Use of a constrained hierarchical optimization dataset enhances knowledge-based planning as a quality assurance tool for prostate bed irradiation

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Purpose: To investigate whether building a knowledge-based planning (KBP) model with prostate bed plans constructed from constrained hierarchical optimization (CHO) would result in more efficient model construction with more consistent output than a model built using plans from a traditional, trial-and-error-based optimization (TEO) technique.

Methods: Three KBP models were constructed from plans from subsets of 58 post-prostatectomy patients treated with intensity-modulated radiation therapy. TEO₅₄ was built from 54 TEO plans, selected to represent typical clinical variations in target and organ-at-risk sizes and shapes. CHO₃₀ and TEO₃₀ were built from the same 30 patients populated with CHO and TEO plans, respectively. The three models were each applied to a new set of 18 patient scans and dose–volume histogram estimates (DVHs) were generated for rectal and bladder walls and compared for each patient.

Results: CHO₃₀ resulted in a significantly tighter range in DVHs ($P < 0.01$) for both the rectal and bladder walls compared with either of the TEO models, indicating less uncertainty in the dose estimation. Plans resulting from KBP optimization using each model were very similar.

Conclusion: Populating a KBP model with CHO data resulted in a high quality model. Since CHO plans can be generated automatically offline in a process that necessitates little to no user interaction, a CHO-KBP model can quickly adapt to changes in plan evaluation criteria or planning techniques without the need to wait to accrue sufficient numbers of clinical TEO plans. This may facilitate the use of KBP approaches for initial or ongoing quality assurance procedures and plan quality audits.

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Key words: constrained hierarchical optimization, intensity-modulated radiation therapy, knowledge-based planning, prioritized optimization, RapidPlan

1. INTRODUCTION

Interobserver variability in radiotherapy plan quality exists.^{1,2} One contributing factor to this variability is that the traditional trial-and-error-based optimization (TEO) algorithms available in most commercial intensity-modulated radiation therapy (IMRT) treatment planning systems collapse all competing optimization objectives into a single function. This often results in suboptimal compromises between target coverage and organ-at-risk (OAR) sparing. Users must perform multiple iterations of the optimization, manually tweaking optimization objectives to achieve what they determine to be the best plan. There is no mechanism to further decrease OAR doses below the clinically defined goals, even if doing so would not harm target coverage or the sparing of other OARs, leaving this decision to the subjectivity of the user.^{3,4}

Different methods have been proposed to increase planning consistency^{5,6} including constrained hierarchical optimization (CHO), also known as prioritized optimization or lexicographic ordering.^{7,8} CHO is an automated planning process developed at Memorial Sloan Kettering Cancer Center. It is based on the optimization technique named hierarchical constrained optimization.^{7,9,10} CHO respects clinical

priorities and produces Pareto optimal plans. The optimization contains three major steps, (a) achieve best planning target volume (PTV) coverage, given all maximum hard constraints; (b) relax PTV coverage slightly to improve OAR structures doses; (c) relax all organ doses to improve fluence smoothness for deliverability.¹¹ CHO has a higher likelihood of achieving Pareto optimality since it uses hard constraints and optimizes in a stepwise order which is predefined by the user. Further OAR dose reduction is sought as long as it does not appreciably hurt higher order constraints. A “slip” parameter is used to reduce the dose to the lower priority OARs with just a slight tradeoff to higher priority constraints.⁹ A disadvantage of CHO is that the methodology is computationally intensive and the IMRT optimization can take hours for a given patient. However, the advantage is that CHO runs with little to no user interaction, so IMRT optimizations can be performed off-hours or in batches.

Another proposed method to improve planning consistency is knowledge-based planning (KBP).^{12,13} This technique uses previous patients’ geometry (e.g., the distance between the PTV and the OAR or the area overlapping between the PTV and the OAR) and the corresponding dose–volume histogram (DVH) information to estimate the

Traditional trial-and-error based optimization

- $TEO_{54} = 26 + 28$
- $TEO_{30} = 26 + 4$

Constrained hierarchical optimization

- $CHO_{30} = 26 + 4$

FIG. 1. Three knowledge-based planning models (TEO_{54} , TEO_{30} , and CHO_{30}) constitute 58 patients in total.

achievable dose sparing of OARs for a new patient. KBP has been utilized both as an optimization tool^{14–16} and a quality assurance tool.^{17–19} Some disadvantages of KBP are that (a) it leads to plans consistent with the prior institutional experience regardless of the quality of that experience, and (b) the model building process can be quite time-consuming, although applying the model to a particular patient is very fast.

We speculated that populating KBP models with CHO plan data would be a method to efficiently produce high quality KBP models for prostate bed irradiation. We investigated this hypothesis by comparing KBP models produced using clinically treated post-prostatectomy patient plans from TEO optimization vs those created using CHO optimization.

2. MATERIALS AND METHODS

2.A. Model construction/input

After appropriate Institutional Review Board review, computed tomography (CT) scans of 58 post-prostatectomy patients, treated with IMRT at our institution from May 2014 to April 2016, were retrospectively selected for inclusion in KBP modeling. The IMRT plans used 7–9 fields with 15 MV x rays and were originally planned in Varian's Eclipse Treatment Planning System (version 11, Varian Medical Systems, Palo Alto, CA) using the dose-volume optimizer algorithm for a prescription dose of 72 Gy over 40 fractions to the prostate bed only. Patients with hip prostheses were excluded from the dataset.

As illustrated in Fig. 1, three KBP models were constructed from subsets of the same 58 patients. As a first step, all CT images and plans were reviewed to ensure that the anatomical segmentations were correct and that the plans met our institutional plan evaluation criteria,²⁰ as described in Table I. The first model, TEO_{54} , contained 54 patient TEO plans, representing typical clinical variations in target and OAR shapes and sizes. TEO_{54} also represented our best effort at creating a KBP model in the manner described by the manufacturer²¹ and in the literature.^{22,23} The second and third models, TEO_{30} and CHO_{30} , were constructed using a subset of 30 patients that had previously been used for a prior study by Tiwari, comparing the quality of TEO and CHO plans.¹⁰ All CHO plans were designed to meet the same planning goals as used for the TEO plans (Table I) and similarly normalized such that the prescription isodose line covers 95% of the PTV volume. TEO_{30} used the original clinically treated plans and CHO_{30} used Tiwari's CHO versions of the plans. TEO_{54} and TEO_{30} were

TABLE I. Post-prostatectomy IMRT planning guidelines and constrained hierarchical optimization constraints and priority levels. Optimization proceeds according to the assigned priority. Lower priority constraints are only met if the higher priority constraints are respected. The prioritization of target coverage and OAR sparing in the algorithm replicates the approach to planning that our human planners are taught and utilize.

Sequence	Constraints	Priority level
1	95% of panning target volume receives 72 Gy ($D_{95\%}$)	1
2	Max. point dose in rectum <74.52 Gy ($D_{max} < 103.5\%$)	1
3	Max. point dose in bladder <77.76 Gy ($D_{max} < 108\%$)	1
4	53% of total rectum volume not exceed 47 Gy ($V_{47 Gy}$)	2
5	53% of total bladder volume not exceed 47 Gy ($V_{47 Gy}$)	3
6	Max. point dose in femoral heads	3
7	High-dose gradient falloff outside planning target volume	4
8	Smooth beam profile	5
9	Incorporate the deliverability issues	6

constructed using the same methodology, the only difference was that TEO_{30} was restricted to the same set of patients as CHO_{30} in order to factor out any potential bias due to patient anatomical differences. Twenty-six of TEO_{30} 's 30 patients were also in TEO_{54} ; the other four were excluded from TEO_{54} due to their identification as outliers during the model building process for TEO_{54} .

KBP model building, including data extraction and model training, was performed using RapidPlan[®], a commercially available KBP tool in the Eclipse Treatment Planning System (version 13.6, Varian Medical Systems). RapidPlan[®] uses linear regression analysis to formulate a relationship between the principle components of geometry-based features and those of the DVH for the patient plans inserted into the model. Outliers in the model were identified as data points with a Cook's distance greater than 10 on the regression analysis and were removed in order to prevent over-fitting. The regression plots for each model are shown in Fig. 2.

2.B. Model evaluation/outputs

The three models were subsequently applied to 18 additional post-prostatectomy patient radiotherapy planning scans. These patients were scanned and treated in the same

FIG. 2. (top row) PTV DVH curves from the plans used as input into the three RapidPlan[®] models. (middle and bottom rows) RapidPlan[®] regression curves for rectal wall and bladder wall. From left to right: Model from 54 patients using traditional trial-and-error-based optimization plans (TEO₅₄), model from 30 patients using traditional trial-and-error-based optimization plans (TEO₃₀), model from the same 30 patients using constrained hierarchical optimization plans (CHO₃₀). Each DVH line and cross mark represent a patient plan in the model. The thick dashed lines in the rectal wall and bladder wall plots represent the linear regression fit while the thin dotted lines represent ± 1 standard deviation. The quality of model fit, as measured by the coefficient of determination (R^2), was highest for CHO₃₀. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 3. The dose-volume histogram estimation bands (DVHE) for the same patient from all three models. From left to right: TEO₅₄ was constructed from 54 patients using traditional trial-and-error-based optimization plans, TEO₃₀ was constructed from 30 patients using traditional trial-and-error-based optimization plans, and CHO₃₀ was constructed from the same 30 patients as TEO₃₀ but using constrained hierarchical optimization plans. Note that the width of DVHEs is smaller for CHO₃₀. [Color figure can be viewed at wileyonlinelibrary.com]

time period using the same techniques but were not used in the construction of the models. IMRT plans were created in Eclipse (version 13.6) using the commercial RapidPlan[®] module and the photon optimizer algorithm (version 13.6). For each model and for each patient's RW and BW,

RapidPlan[®] produced dose-volume histogram estimates (DVHE); a band within which the final optimized DVHs are expected to fall (Fig. 3). These estimates were used to automatically generate optimization objectives in order to produce new plans. The new plans were normalized such that the

prescribed dose of 72 Gy covered 95% of the PTV volume, consistent with our clinical practice, and evaluated at the dose–volume endpoints listed in Table I. The PTV dose uniformity was assessed using the homogeneity index (HI), calculated as $[(D_{2\%} - D_{98\%})/D_{\text{prescr}} \times 100\%]$, where $D_{X\%}$ is the minimum dose to X% of the PTV, and D_{prescr} is the prescribed dose.

TEO₅₄, TEO₃₀, and CHO₃₀ were compared by analyzing the PTV $D_{95\%}$ and HI, and for the RW and BW $V_{47 \text{ Gy}}$ the (a) width of the DVHE band, (b) average of the upper and lower bounds of the DVHE band (i.e., the center of the DVHE band), and (c) resulting DVH after optimization using the KBP models. Single-factor analysis of variance (ANOVA) was used for the statistical comparisons among the three models. A post hoc Bonferroni analysis was further applied to determine the statistical significance of the pairwise differences. Comparisons were declared to be statistically significant at $P < 0.017$ ($\alpha = 0.05/3$).

3. RESULTS

3.A. Model construction/input

The PTV, RW and BW DVH characteristics of the patient datasets used as input for the TEO₅₄, TEO₃₀, and CHO₃₀ models are summarized in Fig. 4. The PTV homogeneity index (HI) and target coverage, described by the $D_{95\%}$, were similar for all three models. The PTV DVH lines are visually tighter for the CHO model input, as shown in Fig. 2.

Figure 4 indicates that the percentage volume of rectal wall receiving at least 47 Gy (RW $V_{47 \text{ Gy}}$) was similar for both TEO models, but significantly lower for CHO₃₀ compared to TEO₃₀. The percentage volume of bladder wall receiving at least 47 Gy (BW $V_{47 \text{ Gy}}$) was similar for all patient datasets. Figure 2 shows that the RW TEO modeling process established little or negative correlations between the geometric and dosimetric characteristics of the input plans while the CHO modeling process established a positive correlation. The coefficient of determination (Fig. 2) of the regression plots was greatest for the CHO₃₀, for both the RW and BW, indicating better fits to the input data.

3.B. Model evaluation/outputs

For the 18 test patients evaluated, CHO₃₀ resulted in significantly tighter DVHEs for BW when compared to both the TEO models and significantly tighter DVHEs for RW compared to TEO₅₄ (Fig. 4). The average of the BW and RW DVHE upper and lower bounds (i.e., the center of the DVHE band) was similar between all three models, although it trended lower for CHO₃₀. The DVHs observed after IMRT optimization with the KBP models (TEO₅₄, TEO₃₀, and CHO₃₀) were similar for all four dosimetric indices reviewed.

4. DISCUSSION

4.A. Model construction/input

The differences observed between the TEO and CHO patient plans used as input into models CHO₃₀ and TEO₃₀ were mainly due to the Pareto optimality achieved in CHO plans, as described by Tiwari et al.¹⁰ CHO will produce a Pareto optimal solution based on the input parameters. The parameters used for post-prostatectomy planning, consistent with the guidelines used by human planners in the TEO approach, are shown in Table I. The improved RW $V_{47 \text{ Gy}}$ for CHO₃₀ over TEO₃₀ reflects a weakness of TEO planning in that, for many cases, further OAR sparing was achievable without compromising target coverage. However, this is often not obvious to a human planner who is likely to stop iterative TEO planning once the optimization objectives have been met. Previous studies have shown that variability between planners exists despite clear plan evaluation criteria and well-documented planning procedures.² Significant decreases in BW $V_{47 \text{ Gy}}$ were not observed. This is most likely because bladder sparing was a level 3 priority in the CHO optimization and that the BW overlaps with much of the PTV in these post-prostatectomy cases.

4.B. Model evaluation/outputs

The widths of the CHO₃₀ DVHE bands were significantly thinner than those for TEO₅₄ for both the RW and BW, reflecting a higher level of confidence in these estimates that arose from greater consistency in the DVH data used to build the CHO model. This can also be observed in Fig. 2 where the CHO model's RW and BW display a narrower standard deviation about the linear regression lines. This is important if one desires to use RapidPlan[®] for plan quality assurance. A large DVHE band that covers a significant portion of the DVH space would not be sensitive enough to differentiate between plans that do and do not correspond to institutional norms. The width of DVHE band for the BW was drastically narrower for the CHO over the TEO models, indicating that CHO may more consistently spare the portion of the BW outside of the PTV, which is the part of the OAR that is subjected to KBP modeling and linear regression analysis.

In addition to analyzing the DVHEs, the three RapidPlan[®] models were also used to generate optimization objectives for subsequent IMRT optimization in order to determine whether the DVH estimated values generated from each model were achievable in practice. The plans resulting from each model were very similar, with no statistically significant differences in PTV HI, PTV $D_{95\%}$, RW $V_{47 \text{ Gy}}$, or BW $V_{47 \text{ Gy}}$. Interestingly, the PTV HI for the optimized results for all three models was smaller than the corresponding HI for the input plans. Since this version of RapidPlan[®] does not estimate DVHs for PTV coverage, this may be a consequence of the photon optimizer used to generate these plans in Eclipse (version 13.6). For all three models, the KBP-optimized RW $V_{47 \text{ Gy}}$ was a few percentage points higher than the center of the DVHE

FIG. 4. Box-and-whisker plots, summarizing the metrics used to compare the three models. The diamonds indicate mean values. The brackets indicate statistically significant differences ($P < 0.017$). TEO₅₄ = model of 54 patients using traditional trial-and-error-based optimization plans; TEO₃₀ = model of 30 patients using traditional trial-and-error-based optimization plans; CHO₃₀ = model of 30 patients using constrained hierarchical optimization plans; PTV = planning target volume, HI = homogeneity index, n = number of individual organs of interest used during the model training or model validation; KBP = knowledge-based planning; D_{95%} = dose received by 95% of the volume, in Gy; V₄₇ Gy = percentage volume of an organ receiving 47 Gy; DVHE = dose-volume histogram estimate. [Color figure can be viewed at wileyonlinelibrary.com]

band, although on average, it was still within the DVHE bounds. Although beyond the scope of this work, further investigation is warranted to determine whether manual adjustment of the RW optimization objective priorities from the RapidPlan[®] autogenerated values might bring the optimized RW doses closer to the center of the estimated range.

There is no significant difference between the DVHs that result from optimizing with the TEO₅₄ and TEO₃₀ KBP models. This result is consistent with what was found by Tol *et al.*, in their study of head and neck KBP models, where they also found, when pooling results, that models built with 30 vs 60 patients delivered similar plans and that more outliers did not necessarily translate into a worse OAR dose.²³

As we have shown, CHO produces a model with RapidPlan[®] DVHs that are as good as, or better than, those from models based on TEO plans. In addition to the dosimetric advantages when used as an optimizer,⁷ CHO is advantageous for the efficient population of KBP models since CHO plans can be produced with little to no user interaction. Therefore, when a new clinical protocol is introduced, a change is made to an existing protocol or a new treatment delivery technique is utilized, CHO can be run automatically on a standard cohort of patient scans to produce the data needed to immediately create or update a KBP model. Using the TEO methodology, one would either have to wait until a sufficient number of patients had been treated in the clinic or

allocate personnel resources to manually reoptimize a sufficient number of plans offline to rebuild the model.

Since both CHO and KBP are available in our clinic, we intend to utilize CHO as our optimization engine since it produces plans at the Pareto front, rather than plans that simply match prior experience. KBP will be used as part of our suite of automated QA tools, flagging plans that are not consistent with the model for further review by the clinical staff. Other QA tools in the suite include an automated plan checker²⁴ and automated treatment delivery verification.²⁵ KBP models built with CHO plans could also be employed as part of a decision support framework to furnish clinicians with estimated dose distributions immediately after segmentation.

5. CONCLUSION

CHO has been noted to be a powerful, efficient, and reliable optimizer for IMRT planning, while KBP models can be used to flag if a given plan is inconsistent with institutional norms; thus, CHO and KBP can be used as complementary technologies. For prostate bed irradiation, KBP models populated with CHO plans are advantageous because (a) they have narrower DVH estimation bands, indicating less uncertainty in the dose estimation and a better ability to differentiate between appropriate and inappropriate plans; and (b) the plans used to build the models can be generated with an automated offline process that requires little to no user interaction, allowing the

KBP models to efficiently maintain their clinical relevance in the face of a continuously evolving clinic.

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CONFLICTS OF INTEREST

Margie A. Hunt and Sean L. Berry hold research grants from Varian Medical Systems for work unrelated to this manuscript.

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