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Technical note

Robustness evaluation of Intensity Modulated Proton Therapy plans using Dose Volume Population Histogram

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ABSTRACT

Purpose: Under geometrical uncertainties, different plan evaluation methods have been suggested but the dose distribution at a specified confidence level being highly desirable is lacking. In this work, we used the DVPH (Dose Volume Population Histogram) tool to evaluate the dose distribution of CTVs and OARs (Organs at Risk) and validate the PTV concept at a certain confidence level.
Methods: The plans were evaluated using PTV DVH and the DVPH approach. The DVPH approach is based on statistical analyzing of multiple CTV DVHs under geometrical errors with corresponding occurring probabilities. The random and systematic geometrical errors, assumed to follow a Gaussian distribution, are simulated by shifting the CT images.
Results: For target doses, the results showed that the minimum dose to PTV does not represent the minimum dose to the CTV. For two prostate cases, the minimum doses reduced from 98% and 95% of prescribed dose from PTV DVH to 89% and 92% of prescribed dose from CTV 90% CL-DVPH (90% Confidence Level-DVPH). This reduction was also seen in head and neck cases, from 95% to 68% and 74% of prescribed dose. For OAR doses, OAR DVHs underestimated the OAR dose receiving.
Conclusions: With the DVPH tool, the results showed that the minimum dose to the PTV is not a representative of the minimum dose to the CTV in IMPT at the 90% confidence level. The OAR DVH does not match any OAR CL-DVPHs.

1. Introduction

A variety of strategies and tools, to ensure and evaluate the radiation treatment plans under uncertainties, have been developed. According to Report 50 of ICRU (International Commission on Radiation Units and Measurements) [1] for photon therapy, PTV (Planning Target Volume) is the geometric volume defined to design the beams and evaluate the treatment plans. The CTV-PTV (Clinical Target Volume-Planning Target Volume) margin ensures the prescribed dose delivered to CTV whilst considering all errors occurring on the treatment day.

Based on the shift invariance assumption, a formula for CTV-PTV margin based on the systematic and random errors was suggested by Stroom et al. [2] and van Herk et al. [3] for photon therapy, Thomas [4] for proton therapy. By considering set up errors along three anatomical axes of the body for head and neck (H&N) cases, Lomax [5] concluded that a simple PTV margin might not be used to account for errors. Different plan evaluation methods using different approaches have been proposed in the past. By assessing some extreme cases, Albertini et al. [6] proposed to use the concept of the 'error bar dose distribution' to assess the planned dose distribution. By statistical approach, Henríquez et al. [7] and then Park et al. [8] suggested that it could use the expected DVH and its standard deviation for plan evaluation.

In our work, we used the Dose Volume Population Histogram tool, abbreviated as DVPH tool, suggested by Nguyen et al. [9] to assess the dose distribution of tumors and organs at risk whilst considering geometrical uncertainties. This tool bases on the direct dose calculations of multiple positions of CTV assuming a Gaussian function for error distribution as proposed by Park et al. [8]. DVPH tool involves two useful parameters in evaluating treatment plans such as DVPH and CL-DVPH. DVPH displays the occurring probability of each dose-volume point, while CL-DVPH displays the DVH at a confidence level selected by users.

2. Materials and methods

2.1. Patients and treatment planning system

For two prostate cases, the prescribed dose is 74 Gy to the ICRU Reference point. The PTV receives doses within −5 and +7 percent of

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Table 1
The dose volume constraints for OARs for rectum and bladder in prostate cases and spinal cord and brainstem in head and neck cases.

	Volume (%)	Dose (Gy)	Maximum dose (Gy)	Reference
Brainstem	< 1	60	54	RTOG 0225
Spinal cord			45	RTOG 0623
Rectum	< 15	75		RTOG 0126
	< 25	70		
	< 35	65		
	< 50	60		
Bladder	< 15	80		RTOG 0126
	< 25	75		
	< 35	70		
	< 50	65		

Table 2
The volume of the CTV receiving doses more than 95% of prescribed dose and the minimum dose to the PTV calculated from PTV DVH and CTV 90% CL-DVPH of two prostate cases.

Cases	PTV From PTV DVH		CTV From CTV 90% CL-DVPH	
	$V_{95\%}$(%)	Dmin(%)	$V_{95\%}$(%)	Dmin(%)
Prostate case 1	100	98	99	89
Prostate case 2	100	95	99	92

the prescribed dose. Dose-volume constraints of rectum and bladder were taken from RTOG 0126 [10] (see Table 1). For two head and neck cases, the prescribed dose is 60 Gy to the ICRU Reference point. The PTV receives doses within −5 and +7 percent of the prescribed dose. The dose constraints of spinal cord and brainstem were taken from the RTOG 0225 [11] and RTOG 0623 [12] (see Table 1).

The beam delivery technique for four cases is spot scanning technique. Proton energies that could be used ranged from 70 MeV to 250 MeV. The range shifter is the last element before the patient with the step of 0.1 cm and could be up to 5 cm. The prostate case 1 used two oblique beam directions with the gantry angles of 70 degrees and −70 degrees. The three remaining cases used two opposed proton beams with the gantry angles of 90 degrees and 270 degrees.

The CTV-PTV margin was computed based on the systematic and random errors using the following formula $2.5\Sigma + a + b + \beta((\sigma^2 + \sigma_p^2)^{0.5} - \sigma_p)$ for all cases [4]. Corrections for planning algorithm error a and for breathing b are equal to zero. The value σ_p = 6 mm and β = 1.6 mm were also referred from Thomas [4]. In this work, $\Sigma = \sigma$ = 4 mm was chosen to model the systematic and random errors for prostate and H&N cases which were consistent to how the DVPH was calculated [9]. As a sequence, with the chosen values of parameters, the isotropic CTV-PTV margins for prostate cases and H&N cases are both 12 mm.

The treatment planning system used in this study is LAP (an abbreviation of Laser Accelerated Proton Beam) [13], an extension for the Computational Environment for Radiotherapy Research (CERR) [14]. The dose calculation algorithm is proton pencil beam algorithm [15] accounting for the effects of heterogeneity. The dose at each voxel is simulated with the help of lookup tables with data obtained from Monte Carlo simulation for the depth dose curve and the lateral spread [16].

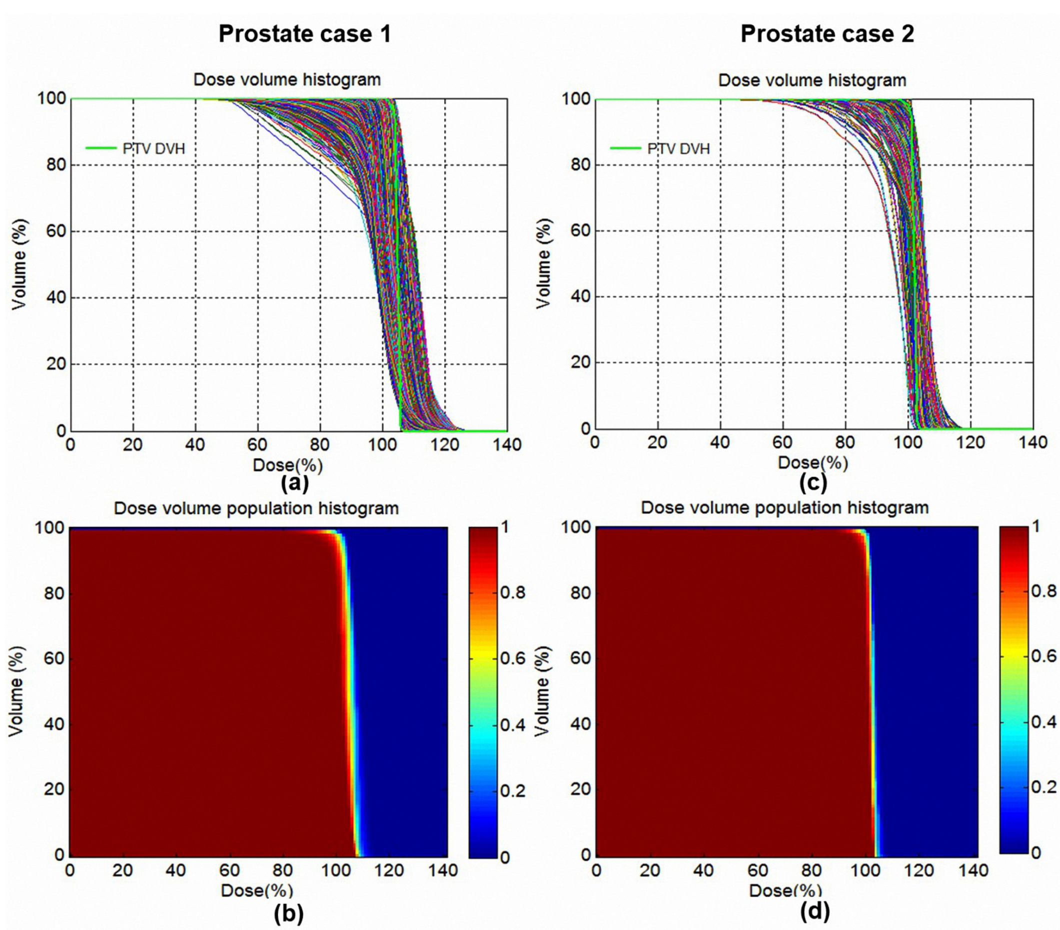

Fig. 1. The 2197 CTV DVHs and CTV DVPH of prostate case 1 (a,b) and prostate case 2 (c,d).

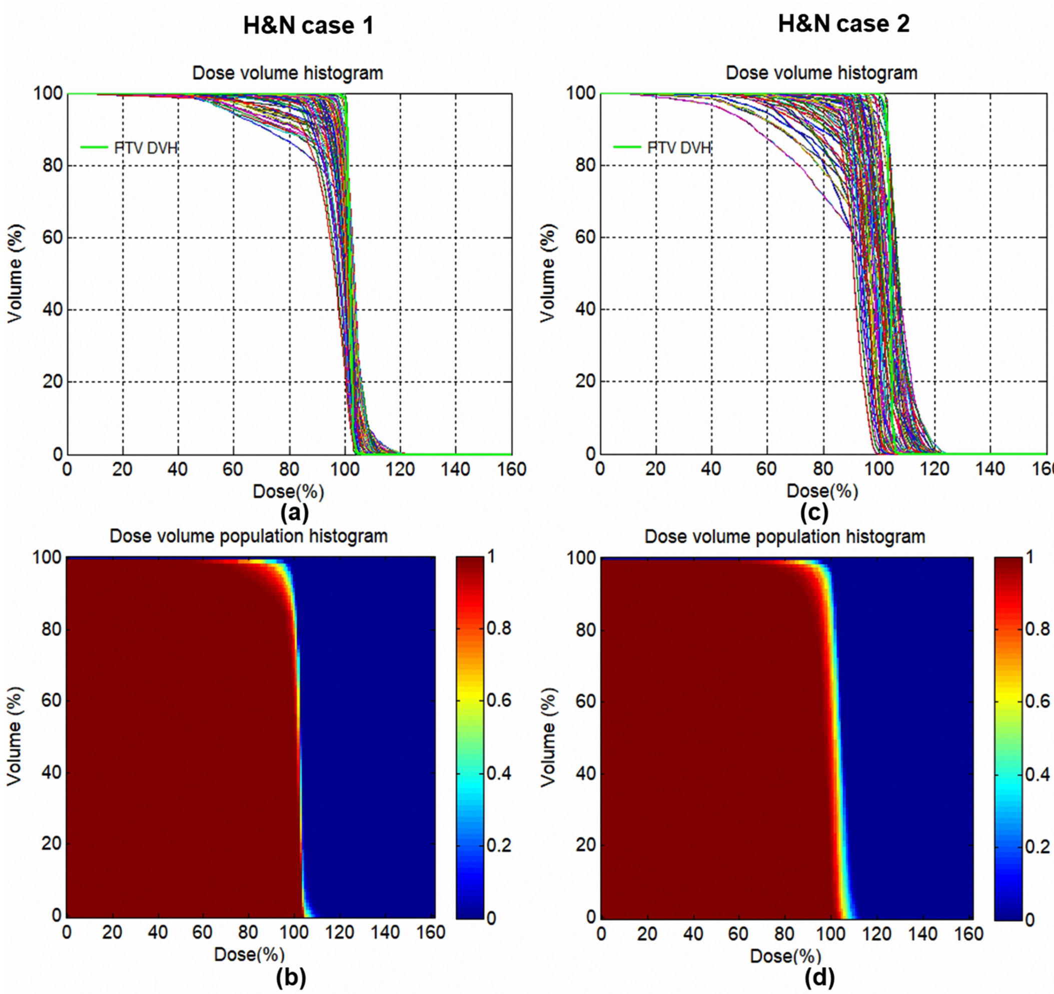

Fig. 2. The 2197 CTV DVHs and CTV DVPH of H&N case 1 (a,b) and H&N case 2 (c,d).

Table 3
The volume of the CTV receiving doses more than 95% of prescribed dose and the minimum dose to the PTV calculated from PTV DVH and CTV 90% CL-DVPH of two H&N cases.

Cases	PTV From PTV DVH		CTV From CTV 90% CL-DVPH	
	$V_{95\%}$(%)	Dmin(%)	$V_{95\%}$(%)	Dmin(%)
H&N case 1	100	95	89	68
H&N case 2	100	95	84	74

For heterogeneity correction, the radiological depth is used instead of the actual depth of each voxel. For the optimization, the Newton method with diagonal Hessian approximation was used to minimize the quadratic deviation of the actual doses from the prescribed doses in all voxels.

2.2. Modeling systematic and random errors

Dose distributions for different systematic and random errors were calculated by recalculating the planned dose distribution in a number of spatially shifted versions of the patient's CT. We used the grid-based method that can deal with both systematic and random errors with assumption that the probability density function (PDF) follows a Gaussian distribution. The mean of zero and the standard deviation of 4 mm for both systematic and random errors [4,9] were used. Each shift in the grid is given a probability derived from its PDF. For 99.7% of the population (i.e. 3 standard deviations), along each axis, the maximum error is 12 mm and the minimum error is −12 mm. With the step of the grid is 2 mm, there are 13 shifts along each axis, so there are total $13 \times 13 \times 13 = 2197$ shifted dose distributions. The cumulative dose distribution at each systematic error considering the effect of random errors was calculated using the same method as presented by Nguyen et al. [9] and described briefly here. At each systematic error s, due to the condition $-12\,\text{mm} \le s + r \le 12\,\text{mm}$, there is a set of values N_r, usually smaller than 2197, of random errors. Thus, at each systematic error s, there are N_r dose distribution with N_r corresponding random probabilities. Summing doses at each voxel weighted by the random probabilities of N_r dose distribution results in the dose distribution at each systematic error. Each dose distribution at each systematic error has a certain probability. There are 2197 systematic errors so there are 2197 dose distributions corresponding to 2197 probabilities. These 2197 dose distributions would be converted to 2197 cumulative DVHs corresponding to 2197 probabilities which were analyzed by DVPH and CL-DVPH.

2.3. The dose-volume population histogram concept for plan evaluation

When evaluating the DVH, planners normally use dose volume constraints such as 'the fractional volume receiving a dose greater than D_i% of the prescribed dose is more than V_j%' for the target or 'the fractional volume receiving a dose greater than D_i% of the prescribed dose is less than V_j%' for OARs. DVPH suggested by Nguyen et al. [9] is the probability of these constraints, i.e. P(V(Di) > Vj) for the CTV or P

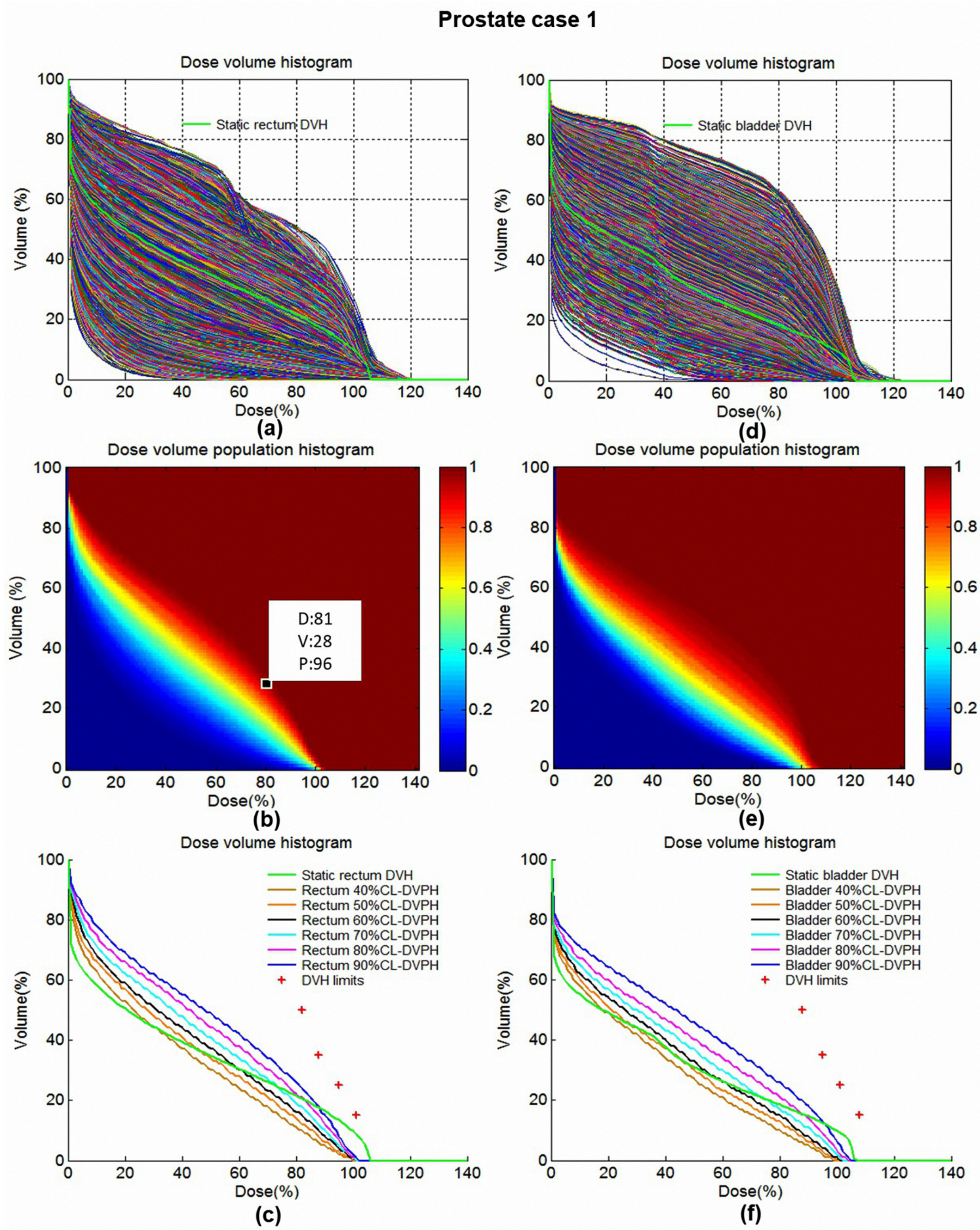

Fig. 3. The 2197 DVHs, DVPH and CL-DVPH of the rectum (a,b,c) and bladder (d,e,f) for the prostate case 1. The results from the prostate case 2 are similar.

(V(Di) < Vj) for OAR respectively, for each dose volume point (Di, Vj). Moreover, the graph of probability of P(V(Di) > Vj) = C or P(V(Di) < Vj) = C with C is a constant for the CTV and OAR correspondingly used to display the DVPH with a specified confidence level, abbreviated as CL-DVPH. This tool allows planners and clinicians to assess the plan quality with a certain confident level, for both the CTVs and OARs.

3. Results

3.1. Robustness of the target volume: effect of planning with safety margins

3.1.1. Prostate cases

The Fig. 1a and c showed the distributions of 2197 CTV DVHs of prostate case 1 and prostate case 2 respectively. The CTV DVHs deviates from the PTV DVH, especially in the low dose region. From the 2197 CTV DVHs, the maximum dose varies from 107% to 128% of the prescribed dose for the prostate case 1 and from 103% to 119% of the prescribed dose for the prostate case 2. The minimum dose varies from 33% to 106% of the prescribed dose for prostate case 1 and from 37% to 102% of the prescribed dose for prostate case 2. These results showed that the plans based on the PTV concept are sensitive to geometrical errors and can vary a lot under geometrical uncertainties.

From the 2197 CTV DVHs, the DVPH was calculated by taking into account of the probability distribution of both systematic and random errors. Fig. 1b and 1d showed the CTV DVPH of two prostate cases. DVPH has one upper boundary with the probability of zero and one lower boundary with probability of 1. The former means that none of the simulated CTV DVHs could be better than the upper boundary. Similarly, the later means, all dose-volume points could be better than the

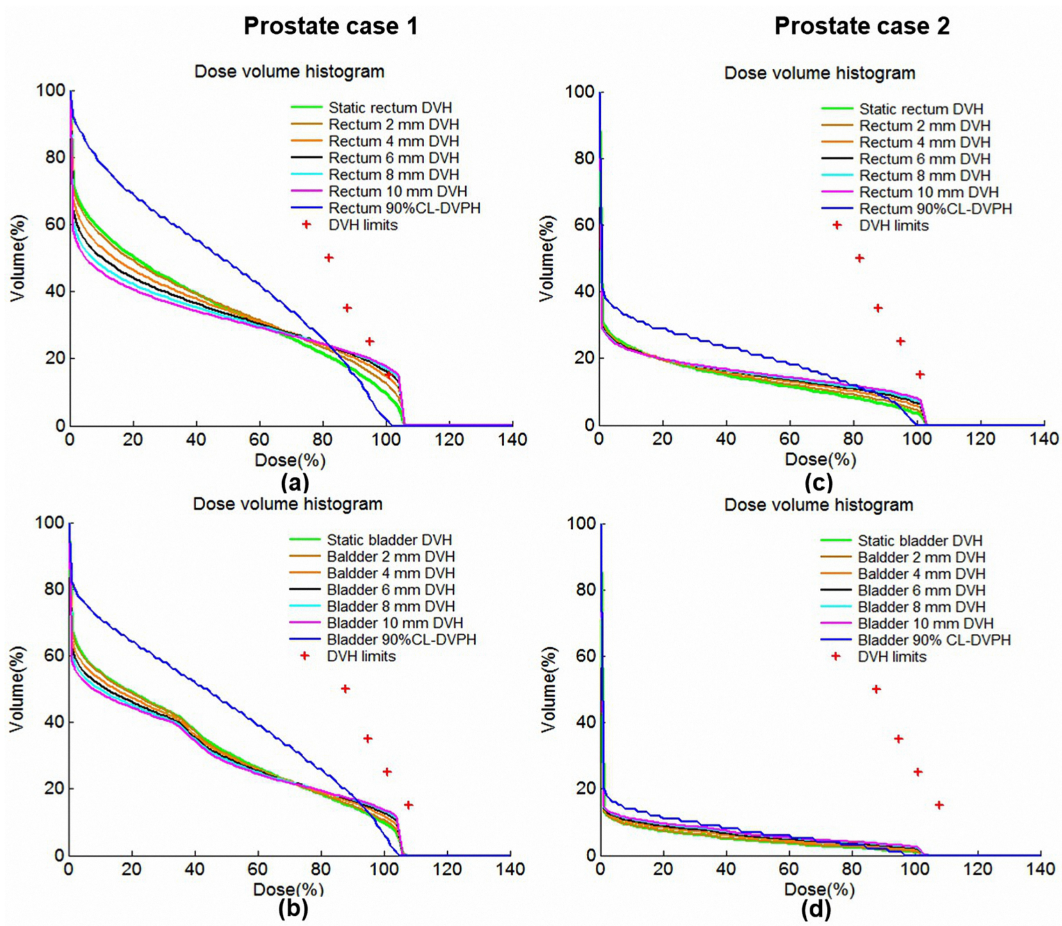

Fig. 4. The rectum & bladder DVHs different margins and the 90% CL-DVPH of prostate case 1 (a,b) and prostate case 2 (c,d).

lower boundary. Thus, dose-volume point might happen in the range from the lower boundary curve to the upper boundary curve. The higher the confidence level, the closer dose volume points (confident level DVPH) is to the lower boundary curve.

To assess the validation of the PTV concept based on the formula suggested by Thomas [4], we made a comparison between the minimum dose to CTV from CTV 90% CL-DVPH and the minimum dose to the PTV from PTV DVH (see Table 2). The minimum doses to the PTV are 98% and 95% of the prescribed dose in comparison to 89% and 92% from CTV DVPH with a 90% confidence level for prostate case 1 and prostate case 2 respectively. In this case, the plan might be accepted if planners use the minimum dose to the PTV criteria. However, the dose to CTV with 90% confidence level might not be accepted with geometrical uncertainties because the plan might result in underdosage to the target. The minimum dose to the PTV does not represent the minimum dose to the CTV at a 90% confidence level.

3.1.2. Head and neck cases

The Fig. 2a and b showed the distribution of 2197 DVHs and the CTV DVPH of H&N case 1. The Fig. 2c and d showed the distribution of 2197 CTV DVHs and the CTV DVPH of H&N case 2. From the PTV DVH, for two H&N cases, the minimum doses to the PTV are both 95% of the prescribed dose (see Table 3). When evaluating using the CTV 90% CL-DVPH, the minimum dose to the CTV are 68% and 74% of the prescribed dose for H&N case 1 and case 2 respectively. An acceptable minimum dose to the PTV does not ensure a good minimum dose to the CTV when considering geometrical uncertainties during the treatment for both cases.

Table 3 showed the comparison of the target coverage of the 95% of the prescribed dose based on two methods of evaluation: From the PTV DVH and CTV 90% CL-DVPH. While the PTV DVH showed an acceptable target coverage (100% for both cases), the CTV 90% CL-DVPH showed an inadequate dose coverage of the CTV (89% and 84% for prostate case 1 and prostate case 2 respectively). The PTV DVH overestimated the dose receiving by the target in the H&N cases by a larger margin than in the prostate cases. This can be observed by looking at 2197 CTV DVHs from both cases. In the H&N cases, the min doses of CTVs were more extended to the low dose region than in the prostate cases. This might due to the fact that the heterogeneity effects are more in a head & neck area than in a prostate area.

3.2. Oars analysis

In OARs analysis, we evaluated the validation of the use of OAR DVH and PRV DVH for assessing the dose to OARs using the OAR 90% CL-DVPH; for instance, the maximum dose for serial structures or dose volume features for the parallel structures. When optimizing the treatment plans based on the PTV concept, we have not added OAR-PRV margin for all OARs for all cases.

3.2.1. Organs with parallel architecture: the rectum and bladder

The parallel architecture organs were investigated including the rectum and bladder of prostate case 1 and case 2. Fig. 3 showed the DVH distribution of 2197 shifts, the DVPH and CL-DVPH of the rectum and bladder for the prostate case 1. From Fig. 3b, the point (81, 28, 96) on DVPH shows that V81% = 28% for 96% of patient population. Compared to the plan requirements V60Gy (V81%) < 50%, the plan is acceptable. Other rectum dose-volume constraints are not violated because V75Gy, V70Gy and V65Gy from rectum 90% CL-DVPH are all lower than the dose volume limits for both cases. Similarly, the

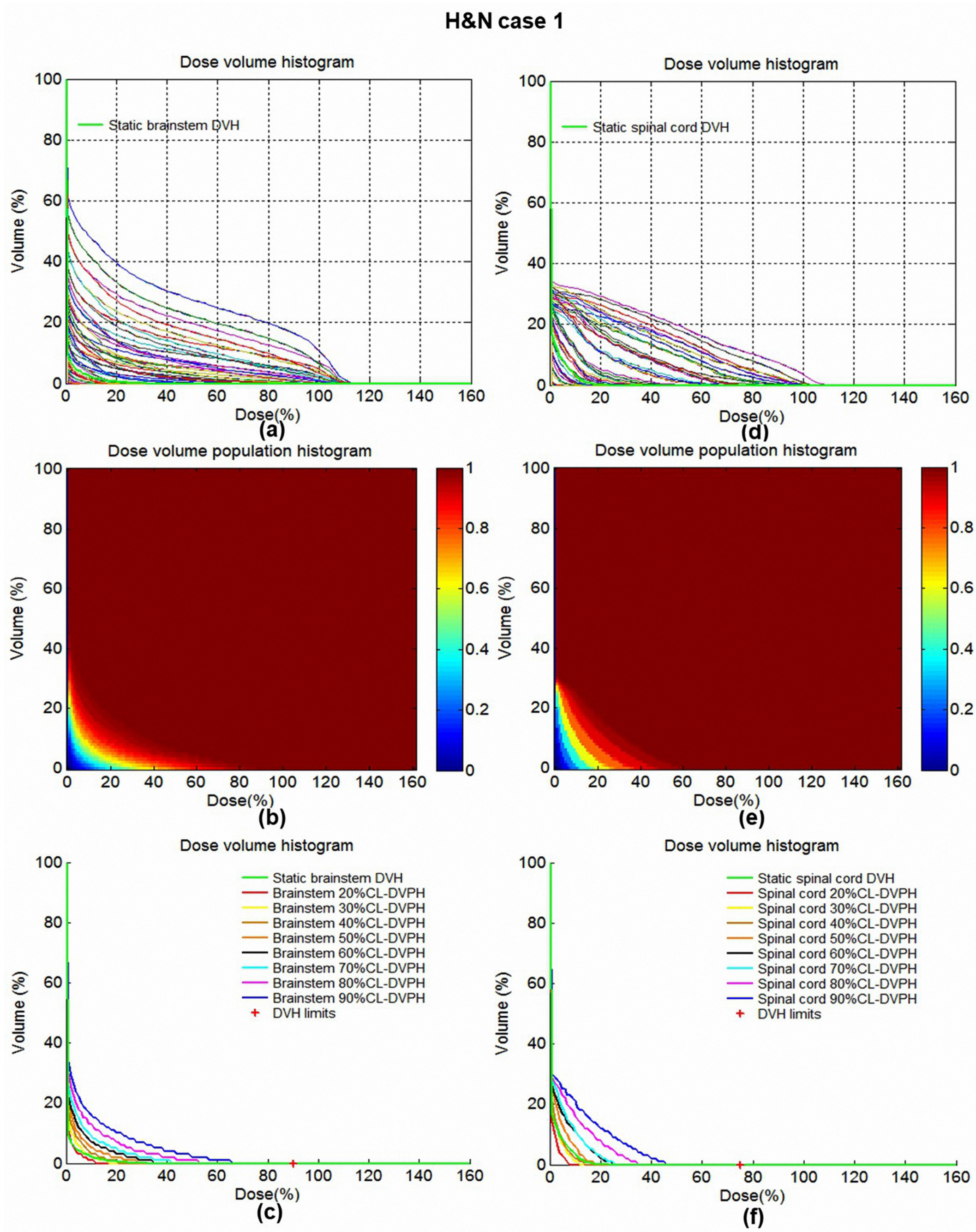

Fig. 5. The 2197 DVHs, DVPH and CL-DVPH of the brainstem (a,b,c) and spinal cord (d, e, f) for the H&N case 1. The results from the H&N case 2 are similar.

treatment plan based on the static bladder DVH does not violate the dose-volume constraints because V80Gy, V75Gy, V70Gy and V65Gy from OAR 90% CL-DVPH is lower than V80Gy, V75Gy, V70Gy and V65Gy limits for both cases.

In order to validate the use of the static rectum & bladder DVHs in plan evaluation, we compared the static rectum & bladder DVHs with the rectum & bladder 90% CL-DVPH. From Fig. 3c, f the static rectum & bladder DVH does not match the OAR CL-DVPH at any certain confidence level. Therefore, using the static rectum & bladder DVH does not reflect the real dose that the static rectum & bladder receiving while geometrical uncertainties occur. In this case, the dose to the rectum and bladder is underestimated for the low dose area and overestimated for the high dose area.

To evaluate the use of OAR-PRV margins for plan evaluation purpose, we compared the PRV DVH with different margins from 2 mm to 10 mm with OAR 90% CL-DVPH of rectum (see Fig. 4). It showed that no PRV DVH can be used to represent the OAR 90% CL-DVPH of the rectum or bladder (see Fig. 5).

3.2.2. Organs with serial architecture: the brainstem and spinal cord

The serial architecture-organs were investigated including the brainstem and the spinal cord of H&N case 1 and case 2. The simulated DVH distribution of brainstem and spinal cord of H&N case 1 varies in the wide ranges for both doses and volumes (see Fig. 4.a and d). The OAR DVPH of brainstem and spinal cord of H&N case 1 was displayed on Fig. 4b and e.

Using the static brainstem DVH (no margin added), the maximum doses are 19.5 Gy and 37.5 Gy for H&N case 1 and case 2 respectively (see Table 4). From the OAR 90% CL-DVPH, these values are 39.6 Gy and 43.8 Gy. The static brainstem DVH underestimates the maximum dose.

Table 4
The maximum dose to the brainstem and spinal cord calculated using different OAR-PRV margins and using OAR 90% CL-DVPH for both H&N cases.

OARs	Cases	The maximum dose (Gy)						
		PRV margin (mm)						90% CL-DVPH
		0	2	4	6	8	10	
Brainstem	H&N case 1	19.5	31.5	46.5	55.5	61.5	61.5	39.6
	H&N case 2	37.5	52.5	61.5	64.5	64.5	64.5	43.8
Spinal cord	H&N case 1	13.5	22.5	28.5	43.5	55.5	61.5	27.6
	H&N case 2	13.5	22.5	40.5	49.5	61.5	64.5	30.6

However, the dose constraint is not violated because of the maximum dose to the brainstem could be 54 Gy, more than the maximum dose from OAR 90% CL-DVPH. For both H&N cases, the maximum dose is 13.5 Gy from the static spinal cord DVHs (without OAR-PRV margin) compared to 27.6 Gy and 30.6 Gy for 90% of the patients from OAR CL-DVPH of the spinal cord. However, two plans are still acceptable because the maximum dose to the spinal cord could be up to 45 Gy.

Moreover, the OAR CL-DVPH could be used to select the appropriate OAR-PRV margin for serial organs. The minimum margins could be added to the brainstem are 4 mm and 2 mm for H&N case 1 and case 2 correspondingly. The minimum margin might be added to the spinal cord is 4 mm for both H&N cases (see Table 4).

4. Discussion

With a statistical method taking into account of both systematic and random errors, DVPH tool has been showed to help planners understand the results more accurately than other methods with the built-in confidence level display, CL-DVPH. Moreover, the simple and effective uses of DVPH are seen when assessing the dose to both targets and organs at risks.

In evaluating the dose to the target, we assumed that the PTV is a representative of the CTV with a 90% confidence level. Since the PTV concept is no longer valid for proton therapy as demonstrated in the study and all previous studies [5–8], what we really need is a method to evaluate the DVH with different confidence levels for all patient geometrical uncertainty distribution not for only some extreme cases. It has been demonstrated in this study that DVPH with CL-DVPH curves is the most sophisticated tool, as suggestion of Lomax [5], allowing planners and clinicians look inside the treatment plan when errors occur at the confidence level as expected.

The DVPH indicates that the PTV might not be used to assess the minimum dose to the CTV in IMPT plans for all four cases studied. The use of a safety margin is still useful to achieve the target coverage for prostate cases, but it is not necessary for head and neck cases due to the heterogeneity density which affects the Bragg peak positions. These results confirmed that the PTV DVH cannot be used reliably for plan evaluation for case where changes in electron density around the targets such as head and neck cases. For the case where changes in electron density is small enough such as prostate cases, the PTV might be used in accessing the dose coverage of CTV.

For parallel organs at risk, the use of OAR DVPH showed that the dose to organ from static OAR DVH is not representative of the dose from DVPH for 90% of the patient population. This is important for close cases where the dose volume point is near the limit. An acceptable plan with static OAR DVH might result in an unacceptable plan with geometrical uncertainties.

The similar results are obtained for serial organs at risk. Besides, planners can use OAR CL-DVPH to estimate the appropriate OAR-PRV margin basing on the comparison between the maximum dose to OAR at different confidence levels and from different OAR-PRV margins, presented as above. Then, the maximum dose to PRV has the appropriate confidence level, more than 90%, resulting in limiting the high dose to the serial organs. However, as it was shown above, the correct margin is not the same for all cases which implied that there is no one OAR-PRV margin recipe which can fit all cases. This is expected because the correct margin is also depending on the dose distribution as well as electron density surrounding the OARs. Using DVPH, especially with 90% CL-DVPH, planners could overcome the need for an OAR-PRV margin and have a tool to better estimate the real dose to the OARs while considering geometrical uncertainties.

Although, our work only considered the systematic and random errors assumed to be Gaussian distributions, making the patient shift relatively to the beams as a whole, any errors and their PDF can be incorporated into the DVPH tool to assess the influence of them on the dose distribution. The bottle neck of using DVPH method is the time it takes to calculate 2197 plans. We used the proton pencil algorithm to calculate the DVPH due to the calculation time [17–19]. However, the more accurate dose calculation algorithm such as Monte Carlo might also be used [20,21]. With the modern calculation using GPU it has been demonstrated that it will take 8 min to calculate 2197 dose distributions using the proton pencil beam algorithm [19]. Thus, the use of DVPH becomes more of a clinical reality as a secondary check to make sure an accepted plan is still acceptable while considering geometrical uncertainties. DVPHs can be calculated in the interval between the time where planners finished plans and physicians performed a final plan review.

In this work, the DVPH is calculated based on a rigid body translational shift, ignoring organ deformation and rotation. For head and neck cases, it has been shown that the target shape and size changes are negligible [22]. For prostate cases, the deformation of the prostate and seminal vesicles is shown to be relatively small compared to organ motion during the course of radiotherapy [23]. However, the above assumption is only valid for the bladder/rectum when a strict emptying protocol is applied [24]. Nevertheless, the DVPH method can be extended to take into account any type of errors. For example, the rectal volume change model suggested by Hoogeman et al. [25] or Price and Moore [26] might be used in the calculation of the rectal DVPH which is a subject for future work.

5. Conclusions

We introduced the prospective of using DVPH tool to present and assess the dose distribution of both targets and organs at risk under the influence of geometrical uncertainties with Intensity Modulated Proton Therapy technique. The results showed that the minimum dose of PTV is not representative of the minimum dose of CTV for both prostate and head and neck cases. For organs at risk volumes, the static OAR DVH underestimates receiving dose when evaluating using dose-volume limits. The DVPH is recommended to be used as a secondary evaluation tool to make sure plans are acceptable under geometrical uncertainties.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2019.09.070.

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