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

The recent article by Das et al. (1) questions the validity of comparing outcome data for patients treated with intensity-modulated radiation therapy (IMRT) treatments across multiple centers because of the inherent heterogeneity of the dose distribution. Their data supporting this assertion consist of the minimum, maximum, median, and isocenter point doses for 803 patients who were treated at five centers. We believe that the spread of the data shown in figures 1–3 of their article misrepresents the clinically relevant variations in IMRT treatments because the dose to any single point does not characterize the treatment dosimetry, as stated both by Das et al. (1) and in the accompanying editorial (2). It would have been better for Das et al. to have evaluated the IMRT treatment plans using the readily accessible dose–volume parameters provided by all of the treatment planning systems included in their study instead of point doses. Dose–volume parameters are widely used in radiotherapy clinical trials to ensure treatment consistency across patients and institutions and are routinely used in the radiotherapy community to assess radiation dose distributions.

As indicated in the editorial (2), a common characterization of the dose distribution is that “95% of the target volume received 100% of the prescribed dose.” National Cancer Institute–sponsored clinical trials that employ IMRT are required to specify the dose in a similar manner. These cooperative group clinical trial protocols also limit the proportion of the target volume that may receive a dose that is substantially greater than that prescribed. The Radiation Therapy Oncology Group protocol 0435 for head and neck cancer (available at: http://www.rtog.org/members/protocols/0435/0435.pdf), for example, specifies that no more than 5% of the planning target volume should receive more than 79 Gy. The protocols also require that the treatment plan meet designated dose–volume criteria for all critical structures. Taken together, these dose specification requirements in clinical trials that employ IMRT permit patient treatments and study outcomes to be evaluated and compared. Certainly, it would be undesirable to follow Das et al.’s suggestion that these dose–volume specifications be replaced with the median dose.

Both clinical significance and achievability were carefully considered in developing the dose–volume specifications used in current radiotherapy clinical trials. Radiotherapy centers in the United States that employ IMRT are generally aware of and follow the treatment site–specific dose–volume guidelines that have been developed by leading treatment centers and listed in clinical trial protocols rather than any of the point dose parameters used by Das et al. This is made feasible by the dose–volume analysis tools provided in all commercial treatment planning systems.

We agree with Das et al. that nationwide guidelines for IMRT dose prescription and reporting are important. However, the guidelines should consist of multiple dose–volume parameters, such as the percentage of the target volume receiving the prescribed dose, the volume receiving a specified dose above the prescribed dose, and the percentage of critical structure volumes receiving a certain dose, rather than Das et al.’s suggestion of median dose. Pooled data analyses can readily assess the mean and standard deviation of these parameters, permitting the generation of highly meaningful radiotherapy dose variability and outcomes data. We believe that the variability found would have been considerably less if Das et al. had analyzed their data using dose–volume parameters instead of point doses.

ARThUR OLCh
Robert LAVEy

References


Notes

Affiliations of authors: Department of Radiation Oncology, Childrens Hospital Los Angeles, and University of Southern California, Los Angeles, CA.

Correspondence to: Arthur Olch, PhD, Childrens Hospital Los Angeles and University of Southern California, Department of Radiation Oncology, 4650 Sunset Blvd, MS #54, Los Angeles, CA 90027 (e-mail: aolch@chla.usc.edu).

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Das et al. (1) assert that their results “suggest that it may not be meaningful to compare clinical outcomes among intensity-modulated radiation therapy (IMRT) patients treated at different institutions.” The research missions of the Radiation Therapy Oncology Group (RTOG) and other multicenter research organizations rely on the validity of such comparisons, and we, as representatives of the RTOG, believe that such comparisons can be made when investigators from different institutions follow the specific guidelines of carefully designed clinical trials. It is not clear to us that the institutions involved in providing the data for the Das et al. report worked under the type of guidelines for dose specifications, planning, and reporting that are provided for RTOG protocols. Our concern is that the radiation oncology community might misinterpret the conclusions of this report to mean that clinical trial groups such as the RTOG are still struggling to bring IMRT under control. This is an interpretation that we would like to strongly refute.

We agree with Das et al. that IMRT is a complex technology. However, we believe that their report overly emphasizes the maximum to minimum dose difference in order to make the point that IMRT produces increased dose heterogeneity relative to three-dimensional conformal radiation therapy (3D-CRT). It is generally accepted that the use of IMRT to bend isodose lines around critical structures will degrade a radiation dose distribution. It is not clear that the information presented by Das et al. properly separates this inherent feature of IMRT from other effects that are not unique to this planning and delivery technique. We do not agree that the dose heterogeneities found among patients treated with IMRT are so different from those found among patients treated with earlier techniques that this is an important topic, but some issues remained to be clarified.

In addition, RTOG protocols that use IMRT determine the maximum and minimum radiation dose limits for protocol compliance by assigning a sampling volume for the high- or low-dose regions. The RTOG uses this approach to avoid reporting of single-voxel anomalies that could give exaggerated dose heterogeneity values. It is possible that Das et al. used the technique of standardizing the sampling volume for the upper and lower dose limits to present the data in their report, but this cannot be determined from the information provided in the manuscript.

In conjunction with the National Cancer Institute–funded Advanced Technology Consortium (ATC), the RTOG has developed the guidelines and procedures necessary to move forward with meaningful clinical trials that use or study IMRT. We do agree with Das et al. that there should be national guidelines for the use of IMRT, but we are surprised that they did not mention that the RTOG and ATC have been actively working to ensure that such guidelines are an integral part of clinical trials.

Reference

Notes
Affiliations of authors: Department of Radiation Oncology, Thomas Jefferson University, Philadelphia, PA (JMG, YX); Department of Radiation Oncology, Emory University, Atlanta, GA (WJC).

Correspondence to: James M. Galvin, DSc, Department of Radiation Oncology, Thomas Jefferson University Hospital, 111 South 11th St, Philadelphia, PA (e-mail: james.galvin@jeffersonhospital.org).

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We read the excellent pattern-of-care study about dose prescription, recording, and delivery of intensity-modulated radiation therapy (IMRT) by Das et al. (1). We feel that this is an important topic, but some issues remained to be clarified.

First, the main result of this study was the variation in the planned dose that was delivered to the patient. It seems that IMRT
possibly provides lower minimal doses to the target when compared to conventional criteria. However, Das et al. do not clarify whether their results were based on the dose to the planned target volume (PTV) or the dose to the clinical target volume (CTV). This information is important for interpreting their result because a dose gradient exists in the peripheral portion of the target such that the dose to the CTV is usually higher than that to the PTV.

Second, radiotherapy dosage was generally prescribed to the PTV, as recommended by the recent International Commission on Radiation Units and Measurements (ICRU) report (2) or Radiation Therapy Oncology Group (RTOG) protocols. For example, one of the dose specifications in RTOG0615 was that PTV70 (CTV70 + margin) will receive 70 Gy in 33 fractions (3). Although the PTV was introduced to ensure delivery of the minimal dose to the CTV, the actual minimal dose to the CTV during a course of radiotherapy is usually higher than the minimal dose to the PTV. To illustrate this point, we performed a simple simulation using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK (4)). The statistical program is provided in an Appendix. We assumed a one-dimensional dose profile, as shown in Figure 1, A. The CTV (diameter = 30 mm) to PTV (diameter = 40 mm) margin was 5 mm, which is typically used in head and neck radiotherapy (3). This margin is usually estimated on the basis of systematic and random errors during radiotherapy (5). On the basis of a review (6), we assumed a value of 2 mm for SDs of both errors in our simulation. We also assumed a radiotherapy course that consisted of 35 fractions. Although the minimal dose to the PTV was only 80% of the prescribed dose, we found that the median actual minimal dose to the CTV was 90% (95% confidence interval = 82% to 98%) of the prescribed dose after 5000 rounds of Monte Carlo simulation. The cumulative probability distribution of the actual minimal dose to the CTV after 35 fractions of radiotherapy is illustrated in Figure 1, B. Therefore, although the minimal dose to the PTV in radiotherapy treatment planning may be low compared with conventional criteria, the actual minimal dose to the CTV after fractionated radiotherapy delivery remains to be investigated in the IMRT era.

Appendix: WinBUGS program for estimation of the actual minimal dose to the CTV after 35 fractions of radiotherapy.

The annotations were preceded by the symbol “#.”

model {
    #N means number of fractions for i in 1:N {
        #actual dose at the margin of CTV in each fraction
        dose_margin[i]<-0.9-0.02*d[i];
        #the actual dose at the margin of CTV is affected by the random and systematic error
        d[i]<-dnorm(mean,0.25);  
        mean<-dnorm(0,0.25);
        #the actual delivered dose at the margin of CTV after N fractions
        mine<-sum(dose_margin[1:N])/N;
        #
        Data
        list(N=35)
    }
}

References


Figure 1. Hypothetical dose distribution in single and fractionated radiotherapy. A) Hypothetical one-dimensional dose profile in a single fraction of radiotherapy. B) Cumulative probability distribution of actual minimal dose to the CTV after 35 fractions of radiotherapy (proportion of the prescribed dose). CTV = clinical target volume; PTV = planned target volume.

Response

We thank Olch and Lavey, Deye et al., Galvin et al., and Chien et al. for their interest in our paper (1) and their willingness to be provoked into a response. The discussion of some of the issues raised is healthy, and it is worthwhile to challenge the assumptions inherent in this topic. We agree that both clinical significance and achievability should be carefully considered in developing the dose-volume specifications used in clinical trials, and that is exactly what we mentioned in the Discussion section of our article [(1); paragraph 2, lines 6–10].

Contrary to what Olch and Lavey have implied, we did not endorse the use of any single point dose but rather the use of the entire dose–volume histogram. On the other hand, it is an undeniable fact that the ICRU-50 (2) has put a lot of emphasis on the reporting of isocenter dose for three-dimensional conformal radiotherapy (3D-CRT). Unfortunately, as we have pointed out, the isocenter dose is simply not meaningful in IMRT. Thus, in addition to the dose–volume histograms of all relevant structures, it is prudent
to find an alternate dose point that can be used for the plan reporting purposes. In light of the variation shown in figure 1 of our article, we suggested that the median dose could be a relevant dose to report in plan comparisons until a better parameter is supported by the clinical findings and advocated by national and/or international guidelines.

We thank Deye et al. and Galvin et al. for their comments and note that we acknowledged the contribution of the RTOG to IMRT, as clearly stated on page 305 in our article (1). Rather than providing the entire dose–volume histogram for 803 patients, we chose only the maximum, minimum, medium, and isocenter doses for our analysis. Picking a maximum dose point at 100%, 99%, 95%, or 90% and a minimum dose point at 10%, 5%, 1%, or 0% of the target volume from the dose–volume histogram is purely arbitrary unless defined and recommended by certain guidelines, as is clearly stated on pages 302–303 in our article (1) and as is also pointed out by Galvin et al. We are aware of various abstracts, a letter to the editor (3), and the contributions of the Advanced Technology Consortium (http://atc.wustl.edu) concerning the variability in clinical trials. It is obvious that there are no concrete guidelines that could be applied to IMRT, as stated by Engler and Rivard (4). And acknowledged by Deye et al. We disagree with Galvin et al. that 3D-CRT and IMRT provide similar dose inhomogeneity. As a result of the inverse planning process, dose variability in IMRT is rather large and dependent on dose–volume constraints, the grid size, the treatment planner, the planning system, and the algorithms used. Certainly, it is another topic for research, and Galvin et al. could provide such data through the RTOG.

Chien et al. point out several issues that require clarification regarding the planning target volume (PTV), the clinical target volume (CTV), and the impact of set-up error in fractionated radiation therapy. Our data did not specify PTV or CTV; instead, we reported the dose deviation from prescription either to PTV or CTV depending on the specification of physicians in each institution. We did not alter the dose reporting solely to PTV, and hence, the interpretation by Chien et al. is not applicable to our study. The second question about set-up error and its impact is also irrelevant in the context of our study. It is well known that additional smearing of the dose–volume histogram takes place with fractionated therapy and increases the dose variation. The RTOG-0615 protocol specifies that at least 95% of the planning target volume receiving 70 Gy (PTV<sub>70</sub>) is covered by the 70-Gy isodose surface, that no less than 20% of PTV<sub>95</sub> receives ≥77 Gy, that no more than 5% of PTV<sub>95</sub> receives ≥80.5 Gy, and that no more than 1% of any distinct PTV<sub>95</sub> receives ≥93% of the prescribed dose, which directly supports our findings in terms of dose variability. Following these criteria for PTV coverage may lead to even wider variation in the maximum and minimum dose to the PTV than what we have reported.

In conclusion, we thank the authors of the correspondences on our article for expressing their concerns, comments, and views about the imperfections associated with IMRT. We believe that figures 1–3 in our article (1) appropriately display the central problem in IMRT plan comparison; certainly guidelines to fix the problem may be forthcoming.

I. J. Das
C. W. Cheng
K. L. Chopra
R. K. Mitra
S. P. Srivastava
E. Glatstein

References

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

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

Present address: Department of Radiation Oncology, Director of Medical Physics, Indiana University School of Medicine, Indianapolis, IN (I. J. Das).

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Response
We note with appreciation the comments of Deye et al. on the recent article by Das et al. (1) and our accompanying editorial (2). The authors make a valid point. The guidance provided to clinical trials by the National Cancer Institute through the Advanced Technology Consortium (ATC) and other mechanisms is valuable. Specifically, the existence of published ATC guidelines for the use of intensity-modulated radiation therapy (IMRT) in multicenter trials and a detailed credentialing process can be credited with ensuring that high standards of dose planning and delivery are already in force in current trials. We did not intend, by omission, to obscure this fact.

We did not refer to the ATC guidelines because our focus was on a different aspect of IMRT plan evaluation and comparison. The ATC guidelines and the credentialing process ensure that the planning and delivery of IMRT by institutions is done with a high degree of accuracy. However, the ATC guidelines do not yet address the question of what constitutes a desirable planning result. Our editorial was concerned with the use of metrics such as minimum and median doses to specify plan quality and with the larger question of how a “good” plan can best be recognized. As we expressed in our editorial, we are wary of the assumption that, for example, minimum planning target volume dose has high merit as a planning metric. The question of which IMRT plan indices should be employed clinically is one that falls outside the scope of the current ATC guidelines. But, as Deye et al. correctly point out, the databases that have been developed by the ATC will allow retrospective analyses that can address connections between dosimetry and outcome, and thus help investigators create a common framework for comparison of IMRT plans.

JOHN WILLINS
LISA KACHNIC
References


Notes

Affiliations of authors: Department of Radiation Oncology, Boston Medical Center, Boston, MA (JW, LK) and Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA (JW, LK).

Correspondence to: John Willins, PhD, Department of Radiation Oncology, Boston Medical Center, Moakley Building, Ste LL100, 830 Harrison Ave, Boston, MA 02118 (e-mail: john.willins@bmc.org).

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