Principles of IMRT

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2.1 Introduction

This chapter describes the basic principles of intensity-modulated radiation therapy (IMRT), providing the necessary background for subsequent clinical chapters. We start by describing the IMRT treatment planning and delivery process, introducing the wide range of different approaches and technologies currently in clinical use. Then, other topics important in the implementation of IMRT are discussed, including quality assurance (QA), facility design, and respiratory motion management. The chapter closes by reviewing some potential advantages and challenges of IMRT.

2.2 Treatment Planning

IMRT relies on many of the same tools for imaging, dose calculations, plan evaluation, QA, and delivery as conventional treatments do. However, some significant differences exist, particularly in the planning and treatment delivery processes. The following sections describe the workflow for the entire IMRT process, from the viewpoint of patients and clinic staff.

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2.2.1 Imaging and Delineation

The first step in the IMRT process, in common with conventional conformal RT, is to obtain images of the patient and delineate the targets and relevant normal tissues on those images. The primary type of imaging used for target delineation and dose calculation is computed tomography (CT), although other imaging modalities such as positron emission tomography (PET) and magnetic resonance imaging (MRI) can also be used. The various volumes that form the skeleton or outline of the treatment plan are described by the International Commission on Radiation Units and Measurements [52–54], and their clinical application is discussed in detail elsewhere in this book. The main volumes to be considered are the gross tumor volume (GTV), which is the gross demonstrable extent and location of the tumor; the clinical target volume (CTV), which includes the tissue that may contain subclinical malignant disease; and the planning target volume (PTV), which is the CTV after geometric expansion to account for uncertainties in the planning and treatment process. Other treatment plan components are the organs at risk (OARs), which are the normal tissues that can suffer radiation damage during treatment; the planning organ-at-risk volume, which is analogous to the PTV, but applied to normal tissues; and the remaining volume at risk, which describes uncontoured parts of the patient. These components are all important in creating an IMRT plan, and they are discussed further in other chapters. IMRT planning also involves the use of "dose-shaping" or "dummy" structures (sometimes called "pseudostructures"), which are nonanatomic structures created by treatment planners to guide optimization of the IMRT plans. One example of such a structure is a ring created around the target, to which the planner sets constraints that keep the dose to this region low. Planners may also add structures to which dose must be reduced after the first plan iteration to cover regions where the dose is too high, such as in a normal tissue or in the target itself. Additional concepts, such as the volume to account for respiratory motion (internal target volume [ITV] [54]), are also important for treating disease at particular anatomic sites (as described in other chapters).

The use of these volume definitions is not unique to IMRT. The quality and accuracy of the delineation of targets and normal tissues, however, require particular attention in IMRT, as this information is the basis for the creation of treatment fluences by inverse-planning algorithms [40]. Structures must be consistent from slice to slice to produce smooth 3D structures. Clinicians or treatment planners must also take care to "clean up" all structures created during the planning process. For example, inadvertent volumes, such as those created if the user accidentally pressed a mouse button when the cursor is not where they wanted it to be, must be removed. Such volumes may represent only a single point that may not be apparent visually, but they can become serious issues when the inverse-planning algorithm attempts to design the fluence that confers dose to them.

2.2.2 Number and Configuration of Radiation Beams

After the necessary structures have been delineated or contoured, the next step in the IMRT process is placement of the treatment beams, including the choice of the number of beams. This step requires determining the treatment isocenter, which may already have been set during the acquisition of scans during treatment simulation. Standard practice for isocenter placement varies among clinics. In some cases, the isocenter is placed in the center of the primary target (e.g., the center of the prostate), but in other cases, the isocenter is placed in a generic location (e.g., the anterior edge of C2 for head and neck tumors). As is true for conventional treatments, shifts may be apparent between the marks on the patient (from the treatment simulation) and the actual treatment isocenter. With IMRT (and unlike most conventional treatments), the isocenter is not necessarily within the treatment volume at all; rather, it may be placed so as to aid image-guided radiation therapy (IGRT) or to avoid geometric restrictions during treatment delivery. For example, when relatively wide targets are to be treated, common practice is to try to place the isocenter so as to minimize the number of adjacent fields needed to cover the entire target (in IMRT, the width of the fields is limited by the length of the multileaf collimator [MLC], as described later in this chapter).

In most planning systems, beams are positioned manually by the treatment planners, although automatic beam placement is also possible [66, 125]. Factors to be considered in beam placement include normal tissue location (e.g., we prefer to minimize beams that pass unnecessarily through the contralateral lung) and the desire to minimize treatment time. Thus, although using more beams provides more degrees of freedom for optimizing the plan, excessive numbers of beams should be avoided because of the additional time needed for treatment (and for plan optimization). Another common practice is to avoid using noncoplanar beams or multiple isocenters. The exact clinical trade-offs (target coverage, normal tissue dose, and treatment time) depend on the clinical situation, but in most cases, the appropriate number of beams is between 7 and 9 [99, 127]. Of course, IMRT may not be delivered as a series of individual beams, but rather may be delivered during a gantry rotation (as in tomotherapy or volume-modulated arc therapy [VMAT]), as described further below.

2.2.3 Treatment Plan Objectives

Once the beam configuration has been determined, the next step is to determine the treatment plan objectives—in other words, the doses that represent the intended treatment, such as target dose and coverage and normal tissue doses. In many cases, these doses come from templates, with standard objectives used for a given clinical site, although the doses can be edited based on individual patient prescriptions or anatomic characteristics. The constraints on those doses may be hard or soft and may be based on dose, dose-volume, or dose-response (e.g., predicted probability of

tumor response), as described below. The desired objectives as specified are often not achieved because the optimizing software tries to balance the requirements of various structures. Thus, specified objectives may be quite different from what is desired. Specifying the objectives, in combination with suitable "penalties," usually leads to an acceptable approximation of what is desired. Penalties and specified objectives are often achieved through experience and may vary among institutions.

An important part of IMRT planning that is hidden from the user is how the inverse-planning algorithm quantifies how well the treatment plan (dose distribution) meets the planners' objectives. The functions used for this task are summarized below.

2.2.3.1 Hard and Soft Constraints

The constraints that the optimization algorithm attempts to meet can be either "hard" or "soft." A hard constraint is one that the treatment plan must meet. For example, the intensities in the fluence cannot be negative in value. In another example, the maximum dose to the spinal cord must not exceed 45 Gy. If the final dose distribution results in a spinal cord dose that exceeds this hard constraint, then the algorithm may automatically scale down the entire dose distribution. A soft constraint is one that could be violated, although violations may incur a penalty. For example, the mean dose to the parotid could be a soft constraint, reflecting our level of understanding of the radiobiology of the parotid and the clinical compromises needed when treating patients. That is, we would like to minimize the dose to the parotid, and we know that maintaining the mean dose at less than 26 Gy will produce less toxicity. However, we also know that a slightly higher dose would be acceptable, and ultimately, we want to treat the tumor and may be willing to sacrifice parotid function to do so. The level of "softness" of a constraint is controlled by the planner by increasing or decreasing its relative weight or penalty.

2.2.3.2 Dose- and Dose-Volume-Based Objective Functions

A simple objective function for optimizing dose distributions could be expressed as a sum of the squares of the differences of desired and computed dose at each point in the volume of interest. Each tissue could be assigned a different weight (or penalty) such that it contributes differently to the overall objective function. For tumors, dose increases (hot spots) and decreases (cold spots) may be important. For normal tissues, only dose increases would be considered. This simple dose-based approach is generally considered insufficient in practice. Radiobiologically, the response of both tumors and normal tissues to radiation is a function of the volume of the tissue that receives each level of dose—hence the common use of dose-volume histograms (DVHs) to assess the quality of radiation therapy plans. DV-based objectives are the most common approach used in IMRT optimization. For each normal structure, the DV constraint can be expressed as the volume of that structure that is allowed to receive a certain dose or higher. Typically, several DV objectives are used for each normal structure. For targets, a constraint is also included that describes the acceptable *minimum* dose to a certain volume, for example, the minimum dose to 95 % of

the PTV. Further, as noted above, each constraint is also assigned a weight that reflects how much it will contribute to the overall objective function.

Notably, the DV constraints that treatment planners often set for plan optimization are not necessarily the same as those they are aiming for in the final treatment plan. Despite extensive and ongoing research into developing treatment plan optimization engines, treatment planning is still an "art" in that treatment planners are often required to "trick" or "massage" the optimization engine to obtain the optimal plan. The process is achieved by varying the DV constraints, varying the relative penalties of the different constraints, and adding dummy structures to help force dose either away from or toward certain areas. Thus, although optimization of a treatment plan is nominally automatic, the experience of the treatment planner is important in determining objectives, priorities, dummy tissues, and beam angles. One approach to mitigate the need for such experience-based artistry is the use of class solutions, which provide a systematic way to plan treatments for specific sites that is consistent and robust. Use of class solutions is particularly promising in the many situations in which objectives conflict [65, 120, 128].

One disadvantage of DV constraints is that each constraint may describe only a single point on the DVH curve. Use of multiple DV constraints can reduce this, and some planning systems actually allow the planner to draw the optimal DVH and then use that to guide the optimization. However, multiple DVHs could, in general, lead to the same dose-response, and another DVH in the space of DVHs of one structure may be more helpful to other structures. Thus, specifying the so-called optimal DVH may not be the ideal solution. One approach to help overcome the limitations of DV-based optimization is to supplement this process with dose-response-based constraints, such as constraints that are based on calculations of tumor control probability, normal tissue complication probability, or equivalent uniform dose [89, 132]. Constraints such as these have the potential advantage of including treatment response in the optimization. Notably, however, in many cases, the treatment response of the irradiated tissues is not well understood.

2.2.4 Optimization of Intensity Distribution

Once the beam configuration and plan objectives are established, the optimum intensity distribution for each beam can be determined. This is achieved through an iterative optimization process as follows. Each radiation ray (beamlet) is traced from the source of radiation through the patient. Only rays passing through the target plus a small margin are considered. The dose at each voxel in the patient is calculated for an initial set of weights for each individual beamlet, and the resulting dose distribution is then used to calculate an objective function that describes how close the current dose distribution is to the goals set by the treatment planner. The effect of a change in the weight of each individual ray or beamlet is then calculated, with the weight increased, decreased, or left the same depending on whether the change would be favorable for the patient. Mathematically, these changes in ray weight are determined from the gradient of the objective function with respect to the

ray weight. Because improvements in the treatment plan are a result of changes in many rays from many beams, only small changes in ray weight may be permitted in any one iteration. This iterative process then continues until no further improvement occurs, at which point the optimization is assumed to have converged on the optimal solution. Most of the optimization algorithms used for IMRT planning use variations of gradient techniques. The large search space of RT plans can contain many local minima [20, 35, 131, 138], and alternative optimization approaches such as simulated annealing can reduce the probability of getting trapped in a nonoptimal local minima [11]. However, this is not a significant issue in clinical practice [67, 131]. Another common practice in clinical treatment planning (depending on the capabilities of the planning system) is to "massage" the optimization in real time by adjusting the constraints and weights as the optimization progresses.

At this point, the optimized intensity modulation must be converted to a deliverable field. Typically, this involves first determining the MLC sequence that will achieve a fluence as close to the optimal fluence as possible, given the physical constraints of the delivery mechanism (including the radiographic properties of the MLCs). The details of this sequencing process are described later in this chapter. Notably, in some situations the optimal fluence and the actual deliverable fluence are sufficiently different that the final dose distribution is compromised.

One approach used in some treatment planning systems to overcome this issue is to directly include the MLC constraints in the optimization process. For example, in direct aperture optimization, only MLC aperture shapes that satisfy the mechanical constraints of the MLC system are considered [1, 33, 108]. In this approach, the final plan typically uses fewer segments (apertures) than other approaches. In other systems, deliverable dose distributions are fed back into the optimizer to further adjust intensity distributions and the resulting leaf positions so that the optimized and deliverable dose distributions are essentially identical.

2.2.5 Dose Calculation

During inverse planning, the dose distribution is recalculated many times. Some compromise between dose accuracy and speed of the dose calculation is necessary because, in general, the faster an algorithm is, the less accurate it is and vice versa. If a fast, inaccurate dose calculation algorithm is used during the optimization, then the final dose calculation (calculated with an accurate algorithm) may well not be the same as the one calculated with the inaccurate algorithm, and it may not even be the optimal solution. Several solutions have been developed to minimize this issue. One approach is to start with a less accurate, fast algorithm to get close to the final solution and then carry out the final iterations using a slower, more accurate algorithm [81, 110]. The less accurate algorithm may be a simple pencil-beam algorithm that may not accurately model the effect of the delivery hardware (e.g., MLCs), as described below. The impact of this approach depends on the anatomic characteristics of the area being treated (e.g., significant heterogeneity in tissue density in the lungs) and the complexity of the treatment plan. The graphics processing unit

recently emerged as an option for reducing the processing time for IMRT optimization and dose calculation [34, 45, 55, 76, 101]. The accuracy of dose calculations in the buildup region, especially with many tangential fields, is particularly important in IMRT, especially for anatomically complex areas such as the head and neck, and additional care is needed when commissioning the treatment planning system [27].

2.2.6 Treatment Plan Evaluation

IMRT dose distributions are usually very conformal, but they can also be very complex and are different from dose distributions in conventional RT. As is true for conventional RT, DVHs are useful tools for summarizing and comparing treatment plans. Unlike conventional RT, the need to review treatment field beam's eye view (including block shape) is usually not important in IMRT, with some notable exceptions (e.g., ensuring that beams do not travel across the top of the shoulders in patients being treated for head and neck cancer). Instead, the complex dose distributions, and clinical compromises that occur near normal tissues, underscore the importance of careful review of the dose distribution for each CT slice.

2.2.7 Special Planning Considerations

Some of the more common planning considerations experienced by clinicians are summarized here. Additional details on IMRT planning for tumors at various sites are given elsewhere in this book.

2.2.7.1 Targets in the Buildup Region

Severe skin reactions, reported in some patients treated with IMRT, can be caused by a variety of factors, including the use of immobilization masks or IGRT couches (both of which can have a "blousing" effect), multiple tangential fields (IMRT typically consists of many fields, many of which are tangential to the patient, unlike traditional treatments), inappropriate strategies during IMRT inverse planning (e.g., including the skin in the PTV expansion), and the inability of the treatment planning system to accurately calculate dose in the buildup regions [23, 27, 28, 44, 63, 118], particularly when the treatment targets are close to the patient's skin. Strategies used to mitigate these effects include delineating the skin as a sensitive structure (and applying a maximum dose constraint during optimization) and pulling the PTV back several millimeters from the body surface; however, care must be taken to avoid unintended consequences such as reduced target coverage [28].

2.2.7.2 Overlap Regions and Pseudostructures

Target volumes (PTVs) will often overlap with critical normal tissues, creating a potential conflict between target objectives and normal tissue constraints. For example, the PTV in head and neck treatments often overlaps with the parotid or other nearby structures. Various solutions to this potential dilemma have been proposed,

including creating dummy (pseudo) structures with no overlap or implementing a priority system in the optimization. As noted previously, pseudostructures (structures that are not necessarily related to specific anatomic structures) are widely used in IMRT planning. Examples include ring structures created around target structures to help force the optimization to minimize dose to surrounding structures; structures created in regions that the planners expect, from experience, that the optimization process may deposit excess dose; and structures created based on isodose lines after initial optimization to remove unwanted high-dose regions (which could be in the target or normal tissues).

2.2.7.3 Hybrid IMRT Approaches

Treatment plans do not have to be constructed only for IMRT or only for VMAT, and many treatment centers combine IMRT and static treatments in therapy for breast cancer [73] or thoracic cancer (cancer of the lung or esophagus). In such cases, hybrid techniques typically concurrently combine static fields (~2/3 of the dose) and IMRT or VMAT fields (~1/3 of the dose) [17, 74]. Potential advantages of this type of treatments include a reduction in the volume of lung exposed to low doses.

2.3 Treatment Delivery

2.3.1 IMRT Delivery Hardware

Several hardware approaches are used to deliver IMRT; the most common involve rotating multileaved slits and moving MLCs and are described below. For the sake of completeness, we also briefly describe the use of compensators and jaws-only IMRT, although these approaches are rarely used for clinical purposes.

2.3.1.1 Compensators

Physical compensators (or compensating filters or modulators) can be used to create complex x-ray fluence distributions. The advantages of physical compensators include not requiring MLCs, with their attendant requirements for commissioning and maintenance (although these benefits are countered by issues related to the accuracy of machining and compensator placement). Other advantages include the finer resolution that is possible with compensators, the less complicated QA, and the lack of interplay effects (interactions between a moving radiation aperture and a moving target) [90], although interplay can be reduced with appropriate planning approaches [24–26]. Similarly, although some of the complexities involved in calculating dose for complex fluences created with MLCs (e.g., transmission, interleaf leakage, and tongue-and-groove effects) do not exist with physical compensators, other issues must be considered such as the effects of beam hardening and scatter from the filter [40]. Currently, at least one company in the United States is creating patient-specific compensators for IMRT (.decimal), and some users create their own [90]. The use of compensators in modern RT is extremely rare.

2.3.1.2 Rotating Multileaved Slit Approaches

The delivery of radiation using a rotating multileaved slit that produces an intensity-modulated fan beam is called tomotherapy [41]. Radiation can be delivered as a series of axial slices, where the patient is translated discretely through the linear accelerator (LINAC) between slices, or in a helical form, where the patient is translated continuously through the LINAC as the LINAC gantry rotates around the patient. These approaches can be considered analogous to axial and helical CT scans. Much of the initial experience with IMRT involved use of an axial tomotherapy system called MIMiC (Nomos) [40]. MIMiC was a binary MLC system, with two banks of pneumatically controlled opposing leaves arranged to give a fan beam of radiation parallel to the rotation of the LINAC. The intensity of the fan beam is modulated by controlling how long each leaf blocks the fan beam. The MIMiC system was an after-market add-on system that allowed centers to add IMRT capabilities to existing LINACs. Its successor still offers similar options (nomosStat; Best nomos, http://www.nomos.com/pdf/nomoSTAT_Bro_03.pdf).

Although axial tomotherapy has remained an after-market add-on system, helical tomotherapy was developed as a purpose-built system, called the TomoTherapy Hi-Art (Tomotherapy Inc). As is true for axial tomotherapy, helical tomotherapy has a fan beam parallel to the gantry rotation plane. In helical tomotherapy, the couch translates through the gantry as the gantry rotates. The pitch (couch movement/fan-beam width) is typically 0.2–0.5.

2.3.1.3 Multileaf Collimators

The vast majority of modern IMRT delivery systems use MLCs, small, individually motorized leaves that can be used to shape or modulate the intensity of the treatment field. Several basic approaches incorporate MLCs into the treatment unit [12], with the MLCs either taking the place of one of the LINAC adjustable jaw pairs or being positioned below the jaws. Common designs have between 10 and 60 opposed leaf pairs, with the width of the MLC in the beam's eye view at the isocenter plane between 2 mm and 1 cm, depending on the manufacturer and model.

The ability of MLCs to shape fields (or segments of IMRT fields) depends on several aspects of their physical design and control mechanism. These include maximum leaf travel (determined by the length of the MLC leaves), maximum field size perpendicular to the MLCs (MLC width × number of MLCs), and whether the leaves on one side can interdigitate with neighboring leaves on the opposite side. These are all important considerations; for example, a machine with small MLCs (such as those used for stereotactic applications) may not be able to cover sufficient length to treat head and neck tumors or large lung tumors.

The x-ray properties of the MLC can also have a significant effect on the dose distribution. Leakage of radiation through the MLCs is much more important in IMRT than in conventional RT because radiation is delivered with narrow openings of the moving leaves of MLCs, and so leakage contributes more to the target dose. For the same reason, scatter from the MLCs is also more important in IMRT than in conventional RT [68, 69].

Another important design consideration is the cross-sectional shape of the MLCs, which is complex because leaves must incorporate divergence in the direction perpendicular to their travel, and adjacent MLCs must overlap to minimize interleaf transmission. Details of this overlap are very important in IMRT, as the exposed stepped sides (known as the tongues) may block or scatter radiation, leading to underdosing the target [40]. This effect can be significant, with reported underdoses as large as 10–25 % [105, 116, 124], as shown in Fig. 2.1. Inclusion of this so-called tongue-and-groove effect in dose calculation algorithms is difficult, so leaf-sequencing algorithms are often designed to minimize this effect (rather than including it in the dose calculation), although some investigators have included this effect in the actual optimization stage [105].

The leaf end shape is also important. It can either be straight, in which case the collimator moves along the circumference of a circle, with the ends of the leaves always remaining along the divergent x-ray beam, or rounded, for designs in which the MCL moves perpendicular to the beam central axis. When MLCs have rounded ends, an offset of 0.4–1.1 mm is present between the edge of the radiation field and the nominal location of the MLC leaf, depending on leaf design, beam energy, and distance from central axis [40]. The effect of this offset must be included in the treatment planning system dose calculations.

The accuracy and precision of MLC positioning are also important. In conventional conformal RT, MLCs are used to define the aperture of the treatment beam, thereby conforming it to the treatment target. When used in this way, an uncertainty in the leaf position of 1–2 mm may be acceptable, because an uncertainty of this size (typically small compared with the total aperture size) has only minimal effects on the radiation output. However, in IMRT the situation is very different. First, the segments can be quite narrow (<1 cm), and uncertainties of only a few tenths of a millimeter can cause errors of several percentage points in delivered dose. Further, the cumulative dose distribution in IMRT comprises contributions from many

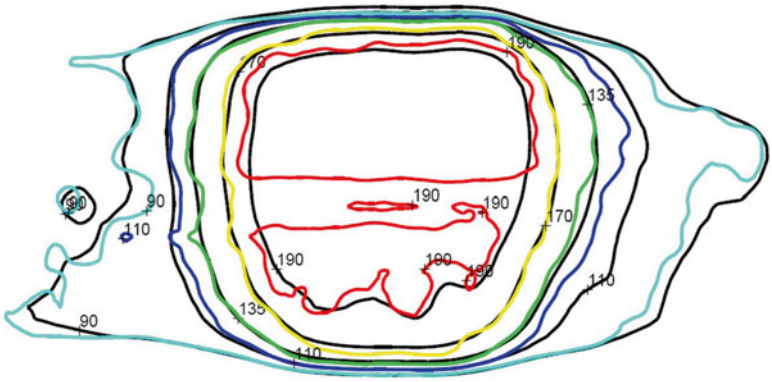

Fig. 2.1 Example of an IMRT case in which the tongue-and-groove effect resulted in a line of reduced dose through the target. *Black isodose lines* show the calculated dose distribution; *colored isodose lines*, the results of film-based IMRT quality assurance

segments. The beam edges move to many different locations during the treatment (i.e., not just at the edge of the target as is the case in conformal treatments), so it is essential that their positional accuracy is maintained to better than a millimeter. Without this level of accuracy, the contributions of the different segments may not sum correctly [40].

2.4 Volume-Modulated Arc Therapy

VMAT is a form of IMRT in which the treatment is delivered in one or more dynamically modulated arcs [5, 16, 93, 94, 104]. As the gantry rotates, the MLCs move, giving a different aperture shape for each angle of the gantry. The rate of rotation of the gantry and the LINAC dose rate can both be modulated during treatment to give the required delivered dose for each gantry angle. The quality of the planned dose distributions that can be achieved is equivalent to those that can be achieved with other forms of IMRT. The plan quality depends on achievable modulation, which, in turn, depends on the gantry speed, number of arcs, or both. The main advantage of VMAT is that the entire treatment can be completed quickly. For example, a typical treatment of two complete 360° arcs, with different couch rotations for each arc, takes less than 2.5 min. This advantage is significant, especially for a busy clinic, and thus we expect that VMAT will become the IMRT delivery technique of choice for most treatments.

2.4.1 Leaf Sequencing

As noted above, some optimization algorithms do not consider the physical characteristics or limitations of the delivery system when calculating the optimal intensity distribution. This optimal intensity is then used to create the MLC leaf positions (leaf positions as a function of time/monitor units [MUs]) that will deliver a fluence that is as close as possible to the optimized distribution.

In step-and-shoot multifield IMRT, modulated delivery is achieved with multiple static MLC segments, with each segment having its own aperture shape and weight (MU). The leaf-sequencing algorithm first coverts the optimized intensity distribution to discrete levels, which are then converted into separate MLC segments (Fig. 2.2). The ideal algorithm will create an MLC sequence for which the summation of all the segments gives a delivered fluence that is close to the optimized fluence, uses the minimum number of segments, and may also minimize the MLC motion between segments. In general, the agreement between the optimized and delivered intensity distribution increases as the number of intensity levels is increased. This process has been shown to increase the target coverage, but it also results in an increase in the number of MLC segments (MLC shapes). Because the beam is turned off as the MLCs move between segments, this can significantly affect the treatment delivery time. The advantage of step-and-shoot delivery is that factors such as MLC speed and dose rate are less important, so the IMRT delivery

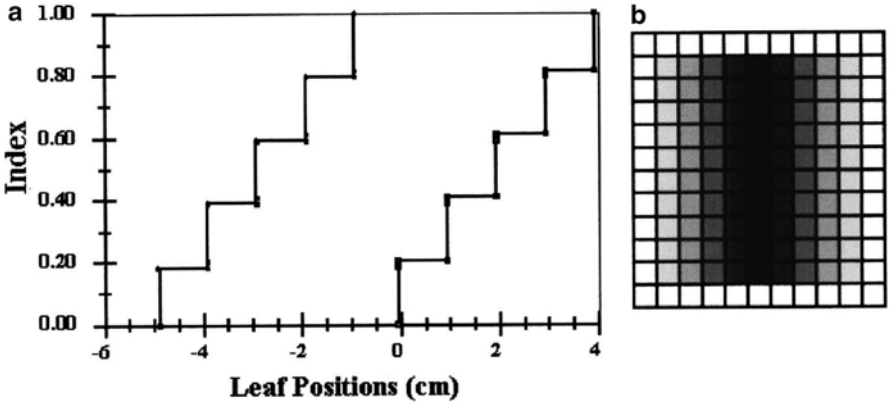

Fig. 2.2 (**a**) Leaf trajectory as a function of dose index for a step-and-shoot IMRT delivery. (**b**) is the resulting fluence map (From Xia and Verhey [133])

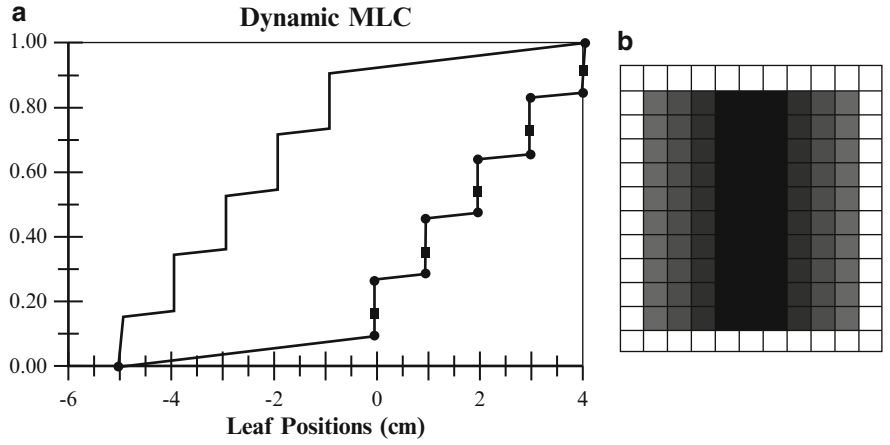

Fig. 2.3 (**a**) Leaf trajectories as a function of dose index for dynamic multileaf collimator (MLC) delivery. (**b**) is the resulting intensity fluence (From Xia and Verhey [133])

is possible with a less advanced treatment machine. Also, importantly, step-and-shoot IMRT typically requires less MUs than dynamic IMRT.

In sliding-window IMRT delivery, the MLCs move across the target volume while the radiation is on [8, 13, 40, 113]. The size of the gap between opposing MLCs and the speed of the MLCs are constantly changing. The dose rate may also be adjusted. Conceptually, the amount of radiation received by a point within the target is proportional to the number of MUs delivered while the system is in the open gap. When the two opposing leaves are far apart, the delivered dose is high; when they are closer together, the delivered dose is reduced (see Fig. 2.3). To account for unexpected variations in dose rate, the position of the MLCs is indexed

to the delivered MUs rather than to time. Advantages of sliding-window IMRT include faster delivery than step-and-shoot IMRT, reduced numbers of MUs, and potentially reduced wear and tear on the MLC mechanism (because motion is mono-directional).

The delivered and ideal fluence can differ for several reasons, including overly complex ideal fluence distributions [80] and practical limitations related to the leaf design (transmission, non-divergent leaf end design, leaf scatter) [99]. Although these limitations reflect the choice of the planning and delivery system, treatment planners can take steps to minimize them. For example, planners should take care not to push the IMRT optimization excessively, as can happen when extreme values of the weights are used for the DV constraints. Some planning systems also allow the planner to control how smooth the ideal fluence will be. One way to monitor fluence complexity is to ensure that the MU per beam is not unusually high. Commonly, the agreement between ideal and deliverable MU decreases as the MU increases. Also, the complex MLC patterns that high-MU fields require can be more difficult for the MLC controller to deliver, resulting in unwanted delays at the time of treatment.

2.4.2 Jaws-Only IMRT

As described above, with MLC-based IMRT, MLCs are used to create many irregular shapes that are superimposed to create a complex fluence pattern. Complex fluences can also be created from many rectangular segments created by the LINAC jaws alone [38, 41]. The main advantage of jaws-only IMRT is the lack of additional complexity and expense of an MLC, which could allow IMRT to be achieved at lower cost. One possible application of this approach could be a low-cost LINAC for low- and middle-income countries, where affordable, reliable RT equipment is desperately needed [47–49]. In modern radiation therapy centers, however, IMRT is dominated by MLC-based delivery.

2.4.3 Image-Guided IMRT

IMRT alone can achieve impressive dose distributions, reducing toxicity to normal tissues. However, the high conformality that can be achieved with IMRT increases the need for image guidance (i.e., IGRT). Moreover, realizing these planned dose distributions over a treatment course lasting days or weeks requires highly accurate patient setup, particularly when taking advantage of tight dose distributions could lead to use of margins as small as 3–5 mm [30]. Many approaches are used for IGRT, including orthogonal (or stereotactic) kilovoltage or megavoltage x-ray imaging and CT imaging (cone beam or CT on rails), and MRI-guided treatments are only a few years away [57, 83, 102, 109]. Specifics of IGRT for IMRT are discussed elsewhere in this book.

2.5 Intrafraction Motion and IMRT

Use of IMRT to treat tumors in regions of the body that experience involuntary intrafraction motion (e.g., tumors in the lung or liver that move with respiration or tumors in the lower abdomen that move with the passing of bowel gas or other involuntary bodily functions) has been controversial for two reasons, namely, the potential for geometric miss and interplay effects between the motion of the tumor and the motion of the machine (gantry, collimator, and MLC) used to create the modulation pattern [10, 107, 136]. Both of these concerns can be managed by appropriate imaging and plan design.

The issue of geometric miss should be addressed by design of appropriate margins (in the same way that all geometric uncertainties are addressed) and the IGRT process (understanding the relationship between the imaging surrogate and the actual target and realizing that this relationship can be influenced by the motion management technique that is chosen). Motion can also be minimized by gating, abdominal compression, or other approaches [56]. Any residual motion should be carefully evaluated and included in the treatment margins.

The issue of the interplay effect has been extensively studied, and although extremely large dose deviations are theoretically possible, such deviations are generally not found in the MLC sequences of real clinical cases. Even when the interplay effect does cause dose deviations from day to day, these deviations average out after a few fractions [26]. Notably, however, treatment planners could potentially create an extremely complicated, overmodulated plan for which the interplay effect can become important. In situations where possible interplay effects are a concern, the dosimetric errors caused by the interplay effect can be reduced by reducing the dose rate [25]. This works because the longer treatment times result in more opportunities for the effects to average out. For the same reason, the interplay effect is not expected to be a significant clinical issue with stereotactic ablative RT (where the doses are high and treatment times are long). Another planning technique shown to reduce the impact of interplay effect for VMAT plans is to use several arcs instead of a single arc [26]. To minimize any interplay effects when moving targets are treated with IMRT (or VMAT), treatment planners should take care to not overmodulate the treatment plan and to use multiple arcs. If these approaches are not possible, a reduced dose rate can be considered.

2.6 Quality Assurance Specific to IMRT

2.6.1 Commissioning and Routine Machine Quality Assurance

Rigorous commissioning of the processes for IMRT planning and delivery is absolutely essential. Nevertheless, the Radiological Physics Center, an imaging and radiation core QA facility based at MD Anderson Cancer Center, has reported that as many as 28 % of institutions failed to meet even the loose criteria of ±7 % dose accuracy or 4 mm distance to agreement in a high gradient when subjecting a head

and neck phantom to IMRT [51]. This is a rather frightening statistic, given that these institutions were obtaining credentials for implementing clinical trials involving IMRT (and presumably thought their planning and delivery process was adequate to treat patients). Although some of the failures resulted from incorrect phantom setup, other reasons include incorrect output factors in the treatment planning system, incorrect CT-to-density conversion, and inadequacies in beam modeling at the leaf ends. The commissioning process involves careful measurement of any physical parameters that the treatment planning system may need (e.g., MLC transmission), evaluation of the mechanical and radiation characteristics of the delivery system (e.g., MLC leaf positioning accuracy) [58], and end-to-end tests. Many of the tolerances (for commissioning or routine QA of IMRT equipment) are different than for non-IMRT machines. For example, step-and-shoot IMRT can involve segments with few MUs; the dose per MU, as well as flatness and symmetry of the beam, should be checked throughout the range of MUs used for IMRT [40, 58].

In addition to measuring individual characteristics of different parts of the delivery process, end-to-end tests are important as well. The American Association for Physicists in Medicine created a series of tests for IMRT commissioning that are designed to represent common clinical treatments. These tests include the measurement of point dose and also dose planes assessed by using the gamma criterion of 3 %/3 mm, the most prevalent standard for acceptance testing and QA [87]. Nine centers (all of which passed the Radiological Physics Center's phantom irradiation) planned, delivered, measured, and analyzed these tests, and the findings were used to create confidence levels for use as reference by other institutions attempting the same tests. Notably, however, despite the common acceptance of 3 %/3 mm as a standard [3], other criteria can be used; moreover, the 3 %/3 mm standard may not be appropriately "tight" for commissioning or for patient-specific QA [22]. Some have proposed a DVH-based metric as the final goal [15].

2.6.2 Patient-Specific Quality Assurance

Each plan in IMRT can be highly complex, and completing patient-specific QA before a patient's treatment is begun is common practice [3, 39, 40, 46, 103, 111]. This process verifies the ability of the treatment planning system to calculate the dose accurately for this patient's plan (which can be done with a secondary dose calculation software package, as used in conventional RT) and the ability of the delivery system to accurately deliver the dose. Typically, the QA process involves comparing a dose plane delivered to a regular phantom with the dose calculated by the treatment planning system for the same geometry [87]. However, correlation can be lacking between conventional IMRT QA passing rates and actual dose errors in anatomic regions of interest [88]. For example, plans can pass planar IMRT QA but still have relatively large dose errors to some of the patient's anatomy. For example, Kruse and colleagues concluded that gamma analysis on a per-plane basis for a set of highly modulated head and neck plans was insensitive for detecting calculational

errors [60]. In a separate study, McKenzie and others found that some devices were relatively insensitive for detecting failing plans [75]. That said, these QA approaches should not be discounted, as they do ensure that no large errors in dose calculation are present. Products are now available that include a calculation of the dose to the patient's anatomy (rather than just to a dose plane in a phantom), although these products are still relatively new [22, 86, 91, 126]. Details on how to commission IMRT QA equipment and processes, equipment choices, and QA criteria are available elsewhere [39, 40, 78].

2.6.3 Process Quality Assurance

As indicated previously, the delivered dose distribution is less likely to match the planned distribution if the plan is excessively complex. Modeling MLCs tends to be more important for complex plans (e.g., the tongue-and-groove effect), and the interplay effect is also more pronounced for complex plans, underscoring the desirability of avoiding these complex plans. Complexity can be quantified in a variety of ways, including average distance between opposing MLCs, but the easiest is probably to quantify the number of MUs for the total plan. Plan MUs depend on a variety of factors, including treatment planning system, IMRT approach (step-and-shoot vs. sliding window), and expectations of the clinicians (tighter constraints or many iterations during the planning process will invariably result in plans with higher MUs). In the example shown in Fig. 2.4, a single, relatively inexperienced treatment planner was responsible for all plans that involved more than 2,000 MUs. Interestingly, this planner's plans tended to have more broken-up isodose lines as well as higher MUs, indicating that optimization engine was being overworked, which probably led to constraints being weighted too strongly. About a year after these data were obtained, the expected plan MUs had dropped significantly.

2.7 Facility Design for IMRT

The number of monitor units required for IMRT plans is much higher than that needed for conformal RT plans (with the exception of VMAT), leading to a significant increase in radiation "leakage." This leakage should be accounted for in shielding calculations by using the so-called IMRT factor, the ratio of average MU per unit prescribed absorbed dose needed for IMRT and the MU per unit prescribed dose for conventional treatments [84, 85]. The IMRT factor is a function of treatment site (being lower for simple plans like breast, higher for more complex plans like head and neck), delivery mode (higher for sliding window than for step-and-shoot IMRT), and treatment planning system (e.g., efficiency of the MLC sequencer). Given the wide range in published values (from 2 to 10 or more), the shielding designer should ensure the use of appropriate values, erring on the conservative

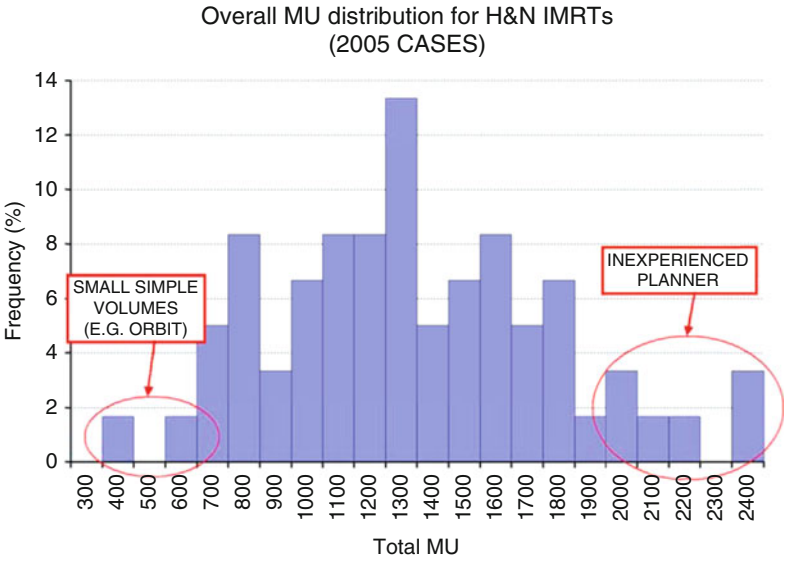

Fig. 2.4 Frequency distribution of total plan monitor units (MUs) in sliding-window IMRT for head and neck treatment at a single institution (These data were obtained in 2005, relatively early in the institution's experience with IMRT; in subsequent years, the total numbers of MUs were lower)

side. An additional consideration when designing a new treatment room is that IMRT tends to require less high-energy beams [95, 112, 119], in which case the high-energy workload may be reduced.

Tomotherapy, which is a special case of IMRT, has a narrow fan beam that is only a few centimeters long; thus, the primary barrier can be much narrower than that required by a conventional treatment unit. The IMRT factor for these units is relatively high, meaning that the secondary shielding barrier may have to be thicker than for conventional treatments [85]. The secondary shielding barrier requirements for scattered radiation are the same in tomotherapy and IMRT as for conventional treatments.

2.8 Advantages and Challenges of IMRT

The ability of IMRT to shape the dose around the target, thereby minimizing dose to adjacent normal structures, is significant, especially for individual patients. However, IMRT also has some limitations. In many cases, these limitations can be mitigated by careful clinical implementation (guided by awareness of the limitations) and future technology developments. Some of the advantages and disadvantages of IMRT are noted briefly below.

2.8.1 Higher Conformality/Margin Reduction

The high degree of conformality possible with IMRT can significantly improve normal tissue toxicity [4, 100, 106, 115, 129, 137], as discussed elsewhere throughout this volume. Combining this high degree of conformality with IGRT offers the potential for further reducing toxicity while maintaining local-regional control [64]. One group successfully reduced PTV margins for patients with head and neck cancer from 5 to 3 mm, reducing the incidence of gastrostomy tube dependence and esophageal stricture but without affecting local-regional control [19]. Image-guided IMRT may also offer the possibility of dose escalation, which can improve control of some tumors [117]. Of course, the risk is that inappropriate reduction in treatment margins will result in geographic miss of the tumor. Little clinical data are available on this issue, but careful understanding of the uncertainties accounted for in the PTV margin is necessary before any reduction is implemented. Even IGRT can still involve significant uncertainties that must be considered, particularly in target delineation [18, 77, 97, 130] and the actual extent of microscopic disease [123], but also in interfraction and intrafraction motion/deformation [121, 122].

2.8.2 Treatment Errors

Error rates in RT have been reported to be less than 1 % per fraction [42, 43, 70]. Moreover, the error rate is often reduced as new technology is introduced. For example, one group showed that the introduction of MLCs reduced error rates relative to "low-technology" machines without MLCs [72]. Error rates with IMRT have also been reported to be lower than those with three-dimensional/conventional RT [71]. One of the main reasons for the lower error rates is that IMRT usually does not involve the use of accessories (e.g., blocks, electron cones), the incorrect use of which is one of the main source of errors in conventional RT. Other reasons are that patients who require urgent treatment (with correspondingly rushed planning) tend to be treated with techniques other than IMRT. Presumably, the extensive patient-specific QA that is carried out for IMRT patients is also important in reducing error rates.

Even though the introduction of new technology tends to reduce error rates, the types of errors change when new technology is introduced. In one analysis, the most common errors with IMRT were found to be related to incorrect data entry (to the record-and-verify system) compared with conventional treatments, for which accessory and setup errors were more common [71]. As integration of the planning system, record-and-verify system, and treatment delivery system improves, the probability of such errors should be progressively reduced. Several IMRT treatment errors have had devastating consequences [50], including a well-publicized case in which a series of computer errors resulted in a patient being treated with MLCs parked in the open position instead of moving across the field to modulate the x-ray intensity. In addition to technology failures, treatment errors can also occur because of the different data needed to commission treatment planning systems for IMRT. For

example, very small fields are possible in IMRT. If these are measured incorrectly (e.g., by using too large a detector), this can result in incorrect treatments [50]. Similarly, the radiation characteristics of MLCs (e.g., transmission) make a larger contribution to IMRT treatments than for conventional treatments, so incorrect entry of these parameters into the treatment planning system can result in incorrect dose calculations. Thus, as is true with any new technology, the clinical implementation of IMRT must be approached cautiously, with an understanding of the risks, full consideration of the workflow/processes, and appropriate staffing levels, training, tools, and techniques. Further guidance on safety considerations in IMRT is available elsewhere [82].

2.8.3 Unanticipated Clinical Consequences

IMRT dose distributions can be quite complex and are unusual in comparison with dose distributions from the pre-IMRT era. For example, depending on the technique or treatment site, high doses may be close to normal tissues, and large volumes of normal tissue may be exposed to low doses. Some of the dose-response data used clinically may have been based on patients who were not treated with IMRT, and care is needed when using such data to evaluate dose distributions from IMRT plans to avoid unanticipated clinical consequences. An example of such consequences was described by Allen and colleagues, who found that IMRT for mesothelioma led to an unexpectedly high rate of fatal pneumonitis [2]. This case highlighted the need for extreme care when applying DVH constraints to new clinical treatment techniques [2, 59].

2.8.4 Out-of-Field Dose and Secondary Malignancies

Patients treated with RT may be at increased risk of developing secondary malignancies caused by radiation outside of the treatment volume (i.e., out-of-field dose) [7, 14, 61]. For example, before the introduction of IMRT, Brenner and colleagues found the absolute risk of secondary malignancies caused by out-of-field dose to be 1.4 % among patients surviving more than 10 years after treatment [14]. Sources of out-of-field dose include photon leakage (proportional to MUs), radiation scattered from the collimators (also related to MUs), radiation scattered within the patient (proportional to target dose) [114], and neutrons, which are produced mostly through high-energy photons interacting with high-Z materials (e.g., tungsten or lead) [62]. Contributions of these factors depend on photon energy as well as distance from the target, with the former MU-dependent sources being most importantly distant from the field edge. Although the higher MUs required for IMRT mean that the risk of secondary malignancy is unavoidably higher, this increase can be minimized to some extent by the choice of IMRT approach (e.g., dynamic IMRT delivery vs. step and shoot) and energy (see Kry et al. [61]).

2.8.5 Concerns About Interplay Effects

The dose delivered to a tumor can vary from day to day when IMRT (whether step and shoot, dynamic, or VMAT) is used to treat moving tumors [9, 12, 29, 37, 107]. This variation results from the interplay between motion of the tumor and motion (or changing aperture shape/position) of the delivery system. As previously discussed, this effect can generally be minimized by careful planning that avoids overly complex plans. That is, for dynamic IMRT, small MLC separation and fast MLC motion should be avoided; for step-and-shoot IMRT, small segments with small MUs should be avoided; and for VMAT, more than one arc should be used. Interplay effects in complex treatment plans can be avoided by reducing the dose rate (and thus reducing the MLC speed and allowing more averaging over the respiratory cycle). In all but the most complex situations, dose deviations average out after several (<5) fractions [26]. Use of IMRT to treat moving targets is discussed in greater detail elsewhere in this volume.

2.8.6 Changes in Workflow

Another potential disadvantage of IMRT is the increased effort needed to create and check each treatment plan. Many factors contribute to the overall time needed to prepare an IMRT plan, including contouring of many more structures than for 3D conformal RT, plan optimization, and phantom planning (for patient-specific QA); the main factor is probably the time spent waiting for the treating physicians to provide target volumes [32]. The need for patient-specific IMRT QA before the first treatment can also add significantly to the effort in preparing a plan for treatment [79, 96]. Selection of the treatment planning system and other tools is important here; for example, some planning systems have better tools for manipulating structures (e.g., cleanup, processing, Boolean operations to combine anatomic structures or to exclude overlapping regions) than others [32]. Similarly, dose calculation times can vary widely between planning systems. Radiation oncology researchers and equipment manufacturers are investing considerable effort in developing segmentation, treatment planning, and general work management tools to improve the workflow of IMRT plan preparation, including reducing variations between users [36, 92, 134, 135], so these potential hurdles to the smooth integration of IMRT are being addressed.

The introduction of IMRT can also make some positive contributions to workflow. For example, forward planning can be extremely difficult. In some cases, only the best treatment planners can create conformal treatment plans that meet the clinical goals of target coverage, minimal dose hotspots, and acceptable normal tissue doses. The process of inverse planning, in which the plan is automatically created based on user-defined dose objectives, can significantly simplify this process. This reduction in planning time with IMRT has been noted by several groups [1, 73]. Also, because IMRT typically uses treatment beams from more directions than most conformal plans, the choice of beam angle is less important. Together, this means

that at least in some cases, IMRT treatment planning is actually easier than planning for conventional treatments. Ongoing developments in multi-criteria optimization and automated plan optimization are further leading to greater planning efficiency and improved consistency and quality of IMRT plans. Multi-criteria optimization techniques allow users to navigate a space of multiple plans favoring individual anatomic structures to trade off competing clinical objectives; automated plan optimization automatically adjusts specified objectives and beam configuration to achieve an improved dose distribution.

2.8.7 Treatment Time

When IMRT was first introduced, the "beam-on" treatment time was significantly longer for IMRT than for treatment that involved conventional static fields. However, this time increase varies widely depending on the delivery technique [6]. Although this disadvantage still exists for some forms of IMRT, the relatively recent clinical introduction of VMAT, in which treatment is delivered with 1 or more arcs around the patient, means that IMRT treatments are much faster than the original forms [21, 31, 93, 98]. In fact, in cases in which conventional treatment would have included electron and photon fields, VMAT treatments are faster than conventional treatments.

2.9 Summary

We have described the basic principles of IMRT planning and delivery, together with the associated advantages and challenges that accompany its use in clinical settings. Subsequent chapters in this volume describe the use of IMRT for tumors at various anatomic sites in further detail.

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