INTRODUCTION

There is rapidly growing interest in applying advanced treatment planning/delivery technologies to improve the therapeutic ratio of external beam radiation therapy (RT). The evolution from two-dimensional (2D) to three-dimensional (3D) conformal planning, and now to intensity-modulated radiation therapy (IMRT) and image guidance (i.e., image-guided radiation therapy [IGRT]), have altered our approach to minimizing normal tissue injury. A broad review of these techniques is presented, with a primary focus on the potential pitfalls of applying these new approaches to minimize normal tissue toxicities. It is critical that physicians understand the power and limitations of these technologies so that they can be optimally exploited to reduce the risks to normal tissues and improve the therapeutic ratio of radiation therapy.

BACKGROUND 2D VS. 3D

In the pre-3D era, physicians prescribed RT without full understanding of the 3D doses and volumes. “Clinically safe” techniques were defined based largely on doses, fractionation, and field sizes/orientations. Experienced physicians relied on their judgment, experience, and qualitative assessment of proposed treatment fields, often without objective quantitative metrics.

Three-dimensional planning tools provide images depicting the beam path through the patient (1, 2). This allows beam orientations/shapes to be more “optimally” selected to improve the therapeutic ratio (i.e., spare normal tissue or increasing target coverage) (1). Alternative treatment beams, and groups of beams, can now be quantitatively compared based on 3D dose and volume data.

Three-dimensional planning is a major advance in radiation oncology because it provides fundamental anatomic and dosimetric information heretofore not available. For any particular case, clinicians often disagree on what should be considered the target volume and what dose to deliver. However, all physicians agree that all of the targeted tissue should be irradiated. Three-dimensional planning facilitates this.

The 3D dose distribution is challenging to comprehend. This has led to the development of representative surrogates of the 3D dose distribution that are easier to understand. The commonly used dose–volume histogram (DVH) takes the 3D dose–volume data, discards all spatial information, and represents it as a 2D graph (3). Because such DVHs can also be difficult to interpret, it is common to extract representative “figures of merit” (e.g., mean dose, or the percent of an organ receiving in excess of a given dose) from the dose distribution (4). The potential shortcomings of DVHs and “figures of merit” are discussed later.

Normal tissue dose–volume limits in the 3D era

One of the great goals of 3D planning was that it would increase our knowledge of the dose–volume dependence of normal tissue injury (5). In large measure this has become true. Table 1 summarizes several sites in which 3D dose–volume data have been successfully related to normal tissue outcomes. Figure 1 illustrates some of the data for several specific organs. Such quantitative information is now widely used during the treatment planning process.

It is often difficult to determine which dosimetric parameter best predicts for organ dysfunction because there is often a strong correlation between the different parameters. In the lung, for example, the correlation coefficient between the competing dosimetric parameters (e.g., mean lung dose,
percentage of lung volume receiving \( \geq 20 \text{ Gy} \) is \( > 0.9 \) \( (8, 9, 13, 36) \). This high correlation is likely due to the use of similar RT techniques within the population of patients studied. When the RT techniques become more diverse \( (e.g., \) with IMRT), the correlation between these parameters may become less strong. Thus it is not clear if parameters that were predictive in the 3D era will remain predictive with IMRT. For the parotid, the mean dose and partial volume thresholds are highly correlated with each other \( (37) \), and thus mean parotid dose is commonly used \( (17, 19) \).

### 3D vs. IMRT

With conventional 3D treatment planning, the entire target is typically encompassed within each beam. Further, each RT beam typically delivers a relatively homogeneous dose throughout the target. Thus significant RT dose is typically received by tissues in the “shadow” of the target as seen in the “beam’s-eye view”. The selection of the beam orientation is critical with 3D planning \( (38–40) \). Wedges can be added to the beam to modify the intensity profile, but are relatively simple and provide only uniform and monotonic modulation of the beam’s intensity \( (e.g., \) the entire anterior part of a lateral beam is given less intensity than the posterior aspect). The 3D dose distribution resulting from the sum of multiple beams with relatively-uniform intensity is typically a convex polygon \( (41) \).

With IMRT, each portion of the beam is modulated to provide a unique intensity to each region of the tumor \( (42–45) \). Thus the dose to normal tissue within the path of the beam can be adjusted. The purposefully nonuniform intensities from several beam orientations combine to deliver the desired 3D dose \( (41, 44–48) \).

The IMRT provides the planner/physician flexibility to modify the 3D dose distribution \( (41, 44) \). Extremely conformal, and purposefully nonuniform, distributions can be generated. The IMRT appears particularly useful for concave targets. Because the entire target does not need to be irradiated by each beam, the number of feasible beam orientations increases. Further, the selection of beam orientations may be less critical for IMRT than for 3D, because the portion of the IMRT-planned beam that “shadows” a critical normal tissue can be given a low intensity. Conversely, IMRT may require a larger number of beam orientations than 3D to yield the desired dose distribution \( (45) \) (Table 2). Fortunately, advanced RT delivery systems readily facilitate this.

### The impact of IMRT on normal tissue doses

The IMRT affords the planner with increased flexibility to more conformally sculpt the RT dose distribution, particularly for concave targets, and hence reduce the risks to normal tissues. For example, encouraging results have been reported for parotid sparing \( (17, 18) \). However, there are several limitations of IMRT that deserve highlighting \( (45, 49) \).

### Incorporation of dose–volume constraints from the 3D era into IMRT optimization

Current dose–volume guidelines were mostly derived in the 3D era, typically from patients irradiated with a modest number of beams, with the normal tissue receiving approximately 2 Gy/fraction. With IMRT, the fraction size delivered to the normal tissue is usually variable, and is typically not 2 Gy per fraction. It is not clear if 3D-era data will be applicable in the IMRT era. This uncertainty is illustrated for the endpoint of pneumonitis.

Historically, the whole lung was thought to be able to tolerate approximately 25–30 Gy using conventional fractionation, without chemotherapy \( (50, 51) \). Several studies from the “early” 3D era successfully related pneumonitis rates to the volume of lung exposed to 20–30 Gy \( (i.e., \) V20 or V30) \( (6, 8) \). When using “conventional beam orientations” \( (e.g., \) 40 Gy opposed anteroposterior, plus 20–30 Gy opposed oblique), the V20 or V30 approximates the volume of lung included in any of the RT beams. The obvious method to reduce the V20 is to treat from additional orientations.

More recent studies, some using a larger number of beam orientations, have implicated the volume of lung receiving 5–13 Gy \( (14, 15) \). Indeed, it is possible that V20 is predictive within the confines of the conventional beam orientations. The use of a larger number of beam orientations may not reduce the normal tissue risks, but rather just alter the parameters that are predictive for toxicity. The IMRT generally requires more beam orientations, and distributes dose to a larger volume of lung. A recent report from Memorial Sloan-Kettering Cancer Center (MSKCC) notes a higher

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**Table 1.** Representative organs where DVH-based metrics have been successfully related to the risk/severity of normal tissue injury

<table>
<thead>
<tr>
<th>Organ</th>
<th>DVH-based metrics*</th>
<th>End point</th>
<th>Representative references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Mean dose, V5, V13, V20, V25, V30, NTCP</td>
<td>Radiation pneumonitis</td>
<td>(6–16)</td>
</tr>
<tr>
<td>Parotid</td>
<td>Mean dose, V15, V30, V45</td>
<td>Salivary flow</td>
<td>(17–19)</td>
</tr>
<tr>
<td>Rectum</td>
<td>V40, V45, V50, V60, V65, V70, Dmax &gt;75 Gy</td>
<td>Proctitis/bleeding</td>
<td>(20–24)</td>
</tr>
<tr>
<td>Liver</td>
<td>NTCP, mean dose, V30</td>
<td>“Liver disease” (RILD)</td>
<td>(25–29)</td>
</tr>
<tr>
<td>Heart</td>
<td>Mean dose, V45, V50, NTCP</td>
<td>“Heart disease” (RIHD)</td>
<td>(30–33)</td>
</tr>
<tr>
<td>Brain</td>
<td>V12, Dmean20</td>
<td>Edema/breakdown of the blood-brain barrier, necrosis</td>
<td>(34, 35)</td>
</tr>
</tbody>
</table>

*Vx is the percent of the organ receiving \( \geq X \text{ Gy} \). For several organs, different dose “thresholds” \( (e.g., \) V20, V30) have been suggested to correlate with injury, as shown.

**Abbreviations:** DVH, dose–volume histogram; RILD and RIHD = radiation-induced liver and heart disease; Dmean20 = the mean dose (in Gray) in a specified volume of 20 cm³ that was given the highest dose; NTCP = normal tissue complication probability computed using a model based on the entire three-dimensional dose distribution.

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rate of pneumonitis in patients treated with IMRT vs. conformal 3D beams (52). Thus care must be taken when applying “3D predictors” in the IMRT era. Conversely, a recent study from the M.D. Anderson Cancer Center (MDACC) suggests lower radiation pneumonitis rates for IMRT vs. 3D (53).

Parallel vs. series organs and the neighborhood effect

It is often useful to categorize normal tissue architecture as either parallel or series (analogous to electrical circuits), because it assists with the selection/creation of models/methods used to analyze DVHs (54). For series organs, injury to any part of the organ may render it dysfunctional (e.g., a bowel stricture affects food mobility throughout the intestine). Conversely, damage to one region of a parallel organ may not significantly alter global function (e.g., injury to a small region of liver, kidney, or lung is often inconsequential).

However, there are data to suggest that the dose delivered to a portion of an organ may have an effect on the RT response to the neighboring portion of that organ, for both parallel and series organs. This is well illustrated by a series of elegant studies by van der Kogel’s laboratory (55). When a 4-mm length of spinal cord was irradiated, the dose to cause paralysis in 50% of the animals (ED50) was 87.8 Gy. If the adjacent cord (both superior and inferior to the 4-mm central area) was given a modest dose of 4 Gy, the ED50 for the central irradiated cord dropped to 61.2 Gy. If the cord on only one side (i.e., superior or inferior, but not both) was irradiated, an intermediate value of 68.6 Gy for ED50 was obtained. A dose of 18 Gy delivered to both sides of the 4-mm zone reduced the ED50 to 30.9 Gy.

Similar data are reported from MSKCC for rectal injury—the risk of injury was dependent on the volume of rectum exposed to approximately 70 Gy and 45 Gy (20, 23). Therefore, increasing the volume of normal tissue exposed to low doses of RT may alter the ability of parts of an organ to tolerate focal areas of high dose. These data challenge the classical segregation of organs into parallel vs. series. Because IMRT tends to increase the volume of normal tissue exposed to a low dose, the widespread use of IMRT may have unexpected sequences on the rate of RT-induced normal tissue injury.

### Dosimetric

The IMRT increases the ability to redistribute the dose within the patient, typically not eliminating incidental normal tissue exposure. For a constant dose delivered to the tumor, the integral dose delivered to the patient is approximately similar for IMRT vs. 3D planning (56–59). The qualitative explanation for this is shown in Fig. 2. For an idealized spherical target within a spherical patient, increasing the number of beams will proportionally increase the volume of normal tissue irradiated, yet similarly proportionally decrease the dose to the irradiated

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**Table 2. Comparisons between 3D-CRT and IMRT**

<table>
<thead>
<tr>
<th></th>
<th>3D-CRT</th>
<th>IMRT</th>
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<tbody>
<tr>
<td>Number of treatment beam orientations</td>
<td>Typically 2–5</td>
<td>Typically more</td>
</tr>
<tr>
<td>Selection of beam orientation</td>
<td>Critical</td>
<td>Less critical</td>
</tr>
<tr>
<td>Shape of resultant therapeutic dose volume</td>
<td>Typically convex</td>
<td>Convex or concave</td>
</tr>
<tr>
<td>Uniformity of the dose to the target</td>
<td>Relatively homogeneous</td>
<td>Can be homogeneous, but often is heterogeneous</td>
</tr>
</tbody>
</table>

**Abbreviations:** 3D-CRT = three-dimensional conformal radiation therapy; IMRT = intensity-modulated radiation therapy.
volume. The integral dose can be reduced by selectively using beam orientations that pass through portions of the patient with lesser “separation” (e.g., the anteroposterior vs. the lateral orientation for tumors in the abdomen or pelvis) or oriented along the “long-axis” of the target.

Nevertheless, because most tumors are relatively spherical in shape, and most patients are relatively cylindrical in shape, the integral dose with different treatment beam orientations should be relatively constant. Indeed, quantitative data based on competing plans generated for patients with cancer of the brain, prostate, and lung, suggest that integral dose is relatively insensitive to the RT technique used (58, 60).

Further, if we pretend to remove the outer shell of the patient, and repeat the exercise shown in Fig. 2a–c on a “reduced patient” leads one to conclude that the integral dose to each “patient shell” is approximately constant (f).

As increased knowledge of the dosimetric predictors of normal tissue injury within the context of IMRT become available, IMRT will allow the planner to redistribute dose to minimize the normal tissue risks. Because the dose–response curve for regional injury is not fully known for many organs, it is unclear how to best exploit IMRT to reduce normal tissue risks. For example, if there is a plateau in such a dose–response curve within the clinical dose range, “trading” a high dose to a small volume for a larger volume at a lower dose (with a constant integral dose) may increase global injury (Fig. 3). Conversely, if there is a threshold dose for regional injury (dashed line), then increasing the volume exposed to a low dose might be beneficial.

**Peer-to-peer quality assurance for 3D vs. IMRT: The application of prior knowledge**

Both 3D and IMRT start with segmentation of a 3D image set to define targets and normal tissues (Fig. 4). For 3D planning, beams and apertures are defined by the planner. Typically, beam orientations resemble conventional beams (48). The experienced physician can apply their prior knowledge to review the beams and 3D dose distribution. The physician can review the beam and doses, and instinctively know if the treatment is safe (i.e., not too large of a risk for normal
Quality assurance from the radiation therapists

With conventional planning, either 2D or 3D, the light projected onto the patient by the shaped field, as seen by the therapist at the machine, generally provides a good representation of the treated volume. Therapists can provide real-time quality assurance regarding what was being treated. Gross errors in setup may be detected by visual inspection of the treatment light field. For example, if a block is inadvertently omitted from a brain field, and the light field is encroaching on the eye, this is readily apparent to the therapists. Similarly, for patients with grossly evident tumors, the light field typically fully encompasses the involved area. Therapists are trained to look at the light field to assess if the treated area matches the prescription (62). With IMRT, there may be little relationship between the setup marks on the skin and the treated volume. This component of quality assurance has thus been reduced.

Not forgetting the simple things

With the recent advances, it is tempting to rely heavily on the technology to minimize normal tissue risks. However, relatively simple techniques to improve the therapeutic ratio of RT should not be abandoned. For example, increasing the physical distance between targets and normal tissues is a powerful way to reduce morbidity. Patient positioning remains critically important for our patients (64). For example, lateral decubital positioning and belly boards can be an effective manner to displace small bowel. When such nonstandard positioning is used, care must be taken to assure that treatment can be set up in a reproducible fashion. Placing bubble wrap within areas of skin folds, or positioning patients to reduce such skin folds, can help to reduce acute skin reactions.

It is often useful for physicians to observe patients in their immobilization device, in the treatment position. Scars, drain sites, skin folds, and other superficial landmarks are often not readily discernible on treatment planning images. This clinical information is often lost if the physician is not intimately involved in the immobilization/planning process. As we become more focused on performing radiation planning on digital images, it is conceivable that patients can proceed through immobilization, planning, and treatment, without intimate “bedside” physician involvement. The degree of respiratory excursion of a superficial target (e.g., the breast) can often be readily discerned by watching the patient breathe. Similarly, the degree of intrathoracic motion, and the location of opacified bowel can often be readily discerned via fluoroscopy. These maneuvers are typically easier, faster, and cheaper than more sophisticated imaging techniques.

Over-reliance on DVHs

Dose–volume histograms are a 2D representation of the 3D dose distribution. Their utility is limited by the ability to accurately segment the images. Multiple studies have demonstrated marked inter-physician differences in image segmentation. Further, DVHs discard all spatial information and inherently assume that all regions of an organ are equally important. This is not true for many organs. For example, the nephrons located closer to the renal hilum have slightly more...
urine concentrating ability than do the cortical nephrons (65). Different regions of the femoral head are particularly important for weight bearing (66, 67). The lower lobe of the lung may be more important than the upper lobe in the genesis of radiation pneumonitis (8, 68, 69). In the diseased lung, areas of emphysema have less perfusion, and are thus less functionally important, than other regions. Regional differences in salivary function have been noted within different parts of the parotid gland (70). Similarly, xerostomia may result from dose to both the parotid gland as well as the minor salivary glands within the oral cavity (71). Specific sub-regions of the pharyngeal musculature may be particularly important for development of dysphagia following treatment of the cancers of the head and neck (72). In routine radiation oncology practice, it is not clear if these spatial variations are meaningful enough to incorporate into the optimization process. The DVHs can be weighted to consider these functional differences, to derive dose–function histograms (73). One could then perform IMRT optimization based on these dose–function histograms (74–76).

The DVHs are only as good as is the anatomic information provided by routine imaging (e.g., computed tomography [CT]). Computed tomography may not accurately reflect the underlying anatomy. The esophagus illustrates this point. On CT, the esophageal circumference is usually seen to vary at different axial levels. This reflects anatomic folds and peristaltic motion that is not well visualized by CT. In reality, the circumference of the esophagus is relatively constant through the chest. In an in-depth analysis of this phenomenon, we demonstrated that DVHs that consider these anatomic realities (and assign the same “importance” of each axial level to the DVH) are better correlated with esophageal toxicity than are traditional DVHs that do not consider this anatomic reality (77). Alternative approaches to considering the longitudinal and circumferential character of the esophageal dose have been suggested (78).

The DVHs of organs at risk are typically considered individually; interactions between organs are usually not considered. There are some data to suggest that such interactions may be important. In a series of elegant experiments in rats, portions of the lung, heart, or both were irradiated with protons. Doses to the heart and lung both appeared to be important determinants of RT-induced shortness of breath, assessed by respiratory rate (79, 80). Several studies in humans note a higher rate of pneumonitis in patients with lower lobe tumors (i.e., those likely with a higher cardiac dose) (8, 68, 69), and hence suggest that there might be an interaction between lung and heart irradiation in the development of “lung” toxicity (31). Potential problems that may arise from the over reliance on DVHs apply to both IMRT and conventional 3D conformal planning.

**Becoming too conformal? The unmasking of our anatomic uncertainties**

The International Commission on Radiation Units and Measurements has defined several volumes to better clarify the uncertainties reflected in the definition of the treated volume (81, 82). This is a useful construct and is outlined in Fig. 5. The successive enlargements from GTV (gross tumor volume) to CTV (clinical target volume), from CTV to ITV (internal target volume), and from ITV to PTV (planning target volume) are meant to reflect our uncertainties regarding microscopic extension, internal motion, and setup accuracy, respectively.

As shown, newer technologies have increased our ability to define, or to reduce these uncertainties. For example, positron emission tomography imaging is assisting with definition of the GTV (83–85). Internal motion is being better quantified with four-dimensional CT, and the ITV can be reduced with respiratory gating or breath-hold techniques (86). Imaging of the patient on the treatment machine increases our knowledge of setup uncertainties (87, 88). Margins for setup uncertainty can be customized for individual patients (89–91), or markedly reduced if imaging is performed and reviewed before each RT session (89, 92). Alternative localization methods can provide similar improvements.

Expansion of the treated volume beyond the GTV reflects these various uncertainties. Historically, physician ignorance regarding the disease extent (a “biologic” uncertainty) was typically believed to be of smaller magnitude than the other uncertainties. Physicians may have derived a level of reassurance that the tumor was included within the irradiated volume because RT field sizes usually far exceeded the size of the known cancer, due largely to the nonbiologic uncertainties. Whether or not this reassurance was justified is debatable. Advances in (for example) imaging of the patient in the treatment room, and tumor tracking, allow a marked reduction in the ITV and PTV margins. Therefore, the physician is now forced to be more specific with GTV and CTV definition. This requires that the physician accurately interpret the diagnostic imaging, understand the limitations and strengths of
the diagnostic tools, and know the likely patterns of tumor spread. Physician uncertainties regarding these issues remain. Care must be taken not to compromise tumor coverage by making the RT fields too tight. The physician needs to balance the risk of normal tissue injury with tumor control. For example, a study from Israel reported an increased rate of local failure with conformal techniques for patients with orbital tumors, likely reflecting marginal misses (93). There presently are no imaging modalities to accurately define the CTV. The CTV definition is based on physician understand-
ing of the tumor biology, anatomic considerations, and bio-
logic/imaging uncertainties (94, 95).

Summary
Modern radiation planning and delivery tools provide the
physician with increased quantitative 3D dose and volume in-
formation, as well as increased flexibility to alter these dose–
volume values. Physicians must understand the power and
limitations of these technologies so that they can be optimally
exploited to reduce the risks to normal tissues and improve
the therapeutic ratio of radiation therapy.

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