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Visualization of a variety of possible dosimetric outcomes in radiation therapy using dose-volume histogram bands

Alexei Trofimov, Ph.D., Jan Unkelbach, Ph.D., Thomas F. DeLaney, M.D., and Thomas Bortfeld, Ph.D.

Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, 02114

Abstract

Purpose—Dose-volume histograms (DVH) are the most common tool used in the appraisal of the quality of a clinical treatment plan. However, when delivery uncertainties are present, the DVH may not always accurately describe the dose distribution actually delivered to the patient. We present a method, based on DVH formalism, to visualize the variability in the expected dosimetric outcome of a treatment plan.

Method—For a case of chordoma of the cervical spine, we compared two intensity-modulated proton therapy plans. Treatment Plan A was optimized based on dosimetric objectives alone (i.e., desired target coverage, normal tissue tolerance). Plan B was created employing a published probabilistic optimization method that considered the uncertainties in patient set-up and proton range in tissue. Dose distributions and DVH for both plans were calculated for the nominal delivery scenario, as well as for scenarios representing deviations from the nominal set-up, and a systematic error in the estimate of range in tissue. The histograms from various scenarios were combined to create DVH-bands to illustrate possible deviations from the nominal plan for the expected magnitude of set-up and range errors.

Results—In the nominal scenario, the DVH from Plan A showed superior dose coverage, higher dose homogeneity within the target, and improved sparing of the adjacent critical structure. However, when the dose distributions and DVH from plans A and B were recalculated for different error scenarios (e.g., proton range underestimation by 3 mm), the plan quality, reflected by DVH, deteriorated significantly for Plan A, while Plan B was only minimally affected. In the DVH-band representation, Plan A produced wider bands, reflecting its higher vulnerability to delivery errors, and uncertainty in the dosimetric outcome.

Conclusions—The results illustrate that comparison of DVH for the nominal scenario alone does not provide any information about the relative sensitivity of dosimetric outcome to delivery uncertainties. Thus, such comparison may be misleading, and may result in the selection of an inferior plan for delivery to a patient. A better-informed decision can be made, if additional information about possible dosimetric variability is presented, e.g., in the form of DVH bands.

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Corresponding Author: Alexei Trofimov, Ph.D. Mailing address: Department of Radiation Oncology, Massachusetts General Hospital, 30 Fruit Street, Boston, MA 02114 Telephone: (617) 724-3655 Fax: (617) 724-0368 atrofimov@partners.org.

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Keywords

visualization of uncertainty; intensity-modulated therapy; proton therapy; inverse treatment planning; multi-criteria optimization

INTRODUCTION

The process of appraisal of a radiotherapy treatment plan is a demanding and time-consuming task: a rather complex 3-dimensional dose distribution has to be reviewed and evaluated in terms of its potential to produce the desired therapeutic outcome in a patient. Historically, the radiation therapy community welcomed approaches that reduced the required amount of data review and simplified its visualization, while minimizing or altogether avoiding the loss of representation and generality in the reviewed body of information. The dose-volume histograms (DVH), first introduced over three decades ago [1], have, in particular, gained acceptance as one of the principal tools in the plan review. While the DVH are completely lacking in spatial information, they allow one to relatively easily evaluate the potential for tumor control, and risk of treatment complications, as indicated by the fractional levels of irradiation of volumes of interest [2,3].

Typically, the DVH are only reviewed for the dose distribution planned for the nominal conditions, that is, the simulated treatment set-up captured by CT or another imaging modality. Numerous reports, however, have demonstrated that the radiation therapy dose delivered to a patient may, in fact, differ from the treatment plan due to deviations and uncertainties during delivery. These include uncertainties in the definition of the target volume [4], estimation of tissue stopping powers [5], errors in dose calculation [6], deviations of patient set-up from the simulated conditions [7,8], inter-fractional anatomical variations [9,10], and intrafractional motion [11].

Thus, due to delivery uncertainties, the limited data used for plan appraisal may not always accurately represent a likely dosimetric outcome of plan delivery to a patient. In the most extreme cases, the limited review criteria may lead to a suboptimal decision regarding the choice of treatment: i.e., a possibility exists that, based on superficial DVH characteristics of nominal plans, an inferior plan could be chosen rather than a more uncertainty-robust plan. This is especially possible in a situation, where relaxed definition of plan objectives may lead to a solution degeneracy [12]: a large number of acceptable solutions, which more or less equally satisfy the planning goals, e.g., produce similar dose-volume histograms, or even nearly identical dose distributions, while employing rather distinct patterns of intensity-modulation.

Recent development and clinical introduction of multi-criteria optimization (MCO) methods yet further underscored the demand for more comprehensive tools for plan intercomparison. In MCO, a variety of distinct plans are generated and a user is provided with tools to navigate between different solutions and combine their elements. Thus, the user arrives at the decision that is optimal not only from the vantage point of mathematical optimization, but also from the clinical experience [13]. While the user is presented with many possible solutions, the decision is still made largely based on the DVH and iso-dose distributions from nominal plans without evaluating the effect of possible delivery errors.

Not surprisingly, shortly after the introduction of the DVH, it has been suggested that, in addition to the nominal dose distributions, “worst case” dose scenarios should also be considered [14]. In the past decade, a significant effort was put in the development of treatment plan optimization methods, which explicitly included delivery uncertainties, either

parametrized as probability functions or considered as individual extreme scenarios. These methods produce plans that are “robust”, i.e., minimally affected by the deviations from the planned set-up or anatomy [15,16,17]. Recognition of the importance of the potential effect of delivery errors required some reconsideration of the way the treatment plans were evaluated, and a number of ideas have been put forward on how to visualize various dosimetric outcomes: display of families of DVH [6,18] and dose distributions for individual error scenarios [10,15], worst-case cases [16,19], and dose variance distributions [8,9].

Below, we present, illustrate, and discuss a concept of DVH bands that allows for visualization of variability in the expected dosimetric outcome of a treatment plan by utilizing the formalism of both the plan evaluation based on dose-volume histograms, and probabilistic robust optimization.

METHODS

Test case

We consider a case of chordoma of the cervical spine, treated with 3D-conformal proton therapy at the F.H. Burr Proton Therapy Center (BPTC). Gross tumor volume (GTV) and clinical target volume (CTV) were contoured by the attending physician. The CTV was expanded non-uniformly from the GTV to include suspected spread of microscopic disease. The CTV was treated to 50.4 Gy in 28 fractions, followed by a boost of 27 Gy in 15 fractions to the GTV. The iso-dose coverage requirement was that a minimum of 97% of the target volume received the prescription dose. No explicit planning target volume (PTV) was defined.

Handling of uncertainties in 3D-conformal proton therapy

Because of the limited range of protons in tissue, PTV margin expansion is not as effective as in photon-based radiation therapy. Instead, proton therapy employs other means, such as range compensator expansion, or “smearing”, distal and proximal range margins to ensure that the errors in the estimated range in tissue and patient set-up do not result in a loss of dose to the target [20]. A systematic error in the proton range may arise due to misestimation of tissue stopping powers from CT data, while intrafractional motion and anatomical variations produce range shifts which can be described as random [19].

At the BPTC, the distal and proximal margins are formed by increasing the range of the spread-out Bragg peak by 3.5%, and expanding the modulation width accordingly. And the compensator smearing radius used for intracranial and head-and-neck targets is typically 3 mm. Thus, in the case of chordoma, with the maximum required range of between 11 and 13 cm depending on the beam direction, the delivered dose distribution is expected to provide the prescribed level of target coverage, as long as the range misestimations do not exceed 5 mm, and set-up misalignments are within 3 mm.

Intensity-modulated proton therapy (IMPT)

IMPT is currently being implemented at the BPTC [21], and its potential application for various sites is under active investigation.

In IMPT, similar to IMRT with photons, non-uniform field contributions, delivered from different directions, combine to produce the desired therapeutic dose distribution that is optimized using inverse planning methods to conform to the clinical prescription. Depending on the definition of dosimetric objectives, choice of the algorithm, as well as the values of input parameters (proton beam characteristics, initial guess of beam weighting, convergence criteria), inverse optimization may produce a variety of clinically acceptable

plans, of comparable quality, namely, yielding similar value of the optimized objective function. This phenomenon is often termed the degeneracy of solution of the inverse planning problem [12,22]. Solution degeneracy in the context of IMPT means that, by adjusting the formulation of objectives and other input parameters, one can generate a variety of plans that would produce similar total dose distributions. However, as illustrated in Figures 1(a) vs. 1(b), the doses delivered by individual fields may differ substantially between such plans.

IMPT treatments can be delivered by scanning a narrow proton pencil beams across the target volume while changing the scanning speed and current intensity to achieve the desired distribution transversally, and adjusting the energy accordingly to reach target tissues located at different depths. Thus, range compensators are not strictly required, but can be used to reduce the number of scanned depth layers.

Generally, intensity-modulation yields higher conformality of proton dose distributions to the target volume and superior sparing of healthy tissue, compared to 3D-conformal therapy, however, because of the spatial dose modulation, IMPT dose distributions may be stronger affected by the delivery uncertainties [8]. Traditional proton therapy techniques of compensator smearing, or range margin expansion are generally not be effective in IMPT, because they do not prevent the deviation in the delivered dose due to misalignment of individual fields. Instead, advanced planning techniques have been put forward that reduce the sensitivity of the IMPT dose to uncertainties [15-17].

IMPT treatment plans

As a part of the research study approved by the Institutional Review Board, IMPT treatment plans were created for the test case of chordoma, using the same dose prescription as specified for the 3D-conformal proton therapy. Planning was performed with the in-house developed software, which offered both conventional and probabilistic algorithms as the option for plan optimization. The software, and the details of the algorithms have been previously described by Unkelbach *et al.* [17]. For convenience, a short summary is given below.

The probabilistic approach considers multiple uncertainty scenarios, and optimizes the expectation value of the delivered dose. Gaussian distributions are used to describe the probability of realization of various random set-up deviations from the plan, as well as deviations from the estimated proton range in tissue. (Although, as discussed above, the range error has a systematic component due to CT conversion to proton stopping powers, the value of this error is not known in any particular case, thus a Gaussian function can be used to describe the distribution of this systematic error for different beam directions and different patient cases.) Range and set-up errors are assumed to be statistically independent. A quadratic objective function (OF) is used to evaluate the conformity of the planned dose to the prescription, and a stochastic gradient descent algorithm is used to optimize the dose, i.e., minimize the OF iteratively. In each iteration, a small set of possible delivery scenarios, i.e., 10 different combinations of set-up and range errors, are randomly sampled according to their relative probability, to calculate the value and the gradient of the OF. As the result, the combined dose distribution conforms to the prescription, to the extent possible, not only for the nominal planning scenario (i.e., no deviations), but also for scenarios describing likely delivery errors.

Two plans were created, which below will be referred to as Plan A and Plan B. Both plans employed the 3D-modulation method, the most common and versatile IMPT planning technique, in which Bragg peak spots from individually weighted pencil beams are distributed throughout the target volume [23]. Both plans used the same beam configuration,

and same set of dosimetric objectives, including minimum and maximum doses to the CTV, and maximum tolerance doses to the critical organs. The beam directions were selected from among those used in the clinical 3D-conformal plan, and included 3 coplanar fields to be delivered with the gantry rotated to 70° (left-anterior), 230° (right-posterior) and 300° (right-anterior), as shown in Figure 1.

Optimization of Plan A was done using the conventional optimization algorithm that did not consider uncertainties of delivery. The dose objective function was evaluated and minimized for the nominal planning conditions alone.

Plan B was optimized with the probabilistic approach, in which the expectation value of the same quadratic objective function was minimized for a variety of sampled delivery scenarios. The probability of delivery errors was approximated as the unbiased Gaussian distribution with the variance $\sigma=3$ mm for the set-up uncertainty in each of 3 dimensions (cranio-caudal (CC), antero-posterior (AP), right-left lateral (RL)), and $\sigma=3$ mm for the deviation from the planned range. With regard to the range uncertainty, for any delivery scenario, it was assumed that a systematic range misestimation would affect all pencil beam positions within a treatment field equally, i.e., all beams penetrating either x mm deeper than planned, or all falling short.

Evaluation of the effect of deviations from the plan during delivery

The effect of errors on delivered dose distribution was estimated in a sensitivity analysis, the method first suggested by Goitein [14] and documented in the optimization literature [10,17]. The sensitivity analysis includes recalculation of the dose distribution for various realizations of 3-dimensional delivery geometry: namely, a shift in the treatment iso-center position for set-up errors, or simulated systematic over- or under-penetration of pencil beams to the planned depth.

The analysis was performed within the optimization software, as the last step of planning. For set-up uncertainties, dose distributions from the optimized plan were recalculated and analyzed for shifts of ± 3 mm (1σ) and ± 5 mm ($\sim 1.7\sigma$) in the three cardinal directions (CC, AP, RL). To evaluate the effect of the range uncertainty, deviations of the same size (1 and 1.7σ) were also applied to the beam penetration depth. Each of the set-up and range errors were considered separately, i.e., only one out of 4 was present in every evaluated scenario: e.g., a 3mm set-up shift alone to the left; a 5 mm shift to the posterior; a 3 mm range overshoot for all beams, etc.

Visualization of uncertainty due to delivery errors in the dose-volume histogram

Dose distributions obtained for various error scenarios were used to calculate dose-volume histograms. Thus, for every error value, e.g., 1σ , 8 histograms were calculated: 2 for range shifts, and 2 for each of AP, CC, and RL shifts. In the next step, the envelope was defined that encompassed the entire set of DVH corresponding to the same absolute size of the error. Below, such envelopes will be referred to as the “DVH bands”.

The generalization being made here is that, for any realized scenario, the DVH would remain within the band as long as the sum-in-quadratures of all errors in different dimensions is smaller than the error threshold for which the bounds were defined. For example, a scenario including a 1mm shift cranially ($\sigma/3$, in our test case), a 2 mm shift posteriorly ($2\sigma/3$), and a 2 mm range overshoot ($2\sigma/3$), with a combined error, obtained by addition in quadratures, of 3 mm (1σ), may be approximated as a weighted combination of 1σ shifts, and thus the DVH will fall within the envelope described by the DVH of respective 1σ -shift scenarios. In the Gaussian distribution, the realization of a scenario within the threshold of 1σ is often described as the result being within “the 65% confidence

interval (CI)", according to its parametrized probability. For deviations within 1.7σ , the corresponding probability of realization is approximately 90%.

RESULTS

For the nominal planning conditions, the total dose distribution for both plans A and B, and the constituent doses delivered by individual fields from 3 different directions, are shown in Figure 1. The corresponding DVHs are compared in Figure 2. For the nominal case, the combined distributions from both plans satisfied the requirements for the prescription dose coverage of the GTV and CTV, as well as the tolerance of the spinal cord (maximum dose of 55 to the center of the cord). Of note is that, in the nominal case, Plan A delivers a more homogeneous dose to the GTV (steeper DVH), and a lower mean and maximum dose to the cord.

By comparing images in the top and bottom rows of Figure 1, from plans A and B, respectively, one may note a difference in the distribution of high dose spots between the two plans, as well as a higher overall uniformity of the field doses with Plan B. In particular, in order to achieve the best possible sparing of the spinal cord, Plan A employed distal gradient of the Bragg peak, which is characterized by a sharper dose fall-off compared to the lateral penumbra. In order to maximize the advantage of the distal penumbra in Plan A, the pencil beams stopped in front of the spinal cord were assigned high relative weights, which resulted in hot spots, visible in Figure 1(a). On the other hand, Plan B, which considered possible miscalculation of the range, as well as set-up shifts, avoided placing high-weight spots proximally to the spinal cord, and used both the distal edge and lateral penumbra to spare the cord. As the results of uncertainty-robust optimization of Plan B, the hot dose spots in Figure 1(b) are located so that range overshoots or transversal shifts would minimally increase the dose to the cord.

The effect of this difference in the distribution of high dose spots can be seen in the analysis of sensitivity of delivered dose to errors. Figure 3 compares the DVH from the two plans for scenarios in which the proton range was either (a) over- or (b) under-estimated by 3 mm. A difference between the nominal DVH of Plan A, and the DVH from the same plan recalculated for a 3 mm shift in the range is particularly large for the spinal cord: the maximum dose is increased from 45.3 Gy in the nominal case (Fig. 2), to 62.5 for the scenario of 3 mm range overshoot (Fig. 3(a)), while for the 3 mm range shortfall the dose is reduced to 39.1 Gy (Fig. 3(b)). For Plan B, the numbers are 54.4, 56.1, and 54.9 Gy, respectively, for the nominal case, 3 mm overshoot and 3mm shortfall. Similarly, the GTV included within the prescription iso-dose (77.4 Gy) was reduced from 97% to 46% for Plan A for the 3mm range shortfall, while for Plan B the reduction was much less substantial: from 97% to 90%. In the case of the 3 mm range overshoot, the maximum dose in GTV increased from 82.9 (107% of prescription) to 89.6 Gy (115%) in Plan A, while it was unchanged at 84 Gy for Plan B (108% of prescription).

A similar effect was observed for larger range shifts of ± 5 mm, as well as in the analysis of sensitivity to set-up shifts. Fig.4 shows the same information presented in terms of DVH probability bands, rather than lines for individual scenarios, as in Figures 2 and 3. The darker-shaded band encompasses (the relatively more likely) variations in the DVH for deviations within 1σ , i.e., 65% CI in the assumed uncertainty model, and the lighter-shaded band shows the scope of variability for errors within 1.7σ (95% CI). Thus, a wider DVH band indicates a higher sensitivity of the delivered dose distribution to the errors of delivery.

DISCUSSION

The evaluation of the effect of delivery uncertainties is an important part of a plan review. However, the task of evaluating a large number of outcome scenarios, dozens of DVH and dose distributions, may be overwhelming for the decision-maker. Simplifying this task requires a method of compact and fair presentation of uncertainties.

One may consider a situation in which a decision-maker is being asked to select one of the two plans for the patient treatment based on the typical set of data displayed in clinical treatment planning systems: the nominal DVH (i.e., Figure 2 alone) and planar dose distributions. A review of the total dose distributions in transversal slices (as in Figure 1) would hardly affect the decision, because the combined doses from two inverse-optimized plans appear rather similar. The reviewer might then likely conclude that Plan A is superior, because it delivers a more uniform dose to the gross tumor volume (GTV), and a lower dose to the critical structure.

However, as Figure 3(a) shows, in a situation in which the proton's penetration in tissue is underestimated, the beams would overshoot the target. In such a case, the Plan A, which emphasizes the sparing of spinal cord with Bragg peak's distal penumbra by placing high-weighted peaks proximally to the cord, would deliver a higher dose to the critical structure. Another relevant consideration is that, when individual doses from IMPT fields are highly inhomogeneous, a range misestimation would also lead to a misalignment between the fields, and increased inhomogeneity of the target dose (e.g., the GTV DVH from Plan A in Figure 3(a)). Further, Figure 3(b) illustrates a potentially very significant reduction of the target coverage in a scenario of the range shortfall in delivery (i.e., overestimation of the range in planning). A noteworthy fact is that the loss of coverage here is due not only to the geographic miss caused by the range shortfall, but also to the increased inhomogeneity of the target dose caused by the field misalignment. Thus, increasing the margin expansions around the tumor would not completely resolve the loss of coverage. After considering the effect of uncertainties on the DVH in Figure 3, one may conclude that Plan B did yield a more robust solution with respect to the proton range uncertainty. Plan B was optimized with a robust probabilistic algorithm, which, compared to Plan A, produced relatively smaller inhomogeneities in doses from individual beams (see Figure 1), and avoided aiming high-weight pencil beams at the cord.

Although various outcome scenarios can be simulated, and the results presented to the decision-maker, analysis of the drastically increased amount of information for review may pose a significant challenge. In the time-constrained environment of the clinic, the sheer size of the additional body of information may possibly even discourage the reviewer from considering the uncertainties altogether. The example shown in Figure 4 summarizes in a compact and legible way all of the information presented in Figures 2 and 3, as well as additional information for the 5 mm range shifts. The difference between the widths of DVH bands for Plan A (Fig. 4(a)) and B (Fig. 4(b)) reflects the higher vulnerability of the former plan to the delivery uncertainties. With this information, not only can the reviewers compare different plans in terms of stability of the target coverage with the prescription dose, but also evaluate whether or not the hot spots of variance are located inside or near the critical structures (i.e., may cause large deviations in maximum dose) or in the target (where it may lead to high inhomogeneity or reduction in coverage).

The example discussed in this paper is from intensity-modulated proton therapy, thus the effect of uncertainties, especially in the estimates of radiological depth and range, is enhanced compared to X-ray based therapy. However, the general concept of DVH bands can be applied to a wide range of modalities of radiation and delivery techniques (including

3D-conformal proton therapy and IMRT), wherever the DVH are used and delivery uncertainties are present.

Visualization of the uncertainty of the outcome can potentially affect not only the selection of a plan for treatment, but also the plan reviewers' confidence in their decisions. Research in spatial data handling [24] indicated that the degree of such influence is affected by the choice of a technique by which the uncertainty is expressed. The techniques to represent uncertainties are generally divided into two categories: extrinsic and intrinsic. Extrinsic representation techniques add geometric objects, such as error bars, or confidence interval bands to represent uncertainty. Intrinsic techniques integrate uncertainty in the display by varying an object's appearance, e.g., brightness, shading, or transparency. (As an example: a darker DVH band in Figure 4 represents a variety of relatively more likely outcomes.) It has been reported that non-technical users are likely to find that intrinsic methods provide a more general visualization of uncertainty, compared to extrinsic representations [24]. The concept of DVH bands as uncertainty intervals, combined with the display of the confidence levels in the form of the color shading, as in Figure 4, combines both the extrinsic and intrinsic visualization techniques.

Various methods of illustrating the uncertainty of delivered dose have been previously used in the literature, including displays of dose distributions and DVH for individual error scenarios [10,16,18], worst-case distributions [17,19], and dose variance distributions [6,8,9]. However, at the moment, their relative utility remains unclear. Clinical evaluation will be needed to determine which of these methods would be the most useful in practice.

CONCLUSIONS

A comparison of DVH for the nominal planning conditions alone does not provide any information about the relative sensitivity of dose distributions to delivery uncertainties. Thus, such a comparison between different plans may be misleading, and result in the selection of an inferior plan for delivery to a patient, based on superficial characteristics of the nominal dose distribution. Evaluating the effect of uncertainties on the delivered dose distribution is an important part in the review of a clinical treatment plan. However, the large amount of information from various error scenarios presents a challenge for the reviewer. The concept of uncertainty visualization proposed and discussed in this paper is the DVH bands, representing a variety of likely dosimetric outcomes, according to their relative probabilities. This additional information in a compact and legible form may be helpful in making better-informed clinical decisions.

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REFERENCES

1. Shipley WU, Tepper JE, Prout GR Jr, et al. Proton radiation as boost therapy for localized prostatic carcinoma. JAMA. 1979; 241:1912–1915. [PubMed: 107338]
2. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991; 21:109–22. [PubMed: 2032882]
3. Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010; 76:S3–9. [PubMed: 20171515]

4. McCormick T, Dink D, Orcun S, et al. Target volume uncertainty and a method to visualize its effect on the target dose prescription. *Int J Radiat Oncol Biol Phys.* 2004; 60:1580–1588. [PubMed: 15590190]
5. Schaffner B, Pedroni E. The precision of proton range calculations in proton radiotherapy treatment planning: experimental verification of the relation between CT-HU and proton stopping power. *Phys Med Biol.* 1998; 43:1579–1592. [PubMed: 9651027]
6. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 1: the potential effects of calculational uncertainties. *Phys Med Biol.* 2008; 53:1027–1042. [PubMed: 18263956]
7. Engelsman M, Rietzel E, Kooy HM. Four-dimensional proton treatment planning for lung tumors. *Int J Radiat Oncol Biol Phys.* 2006; 64:1589–1595. [PubMed: 16580508]
8. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. *Phys Med Biol.* 2008; 53:1043–1056. [PubMed: 18263957]
9. Maleike D, Unkelbach J, Oelfke U. Simulation and visualization of dose uncertainties due to interfractional organ motion. *Phys Med Biol.* 2006; 51:2237–2252. [PubMed: 16625039]
10. Zhang X, Dong L, Lee AK, et al. Effect of anatomic motion on proton therapy dose distributions in prostate cancer treatment. *Int J Radiat Oncol Biol Phys.* 2007; 67:620–629. [PubMed: 17236979]
11. Mori S, Chen GT. Quantification and visualization of charged particle range variations. *Int J Radiat Oncol Biol Phys.* 2008; 72:268–277. [PubMed: 18722277]
12. Alber M, Meedt G, Nüsslin F, Reemtsen R. On the degeneracy of the IMRT optimization problem. *Med Phys.* 2002; 29:2584–2589. [PubMed: 12462725]
13. Hong TS, Craft DL, Carlsson F, Bortfeld TR. Multicriteria optimization in intensity-modulated radiation therapy treatment planning for locally advanced cancer of the pancreatic head. *Int J Radiat Oncol Biol Phys.* 2008; 72:1208–1214. [PubMed: 18954714]
14. Goitein M. Calculation of the uncertainty in the dose delivered during radiation therapy. *Med Phys.* 1985; 12:608–612. [PubMed: 4046996]
15. Unkelbach J, Chan TC, Bortfeld T. Accounting for range uncertainties in the optimization of intensity modulated proton therapy. *Phys Med Biol.* 2007; 52:2755–2773. [PubMed: 17473350]
16. Pflugfelder D, Wilkens JJ, Oelfke U. Worst case optimization: a method to account for uncertainties in the optimization of intensity modulated proton therapy. *Phys Med Biol.* 2008; 53:1689–1700. [PubMed: 18367797]
17. Unkelbach J, Martin BC, Soukup M, Bortfeld T. Reducing the sensitivity of IMPT treatment plans to setup errors and range uncertainties via probabilistic treatment planning. *Med Phys.* 2009; 36:149–163. [PubMed: 19235384]
18. Trofimov A, Bortfeld T. Optimization of beam parameters and treatment planning for intensity modulated proton therapy. *Technol Cancer Res Treat.* 2003; 2:437–444. [PubMed: 14529308]
19. Trofimov A, Nguyen PL, Efstathiou JA, et al. Interfractional variations in the setup of pelvic bony anatomy and soft tissue, and their implications on the delivery of proton therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2011; 80:928–937. [PubMed: 20947266]
20. Bussière MR, Adams AA. Treatment planning for conformal proton radiation therapy. *Technol Cans Res Treat.* 2003; 2:389–399.
21. Kooy HM, Clasio BM, Lu HM, et al. A case study in proton pencil-beam scanning delivery. *Int J Radiat Oncol Biol Phys.* 2010; 76:624–630. [PubMed: 20117294]
22. Albertini F, Hug EB, Lomax AJ. The influence of the optimization starting conditions on the robustness of intensity-modulated proton therapy plans. *Phys Med Biol.* 2010; 55:2863–2878. [PubMed: 20427853]
23. Lomax A. Intensity modulation methods for proton radiotherapy. *Phys Med Biol.* 1999; 44:185–205. [PubMed: 10071883]
24. Deitrick, S.; Edsall, R. The Influence of Uncertainty Visualization on Decision Making: An Empirical Evaluation.. In: Riedl, A.; Kainz, W.; Elmes, GA., editors. *Progress in Spatial Data Handling*. Springer; Berlin: 2006. p. 719-738.

Figure 1.

Dose distributions from intensity-modulated proton therapy plans which used conventional optimization (Plan A), and (b) probabilistic optimization (Plan B). For both plans, the total distributions are shown on the left, and doses delivered from three different beam directions are shown separately. The target volume is designated with a white contour, and organs at risk (parotid glands, spinal cord) are outlined in yellow.

Figure 2.

Dose volume histograms compared for two plans for *nominal* conditions: Plan A optimized using the conventional method, and Plan B obtained with probabilistic optimization.

Figure 3. Dose volume histograms compared between 2 plans, conventional Plan A and probabilistic Plan B, for scenarios in which *delivery deviated from the nominal plan*: (a) a scenario in which the actual range to target was underestimated by 3 mm (resulting in dose overshoot), and (b) for a scenario in which the actual range to target was overestimated by 3 mm.

Figure 4.

An illustration of the use of DVH-bands to visualize the envelope of dose-volume histograms from a variety of likely delivery scenarios for (a) the conventional plan A and (b) probabilistic plan B. Solid lines represent the DVH for the nominal conditions, and the shaded bands designate possible deviations from the planned DVH. The intensity of shading in the bands reflects the relative probability of the outcome, according to the assumed uncertainty model: the darker band corresponds to (more likely) delivery scenarios within 1 standard deviation (SD) from the nominal (e.g., 65% confidence interval (CI)), and the lighter band is for 1.7 SD (90% CI).