Intensity-Modulated Radiation Therapy Dose Prescription, Recording, and Delivery: Patterns of Variability Among Institutions and Treatment Planning Systems

Indra J. Das, Chee-Wai Cheng, Kashmiri L. Chopra, Raj K. Mitra, Shiv P. Srivastava, Eli Glatstein

Background Intensity-modulated radiation therapy (IMRT) is a widely accepted method for radiation treatment to provide a prescribed and uniform dose to the target volume and a minimum dose to normal tissues that is dependent on the IMRT software and the treatment machine. We examined the variation in IMRT dose prescription, treatment planning, dose recording, and dose delivery among cancer patients who were treated with different treatment planning systems at different medical institutions to assess variability in patient care.

Methods We conducted a retrospective analysis of 803 patients who were treated with IMRT between October 2004 and July 2006 for brain, head and neck, or prostate cancer at five medical institutions that used different treatment planning systems. The prescribed dose to the target volume, as recorded in the chart or as noted in the electronic data management system, was extracted for each patient. The planned dose that was delivered to the patient, as represented in the dose–volume histogram, was acquired from each treatment planning system. The actual minimum, maximum, median, and isocenter doses to the target volume were normalized to the prescribed dose and analyzed for each disease site and institution.

Results Of the 803 patients, 12% were treated for brain cancer, 26% for head and neck cancer, and 62% for prostate cancer. The recorded dose variability from prescription was widespread for the minimum, maximum, and isocenter doses. A total of 46% of the patients received a maximum dose that was more than 10% higher than the prescribed dose, and 63% of the patients received a dose that was more than 10% lower than the prescribed dose. At all five institutions, the prostate cancer cases had the smallest dosimetric variation and the head and neck cancer cases had the largest variation. The median dose to the target varied from the prescribed dose by ±2% in 68% of the patients, by ±5% in 88% of the patients, and by ±10% in 96% of the patients. The recorded isocenter dose varied from prescription for all disease sites and treatment planning systems.

Conclusions Substantial variation in the prescribed and delivered doses exists among medical institutions, raising concerns about the validity of comparing clinical outcomes for IMRT. The isocenter dose in IMRT is simply a point dose and often does not reflect the prescription dose that is specified by a selected isodose line encompassing the target volume. This study suggests the need for national and/or international guidelines for dose prescription, planning, and reporting for a meaningful clinical trial in IMRT.

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An improvement in radiation therapy outcomes could be achieved by periodic comparisons of clinical practices through outcome evaluations from clinical trials and studies. For a multicenter study, a meaningful comparison of clinical outcomes in response to radiation treatment requires a standardized process for dose specification. Treatment outcome can be interpreted meaningfully only with accurate knowledge of the reference dose and the dose distribution. National guidelines for clinical reference dosimetry, such as those put forth by Task Groups 21 and 51 of the Radiation Therapy Committee of the American Association of Physicists in Medicine (1,2), recommend that the reference dose (machine output) should not vary by more than ±2% among centers. For patient treatment, the combined dosimetric uncertainty in the target volume (which includes differences in patient setup and

Affiliations of authors: Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA (IJD, EG); Department of Radiation Oncology, Morristown Memorial Hospital, Morristown, NJ (CWC); Department of Radiation Oncology, Kennedy Health System, Sewell, NJ (KLC); Department of Radiation Oncology, Ochsner Clinic Foundation, New Orleans, LA (RKM); Department of Radiation Oncology, Reid Hospital & Health Care Service, Richmond, IN (SPS).

Correspondence to: Indra J. Das, FACR, Department of Radiation Oncology, University of Pennsylvania, 2 Donner Bldg, 3400 Spruce St, Philadelphia, PA 19104 (e-mail: das@xrt.upenn.edu).

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localization, machine calibration, and dose calculation) should be at least within ±5%. Dische et al. (3) showed that a dose difference as small as ±5% may lead to a real impairment or enhancement of tumor response as well as a change in the risk of morbidity to the normal tissues. The variation in dose specification was first recognized as a problem in 1978, when the International Commission on Radiation Units and Measurements (ICRU) provided guidelines for dose specification to the target volume in ICRU Report 29 (4). This report was replaced in 1993 by ICRU Report 50 (5), which included the concepts of target volume, gross target volume, and clinical target volume (CTV) and clearly defined the planning target volume (PTV) and organs at risk. Additional modifications of these concepts were added in ICRU Report 62 (6). The ICRU guidelines provided a standard approach to delineate target volumes and specify radiation dose to facilitate intra- and interinstitutional comparisons of treatment parameters for clinical outcomes in patients treated with three-dimensional conformal radiation therapy (3D-CRT) worldwide. On the basis of clinical outcome data from patients with breast and prostate cancer, ICRU-50 (5) recommended a uniform dose to the target volume within −5% to +7% of the prescribed dose, which was clinically feasible at that time. Traditionally, however, ±10% variation from the prescribed dose is an accepted norm in most clinical practices and is widely used in IMRT.

Great importance was given by the ICRU to the isocenter in 3D-CRT because the machine isocenter (ie, the intersection of the axis of rotation of the machine gantry, the collimator, and the treatment table) can be placed within the target to within ±2 mm for most linear accelerators as recommended by TG-40 guidelines (7). In 3D-CRT, the isocenter is usually the geometric center of the target volume where dose is prescribed and recorded. In IMRT, however, the isocenter can be placed anywhere inside the treated volume, including those locations that may be near a low-dose region or inside an organ at risk, and is mainly used for positioning the patient in the machine, which is critical for dose delivery. ICRU-50 (5) recommended that the radiation dose be documented at the reference point, which is generally the isocenter. Mijnheer (8) pointed out some differences between current practices and ICRU-50 dose specifications. However, it has been generally accepted that in 3D-CRT, the mean dose to the target and the ICRU reference dose are directly correlated with a SD of less than 2% in most disease sites (9).

The emergence of intensity-modulated radiation therapy (IMRT) from nascent technology in the 1980s (10–12) to a well-established modality within just 10 years has opened the doors to its widespread use in the radiation oncology community (13–15). An informal survey that we conducted indicates that, depending on the institution, 30%–60% of cancer patients in the United States are currently being treated with IMRT. IMRT uses inverse planning to generate beamlets (subfield) that produce a variable dose intensity map, whereas 3D-CRT uses forward planning to produce a uniform field of dose intensity. The difference between IMRT and 3D-CRT planning (inverse vs forward planning) is analogous to the difference between bargaining and fixed-price shopping. That is, in IMRT, a treatment planner submits the desired constraints in terms of a cost function and compromises on the outcome (bargains for the price to pay), whereas in 3D-CRT the prescription dose is fixed and the treatment planner directly calculates the input parameter (monitor units) for each treatment field. In IMRT, one usually does not get exactly what is being bargained for (ie, the exact dose distribution as prescribed), but a good treatment planner, like a good bargainer, can get fairly close to the desired initial goal (ie, the desired dose to the target volume while achieving a minimum dose to the adjacent normal tissues). In general, the inverse planning process with current treatment planning systems may not always produce the exact solution but can produce a solution that is close enough to achieve the treatment goals based on the desired constraints. In IMRT, the solution to the cost functions is multifactorial, depending on the complexity of the target and organs at risk. It is not uncommon in radiation therapy to settle on a lower coverage to the PTV to limit the radiation dose to organs at risk. Hence, IMRT planning is more of an art to achieve a compromise solution to the cost function with applied constraints. In IMRT, what is being prescribed may not be achieved exactly by the treatment planning process, an outcome very similar to the bargaining process. The difference between the prescribed

CONTEXT AND CAVEATS

Prior knowledge

Intensity-modulated radiation therapy (IMRT) is widely used to treat cancer because it provides a prescribed and uniform radiation dose to the target while minimizing the radiation dose to normal tissues. In IMRT, many factors, including special software, are required to plan treatments and control the radiation dose during therapy. Variations in these factors can affect the dose and, consequently, the clinical outcome.

Study design

A retrospective analysis of treatment parameters for 803 patients who were treated with IMRT for brain, head and neck, or prostate cancer at five medical institutions that used different treatment planning systems.

Contribution

In IMRT, the prescribed dose rarely corresponded to the planned, or delivered, dose. At all five institutions, dosimetric variation was smallest for the prostate cancer cases and largest for the head and neck cancer cases. The recorded delivered dose varied from the prescribed dose for all disease sites and treatment planning systems.

Implications

The substantial variation in the prescribed and delivered doses that exists among medical institutions raises concerns about the validity of comparing clinical outcomes for IMRT. National and/or international guidelines for dose prescription, planning, and reporting in IMRT are needed.

Limitations

The medical institutions differed with respect to volume delineation, the availability of quality-assurance data for the treatment planning algorithms, and the uniformity of IMRT input constraints. Only five treatment planning systems from five institutions, some of which had limited IMRT planning data in certain disease sites, were included.

and the planned (or delivered) dose is dependent on the treatment planning system and institution and also, more importantly, on the nature and location of the overlapping structures among targets and organs at risk.

The clinical outcome, such as survival and local control, of patients treated with radiation is related to the tumor control probability (TCP), which improves with multimodality imaging for precise tumor delineation, a better knowledge of the normal tissue complication probability (NTCP) (16,17), and with greater attention to patient positioning, total dose, and dose per fraction. IMRT produces a steep radiation dose gradient around the tumor, thus creating a therapeutic advantage that cannot be achieved with conventional 3D-CRT. IMRT uses beamlets or segments via multiple coplanar and noncoplanar treatment fields, depending on the delivery technique and optimization goal. IMRT also requires an absolute reliance on either cumulative or differential dose–volume histograms for the tumor and the organs at risk, which provide information on the dose–volume relationships that are calculated based on user-defined constraints. Such changes have created an additional adjustment to our thinking from the 3D-CRT concept, where dose is defined to a point. Nonetheless, although 3D-CRT was developed to provide a uniform dose to a volume, the dose is actually recorded at a point (5). In addition to requiring attention to such complex issues as patient immobilization, improved volume delineation, organ motion control, and dose delivery, IMRT also requires that the prescribed dose to a volume takes into account tissue tolerance constraints, which are dependent on the total delivered dose.

IMRT optimization results in different shapes of the dose–volume histogram, depending on the treatment planning system algorithm, the beam characteristics of the multileaf collimator (eg, double-focus vs curved-end, 1-cm vs 0.5-cm leaf width), organ constraints, and segmentation parameters, such as the number of beam segments and the dose intensity levels as implemented based on institutional or physician-prescribed guidelines. Although the concept of isocenter in IMRT is still valid in the context of patient setup, its use as a dose specification point (8) has become meaningless due to variable dose specification to the volumes. Furthermore, the radiobiologic consequences for differential dose and dose per fraction as performed in concomitant boost treatment through IMRT require further evaluation and serious consideration because the TCP for a nonuniform target dose is reduced substantially (18,19). These issues raise substantial concerns that need to be addressed through additional international guidelines in the form of ICRU recommendations for IMRT treatment.

As previously reported (20), the shape of a dose–volume histogram for treatment can vary substantially from one patient to another and also from one treatment planning system to another. As a result, dose specification, reporting, and recording could differ substantially among different institutions, thus potentially affecting comparisons of clinical outcomes. The goal of this study was to examine the variation in IMRT treatment planning, dose distribution, and dose delivery among different institutions in terms of the accepted minimum, maximum, and median doses in treatment volume from the optimal plan and the resulting dose to the isocenter. We focused on minimum, maximum, and median dose parameters rather than on the volume of the PTV that received 99%, 95%, and 90% of the prescribed dose because the dose parameters are readily available for all treatment planning systems. Our goal was not to determine whether one institution or treatment planning system was superior to another but rather to identify common characteristics regarding the use of IMRT from a variety of clinical practices and dose optimization algorithms and to determine how dose prescription and the planning dose differs among institutions.

Subjects and Methods

Five institutions participated in this study—University of Pennsylvania (Philadelphia, PA), Morristown Memorial Hospital (Morristown, NJ), Kennedy Health System (Sewell, NJ), Ochsner Clinic Foundation (New Orleans, LA), and Reid Hospital & Health Care Service (Richmond, IN). The participating institutions include a broad range of radiation oncology departments in terms of the number of machines they possess, the number of staff, the number of patients treated per day, and the type of practice (academic vs community based). Each of these institutions uses a different IMRT treatment planning system: BrainScan (BrainLab, Feldkirchen, Germany), CMS-XiO (CMS Inc, St Louis, MO), Eclipse (Varian Medical System, Palo Alto, CA), Oncentra (Nucletron V.B., Veenendaal, The Netherlands), and Pinnacle (Philips Medical Systems, DA Best, The Netherlands). All patients in this study were sequentially selected from each institution and were treated with IMRT between October 2004 and July 2006. The data were collected in full compliance with the Health Insurance Portability and Accountability Act requirements. Proper guidelines were followed for the institutional review board (IRB) at the University of Pennsylvania. This study qualified for exemption from review by the IRB as granted under the US Department of Health and Human Services policy for protection of human subjects 45 CFR 46.101(b) Section 4. Accordingly, only information that was devoid of patient identifiers and demographics and relevant to this study, such as disease site, treatment plan, and dose parameters, was entered into the study database sequentially from each institution. For this study, we collected treatment planning data for 803 patients who had undergone IMRT for brain, head and neck, or prostate cancer at one of the five participating institutions. The distribution of patients by treatment planning system and disease site is shown in Table 1. Some institutions had only limited planning data for one or more disease sites. The type of IMRT cases from each institution reflects the typical clinical practice at the time when the patients were treated and data were collected.

Each of the treatment planning physicists (IJD, CWC, KLC, RKM, SPS) had planned treatment for a minimum of 50 IMRT cases and therefore was considered to be an experienced planner. In this retrospective study, the prevailing institutional IMRT standards were respected and no attempt was made to modify or alter the treatment plans or the clinical practices. The prescription dose to the target volume (primarily the PTV and the CTV) that was recorded in the chart or noted in the record-and-verify system (ie, an electronic data management system that keeps track of every treatment parameter during the entire treatment) was extracted

Table 1. Distribution of patients by treatment planning system and disease site

Institution	Treatment planning system		No. of patients by disease site			
	Company	Model and version	Brain	Head and neck	Prostate	Total
Ochsner Clinic Foundation	BrainLab	BrainScan V5.31	37	59	67	163
Reid Hospital & Health Care Service	CMS Inc	XiO V4.3.1	4	38	105	147
Kennedy Health System	Varian Medical System	Eclipse V7.5	0	2	58	60
University of Pennsylvania	Nucletron V.B.	Oncentra V1.4 Sp3	56	107	119	282
Morristown Memorial Hospital	Philips Medical Systems	Pinnacle V7.4F	0	2	149	151
Total (%)			97 (12)	208 (26)	498 (62)	803 (100)

for each patient. The treatment plan for each patient in this study was reviewed by a physician and a physicist at each institution. For each patient, we extracted the minimum, maximum, and median doses in the target volume and the isocenter dose from the planned dose–volume histogram that was used to treat the patient. The IMRT treatment plans that are delivered to the patients cannot be verified directly. The verification process is performed indirectly on a tissue-equivalent phantom by direct measurements of the point dose and dose distribution of the patient's plan. Accordingly, all patients in this study were verified indirectly by the in-phantom measurements for the accuracy criterion of IMRT dose delivery to an accuracy of ±5% and spatial agreement of planned to delivered isodose lines of ±3 mm. The phantom measurement provides a link between prescription and the dose delivery and is a measure of quality assurance in IMRT. The maximum, minimum, and median doses in the target volume provide a crude estimate of the slope of the dose–volume histogram curve, which defines the quality of the treatment plans included in this study. Even though the dose–volume histogram does not provide spatial information about hot and cold spots (ie, doses higher than 100% in organs at risk and lower than 100% in target volume, respectively) unlike the spatial dose–volume histogram as defined by Cheng and Das (21), it has become customary to use the dose–volume histogram for IMRT optimization and hence it was used in this study. The data presented here reflect the institutional IMRT constraints for patient treatment that has been achieved for the best possible plans by the individual planner.

Retrospectively collected data for all 803 patients were analyzed by normalizing the maximum, minimum, median, and isocenter doses to the prescribed dose (defined as 1.0). Dosimetric deviations from the prescribed dose expressed as a percentage were grouped by disease site, treatment planning system, and ±10% dose intervals (ie, dose deviation bins) for comparison and analysis.

Results

Figure 1 shows the variation in dosimetry among the 803 patients treated with IMRT at the five institutions. This plot is a normalized dose plot that reflects the extent of the variation independent of the prescribed dose, which varied among the three disease sites and among the five institutions (for unnormalized dose plots, see Supplementary Figure 1, available online). The typically accepted IMRT dose variation of ±10% is also shown by the lines drawn at the y-axis at 1.1 and 0.9. The maximum, minimum, median, and isocenter doses to the prescribed target volume showed wide variations among the patients. These doses also varied widely by more than ±10% in individual patients, as reflected by the minimum and maximum doses in the target volume. For example, 46% of the patients received a maximum dose that was more than 10% higher than the prescribed dose, and for some it was as high as 40% higher than the prescribed dose. On the other hand, 63% of the patients received a dose that was less than 10% lower than the prescribed dose, and a portion of the target received a dose close to 0%. The abnormally low dose (ie, <0.9; Figure 1) in the target volume

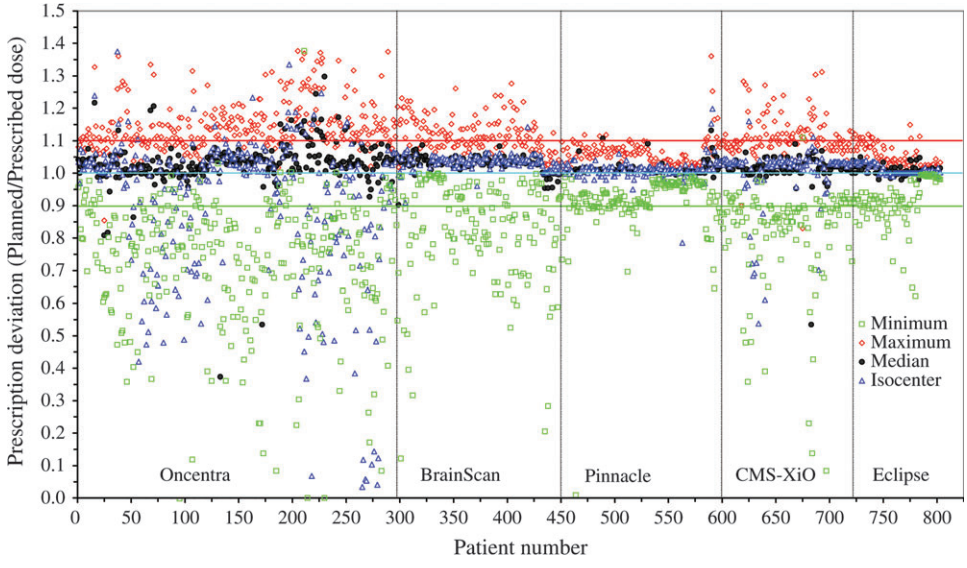

Figure 1. Dosimetric variations between the prescribed and planned doses among 803 patients from five medical institutions with different treatment planning systems. **Vertical lines** separate the data according to treatment planning system (from left to right: Oncentra, BrainScan, Pinnacle, CMS-XiO, Eclipse). The **horizontal line** at 1.0 represents no dose deviation; the **horizontal lines** at 1.1 and 0.9 represent dose deviations of +10% and −10%, respectively, between the planned dose and the prescribed dose.

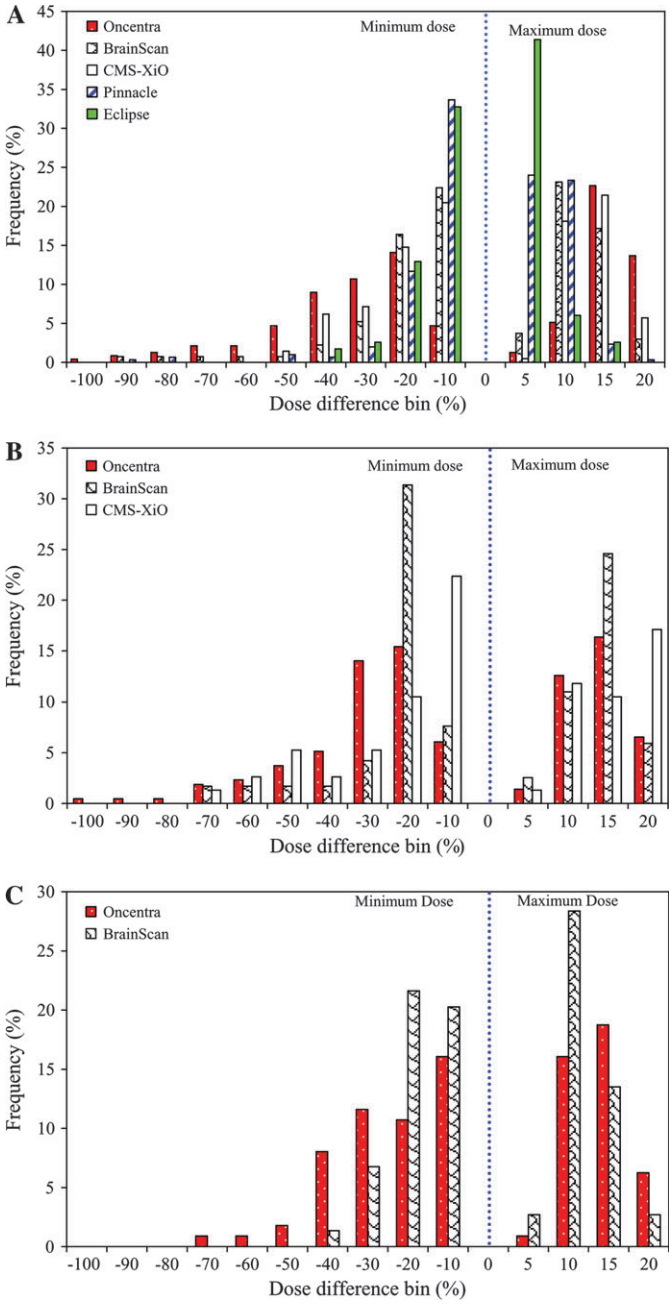

Figure 2. Frequency distribution of the dose differences (prescribed vs planned) among various treatment planning systems for patients with (**A**) prostate cancer, (**B**) head and neck cancer, and (**C**) brain cancer. The dose difference bin is defined as the difference between prescribed and planned dose from maximum and minimum doses and grouped in dose bins for all 803 patients. The **dotted line** at 0% indicates that the prescribed dose and the planned dose are the same.

reported by the minimum dose could be primarily attributed to the target volume being located close to surface or in the buildup region and/or to the presence of an overlapping structure that was planned as an organ at risk in dose optimization. Some treatment planning systems provide sophisticated algorithms that can treat the overlapping structures, in terms of the intersection and union of volumes, either as a target or an organ at risk with appropriate weights in IMRT optimization. Such a decision, however, is institution and physician dependent and usually requires consultation with the planning team. The weighting priorities should be evaluated for each patient based on the structures involved. If an increase in the minimum target dose is required (ie, to a dose that is close to the prescribed dose), then attention should be given to the delineation of PTV by avoiding buildup region and overlapping structures. A well-designed study is needed to evaluate how issues such as location, margin, overlap, and weight affect the quality of treatment plan.

The large dosimetric variation reflected in Figure 1 shows the patterns of dose deviation from prescription as determined by a planned dose–volume histogram in IMRT. Such wide variations in dose planning and delivery suggest that it may not be meaningful to compare clinical outcomes among IMRT patients treated at different institutions. The median dose in the target volume exhibited the smallest variation among the 803 patients. The median dose varied from the prescribed dose by ±2% in 68% of the patients, by ±5% in 88% of the patients, and by ±10% in 96% of the patients. In contrast, the isocenter dose, which the ICRU-50 recommends be documented, showed substantially greater variation among the 803 patients (Figure 1). Even though institutional variations differed somewhat because of differences in disease site distribution, the pattern in Figure 1 shows clear evidence of wide dosimetric variation in radiation treatments using IMRT.

We next examined the frequency of dosimetric variation among the different treatment planning systems according to disease site (ie, head and neck, brain, and prostate). For each disease site and treatment planning system, the maximum and minimum doses were treated as separate entities and were grouped according to the percent difference from the prescribed dose (ie, dose deviation bin) for plotting. The frequency distributions of the patients in various dose deviation bins by treatment planning system are shown in Figure 2. The dashed line at zero separates the minimum and maximum dose bins. In general, the dose spread was more pronounced in the low-dose region than in the high-dose region. The dosimetric spread—which reflects the greater overlap between the target volume and the normal structure(s), low-priority structures, or targets within targets in these patients—was greatest for the head and neck cancer patients, smaller for the brain cancer patients, and smallest for the prostate cancer patients. The dosimetric deviations from the accepted ±10% dose range were 77%, 60%, and 49% for the head and neck, brain, and prostate cancer patients, respectively. Figure 2 also shows that the prescribed dose and the planned and/or delivered dose were never in agreement—that is, the dose bin at zero had no cases. It is obvious that the prescribed dose constraints were rarely met in the final dose calculation. If the constraints had been fully met, the highest values in the frequency distribution would have been near the zero-dose bin. The large frequency spread reflected in dosimetric variation, as shown in Figure 2, illustrates how difficult it is to record the true delivered dose in IMRT. Such a large deviation from prescription in 3D-CRT would have been reported as a misadministration. In IMRT, however, misadministration based on dose deviation is not recognized and is accepted as the result of dose optimization.

The variation in IMRT cost function optimization and final calculated dosimetric results depends on treatment planning systems and on the calculation algorithms that handle inhomogeneity correction. All patients included in this study were treated according

to a treatment plan that adhered to the individual institutional guidelines; however, inhomogeneity corrections in optimization and dose calculations were properly accounted for based on verification and commissioning data for institutional IMRT. Figure 3 shows the percentage of the patient population (frequency distribution) for which the prescribed dose deviated from the planned dose within ±10% according to treatment planning system and disease site. We found an acceptable ±10% dose variation between prescribed and delivered dose only in 11%, 49%, 39%, 81%, and 80% of prostate cancer patients treated with the Oncentra, BrainScan, CMS-XiO, Pinnacle, and Eclipse treatment planning systems, respectively. By contrast, we found an acceptable ±10% dose variation between prescribed and delivered dose in 20%, 21%, and 36% of head and neck cancer patients treated with the Oncentra, BrainScan, and CMS-XiO treatment planning systems, respectively. The frequency distribution could indirectly indicate the relative advantages of different treatment planning systems. For example, for the prostate cancer patients, the Pinnacle and Oncentra treatment planning systems provided a dose that exceeded the ±10% dose criterion to nearly 20% and 80% of the patient population, respectively. Hence, it appears that that the Pinnacle system provides an IMRT treatment plan that is superior to that provided by the Oncentra system. However, such a quick conclusion without a quantitative evaluation of the different planning systems is not reliable because of the multitude of dose–volume histograms for targets and organs at risk and the differences in optimization and dose calculation algorithms (17).

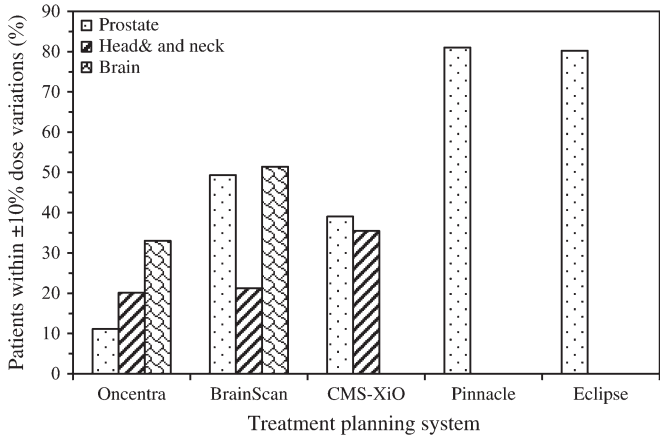

Figure 3. Percentage of patient population within ±10% dose variation (planned vs prescription) for different disease sites and treatment planning systems. Histograms shown are for the treatment planning systems that were used to treat patients with cancers at all three disease sites.

Discussion

IMRT has been shown to provide superior dose distribution for organs at risk compared with 3D-CRT, and hence it has a greater potential to improve the therapeutic ratio and, possibly, to reduce the toxic effects to normal tissues (15). However, in our collective experience, the relatively wider shoulder of the dose–volume histogram for the target volume for IMRT compared with 3D-CRT suggests that IMRT may result in poor and inhomogeneous target coverage. This pattern of a wider shoulder in the dose–volume histogram (spread in maximum and minimum dose) is reflected in the variation in dose delivery as shown in Figure 1 and has also been reported by various investigators (22,23) for head and neck cancer. Boyer et al. (22) reported underdosage in the range of 15%–50% and overdosage in the range of 25%–57%, and Zhou et al. (23) reported an overdosage of 23%. Vineberg et al. (24) also acknowledged the large dosimetric variation between prescription and planning in IMRT and suggested modifying cost functions and treatment planning systems. To our knowledge, no similar studies have been reported for dose variation in the literature for 3D-CRT, except for the large dosimetric deviations that are reported as misadministration. We found that in IMRT the prescribed dose rarely corresponded to the planned, or delivered, dose (Figure 2). Thus, recording the delivered dose becomes inaccurate and ambiguous with respect to the prescribed dose. To eliminate the large variations between the prescribed dose and the delivered dose, a consensus effort by the radiation oncology community and guidelines from national and international radiation organizations are required.

Initial enthusiasm about the better efficacy of IMRT compared with 3D-CRT has also been criticized as premature due to the lack of clinical outcome data (25). Clinical outcomes are complex issues that depend on the dose–volume relationships in the target volume and the organs at risk and require long-term follow-up for the data to mature fully. Some of the problems associated with the radiation outcome may also be attributed to the lack of specific dose guidelines for IMRT outside of a few nationally accepted clinical protocols, such as those endorsed by the Radiation Therapy Oncology Group (www.rtog.org). Thus, each clinic has its own criteria of plan acceptability and dose recording for IMRT that may vary by disease site. This study suggests that the difference between the prescribed dose and the delivered dose is less pronounced in the prostate cancer cases than in head and neck or brain cancer cases for all treatment planning systems (Figures 2 and 3). This is due to multiple structures with competing constraints producing stricter criterion for optimization, depending on the treatment planning system. There are no existing guidelines on what the shape of the dose–volume histogram should be nor do we have a method to compare data from one institution with that from another institution with the same input constraints. This study clearly shows that wide variations between the prescribed dose and the delivered dose exist for patients who receive IMRT through different treatment planning systems. This variability should be further examined in the context of the dose per fraction and the total prescribed dose. For example, a maximum dose in the target volume that is 30% higher than the prescribed dose could signify that the dose per fraction is not the 2 Gy/day that was intended but rather 2.6 Gy/day, which could result in an entirely different clinical outcome. A similar situation could exist in the normal tissues, where the actual dose could be higher than the intended prescribed dose with possible unexpected complications.

Another reason why it is difficult to compare outcome data is because, for most disease sites, target volume delineation varies so much from one institution to the other (26–32). Thus, a good clinical trial should provide clear and explicit guidelines for defining and delineating the target volume, for dose–volume constraints, and for the dose conformality in target volumes. Additional

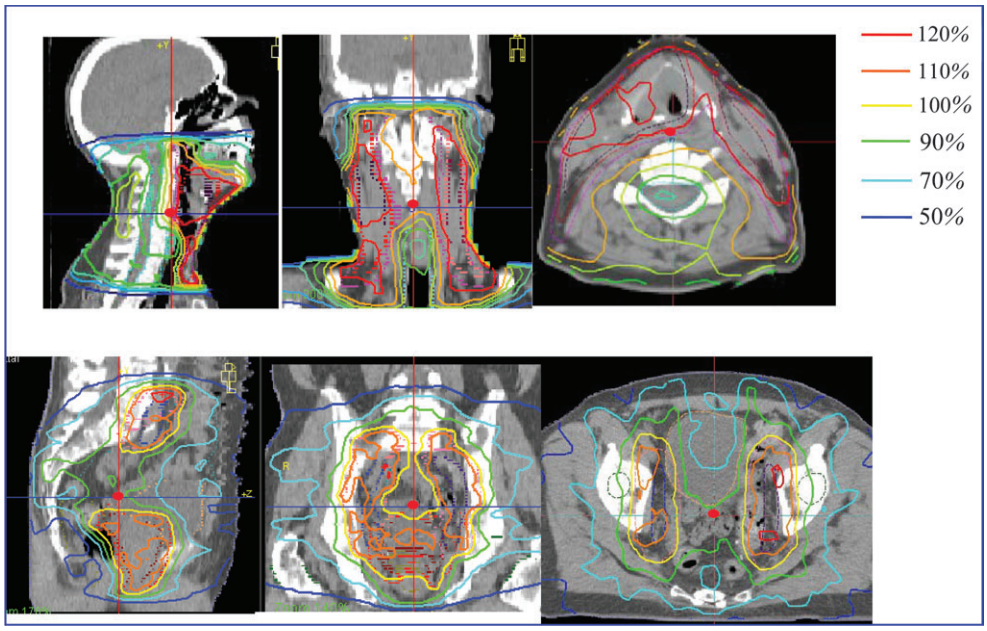

Figure 4. Isodose plots of the intensity-modulated radiation therapy (IMRT) dose distribution in three planes (sagital, coronal, and axial) for a patient with head and neck cancer (**upper panels**) and a patient with prostate cancer (**lower panels**). **Red dots** indicate the location of the isocenter point. The isocenter dose in IMRT is irrelevant because this could be in the region of low dose or in an organ at risk and does not necessarily represent dose to the target volume as is required by the International Commission on Radiation Units and Measurements 50 for dose reporting in three-dimensional conformal radiation therapy. **Colored lines** represent various isodose lines.

quality assurance for the dose prescription, recording, and reporting compliance should also be added and routinely maintained for every clinical trial.

Even though IMRT optimization routines should provide a uniform dose distribution, they also produce greater dose inhomogeneity through steep dose gradients in target volume (22,23) compared with 3D-CRT. The greater dose inhomogeneity is due to the fact that ideal optimized IMRT plans cannot be executed with the use of existing multileaf collimator systems, which differ in design, width, and other physical and mechanical characteristics (33). These differences can result in IMRT plans that vary widely, even those with the best optimization algorithms. Some treatment planning systems may perform slightly better if they are used with a better multileaf collimator. However, regardless of the multileaf collimator design characteristics and the optimization of the algorithm, the prescribed dose will vary from the planned and delivered doses due to the inverse planning process.

Treatment with IMRT is a highly complex process in which the dose varies widely throughout the treatment volume when measured through a phantom plan to verify the actual treatment (34). Our study also suggests that achieving a uniform dose to a target within ±10% is a tall order when treatment planning variations and dose recording are taken into account together with the ±2% in output calibration and the ±5% in IMRT patient dose verification. However, a strict dosimetry guideline for reduction in dose variation would greatly facilitate clinical outcome comparison for patients who are treated with IMRT.

It has been observed that the TCP is substantially reduced when the target dose is nonuniform (18,19). The radiation risk is nonlinear with respect to the radiation dose, and hence, treatment planning system algorithms that produce differing degrees of nonuniformity in the target volume (Figure 1) may lead to different clinical outcomes. Dosimetric information is a proxy for the biologic effect that correlates with the clinical outcome. The variation in dose reporting in IMRT, which is reflective of the nonuniformity of the target dose, could be managed through a concept such as the equivalent uniform dose (18). Even though the equivalent uniform dose has been proposed as a way to overcome the confusion that can arise from the variability in dose per fraction treatment, it has not gained wide acceptability in clinical practice. Various models for TCP and NTCP (16,17) have been proposed during the 3D-CRT era with respect to dose, dose per fraction, volume, and degree of normal tissue complications. However, the proper parameters derived from clinical outcome are still a matter of debate. These models could be useful tools in IMRT for comparing clinical outcomes.

IMRT requires great precision in patient positioning through immobilization and greater reproducibility of the isocenter in patients because of the high dose gradient. The geometric center of the target volume in 3D-CRT is matched precisely with the machine isocenter within ±2 mm. This concept is now fixed within the radiation oncology community through ICRU-50 Report. In IMRT, however, the concept of an isocenter dose is not meaningful because the isocenter can be placed anywhere inside the patient as long as it is reproducible on a daily basis as shown in Figure 4 for a prostate cancer patient and a head and neck cancer patient. Because the isocenter can be located in either the target or in normal tissue, the isocenter dose varies widely from the prescribed dose (Figure 1). Hence, the utility of reporting the isocenter dose in IMRT is limited and has no clinical relevance as it does in 3D-CRT. The isocenter dose or the reference dose, as suggested by ICRU-50, should not be used in IMRT because, in general, it does not relate to the target dose.

Dosimetric variations between the prescribed and the recorded dose could be reduced by establishing international and/or national guidelines on dose prescription and reporting, volume definitions (eg, intersection and union of targets and organs at risk), margin status, and volume extension in buildup region and overlapping structures. Although various radiation societies have undertaken the role of providing educational activities for defining target volumes, it will take time and the effort of the practicing physicians and physicists to achieve this goal. At the present time, however,

this retrospective study shows that IMRT produces relatively greater dose inhomogeneity than 3D-CRT, even though it is theoretically supposed to provide a uniform dose. For clinical trials, the median dose could be used for dose reporting in IMRT given that it is very close to prescribed dose (Figure 1).

This study has several limitations, including the lack of uniformity in volume delineation among institutions, the unavailability of quality-assurance data for the treatment planning algorithms, and the uniformity of IMRT input constraints. This study is also limited to the five treatment planning systems from five institutions, some of which had limited IMRT planning data in certain disease sites, such as head and neck and brain. Given these limitations, it is beyond the scope of this study to provide a rank of merit for any treatment planning systems. Additional work is needed to quantify such differences.

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