PTV-based IMPT optimization incorporating planning risk volumes vs robust optimization

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Purpose: Robust optimization leads to intensity-modulated proton therapy (IMPT) plans that are less sensitive to uncertainties and superior in terms of organs-at-risk (OARs) sparing, target dose coverage, and homogeneity compared to planning target volume (PTV)-based optimized plans. Robust optimization incorporates setup and range uncertainties, which implicitly adds margins to both targets and OARs and is also able to compensate for perturbations in dose distributions within targets and OARs caused by uncertainties. In contrast, the traditional PTV-based optimization considers only setup uncertainties and adds a margin only to targets but no margins to the OARs. It also ignores range uncertainty. The purpose of this work is to determine if robustly optimized plans are superior to PTV-based plans simply because the latter do not assign margins to OARs during optimization.

Methods: The authors retrospectively selected from their institutional database five patients with head and neck (H&N) cancer and one with prostate cancer for this analysis. Using their original images and prescriptions, the authors created new IMPT plans using three methods: PTV-based optimization, optimization based on the PTV and planning risk volumes (PRVs) (i.e., “PTV+PRV-based optimization”), and robust optimization using the “worst-case” dose distribution. The PRVs were generated by uniformly expanding OARs by 3 mm for the H&N cases and 5 mm for the prostate case. The dose-volume histograms (DVHs) from the worst-case dose distributions were used to assess and compare plan quality. Families of DVHs for each uncertainty for all structures of interest were plotted along with the nominal DVHs. The width of the “bands” of DVHs was used to quantify the plan sensitivity to uncertainty.

Results: Compared with conventional PTV-based and PTV+PRV-based planning, robust optimization led to a smaller bandwidth for the targets in the face of uncertainties {clinical target volume [CTV] bandwidth: 0.59 [robust], 3.53 [PTV+PRV], and 3.53 [PTV] Gy (RBE)}. It also resulted in higher doses to 95% of the CTV { $D_{95\%}$: 60.8 [robust] vs 59.3 [PTV+PRV] vs 59.6 [PTV] Gy (RBE)}, smaller $D_{5\%}$ (doses to 5% of the CTV) minus $D_{95\%}$ { $D_{5\%} - D_{95\%}$: 13.2 [robust] vs 17.5 [PTV+PRV] vs 17.2 [PTV] Gy (RBE)}. At the same time, the robust optimization method irradiated OARs less {maximum dose to 1 cm³ of the brainstem: 48.3 [robust] vs 48.8 [PTV+PRV] vs 51.2 [PTV] Gy (RBE); mean dose to the oral cavity: 22.3 [robust] vs 22.9 [PTV+PRV] vs 26.1 [PTV] Gy (RBE); maximum dose to 1% of the normal brain: 66.0 [robust] vs 68.0 [PTV+PRV] vs 69.3 [PTV] Gy (RBE)}.

Conclusions: For H&N cases studied, OAR sparing in PTV+PRV-based optimization was inferior compared to robust optimization but was superior compared to PTV-based optimization; however, target dose robustness and homogeneity were comparable in the PTV+PRV-based and PTV-based optimizations. The same pattern held for the prostate case. The authors' data suggest that the superiority of robust optimization is not due simply to its inclusion of margins for OARs, but that this is due mainly to the ability of robust optimization to compensate for perturbations in dose distributions within target volumes and normal tissues caused by uncertainties. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4774363>]

Key words: robust optimization, IMPT, planning risk volume, robustness evaluation

I. INTRODUCTION

Intensity-modulated proton therapy (IMPT) has a great potential to deliver highly conformal tumoricidal dose to targets while minimizing dose to nearby organs-at-risk (OARs). Multifield optimized (MFO) IMPT is commonly thought to produce the best IMPT plans. In this technique, intensity distributions of spots from all beams are simultaneously optimized to balance target coverage with normal tissue doses and to balance normal tissue doses among themselves. However, the dose distributions of MFO IMPT are particularly sensitive to setup and range uncertainties.^{1,2} Consequently, the effectiveness of IMPT may be significantly degraded.^{3–5}

Current practice in IMPT optimization is to create a margin around the clinical target volume (CTV) to build a traditional planning target volume (PTV).⁶ In doing so, it is implicitly assumed that anatomic variations have a negligible impact on the dose distribution in space.⁷ It is becoming increasingly clear that the resulting dose distribution based on PTV for IMPT is not robust; i.e., the dose distribution actually delivered may be quite different from what is planned.³

There are several published reports on robust optimization,^{7–12} which traces its ancestry back to McShan *et al.*¹³ Our group has also developed robust optimization methodology. Our method takes uncertainties into account during plan optimization via the concept of so-called “worst-case dose distributions.”^{14,15} The uncertainties are modeled in our algorithm as follows. For setup uncertainties, the isocenter of the patient (therefore, both the target and the OARs) is rigidly shifted in the anterior-posterior (A-P), superior-inferior (S-I), and lateral (R-L) directions, yielding six dose distributions and corresponding influence matrixes. For range uncertainties, stopping power ratios are modified by -3.5% and 3.5% to generate two additional influence matrixes corresponding to maximum and minimum proton ranges, respectively. The worst-case dose distribution is then represented by the minimum of the nine doses in each voxel in the CTV and the maximum of the nine doses in each voxel outside the CTV. Our definition of “worst-case” dose distribution is identical to that of Lomax *et al.*⁵ We have found that worst-case robust optimization leads to IMPT plans that are more robust than and superior in optimality to PTV-based optimized plans.^{14,15}

The worst-case robust optimization incorporates setup and range uncertainties, which implicitly adds margins to both the target volume and the OARs; PTV-based optimization, on the other hand, considers only setup uncertainties and adds margins only to the target volume. It might be argued that the improved sparing of OARs from robust optimization may be due to its algorithms’ implicit consideration of setup uncertainty for both OARs and targets. (It should be noted that, additionally, robust optimization is able to compensate for perturbations in dose distributions within target volumes and normal tissues caused by uncertainties, especially for beams passing through complex heterogeneities.)

For photon therapy, International Commission on Radiation Units and Measurements Report 62 suggests that margins be drawn around OARs on planning CT images

to produce planning risk volumes (PRVs); the PRVs, thus, account for geometric uncertainty in the radiation treatment process.¹⁶ Frequently, in the current practice of IMRT and IMPT, OAR margins are omitted.

The purpose of this work is to determine if robustly optimized plans are superior (i.e., it leads to greater sparing of normal structures) compared to those created by PTV-based optimization specifically because the latter does not assign margins to OARs. We tested this idea by comparing the dose distributions and adherence to dose constraints among plans created by robust optimization, PTV+PRV-based conventional optimization, and PTV-based conventional optimization.

II. METHODS AND MATERIALS

II.A. Patient data and beam configurations

We evaluated the relative performance of the optimization algorithms by creating treatment plans for five patients with head and neck (H&N) cancer and one patient with prostate rhabdomyosarcoma who had previously undergone IMPT on a prospective institutional review board-approved protocol at our institution. In all cases, three fields were employed. The prescription doses, target volumes, and beam angles used are listed in Table I. For each patient, three methods of optimization (“worst-case” robust optimization, PTV-based optimization, and PTV+PRV-based optimization) were used to account for setup and range uncertainties. All plans were optimized using the same dose constraints, the same penalties, and the same initial conditions. Setup uncertainties of ± 3 mm for the H&N cases and ± 5 mm for the prostate case and range uncertainty of $\pm 3.5\%$ of the beams’ nominal ranges were assumed in robust optimization. In the conventional optimizations PRVs and PTVs were formed by isotropic expansion of a 3 mm margin for the H&N cases and a 5 mm margin for the prostate case to account for setup uncertainty for the OARs and targets, respectively. The dose grid resolution for all cases was 2.5 mm. The spot arrangements were the same for all three optimization methods (Table II): for all, a margin for “penumbra” was added to allow for the lateral fall-off of dose. The CTV-to-PTV and OAR-to-PRV margins were only for setup uncertainties for PTV- and PTV+PRV-based optimization.

At our institution, the dose-volume constraints H&N irradiations are as follows: for the brainstem, the maximum dose is no greater than 54 Gy (RBE); for the spinal cord, the maximum dose is no greater than 45 Gy (RBE); for the brain, the maximum dose is no greater than 50 Gy (RBE); for the parotids, the mean dose is no greater than 26 Gy (RBE); and for the oral cavity, the mean dose is no greater than 35 Gy (RBE). Similarly, the dose-volume constraints in prostate irradiations are as follows: for the rectum, the volume receiving a dose of 70 Gy (RBE) (denoted by V_{70}) is no greater than 25%; for the bladder, the volumes receiving doses of 65 Gy (RBE) (V_{65}) and 40 Gy (RBE) (V_{40}) are no greater than 25% and 50%, respectively; and for the femoral heads, the volume receiving a dose of 50 Gy (RBE) (V_{50}) is no greater than 10%.

TABLE I. Patient prescriptions, target volumes, and beam angles.

Patient	Number of fractions	Prescriptions (Gy)		Target volumes (cm ³)		Beam angles (gantry, couch)		
		GTV	CTV	GTV	CTV	Field 1	Field 2	Field 3
1	33		66		16.8	245 ⁰ ,0 ⁰	285 ⁰ ,40 ⁰	100 ⁰ ,0 ⁰
2	35	70	66	10.7	45.8	60 ⁰ ,0 ⁰	290 ⁰ ,0 ⁰	320 ⁰ ,0 ⁰
3	30	66	66	3.0	179.1	180 ⁰ ,90 ⁰	310 ⁰ ,30 ⁰	70 ⁰ ,340 ⁰
4	33	70	70	5.2	20.12	290 ⁰ ,20 ⁰	70 ⁰ ,340 ⁰	285 ⁰ ,90 ⁰
5	37	74	74	5.5	20.9	300 ⁰ ,90 ⁰	270 ⁰ ,0 ⁰	75 ⁰ ,0 ⁰
6 ^a	28	50.4	50.4	9.6	42.3	315 ⁰ ,45 ⁰	45 ⁰ ,315 ⁰	180 ⁰ ,0 ⁰

^aProstate case.

II.B. Optimization algorithms

For robust optimization, we compute the objective function value for a given iteration using the worst case dose distribution.^{5,15} We have enhanced the worst-case robust optimization approach proposed by Pflugfelder *et al.*⁸ by modifying the objective function to penalize hot spots within the target.

Our approach to design and compare robustly and conventionally optimized plans differs from those used by many other investigators.^{7–9,17} Many previous investigators optimized conventional plans on the basis of the CTV or compared robustly optimized plans with CTV-based optimized plans. In this work, we chose the PTV as the target for the conventional PTV-based and PTV+PRV-based plans and the CTV as the target for the robustly optimized plan. For details of the algorithms of the PTV-based and robust optimizations, please see Liu *et al.*¹⁵ In Fredriksson *et al.*¹¹ and Chen *et al.*,¹⁰ the PTV was also chosen as the target for the conventional PTV-based plan, and the CTV was chosen as the target for the robustly optimized plan similar to the way we did. The

algorithm used for PTV+PRV-based optimization is the same as for the conventional PTV-based optimization except that PRVs instead of OARs are used in the objective function.

II.C. Plan robustness evaluation

It is important to note that the nominal dose distributions (i.e., without the consideration of uncertainties) from the margin-based optimized IMPT plans do not represent the dose distributions actually realized in the face of uncertainties. To a considerably lesser degree, the same may be true of the robustly optimized plan. Therefore, for valid comparison of results of margin-based optimization and robust optimization, uncertainties must be incorporated into dose distributions.

We used a robustness evaluation technique that displays the envelope of all dose-volume histograms (DVHs) of 21 dose distributions associated with the corresponding range and setup uncertainties, i.e., for each of nominal, minimum, and maximum proton ranges, the isocenter of the patient is at the nominal position and is rigidly shifted in the A-P, S-

TABLE II. Beam parameters used in the optimization of IMPT plans.

Patient	Fields	Axial margins ^a (cm) (proximal, distal)	Lateral margins ^a (cm) (X1, Y1, X2, Y2)	Nominal energy (MeV)	Number of layers	Spot spacing (cm)
1	Field 1	0.0, 0.0	0.9, 0.9, 0.9, 0.8	136.4	43	1.08
	Field 2	0.0, 0.0	0.9, 0.9, 0.9, 0.8	129.2	39	
	Field 3	0.0, 0.0	0.9, 0.9, 0.9, 0.8	159.5	53	
2	Field 1	0.3, 0.3	1.0, 1.0, 1.0, 1.0	131.0	40	0.5
	Field 2	0.3, 0.3	1.0, 1.0, 1.0, 1.0	144.9	42	
	Field 3	0.3, 0.3	0.8, 0.8, 0.4, 0.8	141.6	46	
3	Field 1	0.0, 0.0	1.0, 1.0, 1.0, 1.0	206.3	53	0.7
	Field 2	0.0, 0.0	1.0, 1.0, 1.0, 1.0	203.7	58	
	Field 3	0.0, 0.0	1.0, 1.0, 1.0, 1.0	201.0	54	
4	Field 1	0.0, 0.0	0.9, 0.9, 0.9, 0.9	122.5	24	0.7
	Field 2	0.0, 0.0	0.9, 0.9, 0.5, 0.5	143.2	33	
	Field 3	0.0, 0.0	0.5, 0.9, 0.9, 0.9	153.2	21	
5	Field 1	0.4, 0.8	0.7, 0.7, 0.7, 0.7	206.3	20	0.7
	Field 2	0.6, 0.9	0.6, 0.6, 0.6, 0.6	206.3	29	
	Field 3	0.8, 1.0	0.7, 0.7, 0.7, 0.7	203.7	25	
6 ^b	Field 1	0.2, 0.2	1.0, 1.0, 1.0, 1.0	125.6	51	0.5
	Field 2	0.2, 0.2	1.0, 1.0, 1.0, 1.0	131.0	54	
	Field 3	0.2, 0.2	1.0, 1.0, 1.0, 1.0	131.0	37	

^aMargins are used for placement of spots to ensure target coverage.^bProstate case.

I, and R-L directions, yielding 21 dose distributions (seven per proton range).¹⁸ The DVHs derived by choosing the nominal dose per voxel were also displayed. The “bands” of DVHs are an effective means to illustrate the sensitivity to uncertainties¹⁸—the wider the band, the greater the sensitivity. We computed the width at 50% volume for each DVH band as a quantitative measure of plan robustness. For fair comparison, we renormalized competing plans to have at least 98% of CTV covered by the prescribed dose in the nominal dose distribution and changed other dose distributions accordingly.

II.D. Plan optimality evaluation

To evaluate or compare the optimality of IMPT plans, we used the conventional DVH method with appropriate incorporation of uncertainties. Two DVHs are generated for the target volumes: one by choosing the minimum of the 21 doses in each voxel in the targets and the other by choosing the maximum of the 21 doses in each voxel in the targets. Then, the $D_{95\%}$ (the dose that covers the hottest 95% of the target volume) doses and $D_{5\%}$ (the dose that covers the hottest 5% of the volume) minus $D_{95\%}$, respectively, represent the target dose coverage and target dose homogeneity in the worst-case scenario. The $D_{95\%}$ dose is derived from the former DVH and the $D_{5\%}$ dose from the latter. For the H&N irradiations studied here, we calculated and compared the means of the $D_{95\%}$ and $D_{5\%}$ minus $D_{95\%}$ doses for the five cases from the robustly optimized plan, the PTV-based plan, and PTV+PRV-based plan.

The DVHs for OARs based on the worst-case dose distributions (by choosing the maximum of the 21 doses in each voxel outside the targets) were also generated for the H&N cases. The following dosimetric parameters were used to compare the sparing of OARs: D_{1cc} (the dose that covered the hottest 1 cm³ of the structure volume) for the spinal cord and brainstem, D_{mean} (the mean dose) for the oral cavity and parotids, and $D_{1\%}$ (the dose that covered the hottest 1% of the structure volume) for other organs. We calculated and then compared the means of the evaluation metrics for the corresponding endpoints for those five cases from the robustly optimized plan and the PTV-based and PTV+PRV-based plan.

III. RESULTS

Figure 1 shows the transverse dose distribution for one H&N case. It is clear that the dose distribution in the robustly optimized plan was essentially unaffected by range uncertainty (middle row) and combined range and setup uncertainties (bottom row) compared to those in the PTV-based plan and in the PTV+PRV-based plan. The introduction of the PRVs in IMPT planning did not improve plan robustness compared to only PTV-based planning.

Figure 2 shows the DVH bands of the CTV, brainstem, oral cavity, and optic chiasm for the same H&N cancer case. It is apparent that the CTV DVH bands are narrower for the robustly optimized plans than for the PTV-based and PTV+PRV-based plans [the bandwidths measured at 50% of CTV were 0.59 [robust plan], 3.53 [PTV+PRV plan], and

FIG. 1. Dose distributions in the transverse plane for a representative patient illustrate the insensitivity of the robustly optimized plan (left column) to range and setup uncertainties compared with the conventional PTV+PRV-based optimized plan (middle column) and the conventional PTV-based optimized plan (right column). Top panels (a), (d), and (g) show dose distributions in nominal position; whereas the middle panels (b), (e), and (h) show corresponding data with 3.5% larger range and the bottom panels (c), (f), and (i) are for 3.5% larger range and 3 mm superior shift. Color scheme is CTV- middle shadowed area, Brainstem- bottom shadowed area. Isodose lines (red 100%) in the PTV-based and PTV+PRV-based plans are perturbed to a significantly greater degree than in robustly optimized plan. For instance, CTV is not adequately covered with the prescribed dose in panels (e), (f), (h), and (i).

3.53 [PTV plan] Gy (RBE)}, indicating the reduced sensitivity of the robustly optimized plan to setup and range uncertainties. Sparing of normal tissues was improved by robust optimization (see the following paragraph). However, the addition of PRVs did not improve the robustness of the PTV-based plan, although it did improve normal tissue sparing. In addition, notice that the falloff of the CTV DVH bands is steeper and the maximum dose is lower for the robustly optimized plan than for the other two plans. This result is due to the target-homogeneity-enhancement term used in our robust optimization objective function as well as robust optimization's ability to compensate for dose perturbations.¹⁵

The averaged OAR results of the five H&N cases are shown in Fig. 3 (to the left of the dashed line). The robustly optimized plans minimized the dose to the OARs compared with the PTV-based and PTV+PRV-based conventional plans [D_{1cc} : spinal cord, 24.1 [robust] vs 26.0 [PTV+PRV] vs 28.2 [PTV] Gy (RBE); brainstem, 48.3 [robust] vs 48.8 [PTV+PRV] vs 51.2 [PTV] Gy (RBE); D_{mean} : oral cavity, 22.3 [robust] vs 22.9 [PTV+PRV] vs 26.1 [PTV] Gy (RBE); right parotid, 14.2 [robust] vs 14.7 [PTV+PRV] vs 15.2 [PTV] Gy (RBE); $D_{1\%}$: normal brain, 66.0 [robust] vs 68.0 [PTV+PRV] vs 69.3 [PTV] Gy (RBE); optic chiasm, 48.2 [robust] vs 52.8 [PTV+PRV] vs 53.8 [PTV] Gy (RBE)}. It is apparent that the introduction of the PRV concept during planning improved normal tissue protection, although not as much as robust optimization.

The averaged target dose coverage and homogeneity results of the five H&N cases are also shown in Fig. 3 (to the right of the dashed line). Robust optimization led to better target dose coverage than did PTV-based and PTV+PRV-based conventional planning [$D_{95\%}$ CTV: 60.8 [robust] vs

FIG. 2. Color wash represents the DVH bands for dose distributions covering all setup and range uncertainties for the CTV and various organs in the robustly optimized plan (left column), the PTV-based plan (middle), and the PTV+PRV-based plan (right) for one H&N case. The solid lines are the DVHs for the nominal dose distribution (i.e., without consideration of uncertainties). The narrowness of the CTV bands for the robustly optimized plan relative to the others indicates its superior robustness. Sparing of the brainstem, oral cavity, and optic chiasm was also perceptibly better.

FIG. 3. Left of dashed line: Sparing of OARs resulting from use of the three planning methods. D_{1cc} is shown for the spinal cord and brainstem, D_{mean} for the oral cavity and right parotid, and $D_{1\%}$ for other organs. Right of dashed line: Target (CTV) doses resulting from use of the three methods. CTV $D_{95\%}$ is from the dose distribution obtained by choosing the minimum of the 21 doses in each voxel in the CTV and CTV $D_{5\%} - D_{95\%}$. CTV $D_{5\%}$ is from the dose distribution obtained by choosing the maximum of the 21 doses in each voxel in the CTV.

59.3 [PTV+PRV] vs 59.6 [PTV] Gy (RBE)} with more homogeneous dose distributions { $D_{5\%} - D_{95\%}$ CTV: 13.2 [robust] vs 17.5 [PTV+PRV] vs 17.2 [PTV] Gy (RBE)}. The target dose distributions from the PTV-based and PTV+PRV-based plans were similar. These results are consistent with those from Fig. 2.

Figure 4 shows the DVH bands of the CTV, bladder, rectum, and pubic symphysis for the prostate case. The results and conclusions we drew from the prostate case were consistent with those from the H&N cases.

IV. DISCUSSION

The purpose of this study was to determine whether the improved normal tissue protection achieved with robust optimization^{11,14,15} is due to the margins implicitly assigned to the OARs in the worst-case robust optimization. The results from three different optimization methods (robust optimization, PTV+PRV-based conventional optimization, and PTV-based conventional optimization) indicate that the benefits of robust optimization are not simply due to the implicit expansion of OARs. The PTV+PRV method

Prostate Cancer IMPT Plans

FIG. 4. Color wash represents the DVH bands for dose distributions covering all setup and range uncertainties for the CTV and various organs in the robustly optimized plan (left column), the PTV-based plan (middle), and the PTV+PRV-based plan (right) for the prostate case. The solid lines are the DVHs for the nominal dose distribution (i.e., without consideration of uncertainties). The narrowness of the CTV bands for the robustly optimized plan relative to the other plans indicates its superior robustness. Sparing of the rectum, bladder, and pubic symphysis was also perceptibly better.

can partly improve plan optimality, but it is still inferior to robust optimization in terms of both plan robustness and plan optimality. In other words, robust optimization leads to IMPT plans least sensitive to uncertainties and also the best OAR sparing, target coverage, and dose homogeneity, while the PTV+PRV-based optimization spares normal tissues better than the PTV-based optimization but does not improve plan robustness, target coverage, and target dose homogeneity. The underlying reason is that robust optimization not only incorporates margins but also compensates for perturbations in the middle of the target and overdosing inside normal structures in the face of uncertainties. Thus, the greatest improvement in robustness and optimality would be expected from robust optimization for situations when dose perturbation is high due to complex inhomogeneities along beam paths.

Recently, Albertini *et al.*¹⁹ have also reported that the use of safety margins in conventional IMPT optimization achieved only a marginal improvement in plan robustness in IMPT plans, especially for highly modulated IMPT plans (i.e., have large in-field gradients). They have argued that the degradation within the target is due to misalignments of spots with highly variable intensities. The use of safety margins is an appropriate way to improve plan robustness only if the dose degradation mostly occurs at the edges of the targets but has no effects on the lack of robustness within the targets. Our study is consistent with their results that the use of the safety margin for targets does not improve the plan robustness. We have further demonstrated that similar issues exist for normal structures. That is, adding margins to OARs (thus forming PRVs for OARs) does not improve plan robustness. It does improve normal tissue sparing somewhat but not as

much as robust optimization. The reason, as explained above is that robust optimization compensates for overdosing in normal tissues resulting from incorporation of uncertainties.

It has been argued that improvement in robustness is at the expense of normal tissue sparing.^{7-9,20} We believe that such assertions are due to the fact that comparison of results of robust optimization and conventional optimization does not have uncertainties considered. As emphasized in Sec. II, it is essential that, for comparisons to be valid, uncertainties must be included in dose distributions.

The worst-case dose distribution method proposed by Lomax *et al.*²¹ has its limitation. It accounts for range uncertainties and setup uncertainties along the three major axes. However, it does not consider any nonrigid patient movements, movements in directions other than the major axes, or changes in patient anatomy, which may underestimate the uncertainties. On the contrary, the resulting worst-case dose distribution is composed of the worst dose in each voxel among eight perturbed doses and one nominal dose, which may overestimate the uncertainties. In theory, one can look at all possible perturbed situations with significant computation time. The current approach is more practical. In our robustness evaluation method, we used 21 dose distributions (seven geometrical positions times three proton ranges), rather than nine to evaluate plan robustness in the face of combined uncertainties.

The current study has important clinical implications. Our results show that robust optimization is superior to conventional PTV-based and PTV+PRV-based methods in terms of insensitivity to uncertainties, target coverage, target dose homogeneity, and normal tissue sparing. This further signifies the incapability of PTV-based or PTV+PRV-based planning methods, which are appropriate when the dose distributions are inherently insensitive to uncertainties, as is the case for IMRT,²² to account for uncertainties in proton therapy. It has been shown that target dose inhomogeneity may result in higher probability of local recurrence.²³ This suggests that that the use of robust optimization may improve local control. Furthermore, reduced dose to normal tissues may lead to lower rates of severe toxicities and better quality of life.²⁴

Our results demonstrate the importance of robust optimization. We have implemented dose-based and dose volume-based constraints based on the worst-case dose distribution. However, our method does not explicitly control the degree of the IMPT plan robustness. The next step is to develop a robust optimization method, which is able to control robustness and balance it against plan optimality. This study is under way in our clinic. We are also in the process of implementing robust optimization clinically.

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