Robust treatment planning with conditional value at risk chance constraints in intensity-modulated proton therapy

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(Author listing was corrected after first online publication on January 9, 2017.)

(Received 29 June 2016; revised 7 September 2016; accepted for publication 4 November 2016; published 3 January 2017)

Background and purpose: Intensity-modulated proton therapy (IMPT) is highly sensitive to range uncertainties and uncertainties caused by setup variation. The conventional inverse treatment planning of IMPT based on the planning target volume (PTV) is not often sufficient to ensure robustness of treatment plans. We applied a probabilistic framework (chance-constrained optimization) in IMPT planning to hedge against the influence of uncertainties.

Material and methods: We retrospectively selected one patient with lung cancer, one patient with head and neck (H&N) cancer, and one with prostate cancer for this analysis. Using their original images and prescriptions, we created new IMPT plans using two methods: (1) a robust chance-constrained treatment planning method with the clinical target volume (CTV) as the target; (2) the margin-based method with PTV as the target, which was solved by commercial software, CPLEX, using linear programming. For the first method, we reformulated the model into a tractable mixed-integer programming problem and sped up the calculation using Benders decomposition. The dose-volume histograms (DVHs) from the nominal and perturbed dose distributions were used to assess and compare plan quality. DVHs for all uncertain scenarios along with the nominal DVH were plotted. The width of the “bands” of DVHs was used to quantify the plan sensitivity to uncertainty. The newly developed Benders decomposition method was compared with a commercial solution to demonstrate its computational efficiency. The trade-off between nominal plan quality and plan robustness was investigated.

Results: Our chance-constrained model outperformed the PTV method in terms of tumor coverage, tumor dose homogeneity, and plan robustness. Our model was shown to produce IMPT plans to meet the dose-volume constraints of organs at risk (OARs) and had better sparing of OARs than the PTV method in the three clinical cases included in this study. The chance-constrained model provided a flexible tool for users to balance between plan robustness and plan quality. In addition, our in-house developed method was found to be much faster than the commercial solution.

Conclusion: With explicit control of plan robustness, the chance-constrained robust optimization model generated superior IMPT plans compared to the PTV-based method. © 2016 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12001>]

Key words: Benders decomposition, chance constraints, conditional value at risk (CVaR), intensity-modulated proton therapy (IMPT), robustness

1. INTRODUCTION

Proton therapy is unique because of the sharp falloff of dose deposition beyond the Bragg peak. Intensity-modulated proton therapy (IMPT) is an advanced form of proton therapy that can achieve highly conformal tumor dose coverage and superior sparing of organs at risk (OARs).^{1–4} Proton therapy highly depends on the quality of treatment planning, which involves solving multiple optimization problems⁵ and determining important delivery parameters, such as beam angles, proton energies, and beamlet intensities.

In IMPT treatment planning, the fluence map optimization (FMO) problem focuses on finding optimal beamlet

intensities given beam angles and influence matrix, which records dose contributions from each beamlet of unit intensity to each voxel. The objective of FMO is to deliver the prescribed dose to the tumor while minimizing doses delivered to OARs. Deterministic FMO models, which do not consider range uncertainties, organ motions, and patient setup uncertainties, may produce IMPT plans that are not robust^{6,7} and hence the treatment quality may deteriorate during the beam delivery, resulting in undesired clinical consequence.^{8–12}

As the dose distribution of IMPT is affected much more by uncertainties compared to intensity-modulated radiation therapy (IMRT), robustness is of paramount importance in creating reliable IMPT treatment plans.^{13–16} The conventional

method of adding safety margins to the clinical target volume (CTV) to form the planning target volume (PTV) has been used for decades to mitigate the negative effects of uncertainties in many forms of radiation therapy. However, as pointed out by Liu et al.,¹⁷ the effectiveness of the PTV method is questionable in IMPT planning, as these uncertainties may distort the dose distribution even inside the tumor.

Given that the aforementioned method is inadequate to deal with uncertainties, various robust planning models have been proposed to proactively address the impact of uncertainties in the proton therapy treatment planning and mitigate their negative influences. One research direction was applying stochastic programming techniques. Unkelbach et al.⁹ integrated both range and setup errors based on their probability distributions into a stochastic planning problem for IMPT. Another research direction was applying worst-case robust optimization in treatment planning, in which the worst-case scenario among all possible uncertainty scenarios was chosen for optimization. In IMRT, Chan et al.¹⁸ built a worst-case robust optimization framework which managed the uncertainties caused by respiratory motions. In IMPT, robust optimization had made great progress recently. Pflugfelder et al.¹² developed a worst-case optimization method that addressed both setup and range uncertainties. The worst-case scenario might not be realistic, as the model assumed that each voxel took its worst-case dose independently. This conservativeness was subsequently avoided by a minimax method as described by Fredriksson et al.¹⁹ Other studies^{17,20–22} improved the objective function so that both hot and cold spots in the target were penalized. Recently Chen et al.²³ explored a robust planning model using multi-criteria optimization. Unkelbach et al.¹⁰ compared robust optimization and stochastic programming models and Fredriksson²⁴ included these two types of planning models in a unified framework.

However, nearly all the aforementioned studies adopted quadratic programming with no hard constraints. This is partly because an unconstrained quadratic programming problem simplifies the formulation and facilitates the application of a Newton-like methodology. But the unconstrained optimization problem limits the modeling flexibility. As it does not explicitly include hard constraints in optimization under each uncertainty scenario, the dose-volume constraints for tumors and OARs cannot be guaranteed in each scenario. On the other hand, improving the plan robustness will inevitably sacrifice the plan quality in the nominal scenario (i.e., the scenario without uncertainties considered).⁹ Considering all possible scenarios without ignoring any of them in a planning model may result in an overly conservative plan with unacceptable quality in the nominal scenario. Ideally, a treatment planning model should allow the treatment planner to adjust plan robustness and strike a balance between the two contradictory objectives.

In this work, we focused on the FMO problem for IMPT and proposed a new modeling framework, namely, robust conditional value at risk (CVaR) chance-constrained treatment optimization, to proactively guarantee plan quality in each specific scenario and provide a tool for treatment

planners to actively control the balance between plan robustness and nominal plan quality. Range uncertainty and patient setup uncertainty were accounted for in this work.

The rest of the paper is organized as follows. In section 2, we introduce the new chance-constrained robust treatment planning model for IMPT and the conventional PTV method. Patient data, computational settings, and a solution method of the new model are also described in section 2. In section 3, treatment results from both the chance-constrained robust model and the PTV method are presented. Interpretation and the discussion of the results are given in section 4. Finally, the paper is concluded in section 5.

2. MATERIALS AND METHODS

We introduced the chance-constrained model to assist the treatment planners to adjust plan robustness and strike a balance between plan robustness and the nominal plan quality. The chance-constrained model was initially proposed in the 1950s and has become an important approach to account for uncertainties in multiple areas (power industry, retail industry, etc.).²⁵ A chance-constrained problem takes the form of a regular optimization problem. But a (joint) chance constraint is introduced so that one or several inequalities have to be satisfied with a probability greater than or equal to $1-\varepsilon$, where ε is called the tolerance level. Note that by letting $\varepsilon > 0$ we obtain a flexibility to ignore some scenarios, i.e., the scenarios that are unlikely to happen but seriously worsen the objective value, and avoid compromising the plan quality if so desired.

In order to explicitly control the dose distribution in each scenario, we used CVaR to implement the clinical dose-volume constraints in our model. CVaR is widely applied in finance problems to control risk. Recently it was introduced into IMRT treatment planning to constrain the dose distribution of tumors and normal tissues.^{26,27}

2.A. Robust chance-constrained formulation of the proton FMO problem

In IMPT, tumors are irradiated by multiple beams, each fixed at an incident angle. The set of all tumors was denoted by T and that of all OARs by O . To keep the generality of the model, we suppose that T can have multiple targets. Every beam was decomposed into many small beamlets. We denoted the set of all beamlets in all beams by J . In our work, all tumors and OARs were discretized into sets of voxels. CTV_t was used to denote the set of all voxels in the CTV of tumor t in T . V_n was the set of all voxels of the OAR n in O . Prescription dose of the tumor t and dose constraints of OAR n were represented by D_t^0 and D_n^0 , respectively. The dose received by voxel i of tumor t was denoted by D_{ti} and that received by voxel i of OAR n was denoted by D_{ni} . The intensity of each beamlet $j \in J$, d_j , was the decision variable. In the influence matrix, its element k_{ij} was the dose contribution of the beamlet j of unit intensity at voxel i . Therefore, D_{ti} and D_{ni} were calculated using the equations $D_{ti} = \sum_{j \in J} k_{ij} d_j$ and $D_{ni} = \sum_{j \in J} k_{ij} d_j$.

Various uncertainties, including range and setup uncertainties, may perturb the influence matrix and hence the dose. Let Ω be the set of all possible uncertainty scenarios. We used ω_0 to stand for the nominal scenario. In uncertainty scenario, $\omega \in \Omega$, $D_{ti}(\omega)$, and $D_{ni}(\omega)$ were the doses corresponding to uncertainty scenario ω . Let d be the vector of d_j for all j and $f_t(d)$ and $f_n(d)$ be the parameters describing dose distributions of tumor t and OAR n , respectively. Correspondingly, $f_t(d, \omega)$ and $f_n(d, \omega)$ were the values of $f_t(d)$ and $f_n(d)$ under uncertainty scenario $\omega \in \Omega$. Our chance-constrained formulation for IMPT planning is as follows:

$$\begin{aligned} \min & \sum_{t \in T} \left(\frac{\alpha_t}{|CTV_t|} \sum_{i \in CTV_t} |D_{ti}(\omega_0) - D_t^0| \right) \\ & + \sum_{n \in O} \left(\frac{\alpha_n}{|V_n|} \sum_{i \in V_n} (D_{ni}(\omega_0) - D_n^0)^+ \right) \\ \text{s.t.} & \end{aligned} \quad (1)$$

$$P\{L_t \leq f_t(d) \leq U_t \ \forall t \in T\} \geq 1 - \varepsilon \quad (1)$$

$$f_n(d, \omega_0) \leq U_n \ \forall n \in O \quad (2)$$

$$d_j \geq 0 \ \forall j \in J.$$

Note that $f_t(d)$ has different values under different uncertainty scenarios. The chance constraint Eq. (1) ensures that dose distribution requirements for tumors are satisfied with a probability P no less than $1 - \varepsilon$, where P stands for the probability of the corresponding constraints to be satisfied. The underlying assumptions about random scenarios and the associated probabilities will be introduced in section 2.D. And L_t and U_t are the lower and upper constraints of the tumor dose distribution, respectively. It is worth pointing out that when $\varepsilon = 0$, Eq. (1) reverts to a conventional constraint, and when $\varepsilon = 1$, the constraint Eq. (1) may be ignored. We use constraints in Eq. (2) to control the OAR dose distribution, where U_n is the upper constraint of the OAR dose distribution. The objective function of the above optimization model takes a linear form^{18,28,29} and is the weighted sum of difference values between the real doses and the prescribed doses for all voxels in tumors and organs under the nominal scenario ω_0 . We use α to denote the penalty weight for tumor or organs in the objective function. The function $()^+$ is conventionally defined, i.e., it is $(D_{ni}(\omega_0) - D_n^0)$ if $(D_{ni}(\omega_0) - D_n^0) > 0$ and 0 otherwise. The optimal objective value reflects the optimal plan quality we can achieve. A smaller optimal objective value means a better plan quality.

The formula $f_t(d)$ was implemented as the dose-volume constraints for tumors and OARs using CVaR.²⁶ For tumor $t \in T$, the abstract form $L_t \leq f_t(d) \leq U_t$ in the constraint Eq. (1) is defined as:

$$\underline{\rho}_t - \frac{1}{(1 - \tau)|CTV_t|} \sum_{i \in CTV_t} (\underline{\rho}_t - D_{ti})^+ \geq \gamma_t^l D_t^0 \quad (3)$$

$$\bar{\rho}_t + \frac{1}{(1 - \tau)|CTV_t|} \sum_{i \in CTV_t} (D_{ti} - \bar{\rho}_t)^+ \leq \gamma_t^h D_t^0, \quad (4)$$

where τ is used to control the percentage of the high dose-volume relative to the total volume of CTV_t and $\underline{\rho}_t$ and $\bar{\rho}_t$

are auxiliary variables. The constraint Eq. (3) indicates that the average dose of the subset of the target t with the percentage volume of $(1 - \tau)$ receiving the lowest amount of radiation dose must be at least $\gamma_t^l D_t^0$. Similarly, the constraint Eq. (4) means that the average dose of the subset of the target t with the percentage volume of $(1 - \tau)$ receiving the highest amount of radiation dose must be at most $\gamma_t^h D_t^0$. By setting γ_t^l and γ_t^h close to 1, we can achieve good tumor dose distribution as shown in Romeijn et al.²⁶ Similarly, for organ $n \in O$, its constraint Eq. (2), $f_n(d, \omega_0) \leq U_n$ is expressed as:

$$\bar{\rho}_n + \frac{1}{(1 - \tau_n)|V_n|} \sum_{i \in V_n} (D_{ni}(\omega_0) - \bar{\rho}_n)^+ \leq U_n^0. \quad (5)$$

U_n^0 may simply be set as the maximum dose allowed by $(1 - \tau_n)$ percentage volume of OAR n .

2.B. Reformulation of the robust chance-constrained model and its solution methods

In general, chance-constrained optimizations are challenging to solve. However, if we suppose that Ω is a finite discrete set, we can replace constraint Eq. (1) with the following linear constraints and convert the chance-constrained model to a solvable mixed-integer programming (MIP) problem after introducing a binary variable for each scenario:

$$L_t - Mz_\omega \leq f_t(d, \omega) \leq U_t + Mz_\omega \ \forall t \in T, \omega \in \Omega \quad (6)$$

$$\sum_{\omega \in \Omega} p_\omega z_\omega \leq \varepsilon \quad (7)$$

$$z_\omega \in \{0, 1\} \ \forall \omega \in \Omega, \quad (8)$$

where M is a large number relative to other parameter values. Specifically, the enforcement of the constraint in scenario ω with probability p_ω is determined by the binary variable z_ω . From Eq. (6), if $z_\omega = 0$, the constraint has to be satisfied for ω . When $z_\omega = 1$, it can be ignored because of the big M . Eq. (7) is added so that the constraint Eq. (1) can be satisfied with a probability greater than or equal to $1 - \varepsilon$.

In the objective function, nonlinear terms such as absolute values and Heaviside functions can be easily linearized. Therefore, our chance-constrained IMPT planning problem may be solved using commercial solvers such as (IBM CPLEX version 12.5, Armonk, New York, USA). This process however is slow. In order to improve computational efficiency, we designed a customized Benders decomposition algorithm. Rather than considering all variables simultaneously, Benders decomposition divides the original problem into a simpler master problem, which contains only integer variables at the beginning, and a subproblem, which only includes continuous variables. In the solution process, new constraints (i.e., Benders cuts) describing the shape of the feasible region of the subproblem are iteratively generated and added to the master problem. The solution of the master problem will approach that of the original problem after iterations.^{30,31}

2.C. PTV-based formulation of the proton FMO problem

Our new robust chance-constrained model was benchmarked with a PTV-based formulation. For the PTV-based formulation, we used the same objective function as that of the robust chance-constrained model except that the tumor voxels are from the PTV of the tumor t , denoted by PTV_t .

$$\min \sum_{t \in T} \left(\frac{\alpha_t}{|PTV_t|} \sum_{i \in PTV_t} |D_{ti}(\omega_0) - D_t^0| \right) + \sum_{n \in O} \left(\frac{\alpha_n}{|V_n|} \sum_{i \in V_n} (D_{ni}(\omega_0) - D_n^0)^+ \right)$$

The PTV was formed by uniform expansion of CTV by 3 mm for the head and neck (H&N) case and 5 mm for the lung and prostate cases. The PTV-based optimization is unconstrained. It does not consider range uncertainties and it considers setup uncertainties implicitly as they were taken into consideration by the PTV margin. The PTV-based formulation optimizes dose distribution so that the difference between target doses and actual doses of tumors and organs is minimized under the nominal scenario.

PTV-based model can be directly solved by commercial solvers effectively.

2.D. Patient data and computational setting

In this exploratory study, the effectiveness of our model was benchmarked on three clinical cases including one prostate cancer, one lung cancer, and one H&N cancer. Table I lists the planning parameters of the three cases. Each of the three cases has one target.

We used a discrete set Ω to describe the setup and range uncertainties (similar to the worst-case approaches^{12,32,33}). For the H&N and the lung cancer cases, nine scenarios (eight perturbed plus the nominal) were obtained as follows. The interfractional patient setup uncertainties were simulated by shifting the isocenter of the patient in the anteroposterior (A-P), superior-inferior (S-I), and right-left (R-L) directions by 3 mm for the head and neck cancer case and 5 mm for the

other two cases, yielding six scenarios. Range uncertainties were simulated by scaling the stopping power ratios by $\pm 3.5\%$ to generate two additional scenarios. The influence matrix for the corresponding uncertainty scenario was recalculated using an in-house developed treatment planning system.^{4,17} For the demonstration purpose, we assumed that the nominal scenario had the probability of 0.6 and each of these eight uncertainty scenarios had the probability of 0.05. In this study ε was set to be 0.05, therefore only one scenario was allowed to be ignored. The ignored scenario was determined by the optimizer automatically to achieve the best balance between plan quality and plan robustness under all uncertainty scenarios given the tolerance level ε .

To demonstrate the effectiveness of our method, we also considered 21 uncertainty scenarios (20 perturbed plus the nominal) for the prostate cancer case. For each of the proton ranges (nominal, minimum, and maximum), the isocenter of the patient was rigidly shifted in the A-P, S-I, and R-L directions, respectively, yielding 18 dose distributions (6 per proton range). The other two were obtained from minimum and maximum proton ranges with the patient at the nominal position. Again for the demonstration purpose, here every uncertainty scenario was assumed to have a probability of 0.02. In this case, ε was set as 0.04, therefore two scenarios could be neglected.

We generated two plans for each of the three clinical cases: one using the PTV method and the other using the robust CVaR chance-constrained treatment planning with the target as the clinical target volume (CTV). For all the three cases, we used 21 scenarios to evaluate the quality of a plan regardless of whether the plan is obtained by 21 scenarios (prostate cancer case) or 9 scenarios (H&N and lung cancer cases).

Dose-volume histogram (DVH) indices comparing CTV dose coverage, homogeneity, and OAR sparing were evaluated. $D_{95\%}$ (the dose covering the highest 95% of the structure's volume) and $D_{5\%}$ (the dose covering the highest 5% of the structure's volume) were derived from the CTV DVH. $CTV D_{95\%}$ and $D_{5\%} - D_{95\%}$ were used to assess CTV dose coverage and homogeneity, respectively. The lowest dose covering a percentage of the structure's volume ($D_{\%}$) and the percentage volume of a structure that receives at least a certain amount of dose (V) were compared for OARs, which were derived from an OAR's DVH. For the prostate cancer case, V_{70} of rectum and V_{65} and V_{40} of bladder were compared. For the H&N cancer case, $D_{1\%}$ of brainstem, brain, and spine, mean doses of parotids and oral cavity were compared. For the lung cancer case, we used $D_{1\%}$ dose for the spinal cord and V_{20} and mean dose of the normal lung.

2.E. Robustness quantification

To evaluate and compare IMPT plans, we used a robustness quantification technique that displayed the envelope of all DVHs in band graphs of the 20 dose distributions corresponding to the scenarios of range and setup uncertainties.^{21,34} For convenience, the DVHs of nominal scenarios

TABLE I. Parameters of the three clinical cases. It shows number of beamlets in each beam, prescription dose (Gy[RBE]), and values of parameters in the CVaR constraints.

Cancer cases	Beamlets	D_t^0 (Gy)	τ (%)	γ_t^l	γ_t^h
Prostate	Beam 1: 1495	76	20	0.99	1.015
	Beam 2: 1497				
Lung	Beam 1: 7250	74	20	0.99	1.01
	Beam 2: 6075				
	Beam 3: 6211				
	Beam 4: 7164				
Head and neck	Beam 1: 2107	66	20	0.99	1.01
	Beam 2: 1993				
	Beam 3: 2227				

were also displayed in the robustness quantification. The nominal DVH curve was drawn by a red line. In the chance-constrained model, the DVH curves associated with the ignored scenarios were drawn by black lines. This robustness quantification technique was effective at determining an IMPT plan's sensitivity to uncertainties.

3. RESULTS

3.A. Comparison of plan quality

Table II shows the tumor DVH indices achieved by our robust chance-constrained method and the PTV method. To measure tumor dose coverage, the first row, entitled Nominal $D_{95\%}$, shows the $D_{95\%}$ of tumor of the nominal scenario. The second and the third row list the lowest (worst-case) and average $D_{95\%}$ of tumor among all scenarios, respectively. They represent the dose coverage of the tumor under uncertainties. The fourth to sixth row show $D_{5\%}-D_{95\%}$ of the nominal, largest (worst-case) $D_{5\%}-D_{95\%}$, and average $D_{5\%}-D_{95\%}$ of all scenarios, respectively. They represent the dose homogeneity of the tumor under uncertainties. In the last three rows, we chose the width of the DVH band to quantify the plan robustness under uncertainty; it was calculated as the DVH band widths at $D_{95\%}$, $D_{50\%}$, and $D_{5\%}$.

Due to the nature of chance constraints, the unlikely and thus "ignored" scenarios were not considered in the optimization. However, we evaluated the generated plans' quality using all 21 scenarios (the nominal and 20 uncertain scenarios).

Figure 1 shows the DVH bands derived from the two methods to illustrate the sensitivity of treatment plans to uncertainties.

For prostate and lung cancer cases, $D_{95\%}$, $D_{5\%}-D_{95\%}$, and the DVH band width from the chance-constrained model

were uniformly better than those from the PTV method (as graphically shown by Fig. 1).

For the H&N cancer case, the plan from the chance-constrained model had slightly smaller nominal $D_{95\%}$ and slightly bigger nominal $D_{5\%}-D_{95\%}$, while all other indices from the chance-constrained model still outperformed those from the PTV method.

The OAR DVH indices for each case are listed in Table III. We presented the values in the nominal scenario and also presented the average and the worst-case values considering all scenarios (including the ignored scenarios).

For the prostate cancer and lung cancer cases, the OAR sparing requirements could be satisfied for both the chance-constrained model and the PTV method. Our chance-constrained model delivered smaller doses to all normal organs considered. For the challenging H&N cancer case, the ipsilateral parotid had to be compromised. With the exception that the worst-case $D_{1\%}$ of brain stem was slightly higher, the chance-constrained method gave superior OAR sparing than the PTV method for all other organs.

3.B. Relationship between plan robustness and nominal plan quality

In Fig. 2, we showed the relationship between the tolerance ε and corresponding optimal objective value for the prostate cancer case with eight scenarios considered. The curve was decreasing between $\varepsilon = 0$ and 0.3 and purely a horizontal line between $\varepsilon = 0.3$ and $\varepsilon = 1.0$. The DVH curves of the tumor for all scenarios with $\varepsilon = 0$ and $\varepsilon = 0.05$ are shown in Fig. 2.

3.C. Computational performance

For our robust chance-constrained model, the introduction of binary variable z (thus MIP) might greatly prolong the optimization time. For example, the solver, CPLEX version 12.5, was unable to find a solution for the lung cancer case within a reasonable time frame. As shown by Table IV, our Benders decomposition algorithm dramatically sped up the optimization compared to the commercial solver CPLEX.

4. DISCUSSION

The robust chance-constrained model can yield clinically acceptable plans as demonstrated in the three clinical cases. Dose-volume constraints of tumors and OARs in the presence of uncertainties were satisfied by explicitly adding CVaR chance constraints in every uncertainty scenario.

Our robust chance-constrained model outperformed the PTV method in terms of tumor coverage, homogeneity, and plan robustness. Even when the ignored extreme scenarios were considered, $D_{95\%}$, $D_{5\%}-D_{95\%}$, and the DVH bandwidths of the tumor from our model were mostly better than the results obtained using the PTV method. For the OAR sparing, the dose-volume constraints were easily met by both methods for most clinical cases. However, in the challenging

TABLE II. Comparison of tumor dose-volume histograms (DVHs) of the chance-constrained method (CC) and the PTV-based method (PTV). The values are derived from the dose-volume histograms (DVH) curves for all the 21 scenarios. Besides the nominal case, the value for the worst case and the average (Avg) over all scenarios are also listed. $D_{95\%}$, $D_{5\%}-D_{95\%}$, and DVH band indicate tumor dose coverage, homogeneity, and robustness, respectively.

	Prostate		Head and neck		Lung	
	CC	PTV	CC	PTV	CC	PTV
Nominal $D_{95\%}$ (Gy)	72.6	72.1	63.8	64.3	73	71.8
Min $D_{95\%}$ (Gy)	66.1	57.1	55.9	53.7	61.1	58.5
Avg $D_{95\%}$ (Gy)	72.4	67.5	61.8	60.2	68.6	67
Nominal $D_{5\%}-D_{95\%}$ (Gy)	8.5	10.1	4.5	3.4	3.1	4.2
Max $D_{5\%}-D_{95\%}$ (Gy)	14.8	25.2	14.4	16.2	16.4	19.1
Avg $D_{5\%}-D_{95\%}$ (Gy)	7.9	16.7	7.5	11.2	8.7	12
$D_{95\%}$ DVH band	8.4	15	7.9	10.6	11.9	13.3
$D_{50\%}$ DVH band	1.2	5.4	0.6	4.4	0.6	4.8
$D_{5\%}$ DVH band	1.9	6.7	2.5	8.3	1.8	6.2

FIG. 1. Tumor dose DVH for the three cases. From top to bottom: 21-scenario prostate cancer, head and neck cancer, and lung cancer. Plans of the chance-constrained model are (a), (c), and (e), and plans of the planning target volume (PTV) model are (b), (d), and (f). Blue area represents the DVH bands of all random scenarios. The red line is for the nominal dose distribution. The black line is for the ignored scenario in the chance-constrained model. The narrowness of the DVH bands from the chance-constrained model indicates improved robustness. The dose is normalized to the prescription dose. [Color figure can be viewed at wileyonlinelibrary.com]

H&N cancer case, our method demonstrated its superiority over the PTV method by greatly improving the protection of critical organs under the nominal and perturbed scenarios. In clinical practice, the chance-constrained IMPT robust treatment planning may enhance the reliability of tumor dose distribution and hence decrease the chance of local recurrence. At the same time, improved OAR protection should lead to fewer complications and better quality of life for patients.

Even though only nine scenarios were used in the chance-constrained robust optimization (for the H&N and lung cases), we used 21 uncertainty scenarios in the plan evaluation. We found that with 21 uncertainty scenarios considered they were still able to generate better dose distributions for tumor and organs compared to the PTV method.

By introducing the adjustable tolerance level ε , we can flexibly ignore some extreme scenarios and avoid overly

conservative plans. A small tolerance level can ensure good plan robustness but may inevitably compromise the nominal plan quality given the same optimization target.⁹ In this work, we investigated the relationship between plan robustness and nominal plan quality. In Fig. 2, it can be seen that relaxing the tolerance level cannot always improve the nominal plan quality, as at some point ($\varepsilon = 0.3$) it will saturate. In other words, when six scenarios (out of eight) were allowed to be ignored, the objective value reached its lowest possible value (best plan quality). After that, the plan quality under the nominal scenario, i.e., the objective value, could not be further improved when we further relaxed the tolerance level ε . By taking a closer look at the results, we found that the only two scenarios considered in the model at $\varepsilon = 0.3$ are those for the shifts in the R-L direction (setup errors). The horizontal line after $\varepsilon = 0.3$ indicates the nominal plan quality is insensitive

TABLE III. Comparison of organs at risk (OARs) sparing from the chance-constrained method (CC) and the PTV-based method (PTV). The values are derived from the dose-volume histograms (DVH) for all the 21 scenarios. Besides the nominal case, the maximum dose (Worst-case), and the average (Avg) overall scenarios are also listed. MLD stands for the mean dose.

		Prostate (large)			Lung		
		Rectum V ₇₀ (%)	Bladder V ₆₅ (%)	Bladder V ₄₀ (%)	Spinal cord D _{1%} (Gy)	Lung V ₂₀ (%)	Lung MLD (Gy)
PTV	Nominal	1.8	7	3.3	3.1	29.6	10.4
	Average	4.7	3.4	6.8	4.5	30.1	10.4
	Worst-case	11.4	6.3	10.2	10.2	33.7	11.9
CC	Nominal	1.7	6.3	2.6	1.7	27.6	9.3
	Average	2.3	2.7	6.4	2.7	27.7	9.3
	Worst-case	8.2	5.1	9.4	8.9	31.5	10.6

		Head and neck					
		Brain stem D _{1%} (Gy)	Brain D _{1%} (Gy)	Spine D _{1%} (Gy)	Parotid MLD (Gy) (contralateral)	Parotid MLD (Gy) (ipsilateral)	Oral cavity MLD (Gy)
PTV	Nominal	23.6	23	38.4	8.9	42.8	0.2
	Average	22.6	22.7	38.8	9.1	42.8	0.2
	Worst-case	25.6	24.9	44.4	11.2	48.6	0.3
CC	Nominal	19.9	15.2	32.1	6.9	30	0.2
	Average	21.3	15.3	32.9	7	30.2	0.2
	Worst-case	28.2	16.8	38.4	8.4	36.4	0.2

FIG. 2. Relationship between objective value and tolerance level ϵ . As the tolerance level ϵ becomes larger, the objective value becomes smaller, i.e., the nominal plan quality becomes better. This is because a larger ϵ means that the plan is less robust and more scenarios can be ignored in optimization. When six of eight scenarios are allowed to be ignored ($\epsilon = 0.3$), the objective value reaches its lowest value and cannot be further. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE IV. Comparison of computational time. For the Benders decomposition (BD) method we also show the number of iterations.

	Cplex Time (s)	BD Time (s)	Iteration
Prostate (21 sce)	36,660	18,111	56
H&N (8 sce)	520,986	28,357	8
Lung (8 sce)	NA	67,893	8

sce, scenarios.

to these two scenarios. This is consistent with the observations and explanations reported in previous researches.⁹ The graph suggests that this method makes it possible for treatment planners to explicitly control plan robustness as the tolerance level ϵ is adjustable by the treatment planner. This capability is desired in the clinic. In addition, the graph can guide treatment planners in finding the optimal balance between plan quality and plan robustness.

A multi-objective optimization method may help us study the conflicting objectives more rigorously. A quadratic objective function can penalize the errors more effectively than the linear one and has the potential to further improve the plan robustness and quality. However, more advanced solvers or algorithms are needed to solve complicated chance-constrained models. The computational performance of our method is limited in large-scale 21-scenario H&N cancer and lung cancer cases. In the future, we will develop new methods to enhance the computational efficiency and apply the chance-constrained robust optimization framework to more clinical cases.

5. CONCLUSION

We proposed a robust chance-constrained IMPT planning scheme to proactively hedge against the negative influence of uncertainties. The chance constraint took the form of CVaR, which was shown to well represent the dose-volume constraints in clinical practice. The model was then reformulated into a tractable MIP model that was efficiently solved by an in-house developed algorithm.

The performance of the robust chance-constrained model was benchmarked on three clinical cases. We found that the treatment plan generated using our robust CVaR chance-constrained model achieved better tumor dose coverage, homogeneity, and robustness than the PTV-based planning method. In addition, OAR sparing, which is crucial in radiotherapy of cancer patients, was improved using our novel method. By studying the relationship between the tolerance level and optimal objective value, we found a tool that may help obtain a good balance between plan quality and

robustness by adjusting the tolerance level. Chance-constrained models are challenging to solve and thus the computation performance for clinical cases is slow. The computational efficiency of our model needs to be improved for future clinical use.

ACKNOWLEDGMENT

This research was supported by the National Cancer Institute (NCI) Career Developmental Award K25C

A168984, the Fraternal Order of Eagles Cancer Research Fund Career Development Award, the Lawrence W. and Marilyn W. Matteson Fund for Cancer Research, Mayo Arizona State University Seed Grant, and the Kemper Marley Foundation.

CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to disclose.

APPENDIX

TABLE AI. PARAMETERS AND VARIABLES.

Indices and sets		Model parameters	
t	Index for tumors	D_t^0	Prescription dose of tumor t
n	Index for organs	D_n^0	Dose constraint of OAR n
i	Index for voxels	D_{ti}	Dose to voxel i of tumor t with no randomness considered
j	Index for beamlets	D_{ni}	Dose to voxel i of organ n with no randomness considered
ω	Index for uncertain scenarios	k_{ij}	Dose contribution of beamlet j (unit intensity) at voxel i
T	Set of tumors	$f_t(d)$	Parameter describing dose distribution of tumor t
O	Set of OARs	$f_n(d)$	Parameter describing dose distribution of organ n
J	Set of all beamlets	α_t	Weight of dose errors in tumor t
CTV_t	CTV of tumor t	α_n	Weight of dose errors in organ n
V_n	Set of all voxels in organ n	$ CTV_t $	Number of voxels in the CTV of tumor t
Ω	Set of all uncertain scenarios	$ PTV_t $	Number of voxels in the PTV of tumor t
PTV_t	PTV of tumor t	$ V_n $	Number of voxels in organ n
Random factors		$P\{\}$	Probability
$D_{ti}(\omega)$	Dose to voxel i of tumor t in scenario ω	ε	Tolerance level of the chance-constrained model
$D_{ni}(\omega)$	Dose to voxel i of organ n in scenario ω	L_t	Lower bound requirement of $f_t(d)$
$f_t(d, \omega)$	Value of $f_t(d)$ in scenario ω	U_t	Upper bound requirement of $f_t(d)$
$f_n(d, \omega)$	Value of $f_n(d)$ in scenario ω	U_n	Upper bound requirement of $f_n(d)$
Decision variables		ρ_t	Auxiliary variable in $CVaR$ constraint
d_j	Intensity of beamlet j	τ	Parameter controlling the size of partial volume in $CVaR$ constraint
d	Vector of d_j for all j	γ_t^l	Parameter controlling the dose of partial volume in $CVaR$ constraint
z_ω	Variable indicating if scenario ω is considered in optimization	γ_t^h	Parameter controlling the dose of partial volume in $CVaR$ constraint
		$\bar{\rho}_n$	Auxiliary variable in $CVaR$ constraint
		τ_n	Parameter controlling the size of partial volume in $CVaR$ constraint
		U_n^0	Upper bound requirement of $f_n(d, \omega_0)$
		M	Constant with big value
		ω_0	The nominal scenario
		p_ω	Probability of scenario ω

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