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Introducing New Technologies into the Clinic

Benchmark Dose-Volume Histograms for Prostate Cancer as a Paradigm

Srinivasan Vijayakumar · Samir Narayan ·
Claus Chunli Yang · Philip Boerner · Rojymon Jacob ·
Mathew Mathai · Rick Harse · James Purdy

Department of Radiation Oncology, University of California, Davis Cancer Center,
Sacramento, Calif., USA

Abstract
Introducing new technologies into radiation oncology clinical practices poses very specific logistical dilemmas. How do we determine that a new technology's dose distribution is better than the 'standard' and what are the methods that can be applied to easily compare the 'new' with the 'old'? We consider how the benchmark dose-volume histogram (DVH) can serve as a conceptual model to approach these issues. Comparing dosimetric differences using benchmark DVHs helps a 'global' comparison of the area under the curve that is intuitive, relatively efficient and easily implemented. These concepts, applied in prostate cancer in this communication, have wider applications in other disease sites and in the introduction of technologies beyond intensity-modulated radiation therapy.
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The Benchmark Dose-Volume Histogram

The introduction of new technologies into our clinical practice of radiation oncology poses very specific logistical dilemmas. At what point can one say that the new technologies offer potential advances in treatment outcomes? How often can these potential outcomes be expected? In daily clinical work, these questions eventually resolve to: will a specific patient's problem be aided by the use of the new technology? New technologies are often accompanied by added technical costs, staff time in implementation, and practical concerns regarding the reliability of the

new processes and their outcomes. New technologies designed for clinical use, though acquired with considerable cost and effort, will likely suffer deferment of use on a day-to-day basis unless quantitative measures permit a clear definition of their new and immediate roles in improving outcomes for specific patient groups.

Dose-volume histograms (DVHs) are generated during the treatment planning process [1–3], and assist in defining the dose distributions of rendered plans to regions of interest. In comparing rival plans, DVHs can be used for making treatment decisions in therapy by comparing the dose distributions to normal and tumor tissues. In so doing, DVHs can objectively compare the treatment technologies themselves, their role for individual patients, and ultimately their role in the technical environment of individual treatment clinics, each with its unique army of diverse technologies.

The benchmark DVH is a conceptual model to facilitate an efficient way to define the relative role of a new radiation delivery technology. A *benchmark* is a standard of measurement or evaluation, 'a point of reference for judging value, quality, change or the like; standard to which others can be compared'. By using the benchmarking of DVHs as a strategy, one can objectively define a path of progress in improving radiotherapy dose distributions, and utilizing the new technologies that provide those improved dose distributions.

A new technology may give a better dose distribution to the planning target volume (PTV), and thus to the gross tumor volume (GTV) and clinical target volume (CTV). This might be either a more uniform dose distribution or a biologically advantageous dose gradient ('hot spot') within the PTV that could potentially improve outcomes. In addition, a new technology could be instrumental in reducing doses to critical tissues. In turn, these dosimetric advantages can improve outcomes, including survival, local control, quality of life, and toxicity endpoints. The new technology might also be more efficient or cost less. Benchmarks can help assess all of these important considerations.

Important questions remain in the development of new intensity-modulated radiation therapy (IMRT) approaches for radiotherapy. For example, are IMRT plans always better than conventional or three-dimensional conformal radiation therapy (3DCRT) plans? How does one quantitatively compare IMRT with other plans? How much additional time is required for IMRT in terms of planning treatment, monitoring quality assurance, and delivering therapy? What additional resources are needed for its implementation and confirming its reliability? Which patients should receive this new technology and which will not benefit from it? How can exact guidelines for use be developed? More generally, why would one want to change to a new technology when an older technology may appear adequate? These questions are universal for the introduction of any new technology into our clinics. The differences that can be defined by benchmark DVHs can lead

Table 1. Considerations regarding the value of IMRT compared with 3DCRT

Consideration	Response
Better dose distribution?	yes
Lower doses to the critical tissues?	yes
Improved outcomes?	
Survival	unknown
Local control	yes
Quality of life	possibly
Fewer toxicities	yes
More efficient than 3DCRT?	no
Lower cost (decreased staff levels)?	no

not only to approval of new treatment plans, but also to the justification for the new planning and delivery processes themselves and their requirements for implementation. Benchmark DVHs can provide objective measures for the specific roles of new technologies in the radiotherapy clinic.

This discussion will illustrate these concepts using prostate cancer therapy as a model.

The Benchmark Dose-Volume Histogram and Prostate Cancer

In prostate cancer treatment, dose escalation beyond 70 Gy is becoming routine practice. This is made possible with the use of 3DCRT and more recently with the implementation of IMRT. Dose escalation, however, is often limited by rectal and bladder toxicity. Although accuracy in delivering high doses to the target and low doses to the surrounding structures is complicated by rectal dose/volume variation due to organ motion and daily repositioning errors, the likelihood of late rectal or bladder toxicity is initially investigated through evaluation using the DVH.

One of the questions regarding prostate cancer radiotherapy is whether IMRT always leads to a better dose distribution to the PTV, meaning a more uniform dose or higher dose within the CTV/GTV, than occurs with 3DCRT. Second, does IMRT lead to lower doses to the critical tissues such as the rectum, bladder, penile tissues, and femoral heads/hip joints? Third, has IMRT improved outcomes, including survival, local control, quality of life, and lower toxicity? Table 1 provides some of the commonly acknowledged answers to these questions.

However, are these answers applicable to every prostate cancer patient treated today? A response to this requires quantification of the potential benefit of IMRT specific to an individual case, and is aided by standards for comparison. In this

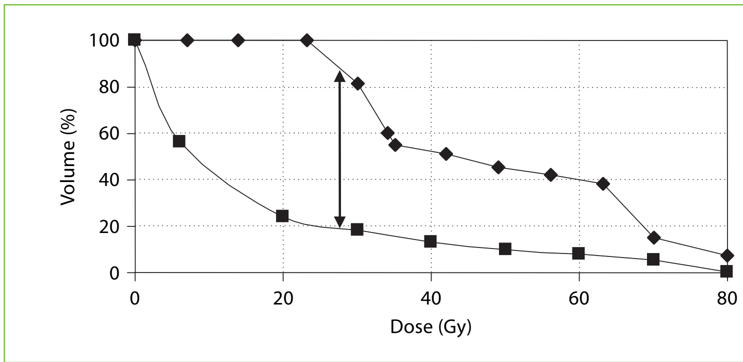

Fig. 1. Upper and lower range for bladder DVHs reported by 9 institutions in the literature.

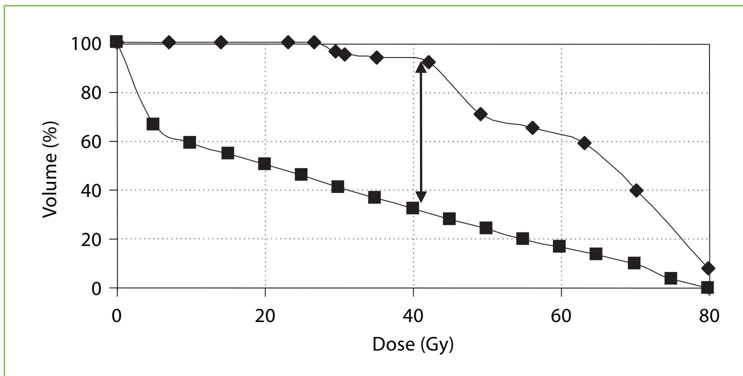

Fig. 2. Upper and lower range for rectal DVHs reported by 9 institutions in the literature.

paper, a systematic approach toward this will be presented, showing an organization of existing data on prostate therapy DVHs that should prove useful for evaluating IMRT treatment plans and expected outcomes. These concepts may be applied in other clinics for their prostate cancer therapy planning, and may be applied for other tumor sites and other technologies as well.

Benchmark Dose-Volume Histogram Data for Defining Prostate Cancer Therapy

Bladder and Rectum DVH Results in the Literature for Prostate Radiotherapy
Published DVH analyses for bladder or rectum volumes, treated using modern radiotherapy approaches for prostate cancer, are shown in figures 1 and 2. They reveal a wide range of results. These grouped data cannot be used directly to eval-

uate a single institution's DVH results. Each institution has its own set of protocols in performing simulations, positioning patients, defining targets, expanding PTV margins, and so forth. For example, some institutions use enemas to evacuate the rectum before planning treatment, and this alone could have an influence on an institution's DVH patterns for rectal volume that does not reflect any contribution of IMRT. Some institutions use intravenous contrast and some do not. Some institutions treat patients in the prone position, whereas the majority of institutions use the supine position. Therefore, the institutions must develop their own benchmark DVHs to compare their work and technologic development, and to correlate them with their outcomes once sufficient follow-up has been obtained.

There are a number of ways clinicians can analyze DVH data to optimize planning. For example, one might evaluate the mean dose to the rectum, or the rectal volume receiving more than 70 Gy, or other measures. In the experience of several groups including ours, the ideal way is to utilize the whole DVH curve, because even the lower therapy doses may significantly contribute to normal tissue complications.

At least three published studies show the importance of evaluating the area under the curve. In one, Huang et al. [4] at the MD Anderson Cancer Center examined the dosimetric, anatomical and clinical factors that may lead to late rectal toxicity after 3DCRT by retrospectively analyzing DVHs. The study was comprised of 163 patients with stage T1–T3 disease and treated from 1992 to 1999. Treatments delivered isocenter doses of 74–78 Gy, and patients were followed for a median of 62 months. To score late rectal complications, the investigators used modified Radiation Therapy Oncology Group criteria, and correlations were made at 6 years following therapy for grade 2 or higher toxicities. At 6 years, grade 2 or higher toxicities were seen in 25% of patients. Factors that correlated with late rectal toxicity included dose and volume effects: the overall percent volume of the rectum irradiated and the dose prescribed. Analyzing specific doses, there was a significant correlation of toxicity with the volume of rectum treated. Importantly, this correlation existed at several dose points, including the volume of the rectum receiving 60, 70, 75.6 and 78 Gy.

Additionally, the percentage of rectal volume treated correlated significantly with the incidence of rectal complications, as well as the absolute rectal volume, both at 70, 75.6 and 78 Gy. According to their univariate analysis, maximal dose to the CTV, maximal dose to the rectum, maximal dose to the rectum as a percentage of the prescribed dose and maximal dose delivered to 10 cm^3 of rectum were all important. The only clinical variable that was important was a history of hemorrhoids. Through DVH analysis, this study found a dose/volume correlation for developing late rectal complications, and this correlation was observed at multiple dose levels indicating that the curve itself must be considered rather than any individual dose point on the curve.

Table 2. Association of total rectal wall volume (VRW) with rectal bleeding, at the Memorial Sloan-Kettering Cancer Center

Dose and correlation with rectal bleeding	
70.2 Gy	p = 0.06
75.6 Gy	p = 0.01
Patients with similar VRWs, and volume exposed to 46 Gy	
70.2 Gy	p = 0.02
75.6 Gy	p = 0.005
Patients with volume exposed to 77 Gy	
75.6 Gy	p < 0.005

A second important study, from the Memorial Sloan-Kettering Cancer Center [5], looked at late rectal bleeding after 3DCRT, and specifically at the rectal wall DVHs. A total of 266 and 320 patients were treated with doses of either 70.2 or 75.6 Gy, respectively, using six-field coplanar beams. Patients were scored as having rectal bleeding or not depending on whether they showed this complication by 30 months. Within the eligible group, rectal bleeding occurred in 13 patients after 70.2 Gy and in 36 patients after 75.6 Gy. For comparison, investigators took cohorts of 39 and 83 patients from a random sample of eligible nonbleeding patients at 70.2 and 75.6 Gy, respectively. They then performed a multivariate analysis, looking at rectal wall DVH correlations, to investigate what the predictive variables might be (table 2). For patients with bleeding, the area under the rectal DVH curve (using average percent volume) was significantly greater than for patients without bleeding, for both dose groups. In both, the volume exposed to 46 Gy was very important in influencing rectal bleeding rates, indicated with significant p values. Also, the percent volume receiving 77 Gy was significant for the patients receiving 75.6 Gy. This study shows that even at 46 Gy, the absolute volume or percent volume of the rectum helps predict complications.

To guide dose escalation in prostate cancer treatment, variations in the rectal dose/volume relationship must be considered as well. In a third related study, Yan et al. [6] examined the influence of variations in rectal volume, shape, size and position between patients and in the same patient on different treatment days. This retrospective study took different PTV constructions and evaluated the effect of rectal complications on them. In 30 patients, treatment plans were generated (a four-field box beam arrangement) for each of three different PTVs: PTV with a 0.5-cm uniform margin from CTV, a 1.0-cm margin, and a patient-specific PTV constructed using treatment imaging feedback. The investigators found that sensitivity of the risk of rectal complication to rectal dose/volume variation strongly depended on both the CTV-to-PTV margin and the prescription dose (table 3) in addition to other factors.

Table 3. Factors causing rectal complications, in order of importance

1	Margin expansion, CTV to PTV
2	Prescription dose
3	Rectal volume
4	Rectal dose
5	Shape/size of rectum
6	Position of rectum

William Beaumont Hospital [6].

Using DVH Results to Strategize the Introduction of New Technologies
Clinical analyses of DVH results can be used to model improvements in our technologies and their clinical roles. Building upon these earlier studies of prostate cancer DVHs, the approach used at UC Davis to introduce IMRT for prostate cancer patients is outlined in table 4 [7, 8].

The hypothesis was that IMRT was likely to give a better dose distribution in a majority of patients but not in all patients. The percentage of patients in whom IMRT would not be different than 3DCRT was not known when examined 2–3 years ago. One way to ascertain an improved dose distribution is to compare 3DCRT with IMRT in each patient. However, this would be extremely resource intensive. By developing benchmark DVHs, one can create a more efficient method of comparing new IMRT plans with more traditional plans. This approach is equally applicable to the evaluation of other new technologies (for example, helical tomotherapy might be compared with linear accelerator-based IMRT). What follows is a description of the introduction of IMRT in a planned and phased way at UC Davis, which helped to optimize its use of resources and may be helpful for other institutions.

The strategy was to create individual 3DCRT and IMRT plans for a certain number of patients. The expectation was that patients would be treated using IMRT only if the dose distributions were better than those with 3DCRT. Benchmark DVHs were then developed after a certain number of cases and used for future comparisons. To define this benchmark standard, 97 treatment plans were used from 66 patients with prostate cancer treated at UC Davis between 2000 and 2003. Thirty-five patients, treated before routine implementation of IMRT, were treated with 3DCRT. Both 3DCRT and IMRT plans were developed for the remaining 31 patients. In order to develop baseline data, DVHs from prior work at the University of Illinois at Chicago were used to accomplish some of the average DVHs, since their outcomes were known [Vijayakumar, S., pers. commun.].

Table 4. UC Davis hypotheses, strategy and experience [8]

Hypotheses	Strategy	Experience
IMRT is likely to give better dose profiles in a majority of patients, but not all patients (the percentage in whom it may not be different than 3DCRT was unknown)	Perform 3DCRT and IMRT plans for a certain number of patients	97 treatment plans were generated on 66 patients with prostate cancer treated at our institution between April 2000 and December 2003
One way to ascertain an improved dose profile is by comparing 3DCRT vs. IMRT in each patient (however, this would be resource intense over time)	Treat those with IMRT if the dose profile is better than 3DCRT	35 patients were treated before the routine implementation of IMRT with 3DCRT
Developing benchmark DVHs will allow for a more efficient way to compare IMRT to more traditional treatment plans	Treat with 3DCRT if dose profiles are comparable (this saves resources)	Both 3DCRT and IMRT plans were developed for the remaining 31 patients
A class solution for comparing rival plans can save resources and can make the implementation of any new technology more efficient	Develop benchmark DVHs after a certain number of cases and then use the benchmark DVH for comparison	Bladder and rectum DVH data were summarized to obtain an average DVH for each technique and then compared using two-tailed paired t test analysis (fig. 3–9)

In accordance with our methods, a dose of 74 Gy in 37 fractions was prescribed to the 95% isodose surface and the dose was normalized to the isocenter. Bladder and rectum DVH data were summarized to obtain an average DVH (fig. 3, 4) for each technique, and then compared using a two-tailed paired t test. Target volumes (GTV, CTV and PTV), as well as critical tissues, were recontoured if necessary when this analysis was done, so that there was uniformity in the delineation of target volumes [7, 8].

The mean dose for 3DCRT patients was 28.8 versus 26.4 Gy for IMRT. Examining the volume receiving 70 Gy next, similar results were found. In the results for the rectum, there was an advantage for IMRT over 3DCRT both for the mean dose and volume receiving 70 Gy. For those patients who had both prostate and seminal vesicles treated, IMRT gave an advantage in terms of both the mean dose and volume receiving 70 Gy for both bladder and rectum. The mean dose to the bladder was 27.5 Gy for 3DCRT patients compared with 25.9 Gy for IMRT. Finally, in those patients receiving treatment to the prostate only, there again were advantages for IMRT for bladder and rectum [8]. For example, the mean dose to the bladder was