32] followed in 1955 by the initial 6-MV linear accelerator installed by Kaplan, Ginzton, and co-workers at Stanford.[33] The significant increase in depth dose (see Fig. 2) associated with Cobalt, 4- and 6-MV photons, compared to orthovoltage x rays, dramatically increased the practicality of many of the multi-field crossfiring treatment techniques. As described by Kaplan:[34] "We are no longer dependent on the limitations of skin tolerance. We can use the beam like a rifle in aiming at quite small lesions inside the body, and carefully avoiding nearby vital tissues and organs... . We have been enabled to

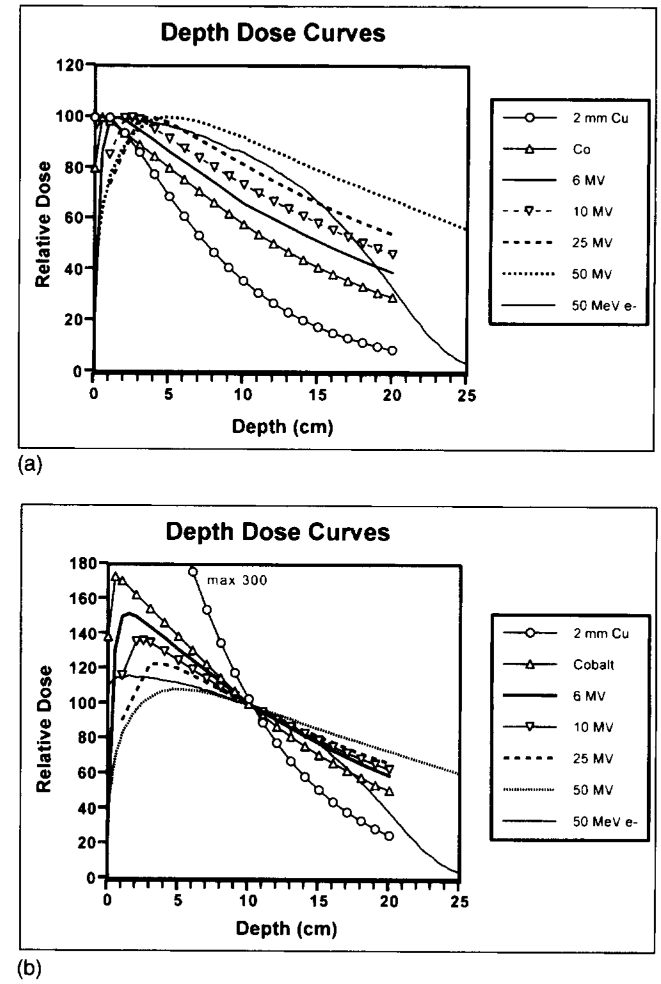

FIG. 2. Depth doses for different energy beams [Orthovoltage (2 mm Cu), Co60, 6, 10, 15, 25, and 50-MV and 50-MeV electrons] for 10×10 fields. All data from Ref. 151 except the 50-MV photons and 50-MeV electrons, measured on the racetrack microtron system. (a) Depth dose curves normalized at their individual maximums. (b) Same curves normalized at a depth of 10 cm to demonstrate the relative doses delivered to surface and deep regions relative to a target at a depth of 10 cm.

undertake much more diversified and more aggressive kinds of treatment which can deliver tumoricidal doses to tumours in virtually every region of the body."

The acceptance of isocentrically mounted cobalt machines and linear accelerators allowed the straightforward and precise application of multi-field cross-firing treatments, but it also limited the flexibility of the orientations used for the treatment. The early pioneers in the orthovoltage era often used many different treatment beams, oriented at whatever angle to the patient was appropriate, as well as complex mechanical devices to orient the x-ray tube appropriately.[35] These early x-ray machines with relatively small treatment heads could be supported by a mechanism with many degrees of freedom and were quite flexible. In contrast, the isocentrically mounted cobalt machine or linear accelerator which arrived in the 1950s was forced to rotate around an isocenter, with the only additional angular degree of freedom provided by an isocentrically mounted treatment couch. With the introduction of these machines, treatment delivery began to be constrained into "the tyranny of the axial plane." Only in recent years, with the renewed interest and capabilities in so-called "non-coplanar" treatment plans,[6,36–39] has treatment delivery again begun to include the third (nonaxial) dimension for treatment delivery.

While the majority of the field worked with linear accelerator machines, the therapeutic use of cyclotrons and other machines originally developed for physics research continued. The quite unique dosimetric and/or radiobiologic properties of protons, pions, heavy particles, and neutrons have led to numerous specific treatment delivery techniques which take advantage of the specific properties of the particular particles.[40] Many advanced concepts associated with modern conformal therapy delivery techniques, including patient positioning and localization,[41,42] treatment planning,[43–45] and radiobiologically related analysis of treatment results[46,47] were pioneered by the proton and heavy particle treatment groups at Harvard/Massachusetts General Hospital, and the Lawrence Berkeley Lab.

V. COMPUTERIZED TREATMENT PLANNING

As early as 1954, the possibilities for using the developing new computer technology to assist in treatment planning computations were first investigated.[28] In 1955 Tsien published the first paper associated with this new field of computerized treatment planning,[48] and within the next years, numerous systems were developed and reported in the literature.[49–54] Developments of increasing sophistication continued during the 1970s, including the work of Cunningham,[25] and Bentley and Milan.[55]

This early work on computerized treatment planning was clearly an essential step toward the ability to plan and perform conformal therapy, as it allowed (for the first time) the physician and treatment planner to design and evaluate the dose distribution in a quantitative manner. Beams could be arranged and modified in order to improve the dose distribution within the target. The lack of sophisticated anatomical input data describing the external patient shape, tumor, and normal tissues was generally coupled, however, with an equally limited and fairly two-dimensional view of the radiation beam and the associated dose distribution. Although a number of early treatment planning developments attempted a fairly three-dimensional approach to parts of the treatment planning process,[50,52] the technology was not available to fully implement real 3-D approaches.

VI. EARLY CONFORMAL THERAPY TECHNIQUES

It has been known for many decades that delivering a high dose to the tumor was critical if the tumor was to be controlled. In addition, it was also clear that typically the probability of complications increases with radiation dose, and often with the volume (or area, for skin) of tissue which is irradiated. The basic concepts of conformal therapy were elucidated quite early in the century: one wants to treat the tumor to a high dose, while at the same time minimizing the dose to normal tissues. Several different conformal therapy treatment techniques conceived in the 1950s and 1960s were specifically aimed at accomplishing that objective. These approaches were, as stated by Green in 1965,[56] "the logical sequence of development over the past twenty five years."

One of the most important pioneers in the field of conformation therapy was Shinji Takahashi, working in Nagoya, Japan. In 1965 Takahashi published a monograph entitled "Conformation Radiotherapy: Rotation Techniques as Applied to Radiography and Radiotherapy of Cancer,"[57] which elucidated many of the central concepts of both conformal treatment delivery and the use of 3-D treatment planning of those treatments. Takahashi and co-workers designed and used "geared sectional collimators" (early multileaf collimators), employed dynamic conformal therapy treatments with a mechanical control system to make the beam shape conform to the shape of the target as the machine rotated about the patient, used orthogonal light beams to specify patient alignment with the machine isocenter, and made extensive use of 3-D models of the tumor (based on various kinds of tomography) for planning and delivery of the conformal therapy.[57] Takahashi's work has continued at a number of research centers throughout Japan.[58–61] Similar work with rotational conformation therapy, using early multileaf collimators, also took place in other centers, notably Perry and co-workers.[62] The development of synchronous shielding devices similar to that of Takahashi also occurred independently at the MIT–Lahey Clinic in the late 1950s by Proimos, Wright, and Trump.[63–67]

Another early approach to conformal therapy by Green, Jennings, and others at the Royal Northern Hospital (and later the Royal Free Hospital) in England was based on experience with various kinds of moving beam therapy. Known as the "Tracking Cobalt Project,"[14] this work attempted to track the path of disease spread, particularly along lymph node chains. First reported in the late 1950s,[68] and summarized by Jennings,[14] a series of mechanical, electronic, and finally computer-controlled treatment machines were developed. With these machines, the isocenter of the machine's rotational therapy was moved through the patient by moving the treatment table. By 1980, the computer-controlled version of the tracking system was in clinical use.[69] A statement by Brace in a 1981 paper is quite interesting: "The major obstacle to the routine use of conformation therapy is treatment planning."[69]

A logical extension of this kind of approach to conformal therapy continued in Boston at the Joint Center for Radiation Therapy (JCRT) by adding computer control to a modern linear accelerator. The treatment table, gantry, collimator, collimator jaws, dose rate, and other parameters could be controlled dynamically while the beam was on. Using this device, the JCRT achieved the delivery of what is now called "dynamic conformal therapy."[13,70–72] The JCRT work is quite important in the evolution of the current approaches to computer-controlled conformal therapy.

VII. CT-BASED AND 3-D TREATMENT PLANNING

The introduction of the CT scanner in the early 1970s is one of the key leaps in the development of modern conformal therapy. For the first time, a full set of anatomical information describing the individual patient in three dimensions became available for the radiation oncologist to use in planning the patient's treatment. Within a few years, CT scans began to be used as the anatomical input for the treatment

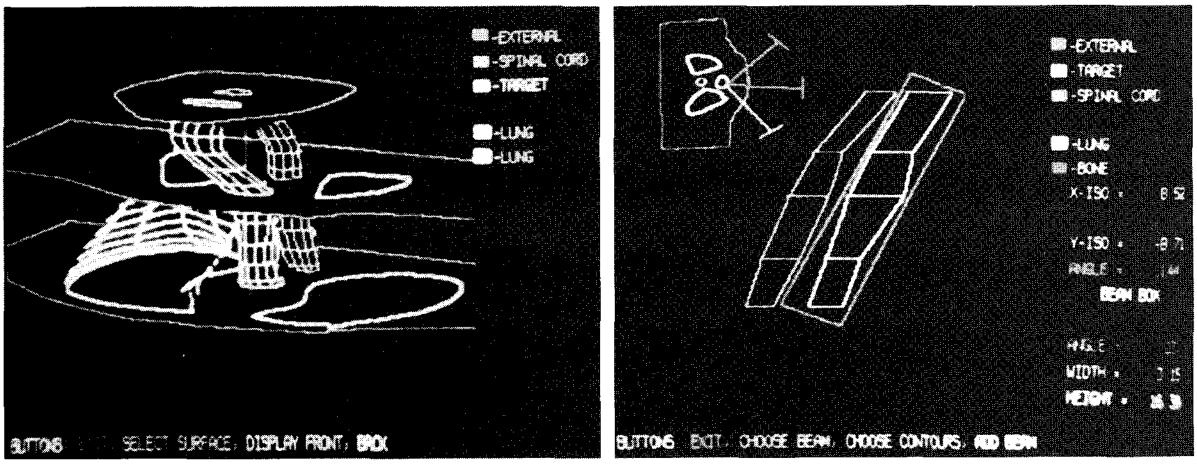

FIG. 3. Early 3-D treatment planning displays, reprinted in black and white from McShan *et al.* (Ref. 88). The first figure shows a 3-D graphical view of the anatomy of an esophagus case, while the second shows one of the first beam's eye view displays, along with the use of shielding for the spinal cord which was designed using the BEV display.

planning process, and this use was soon evaluated.[73–75] Furthermore, the electron density information which is directly obtained from the CT scans contained an accurate description of the various densities which are distributed throughout each patient. For the first time, it became possible to evaluate the practical importance of density corrections in dose calculations. Density correction methods had been studied for many years, but it was only with the introduction of CT that these methods (and future improvements) could really be important clinically. Cunningham summarized this work in 1983.[76] An excellent summary of early CT-based treatment planning work has been published by Ling.[77] MR imaging also has been used to help define the anatomy for the planning process. Although initially it appeared that quantitative use of MR would be difficult,[78,79] methods to allow the registration of the MR with CT (or other) datasets became available.[80–83] MR has become a routine part of 3-D treatment planning in some institutions.[84,85]

After the widespread distribution of CT-based treatment planning systems, the continually increasing power of modern computers, graphics processors, and software led to reconsideration of the three-dimensional aspects of the treatment planning process. The first modern "3-D planning" work began with the use of 3-D computer graphics in the late 1970s (Fig. 3), and included the pioneering of concepts such as the Beam's Eye View.[44,45,86–89]

The first routine clinical use of 3-D treatment planning began in 1986,[90–95] and numerous different 3-D planning systems have been reported in the literature since that time.[96–99] With the continued development and clinical experience with 3-D planning, the concepts of conformal therapy treatment gained real impetus. Beam's Eye View-based targeting of the tumor (shaping the beam aperture based on the geometric shape of the target) is being supplanted with full conformal therapy. In the latter, the high dose volume is truly conformed to the shape of the target volume by modifying fields and aperture shapes so that the desired isodose surface conforms tightly to the target volume in three dimensions. The use of dose volume histograms to analyze the resulting 3-D dose distributions[100,101] soon was enhanced by the availability of normal tissue complication probability (NTCP) models,[46,47] and then with clinical NTCP data.[102–104]

VIII. MODERN COMPUTER-CONTROLLED TREATMENT DELIVERY AND CONFORMAL THERAPY

As the 3-D treatment planning revolution was occurring, the first treatment machine designed to perform computer-controlled conformal radiation therapy (CCRT), the Scanditronix MM50 racetrack microtron, was developed in Sweden.[105–107] The MM50 includes a fully computerized control system, a computer-controlled multileaf collimator,[108] photon and electron beams up to 50 MeV,[109,110] and a unique computer-controlled point-scanned electron and photon beam.[105,111] In recent years, most other accelerators have used computers as part of their accelerator control systems, and use of the computer-control capabilities has begun to be introduced. See, for example, the dynamic wedge implementation described by Leavitt.[112] While some systems like the racetrack microtron are designed for use with segmental therapy (the machine can automatically deliver radiation with a series of fixed "segments" or treatment ports), other machines are aimed more are pursuing "dynamic" therapy, in which the machine is moving while delivering beam.[3]

The most recent contribution to the spread in interest in CCRT has been the widespread availability of computer-controlled multileaf collimator (MLC) systems. A MLC consists of two sets of thin tungsten leaves (typically up to 40 leaves on each side of the collimator)[5,113,114] which are moved in and out of the beam by computer control. With a MLC, one can set shaped apertures for the beam under control of the computer, rather than being forced to enter the treatment room between each treatment field in order to place a new block aperture into the machine.

The combination of a computer-controlled MLC with the other computer-control capabilities of modern control systems can result in a treatment machine which is capable of very sophisticated conformal therapy treatments. However, use of a MLC for field shaping does not automatically result in conformal therapy. In fact, a simple substitution of MLC shapes for focused block shapes, without changing any other aspect of the plan, will always lead to a slightly worse dose distribution with the MLC.[115] The additional penumbra associated with the jagged beam edge due to the leaves of the MLC will always increase the dose outside the target, or decrease the dose inside the target volume, or both. The importance of these effects is currently a matter of some debate.[5]

True conformal therapy requires not only that the high dose volume be shaped (or conformed) to the three-dimensional shape of the target volume, but it also must minimize the dose to surrounding normal tissues. The "block replacement" mode of MLC use, in which field shaping based on lead alloy blocks is simply replaced by similar field shaping using the MLC, is quite different from conformal therapy. To perform conformal therapy with a MLC in general involves optimizing the individual MLC leaf positions for each of the fields in the treatment plan to obtain adequate target coverage and maximal normal tissue sparing. Concepts like the equivalent penumbra[116,117] can be used to design reasonable MLC shapes when operating in block replacement mode. For conformal therapy, a number of different methods for MLC shaping have been described,[5] but all of these methods are geometry based. A more sophisticated and dosimetrically based optimization of individual leaf positions will be required for MLC conformal therapy if one wants to avoid iterative dose calculations.

For true conformal therapy, the MLC and computer control open up a wide variety of possibilities for improving the dose distributions with which patients are treated. Computer control of the treatment machine helps return the flexibility with which radiation was directed toward the tumor in the beginning of the century, and offers increased accuracy, speed and ease when applying such fields to the patient. The MLC adds the additional control of individualized beam apertures from each different angle (Fig. 4). In addition, computer control capabilities open up the possibilities of modulation of the intensity distribution of each beam, using various segmental [115,118–120] or dynamic[105,121–123] techniques. Even relatively simple intensity modulation techniques, such as the multi-segment MLC-based technique used in our institution, have the capability of dramatically improving our ability to deliver the required dose to the tumor, while minimizing dose to normal tissues. The benefits of intensity modulation have long been known, as shown by the use of compensators.[124] These capabilities are now combined with other benefits of computer-controlled operation, and with the more sophisticated treatment planning and plan optimization approaches. Examples of the latter include the inverse planning method[125,126] and autonomous optimization methods such as simulated annealing.[127–129]

The treatment delivery process must be evaluated and modified to make possible the delivery of sophisticated computer-controlled conformal radiation therapy (CCRT) in the clinic in a routine way. One of the most critical aspects of the design of a CCRT delivery process involves study of the entire system, and creation of a model for the delivery process.[3,130,131] Various other aspects of the problem are quite important, including treatment delivery planning,[132,133] how the user and computer-controlled machine should interact,[134,135] collision avoidance issues,[132,133,136] and the database and electronic chart issues for these very complex plans.[137,138] Verification methodologies, such as the graphical checks incorporated into our Computer-Controlled Conformal Radiotherapy System (CCRS) (Fig. 5), are another important clinical requirement. CCRT plans are often too complex for the usual qualitative checks by the treatment therapists to be adequate verifications, even if supplemented with a computer verification system. The use of electronic portal imaging systems[139] to provide on-line verification of patient positioning and/or treatment portals is another critical part of a complete CCRT delivery scheme.

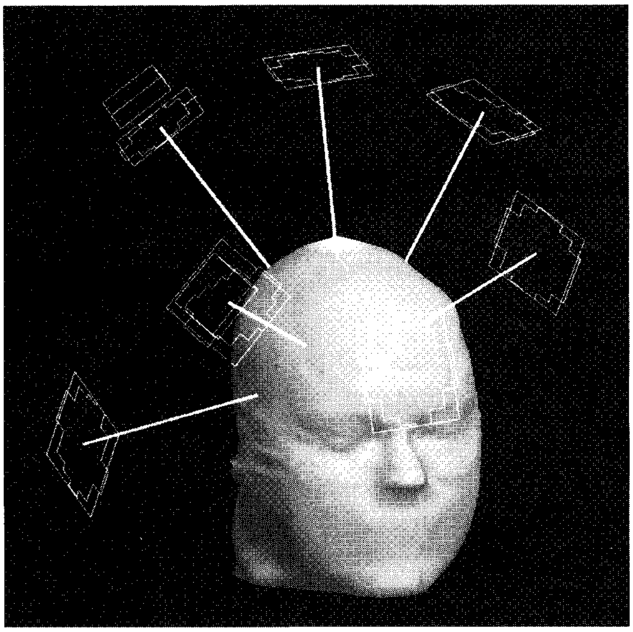

FIG. 4. Non-coplanar treatment plan for a brain tumor. Each field or segment is designed with a separate MLC aperture so that the dose distribution conforms to the target volume shape in 3-D.

Clinical application and analysis of modern 3-D treatment planning and conformal therapy treatments are finally determining some of the dosimetric relationships which will allow the true optimization of radiation treatments. The individualized 3-D description of each patient which is provided by CT, MR, and other modern imaging modalities, combined with the use of 3-D treatment planning, document the relationship between the 3-D dose distribution, the volume and fractionation of dose delivered to the tumor and to the various normal tissues. Thus, for the first time, one has a quantitative record of the dosimetric situation for each patient. When combined with clinical follow-up studies that evaluate tumor control and normal tissue complications, the relationships between dose, volume, complications, and tumor control can be studied in a quantitative way.

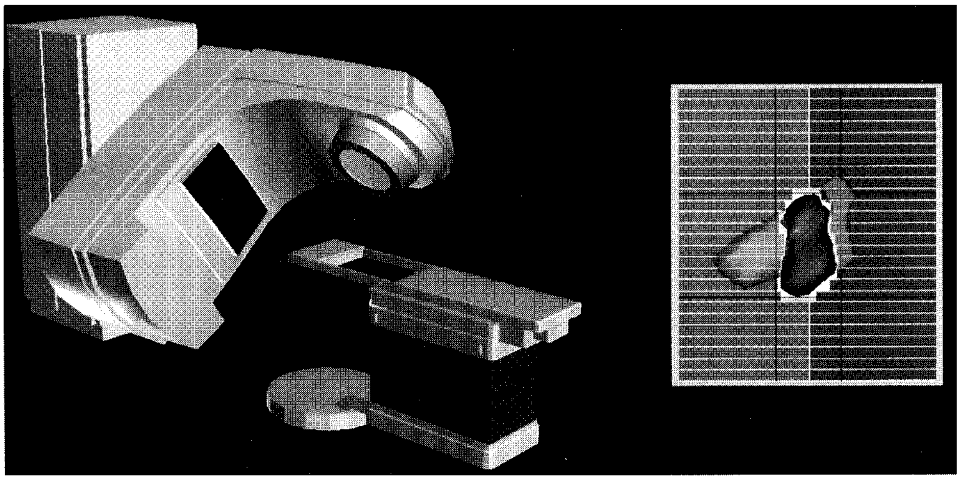

FIG. 5. Graphical simulator for computer-controlled machine and MLC used to plan treatment delivery procedure, for simulation of the proposed treatment (including collision checks), and as part of a complete treatment delivery and verification system for computer-controlled conformal radiation therapy (Refs. 130 and 132). This image shows the Clinac 2100-CD (Varian Oncology Systems, Palo Alto, CA).

Numerous dose escalation trials based on 3-D treatment planning and conformal therapy are currently attempting to determine the doses which can actually be used to treat various tumors and sites. The studies include dose escalation for the prostate,[140,141] liver,[103,142–145] brain, nasopharynx,[146] and for the lung.[104,147–149] These phase I trials aim to determine the maximum tolerated dose[150] for the treatment techniques which are available. After the maximum tolerated doses are defined, phase II and III studies will begin to test the efficacy of the new treatment strategies.[150]

IX. SUMMARY

In a certain sense, the dose escalation studies currently in progress return us to the very early applications of radiation therapy, when the amount of radiation which should be used for a particular situation was not known. Then, the new modality was routinely used in a very empirical way to try to improve the clinical situation. Now, we attempt to determine the maximum tolerated doses, normal tissue complication probabilities, and tumor control probabilities for our available treatment techniques. In addition, we attempt to improve our capabilities for treatment planning, optimization, and delivery of the treatments in order to maximize tumor control and minimize the complication probability.

Our current attempts to find out how to optimize the dose distribution, how to choose the dose to be delivered, and how to minimize complications are certainly not new. The first pioneers were, however, hampered in their efforts. They had no way to compare doses, and did not have the careful quality control efforts which accompany most clinical treatments and studies which are now undertaken. Early workers could not really identify or localize tumors unless they were superficial, in contrast to our ability to image the entire 3-D anatomy of the patient, and our 3-D visualization tools which can be used to look inside the patient with very high precision. Although the early treatment machines allowed a high degree of flexibility in directing the radiation beam at the tumor, our use of computer-controlled machines has now allowed us to regain much of that flexibility, with a much higher degree of precision and control. The development and use of CT-based treatment planning, followed by 3-D treatment planning, has allowed the development of quite sophisticated treatment approaches that include techniques which were unavailable to the early workers in the field.

The present work on conformal therapy, using modern 3-D planning and computer-controlled treatment delivery systems to perform studies of dose escalation and minimization of normal tissue complications, is based on extensions of many concepts developed by the pioneers in the field of radiation therapy. Our challenge is now to use all these modern tools and capabilities in an appropriate way. We must find the best ways to treat our patients, maximizing the benefit while minimizing the costs. Much basic data on tissue tolerance and tumor control must be obtained, to provide a broad basis for our clinical decisions. We need to investigate the use of expensive modern technologies, and then test whether there are benefits from their use.[150] This requires careful comparative studies, designed so that they will actually answer the relevant questions. Once the new technologies are perfected, these studies will help us continue the impressive string of improvements and achievements which has accompanied the first hundred years of the therapeutic use of those new rays discovered by Roentgen a century ago.

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ABOUT THE AUTHOR...

Benedick A. Fraass, Ph.D., *is Professor and Director of Radiation Physics in the Department of Radiation Oncology in the University of Michigan Medical Center in Ann Arbor, Michigan. Dr. Fraass did his undergraduate work in physics at Stanford University, and completed M.S. and Ph.D. degrees in low temperature solid state physics at the University of Illinois, Champaign–Urbana. In 1980 he began his career in Medical Physics at the Radiation Oncology Branch of the National Cancer Institute in Bethesda, Maryland. During his* $4\frac{1}{2}$ *years at the NIH, he was involved with research in total skin electron dosimetry, field matching, electron interoperative therapy, peripheral dose issues, and various aspects of treatment planning. In 1984, Dr. Fraass moved to Ann Arbor with Dr. Allen Lichter, M.D., to lead the physics group in the Radiation Oncology Department at the University of Michigan. Along with collaborators Dan McShan, Ph.D., Randy Ten Haken, Ph.D., and many others, Dr. Fraass has been responsible for development, clinical implementation, and research on 3-D treatment planning, computer-controlled treatment delivery, and clinical conformal therapy.*