Comparisons of treatment optimization directly incorporating random patient setup uncertainty with a margin-based approach

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The purpose of this study is to incorporate the dosimetric effect of random patient positioning uncertainties directly into a commercial treatment planning system's IMRT plan optimization algorithm through probabilistic treatment planning (PTP) and compare coverage of this method with margin-based planning. In this work, PTP eliminates explicit margins and optimizes directly on the estimated integral treatment dose to determine optimal patient dose in the presence of setup uncertainties. Twenty-eight prostate patient plans adhering to the RTOG-0126 criteria are optimized using both margin-based and PTP methods. Only random errors are considered. For margin-based plans, the planning target volume is created by expanding the clinical target volume (CTV) by 2.1 mm to accommodate the simulated 3 mm random setup uncertainty. Random setup uncertainties are incorporated into IMRT dose evaluation by convolving each beam's incident fluence with a $\sigma=3$ mm Gaussian prior to dose calculation. PTP optimization uses the convolved fluence to estimate dose to ensure CTV coverage during plan optimization. PTP-based plans are compared to margin-based plans with equal CTV coverage in the presence of setup errors based on dose-volume metrics. The sensitivity of the optimized plans to patient-specific setup uncertainty variations is assessed by evaluating dose metrics for dose distributions corresponding to halving and doubling of the random setup uncertainty used in the optimization. Margin-based and PTP-based plans show similar target coverage. A physician review shows that PTP is preferred for 21 patients, margin-based plans are preferred in 2 patients, no preference is expressed for 1 patient, and both autogenerated plans are rejected for 4 patients. For the PTP-based plans, the average CTV receiving the prescription dose decreases by 0.5%, while the mean dose to the CTV increases by 0.7%. The CTV tumor control probability (TCP) is the same for both methods with the exception of one case in which PTP gave a slightly higher TCP. For critical structures that do not meet the optimization criteria, PTP shows a decrease in the volume receiving the maximum specified dose. PTP reduces local normal tissue volumes receiving the maximum dose on average by 48%. PTP results in lower mean dose to all critical structures for all plans. PTP results in a 2.5% increase in the probability of uncomplicated control ($P+$), along with a 1.9% reduction in rectum normal tissue complication probability (NTCP), and a 0.7% reduction in bladder NTCP. PTP-based plans show improved conformality as compared with margin-based plans with an average PTP-based dosimetric margin at 7100 cGy of 0.65 cm compared with the margin-based 0.90 cm and a PTP-based dosimetric margin at 3960 cGy of 1.60 cm compared with the margin-based 1.90 cm. PTP-based plans show similar sensitivity to variations of the uncertainty during treatment from the uncertainty used in planning as compared to margin-based plans. For equal target coverage, when compared to margin-based plans, PTP results in equal or lower doses to normal structures. PTP results in more conformal plans than margin-based plans and shows similar sensitivity to variations in uncertainty. © 2009 American Association of Physicists in Medicine. [DOI: [10.1118/1.3176940](https://doi.org/10.1118/1.3176940)]

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I. INTRODUCTION

In external beam radiation therapy, the current method of compensating for patient positioning uncertainties is to apply margins around the contoured patient structures.^{1,2} Treatment dose levels are planned to be delivered to the margin-expanded region around the target while doses are limited within the margin-expanded regions around critical structures. Margins are intended to ensure that the target is covered when subject to "reasonable" random and systematic patient position variations and that critical structures are

similarly spared when subject to such variations. If the clinical target volume (CTV) margin is insufficient, the CTV can move outside of the expected treatment region resulting in underdosing of the target and poor tumor control. Similarly, if a planning organ at risk volume (PRV) margin is insufficient, normal tissue and critical structures can move into regions receiving treatment dose levels resulting in unnecessarily high doses to these structures, which may result in greater complications. The addition of a margin reduces the likelihood of the target being outside of the treatment region; however, this also increases the likelihood that normal tissue

or critical structures will fall within the treatment dose region. In order to meet the goals of margin-based planning, formulas have been created to determine the size of suitable margins.^{3,4} An example is the margin formula of van Herk *et al.*,⁴⁻⁶ which specifically aims for 90% of patients to receive 95% of the prescribed treatment dose.

Patient treatment involves many sources of positioning uncertainty. Random uncertainty stems from daily changes in patient positioning and patient anatomy. Systematic uncertainty represents a shift from the mean of the expected patient position. Random uncertainty results in a blurring of the dose distribution. Systematic uncertainty results in an unknown shift in the dose distribution. Given these differences, the methods of including the effects of these uncertainties into the dose distribution differ. Random uncertainties can be compensated for by multiple sampling of the patient position or by convolution. Systematic uncertainties do not lend themselves to convolution-based solutions. Fortunately, modern advances in image guidance have decreased the systematic and random uncertainties present in radiation therapy. Implanted markers, portal image-based setup, and cone-beam CT are just a few of the methods that show potential to decrease setup errors.⁷⁻¹² Systematic uncertainties can be significantly reduced using repeated imaging adaptive setup protocols such as those used by Yan *et al.* and Hoogeman *et al.* that indicate that use of four to six initial portal or CT images can estimate and effectively reduce systematic setup errors.^{13,14} While adaptive setup protocols can significantly decrease systematic uncertainty, random uncertainties are less effectively reduced using these methods.¹⁴

In IMRT planning, the margin-expanded planning target volume (PTV) acts as a surrogate for the CTV, the actual position of which varies from fraction to fraction. With the patient setup uncertainty added over several treatment fractions, ensuring coverage or sparing of the margin-expanded volume should ensure coverage or sparing of the underlying structure of interest. In margin-based planning, the dose distribution of the expanded structure is intended to be representative of the underlying structure when expected setup uncertainties are considered.⁴ However, with knowledge of the setup uncertainty and tissue motion distributions, the PTV surrogate can be removed and planning can be done directly on the CTV. Probabilistic treatment planning (PTP) attempts to ensure coverage of the target without addition of explicit margins by incorporating an uncertainty model directly into the plan optimization process. Several authors have studied PTP.¹⁵⁻³¹ The general finding of these studies is that PTP reduces normal tissue and organ at risk (OAR) doses while maintaining the same target coverage as margin-based plans.

The purpose of this study is to implement a method of incorporating random uncertainty into treatment planning and to compare this method with margin-based planning. Plans are generated using standard dose-volume histogram (DVH)-based criteria for prostate planning on a large population of patients including many structures with criteria defined in RTOG0126. The simplicity of the proposed method allows for arbitrary optimization objective functions to be

defined in the treatment planning system (TPS). Comparison metrics include DVH analysis, mean dose, tumor control probability (TCP), normal tissue complication probability (NTCP), and coverage probability. Systematic errors are not considered within this optimization. It is assumed that systematic errors are substantially reduced by application of an adaptive therapy protocol,¹⁴ and any remaining systematic uncertainty in a structure's position is incorporated into the structure contours. Fluence convolution is used to approximate the effects of random patient setup errors over multiple fractions of dose delivery. The validity of the fluence convolution assumption is tested by sampling different possible treatment scenarios. The sensitivity of the optimized result to changes in the patient's random setup uncertainty from that applied within the optimization is also studied.

This paper deviates from previous PTP work in that it uses existing objective functions directly within the commercial TPS. Additionally, fluence convolution is used to simulate the effect of random errors instead of dose convolution during the plan optimization, typical DVH-based objective functions are used instead of custom TCP-based objective functions, and a large patient population is used to demonstrate statistical significance of the similarity in dose coverage for the CTV and the dose reduction to normal tissues for PTP. This study compares PTP to margin-based planning, showing differences using the DVH metrics used in optimization. Models for $P+$, TCP, and NTCP are used to compare plan quality. Dosimetric margins are computed for both methods to evaluate conformity changes between methods. Finally, sensitivity analysis is conducted to verify that PTP is not highly sensitive to inaccuracies in the patient uncertainty distribution estimate.

II. MATERIALS AND METHODS

Patient imaging data and structure contours used in this study are derived from 28 in-house prostate patients. In accordance with our institutional review board protocol, all patient identifiable information is stripped from each data set prior to use in the study. Since this study employs a paired comparison between two planning methods that are unrelated to the treatment plans used for the actual patient treatments, the plans that were used for patient treatment are deleted. Additional structure contours are added as needed.

For each patient image set, IMRT treatment plans are developed using Philips Medical Systems Pinnacle³ 8.1w research version (Philips Medical Systems, Fitchburg, WI). The research version allows for the in-house code to be incorporated into the planning system by way of plugins. Dose is calculated using the adaptive convolution algorithm with a dose grid of $2 \times 2 \times 2$ mm³. The IMRT plans are optimized with direct machine parameter optimization (DMPO). Each patient is planned with seven beam angles of 30°, 80°, 130°, 180°, 230°, 280°, and 330° in IEC coordinates. Patients are each planned according to criteria specified by RTOG0126, an external beam radiation therapy prostate carcinoma dose

TABLE I. Optimization criteria used for generating patient plans, based on RTOG0126. Values of “Max.” for the volume indicate that the specified dose should not be exceeded anywhere within the volume.

Structure	Dose (cGy)	Volume
Target	>7920	98%
	<8470	2%
Rectum	<6000	50%
	<6500	35%
	<7000	25%
	<7500	15%
	<8470	Max.
Bladder	<6500	50%
	<7000	35%
	<7500	25%
	<8000	15%
	<8470	Max.
Left femur	<3500	50%
	<5000	Max.
Right femur	<3500	50%
	<5000	Max.
LNT	<5000	Max.

escalation protocol. The plan optimization criteria are shown in Table I. Each virtual patient is planned to be delivered over a course of 30 treatment fractions.

Two planning approaches are used, traditional margin-based planning and PTP. For margin-based planning, a PTV is created using a 2.1 mm margin around the CTV. This is in accordance with the margin formula of van Herk *et al.*^{4–6} which recommends a margin of $M=2.5\Sigma+0.7\sigma$. With an assumed random uncertainty of $\sigma=3$ mm and no systematic uncertainty ($\Sigma=0$), the recommended margin is $M=2.5(0)+0.7(3)=2.1$ mm.

The 3 mm random setup uncertainty is representative of those used in related literature^{4,6,15,17,30,32} and is consistent with, though somewhat larger than, what is observed in in-house internal marker-based daily alignment protocol. Reported random setup uncertainty values have significant variation, ranging from 0.9 to 5.1 mm. We believe that the exact value for the assumed random uncertainty is not required for the comparisons performed in this study. The simulations assume that the value of the uncertainty is known and plan according to this known value. Afterwards, the final dose for the treatment course is computed with the same uncertainty as in planning. Both arms of the study use the same random uncertainty assumption. This eliminates the need for knowledge of the exact value of real patient uncertainty. In actual clinical application of the proposed methods, in-house measurements of setup uncertainty would be required.

Standard margin-based plans are optimized using the criteria specified above. In margin-based planning, the target is the PTV. A pseudovolume termed local normal tissue (LNT), which is a ring extending from 2 cm outside of the CTV to 4 cm outside of the CTV, is used by the optimization process to attempt to reduce dose outside of the target. After optimi-

FIG. 1. PTP optimization flow using fluence convolution used in this study.

zation is completed, dose for the margin-based plan is recalculated using fluence convolution, as discussed below, to generate the dose distribution representative of the patient subject to random setup uncertainties over the 30-fraction treatment.

PTP-based plans are optimized using the same criteria as the margin-based plans with the exception of the target structure criterion. For PTP, the CTV is used as the target structure in planning rather than the PTV. A flow chart describing the PTP optimization process is shown in Fig. 1. During each iteration of the optimization, an in-house written plugin is used to convolve each beam's incident fluence with a $\sigma=3$ mm Gaussian during the dose computation process. The dose resultant of the convolved fluence is then used by the optimizer to determine the next update to the fluence matrix. Fluence updates are performed on an unconvolved representation of each beam's fluence matrix. After optimization is completed, the dose distribution is representative of the dose distribution of a patient subject to random uncertainty.

The convolution plugin operates by intercepting the intensity-modulated fluence before casting the fluence through the patient geometry. The plugin convolves the fluence with a kernel representing the probability density function (PDF) of the random patient positioning uncertainty, assumed to be a Gaussian kernel for this study. This efficiently simulates the effect of uncertainty over an entire fractionated treatment course, with an infinite number of fractions. The convolved fluence is then passed back to the dose calculation engine. The resultant dose distribution is the result of a con-

TABLE II. Parameters used in TCP and NTCP evaluations. Values are equivalent to the default values given by the Pinnacle TPS (Refs. 40–42).

Type	ROI	Organ/tumor	End point/stage	D_{50}	Gamma	Alpha/beta	Seriality
TCP	CTV	Prostate	Stage B	5270	4.2	10	
NTCP	Bladder	Bladder	Contracture	8000	3	3	0.18
NTCP	Rectum	Rectum	Necrosis/stenos	8000	2.2	3	1.5
NTCP	Left femur	Femur	Necrosis	6500	2.7	3	1
NTCP	Right femur	Femur	Necrosis	6500	2.7	3	1
NTCP	LNT	Normal tissue	Necrosis	6500	2.8	3	1

volved fluence. Fluence convolution-based dose calculations are used in the PTP optimization process and in the comparative analysis for margin-based plans.

Fluence convolution is technically only valid for an infinite number of fractions. Unkelbach and Oelfke²⁷ demonstrated that PTP methods that optimize the expectation value of the dose can yield undesirable dose undulations when delivered in a finite number of fractions. Therefore, they required a variance reduction term in the objective function to minimize these undulations.

To determine if our optimization results show such undulations, we perform postoptimization treatment delivery simulations to simulate multiple 30-fraction treatment courses for a single patient. This is similar to the stochastic method used by Craig *et al.* to validate dose convolution.³³ A single treatment course is simulated by computing the total dose for 30 fractions, where each fraction is simulated by shifting the fluence by a random value sampled from a $\sigma=3$ mm Gaussian and computing the dose. The dose from each fraction is summed to produce a distribution representative of the dose accumulated over an entire treatment course. This process is repeated 100 times to produce a total of 3000 fractions representing 100 treatment courses. The results of these treatment courses are then compared to a treatment course computed using fluence convolution. For each total treatment dose, the difference in DVH results from the convolution method is computed. Validation of convolution is shown on both PTP-based and margin-based optimized fluences.

For evaluation of the clinical acceptability of the automatically generated treatment plans, both PTP-based and margin-based plans are reviewed by a physician. The physician determines if each plan is clinically acceptable and chooses the preferred plan for treatment.

Comparisons between plans are conducted based on the dose that incorporates the expected random daily setup errors. For each structure, plans are compared based upon the dose-volume criteria specified during optimization. The volume receiving the prescription dose and the dose received by the prescription volume are computed at each point specified in the plan criteria. Plan criteria that are completely satisfied by the optimized dose distribution are excluded from the analysis as the optimizer does not attempt to improve the plan beyond the defined criteria. For example, given the objectives used in this study, if the dose to the bladder is below 65 Gy the planning objective would be met; therefore, this

criterion would not be reported. Since the dose distributions used in this evaluation include the effects of random errors, both margin-based and PTP methods use the CTV in the DVH analysis. The PTV is only used in the optimization process for margin-based planning as it is only a surrogate for the complete treatment dose on a static plan. In addition to dose-volume metrics used as optimization objectives, the mean dose to each structure is computed.

For each of the structures specified in the plan criteria, TCP and NTCP indices are computed. These are computed using the Biology tool available under the Plan Evaluation menu in Pinnacle. Parameters for TCP/NTCP indices are equal to the defaults for each given organ in the Biology tool. Table II displays these values. TCP is computed for the target structure and NTCP is computed for normal tissue structures. Additionally $P+$ is computed for each plan. $P+$ is a composite measure incorporating all TCP and NTCP indices from the plan into a single metric which represents the probability of uncomplicated tumor control. For these metrics, an increase in TCP or $P+$ is considered beneficial while a decrease in NTCP is preferred.

The conformity of the plans is quantified by computing the dosimetric margin distribution (DMD).³⁴ The DMD is a generalization of the ICRU conformity index² that measures the distance a structure can move before crossing a given isodose line in different directions. DMD evaluations are performed on the fluence-convolved dose distributions for the CTV to both the 90% prescription line (7100 cGy) and the 50% prescription dose line (3960 cGy). The DMD is obtained from 146 equispaced directions around the CTV. The 50% isodose line is evaluated since it corresponds to the irradiated volume² and conventionally indicates the location of the edge of the treated volume.

Clinically, the random component of the setup uncertainty varies from patient to patient and is unknown at the time of planning. The sensitivity of the plans generated assuming a $\sigma=3$ mm random uncertainty to deviations in patient-specific random uncertainty value σ_T is studied by evaluating the dose distributions corresponding to halving ($\sigma_T=1.5$ mm) and doubling ($\sigma_T=6$ mm) the uncertainty used during the plan optimization. DVH indices are compared and the number of plan objectives met by each is scored.

TABLE III. Minimum, maximum, range, mean, and standard deviation of DVH criteria observed over the 100 simulated treatment courses for the CTV and LNT structures compared with convolution. Average difference is the convolution value minus the mean of the simulated treatment courses. RMS value is the sum of the squared differences of each simulated course from the convolution value. Simulated treatment course values are the difference from convolution for volumes and the percentage difference relative to convolution for doses.

				Simulated treatment courses					
				Min. (%)	Max. (%)	Range (%)	Average (%)	RMS (%)	Standard deviation (%)
Convolution									
Margin based	CTV	V_{7920}	98.0%	−0.7	0.6	1.3	0.0	0.3	0.3
		D_{98}	7920 cGy	−0.2	0.2	0.5	0.0	0.1	0.1
		V_{8470}	0.4%	−0.4	0.8	1.2	0.1	0.3	0.3
		Max.	8506 cGy	0.0	0.1	0.1	0.0	0.0	0.0
	LNT	V_{5000}	1.1%	−0.1	0.1	0.2	0.0	0.0	0.0
PTP based	CTV	V_{7920}	97.5%	−2.1	1.0	3.0	−0.1	0.6	0.6
		D_{98}	7890 cGy	−1.8	0.7	2.5	−0.1	0.5	0.5
		V_{8470}	0.0%	−1.6	1.5	3.1	0.3	0.6	0.6
		Max.	8470 cGy	−0.2	0.3	0.5	0.1	0.1	0.1
	LNT	V_{5000}	0.7%	−0.1	0.1	0.1	0.0	0.0	0.0

III. RESULTS

The suitability of using fluence convolution to simulate the 30-fraction treatment delivery for plan evaluation and plan optimization is shown in Table III. The variability of margin-based and PTP-based plans for one hundred 30-fraction delivery simulations and deviations from convolution are evaluated using the planning DVH criteria. For margin-based plans, the convolved dose differs by <0.1% from the average dose from treatment simulations. The volume receiving the prescription dose after convolution differs by 0.02% from the volume receiving the prescription dose from treatment simulations. The <0.1% variability in dose observed is much smaller than the 2%–3% accepted variability in beam delivery^{35,36} and is therefore considered clinically acceptable. The maximum and minimum doses deviations are also well within a 2% tolerance. For PTP-based plans, the difference between the convolution and the average of the treatment simulations is with 0.1% in dose and 0.3% in volume. The 0.5% variability of the PTP-based plans for the treatment simulations is larger than the 0.1% observed for the margin-based plans but still well within a 2% tolerance. The maximum deviation is also larger but within tolerance. One treatment course simulation varies by 2.1% from the convolution volume at 7920 cGy. For both methods, all critical structures aside from the LNT structure remain below plan criteria for all simulations. The LNT volume in simulated treatment courses differs by less than 0.1% from convolution for both methods. While each simulated random treatment course yields slightly different doses, the variation is within typical clinical tolerances. In this study, 100% of simulations produce dose distributions that deliver >7524 cGy (95% of the prescription dose) for both PTP-based and margin-based plans. This exceeds the 90% of patients expected when using the margin formula of van Herk *et al.* and is due to the fact that only random setup uncertainties are considered.

Margin-based planning and PTP planning are successfully

completed on all patient plans. A comparison of isodose profiles on a transverse slice through the isocenter for one patient with PTP-based and margin-based (with and without convolution) plans is shown in Fig. 2. As is typical in dose-volume based optimization, final plans result in a trade-off between the objective function criteria, with not all treatment objectives being fully met. All plans meet the specified criteria for left femur and right femur using both methods. One margin-based planning patient and a different PTP patient exceed the bladder maximum dose objective. All other bladder objectives are met for all patients. One PTP patient exceeds the 8470 cGy rectum maximum dose objective by 0.3 cGy. Two margin-based plans and two PTP-based plans exceed the rectum 7500 cGy objective (by 36 and 3 cGy for the margin-based plans and by 5 and 103 cGy for the PTP-based plans; the 3 and 103 cGy deviations are for the same patient). All other rectum objectives are met for all patients.

Physician review of the plans indicates that the PTP-based plan is preferred over the margin-based plan for 21 out of 28 total patients. For one patient, the clinician indicated that there is no preference between plans. For two of the patients,

FIG. 2. Typical isodose profiles on a transverse slice passing through the isocenter for (a) the optimized margin-based plan, without inclusion of the effect of the random patient setup errors, (b) the optimized margin-based plan, with inclusion of the random patient setup errors, and (c) the PTP-based plan, which inherently incorporates the effect of random patient setup errors.

FIG. 3. (a) The percentage difference in the CTV doses to 98% of the volume between the margin-based and PTP-based plans for each patient. The average difference of -0.5% is indicated by the small bar. Negative values indicate a lower dose for the PTP-based plans. 0.5% corresponds to a 39.6 cGy difference. (b) The percentage difference in the LNT volumes receiving 5000 cGy. The average difference of -48% is indicated by the small bar. Negative values indicate a lower volume for the PTP-based plans. 48% corresponds to a 409 cc reduction in volume. (c) The percentage difference in the local normal tissue maximum doses between the margin-based and PTP-based plans for each patient. The average difference of -1.9% is indicated by the small bar. 1.9% corresponds to a 120.7 cGy difference.

the margin-based plan is preferred due to a slightly greater amount of the rectum exposed to high doses in the PTP plan. For four of the patients, the physician rejected both of the autogenerated plans due to the high dose to the critical structures. For two additional patients, the physician would reject only the margin-based plan. None of the PTP-based plans are rejected without the margin-based plan for the same patient being rejected. In a true clinical setting, optimization parameters for failing plans would have been modified to meet the planning criteria; however, for consistency, standard criteria are used for all plan evaluations in this study. Histograms of per-patient deviations in the dose-volume indices, $\Delta = 100(1 - D_{V_x}^{\text{PTP}}/D_{V_x}^{\text{MP}})$ or $\Delta = 100(1 - V_{D_y}^{\text{PTP}}/V_{D_y}^{\text{MP}})$, where D_{V_x} is the dose received by V_x percentage of the volume for the structure indicated and V_{D_y} is the volume receiving a dose of

FIG. 4. (a) The percentage difference in CTV mean dose between the margin-based and PTP-based plans for each patient. The average difference of 0.7% is indicated by the small bar. Negative values indicate a lower dose for the PTP plans. 0.7% corresponds to a 60.1 cGy difference. (b) The percentage difference in LNT mean dose between the margin-based and PTP-based plans for each patient. The average difference of 12.9% is indicated by the small bar. 12.9% corresponds to a 268 cGy difference.

D_y for the structure indicated, are shown in Fig. 3. Summary results of DVH analysis are shown in Table IV. Averaged over all patients, the CTV D_{98} is 0.5% lower for PTP as compared to margin-based planning. The CTV volume receiving 7920 cGy does not differ significantly for this objective ($p=0.092$). All p values are obtained from a two-tailed paired t test. The maximum 8470 cGy dose objective shows no significant differences between PTP- and margin-based planning ($p=0.44$). PTP shows a 48% decrease in volume receiving the 5000 cGy maximum dose objective for LNT with $p<0.0001$. There is a 1.9% decrease in the maximum dose delivered to the target with $p=0.0095$.

Histograms of per-patient deviations in the mean dose, $\Delta = 100(1 - \bar{D}^{\text{PTP}}/\bar{D}^{\text{MP}})$, where $\bar{D}$ is the mean dose delivered to the structure indicated, are shown in Fig. 4. Summary results of mean dose analysis are shown in Table V. The CTV on average receives a slightly higher mean dose ($+0.74\%$, $p<0.0001$). PTP results in a significantly ($p<0.0001$) lower mean dose to critical structures. Mean doses to all critical structures on all patient plans are reduced compared with margin-based plans as follows: Bladder, -14.2% ; rectum, -8% ; left femur, -11.3% ; right femur, -11% ; and LNT, -12.9% .

Histograms of absolute per-patient deviations in the $P+$, TCP, and NTCP, $\Delta = B^{\text{PTP}} - B^{\text{MP}}$, where B is the $P+$, TCP, or

TABLE IV. Mean, maximum, minimum, and p value for the difference in doses and difference in volumes between margin-based and PTP-based plans for the listed objectives. Plan objectives not listed were met by both methods for all plans. Δ is used to indicate “difference in.”

Structure	Dose (cGy)	Volume (%)	Δ dose (%)	Max. (%)	Min. (%)	p	Δ volume (%)	Max. (%)	Min. (%)	P
Target	>7920	98	-0.5	0.6	-2.4	0.0013	-0.4	4.7	-3.0	0.0916
	<8470	2	0.1	1.4	-0.7	0.1040	66.6	780.1	-86.6	0.4415
Rectum	<7500	15	a							
	<8470		b							
Bladder	<8470		c							
LNT	<5000		-1.9	4.9	-10.0	0.0095	-47.9	50.2	-94.4	<0.0001

^aAll plans met objectives except for two PTP-based plans and two margin-based plans.

^bAll plans met criteria except for one PTP-based plan.

^cAll plans met criteria except for one PTP-based plan and one margin-based plan.

TABLE V. Mean, maximum, and minimum differences in mean doses between margin-based and PTP-based plans, with associated p values for objective structures. Δ is used to indicate “difference in.”

Structure	Δ mean (%)	Max. (%)	Min. (%)	p
CTV	0.7	2.0	-1.2	<0.0001
Rectum	-8.0	-1.6	-15.5	<0.0001
Bladder	-14.2	-4.5	-26.4	<0.0001
Left Femur	-11.3	-5.0	-20.6	<0.0001
Right Femur	-11.1	-3.0	-18.5	<0.0001
LNT	-12.9	-9.9	-18.2	<0.0001

NTCP value for the structure indicated, are shown in Fig. 5. Summary results of $P+$, TCP, and NTCP analysis are shown in Table VI. The PTP-based plans on average show an absolute increase in $P+$ of +2.5% over margin-based plans. ($p=0.0002$). The TCP for both PTP-based and margin-based plans are equal at 99.9% for all but one plan. That plan shows an increase in TCP of 0.01% from 88.1% to 89.2% for the PTP-based plan. The rectum NTCP decreases for PTP-based plans by an average of 1.9% with $p=0.0014$. Rectal NTCP differences range from an increase of 2.8% to a decrease of 7% for PTP. Bladder NTCP values decrease on average by 0.7%, $p<0.0001$. LNT NTCP is decreased by 0.06%, $p=0.0028$. The left and right femurs for all patients for both PTP-based and margin-based plans have 0 NTCP.

FIG. 5. (a) The absolute difference in $P+$ between the margin-based and PTP-based plans for each patient. The average difference of 2.45% is indicated by the small bar. Positive values indicate a better treatment outcome for the PTP-based plans. (b) The absolute difference in rectum NTCPs between the margin-based and PTP-based plans for each patient. The average difference of 1.9% is indicated by the small bar. Negative values indicate a lower complication rate for the PTP-based plans. (c) The absolute difference in bladder NTCPs between the margin-based and PTP-based plans for each patient. The average difference of 0.7% is indicated by the small bar. (d) The absolute difference in LNT NTCPs between the margin-based and PTP-based plans for each patient. The average difference of 0.06% is indicated by the small bar.

FIG. 6. Dosimetric margin distributions for sample (a) margin-based plan and (b) PTP-based plan. The average dosimetric margin for margin-based plans is 9.8 mm as indicated by the bar on (a). The average dosimetric margin for PTP plans is 7.2 mm as indicated by the bar on (b).

For all patients, PTP gives 0 NTCP for LNT. Five margin-based plans have an NTCP of 0.01 for LNT; all other plans have 0 NTCP for LNT.

A histogram of the 7100 cGy DMDs for the margin-based and PTP-based plans for a sample patient is shown in Fig. 6. Table VII shows the summary of the DMD values. For each patient, the average dosimetric margin for the PTP-based plans is less than that for the margin-based plans. The average dosimetric margin over all patients at 7100 cGy shows a significant ($p<0.0001$) difference between margin-based (0.90 cm) and PTP-based (0.65 mm) plans. For 25 out of 28 patients, the dosimetric margin at 7100 cGy for PTP-based plans is smaller than that of the margin-based plans in all of the 146 evaluated directions. The average dosimetric margin over all patients at 3960 cGy shows a significant ($p<0.0001$) difference between margin-based (1.90 cm) and PTP-based (1.60 cm) plans. For 27 of the patients, the dosimetric margin at 3960 cGy for PTP-based plans is smaller than that of margin-based plans in all of the 146 evaluated directions. PTP produces plans that are more conformal resulting in smaller dosimetric margins and a reduction in doses outside of the target. For PTP-based plans a slight increase (1.6%) in monitor units is observed compared to margin-based plans; this indicates little increase in the complexity of PTP-based plans.

The sensitivity of the structure dose coverage to the setup uncertainty estimate used in optimization is tested for both margin-based and PTP-based plans. Table VIII displays the difference in mean dose when the patient-specific random setup uncertainty σ_T is double and half the value that is used for the optimization. If the patient setup uncertainty is decreased with respect to the estimated uncertainty used during planning ($\sigma_T < \sigma$), mean dose for both PTP-based and margin-based plans increases for all structures except the LNT structure which reports a lower mean dose from both methods. With increased setup uncertainty during treatment, the converse holds true. These results are consistent with a decrease/increase in the dose blurring as the setup uncertainty is reduced/increased. Table IX compares the plans using the optimization DVH indices for unmet criteria. Again, consistent with dose blurring, as treatment uncertainty increases, the dose to the target decreases and deviation between target simulation dose increases. Dose to critical structures decreases as well as the deviation between OAR

TABLE VI. Mean, maximum, and minimum differences in $P+$, TCP, and NTCP between margin-based and PTP-based plans with associated p values for objective structures. Δ is used to indicate “difference in.”

Structure	Type	Δ mean (%)	Max. (%)	Min. (%)	P
All	$P+$	2.45	7.60	-2.10	0.0002
CTV	TCP	0.01	0.30	0.00	0.3262
Rectum	NTCP	-1.88	2.80	-7.00	0.0014
Bladder	NTCP	-0.67	0.00	-2.60	<0.0001
Left femur	NTCP	0.00	0.00	0.00	—
Right femur	NTCP	0.00	0.00	0.00	—
LNT	NTCP	-0.06	0.00	-0.40	0.0028

simulation dose as uncertainty increases. For $\sigma_T=6$ mm, all PTP- and margin-based plans failed to meet the CTV $D_{98} \geq 7920$ cGy dose criteria; however, eight PTP and six margin-based plans that initially failed to meet the CTV $D_{\max} < 8470$ cGy then met the criteria, consistent with dose blurring. With $\sigma_T=6$ mm, no critical structure doses exceeded planning criteria. For $\sigma_T=1.5$ mm, 23 PTP plans and 10 margin-based plans that initially did not fully meet the CTV $D_{98} \geq 7920$ cGy criteria then met the criteria. However, two additional PTP and four additional margin-based plans failed to meet the $D_{\max} < 8470$ cGy criteria. Furthermore, four additional OAR criteria were not met with $\sigma_T=1.5$ mm for both the PTP- and margin-based plans. Adequate coverage is achieved if the uncertainty during treatment is less than or equal to the uncertainty used during the planning process for either margin-based planning or PTP. When the uncertainty during treatment is greater than the uncertainty used during the planning process, both methods have reduced coverage. These results demonstrate that if uncertainty is underestimated, PTP methods will produce acceptable coverage. In the case of uncertainty being overestimated, neither PTP- nor margin-based planning will produce the required coverage. In both PTP- and margin-based planning, if there is low confidence in the uncertainty estimate, it is best to overestimate the uncertainty to ensure coverage.

IV. DISCUSSION

In this study, a simple method for incorporating random patient setup uncertainty into plan optimization is implemented. This method does not require changing the objective functions used in optimization. The results show that PTP-based plans produce similar target coverage to margin-based

plans while reducing dose to critical structures and LNT and produce more conformal plans without increasing complexity. This simple method of incorporating random errors into treatment optimization is significant since it is a straightforward method to improve the therapeutic ratio that can be implemented into an arbitrary optimization system.

PTP allows for uncertainties to be handled directly by the optimizer. This allows an optimal solution to be generated that does not require the addition of margins. PTP optimized plans result in a tighter dosimetric margin around the target. Margin-based plans using a fixed expansion tend to generate effective dosimetric margins that are larger than the planning margin.³⁴ This larger margin results in more normal tissue receiving therapeutic doses.

Our findings that PTP reduces normal tissue doses and NTCP are similar to the findings of previous studies. For focal liver tumors, Balter *et al.* reported that convolving the dose with a population-based random Gaussian can reduce the effective treatment volume by 6%–8% as compared to a margin-based approach.³⁷ Yang *et al.* reported that incorporating uncertainty around targets and OARs by way of a score function composed of scores on multiple shifted planning scans weighted by their probability resulted in greater OAR sparing when compared to margin-based approaches, including methods that incorporate a PRV margin.³¹

As is demonstrated in Fig. 2, incorporating the effects of random setup errors into the dose evaluation results in a blurring of the patient dose distribution. This finding is in agreement with numerous previous authors.^{6,38} Although it is trivial to incorporate such a blurring into the dose calculation and display process and require very little additional computational overhead, clinically, no treatment planning systems

TABLE VII. Mean, maximum, and minimum dosimetric margins for 7100 and 3960 cGy for both margin-based and PTP-based plans with p values of the difference between margin-based and PTP-based plans.

Dose	7100 cGy			3960 cGy		
	Mean (cm)	Max. (cm)	Min. (cm)	Mean. (cm)	Max. (cm)	Min. (cm)
Margin	0.90	1.63	0.37	1.90	4.11	0.92
PTP	0.65	1.47	0.17	1.60	3.67	0.62
P	<0.0001			<0.0001		

TABLE VIII. Differences in the structure mean dose values when the patient plan is subject to half ($\sigma_T=1.5$ mm) and double ($\sigma_T=6$ mm) the estimated ($\sigma=3$ mm) random uncertainty used during the optimization for margin-based and PTP-based plans.

		Half (%)	Double (%)
Margin	Bladder	0.3	-1.0
	CTV	0.2	-1.6
	LNT	-0.4	1.8
	Left femur	0.3	-1.1
	Right femur	0.4	-1.3
	Rectum	0.3	-1.0
PTP	Bladder	0.1	-0.2
	CTV	0.4	-2.6
	LNT	-0.3	1.6
	Left femur	0.3	-1.2
	Right femur	0.4	-1.3
	Rectum	0.3	-1.0

do this. Currently, plans are presented to the physician showing isodose profiles and DVHs as if the patient is in an identical treatment position with respect to the beams during each treatment delivery. By viewing a static dose distribution, the gradients in the dose distributions evaluated by the clinicians are sharper than what is actually achieved during multifractional treatment delivery. A method more representative of the actual patient dose is to include the best estimate of the random component of the random patient setup uncertainty into the dose calculation, either using the fluence convolution³⁹ or dose convolution³⁸ approaches prior to displaying isodose and DVHs. For margin-based planning, such analysis would require evaluating DVHs for structures with margins added that only account for systematic setup errors or evaluation of the coverage probability. It is possible, though not quantifiable at this point, that displaying a more clinically realistic dose distribution to the clinician could alter treatment planning decisions.

For the purposes of this study, other than the sensitivity study, exact knowledge of the random uncertainty distribu-

tion was assumed. Exact knowledge of the random uncertainty distribution can only be had after an entire treatment course has been completed. Random uncertainty estimates are commonly obtained from a large population of similar patients. Additionally from a large population of patients, the uncertainty in the random setup uncertainty estimate can be obtained. With knowledge of the uncertainty in the random uncertainty estimate, a planning setup uncertainty can be chosen based upon a percentage of the uncertainty distribution. It may be the case that the best value used in planning is the N th percentile of the distribution of uncertainty estimates, where N is the percentage of patients. For this case, 90% would correspond with the margin formulations of van Herk *et al.*⁴⁻⁶

In this study, we assume that systematic setup uncertainties are negligible. While clinically unrealistic, use of adaptive therapy setup protocols,^{13,14} where the patient position is imaged for the first several (approximately five) fractions, then repositioned based on the systematic error derived from those measurements, has been shown to significantly reduce systematic setup errors. Even if systematic errors persist, the methods used in this study are still relevant. When systematic errors remain, a margin can be added around the structures to account for systematic uncertainty alone while allowing PTP to account for random uncertainty.

While this study only accounted for random rigid patient setup variations, other random uncertainties such as intrafraction motion that can be modeled using a PDF could be incorporated using similar methods. Evaluation of these uncertainties is left to future studies.

V. CONCLUSIONS

A PTP method that directly incorporates random uncertainty into the standard IMRT optimization of a commercial TPS has been implemented and tested. PTP results generated using this implementation are compared with margin-based plans. PTP-based plans show similar coverage to the margin-based plans. A small reduction in the dose to the target planning objectives is observed but dose to the local normal tissue structure is significantly reduced. OARs and LNT show

TABLE IX. Mean dose and standard deviation over 28 patients for the listed criteria for plans optimized with $\sigma=3$ mm but recomputed with $\sigma_T=1.5$, 3, and 6 mm. As uncertainty increases, the dose at target objectives decreases and vice-versa. As uncertainty increases, the dose at OAR objectives decreases and vice-versa. Objectives not listed were met by all plans.

		1.5 mm		3 mm		6 mm	
Dose		PTP	Margin	PTP	Margin	PTP	Margin
CTV	98% (cGy)	8005	7974	7878	7930	7198	7494
	Standard deviation (cGy)	48	30	69	38	153	133
Rectum	25% (cGy)	5441	5797	5382	5743	5193	5554
	Standard deviation (cGy)	864	796	852	783	805	743
Rectum	15% (cGy)	6507	6811	6434	6734	6189	6486
	Standard deviation (cGy)	744	672	727	650	669	600

decreased mean dose using PTP methods as compared to margin-based methods while target mean dose slightly increases. Biological indices indicate that PTP has a similar TCP with reduced NTCP resulting in a higher $P+$. Effective dosimetric margins are smaller in PTP-based plans as compared to margin-based plans indicating more conformal plans. PTP produces plans that maintain similar target coverage while reducing dose to all other structures.

The use of fluence convolution to simulate the dose blurring effect of the 30-fraction treatment courses is valid. Compared with average from delivery simulations, fluence convolution-based target doses and volumes differed by $<0.1\%$. Use of convolution instead of simulation during optimization is within clinical tolerance.

The sensitivity of PTP-based plans to deviations in the patient-specific uncertainty with respect to that used in planning is comparable to the sensitivity of margin-based plans. For both margin-based and PTP methods, if the setup uncertainty is less than what was used for planning, dose increases to the target and to nearby critical structures due to sharpening of the dose distribution. If the setup uncertainty is larger than what is used for planning, dose decreases to the target and to nearby critical structures due to blurring of the dose distribution.

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