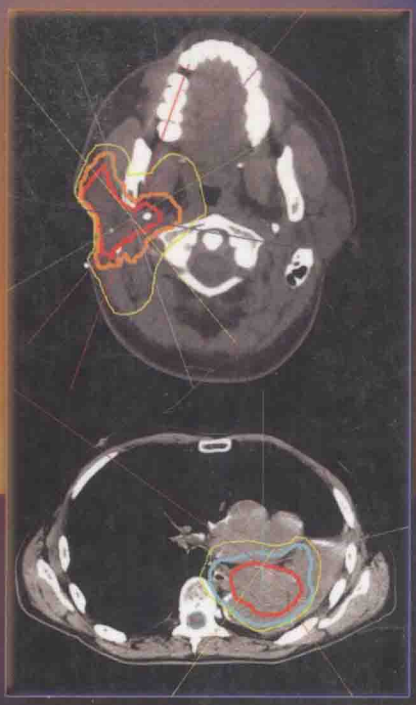

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Radiation Oncology Management Decisions

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RADIATION ONCOLOGY MANAGEMENT DECISIONS

THIRD EDITION

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RADIATION ONCOLOGY MANAGEMENT DECISIONS

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PREFACE

Since the second edition of *Radiation Oncology Management Decisions* (*ROMD*), substantial strides have been made in the delivery of radiation treatment to the oncology patient. Image-guided techniques, summarized here in Chapters 3, 4, and 6, are rapidly being incorporated into clinical practice to move closer to the goal of maximum eradication of tumor while preserving normal function of adjacent tissues and organs. Radiation oncologists and treatment planners have a growing list of three-dimensional techniques, especially intensity-modulated radiation therapy (IMRT) and image-guided brachytherapy. In addition, there now are so-called four-dimensional protocols, which incorporate temporal modulation to address long-standing difficulties, such as organ motion during irradiation.

This third edition is designed, as were its predecessors, to be a bridge for students and practitioners to connect questions arising in the clinic to the comprehensive texts and the research journals. In that regard, this volume includes the AJCC 7th edition TNM staging classification definitions for each organ or disease site. In February 2010, the *International Journal of Radiation Oncology Biology Physics* issued a supplemental volume devoted to the results of the QUANTEC reviews on radiation damage to normal tissues experienced during tumor treatment. We have presented brief summaries of the dose recommendations from the QUANTEC papers for the organ systems selected by the QUANTEC steering committee.

While new material focuses on the cutting-edge advances in the field, we have not eliminated all the older figures or practice guidelines. Particularly in the developing world, resources do not permit the acquisition of the latest multimillion dollar machines and the associated computing infrastructure. Yet practitioners in those areas still have patients in need, and the older methods can still provide therapeutic efficacy or at least palliation for the advanced cancer patient. Comments and suggestions are, of course, welcome.

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CONTENTS

1 Fundamentals of Patient Management

MANAGEMENT OF THE PATIENT WITH CANCER

- The optimal care of patients with malignant tumors is a multidisciplinary effort that combines the classic modalities of surgery, radiation therapy, and chemotherapy.
- The role of the radiation oncologist is to assess all conditions relative to the patient and tumor, systematically review the need for diagnostic and staging procedures, and, in consultation with other oncologists, determine the best therapeutic strategy.
- Radiation oncology is the clinical and scientific discipline devoted to the use of ionizing radiation in the management of patients with cancer (and other diseases), the investigation of the biologic and physical basis of radiation therapy, and the training of professionals in the field.
- The aim of radiation therapy is to deliver a precisely measured dose of radiation to a defined tumor volume with minimal damage to surrounding healthy tissue.

PROCESS OF RADIATION THERAPY

The goal of therapy should be defined at the onset of therapeutic intervention:

- *Curative*: There is a probability of long-term survival after adequate therapy; some side effects of therapy, although undesirable, may be acceptable.
- *Palliative*: There is little hope of survival for extended periods. Symptoms producing discomfort or an impending condition that may impair comfort or self-sufficiency require treatment. Relatively high doses of irradiation (sometimes 75% to 80% of curative dose) are required to control the tumor for the survival period of the patient.

BASIS FOR PRESCRIPTION OF IRRADIATION

- Evaluation of tumor extent (staging), including diagnostic studies.
- Knowledge of pathologic characteristics of the disease.
- Definition of the goal of therapy (cure or palliation).
- Selection of appropriate treatment modalities (irradiation alone or combined with surgery, chemotherapy, or both).
- Determination of optimal dose of irradiation and volume to be treated, according to anatomic location, histologic type, stage, potential regional nodal involvement (and other tumor characteristics), and normal structures in the region.
- Evaluation of patient's general condition, plus periodic assessment of tolerance to treatment, tumor response, and status of normal tissues treated.
- The radiation oncologist must work closely with physics, treatment planning, and dosimetry staffs to ensure greatest accuracy, practicality, and cost benefit in the design of treatment plans.
- The ultimate responsibility for treatment decisions, technical execution of therapy, and consequences of therapy always rests with the radiation oncologist.

RADIATION TREATMENT PLANNING

- Different radiation doses are required for given probabilities of tumor control, depending on the tumor type, the initial number of clonogenic cells present, the extent of disease to be treated (2), and the inclusion or exclusion of additional therapeutic modalities (e.g., surgery and/or chemotherapy) in the overall treatment plan.
- International Commission on Radiation Units and Measurements Reports Nos. 50 and 62 define the following treatment planning volumes (7,8):
  - *Gross tumor volume (GTV)*: All known gross disease, including abnormally enlarged regional lymph nodes. To determine GTV, appropriate computed tomography (CT) window and level settings that give the maximum dimension of what is considered potential gross disease should be used.
  - *Clinical target volume (CTV)*: Encompasses GTV plus regions potentially harboring microscopic disease.
  - *Planning target volume*: Provides margin around CTV to allow for internal target motion, other anatomic motion during treatment (e.g., respiration), and variations in treatment setup. This does not account for treatment machine beam characteristics.
- Treatment portals must adequately cover all treatment volumes plus a margin to account for beam physical characteristics, such as penumbra (Fig. 1-1).
- Simulation is used to accurately identify target volumes and sensitive structures, and to document configuration of portals and target volume to be irradiated.

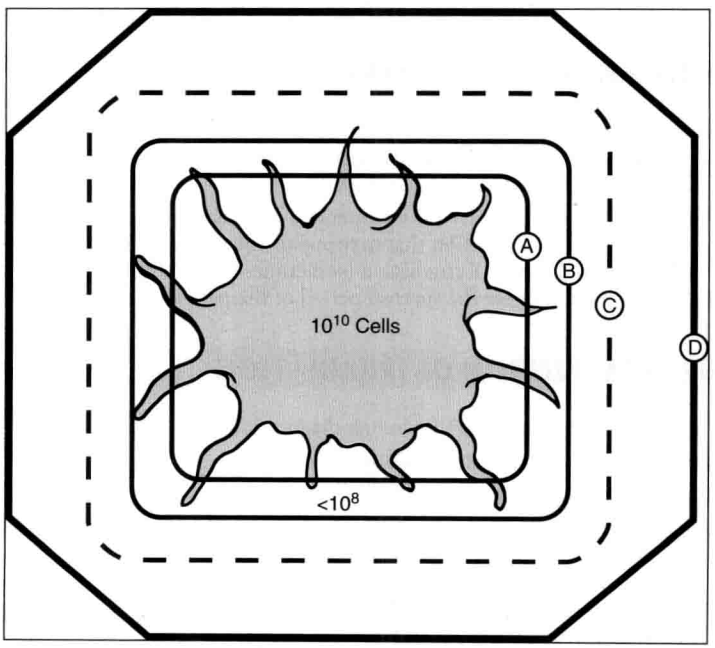

FIGURE 1-1 Schematic representation of "volumes" in radiation therapy. The treatment portal volume includes tumor volume, potential areas of local and regional microscopic disease around tumor, and a margin of surrounding normal tissue. *A* shows gross tumor volume, *B* shows CTV, *C* shows planning treatment volume, and *D* shows treatment portal volume. (Modified from Halperin EC, Perez CA, Brady LW. The discipline of radiation oncology. In: Halperin EC, Perez CA, Brady LW, eds. *Principles and Practice of Radiation Oncology*, 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2008:2–75, with permission.)

- Treatment aids (e.g., shielding blocks, molds, masks, immobilization devices, compensators) are extremely important in treatment planning and delivery for optimal dose distribution. Repositioning and immobilization devices are critical because effective irradiation is that which accurately hits the clonogenic tumor cells.
- Simpler treatment techniques that yield an acceptable dose distribution are sometimes preferred over more costly and complex ones, which may have a greater margin of error in day-to-day treatment.
- Accuracy is periodically assessed with portal (localization) films or on-line (electronic portal) imaging verification devices, which may be 2-D (e.g., port films) or 3-D (e.g., on-board kV or MV cone-beam CT imaging) based systems. Portal localization errors may be systematic or may occur at random.

Three-Dimensional Treatment Planning

- CT simulation allows more accurate definition of target volume and anatomy of critical normal structures, three-dimensional (3-D) treatment planning to optimize dose distribution, and radiographic verification of volume treated (12,14).
- Advances in computer technology have augmented accurate and timely computation, display of 3-D radiation dose distributions, and dose-volume histograms that yield relevant information for evaluation of tumor extent, definition of target volume, delineation of normal tissues, virtual simulation of therapy, generation of digitally reconstructed radiographs, design of treatment portals and aids, calculation of 3-D dose distributions and dose optimization, and critical evaluation of the treatment plan (15).
- Dose-volume histograms are useful in assessing several treatment plan dose distributions and provide a complete summary of the entire 3-D dose matrix, showing the amount of target volume or critical structure receiving more than the specified dose. They do not provide spatial dose information and cannot replace other methods of dose display.
- 3-D treatment planning systems play an important role in treatment verification. Digitally reconstructed radiographs based on sequential CT slice data generate a simulation film that can be used in portal localization and for comparison with the treatment portal film for verifying treatment geometry.
- Increased sophistication in treatment planning requires parallel precision in patient positioning and immobilization, as well as in portal verification techniques (17). Several real-time, on-line verification systems allow monitoring of the area to be treated during radiation exposure.
- Computer-aided integration of data generated by 3-D radiation treatment planning with parameters used on the treatment machine, including gantry and couch position, may decrease localization errors and enhance the precision and efficiency of irradiation.

Intensity-Modulated Radiation Therapy

- Intensity-modulated radiation therapy (IMRT), a relatively newer approach to 3-D treatment planning and conformal therapy, optimizes delivery of irradiation to irregularly shaped volumes through complex forward or inverse treatment planning and results in modulated fluence of multiple photon beam profiles.
- Inverse planning starts with an ideal dose distribution and results in, through trial and error or multiple iterations (simulated annealing), the desired beam characteristics (fluence profiles). It produces the best approximation to the ideal dose defined in a 3-D array of dose voxels organized in a stack of 2-D arrays.
- Approaches to IMRT include the following:
  - The step-and-shoot method, which employs a linear accelerator and multileaf collimator that breaks each treatment field into a set of smaller subfields. Each subfield is delivered one at a time in a predefined sequence. After a subfield is treated, the beam is shut off, the MLC leaves are repositioned for the next subfield and the beam is turned on again.
  - Dynamic computer-controlled IMRT is delivered when the configuration of the portals with the MLC changes at the same time that the gantry or accelerator changes positions around the patient.

  - In helical tomotherapy, a photon fan beam continually rotates around the patient as the couch transports the patient longitudinally through a ring gantry (9). The ring gantry enables verification processes for helical tomotherapy; the geometry of a CT scanner allows tomographic processes to be reliably performed. Dose reconstruction is a key process of tomography; the treatment detector sinogram computes the actual dose deposited in the patient. The lengths of the MLC in helical tomotherapy are temporally modulated or binary because they are rapidly driven either in or out by air system actuators rather than by beams slowly pushed by motors driving lead screws, as in the conventional MLC.
  - The robotic arm of the IMRT system Cyberknife (Accuray, Sunnyvale, CA) consists of a miniaturized 6-MV photon linear accelerator mounted on a highly mobile arm and a set of ceiling-mounted x-ray cameras to provide near real-time information on patient position and target exposure during treatment.
- The majority of IMRT systems use 6-MV x-rays, but energies of 8 to 10 MV may be more desirable in some anatomic sites to decrease skin and superficial subcutaneous tissue dose.

PROBABILITY OF TUMOR CONTROL

- Various levels of irradiation yield different probabilities of tumor control, depending on the histology and number of clonogenic cells present. Numerous dose response curves for a variety of tumors have been published with higher doses of irradiation producing better tumor control.
- For every increment of irradiation dose, a certain fraction of cells will be killed; the total number of surviving cells is proportional to the initial number present and the fraction killed with each dose (5).
- For subclinical disease (deposit of tumor cells too small to be detected clinically or even microscopically), doses of 45 to 50 Gy will result in disease control in more than 90% of patients (6).
- Microscopic tumor, such as at the surgical margin, is not subclinical disease; cell aggregates 10^6 per cm^3 or greater are required for the pathologist to detect them. These volumes must receive higher doses of irradiation (e.g., 60 to 65 Gy in 6 to 7 weeks) (6).
- For clinically palpable tumors, doses of 65 (for T1 tumors) to 75 to 80 Gy or even higher (for T4 tumors) are required (1.8 to 2.0 Gy per day, five fractions weekly) (6).
- A boost is an additional dose administered through small portals to residual disease; it is given to obtain a similar probability of control as for subclinical aggregates.
- Portals can be progressively reduced in size (i.e., the "shrinking-field" technique) to administer higher doses to the central portion of the tumor, where more clonogenic cells (presumably hypoxic) are present, in contrast to the smaller doses required to eradicate disease in the periphery, where a lower number of better oxygenated tumor cells are assumed to be present.

NORMAL TISSUE EFFECTS

- Ionizing radiation induces various changes in normal tissues, depending on the closely interrelated factors of total dose, fractionation schedule (daily dose and total radiation course time), and volume treated. For many normal tissues, the necessary dose to produce a particular sequela increases as the irradiated volume of the organ decreases.
- Higher tolerance doses (TDs) than initially reported have been observed in some organs, stressing the importance of updating information in light of more precise treatment planning and radiation delivery systems and more accurate evaluation of treatment sequelae (4). Tolerance curves for multiple organs have been developed (3).
- The $TD_{5/5}$ is the dose of radiation that could cause no more than a 5% severe complication rate in a particular organ or organ system within 5 years of treatment.
- An acceptable complication rate for moderate to severe injury is 5% to 15% in most curative clinical situations.

- Less clinically significant sequelae occur in 20% to 25% of patients, depending on irradiation dose and the proximity of organs at risk to the target volume.
- The effects of irradiation are described based on the time in which they are observed: *acute* (first 6 months), *subacute* (second 6 months), or *late*. The gross manifestations depend on the kinetic properties of the cells (e.g., slow or rapid renewal) and the dose given.
- Depending on their cellular architecture, organs are classified by functional subunits either in series (e.g., the spinal cord), in which injury of a segment results in a functional deficit of the distal organ, or parallel (e.g., lung, kidney), in which injury of a segment is compensated by function of unaffected adjacent segments.
- Combining irradiation with surgery or various systemic agents frequently modifies the tolerance of normal tissues to a given dose of irradiation, possibly requiring adjustments in treatment planning and dose prescription.
- Radioprotectors, such as amifostine, improve the tolerance of certain normal tissues to a given dose of irradiation, thereby decreasing the likelihood of potential treatment-related morbidities (e.g., xerostomia in patients irradiated for head and neck cancers or pneumonitis in patients with lung or esophageal cancer).

THERAPEUTIC RATIO (GAIN)

- An optimal irradiation dose will produce maximal probability of tumor control with minimal frequency of complications (sequelae of therapy).
- The more the curves of tumor control probability and complication probability diverge, the more favorable the therapeutic ratio.

DOSE-TIME FACTORS

- Fractionation of irradiation with prolongation of radiation course spares acute reactions because of compensatory proliferation of the acute responding tissues.
- A prolonged course of therapy decreases early acute reactions but does not protect against serious late damage to normal tissue. In addition, it may allow the growth of rapidly proliferating tumors and may be inconvenient for the patient.
- For tumors with short potential doubling times, overall treatment course times of less than 6 weeks are optimal. More slowly proliferating tumors can be treated with longer overall courses.
- Late damage is dictated predominantly by radiation fraction size (rather than overall radiation course treatment time).

Prolongation of Overall Treatment Time, Tumor Control, and Morbidity

- The total irradiation dose required to produce a given probability of tumor control must be increased when fractionation is prolonged beyond 4 weeks because of repopulation of surviving cells. Withers et al. (20) estimated that the dose of irradiation is to be increased by 0.6 Gy for every day of interruption of treatment. Taylor et al. (18) estimated the increment, in isoeffect dose per day, to be larger than 1 Gy in squamous cell carcinoma of head and neck.
- The Radiation Therapy Oncology Group reported no therapeutic advantage in studies of split-course radiation in head and neck, uterine cervix, lung, or urinary bladder tumors; tumor control and survival were comparable to those with conventional fractionation. Late effects were slightly greater in the split-course groups. Single institution reports suggest that tumor control may be compromised by split-course regimens (10,11).

Linear-Quadratic Equation (α/β Ratio)

- Formulations of dose-survival models have been proposed to evaluate the biologic equivalence of various doses and fractionation schedules, based on a linear-quadratic survival curve:

  $\text{Log}_e\ S = \alpha D + \beta D^2$

  in which α represents the linear (first-order–dose-dependent) component of cell killing, and β represents the quadratic (second-order–dose-dependent) component of cell killing. β represents the more reparable (over a few hours) component of cell damage. The dose at which the two components of cell killing are equal is the α/β ratio.
- The shape of the dose-survival curve with photons differs for acutely and slowly responding normal tissues.
- Acutely reacting tissues have a high α/β ratio (between 8 and 15 Gy), whereas tissues involved in late effects have a low α/β ratio (1 to 5 Gy). Values obtained in animal experiments and clinical studies have been summarized (19) (see Table 5-2).
- A biologically equivalent dose (BED) can be obtained using this formula:

  $\text{BED} = nd\,[1 + d/(\alpha/\beta)]$

  in which n = number of fractions and d = dose per fraction (fractionation).
- If one wishes to compare the two treatment regimens (with some reservations), the following formula can be used:

  $n_1 d_1[1 + d_1/(\alpha/\beta)] :: n_2 d_2[1 + d_2/(\alpha/\beta)]$

  in which $n_1 d_1$ = known total dose (reference dose), $n_2 d_2$ = new total dose (with different fractionation schedule), d_1 = known fractionation (reference), and d_2 = new fractionation schedule.

COMBINATION OF THERAPEUTIC MODALITIES

Preoperative Radiation Therapy

- *Rationale*: Preoperative radiation therapy potentially eradicates subclinical or microscopic disease beyond the margins of surgical resection, diminishes tumor implantation by decreasing the number of viable cells within the operative field, sterilizes lymph node metastases outside the operative field, decreases potential for dissemination of clonogenic tumor cells that might produce distant metastases, and increases the possibility of resectability.
- *Disadvantage*: Preoperative radiation therapy may interfere with normal healing of tissues affected by radiation.

Postoperative Irradiation

- *Rationale*: Postoperative irradiation may eliminate residual tumor in the operative field by destroying subclinical foci of tumor cells after surgery. This is achieved through the eradication of adjacent subclinical foci of cancer (including lymph node metastases) and the delivery of higher doses than with preoperative irradiation; a greater dose is directed to the volume of high-risk or known residual disease.
- *Disadvantages*: Delay in initiation of irradiation until wound healing is completed and vascular changes produced in tumor bed by surgery may impair radiation effect.

Irradiation and Chemotherapy

- *Enhancement* is any increase in effect on tumor or normal tissues greater than that observed with either modality alone.
- Calculation of the presence of additivity, supraadditivity, or subadditivity is simple when dose response curves for irradiation and chemotherapy are linear.