Uncertainty incorporated beam angle optimization for IMPT treatment planning

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Purpose: Beam angle optimization (BAO) by far remains an important and challenging problem in external beam radiation therapy treatment planning. Conventional BAO algorithms discussed in previous studies all focused on photon-based therapies. Impact of BAO on proton therapy is important while proton therapy increasingly receives great interests. This study focuses on potential benefits of BAO on intensity-modulated proton therapy (IMPT) that recently began available to clinical cancer treatment.

Methods: The authors have developed a novel uncertainty incorporated BAO algorithm for IMPT treatment planning in that IMPT plan quality is highly sensitive to uncertainties such as proton range and setup errors. A linear programming was used to optimize robust intensity maps to scenario-based uncertainties for an incident beam angle configuration. Unlike conventional intensity-modulated radiation therapy with photons (IMXT), the search space for IMPT treatment beam angles may be relatively small but optimizing an IMPT plan may require higher computational costs due to larger data size. Therefore, a deterministic local neighborhood search algorithm that only needs a very limited number of plan objective evaluations was used to optimize beam angles in IMPT treatment planning.

Results: Three prostate cancer cases and two skull base chordoma cases were studied to demonstrate the dosimetric advantages and robustness of optimized beam angles from the proposed BAO algorithm. Two- to four-beam plans were optimized for prostate cases, and two- and three-beam plans were optimized for skull base cases. By comparing plans with conventional two parallel-opposed angles, all plans with optimized angles consistently improved sparing at organs at risks, i.e., rectum and femoral heads for prostate, brainstem for skull base, in either nominal dose distribution or uncertainty-based dose distributions. The efficiency of the BAO algorithm was demonstrated by comparing it with alternative methods including simulated annealing and genetic algorithm. The numbers of IMPT plan objective evaluations required were reduced by up to a factor of 5 while the same optimal angle plans were converged in selected comparisons.

Conclusions: Uncertainty incorporated BAO may introduce pronounced improvement of IMPT plan quality including dosimetric benefits and robustness over uncertainties, based on the five clinical studies in this paper. In addition, local search algorithms may be more efficient in finding optimal beam angles than global optimization approaches for IMPT BAO. © 2012 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4737870>]

Key words: beam angle optimization, IMPT, uncertainty

I. INTRODUCTION

The selection of treatment beam angles by which the treatment fields are delivered forms a crucial optimization problem in radiation therapy treatment planning, i.e., beam angle optimization (BAO). Optimal beam angles are those that achieve the best possible dose distribution in the treatment volume, i.e., homogeneous high dose in the target volume and minimal dose in surrounding normal tissues. However, most commercial treatment planning systems used by hospitals have not included a BAO routine mainly due to its impractical compu-

tational difficulty. For the conventional intensity-modulated radiation therapy with x ray or photons (namely, IMXT) in current clinical practice, beam angles manually selected by planners based on trial and error have been able to create acceptable treatment plans for various cancer sites. This is only possible because of long accumulated experiences with a large number of clinical cases. And yet for the intensity-modulated proton therapy (IMPT) that has only become available in few hospitals, clinical cases are very limited. Although initial studies^{1,2} have illustrated the importance of BAO for particle therapy treatment planning, determining quality beam

angles for IMPT treatment planning is an open question in both the practice and the research domain.

The BAO problem in radiotherapy treatment planning is typically a large-scale combinatorial optimization problem. As it is highly nonconvex and many local optima may exit, previous studies have extensively investigated different global optimization algorithms for solving the BAO problem, such as simulated annealing,^{3–6} genetic algorithms,^{7–9} multiresolution exhaustive search,^{10,11} artificial neural network,¹² particle swarm,¹³ nested partitions,¹⁴ etc. Although those global algorithms may avoid local optima theoretically, they cannot guarantee quality solutions unless a significant number of iterations are allowed. While most previously published studies on BAO were designated for IMXT, algorithms introduced might be more difficult to hold their efficiency in implementation for IMPT. There may be two explicit causes. First, it is much more expensive to compute a score for an incident beam configuration in IMPT planning than that in IMXT because of larger data size.¹⁵ The dose influence data for IMPT must contain information of scanning spot depth which is an additional dimension beyond typical IMXT data. Second, the BAO search space can be much smaller in IMPT planning than that in IMXT. While IMPT often includes only two to three beams for treating most cancer sites, five to nine beams are typical in IMXT. For example, in the selection out of 36 equispaced coplanar beams with 10° interval, there are a total of 630 ($_{36}C_2$) possible combinations if two beams are desired for IMPT, whereas there are a total of 8 447 680 ($_{36}C_7$) possible combinations if seven beams are desired for IMXT. Here the increase of search space size is over 13 000 times. Stochastic-based optimization algorithms, e.g., simulated annealing and genetic algorithm, can be ideal for problems with very large search space. However, their advantages over greedy deterministic optimization algorithms with relative quick convergence may need to be investigated for problems with smaller search space such as BAO for IMPT.

Another critical distinction in IMPT planning can be the importance of plan robustness over delivery uncertainties which is usually absent in IMXT plan optimization. As protons deliver most of their dose at their Bragg peaks, misplaced Bragg peaks can easily cause underdosing in the target volume and overdosing in normal tissues.^{16–18} Therefore, IMPT plan can be very sensitive to treatment delivery uncertainties. The ultimate delivered dose distribution can be greatly deviated from the prescribed dose if uncertainties are not considered in the treatment planning process. There are two major sources of uncertainties. First, it is the range uncertainty of proton beams that can be caused by CT artifacts, the conversion from Hounsfield units to stopping powers, and geometric changes of the patients such as weight gain or loss, and so on.¹⁸ Second, the patient setup uncertainties. They can be caused by the misalignment of patient positions or tissue density heterogeneities.¹⁴ Various studies on the impact of different uncertainties such as system errors, organ motion, patient positioning on IMPT plan quality have been reported.^{17,19–22} Optimization models used in these studies were mainly based on quadratic programming (QP). They can be computationally challenging to solve if constraints for dose

requirements were added. Even only the non-negative constraints for spot intensities can introduce significant complexity to a QP model.

In this study, an uncertainty incorporated linear programming (LP) model is formulated to optimize an IMPT plan. We use a deterministic scenario-based approach similar to the one used by Pflugfelder *et al.*¹⁷ to account for uncertainties. The LP objective value thus indicates a merit score of a set of beam angles used. Uniformity constraints for doses of target voxels and upper bounds for doses of organs at risk (OAR) voxels are also imposed. We introduce a local neighborhood search (LNS) algorithm to optimize beam angles with fast convergence. The solution quality is compared with alternative algorithms and demonstrated on three prostate cases and two skull base chordoma cases.

The rest of this paper is organized as follows. Section II describes an LP model for optimizing a robust fluence map and the local neighborhood search algorithm for finding the optimal treatment beam angles. Section III presents the application of our proposed methods on phantom and clinical cases. Section IV discusses the insights of obtained results and Sec. V concludes this paper.

II. MATERIALS AND METHODS

II.A. Robust fluence map optimization model

We use a worst-case approach to account for systematic uncertainties and errors of IMPT delivery in our optimization model. Uncertainty-based scenarios of dose contribution are calculated independently. The model sets the dose calculation constraints in the most conservative way so that the resulting plan can represent the worst plan quality if included uncertainties were present. The idea of the worst-case dose distribution was introduced by Lomax *et al.*²³ It can be obtained based on different dose distributions for different scenarios, e.g., different ranges of proton beams and setup errors of isocenter. If a voxel is located within the target volume, the dose of this voxel is set as the minimum of all dose distributions in the worst-case dose distribution calculation. If a voxel is located in the surrounding normal tissues, the dose of this voxel is set as the maximum of all dose distributions. Although the worst-case dose distribution is physically invalid, it provides a lower bound of the worst treatment plan quality.¹⁷ For illustration, suppose that there are r dose distributions representing various scenarios caused by uncertainties, and the dose contribution parameter becomes $d_{p,a,b,r}$. Thus, the worst-case dose distribution can be calculated as follows:

$$D_{p \in T} = \min_r \left\{ \sum_{a,b} (x_{a,b} \cdot d_{p,a,b,r}), r = 1, 2, \dots, p \in T \right\}, \quad (1)$$

$$D_{p \in S \cup N} = \max_r \left\{ \sum_{a,b} (x_{a,b} \cdot d_{p,a,b,r}), r = 1, 2, \dots, p \in S \cup N \right\}, \quad (2)$$

where we define the decision variable of our IMPT fluence map optimization (FMO) model is the scanning spot weight $x_{a,b}$ of beam angle a at spot position b , where $a \in \mathcal{A}$, $b = 1, 2, \dots, B_a$, and B_a represents the maximum number of spots delivered at angle a . Let $d_{p,a,b,r}$ denote the r th dose contribution from pencil beam (a, b) to voxel p , where $p \in (T \cup S \cup N)$, and T , S , and N are three sets of voxels in the tumor target, OARs, and normal tissues, respectively. The total dose D_p that a voxel p with uncertainty scenario r receives is

$$D_p^r = \sum_{a,b} (x_{a,b} \cdot d_{p,a,b,r}). \quad (3)$$

Thus, given a set of selected treatment beam angles, $\bar{\mathcal{A}} \in \mathcal{A}$, the FMO model can be formulated as follows:

$$\min_x f(D), \quad (4)$$

subject to

$$D_p^r = \sum_{a,b} (x_{a,b} \cdot d_{p,a,b,r}) \quad \forall p \in (T \cup S \cup N), \quad (5)$$

$$L_T \leq D_p^r \leq U_T \quad \forall p \in T, r = 1, 2, \dots, \quad (6)$$

$$D_p^r \leq U_{S_i} \quad \forall p \in S_i, r = 1, 2, \dots, \quad (7)$$

$$0 \leq x_{a,b} \quad \forall a \in \bar{\mathcal{A}}, b = 1, 2, \dots, B_a, \quad (8)$$

$$\begin{aligned} f(D) = & w_T^- \left(\lambda_T \cdot e_T - \min_r \{D_T^r\} \right)_+ \|_1 \\ & + w_T^+ \left(\max_r \{D_T^r\} - \lambda_T \cdot e_T \right)_+ \|_1 \\ & + \sum_i w_{S_i} \left(\max_r \{D_{S_i}^r\} - \lambda_{S_i} \cdot e_{S_i} \right)_+ \|_1, \end{aligned} \quad (9)$$

where $(\cdot)_+$ denotes $\max\{\cdot, 0\}$ and e_T and e_{S_i} denote vectors of ones ($S_i \in S$, indicating voxel set for each OAR included). The parameters λ_T (e.g., the prescribed dose) and λ_{S_i} (e.g., zero dose) are soft bound control parameters, i.e., only penalizing target dose deviated from λ_T ($L_T \leq \lambda_T \leq U_T$), and OAR dose over λ_{S_i} ($\lambda_{S_i} \geq 0$). Weight factors, including w_T^+ , w_T^- , and w_{S_i} , are assigned for priorities of different optimization objectives. The values of these parameters are configured according to the treatment planner's preference. Note that the above LP model [Eqs. (4)–(8)] becomes a conventional FMO model when no uncertainty is considered, i.e., with r only indicating nominal scenario of dose distribution and $r = 1$. The dose contribution matrix $d_{p,a,b,r}$ was calculated using our in-house developed dose calculation algorithm.^{15,24–26}

II.B. Local neighborhood search algorithm for BAO

A local neighborhood search algorithm is introduced to find a local optimal solution subject to the neighborhood definition for a given starting feasible solution. In our implementation, the neighborhood of a beam angle set is defined by a one-angle-exchange algorithm.²⁷

The local search procedure first enumerates all elements of the neighborhood of a starting feasible solution. Next, one beam from the feasible solution set is selected. For its given angle, one angle from the neighborhood set is selected and exchanged with the angle from the current solution set, and the objective function is evaluated with this new angle set. We repeat this procedure until all angles in the neighborhood set are evaluated. The current solution is then updated with one yielding the most improvement in objective function value among those elements. This process continues with next angle in the current solution set until no more improving solutions exist.

Regarding to the beam angle set in the search space for the BAO problem, we consider a neighbor of a set by substituting one and only one angle of the set with a neighbor of that angle. This is the *1-Exchange*.²⁷ Note that the neighborhood size may increase exponentially if two or more elements of the vector are changed to form the vector's neighbor. Given a starting solution $\bar{\mathcal{A}}$, where $\bar{\mathcal{A}} \subset \mathcal{A}$, $|\bar{\mathcal{A}}| = n$, we define the neighborhood of $\bar{\mathcal{A}}$, $N(\bar{\mathcal{A}})$ as

$$\begin{aligned} N(\bar{\mathcal{A}}) = \{ \bar{\mathcal{A}}' : \bar{\mathcal{A}}' = \bar{\mathcal{A}} \cup \{a_j\} \setminus \{a_i\}, \\ \text{for } a_j \in \Theta(a_i), a_i \in \bar{\mathcal{A}} \}. \end{aligned} \quad (10)$$

We consider the neighbors of a fixed beam angle a_i as angles that are geometrically located within a_i 's adjacent area and a_i 's opposite direction, since those angles have similar contributions as a_i to the treatment plan in our observation. In addition, the beam angles possess the particular cyclicity. We take modular arithmetic for angles with 360, e.g., $(-20 \bmod 360) = 340 = 340$, or $(420 \bmod 360) = 60$. Thus, for $a_i \in \mathcal{A}$, the neighborhood of a_i , $\Theta(a_i)$, is defined as

$$\begin{aligned} \Theta(a_i) = \{ a'_i : a'_i = [a_i - \theta_0, a_i + \theta_0] \cup \{a_i + 180^\circ\}, \\ \text{for } a'_i \in \mathcal{A} \text{ and } a'_i \notin \bar{\mathcal{A}} \bmod 360^\circ, \end{aligned} \quad (11)$$

where θ_0 is a parameter that determines the size of $\Theta(a_i)$. Assume that we have 36 equispaced candidate beam angles in a solution pool $\mathcal{A} = \{0, 10, 20, \dots, 350\}$ and two angles are selected as a current solution set $\bar{\mathcal{A}} = \{40, 230\}$. Based on the beam angle neighborhood definition [Eq. (11)], if $\theta_0 = 20$, the neighbors of angle 40 are located within its proximal region $[40 - 20, 40 + 20]$, i.e., $[20, 60]$, and in its opposite direction $40 + 180$, i.e., 220. The angle 40 itself is excluded of course. So, $\Theta(40) = \{20, 30, 50, 60, 220\}$. In the same way, if $\theta_0 = 30$, $\Theta(230) = \{200, 210, 220, 240, 250, 260, 50\}$. Therefore, a larger θ_0 indicates a larger sized beam angle neighborhood set.

The LNS algorithm for solving the BAO problem starts with a given beam angle set $\bar{\mathcal{A}}_0 \in \mathcal{A}$ ($|\bar{\mathcal{A}}_0| = b$) as the current solution and its corresponding objective value of the FMO model. Initially, the index i is initialized to 0. The FMO model is iteratively solved using each of the neighboring angle sets $N(\bar{\mathcal{A}}_i)$ defined by Eq. (10). All resulting objective values are recorded. If the lowest value is less than $z(\bar{\mathcal{A}}_i)$, update the corresponding angle set as the current solution and update the index, $i = i + 1$. The algorithm continues to search $N(\bar{\mathcal{A}}_i)$ for an improving objective value. When no improving solution exists, the algorithm terminates the process and accepts the

TABLE I. Patient data and prescriptions for prostate cancer and skull base chordoma cases.

Site	Case	Prescription (Gy)	Number of voxels			
			CTV	Rectum	Bladder	Femoral heads
Prostate	1	76	2955	2522	4003	6727
	2	76	2308	2460	4563	5111
	3	76	3313	2449	4788	8413
Skull base			CTV	Brain	Brainstem	Cord
	1	74	3279	97 981	1954	1194
	2	74	1904	16 681	413	238

current solution as the local optimum. The LNS algorithm thus takes the following form:

0. Start with $\bar{\mathcal{A}}_0$, $z(\bar{\mathcal{A}}_0)$, $i = 0$;
1. *do* {
2. Generate neighborhood $N(\bar{\mathcal{A}}_i)$;
3. Search all sets in $N(\bar{\mathcal{A}}_i)$, and save the set with the lowest objective value as $\bar{\mathcal{A}}_{i+1}$;
4. Set $i = i + 1$;
5. } *while* $z(\bar{\mathcal{A}}_i) < z(\bar{\mathcal{A}}_{i-1})$;
6. Stop. The final local optimal solution is $\bar{\mathcal{A}}^* = \bar{\mathcal{A}}_{i-1}$ and $z^* = z(\bar{\mathcal{A}}_{i-1})$.

Note that the starting solution to the LNS algorithm can be any set of angles. A simple starting solution can be a set of equally spaced beam angles. For example, if $A = \{0, 10, 20, \dots, 350\}$ and $n = 4$, then $\bar{\mathcal{A}}_0$ can be $\{0, 90, 180, 270\}$, $\{10, 100, 190, 280\}$, $\dots$, or $\{80, 170, 260, 350\}$.

II.C. Setup for patient studies

We implemented our BAO algorithm on three prostate cancer cases and two skull-based chordoma cases. All cases were selected from our patient database at our institution retrospectively. For prostate cases, 36 equispaced coplanar beam angles were considered as candidate beam angles for selecting different numbers of optimal treatment angles. The prescribed dose to the clinical target volume (CTV) for irradiating the prostate tumor was set at 76 Gy. The dose volume requirements for the OARs were as follows: less than 25% of the rectum and bladder were allowed to receive 70 and 65 Gy or more, respectively. For skull base cases, 36 equispaced coplanar and eight manually selected noncoplanar beam angles were considered as candidates. The gross treatment volume (GTV) was used for case 1 to optimize plans with a prescription dose of 74 Gy. Meanwhile, the CTV was used for case 2 with a prescription dose of 66 Gy. The maximum dose for the brainstem was set at 60 Gy for both cases. The numbers of voxels in major volumes of interest are listed in Table I. In all cases, eight scenarios of uncertainties were considered in this study, including ± 5 mm (for prostate cases) or ± 3 mm (for skull base chordoma cases) setup errors for each of x, y, and z directions and skull base chordoma cases, respectively, and $\pm 3.5\%$ of range uncertainties over beam direction. The proposed BAO algorithm was modeled in general algebraic modeling system (GAMS) and MATLAB. The LP relaxation models were

solved using the interior point method in CPLEX v12.1 (IBM, Armonk, NY). All computations in this study were performed on a 64-bit Linux machine with an eight-core Intel Xeon 3 GHz processor (a single core was used in calculation) and 24 GB memory. For all patient studies, nominal and worst-case dose distributions are computed and evaluated to examine the optimized beam angles.

III. RESULTS

Beam angles optimized by our robust BAO algorithm for the three prostate cancer cases were listed in Table II. Optimized two-beam plans were $\{60, 270\}$, $\{90, 310\}$, and $\{50, 270\}$ for case 1, case 2, and case 3, respectively. While the conventional angle plan for treating prostate includes two parallel-opposed lateral beams, i.e., $\{90, 270\}$, optimized two-beam angle plans in this study contained one lateral angle (either 90 or 270) and one anterior oblique angle (310, 60, or 50). Optimized three-beam plans were $\{60, 270, 310\}$, $\{50, 90, 300\}$, and $\{50, 270, 310\}$, and four-beam plans were $\{50, 100, 230, 310\}$, $\{60, 100, 260, 310\}$, and $\{50, 110, 270, 320\}$ for case 1, case 2 and case 3, accordingly.

Figure 1 compares dose volume histograms for the CTV, rectum, and bladder for plans with conventional and optimized two-beam angles for the prostate case 1. The panel (a) shows the results from two conventional lateral-opposed angles and the panel (b) shows the results from two optimized angles. While the solid lines in Fig. 2 are based on the nominal dose distribution, the dashed lines are based on the worst-case dose distribution. For both dose distributions, plans with optimized angles demonstrated better rectum sparing over plans with bilateral beam angles. The dose coverage on the CTV showed almost equally good homogeneity in both angle plans. There were less differences of bladder sparing between two angle plans. We observed that the plans with optimized treatment angles were better at sparing the rectum than the $\{90, 270\}$ plans in all prostate cases. Mean-

TABLE II. Optimized two-, three-, and four-beam solutions for three prostate cancer cases.

Case	Two-beam	Three-beam	Four-beam
1	60,270	60,270,310	50,100,230,310
2	90,310	50,90,300	60,100,260,310
3	50,270	50,270,310	50,110,270,320

(a) Conventional angle plan {90,270}

(b) Optimized angle plan {60,270}

FIG. 1. Dose volume histograms for CTV, rectum, and bladder for IMPT plans with (a) conventional and (b) optimized two-beam configurations for the prostate cancer case 1. Solid and dashed lines are based on nominal and worst-case dose distributions, respectively.

while, the {90,270} plans were marginally better at sparing the bladder than plans with optimized in two cases. By comparing the difference between nominal and worst-case dose distributions, plans with both conventional and optimized beam angles demonstrated similar robustness as shown in Fig. 1. Figure 2 shows the mean dose on the rectum, the bladder and the femoral heads for all three cases. Almost all mean dose values were reduced by optimized angle plans. An average reduction of 4.0 Gy for the rectum and 6.0 Gy for the femoral heads were achieved. However, there was an average increase of 0.6 Gy for the bladder.

We further analyzed the data of the irradiated volumes at different dose levels in all prostate cases under worst-case dose distributions in plans with conventional two-beam angles ({90,270}), and optimized two- and three-beam angles. Table III lists the normalized rectum and bladder volumes re-

FIG. 2. Mean dose on OARs for IMPT plans with conventional (solid dot with outline) and optimized (solid dot without outline) two-beam configurations for three prostate cancer cases.

ceiving doses more than 30, 40, 50, 60, and 70 Gy; and the normalized volumes of femoral heads receiving doses more than 30, 35, 40, and 45 Gy. In all three cases, the volumes of rectum receiving doses more than 30, 40, 50, 60, and 70 Gy in the conventional two-beam angle plans were reduced by optimized two-beam angle plans, respectively. The improvement of rectum sparing by optimized three-beam angle plans over optimized two-beam ones was also consistent in all dose levels and all cases. More significant improvements of sparing femoral heads by using optimized angles were also shown in the dose volume data for all cases. However, the volumes of bladder receiving doses of 30, 40, 50, 60, and 70 Gy in the {90,270} plan were slightly increased by optimized two- and three-beam angle plan in three cases. In addition, there was no pronounced improvement found in plans with optimized four-beam angles over three-beam plans in all cases.

In order to analyze the convergence rate of the proposed LNS algorithm, we tracked objectives improved each iteration until the algorithm terminates. We also implemented a simulated annealing (SA) algorithm⁵ and a genetic algorithm (GA) (Ref. 7) to compare with LNS. Figure 3 shows the progression of objective convergence for the LNS, SA, and GA algorithms implemented on the prostate cancer case 1. Note that, globally optimal solutions were found by exhaustive search for both the two- and three-beam BAO cases. They are also shown by dashed-dotted lines in Fig. 3. When two-beam angles were optimized from 36, all three algorithms converged at the global optimum. While LNS terminated after 64 iterations, SA and GA terminated after 125 and 380 iterations, respectively [see Fig. 3(a)]. When three-beam angles were optimized from 36, LNS and SA found the same near globally optimal solution (objective values were 0.3111, where the global optimum is 0.3103), and the GA solution was relatively worst (objective value was 0.4008). The LNS was also the first to converge among three algorithms. LNS, SA, and GA run 63, 128, and 300 iterations, accordingly. Note that each iteration

TABLE III. Dose volume data of worst-case dose distributions for plans with conventional two beams, optimized two beams, and optimized three beams for three prostate cases.

ROI	Statistic	Case 1			Case 2			Case 3		
		Conventional two beams (%)	Optimized two beams (%)	Optimized three beams (%)	Conventional two beams (%)	Optimized two beams (%)	Optimized three beams (%)	Conventional two beams (%)	Optimized two beams (%)	Optimized three beams (%)
Rectum	V30Gy	23.8	17.9	16.5	31.8	23.9	24.1	26.5	18.9	18.1
	V40Gy	19.7	14.1	13.3	27.1	20.6	20.3	22.4	16.2	15.4
	V50Gy	15.1	12.3	11.4	21.8	16.7	17.2	17.8	13.7	13.8
	V60Gy	12.9	9.6	8.9	17.3	13.1	11.8	14.4	10.6	10.3
	V70Gy	8.3	6.3	6.2	11.6	7.8	7.5	9.9	8.2	7.8
Bladder	V30Gy	20.2	21.5	21.8	18.1	20.5	18.4	25.6	27.7	27.9
	V40Gy	17.3	18.4	18.9	15.8	17.0	16.0	21.1	24.5	24.6
	V50Gy	14.6	15.8	16.2	13.9	13.8	13.3	19.7	21.0	20.8
	V60Gy	10.1	10.9	11.2	11.0	10.8	10.8	14.3	17.9	17.9
	V70Gy	7.8	7.9	7.9	8.2	8.1	7.7	12.0	12.4	13.1
Femoral heads	V30Gy	39.5	31.7	6.8	42.2	29.4	7.3	40.1	28.2	6.2
	V35Gy	15.3	8.2	3.3	14.1	7.6	1.9	17.8	15.7	2.9
	V40Gy	0.9	0.7	0.7	0.9	0.1	0.8	1.1	0.7	0.8
	V45Gy	0	0	0	0	0	0.1	0	0.1	0.1

in which a LP model is solved took CPU times ranging from 1 to 2 min.

We also implemented our robust BAO algorithm on two skull base chordoma cases (see Fig. 4 for geometries). Optimized two-beam plans were {70,290} and {80,(280,50)} for case 1 and 2, respectively. Optimized three-beam plans were {60,280,330} and {60,(280,50),(320,90)}, accordingly. Note that a noncoplanar beam (a,b) indicates a beam in gantry angle a and couch angle b. Figure 5 compares dose volume histograms for the GTV and the brainstem for plans with conventional [panel (a)] and optimized [panel (b)] two-beam configurations for the skull base chordoma case 1. While solid lines indicate the nominal dose distribution, the dashed lines indicate the worst-case dose distribution in Fig. 5. For both dose distributions, plans with optimized angles demonstrated better homogeneous dose coverage on the GTV and improved brainstem sparing over plans with bilateral beam angles. Note that the cord was not shown in the comparison, since there were hardly differences of cord sparing between two angle plans. By comparing the difference between nominal and worst-case dose distributions, the plan with optimized angles demonstrated better robustness over the plan with conventional angles. We also observed similar dosimetric advantages of optimized angles for three-beam plans for both cases.

For studies presented in this paper, the calculation times of the proposed algorithm ranged from about 60 to 80 min for prostate cases (including two- and three-beam plans), and from about 20 to 30 min for skull base chordoma cases (including two- and three-beam cases).

IV. DISCUSSION

Although the BAO problem has been extensively studied in conventional radiation therapy with photons, its indication

in IMPT treatment planning has been rarely reported. This paper focuses on an initial investigation on the IMPT BAO problem. It is the first work in literature to study the BAO as well as BAO incorporated with robust optimization in literature for IMPT to our knowledge. Two primal distinctions of this problem comparing IMPT with IMXT were addressed in this work. First, the sensitivity to uncertainties was tackled by a robust IMPT plan optimization model. Instead of using nominal dose distributions, robustly optimized dose distributions were compared to find improved angle configurations. Second, as IMPT requires much less numbers of treatment beams, a typical reduced search space was handled by a deterministic local neighborhood search optimization algorithm. Stochastic global algorithms such as simulated annealing and genetic algorithm require a large number of iterations to guarantee convergence. We showed that the proposed local neighborhood search algorithm could greatly reduce the number of iterations required by simulated annealing and genetic algorithm without compromising solution quality.

Our study on clinical cases for two cancer sites, i.e., prostate and skull base, demonstrated that the proposed BAO algorithm might be able to automatically find quality IMPT treatment beam angles without manual trial-and-errors. In addition, nonintuitive beam angles may be identified by the algorithm to achieve dosimetric advantages over plans with intuitive beam angles. For example, optimized angles 50, 60, and 310 are all nonintuitive but plans with these angles improved rectum and femoral heads sparing significantly than plans with conventional bilateral angles (90 and 270) in our studies for prostate cases. The difficulty for intuitively selecting optimal beam angles can increase exponentially when desired numbers of angles are more than two or noncoplanar angles are included. Previous researchers have illustrated that optimal beam angles can often be nonintuitive in IMXT treat-

FIG. 3. Illustration of objective value convergence for different BAO algorithms including LNS, SA, and GA. Global optima are shown by dashed-dotted lines.

ment planning.²⁸ Our initial investigation here confirmed that it might also be the case for IMPT planning.

The current clinical practice of IMPT prostate treatment typically uses only two parallel-opposed lateral beam angles. Anterior, posterior, and oblique angles are avoided due to their uncertainty risks.²⁹ This practice may be because current commercial treatment planning systems have no robust optimization capabilities. With the help of robust optimization,^{17,30–32} optimized angles, such as anterior oblique angles found in our study for prostate treatment, have the potential to be ultimately used in clinical treatment so that plan quality may be improved. From the perspective of modality other than inverse plan optimization, some recent studies have investigated that anterior, posterior, and oblique angles could be safely included in clinical prostate treatment with a better proton range control technique.³³ The primary gains of using those angles were significant improvement on sparing

FIG. 4. CT slices in a transverse plane for two skull base chordoma cases. Panels (a) and (b) show case 1 and 2, respectively. GTV (case 1), CTV (case 2) and brainstems are contoured by solid lines. Equally spaced beam angles that target GTV or CTV are demonstrated by white lines.

rectum and femoral heads,³³ which were also found in this work.

We observed that the optimized beam angles in our clinical studies for prostate were consistently characteristic from patient to patient. For example, lateral angles, 90 and 270, and anterior oblique angles, 60 and 310 were mostly selected in optimized angle plans with different numbers of beams (Table II). Although optimal beam angles may be patient specific, information on preferred angles may be added into BAO algorithms and improve their efficiency. Furthermore, it is promising that class solutions of beam angles for certain cancer types might be revealed if extensive clinical studies will be carried out. Previous studies have suggested that beam angle class solutions are of great importance in clinical practice because they may significantly reduce the effort for beam placement in IMXT treatment planning.³⁴ For IMPT planning, the validation of class solutions for simple cancer sites such as prostate would bear on great importance in clinical routines.

(a) Conventional angle set {90,270}

(b) Optimized angle set {70,290}

FIG. 5. Dose volume histograms for GTV and brainstem for IMPT plans with (a) conventional and (b) optimized two-beam configurations for the skull base chordoma case 1. Solid and dashed lines are based on nominal and worst-case dose distributions, respectively.

The local search framework developed in this work for solving the IMPT BAO problem can be important for current investigation on improving IMPT plan quality. This automatic tool can be equipped with any IMPT optimization models other than the one used here. Besides conventional nominal optimization models, various robust optimization models have been studied, including deterministic,^{17,31} probabilistic,^{32,35} and multiobjective³⁰ oriented ones. Treatment planners may select any of those optimization models according to their best interest and fit it into the proposed BAO framework to obtain optimal beam angles. Therefore, benefits of those well-developed optimization models may be maximized by including not only beamlet intensity but also beam angle selection variables.

V. CONCLUSION

This study focuses on the BAO problem in IMPT treatment planning. We introduced an uncertainty-incorporated BAO algorithm for IMPT. The worst-case optimization approach was used to optimize robust treatment plans in the most conservative manner. The beam angles are optimized by the uncertainty-incorporated BAO algorithm for achieving not only dosimetric benefits but also robustness against uncertainties. We have demonstrated the algorithm performed well in finding quality beam angles on three prostate cancer cases and two skull base chordoma cases. The efficiency of the local search strategy was also demonstrated by comparing it with alternative BAO algorithms. However, more patient studies are necessary to further validate the algorithm and understand the physical rationalities of preferable beam angles for IMPT.

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