Routine 3D Treatment Planning: Opportunities, Challenges, and Hazards

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Three-dimensional (3D) treatment planning refers to the use of software and hardware tools to design and implement more accurate and conformal radiation therapy. This is a major advance in oncology that should lead to

Introduction

In an ideal world, radiation treatment beams would fully encompass the target tissue and exclude all nontarget normal tissues. In practice, however, this is impossible due to the intimate relationship between tumors and surrounding normal structures. Radiation treatment planning, therefore, is based on a compromise between tumor and normal tissue considerations. The radiation oncologist's traditional approach to this problem is to:

(1) Review appropriate clinical and radiographic information to identify targets.
(2) Choose appropriate treatment beam orientations.
(3) Under fluoroscopic guidance, orient the treatment beams onto the patient so that the fields include the defined target volume, and obtain simulation films.
(4) Shape treatment beams based on the clinician's knowledge of the location of the target and normal tissues, typically by drawing on the simulation films.

This traditional approach, however, has several limitations. First, it is extremely difficult for most radiation oncologists to accurately assimilate complex three-dimensional (3D) anatomic data such as that obtained with computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT), unless the target is bound by radiographic landmarks (for example, the sella). The inability to precisely understand the often complex 3D relationships among a variety of structures limits the physician's ability to conceive of "optimal" beams. Second, because 3D diagnostic information is usually conveyed with a series of axial images, it is easier to conceive of beams that lie within the transverse plane. Nonaxial beams may be therapeutically advantageous, but they are more difficult to visualize, and may be underutilized by the radiation oncologist. Third, even if the "optimal" beam is conceived, it is very difficult to accurately set up that beam in the simulator room. The physician is limited by the need to relate the 3D diagnostic data to the planar fluoroscopic images.

Fundamentals of 3D Treatment Planning

Three-dimensional treatment planning broadly refers to a variety of tools and procedures that facilitate the use of 3D data during the planning process. Different approaches to this process have been taken.[1-4] In 1991, we implemented an approach to 3D treatment planning at Duke University that was developed and initially implemented at the University of North Carolina (UNC) in the 1980s. Initial clinical results from UNC have been reported.[5-7] A brief outline of the process used at Duke is as follows:

(1) Three-dimensional imaging (eg, CT) is obtained with the patient in an immobilization device that is used throughout treatment. A reference coordinate system is defined and marked on the immobilization device (and, possibly, on the patient as well).
(2) The patient returns home and the treatment planning proceeds on 3D imaging data sets.
(3) Structures of interest, targets, and normal tissues are identified on the images.
(4) Treatment-planning software (initially GRATIS [Sherouse Systems Incorporated], and more recently, PLUNC [Plan University of North Carolina]) is used to view the 3D relationship between

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Page 1 of 10
structures of interest from any direction (including axial and nonaxial orientations). Information from
different diagnostic imaging modalities can be viewed.
(5) Beam orientations are selected and beams are shaped, based on the projection of the structures
of interest as seen along the beam’s-eye view.
(6) Doses are calculated and adjustments in beam weights, wedges, blocks, and beam orientations
are made as desired in an iterative fashion.
(7) Digitally reconstructed radiographs of each beam are generated (including the block shape and
desired structures) and can be used in lieu of physical simulator films.
(8) Setup instructions to facilitate the implementation of treatment beams at the physical simulator
and treatment machine are provided and include field size, gantry, collimator, and table position
(relative to the predetermined coordinate system).

The 3D treatment planning tools evolved, in part, as use of the systems identified areas that needed
improvement. Recent additions to the planning software include the use of predetermined beam
templates, viewing of real-time digitally reconstructed radiographs, and the ability for multimodality
imaging.[8]

Performing the treatment planning on the image data set reduces the stress and associated practical
limitations of having the patient on the simulator table. Planning that considers beams from any
orientation can be performed at a comfortable pace. The information provided by the treatment
planning system parallels that provided by the physical simulator. Thus, the physical simulation may
be omitted.

In most instances, however, a physical simulation is performed to obtain a set of simulator films (that
do not have the reconstruction artifact of the digitally reconstructed radiographs) and, in some
cases, to verify that the beams are implementable and clinically appropriate. An additional
consideration is that the physical simulation provides an opportunity to assess
respiratory/diaphragmatic movements not readily appreciated on the CT data set.

If the physical simulation is omitted, the first day on the treatment machine essentially serves as the
simulation and will generally take more time than a typical treatment. Thus, the choice to skip the
session in the physical simulator is related to time restrictions on use of the simulator vs use of the
treatment machine.

The goals of this article are to:
(1) Describe our initial experience with 3D radiation treatment planning in approximately 1,500
patients.
(2) Report the results of a physician survey assessing the perceived utility of 3D treatment planning
in 856 of these patients.
(3) Review the rationale for, and our experience with, incorporating physiology into the 3D planning
process.
(4) Discuss some of the challenges and hazards of 3D planning.

Initial Clinical Experience and Survey Results

The number of patients who underwent 3D treatment planning per year from 1991 through 1998 is
shown in Figure 1. For the 856 patients treated between March 1995 and 1998, the treating
physicians were asked to qualitatively assess the perceived benefits of 3D treatment planning for
each case. Surveys were delivered immediately following completion of radiation therapy, and 80%
of the surveys were returned.

The questions and a summary of the results are shown in Table 1. The rate of affirmative answers to
the questions is a minimum value since all missing answers were assumed to be negative. The
results reported are for the entire patient population and for the largest subsets of patients (ie, those
with lung, prostate, and brain tumors).

For patients with prostate cancer, the use of 3D planning tools altered the shape of the radiation
beams, but generally not their orientation. For patients with lung cancer, 3D planning tools led to
atypical beam orientations and gave the physician confidence to treat patients with unconventionally
high radiation doses. No notable differences were seen over time, probably because the surveys
were started several years after the implementation of 3D planning (ie, after the steep learning
curve).

The extra time spent by the physician per prostate cancer case was only 30 minutes, probably due
to the use of a conventional four-field box technique in almost all cases. The brain and lung cancer
cases required more time since unusual beam orientations, typically with field reductions, were
commonly used.
The utility of 3D treatment planning is not limited to dose escalation. In fact, a better understanding of the 3D anatomic relationships between the target and normal tissues likely improves the treatment planning process, even when conventional beam orientations and target doses are used. Simply placing the treatment isocenter and beams in their intended location is a worthwhile goal, as illustrated by the survey results: Sixty-seven percent of the surveys indicated that the additional effort was worthwhile, even though dose escalation was performed in 20% of cases. In about 65% of cases, it was believed that 3D planning reduced the volume of normal tissue irradiated and improved the therapeutic ratio. This rate was lowest in patients with brain tumors, since they frequently were treated with large opposed lateral fields.

Although it is beyond the scope of this article to outline the potential benefits of 3D planning at all disease sites, our experience with the process at certain sites deserves mention. For cancers of the paranasal sinuses, a comparison of 3D planned beams to conventional beam arrangements suggests a dramatic benefit attributable to 3D planning. The software allows the use of nonaxial beams that markedly reduce the dose to the optic structures.[9] The 3D tools facilitate the use of conformally shaped tangent fields that limit the volume of heart irradiated in patients with breast cancer.[10-11] We have developed beam “bouquets,” multiple noncoplanar beams that provide rapid dose gradients at target edges similar to what can be achieved with radiosurgery arcs.[12-14]

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**Incorporating Physiology Into the 3D Planning Process**

Advances in 3D planning provide substantial dose information not previously available. This has led to multiple studies relating the 3D dose distribution to outcome (assessing, for example, normal tissue complication probability and tumor-control probability).[15-21] Since it is extremely cumbersome to consider the entire dose distribution as a 3D data set, it has been customary to condense this information into a dose-volume histogram. This data-reduction scheme discards all the spatial information in the initial 3D dose distribution. An inherent assumption in this approach is that different regions of an organ are equivalent, that the delivery of 40 Gy to 10% of the lung will result in the same outcome regardless of which 10% of the lung is irradiated.

This may be a reasonable assumption for organs that are parallel in structure (eg, liver, kidney, lung). However, for organs in which function is not uniformly distributed (eg, heart, brain, bone), this is not a valid assumption. It is unreasonable to expect dose-volume histograms to be highly predictive of outcome, as this measure does not reflect heterogeneity in function and/or architecture of tumors and normal tissues. Accurate predictors of outcome should consider the physiology of the structure in question (Figure 2). The limitations of traditional dose-volume histograms are described below.

**Tumor Heterogeneity**

Tumors vary in clonogen density and viability. In a large tumor with central necrosis, the dose delivered to the central region is probably not related to the tumor-control probability because the cells at the tumor’s center are generally not viable. Other regions of the gross target volume may be densely packed with viable tumor cells.[22]

Conversely, the periphery of the planning target volume is likely sparsely populated with tumor cells. The rate of clinical response might be related to the dose administered to the gross target volume (since that is what can be seen or palpated), whereas the ultimate control rate is related to the dose delivered to the entire clinical target volume at risk.

In addition, it is possible that tumor responses are partly related to radiation injury to the tumor vasculature (which is also not uniform throughout the target). These factors might make it difficult to relate the dose-volume histogram to tumor-control probability.

**Normal Tissue Heterogeneity**

Many normal tissues have spatial heterogeneities in function. For example, the macular region of the eye is more important for vision than are the more peripheral regions of the retina. The left ventricle of the heart is more important for cardiac output than are other regions of the organ. Models that consider such fundamental anatomic/physiologic factors are likely to be better able to relate the 3D dose distribution to the normal tissue complication probability than are conventional dose-volume histogram reduction approaches.

**Architecture**

We have found it to be instructive to categorize normal tissues based on their architecture (parallel vs series) and their functional distribution (uniform vs heterogeneous) (Table 2).[23] Methods to
relate 3D dose distribution with normal tissue complication probability should consider these differences.

For parallel organs, whole-organ dysfunction generally occurs when a critical fraction of the subunits (eg, nephrons, alveoli) are injured. For series organs, injury to one segment can cause whole-organ dysfunction. Most parallel organs are considered to have uniform function throughout. However, this might not be true. Function is fairly uniformly distributed in the healthy lung, but can be very heterogeneous in diseased lung (eg, in a patient with emphysema).[23] Similarly, the concentrating ability of nephrons varies, depending on their location relative to the medulla.

Normal tubular tissues (eg, rectum, esophagus) are challenging in radiation treatment planning. Traditional dose-volume histograms do not consider the radial-longitudinal distribution of dose and, therefore, might not be predictive of outcome.[24] This is graphically illustrated in Figure 3.[25] Each of the three dose distributions shown has the same dose-volume histogram. The first illustrated dose distribution might result in no normal tissue reaction, whereas the middle pattern might result in a small ulceration, and the third might result in a stricture.

We have considered the longitudinal and radial character of the dose distribution within the esophagus and rectum in a series of 82 patients with lung cancer and 91 patients with prostate cancer, respectively. The preliminary analysis of these populations suggests that the radial-longitudinal characteristics of the dose distribution might provide information predictive of treatment outcome beyond that provided by conventional dose-volume histogram-derived parameters.[26,27]

Functional Imaging in Patients With Lung Cancer

For the last several years, we at Duke have incorporated physiology into treatment planning for patients with lung cancer. For target identification, PET scans (with F-18 fluorodeoxyglucose) have been used to better delineate areas of metabolic hyperactivity. In an analysis of 35 patients who had PET scans as part of the treatment planning process, the scan modified the treatment beam in 34% of cases.[28] The target volume was frequently enlarged to include equivocally sized lymph nodes that appeared hyperactive on PET. The union of CT and PET abnormalities were typically used as the target volume.

Single-photon emission computed tomography lung perfusion images have been used since 1992 as a means of identifying functional regions of the lung. The goal here is to design radiation beams that purposely exclude the better-functioning regions of the lung. This is only practical when the target volume is small (such that there is a great flexibility in beam orientation) and preradiotherapy pulmonary function is extremely poor (since there is a desire to minimize incidental pulmonary irradiation). In our analysis of 104 patients who had SPECT scans performed as part of their treatment planning process, 11% had their beams altered based on the SPECT information. This rate was higher in patients with very poor preradiotherapy pulmonary function.[28,29]

Our experience with SPECT scans led to the development of dose-function histograms. The potential advantage of dose-function histograms over dose-volume histograms is that the former representation recognizes the functional heterogeneities that exist in patients with lung cancer (generally due to emphysema). Nevertheless, dose-function histograms still lack spatial information. Furthermore, SPECT perfusion scans image function at a given point in time and do not assess potential function. If there is poor blood flow in a region of the lung due to compression of central blood vessels by a central lung tumor, then these regions of lung might reperfuse following therapy.[29]

Quantification of Radiation-Induced Lung Injury

For parallel organs such as the lung, regional injury should be related to regional dose, and changes in whole organ function are likely related to the sum of regional injuries. To test this hypothesis, we are performing studies that relate the regional radiation dose to changes in regional lung function.[30] We use regional blood flow, assessed by SPECT lung perfusion imaging, as a surrogate for function. Regional lung dose is calculated to reflect tissue-density heterogeneity. These studies are possible only with sophisticated 3D planning software that allows accurate dose calculation and registration of SPECT images with the dose map. An identical technique has been employed by Dr. Lebesque and colleagues at the Netherlands Cancer Institute.[31,32]

A dose-response curve for radiation-induced regional lung dysfunction derived from 50 patients is shown in Figure 4.[33] The details on how these data are generated are reported elsewhere.[30] The dose-response curve appears to plateau in the > 60 Gy range at ~70% reduction in perfusion. This implies that 70% is the maximal measurable reduction in regional perfusion detectable with this technique. This might be related to the SPECT reconstruction technique used and additional studies are underway to improve SPECT quantification.
Alternatively, persistent perfusion within the high-dose region may be due to movement of the lung following irradiation. If the lung in the high-dose region scars and retracts, the adjacent still-perfused lung may move into the high-dose space. This is a shortcoming of this approach. Dose-response data from the Netherlands group, included for reference, are similar to our data.

Once the dose-response curve for regional injury is well defined, one should be able to multiply a differential dose-volume histogram by the dose-response curve to predict changes in whole-organ function.[34,35] This approach might overestimate the degree of lung injury because nonirradiated regions of the lung might, at least in part, compensate for the radiation damage within the irradiated field.

### Challenges and Hazards of 3D Planning

During the past 7 years, we have identified several challenges and hazards associated with routine 3D planning. These are outlined and briefly discussed below. As part of our quality assurance program at Duke, errors in patient planning/setup are monitored. Where appropriate, the frequency of such errors is noted.

#### Target Localization

In some clinical situations, it is difficult and perhaps impossible to clearly identify the target tissues on CT. These situations may not be conducive to routine 3D treatment planning and may require special attention. Some of this problem has been addressed with the use of image fusion techniques that allow, for example, the use of diagnostic MRI and/or nuclear medicine imaging (such as PET) to be merged with the CT data set in order to better identify target volumes.[8] In several clinical situations, however, targets are not well identified on any readily available imaging study, and target volumes are better defined on a clinical basis.

For example, in patients with cancers of the floor of the mouth or tongue being treated postoperatively, it is often quite difficult to accurately contour target volumes on imaging studies. Similarly, the buccal mucosa can be difficult to identify radiographically. It is, therefore, important to place radio-opaque markers on clinical landmarks at the time of imaging in order to incorporate such clinical information into the 3D planning process. In one of our earliest patients to have 3D planning at Duke, the target volume was contoured incorrectly on the wrong side. The target volume in the floor of the mouth was not clearly visible on the planning CT scan, and the error was not noted until the time of physical simulation.

#### False Sense of Security

Improved anatomic information may give the physician a false sense of security and lead to a tendency to use tight margins. Careful attention to beam penumbra, limitations in immobilization, and physiologic mobility of internal structures must be considered when margins are placed around target volumes.

It is important not to lose sight of the biological realities of many of the tumors we treat. Cancer, by its very nature, is often invasive to surrounding adjacent structures. The use of tight, conformal beams in these situations might not be clinically appropriate (Figure 5). An important goal of 3D treatment planning is to more accurately locate and define margins around the target—not necessarily to narrow the margins.

#### Margins Without Biological Rationale

Once the target area is defined and a beam orientation is selected, it is convenient to use an auto-contour tool to set the beam aperture (thereby allowing for a margin around the target). This approach assumes that the desired margin in each direction is equivalent. In many clinical situations, however, the extent of microscopic tumor spread might not be uniform, as illustrated in Figures 6 and 7.

#### Extensive Preplanning and the Auto-Plan Phenomenon

Consider a patient with lung cancer. In conventional treatment, it is customary to simulate the anteroposterior/posteroanterior (AP/PA) fields at the start of treatment, and, after the initial 4 weeks of therapy, to bring the patient back to the simulator for the off-cord oblique simulation. This sequential approach reduces the risk of confusing treatment setup marks, beam templates, blocks, setup instructions, and so forth.

With 3D treatment planning, however, it is quite simple to perform the boost simulation at the same time as the initial simulation. Thus, when the patient begins initial AP/PA treatment, the therapist operating the machine is presented with a multitude of beam information, much of which will not be used for several weeks.

This is a potential area of confusion and hazard, since it is possible for setup instructions, beam
templates, and radiographs to be inadvertently interchanged. We know of two patients whose initial treatment was delivered incorrectly because the wrong setup marks were used. To address this issue, it is critical to clearly label all boost fields as such, and perhaps file the appropriate paperwork in a separate location on the treatment chart to avoid confusion. We now systematically use black to denote reference marks added at the time of CT, and other colors to mark treatment fields. No similar errors have been identified since 1996.

In addition, a patient's body contour may change during therapy. If patients undergo repeated physical simulation, it would be routine for the simulator technologist to remeasure a separation, and assess the contour. This, however, might not be the case for patients who have had all of their treatment beams planned at the commencement of treatment. Doing all of the planning at the start of therapy does not allow one to adjust the boost fields to reflect anatomic changes that occur during the initial portion of therapy. For example, reexpansion of a region of the lung in response to tumor shrinkage may cause shifts in the mediastinal structures.

**It Must Be Right—The Computer Says So**

At the start of our clinical practice with 3D treatment planning, there was a sense among physicians, dosimetrists, physicists, and radiation therapists that the plan and beam *must* be right; it was done on the computer. This clearly is not the case. Human error will remain a potential quality assurance issue in radiation oncology. If anything, the 3D planned treatment beams tend to be more complicated than conventional beams. Therefore, extreme care should be taken when implementing a 3D plan, and quality assurance procedures should be tighter than for conventionally treated patients.

**Not Following Treatment Setup Instructions (or “This Can’t Be Right”)**

Three-dimensional planned beams are often complex, requiring unusual collimator, table, gantry, wedge, and block positions. The numerous parameters that need to be set may increase the risk of setup errors. Even if setup instructions are fully understood, there is a tendency to disbelieve that they are correct when they deviate markedly from conventional techniques.

Since 1992, we have identified seven occasions at Duke when radiation therapists have deviated from the prescribed 3D setup instructions in order to make the parameters conform with traditional methods (e.g., placing a wedge in a typical orientation). Thus, when new 3D techniques are instituted, therapists need to be educated to avoid these problems.

**Doing Something New Without Realizing It**

In some clinical situations, we may believe that we are providing coverage of a particular structure with conventional techniques. We then proceed to provide the desired coverage, as seen in 3D, to do what we thought we were doing (or perhaps intended to do) with two-dimensional techniques. An example of this is elective mediastinal irradiation with AP/PA fields in patients with lung cancer or tangent fields for patients with breast cancer. During the 3D planning process, one might place a 1.5-cm geometric margin around the clinical target volume (including the mediastinum or glandular breast tissue). This generally will result in treatment beams that are larger than traditional fields. This new beam might not be questioned because it was planned on the 3D planning system and, therefore, assumed to be correct.

**Immobilization/Skin Sparing**

A cornerstone of 3D treatment planning is reproducing the patient’s position during diagnostic scans and therapy. Although aggressive immobilization systems improve reproducibility of patient position, they may have negative dosimetric consequences. Immobilization devices generally reduce skin sparing and may cause increased skin reactions (Figure 8). This is related to the beam energy, total dose, type of immobilization device, and construction method used. We have used a Plexiglas sheet under the immobilization cradles in many patients in order to provide support for the often large cradles. The degree of skin reaction appears to have been reduced with the elimination of this sheet.

**Immobilization Devices Covering Surface Anatomy**

Clinical landmarks are very important in radiation oncology. The use of 3D treatment planning minimizes, and often prevents, the use of surface anatomy. It is reassuring to go into the simulator or treatment room and palpate a mass (e.g., in the buccal space) to be sure that this is included within the treatment field. This is not possible with the head-and-neck immobilization systems that are often used. A similar situation occurs with surgical scars, postoperative induration, and palpable neck nodes.

When particular surface landmarks might be helpful in the treatment planning process, it is imperative to mark these with radio-opaque markers at the time of the treatment planning scan so that this information can be used during the treatment planning process. The relationship between
anatomic landmarks and treatment fields can be verified at the physical simulation and is one of the reasons to perform a physical simulation following computer-based treatment planning.

**Immobilization Devices Altering the Body Contour**

Some immobilization devices may have a negative impact on body contour. An example of this effect is seen in a patient receiving tangential therapy to the right breast ([Figure 9](#)). The lateral aspect of the cradle has displaced some of the subcutaneous tissue anteriorly. This not only increased the separation along the treatment beam (compared to what it would have been without the immobilization device), but also produced an additional skinfold. Modification of the cradle can eliminate this effect.

**Reliance on Contoured Structures and Digitally Reconstructed Radiographs**

If a particular structure of interest is not contoured on the treatment planning scan, it may be forgotten when the treatment beams are designed. At the time of physical simulation or the start of treatment, the treating physician will occasionally say, “I wonder how much of the... is in the radiation field?” The anatomic information can be retrieved and the beam modified as necessary, but usually with a fair degree of effort.

One of our patients had a reduced treatment field planned toward the end of their initial fields, based on information seen on the digitally reconstructed radiographs from the initial treatment beams. The physician did not realize that the spinal cord was in the reduced field because its contours were not printed on the digitally reconstructed radiograph. The presence of the spinal cord in the field was not realized until the portals of the reduced field were reviewed.

The converse is also true. Extra effort may be expended adjusting fields to fully exclude a critical normal structure (eg, the optic chiasm), thus occasionally reducing the margin around the target and/or complicating treatment. This clearly is justified if the incidental dose is likely to cause injury. However, it is tempting to adjust fields in this manner even when the doses are low.

One of the great benefits of digitally reconstructed radiographs over routine simulator films is that the 3D anatomic information can be printed onto the digitally reconstructed radiograph. The presence of this anatomic information, however, often obscures the anatomic landmarks that are used to compare portal films to simulation films. Thus, bringing the patient to the physical simulator for an additional set of films and/or printing two sets of digitally reconstructed radiographs (one with and one without the 3D-defined structures outlined) is helpful when checking portal films.

**The Dose Must Go Somewhere**

Dose-volume histograms are commonly used to compare radiation treatment beams designed using traditional techniques with those planned using 3D tools. The structures chosen for the dose-volume histogram comparison are typically those that are incidentally irradiated using traditional methods. Thus, at times, the dose-volume histograms for all normal tissues evaluated will look “better” (ie, predictive of less risk of normal tissue injury) with 3D-planned beams than with traditional beams. Nevertheless, it is important to remember that the dose must go somewhere and that dose-volume histograms of other structures must be worse with the 3D-planned beams than with traditional beams.

**Conclusions**

Three-dimensional radiation treatment planning is a major advance in oncology. This technology affords great opportunities for more accurate radiation treatment planning. It facilitates the design of more conformal radiation treatment beams, and might facilitate a safe dose escalation for many tumor sites. However, as with any new technology, extreme care must be taken when introducing it into the clinic.

Based on our experience with approximately 1,500 patients, we have outlined several challenges and hazards associated with the implementation of routine 3D treatment planning. Incorporation of physiologic and anatomic information into the treatment planning process should further exploit the potential benefits of 3D planning. Physiologically based studies are underway to relate 3D dose distribution to outcomes.

**References:**


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