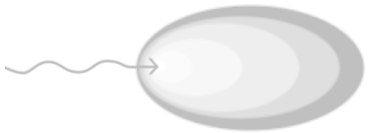
Chapter 1

Advances in Modern Radiation Therapy



Jacob Van Dyk

1.1 Introduction

Modern radiation therapy continues to progress at an unprecedented rate. The present rapid evolution is primarily related to the very significant advances in the modern technology of radiation oncology. This development is strongly linked to the evolution of computer technology and the corresponding advances in diagnostic imaging equipment. New "buzz words" have evolved in the last two decades, such as "three-dimensional conformal radiation therapy" (3-D CRT), "4-D radiation therapy," "intensity-modulated radiation therapy" (IMRT), "tomotherapy," "treatment gating," "breathing control," "adaptive radiation treatment," "inverse treatment planning," "multileaf collimation," and "image segmentation." Volume 1 of *The Modern Technology of Radiation Oncology: A Compendium for Medical Physicists and Radiation Oncologists* [85] provides a detailed description of all the technologies associated with radiation oncology, including the design details, as well as procedures for acceptance, commissioning, and quality assurance. This book, volume 2, provides an update on the recent evolution of the technology of radiation oncology, especially the advances that have taken place in the last 3 to 5 years. This chapter provides an overview of some of the recent advances, while subsequent chapters address the major developments in significant detail.

1.2 Historical Review of Radiation Therapy and IMRT

A brief historical review of radiation therapy was provided in chapter 1 of volume 1 [84]. In this section, a more detailed review is given specifically of the evolution of IMRT, today's standard for state-of-the-art radiation treatment. The goal of radiation therapy has always been to maximize the probability of controlling the tumor and minimizing normal tissue complications. The achievement of this goal is the key component driving the technological developments. While the increases in the energies of radiation producing machines from orthovoltage x-rays to cobalt-60 gamma rays and megavoltage accelerators have been a major component of these technological developments, field shaping and dynamic beam motions have contributed as well. Historically, five phases of radiation therapy development have been described [83]. These have evolved at different rates in different countries or even different institutions within the same country (Table 1.1).

It is interesting to note that it was not long after the implementation of megavoltage radiation therapy in the 1950s that sophisticated dose delivery and field shaping concepts were described in the literature. Johns et al. [35] described the development of isocentric rotational cobalt-60 machines. As early as 1965, Takahashi [77], in Japan, described some of the important concepts of 3-D CRT and IMRT delivery. He described the first use of a multileaf collimator (MLC), which he called a "geared sectional diaphragm" (Figure 1.1). The group at the Massachusetts Institute of Technology first developed asynchronous beam shaping devices [65,93]. In England the group at the Royal Northern Hospital [23] developed the tracking cobalt unit using simultaneous moving couch and gantry to generate conformal dose distributions. This was later extended by Davy and Brace in the 1970s and 1980s [17]. Similar work was also performed by the group at the Joint Center in Boston, using a linear accelerator [5].

From a conceptual perspective, Brahme and coworkers [6] and Cormack [9] independently presented many of the basic concepts related to developing shaped or intensity-modulated dose distributions. Some of the concepts were implemented in Sweden on a 50 MeV racetrack microtron. The actual "routine" implementation of IMRT was made possible by the commercial availability of computer-controlled MLCs and the corresponding inverse planning software required to define the multiple positions of each leaf during a segmented or dynamic delivery procedure [26]. Today, IMRT with inverse treatment planning is available in multiple institutions even in the smaller nonacademic clinics, especially in the United States, where significant reimbursement is available for such complex treatment procedures. Chapter 6 of this volume gives a detailed review of the present status of IMRT. The increase of IMRT activity in the past decade can be seen in Figure 1.2, which shows a plot of the number of publications on IMRT versus year.

1.3 The New Process of Radiation Treatment

The steps in the process of conventional radiation therapy, the technologies used, and the professionals involved were described in detail in chapter 1 of volume 1 of *The Modern Technology of Radiation Oncology* [84]. This section highlights the differences between 3-D CRT and IMRT. Figure 1.3 is a block diagram showing the major steps in the radiation therapy planning and treatment process for both conventional 3-D CRT and IMRT. The white boxes indicate that these specific steps are very similar, although with IMRT and escalating doses, there are greater concerns for precision and accuracy in patient immobilization, and a greater need for better resolution in all dimensions when imaging the

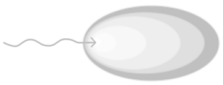


Table 1.1

The Major Phases of Major Technological Developments in Radiation Oncology [Adapted with permission from [83].]

PHASE	TIME	TECHNOLOGY	ISSUES/BENEFITS
1	1895–1940s	100–400 kV x-rays	Nonuniform doses to deep-seated tumors; skin toxicity; bone toxicity
2	1950s	Cobalt-60 4–8 MeV linacs 20–30 MeV betatrons	Megavoltage photons provide skin sparing; improved dose uniformity in the target and reduced doses to normal tissues; increased manual treatment planning
3	1960s–1970s	Multimodality linacs Computerized radiation treatment planning systems Simulators	Increased availability of linacs; increased use of computerized treatment planning; introduction of simulators; increased physics human resources to support the technologies; more systematized and comprehensive quality assurance
4	1970s–1980s	CT[1] combined with 3-D treatment planning	Improved targeting; reduced complications; improved dose computations
5	1980s–present	Development of computer-controlled dynamic treatments (IMRT[2]) Further improvements in imaging with CT simulators, MRI,[3] PET,[4] PET-CT	Allows dose escalation with increased probability of tumour control and reduced probabilities of normal tissue complications

[1] CT=computerized tomography.
[2] IMRT=intensity modulated radiation therapy.
[3] MRI=magnetic resonance imaging.
[4] PET=positron emission tomography.

patient, allowing for better target volume delineation and 3-D display. The gray-shaded boxes indicate components in the process that have significant differences between 3-D CRT and IMRT. Thus, the definition of treatment planning constraints for IMRT is dependent on the mathematical objective functions that are used and their dependence on "importance" factors or "weighting" factors associated with normal tissue constraints. (See chapters 4 and 5 of this volume.)

IMRT differs from 3-D CRT in two very significant ways. First, IMRT uses an iterative plan optimization process, generally known as "inverse planning." Second, it uses intensity-modulated beams that can be delivered in a dynamic MLC (dMLC) mode or in a segmented MLC (sMLC) mode (i.e., multiple stationary fields with different MLC configurations). Both the inverse planning and the IMRT delivery are shown as "black boxes" to illustrate that, from a user's perspective, it is a "hidden" automated process by which the optimization is performed and the dose is delivered. Thus, while in the past the treatment planner would place the beam directions on the plan "manually" and perform the relative beam weightings and insert the appropriate beam modifiers, the new process provides a fully optimized plan automatically. Of course, the results of this automated process are very dependent on the constraints provided by the user. Similarly, in the past, radiation therapists (technologists) have positioned the patient and rotated the gantry to generate the required beam directions. The IMRT approach may require the therapist to set beam directions, but the dose delivery is with multiple beam segments or dMLC delivery. It can also be delivered while both the MLC and the gantry are moving dynamically. Thus, again, from a radiation therapist's perspective, he or she has to believe that it is being delivered accurately; hence, the

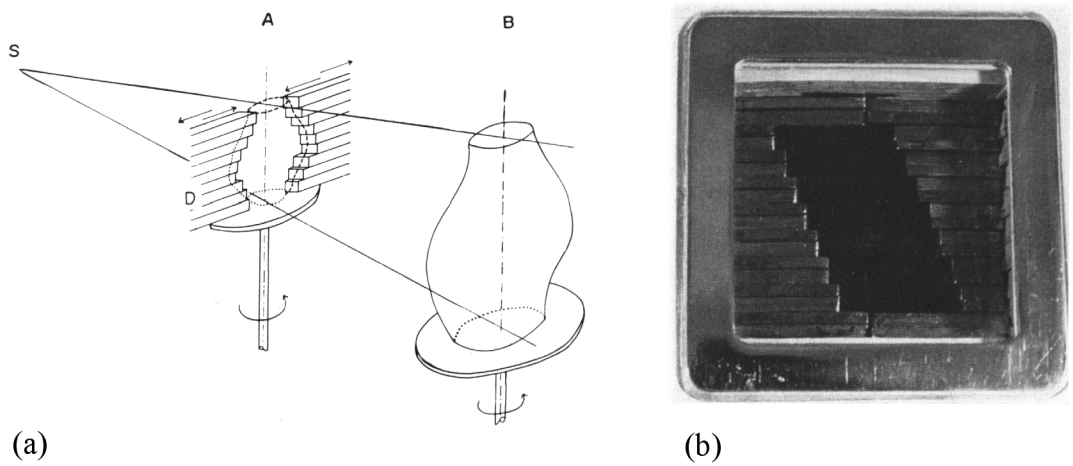


Figure 1.1
(a) Schematic of early (1965) MLC concept called "geared sectional diaphragm." (b) Picture of "sectional diaphragm." [Reproduced with permission from [77].]

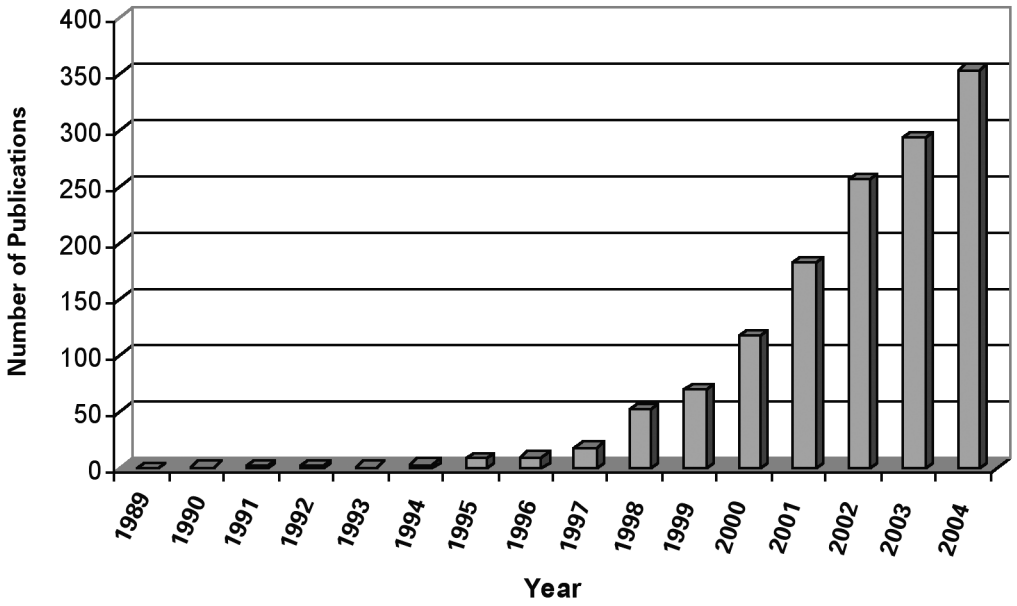


Figure 1.2
The number of publications on IMRT by year. These data were obtained by performing a PubMed search on the National Library of Medicine Web site for "intensity modulated radiation therapy OR IMRT OR intensity modulated radiotherapy" in May 2005.

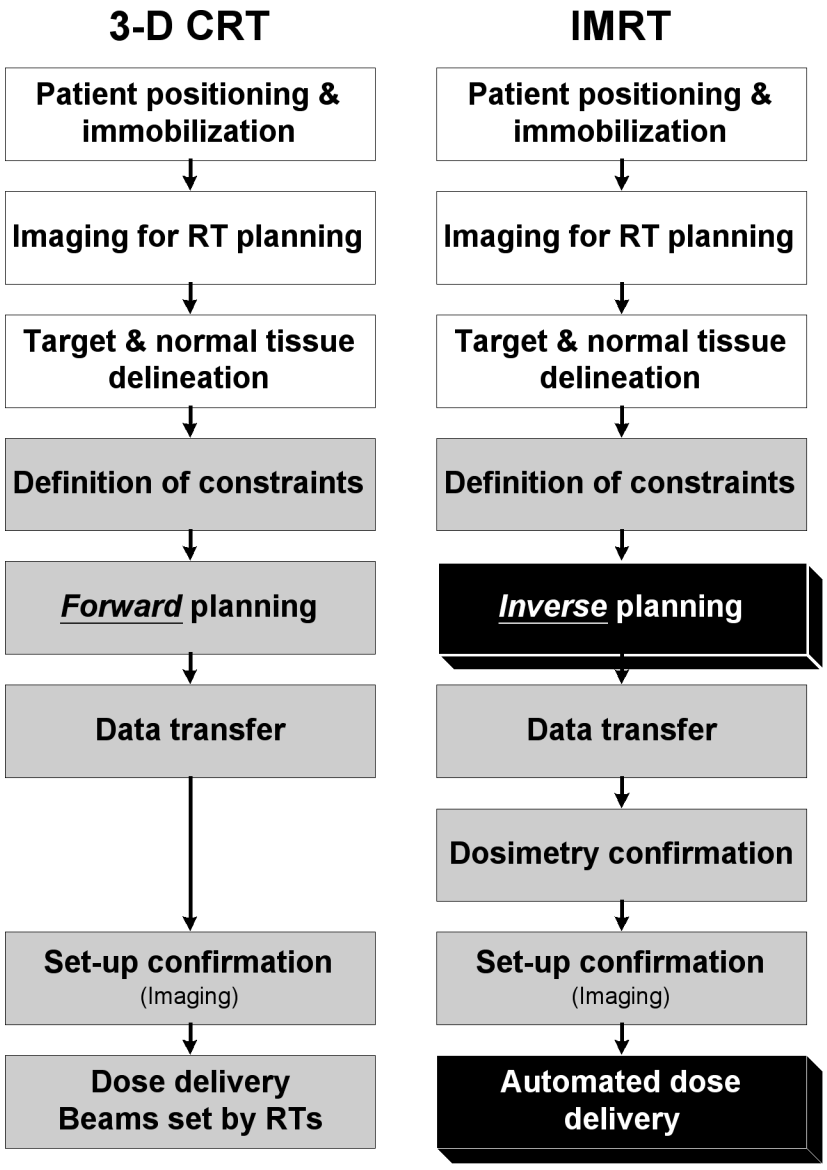


Figure 1.3
Comparison of the steps in the radiation treatment planning and dose delivery procedures for 3-D CRT and IMRT. The gray shading indicates that there are differences between the corresponding steps in 3-D CRT and IMRT. The black emphasizes that there are things that happen automatically and from the user's perspective behave like a "black box."

"black box" concept for both the inverse planning and dose delivery parts of the new radiation treatment process.

1.3.1 Patient positioning, immobilization, and adaptive treatment

Since IMRT provides more controlled and better-shaped dose distributions with large dose gradients between the target and the critical tissues, higher doses can be delivered to the tumor while at the same time providing adequate sparing of the normal tissues. This dose escalation, however, also requires improved precision in patient setup to ensure that the higher doses do not inadvertently irradiate normal tissues or that the tumor is underdosed. Thus, a lot of effort is generated to improve precision.

Verhey and Bentel, in chapter 3 of volume 1 [89], have described various methods of patient positioning and immobilization in detail. The implementation of these methods has not changed much in the last five years. However, what has advanced is the use of various imaging techniques to guide patient setup on a daily basis (see chapter 7 of this volume). Thus, ultrasound is now used in many clinics to guide the localization of the prostate on a daily basis [39]. Some larger academic institutions have installed a computed tomography (CT) scanner in the therapy room so that the patient is scanned before treatment to localize the tumor and to realign the patient (or the treatment) if necessary. An automated couch registration procedure is used to move the patient from the CT scanner to the therapy machine [96]. Most recently CT scanning capabilities have been implemented on the radiation therapy machines. Helical tomotherapy is one such modality that uses the megavoltage x-rays from the same source both to image and to treat [48,60]. This has been described in chapter 15 of volume 1 [60]. Cone beam CT is now also commercially available (see chapter 7 of this volume). It uses a separate kilovoltage x-ray source and flat panel detector to measure the transmitted radiation through the patient in a 360° rotation to generate kilovoltage CT images. These methods of daily online imaging provide the capability of adapting the treatment to the "target of the day." This approach has become known as "image-guided radiation therapy." While these procedures are now in clinical practice in some institutions, the next level of sophistication is to reoptimize the treatment based on the "target of the day" and the location of the normal tissues of the day. This will be true "adaptive radiation therapy."

Today's software and computer technology are not yet fast enough to do this in real time, at least not for external beam therapy. Real-time optimization is now being practiced for prostate brachytherapy, where dose distributions are automatically updated as new radioactive seeds are injected into the patient (see chapter 10 of this volume). As computer technology advances we can expect that real-time reoptimization with new MLC and/or IMRT configurations will also be developed for the optimized treatment of the day.

1.3.2 Imaging for target delineation

One of the very important steps of the radiation treatment planning process is the definition of the target that is to receive a high radiation dose. Multiple studies have shown that there can be tremendous inter- and intraobserver variation in the definition of the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV), dependent on the individual physicians, the clinical treatment site, the imaging modality that is used, and the training of the physicians [41,45,75,76,81,94]. Indeed, it can be argued that this is one of the greatest uncertainties in the total radiation treatment process as defined in Figure 1.3. Table 1.2 is adapted from Battista and Bauman [4] and summarizes the various imaging techniques in a matrix of contributions to radiation oncology, with new and expanding roles of functional diagnostic imaging [7,78] (see chapter 2 of this volume), verification imaging (see chapter 13 of volume 1 [58] and chapter 7 of this volume), and dosimetric imaging. These ideas have been further expanded by the concept of biological target volume (BTV) as proposed by Ling et al. [42], where different doses ("dose sculpting" or "dose painting") can be delivered to subvolumes of the malignant target, dependent on their metabolic, functional, physiological, genotypic, and phenotypic makeup as determined by various imaging modalities. The new imaging technologies now come in combination gantries (e.g., PET/CT, SPECT/CT), facilitating direct image registration (see chapter 2 of this volume). Much research is now underway in molecular imaging to develop means of assessing tumor signaling pathways to gain further insight as to the nature of the disease.

1.3.3 Definition of constraints

Developing an optimum treatment plan, which maximizes tumor control and minimizes normal tissue complications, involves the definition of the goals of the plan. Usually, a physician defines the dose to be delivered to the tumor, perhaps with a range of acceptability, e.g., 70 Gy with upper and lower limits of +7% and −5%. Along with the tumor prescription, the physician also defines the dose limits to normal tissues. In the past, physicians would often indicate a maximum tolerable dose, e.g., no more than 50 Gy in 20 fractions to the spinal cord. With 3-D CRT, much more dosimetric information is provided by dose-volume histograms (DVHs), which present relevant dose data in 3-D as a function of organ or tumor volume. With this 3-D information, it has become much more plausible to define partial volume constraints, e.g., no more than 25 Gy to 25% of the lung. This can be extended even further by defining constraints that represent several points on a DVH. With 3-D CRT, these constraints are met by comparing several plans with altered beam configurations that have been calculated by a forward planning process. With IMRT, forward planning is much more difficult, if not impossible, in view of all the possible field configurations that can be defined by the computer-controlled location of the MLCs. Because of the automated nature of inverse planning (see section 1.3.4), even the constraints can be defined as "hard" constraints, i.e., very important, or "soft" constraints, i.e.,

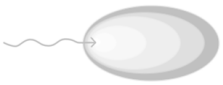


Table 1.2
Multimodality Imaging [Adapted with permission from [4].]

FEATURE	SIMULATOR	CT	MRI	MRS	SPECT PET	ULTRASOUND	PORTAL IMAGING
Open gantry	✔	(✔)	✔		(✔)		✔
Projection	✔	✔	(✔)				✔
Tomography	✔*	✔	✔		✔	✔	
Beam's-eye view	✔	✔	✔				✔
Fluoroscopy	✔					✔	(✔)
Surface contours	✔	✔	✔			✔	
Electron densities		✔					
Vasculature	✔	✔	✔			✔	
Gross tumor volume	✔	✔	✔		✔	✔	(✔)
Organs at risk	✔	✔	✔		✔	✔	(✔)
Clinical target volume				✔	✔		
Planning target volume	✔	✔					(✔)
Biological target volume			✔	✔	✔		
Verification		✔				✔	✔
3-D dosimetry		✔	✔	(✔)			

Bracketed (✔) denotes "under development" and ✔* denotes that it is available in a limited form.

CT=Computed tomography
MRI=Magnetic resonance imaging
MRS=Magnetic resonance spectroscopy
SPECT=Single photon emission computed tomography
PET=Positron emission tomography

would like but not absolutely essential. Thus constraints for specific normal tissues can also be given "weighting" factors or "importance" factors that are then used by the algorithm to aid with the automated optimization process. It is interesting that inverse treatment planning uses an objective function to allow for an automated optimization process. However, the definition of constraints that include weighting factors or importance factors is still a very subjective process. Often these constraints must be developed specifically for individual techniques to yield plans that are acceptable to the radiation oncologist. These "class solutions" are an important aid to make the optimization process more efficient.

1.3.4 Forward or inverse planning

Conventional planning is considered a *forward* planning process, i.e., the dose is calculated to tissues within the body using relevant information about the patient and the radiation beam. Then an optimal treatment plan is chosen by comparing a series of forward-planned dose distributions and selecting the one that best meets the criteria defined by the radiation oncologist, i.e., the constraints of the plan. In forward planning, the optimization is considered a "manual" process, since the treatment planner has to make specific adjustments to the treatment variables, such as beam directions, shapes, wedges, and compensators. In *inverse* planning, a desired dose distribution is defined (i.e., by the definition of constraints), and the computer calculates the required beam intensities and shapes to best meet the specified dose distribution or treatment objectives. With inverse planning, the user does not directly optimize or readjust beam intensities. If, however, the optimized plan is not considered acceptable, then the planner has to modify the dose-volume constraints and restart the

optimization process. The forward planning process yields dose distributions that are much more intuitively obvious, as opposed to inverse planning, where a computer algorithm defines the "optimum" dose distribution. It is for this reason that Figure 1.3 shows inverse planning as a "black box."

Central to the inverse planning algorithm is an *objective function*—a mathematical function that describes the quality of a treatment plan. Various mathematical procedures have been developed to minimize the objective function, usually by going through some type of iterative process. Objective functions can be based on dose criteria, dose-volume criteria, or biological criteria (see chapter 5 in this volume for the latter). While the use of a biologically based objective function is more relevant in principle, it is generally recognized that the state of biological modeling needs further enhancement and that radiobiological response data need reduced uncertainties before these are used routinely in the clinical environment.

1.3.5 Data transfer and dosimetry confirmation

Once the optimized treatment plan has been developed and approved by the radiation oncologist, the plan must be documented and the plan parameters must be transferred to the treatment unit. Because IMRT treatment plans involve very many MLC settings in addition to multiple other machine-related parameters, a wealth of information must be transferred from the treatment planning computer to treatment machine. Thus, there is a major dependence on electronic data exchange. This data exchange is greatly facilitated by the DICOM and DICOM-RT standards. However, integrity of the transferred data must be evaluated routinely, if not for every plan that is produced.

IMRT quality assurance (QA) consists of two major components [46]. First, machine QA must be performed as part of the commissioning process and then continuously reviewed to ensure consistency is maintained. Second, patient-specific QA must be performed to verify the intensity-modulated fields for an IMRT delivery for individual patients. This can be done in a number of ways. One approach is to recalculate the dose distribution on a phantom using all the treatment parameters that were determined for the patient plan. Using the patient plan data and transferring them to the machine, a plan can be delivered to the phantom after appropriate dosimeters (e.g., film, ionization chambers, thermoluminescent dosimeters (TLD), MOSFETs, diodes) have been placed in the phantom. The resulting measurements after the dose is delivered can then be compared directly to the calculations performed on the phantom. This tests the total treatment process. Alternatively, one can compare measured and calculated point doses on a flat homogeneous phantom for each of the individual patient fields [46]. This provides a monitor unit (MU) check, although it does not check the validity of the total plan in its composite form. Another process for assessing the MU accuracy is to use an independent software package to generate MUs for specific field configurations.

1.3.6 Treatment setup confirmation

It is obvious that the patient position that was used during the imaging for radiation therapy planning must be reproduced at the time of treatment for each individual treatment fraction. It is also well recognized that this is one of the major challenges in radiation treatment. Patients, being fairly elastic and pliable, tend to change shape from day to day, especially over a course of treatment with 30 to 40 fractions given over 6 to 8 weeks. This results in considerable uncertainty in locating the beam on the target and avoiding unwanted normal tissue irradiation. This uncertainty has been accommodated by leaving a margin around the region to receive a high dose using the PTV concept [30]. However, if the margin size can be reduced, less normal tissue will be irradiated, with the potential for escalating the tumor dose. There are various methods available to aid patient setup reproducibility. The conventional approach is to use three-point laser alignment on specific skin marks or tattoos. This, however, does not address internal tumor or organ motion. The next level of sophistication is to use portal imaging, either with film or with an electronic portal imager, to align the beam with respect to bony anatomy (see chapter 13 of volume 1 [58]). If film is used, then, for practical reasons, this alignment can only be used a few times during a course of treatment. If real-time electronic portal imaging is used, then this alignment can be performed on a daily basis. With such bony alignment, the tumor and normal tissue positions do not always remain constant with respect to the position of the bony structures. For this reason, some tumor sites use radiopaque fiducial markers, such as metallic seeds, injected in the target tissues, to truly assess the alignment of the target on an electronic portal image. An example of this is the use of gold seeds within the prostate, as published by Alasti et al. [3]. The use of such fiducial markers allows for online corrections to localize the tumor within the high-dose region of the beams on a daily basis. However, neither variation in target shape nor the location of critical normal tissues can be assessed on a daily basis using this approach.

As indicated in section 1.3.1, the most sophisticated approach is to generate daily 3-D image data of

the entire region requiring irradiation. The various approaches for this are addressed in detail in chapter 7 of this volume. In brief, several options are possible. One approach is to place a conventional CT scanner in the room with the accelerator [38]. A full set of CT images is taken to determine the location of the target and the normal tissues in three dimensions. Kuriyama et al. [38] report a positional accuracy of under 0.5 mm. Another approach is to generate CT images directly on the radiation therapy machine. To this end, various authors have reported on the development of generating megavoltage CT scans on a conventional linear accelerator used for radiation treatment, either using a single slice approach [59,69] or using a cone beam technique [56]. More recently, a cone beam CT approach has been described in which an independent kilovoltage x-ray beam and detector system was mounted on the gantry of a standard linear accelerator [33]. Perhaps the most sophisticated approach has been developed by Mackie and his group [48,60], in which the machine is specially designed for both IMRT delivery and onboard CT imaging. The technology is known as helical tomotherapy, reflecting its helical slice imaging and delivery capabilities. Each of these in-room or onboard CT imaging capabilities allows for the daily alignment, in three dimensions, of the target and normal tissues with respect to the original planning images. While these technologies allow the alignment of targets and normal tissues within the patient, they do not yet account for the possible changes of shape of the target or the normal tissues. Ideally, one would like to be able to generate a real-time reoptimized treatment plan to account for the shape and location of the target and the normal tissues of the day. While this is not achievable with today's optimization algorithms due to their slowness, it is anticipated that this will be a major focus for research and probably will become reality in the future.

1.3.7 Dose delivery

Again considering Figure 1.3, in conventional dose delivery procedures, the radiation therapist sets up the patient and each individual beam direction. The field shape may be determined by the MLC settings. If necessary any ancillary devices (e.g., wedges, compensators, shields, bolus) are inserted into the beam, the number of MUs is set on the control console, and the patient is treated. From a QA perspective, the radiation therapist (technologist) can observe each setup parameter and confirm that these make sense and are consistent with the treatment plan.

For IMRT dose delivery, this QA check by the therapist is much more difficult. The treatment may involve moving MLCs while the beam is on and, for some techniques, while the gantry is moving. Clearly this makes it impossible for the therapist to check that the delivery is given as intended. Hence, this component of the treatment process, as shown on Figure 1.3, is shown as a "black box." For this process, it is important that there is a pretreatment confirmation of the plan, as described earlier, and that there is sufficient electronic redundancy to ensure that the delivery is carried out as intended.

In addition to the assurance that the treatment is carried out as intended, there also has to be sufficient pretreatment commissioning to account for issues related to the dosimetry associated with small fields when using MLCs, e.g., MLC curved ends, MLC transmission both inter- and intraleaf, MLC leaf speeds, MLC position calibration, head scatter, etc. These issues are discussed in detail in chapter 6 of this volume.

1.4 Potential Impact of the Modern Technology of Radiation Oncology on Predicted Treatment Outcome

Our group at the London Regional Cancer Program (London, Ontario, Canada) has been performing research on optimizing radiation therapy by the assessment and reduction of treatment-related uncertainties. We hypothesize that modeling the propagation of these uncertainties will allow (1) for the identification of those uncertainties that most significantly impact clinical outcome, and (2) simulation of strategies to reduce uncertainties and improve the therapeutic ratio to allow a safe increase in tumor control probability (TCP) while minimizing normal tissue complication probabilities (NTCP). Our overall goal is to develop and implement a methodology that is capable of incorporating uncertainty information in the clinical treatment plan evaluation process and in the prediction of clinical outcome, thus providing a tool to aid the optimization process.

We have modeled organ motion and patient setup uncertainties especially for external beam treatment of cancer of the prostate [11–13,15]. Table 1.3 provides a brief overview of some of the research results that provide input into the overall radiation therapy optimization process.

Our recent research has evaluated the impact of variations in patient setup from day to day on the actual dose delivered to specific tissue voxels and then the conversion of this "real" dose delivery to a radiobiological response. By using this methodology we were able to determine the potential clinical benefits of different patient setup and image guidance strategies. By way of example, a brief summary of one component of this

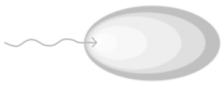


Table 1.3

Summary of Uncertainty Analysis for Various Situations in the Radiation Treatment Process as Performed by Our Group at the London Regional Cancer Program

UNCERTAINTY ISSUE	SOME OBSERVATIONS AND KEY CONCLUSIONS	REF.
Definition of margins for defining target volumes accounting for random and systematic uncertainties	Effects of systematic uncertainties are not always linear. Effects of systematic uncertainties when small are negligible but predominate when large; therefore, should attempt to minimize systematic uncertainties to predefined levels. Non-uniform margins should be used where geometric uncertainties are anisotropic and/or organs at risk may be spared.	[11]
Limitations in convolution calculations due to the shift invariance assumption	Errors near the patient surface are significant (>20%). Our modification to the convolution method greatly improves accuracy near surfaces (<5%). Especially relevant for targets in the head and neck and breast regions.	[12]
Limitations in convolution calculations due to the assumption of infinite number of fractions	For conventional fractionation schemes, the error in using convolution to generate plan evaluation parameters is smaller than the maximum error in the dose distribution.	[13]
Impact of geometric uncertainties on hypofractionated external beam prostate treatments	Intuitively one expects that geometric uncertainties will have greater impact when fewer fractions are used. This analysis suggests that the magnitude of the impact is small. It does not appear that geometric uncertainties will limit the potential therapeutic gains of hypofractionated external beam prostate treatments.	[15]
Impact of treatment uncertainties on modern IMRT compared to 3-D CRT	Contrary to the widely held belief, conformal dose distributions with steep dose gradients, such as the IMRT plans, are not always deteriorated by random geometric uncertainties. The consideration of geometric uncertainties can change the perception of a treatment plan considerably.	[15,16]
Generation of composite dose distributions accounting for organ motion in daily setups	By using an image warping technique, we have been able to generate composite dose distributions to individual tissue voxels accounting for daily variation in patient setup. For a clinical prostate case, we demonstrate that there are significant localized dose differences (>10%) in a single fraction, as well as in 15 cumulative fractions, when compared to the planning dose distribution, assuming no changes in anatomy.	[68]
Treatment plan optimization using different DVH reduction schemes and different radiobiological models	Whenever the preferred Lyman scheme [47] was used to reduce the DVH, competing plans were indistinguishable as long as the mean dose was constant. The effective volume DVH reduction scheme did allow us to distinguish between these competing treatment plans. However, plan ranking depended on the radiobiological model used and its input parameters.	[54]
Evaluation of the assumption in radiobiological NTCP calculations of uniform effect per unit volume.	A differential response in different lung regions was evaluated in rodents. If the existence of these effects is proven in humans, it will require the incorporation of geometrical and directional information in normal tissue complication probability calculations for lung—considerations that are ignored in present approaches using conventional DVHs.	[52]

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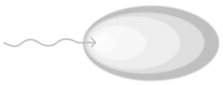

Table 1.3
Continued

UNCERTAINTY ISSUE	SOME OBSERVATIONS AND KEY CONCLUSIONS	REF.
Generation of dose-volume response data for radiation pneumonitis from a cohort of thymoma patients	Dose-volume response data were generated for the thymoma patients and compared to other published data. Significant variations occur among the published data. Mean dose in lung strongly correlated with lung complications that manifest clinically, and the determination of the dose-volume dependence is affected by the choice of endpoints, i.e., whether based on clinical symptoms or radiographic changes not accompanied by clinical symptoms.	[55]
Evaluation of the impact of uncertainties on the generation of dose-volume response data.	Our findings have implications for the use of existing clinical data that have unavoidable inherent uncertainties characteristic of older technologies. These may not be predictive of the therapeutic gain to be expected from new dose delivery technologies in which such uncertainties will be substantially reduced. Even if the uncertainties are known, it is not possible to extract the underlying dose-response parameters.	[53]
Characterization of prostate motion using implanted fiducials with portal imaging and CT scanning	Quantified the extent of systematic and random organ motion in prostate patients with conventional treatment setup. Unexpected systematic error detected attributable to the urethrogram.	[43,44]
Inter- and intraobserver variation in target volume delineation and differences in target volume delineation by imaging modality	Quantified the measurement of prostate volume and length of 10 patients, 7 observers each contouring twice on CT, MR, and ultrasound. Determined volume ratios and inter- and intraobserver standard error of the mean by imaging modality.	[70]

research is given here as an illustration of the potential benefits of the implementation of modern technology of radiation oncology on clinical outcome.

We simulated patient treatments by importing the beam arrangement from the treatment plan into multiple repeat CT studies acquired during the treatment course of five prostate cancer patients. The repeat CT studies each represented a daily patient treatment setup on the therapy machine. The dose distribution was calculated on each CT study, thus representing the dose delivered to the patient on that day. This specific day's dose distribution was then mapped back to the planning CT study using a contour-driven thin-plate spline algorithm [66,67]. Figure 1.4a shows an example color wash dose distribution that we normally obtain at the time of treatment planning using a six-field conformal technique. Figure 1.4b shows a similar dose distribution on a CT image taken on the first day of treatment. The internal contours represent the prostate and the rectum. It is obvious that the rectum is enlarged compared to the planning CT study and that the prostate is displaced anteriorly. Figure 1.4c shows the dose distribution of Figure 1.4b, but mapped back to the planning CT scan using the warping algorithm. This represents the dose delivered to the tissue voxels as seen on the planning image. Figure 1.4d is a dose difference map comparing the distribution of dose as "actually" delivered to specific tissue voxels on the first treatment day to the planned dose distribution. For one fraction the dose differences could be as large as 40% to 60% to some tissue voxels. In this example, the dose to the rectum is significantly higher, as is obvious from the change of the rectum location, and the dose anterior to the prostate is significantly lower.

Using this approach, various patient setup scenarios were compared to assess the impact of image guidance on radiation treatment precision using this six-field conformal technique. These scenarios included (1) daily alignment to skin marks, thus representing a conventional beam setup without image guidance; (2) alignment to bony anatomy for correction of daily patient setup error, as would be done by electronic

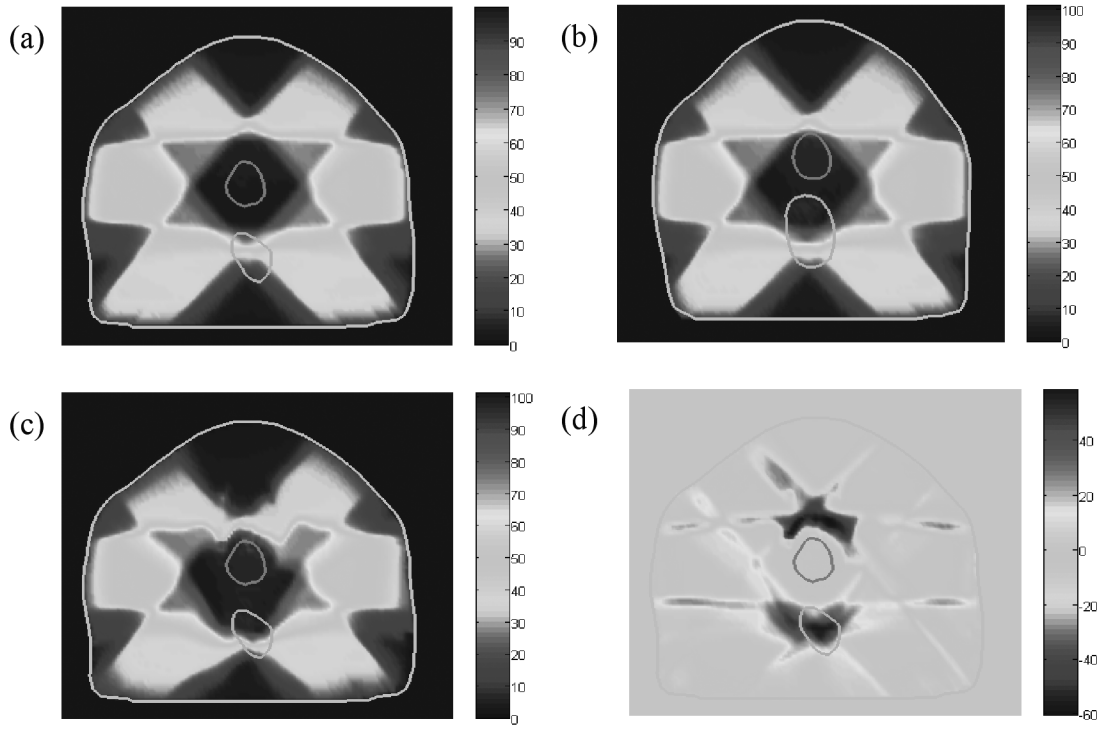

Figure 1.4
(a) Dose distribution as obtained at treatment planning. Note the prostate and rectal contours. (b) The dose distribution as obtained on the first day of treatment. (c) The dose distribution from (b) as mapped onto the planning CT study using the warping algorithm. (d) The dose difference distribution by subtracting the distribution in (c) from that in (a). SEE COLOR PLATE 1.

portal imaging; and (3) alignment to the "CTV of the day" for correction of interfraction tumor motion. A fourth situation was also assessed by repeating treatment scenario (3) with a reduced CTV to PTV margin. Figure 1.5 shows the impact of different image guidance strategies using dose difference maps for (a) daily alignment to laser marks, (b) daily alignment to bony landmarks using, for example, electronic portal imaging, and (c) some form of image guidance to align the beams to the CTV. These data, however, are for one fraction only. Table 1.4 shows the results when such data are accumulated over 15 fractions (only 15 sets of treatment CT studies were available in this analysis). Clearly, there are very significant differences in dose to the patient as determined from the calculation obtained during conventional treatment planning compared to what is actually delivered to the patient when accounting for daily geometric changes that occur as a result of organ motion and deformation.

The use of daily realignment gives the opportunity to reduce the margin size since, in principle, the beams will more closely align with the target. Daily realignment to the tumor combined with reducing the margin size from 1.0 cm to 0.5 cm resulted in an average escalation in tumor dose of 9.0 Gy in an original prescription dose of 70 Gy for all static plans while keeping the normal tissue constraints the same. However, the escalated prescription dose was 13.8 Gy when accounting for changes in anatomy by accumulating daily doses using nonlinear image registration techniques. The results from this work provide quantitative information on the effectiveness of image-guided treatments and may guide decisions as to when and how to implement adaptive treatments.

A further evaluation of the quantitative benefits of image guidance was performed by our group [73]. The purpose of this specific study was to evaluate various image-guided target localization techniques for daily patient setup, as described above, and their potential impact on the outcome of prostate cancer radiation therapy to mitigate against geometric uncertainties, in terms of TCP and NTCP. Figure 1.6 summarizes results of a dose escalation analysis considering conventional fractionation. For the TCP calculations, the results were

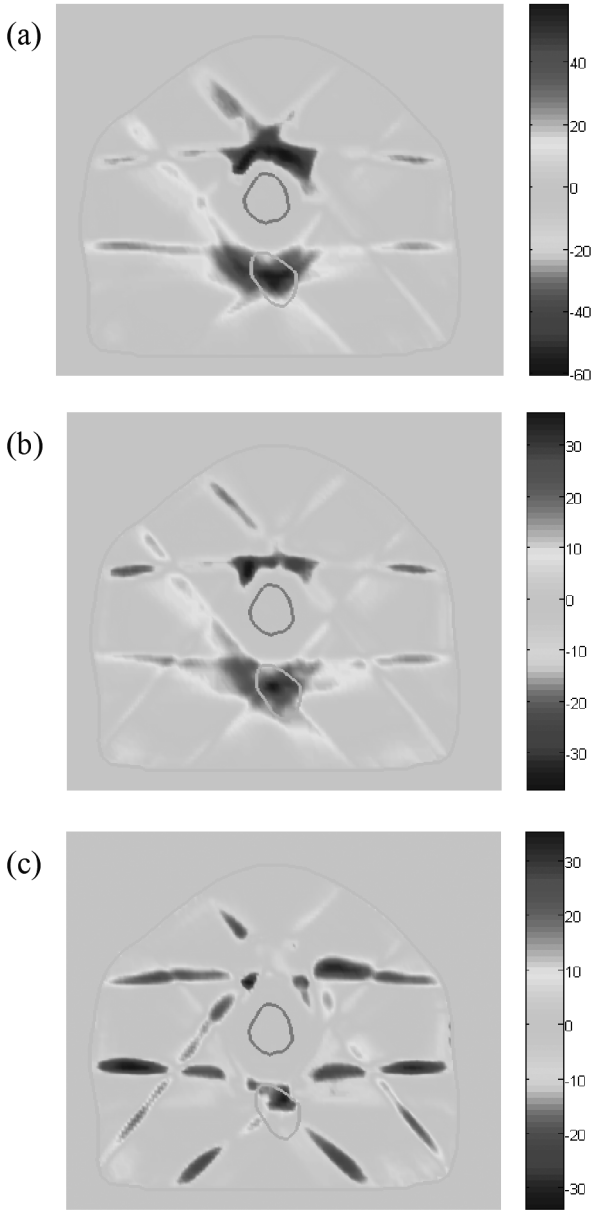

Figure 1.5
Dose difference maps for one fraction comparing treatment on day one to the planned dose distribution for (a) daily alignment to laser marks, (b) daily alignment to bony landmarks using, for example, electronic portal imaging, and (c) some form of image guidance to align the beams to the CTV. SEE COLOR PLATE 2.

generally quite consistent for each setup guidance technique except when the margin was reduced with the tattoo setup technique, which resulted in a significantly lower TCP. For NTCP of the rectum, it is clear that the image-guided technique ("CTV align") with reduced margin size results in the lowest NTCPs. Thus, as expected, the most effective way to reduce NTCP was to reduce the margin size from 10 to 5 mm combined with the use of image guidance. If one assumes that a 5% rectal complication rate is acceptable for prostate treatments, then it can be seen on the figure that significant target dose escalation is possible with a corresponding increase in TCP using more advanced image guidance procedures.

It is studies such as these that will ultimately provide the optimized form of radiation treatment. Clearly, the use of image guidance along with accurate radiobiological models for treatment optimization will become standard practice in radiation treatment.

1.5 QA Considerations

The increased complexity of the modern technology of radiation oncology places greater pressures on QA and quality control to ensure that patients are treated safely. The International Organization for Standardization (ISO) defines QA as "all those planned and systematic actions necessary to provide adequate confidence that a product or process will satisfy given requirements for quality" [32]. There are two major components to this definition of QA. The first is that there has to be some quantitative measure that determines whether a product or process has met the desired standard. Second, if the product does not comply with the standard, then there must be a defined process to bring the product in line with the standard. ISO also defines quality control (QC) as "the regulatory process through which the actual performance is measured, compared to existing standards and finally the actions necessary to keep or regain conformance to the standard" [32]. Thus, QA is the plan and definition of systematic actions and QC is the actual measurement and assessment process.

While the ISO has provided a generic definition of QA and QC for *any* product or process, for radiation therapy there are two very major considerations. The first of these is that the *treatment is carried out accurately* and that all uncertainties are kept to acceptable levels. The second consideration relates to *the avoidance of treatment errors* or treatment misadministrations.

1.5.1 Treatment accuracy in modern radiation therapy

It is generally well recognized that the goal of radiation therapy is to deliver a dose of radiation to the target volume with an overall accuracy of 5% [19,29,51]. (See also chapter 9 of this volume.) However, there are several issues to consider when the

Table 1.4

Percent Dose Differences Comparing Planning Dose Data to Specific Tissue Volumes over a Course of 15 Fractions [Data from [67].]

STRUCTURE	LASER SETUP	SETUP CORRECTED	CTV REALIGNMENT
Prostate[1]	−5.5	−1.4	−1.4
Rectum[2]	+32.7	+19.5	+5.9
Bladder[2]	+35.7	+35.2	+39.2

[1] For a single voxel.
[2] For a 2 cm^3 volume.

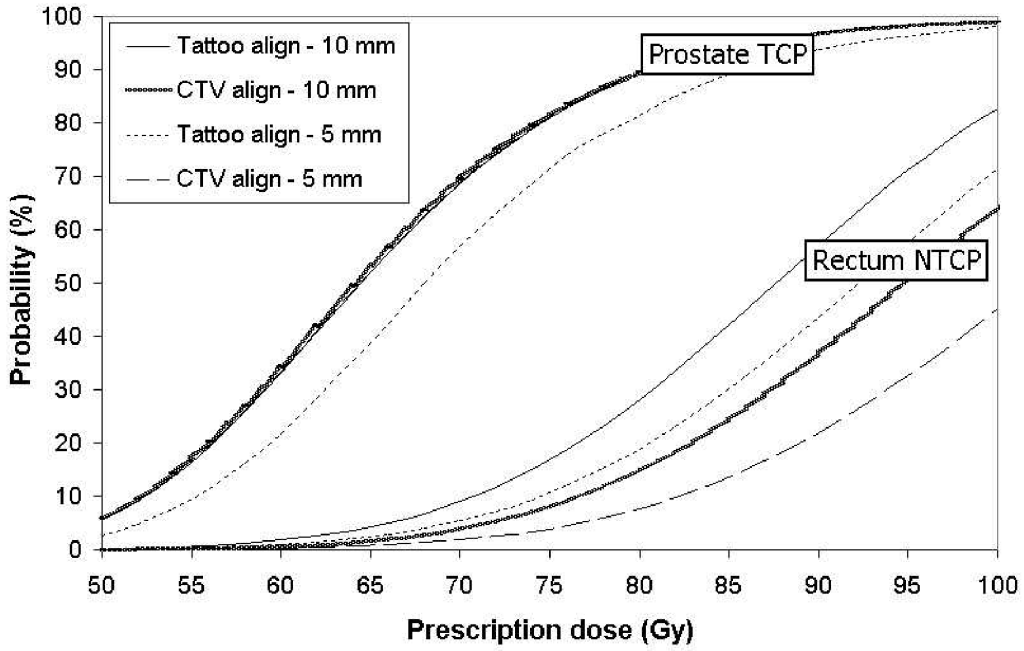

Figure 1.6
Comparison of TCP and NTCP calculations for various patient setup and image guidance strategies. "Tattoo align" refers to daily setup using lasers to skin tattoo marks, and "CTV align" refers to the use of some image guidance technique such as "on board" kilovoltage CT, or megavoltage CT as provided by helical tomotherapy, or ultrasound. Significant target dose increases are possible if rectal complication level is held constant, thus resulting in the potential of significant increases in TCP.

accuracy of 5% is quoted. First, while, in general, 5% is the desired goal, there may be circumstances where 5% accuracy is not entirely necessary or where it might be quite "costly" to achieve. "Costly" here could consider the financial cost of treatment or it could consider the cost to the patient in terms of preparation time or setup time for a more accurate treatment. For example, one could argue that a quick emergency treatment for palliation purposes might not need the rigor required for a high-dose, radical treatment. A philosophy that is analogous to the ALARA principle in radiation safety could be considered in radiation therapy (i.e., in radiation safety, one plans to allow radiation doses to any individual to be

"as low as reasonably achievable [ALARA], social and economic factors being taken in to account"). Thus, we should use a philosophy of "as accurate as is reasonably achievable (AAARA or A^3RA), technical and biological factors being taken into account."[1] This implies that perhaps 5% accuracy is not required under all circumstances. Under some conditions the accuracy should be better than 5% and under other circumstances a larger uncertainty might be acceptable or realistic. Examples of the latter could include total body irradiation (although one wants to ensure that the dose to some critical organs at risk is understood to an accuracy of 5% or better), some palliative treatments (e.g., spinal cord compression or half body irradiation for widespread disease), and some forms of brachytherapy. Furthermore, in some regions of dose delivery, a 5% accuracy in dose delivery will be very difficult to achieve. Examples of this include regions near, or in, the penumbra, or regions outside of the penumbra where the dose is rather low, or in the buildup region where the issues of electron contamination are very difficult to model accurately. Indeed, different ranges of accuracy have been quoted by various reports defining criteria of acceptability for treatment planning computers [21,27,86,88]. Also, the criteria of acceptability for regions with rapidly changing dose gradients are quoted in spatial units of distance to agreement (in millimeters) rather than in units of relative dose. Note that the AAARA principle is not an argument for "sloppy" radiation therapy. Rather it is an argument for the realistic issues associated with radiation treatment and a recognition that the determination of the radiation dose delivered to any point in the patient to an accuracy of 5%, at the present time, is unrealistic.

However, when we do aim to achieve an overall accuracy of 5% in dose delivery to a reference point in the patient, there are a number of subcomponents to the treatment process that each will require its own level of accuracy. One relatively simple example of this is illustrated in Table 1.5. The numbers in Table 1.5 refer primarily to dose delivery within high-dose regions such as the PTV. The "overall uncertainty" is determined by adding the uncertainties associated with each subcomponent in quadrature.

In view of these comments about dose delivery accuracy, a question needs to be asked about whether there are any changes in accuracy requirements with modern radiation therapy using such techniques as 3-D CRT or IMRT. As we reduce our safety margins around the CTV to generate the PTV, and as we escalate prescription doses, there is an increased concern about normal tissue complications. As a result, the spatial accuracy associated with beam direction and dose delivery to specific tissue volume elements (voxels) needs to be better than it has been for conventional therapy. Thus, improved immobilization procedures are required. Techniques for this have been discussed in detail by Verhey and Bentel (see chapter 3 of volume 1 [89]). Furthermore, chapter 8 of this volume describes issues associated especially with thoracic treatments where the effects of breathing motion are considerable. Methods of mitigating against these effects are described in detail in that chapter and are now being implemented by a number of cancer centers.

[1] A similar concept was described by Van Dyk in 1983 [82] in the context of large-field radiation therapy. At that time, it was described as the APARA (as precise as reasonably achievable) principle; however, for interinstitutional comparison, accuracy is more important than precision.

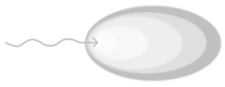

Table 1.5

Examples of Accuracy Requirements in Subcomponents of Radiation Therapy Dose Determination Process

	UNCERTAINTY TYPE	ESTIMATED UNCERTAINTY (%)
1	Absorbed dose to reference point in water	2.5
2	Determination of relative dose (measurement away from reference point)	2.5
3	Relative dose calculation (using the treatment planning computer)	2.5
4	Patient irradiation	2.5
	Overall uncertainty in dose delivery	**5.0**

1.5.2 The avoidance of errors in radiation treatment

As indicated above, there are two considerations that rationalize the need for QA in radiation therapy: the first has to do with ensuring treatment accuracy and the second deals with the avoidance of treatment errors.

Treatment errors in medicine go by various names including "treatment misadministrations," "treatment incidents," "treatment accidents," "unusual occurrences," "treatment discrepencies," and "adverse events." In 2000, the Institute of Medicine in the United States published a detailed report on treatment errors in medicine, in general, entitled "To Err is Human: Building a Safer Health System" [37]. They define treatment errors as "the failure of planned action to be completed as intended" (i.e., error of execution) or "the use of a wrong plan to achieve an aim" (i.e., error of planning). They estimate that there are about 44,000 to 98,000 people in the United States who die annually from medical errors. These deaths represent more than annual deaths from motor vehicle accidents, or patients who die from breast cancer, or deaths from AIDS. The estimated total annual cost of these errors is $38 to $50 billion per year. The most common types of errors are categorized as being related to "technical" (44%), "diagnosis" (17%), "failure to prevent injury" (12%), and "use of drugs" (10%).

The discussion of medical errors has become more public in recent years. This is clear from two major reports on errors in medicine in the United States published in the early 2000s [37,72]. Similar trends have been observed in radiation therapy. Indeed, the 2001 European Society of Therapeutic Radiation Oncology (ESTRO) Gold Medal Lecture was entitled "Irradiation Accidents: Lessons for Oncology?" [10] Furthermore, the International Atomic Energy Agency (IAEA) and the International Commission on Radiological Protection (ICRP) published reports in 2000 on "lessons learned from accidental exposures" and "prevention of accidental exposures" in radiation therapy, respectively [28,31]. More recently, individual institutions have published summaries of their own recorded/reported error rates [24,95]. Huang et al. [24] concluded that new technology can produce new ways for errors to occur, necessitating ongoing evaluation of QA for radiation therapy.

The recent reviews of accidental exposures in radiation therapy by international committees [28,31] provide some clear lessons that should be recognized by the professionals involved in prescribing, calculating, and delivering radiation treatments. The IAEA report [28] describes 92 accidental exposures in radiation therapy and highlights some lessons that can be learned from the review of these accidental exposures. Table 1.6 summarizes the number of specific types of errors that they reviewed. The information on these accidental exposures was derived from reports to regulatory authorities, professional associations, or scientific journals, or the incidents became known through other publications.

Similarly, the ICRP report [31] reviews a number of case histories of major accidental exposures of patients undergoing radiation treatment, with the intent of preventing such accidents from recurring in other institutions.

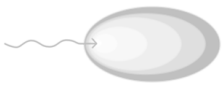

Table 1.6

Summary of Types of Accidental Exposures Reported by the IAEA [Data from [28].]

CATEGORIES	NUMBER OF ACCIDENTS
Radiation measurement systems	5
Machine commissioning/calibration	15
External beam: treatment planning, patient setup, treatment	26
Decommissioning of teletherapy equipment	2
Mechanical/electrical malfunctions	4
Brachytherapy low dose rate sources/applicators	29
Brachytherapy high dose rate	3
Unsealed sources	8
Total	92

It is not possible to address the details of the IAEA and ICRP reports in this chapter; however, it is possible to highlight the broad issues associated with occurrence of such accidents:

- Insufficient education
- Lack of procedures/protocols as part of a comprehensive QA program
- Lack of supervision of compliance with a QA program
- Lack of training for "unusual" situations
- Lack of a "safety culture"

Insufficient education will result in lack of awareness. Accidents can happen due to inattention to details and lack of alertness. This can be exacerbated by situations where personnel work in less than ideal conditions, in understaffed departments with long working hours and high patient throughput.

Accidents are also more likely to happen when there is a lack of policies, procedures, and checks in the treatment system. Furthermore, there needs to be constant vigilance to ensure that the procedures that have been developed are fully implemented, or if the procedures are changed, that the documentation is updated appropriately.

Errors are also more likely to happen when the staff are not trained appropriately or lack proper qualifications. Furthermore, staff at all levels need to be made aware of the distinction between standard procedures and unusual situations. Whenever unusual situations occur, staff should always be encouraged to ask questions, and no question should be considered a "stupid" question. An open attitude to uninhibited questions leads to a positive safety culture. A discouragement of questions or a negative attitude to questions leads to a negative safety culture.

It is also important that responsibilities and lines of authority are defined clearly so that there are no gaps or ambiguities as to who is responsible for specific tasks. In chapter 2 of volume 1 [87], a clear description was given of the need for a QA committee that includes representation of the major professionals involved in radiation treatment.

Radiation professionals need to realize that major radiation accidents are possible in any clinic. The minimization of such accidents is strongly dependent on the QA structure of the clinic, on the professional education of the staff, on onsite training for the use of new technologies as they are brought into the clinic, and on the attitude related to QA, especially by those who have more responsibility and authority. The combination of these issues generates a very positive radiation safety culture, with the result that there will be due diligence by all staff involved in treating patients with radiation therapy.

One approach to minimize the possibility of accidents is to use "defense in depth." This is defined as the application of more than one single protective measure for a given safety objective such that the objective is achieved even if one of the protective measures fails. Defense in depth can be viewed as several layers of safety provisions, such as physical components and procedures. For this multilayered accident prevention to work, these layers need to be independent of each other. The following is an example of such multilayers for a specific incident. One of the reported errors consisted of mistakenly inverting the SSD correction in the MU calculation. If only one calculation is done before the patient is treated then this would be considered a single layer between the actual calculation and the dose delivery. A layer can be added by performing an independent check of the MU calculation by another individual. A further layer can be added by doing a weekly chart check for "reasonability" of the result. In vivo dosimetry would add a further layer. Having a detailed write-up on MU calculation procedures would be equivalent to another layer, assuming, of course, that the written procedures are referred to regularly. Another layer would be added if the staff are well trained in recognizing that a shorter treatment distance means less MUs for the same dose.

The following is a series of questions that serve as a checklist for accident or error prevention in radiation therapy. These evolved out of the IAEA report [28]. Note that these are only examples of some of the issues that need to be considered.

- Organization, Functions, and Responsibilities
  - Have all necessary functions and responsibilities been allocated?
  - Are all functions and responsibilities understood?
  - Is the number of staff commensurate to workload?
  - Is this number reassessed when workload increases, or when new equipment is purchased?
- Education and Training
  - Is every member of staff educated and trained according to their responsibilities? Is this education and training documented?
  - Is there a program for continuing and individual development?
  - Are lessons from accidents and their prevention included in continued training?
  - Are there provisions for additional training (new equipment, new procedures)?
  - Are emergency plans exercised as part of the training?
- Acceptance Testing and Commissioning
  - Is there a program for formal acceptance of equipment in place?

  - Is it carried out according to international or national standards?
  - Is there a program of commissioning in place?
  - Does it include treatment equipment as well as treatment planning systems, simulators, and other ancillary equipment?
- QA Program
  - Is a program of QA established?
  - Is the program based on accepted protocols? Which ones?
  - Are all tasks associated with QA clearly assigned to the right persons?
  - Are the necessary tools and instruments available?
  - Are audits part of the QA program?
- Communication
  - Is a communication policy in place and understood by staff?
  - Is reporting of unusual equipment behavior required?
  - Is reporting of unusual patient reactions required?
  - Are procedures in place for equipment transfer from maintenance back into clinical use?
- Patient and Site Identification
  - Are there procedures to ensure correct identification of the patient and clinical treatment site?
  - Is there a protocol for the patient's chart check?
- External Beam Calibration
  - Are there provisions for initial beam calibration?
  - Is independent verification in place, foreseen, and planned?
  - Is there an accepted protocol? Which one?
  - Is a program for follow-up calibration in place?
  - Is participation in an audit program part of the QA program?
- External Beam Treatment Planning and In Vivo Dosimetry
  - Are treatment planning systems included in the program of acceptance and testing?
  - Is treatment planning documented according to accepted protocols?
  - Are crosschecks and redundant and independent verification included?
  - Has a system for in vivo dosimetry been considered?

As summarized in IAEA TRS-430 [27], the major issues that relate to QA and avoidance of errors in radiation therapy can be summarized by four key words:

1. Education
2. Verification
3. Documentation
4. Communication

Education

In the treatment planning context, education is required both at the technical/professional level, in terms of usage of the treatment planning system, and at the organizational level, with respect to institutional policies and procedures. A very important component of education relates to understanding software capabilities and limitations. Especially relevant here are issues that relate to dose calculation normalization procedures, treatment setup parameters as used by the computer compared to the actual treatment machine, time or MU calculations, and inhomogeneity corrections. A misinterpretation of any of these calculation procedures can potentially yield significant treatment errors. In brachytherapy, issues of significant concern relate to source activity specification and how the algorithm uses this specification.

Verification

Nearly 60% of the reported errors that related to treatment planning involved a lack of an appropriate independent secondary check of the treatment plan or dose calculation. Clearly, verification is also required when calibrating radiation therapy machines, especially for newly installed machines in the department. Such calibrations should be repeated completely independently, with an independent person and an independent detector/electrometer system (see chapter 9 of this volume).

Documentation

Clear documentation is required of each patient's individual treatment plan, and of departmental policies and procedures.

Communication

Open communication among staff members is essential for all aspects of treatment, since various people at various professional levels are involved in the treatment process. Poor communication was a key factor in a number of the errors reported.

1.6 The Future of the Modern Technology of Radiation Oncology

In its simplest form, the aim of radiation therapy is to cure the tumor without harming the patient. The science and technology involved in achieving this aim are multidisciplinary and multifaceted. While the aim of radiation therapy has not changed since the discovery of ionizing radiation in 1895, the focus and emphasis has changed dramatically over the years, depending on the state of understanding of the biology and on the avail-

ability of the latest technology. Earlier in this chapter, reference was made to the five phases in the evolution of the technology of radiation oncology (Table 1.1). During this period there has also been an evolution in the understanding of the basic biology of cancer, the radiobiology of the treatment of this disease, and the clinical results associated with treatment advances. We are now evolving into a phase in which advances will take place through an integration of knowledge from basic biology, radiation oncology, technology, and clinical medicine. In a summary of the International Conference on Translational Research held in 2003, Coleman [8] referred to the five components of radiation oncology that, when brought together, provide advances in cancer treatment and prevention. He categorized these areas of expertise into basic science, imaging, mathematical and biological models, biology-based therapy, and technology. Figure 1.7 is reproduced from his paper and summarizes the contents of each of these "pillars."

As shown in Figure 1.7, underpinning the entire field are education, training, and mentoring—particularly for trainees and young faculty—and service, collaboration, and dedication to mission—intangibles that add value for patients and society. Coleman goes on to describe each of these pillars in significant detail based on the deliberations at this conference. It is interesting to note that even in this and the previous volume of *The Modern Technology of Radiation Oncology* [85], each of these pillars has been addressed to different degrees. Components of basic biology are a necessary understanding for radiobiological modeling in treatment planning (chapter 5, this volume). Imaging for therapy planning plays a major role in radiation therapy ("If you can't see it, you can't hit it. If you can't hit it, you can't cure it."[2]) and is addressed in chapters 5 and 7 of volume 1 and in chapter 2 of this volume. Of course modeling is involved in dose computations, as is radiobiological modeling (chapters 8, 12, and 15 of volume 1 and chapters 3, 4, 5, 6, and 10 of volume 2). Biological treatment was addressed in chapters 22, 23, 24, and 25 of volume 1.

[2] This is a quote that was often used by the late William E. Powers (internationally recognized radiation oncologist) and the late Harold E. Johns (internationally recognized medical physicist).

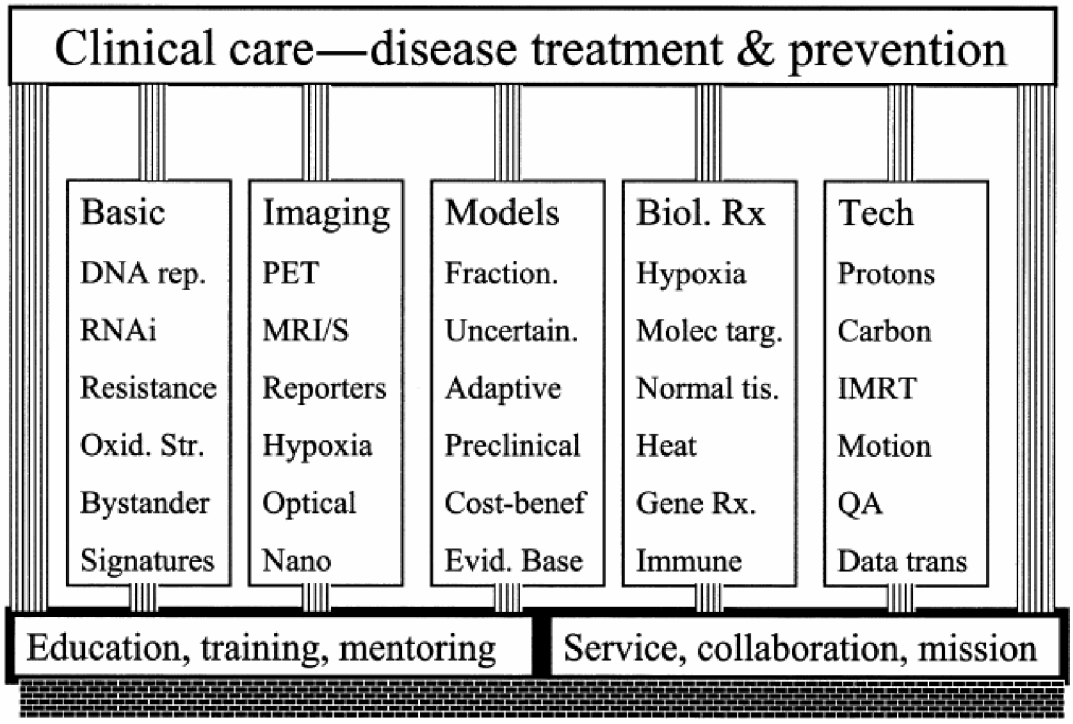

Figure 1.7
Coleman's pillars for advances in clinical care. The five areas that support patient care are basic science, imaging, mathematical and biological models, biologically based therapy, and technology. [Figure reproduced with permission from [8].]

Finally, the technology of radiation oncology is addressed throughout both volumes of this series. As Coleman points out, while the five pillars are partly "self-sustaining fields," the common goal is clinical care.

So what is it that we can expect to see in the next decade? Predicting the future, of course, is based on past experience and how this may be projected into the future. There have been a number of workshops within the last few years that have addressed future research directions and priorities in radiation oncology. A review of these workshops will give some sense as to the direction that the field is taking, although there is very little sense as to how fast we will get there. Battista and Bauman [4] provided an interesting perspective on the future of IMRT in the proceedings of the 2003 AAPM Summer School on Intensity Modulated Radiation Therapy: The State of the Art. They first point out that the underlying hypothesis of advanced technologies such as IMRT is that loco-regional control of cancer remains a significant barrier to cancer cure for many common cancers [40,79]. They looked at the cost-benefit ratio as a good prognostic indicator for the longevity of a new product, process, or service. Figure 1.8 is adapted from their chapter and illustrates a qualitative ranking of various technologies and techniques, including IMRT, versus the technical complexity and cost required for implementation. The evolution from the kilovoltage era to the megavoltage era resulted in significant gains at a relatively low cost. As indicated in Table 1.1, the advent of x-ray CT scanning led the way for 3-D imaging and treatment planning. Computer-controlled accelerator technology with MLCs allowed the capability of intensity-modulated arc therapy in a forward-planned mode (SIMAT) [92] or using inverse planning (IMAT, IMRT) [26,97]. Finally, the move into high linear energy transfer (LET) particles offers radiobiological advantages with relative radiobiological effectiveness (RBE) and oxygen enhancement ratio (OER) differentials.

In 2001, Herman Suit [74] appropriately pointed out that there are two basic strategies to increase the efficacy of radiation therapy. The first is to reduce the treatment volume, i.e., irradiate a smaller volume of normal tissue while irradiating the defined target volume in each treatment session. This strategy not only includes techniques of treatment planning and delivery, but also the ability to define the anatomic margins and topographic distribution of clonogen number and radiation resistant foci in the tumor. The second is to increase the differential response between tumor and normal tissue by taking advantage of things like chemotherapeutic drugs, biologic agents, and genetic and proteomic techniques. The former are within the realm of near future reality, i.e., in the next 10 years. The latter could potentially result in larger gains but are likely to yield results in the more distant future.

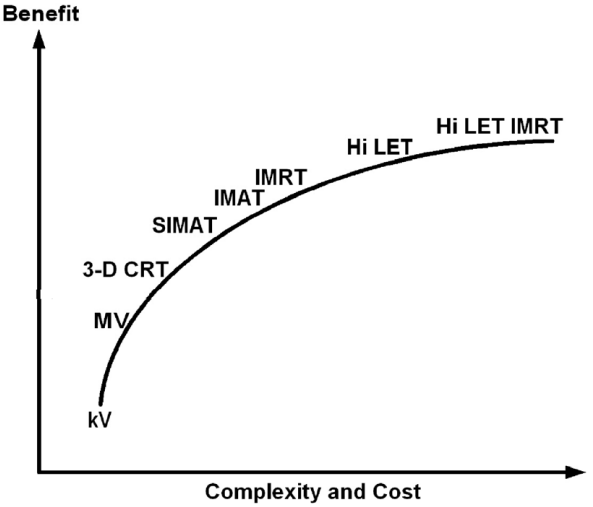

Figure 1.8
Schematic of benefit versus cost achieved with technical advances in radiation therapy. kV, kilovoltage x-rays; MV, megavoltage x-rays; 3-D CRT, 3-D conformal radiation therapy; SIMAT, simplified intensity-modulated arc therapy (forward planned); IMAT, intensity-modulated arc therapy (inverse planned); IMRT, intensity-modulated radiation therapy; Hi LET, High LET charged particle radiation therapy; Hi LET IMRT, High LET charged particle intensity-modulated radiation therapy. [Adapted with permission from [4].]

So what are the factors that are likely to be implemented in the next decade, which will aid in the reduction of treatment volumes with the corresponding potential for increases in target doses?

1.6.1 Improved imaging technologies for target and normal tissue definition

Section 1.3.2 and Table 1.2 have already summarized the potential gains from using a variety of imaging technologies dependent upon specific clinical situations. Many of the imaging modalities listed in Table 1.2 are becoming more readily available to radiation oncologists. PET/CT units, MRI, MRS, and ultrasound will be used selectively for specific clinical sites to aid in target definition and definition of subregions within the tumor that may need a preferential increased dose compared to the rest of the target volume. Chapter 2 of this volume clearly defines the advantages of these various imaging modalities. It is likely that within the decade, many cancer patients will be imaged by more than one modality to aid in the definition of regions to be irradiated and

regions to be spared. What is not clear yet is how specific these imaging technologies will be. For example, will imaging allow for the clear definition of hypoxic regions for many tumors within the decade?

1.6.2 Increased use of image registration/fusion technologies

Based on the use of multiple imaging modalities, it is clear that software is required to correlate and register these images, such that they can be compared directly. This software already exists and is being used routinely for combined modality scanners such as PET-CT scanners. Furthermore, most virtual simulation software now allows the import of images from different sources for direct comparison using image registration/fusion techniques. Added to this is imaging for therapy verification using image guidance technologies, each of which will require image registration comparing the patient setup (image) of the day with the planning images. We already see these technologies in clinical practice with the use of megavoltage CT on helical tomotherapy, with cone beam kilo- or megavolotage CT on conventional accelerators, and with ultrasound guidance. It is likely that within the decade, many of our patients will be treated with the application of image registration either as part of the planning process or as part of the dose delivery process.

1.6.3 Increased use of IMRT with improved optimization algorithms

IMRT is now a technology that is potentially available in various forms in the vast majority of clinics in North America. In this volume, chapter 4 describes the recent advances in inverse planning algorithms, and chapter 6 describes the clinical application of IMRT. It is expected that IMRT will be standard practice within the decade and that the majority of radical cases will be treated with some form of IMRT.

One of the major issues in optimizing treatment plans using inverse planning is the definition of objective functions and corresponding constraints for these objective functions. To date, most of these functions and constraints are based on dose-volume objectives (see chapter 4). It is intuitively clear, however, that radiobiological relevance exists within radiobiological models and the use of radiobiological objectives. As indicated in chapter 5 in this volume, these models are being developed at a rapid rate; however, at this stage they should be used guardedly and certainly not yet for routine treatment planning. The knowledge of clinical data remains limited, such that the predictive capabilities tend to be assessed over only a small range of conditions. Furthermore, the uncertainties in the predicted clinical responses are still very large. For the present time these models should be used only with the full understanding of the ramifications of the model predictions. While it is likely that their use will be increased over the next decade, especially in the context of developing dose-escalation protocols, it is not clear that enough new radiobiological data will be generated with sufficiently small uncertainties to allow them to be used routinely in all clinical settings.

As part of the enhancements of optimization models, more emphasis will be placed on uncertainty estimates, both for patient cohorts and for individual patient treatments. An example of such analysis was described by Deasy et al. [18] in the context of the effect of plan evaluation of uncertainty in tolerance limits. This is an area of research by our group, as well as at other academic institutions. The results of this research should provide a significant aid to the optimization process over the next decade.

1.6.4 Increased use of 4-D imaging and breathing-controlled treatment

The technology now exists for 4-D CT scanning such that we can obtain images of the patient during individual phases of the breathing cycle (see chapter 8, this volume). Furthermore, these data can be used to develop treatment plans for patients with reduced CTV to PTV margins, thereby reducing normal tissue irradiation, thus allowing for increased target doses. Furthermore, the application of breathing control or gated treatment is possible. Thus, while these technologies exist, albeit at an embryonic stage, their application will be greatly increased over the next decade.

1.6.5 Increased use of image guidance for reproducible patient setups

As has already been alluded to in this chapter, image guidance is playing an increasing role as part of the daily patient setup procedure. Chapter 7 of this volume provides a recent update on chapters 13 [58] and 15 [60] of volume 1. These techniques have become an essential component of reducing the volume of normal tissues irradiated and allowing dose escalation with IMRT treatments.

1.6.6 Increased use of particle therapy

Herman Suit [74] argues strongly that the use of intensity-modulated proton therapy (IMPT) is the ultimate in low-LET external beam radiation therapy. The physics of proton therapy has been discussed in detail by Moyers in

chapter 20 of volume 1 [57]. With the added capability of IMPT, Suit [74] argues that because of the dose distribution advantages of proton beams, it is likely that they will replace photon beams over the next two to three decades. This trend appears to already be in progress considering the number of new proton therapy facilities that have recently been implemented or are to be implemented in the near future (in 2003, 23 proton facilities were in existence and 22 were being planned [50]). However, at this time the cost of proton therapy remains prohibitive, and unless new and less expensive proton sources are obtained, it will take a significant time before photon beam therapy is replaced by proton beams. However, recent research by Fourkal et al. [20] indicates the possibility for laser-generated IMPT as a potential for making proton therapy cost-effective.

While heavy ion therapy is another evolving technology that has been pursued by the Germans and Japanese [34], there is a growing interest by the Europeans in light ion therapy [80]. Light ion beam therapy may allow a somewhat better geometric precision in dose delivery compared with proton beams, since the penumbra and the Bragg peak decrease with increasing atomic number. Turesson et al. [80] give three reasons why therapy with light ion beams with atomic numbers in the range of $Z = 2$ to $Z = 6$ might be more advantageous than heavy ion beams with $Z \geqslant 7$. First, the LET for heavier ions is quite high, also in regions of normal tissue irradiation, thus increasing the risk of complications. Second, heavy ions fragment into lighter ions that have ranges beyond the Bragg peak, thus leaving a "tail" in the depth-dose distribution. Third, it is argued that there is an increasing risk that higher LET radiation could result in "cold spots" in the dose distribution, thus risking tumor recurrence. A major concern about ion beams with particles heavier than protons is that their RBE is not as well understood. Indeed, the RBE is dependent on the cell types being irradiated and on the location within the depth-dose curve. Thus, while light ion beams are being developed and implemented in a number of European centers, they will not likely comprise a large component of radiation therapy treatments over the next decade.

1.6.7 Increased use of brachytherapy

Battista and Bauman [4] indicated that brachytherapy was the first method to achieve "conformal radiation therapy," and well before external beam CRT. The use of high-dose-rate brachytherapy technology (see chapter 18, volume 1 [22]), as well as low dose rate implants, especially as used for prostate cancer treatments (see chapter 10, this volume), has increased significantly in the last decade and is likely to increase even more in the next decade. Brachytherapy for partial breast irradiation is also a growing trend [62,64,90]. Vicini and Arthur [90] conclude that accelerated partial breast irradiation using brachytherapy has great potential to overcome many of the barriers that have prevented women from pursuing standard breast-conserving therapy and thus could find a significant increase in usage during the next decade.

The use of 3-D ultrasound (see chapter 7 of volume 1 [63]) combined with the introduction of robotics provides the potential for advancing brachytherapy applications even further [91].

1.6.8 Increased QA

As a result of the increased complexity of the multiple components associated with the modern technology of radiation oncology, there is clearly a need for increased activity associated with the commissioning and QA of these new technologies. QA was addressed in a generic sense in chapter 2 of volume 1 [87], and some recent issues were addressed in section 1.5 above. Modern tools for commissioning and QA are evolving to address the 3-D and 4-D nature of the new treatment techniques. Figures 1.9 through 1.13 demonstrate new phantoms and techniques developed by our group as examples of addressing QA associated with the new technologies. Figure 1.9 shows a commercial phantom used to assess the image display components of beam geometries as used on 3-D virtual simulators and treatment planning software [14,49]. Figure 1.10 shows a multicomponent "body" phantom used for volume assessments as would be used in DVH determination, for autocontouring tools, for automargining tools, for IMRT dose delivery assessment, for patient-specific dosimetry, for CT number to electron density conversion, and a number of other tests. Figure 1.11 shows an IMRT verification phantom that can hold films or ionization chambers. Figure 1.12 shows the prototype model of a moving "lung" phantom for assessing gating capabilities and reproducibility. It is clear that with IMRT, individualized, patient-specific QA is required largely to address the concerns of the "black boxes" in Figure 1.3. Either the commissioning or the patient-specific QA can be aided by the use of 3-D dosimetry. Figure 1.13 shows the latest commercial tools for 3-D gel dosimetry using optical CT as the readout process to generate 3-D dose distributions [36]. Clearly, tools of this nature will continue to evolve as treatment technology becomes more complex.

1.6.9 Increased need for medical physicists

It is clear from the earlier parts of this chapter that the need for well-trained and highly specialized medical

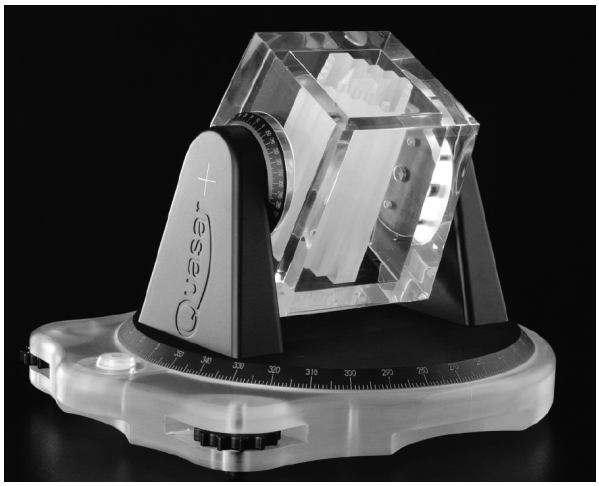

Figure 1.9
Phantom used to assess beam display accuracy on CT-simulator virtual simulation stations or on treatment planning computers [14,49]. [Picture courtesy of Modus Medical Devices, Inc.]

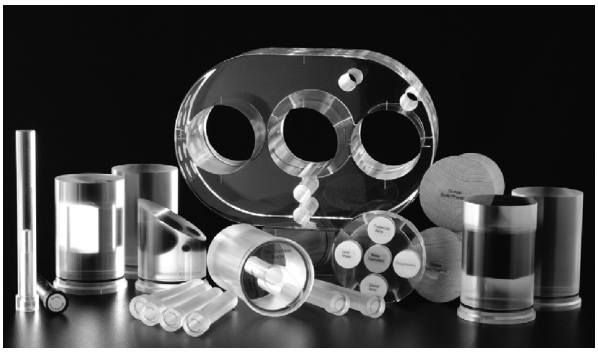

Figure 1.10
Phantom for assessing multiple nondosimetric as well as dosimetric components of treatment planning systems. The following are some nondosimetric features that can be assessed: geometric accuracy of 2-D images and 3-D image reconstructions; 2-D and 3-D measurement tools including volume calculation accuracy; automatic, semiautomatic, and manual boundary identification tools; automargining tools; representation and manipulation of contoured patient anatomy; DVHs; conversion of CT numbers to relative electron densities; comparison of display on CT simulators, radiation treatment planning systems, and other imaging work stations; image transfer, storage, retrieval, DICOM tools on all workstations. The following dosimetric components are also possible: ion chamber locations include on-axis and multiple off-axis locations for measurements in low- and high-dose gradient regions; blank acrylic inserts for homogeneous density tests; two lung equivalent inserts and a spine equivalent rod for a variety of inhomogeneous density tests with precisely determined, near anthropomorphic geometry; a sphere representing a prostate volume for contouring and automargining assessment; light field alignment tests. [Picture courtesy of Modus Medical Devices, Inc.] SEE COLOR PLATE 3.

physicists is increasing. Not only is the technology becoming extremely complex, but, in addition, the patient population continues to increase as well, especially as a result of the postwar baby boom and an aging population. As Battista and Bauman [4] have indicated, the expected patient population growth rate is approximately 2.5% per year over the next decade, while medical physics staff growth rates may be more realistically estimated at 5% per year to account for the increased workload associated with the increased sophistication and complexity of the modern technology of radiation oncology.

In a recent "point/counterpoint" in the journal *Medical Physics,* the proposition was, "Over the foreseeable future, the growth in technical complexity of radiation therapy will continue to drive the demand for more medical physicists." Arguing for the proposition was Saiful Huq [25], and against the proposition, Jason Sohn [71]. Huq [25] quoted from the American College of Radiology survey [61] in the United States, which showed that between 1983 and 1994 the number of full-time equivalent (FTE) physicists increased by 60%. The Abt studies of medical physicist work values [1,2] showed that between 1995 and 2003, practices offering remote-controlled afterloading brachytherapy increased from 46% to 66%, the availability of MLCs increased from 19% to 79%, and electronic portal imaging rose from 20% to 53%. Technology-intensive procedures such as prostate seed brachytherapy rose to 89%, 3-D CRT (non-IMRT) to 92%, coronary vascular brachytherapy to 74%, and record and verify systems to 87%. The median relative work estimates for a qualified medical physicists increased by a factor of 12 for IMRT treatment planning, 14 for special medical physics consultation, and 16 for IMRT special physics consultation [2]. As Huq points out, these numbers indicate that the discipline of radiation oncology is continually changing in response to technology, practice, and state and federal regulations. However, Sohn [71] contends that as the radiation therapy technologies mature, converging treatment systems will be less complicated, require less space, and eventually reduce the demand on physicists. Thus, streamlining of physics activities will decrease the demand for physicists. While these are interesting conjectures, experience over the last three decades—three decades in which we have experienced tremendous technological developments—has shown contin-

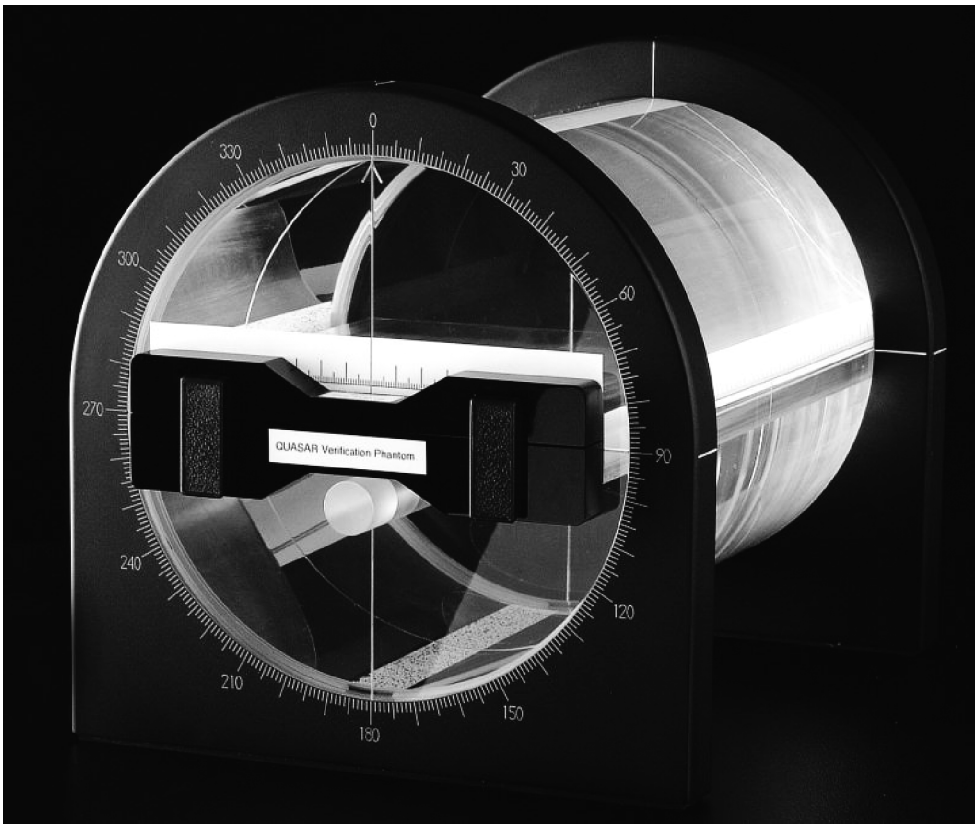

Figure 1.11
The verification phantom comprises a cylindrical phantom, a film cassette, and several inserts for holding and positioning an ion chamber at any point along the diameter of the phantom. The film cassette holds half-sized sheets of film and can hold either one or two of these sheets at a time. Inserts are available for ion chambers from several major suppliers. The 360° rotation of the cylinder allows the films to be placed orthogonal to the beam direction or ion chambers to be placed at any desired location. [Picture courtesy of Modus Medical Devices, Inc.]

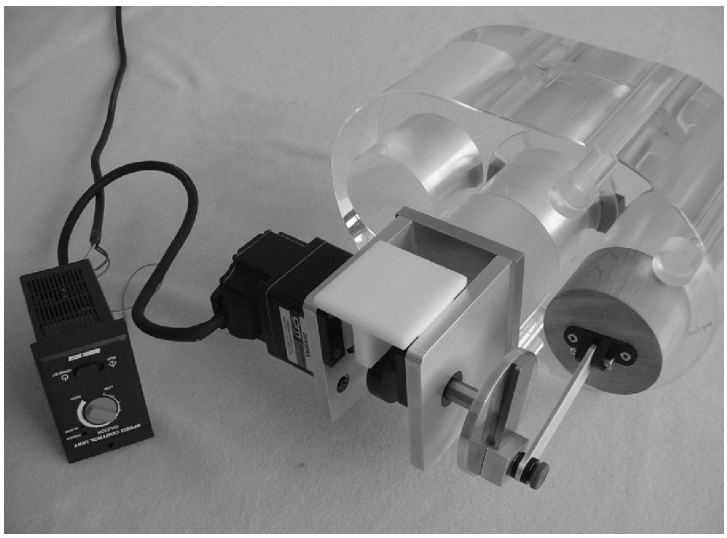

Figure 1.12
Prototype model of a moving "lung" phantom for assessing gating capabilities and reproducibility. The white platform near the center of the phantom is for positioning the Varian RPM® (Varian Medical Sysyems, Palo Alto, CA) gating block normally placed on the patient's chest. By using different cams under this platform, different breathing styles can be simulated. The moving "lung" has an insert for small dosimeters such as MOSFETs to assess the quality of the gating system on the linear accelerator. [Picture courtesy of Modus Medical Devices, Inc.]

(a) (b)

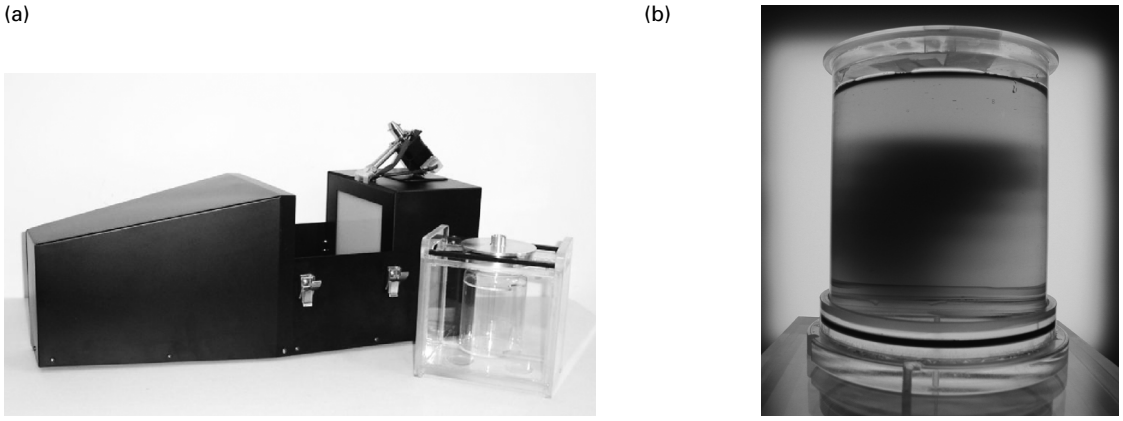

Figure 1.13
(a) Picture of the optical CT scanner used for generating 3-D dose distributions from gel dosimetry [36]. [Picture courtesy of Modus Medical Devices, Inc.] (b) Gel showing color change due to 3-D dose delivery. [Picture courtesy of Kevin Jordan and Jerry Battista.] SEE COLOR PLATE 4.

ued increase in the demands on medical physicists and the increased need for medical physicists. Based on these three decades and based on the advancing nature of the complexity of the technology of radiation oncology, it is likely that there will be a greater demand for, and demand on, medical physicists.

1.7 Summary

The modern technology of radiation oncology continues to progress at an unprecedented rate. The need for these advancements is based on the underlying assumption that the new, complex technologies will improve locoregional control of cancer and therefore cure more patients. Research has shown that improvements in patient setups using image guidance technologies has the potential for dose escalation, with a corresponding increase in predicted local control, while maintaining the same level of normal tissue complications. Although clear proof of improvements in long-term survival remain to be obtained, examples of improvement in biochemical control for prostate cancer while reducing rectal complications have been published [40,79].

The new technologies result in new demands on the total QA process for radiation treatment. Additional steps and more accuracy are required in patient setup. QA procedures need to be enhanced because significant components of the treatment process are performed "automatically," resulting in dose delivery techniques that are no longer intuitively obvious. Thus, the user needs to develop confidence that the class solutions to QA procedures will be sufficient to check the built-in safety devices on modern treatment technologies. Especially because of these added complexities, significant emphasis needs to be placed on four key components of any QA program: education, verification, documentation, and communication. Furthermore, it is important that a "safety culture" be nurtured within the radiation program and throughout the organization.

Predictions over the next decade project an increased use of imaging for therapy planning, an increased use of software tools to register images from multiple imaging sources, and an increased demand for IMRT with the application of image guidance for daily setups. 4-D imaging with breathing-controlled or gated therapy will be applied more frequently to thoracic tumors. There will likely be increased applications of brachytherapy. Particle therapy, especially protons, will also gain in activity, although these will likely be limited to larger academic institutions since the costs are still prohibitive. Significant expansions in these programs are likely to occur beyond the next decade.

All of these advances in modern technology, and a growing patient population, will place greater demands on the number of medical physicists required, as well as the need for sophistication of education and training to deal with these advanced technologies.

Ultimately these advances in the technology of radiation oncology will benefit the cancer patient by improving the likelihood of cure with reduced complications, resulting in a better quality of life.

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