Knowledge-based planning

Cross-institutional knowledge-based planning (KBP) implementation and its performance comparison to Auto-Planning Engine (APE)

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Background and purpose: To investigate (1) whether a plan library established at one institution can be applied for another institution’s knowledge-based planning (KBP); (2) the performance of cross-institutional KBP compared to Auto-Planning Engine (APE).

Material and methods: Radboud University Medical Center (RUMC) provided 35 oropharyngeal cancer patients (68 Gy to PTV 68 and 50.3 Gy to PTV 50.3) with clinically-delivered and comparative APE plans. The Johns Hopkins University (JHU) contributed a three-dose-level plan library consisting of 179 clinically-delivered plans. MedStar Georgetown University Hospital (MGUH) contributed a KBP approach employing overlap-volume histogram (OVH-KBP), where the JHU library was used for guiding RUMC patients’ KBP. Since clinical protocols adopted at RUMC and JHU are different and both approaches require protocol-specific planning parameters as initial input, 10 randomly selected patients from RUMC were set aside for deriving them. The finalized parameters were applied to the remaining 25 patients for OVH-KBP and APE plan generation. A Wilcoxon rank-sum test was used for statistical comparison.

Results: PTV68 and PTV50.3’s V95 in OVH-KBP and APE were similar (p > 0.36). Cord’s D 0.1 cc in OVH-KBP was reduced by 5.1 Gy (p = 0.0001); doses to other organs were similar (p > 0.2).

Conclusion: APE and OVH-KBP’s plan quality is comparable. Institutional-protocol differences can be addressed to allow cross-institutional library sharing.

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Knowledge-based planning (KBP) has proven to be an effective way in improving planning efficiency and plan quality in radiotherapy inverse planning [1–16]. A key pre-requisite of KBP is to compile a sufficiently large number of high quality plans to build a predictive model. As reported by Boutilier JJ et.al [16], more than one hundred plans are necessary to build a prostate library to cover the range of prostate-rectum and prostate-bladder anatomical variations; in addition, individual library plan review is necessary to remove dosimetric outliers (plans with inferior quality) to ensure model robustness [5,15]. It may take a few years to collect sufficient number of quality plans at a medium sized academic institution to construct a robust model. A method facilitating plan library building is therefore desired to allow broad adoption of KBP.

This study proposes cross-institutional library sharing in KBP, which allows centers to utilize an established library from another institution to generate their KBP plans, instead of building their own library and developing their own model. We hypothesize that by allowing library sharing, target coverage and organs-at-risk (OAR) sparing achieved at the established library could be obtainable at other centers. However, the present KBP studies are mostly based on single-institutional experience [1–7,9–14], where a site-specific clinical protocol (beam configuration, contour specification, prescription, and planning guideline) consistently across library and future patients is followed. How a plan library established at one institution with a different protocol can be transferred to another institution for quality planning remains unknown and warrants investigation.

The KBP is only one of several auto-planning approaches that have been developed. Recently, an alternative approach, called Auto-Planning Engine (APE) [17,18], has been commercialized in Pinnacle v.9.10 TPS (Philips Radiation Oncology, Madison, WI). Unlike KBP, which requires a plan library, APE relies on the
understand the clinical acceptability. This study aims to take on the dual tasks of: (1) investigating whether institutional-protocol differences can be addressed to allow plan library sharing in cross-institutional KBP implementation, and (2) capabilities and relative strengths/weaknesses of KBP compared to APE. This study focuses on SIB-IMRT for oropharyngeal cancer, and is a joint effort of three academic institutions: MedStar Georgetown University Hospital (MGUH, Washington, D.C.), Radboud University Medical Center (RUMC, Nijmegen, The Netherlands) and the Johns Hopkins University (JHU, Baltimore, MD). Specifically, (1) RUMC provided a patient data pool of 35 oropharyngeal cancer patients, including clinically-delivered and corresponding comparative APE plans. (2) JHU contributed a patient library consisting of 179 clinically-delivered plans with different protocol than RUMC. (3) MGUH provided a KBP approach employing overlap-volume histogram (OVH-KBP), where the JHU library was used to generate RUMC patient's KBP plans. Finally, cross-institutionally generated KBP plans were compared to APE plans following RUMC guideline. In accordance with HIPAA (The Health Insurance Portability and Accountability Act of 1996), all patient data were anonymized following appropriate governance requirements.

Materials and methods

Study design

Since clinical protocols adopted at RUMC and JHU are different (see Table 1) and both KBP and APE require certain users' pre-set planning parameters as initial input to start optimization, 10 randomly selected patients from the accrued 35 patients were set aside as a training group for deriving them. For OVH-KBP, although OAR’s DVH objectives are predicted from a library and applied as optimization goals, users still need to determine non-OAR structures’ optimization goals for controlling target homogeneity, conformity, and steepness of dose fall-off outside targets [2]. For APE, although a progressive optimization algorithm is used to search for optimal solutions during optimization [17,18], users’ input is required to set initial optimization values (or treatment technique as called in APE). In training cycles, the non-OAR structures’ optimization goals used in OVH-KBP and APE’s treatment technique were determined.

The determined planning parameters were then applied to the remaining 25 patients (testing group) to generate OVH-KBP and APE plans, using Pinnacle v.9.10 TPS and the RUMC beam configuration as shown in Table 1. Their dosimetric results were compared following RUMC guideline using a Wilcoxon rank-sum test. The statistical significance level was set as p < 0.05. Additionally, a RUMC radiation oncologist (T. Dijkema) reviewed iso-dose distributions and DVH curves of OVH-KBP and APE plans and compared them with corresponding clinically-delivered plans to determine their clinical acceptability.

RUMC’s protocol & APE plan generation

Patients were treated with a two-dose-level, SIB-IMRT scheme (68 Gy to PTV\textsuperscript{68} in 34 fractions, and 50.3 Gy to PTV\textsuperscript{50.3}). Clinically-delivered plans were manually created by RUMC staffs using Pinnacle v.9.0 TPS following the protocol described in Table 1. APE requires users to provide the following optimization presets: (a) derived structures; (b) iso-center; (c) prescription; (d) beam configuration; (e) targets/OARs’ optimization goals [17,18]. Specific to this study, the derived structures, iso-center, beam configuration and prescription used in RUMC protocol were directly applied to the presets. The optimization goals in item (e) were determined in training cycles. The finalized presets used to generate testing patients’ APE plans are shown in Supplemental materials.

OVH-KBP

OVH-KBP is a geometry-driven approach utilizing target-OAR Euclidean distance and dose distribution of prior plans to establish a predictive model to estimate new patients’ OAR doses [1–3]. It assumes that for the same protocol across patients, the dose to an OAR’s voxel decreases with increasing distance from target surface. For a specific target-OAR pair, the OVH is defined as a cumulative distribution function relating an OAR’s voxel to a target-OAR’s distance. Fig. 1 shows the relation between OVH and DVH for a target-OAR pair. A cohort of prior plans containing OVH and DVH information is required to build the model.

A unique feature of this study was to use a plan library from JHU as a model to predict achievable OARs’ doses for RUMC’s patients. Specifically, a RUMC patient’s target-OAR distance was compared to the cohort of corresponding target-OAR distance in the JHU library. From this comparison, the library was used to estimate the patient’s OAR doses, which were applied as OAR’s optimization

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Protocol differences between RUMC and JHU.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beam Configuration</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>JHU</strong></td>
</tr>
<tr>
<td>7 standardized angles</td>
<td>9 standardized angles</td>
</tr>
<tr>
<td>Maximal segments per plan: 60</td>
<td>Maximal segments per plan: 120</td>
</tr>
<tr>
<td>Minimal area per segment (cm(^2)): 10</td>
<td>Minimal area per segment (cm(^2)): 4</td>
</tr>
<tr>
<td>Elekta Synergy</td>
<td>Elekta Infinity</td>
</tr>
<tr>
<td>Prescription</td>
<td></td>
</tr>
<tr>
<td>Two-dose-level: 68 GY and 50.3 Gy</td>
<td>Three-dose-level: 70 Gy, 63 Gy and 58.1 Gy</td>
</tr>
<tr>
<td>2 Gy/fraction in 34 fractions to PTV\textsuperscript{68}</td>
<td>2 Gy/fraction in 35 fractions to PTV\textsuperscript{70}</td>
</tr>
<tr>
<td>PTV\textsuperscript{68} and PTV\textsuperscript{50.3}, V\textsubscript{68} &gt; 95%</td>
<td>PTV\textsuperscript{70}, PTV\textsuperscript{63} and PTV\textsuperscript{51.1}, V\textsubscript{63} &gt; 95%</td>
</tr>
<tr>
<td>3-mm expansion from CTVs</td>
<td>5-mm expansion from CTVs</td>
</tr>
<tr>
<td>PTV\textsuperscript{68} volume in cc: 194 ± 136; [71,625]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>PTV\textsuperscript{70} volume in cc: 171 ± 150; [26,790]&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PTV\textsuperscript{50.3} volume in cc: 585 ± 135; [384,898]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>PTV\textsuperscript{63} volume in cc: 349 ± 205; [98,1075]&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>PD[PTV\textsuperscript{68}, PTV\textsuperscript{50.3}] &lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
<td>PD[PTV\textsuperscript{70}, PTV\textsuperscript{63}, PTV\textsuperscript{51.1}] &lt; 0.001&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- DMPO (Direct Machine Parameter Optimization)
- D\(_x\) = average dose to x Gy
- D\(_y\) = mean dose
- D\(_{mean}\) = mean dose
- V\(_{x}\) = volume corresponding to x Gy
- V\(_{y}\) = volume corresponding to y Gy
- cc\(_x\) = cm\(^3\)
- N/A = not considered.

<sup>a</sup>Common features—6 MV; DMPO (Direct Machine Parameter Optimization) with Adaptive Convolution; 4 mm dose grid size; minimal MU per segment is 5.

<sup>b</sup>Wilcoxon’s rank-sum test for volume comparison; p < 0.05 indicates statistical significance.
goals for RUMC's patients. However, the protocol differences, as shown in Table 1, introduced uncertainties in applying the JHU's library to RUMC's KBP and were investigated.

Using the JHU's library in RUMC patient's OVH-KBP

The JHU library contained OVH and DVH information of clinically-delivered SB-IMRT plans of 179 patients with a prescription scheme as: 70 Gy in 35 fractions to PTV 70, and 63 Gy and 58.1 Gy to PTV 63 and PTV 58.1. The details of the library have been discussed in a previous publication [2].

The following institutional-protocol differences (Table 1) were investigated in training cycles, and the results were used to determine the test patients' OVH-KBP's planning parameters:

1. Beam configuration. As reported in [19,20] and based on our planning experience, dosimetric results generated by 7 and 9-beam IMRT are comparable with non-significant, more homogenous target dose in 9-beam IMRT. Since RUMC guideline was used in the comparison, RUMC's 7-beam configuration was selected.

2. Number of PTVs and their dose coverage specification. Since OAR's doses depend on achieved target's doses, the doses in JHU's three-dose-level (70 Gy, 63 Gy and 58.1 Gy) plans are scaled down to estimate the OAR's doses in RUMC's two-dose-level (68 Gy and 50.3 Gy) plans. The scaling-down is based on the following assumptions: a) OAR's doses depend only on its distance to low-level PTV (PTV50.3 in RUMC and PTV58.1 in JHU); of note, this assumption may be invalid if the OAR's volume is large. A cohort of prior plans with known DVH and OVH is used to establish the normalization from RVH to OAR's doses. The above figures show that the distance in RUMC's patients is a subset of JHU.

3. PTV-OAR distance at a specific volume. Table 1 shows that average distance PTV50.3 to PTV58.1 is 353 cc larger than RUMC's PTV50.3 with p < 0.001. Since OVH is a spatial descriptor characterizing the distance between a target and an OAR, the effect of PTV size on the distance warrants investigation.
Finally, a previously developed [2], auto-planning application incorporating the above factors was built into Pinnacle v.9.10 TPS for generating testing patients' OVH-KBP plans.

Results

The number of individual plans of the 25 testing patients achieving RUMC’s dose/volume criteria and their statistical results are shown in Table 2. Fig. 3 shows the average DVH curves of the plans. For planning efficiency, each OVH-KBP and APE plan was fully automatically generated in less than 15 min without human interventions.

PTV coverage

Table 2 shows that for PTV68, four APE plans and two OVH-KBP plans did not meet the target constraint $V_{95} \geq 95\%$ with smallest $V_{95} = 94.2\%$; for PTV50.3, one OVH-KBP plan did not meet the constraint with $V_{95} = 93.8\%$, while all APE plans achieved it. On average, $V_{95}$ in the two sets of plans were similar: PTV68's $V_{95}$ was 96.5% in APE plans and 97% in OVH-KBP plans with $p = 0.36$; PTV50.3 $V_{95}$ was 97.8% in APE plans and 97.6% in OVH-KBP plans with $p = 0.6$.

OAR sparing

Table 2 shows that dose constraints for the cord ($D_{0.1 \text{ cc}} \leq 50 \text{ Gy}$) and brainstem ($D_{0.1 \text{ cc}} \leq 54 \text{ Gy}$) were all achieved. On average, cord's $D_{0.1 \text{ cc}}$ in OVH-KBP plans was 5.1 Gy less than APE plans with $p = 0.0001$; brainstem's $D_{0.1 \text{ cc}}$ in APE plans was 1.2 Gy less than OVH-KBP plans with $p = 0.6$. For other OARs, dose constraints were not achieved in the majority of plans, and their mean doses were similar.

RUMC radiation oncologist’s preference

Without identification of the sources, the RUMC radiation oncologist reviewed iso-dose distributions and DVH curves of each OVH-KBP and APE plan and compared them with the corresponding clinically-delivered plan to determine their clinical acceptance. The evaluation lead to the following conclusions: (1) differences in OAR sparing were small or not clinically relevant; (2) the oncologist preference for the 25 patients' APE and OVH-KBP plans was: neither plan was clinically acceptable for one patient due to oncologist preference for the 25 patients’ APE and OVH-KBP plans, while all patients favored at least one plan.

Discussion

Presently, several strategies exist for auto-planning, which can be classified into two categories. One is optimization algorithm-driven, e.g., APE [17,18], Erasmus-iCycle [20,21], Multi-Criteria Optimization [22], Heuristic Optimization [23], and MdaccAutoPlan [24]. Another is KBP built upon a plan library, e.g. OVH-KBP [1–3], RapidPlan [4–7], and beams-eye-view (BEV)-KBP [8]. Both categories have been investigated by various researchers. However, to the best of our knowledge, no studies have been performed to compare the performance of these two categories (APE vs. KBP), and no KBP studies have been conducted in cross-institutional library sharing. This study demonstrates that plan quality resulted from APE and KBP is comparable. It reveals that institutional-protocol variations can be appropriately addressed to allow dosimetric results achieved at one institution to be obtainable at other institutions. Note, JHU library quality and its model accuracy have been established in [1–3] and will not be discussed here.

The primary methodological difference between KBP and APE is the way how the targets/organ’s optimization goals are handled. In KBP, the goals are predicted from a plan library utilizing anatomic feature matching. Since they are geometry-specific and their trade-offs have been considered in prior planning session, they are achievable for new patients. Those goals are directly applied to TPS’s optimizer, and no further adjustments are needed during optimization. Thus, the performance of KBP depends on the quality of library and robustness of its predicting algorithm. On the other hand, APE employs pre-set, generic optimization goals for patients with the same protocol. Those generic goals are protocol-specific, rather than patient-specific as in KBP. During optimization, an iterative algorithm is utilized to automatically adjust the goals to arrive at or surpass them if possible. Therefore, the APE solutions are constrained by the robustness of the iterative algorithm and proper selection of the generic goals.

It would be interesting to develop a hybrid planning solution combining the advantages of KBP and APE. A merit of KBP is to provide individualized, geometry-specific optimization goals to a TPS’s optimizer. In contrast, APE is optimization algorithm-driven, employing an iterative process to adjust pre-set optimization goals.

Table 2

<table>
<thead>
<tr>
<th>RUMC guideline</th>
<th>Criteria</th>
<th>APE</th>
<th>OVH-KBP</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTV68</td>
<td>$V_{95} \geq 95%$</td>
<td>21</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>PTV50.3</td>
<td>$V_{95} \geq 95%$</td>
<td>25</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Cord</td>
<td>$D_{0.1 \text{ cc}} \leq 50 \text{ Gy}$</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Brainstem</td>
<td>$D_{0.1 \text{ cc}} \leq 54 \text{ Gy}$</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Larynx</td>
<td>$D_{\text{mean}} \leq 30 \text{ Gy}$</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>$D_{\text{mean}} \leq 20 \text{ Gy}$</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>I parotid</td>
<td>$D_{\text{mean}} \leq 20 \text{ Gy}$</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C parotid</td>
<td>$D_{\text{mean}} \leq 40 \text{ Gy}$</td>
<td>7</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>I Submandibular</td>
<td>$D_{\text{mean}} \leq 40 \text{ Gy}$</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>C Submandibular</td>
<td>$D_{\text{mean}} \leq 40 \text{ Gy}$</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>MU/fraction</td>
<td>Not considered in planning</td>
<td>664</td>
<td>71</td>
<td>652</td>
</tr>
</tbody>
</table>

Abbreviations: $V_{95}$ = percentage volume receiving 95% of prescription dose; $D_{0.1 \text{ cc}}$ = dose corresponding to 0.1 cc; $D_{\text{mean}}$ = mean dose; cc = cm$^3$.

1: Number of the individual plans achieving the criteria.

*: Average ± standard deviation.

p: Wilcoxon rank-sum test; $p < 0.05$ indicates statistical significance.

$p_a$: p value between APE and OVH-KBP plans.

$p_b$: p value between APE and clinically-delivered plans.

$p_c$: p value between OVH-KBP and clinically-delivered plans.
to a desired direction if possible. A potential research topic of interest would be to integrate KBP and APE into a single optimization, in which KBP provides individualized optimization goals to APE’s optimizer and APE’s iterative algorithm is used to further refine them if possible.

It should not be surprising that the achieved cord’s $D_{0.1\,cc}$ in OVH-KBP is 5.1 Gy lower than APE since the JHU’s protocol has a much more aggressive sparing goal: cord $4\,mm\,D_{0.1\,cc} \leq 44\,Gy$ in JHU vs. cord’s $D_{0.1\,cc} \leq 50\,Gy$ in RUMC. However, the RUMC oncologist did observe increased oral cavity doses in OVH-KBP over APE plans, which could be due to cord’s “over-sparing” in OVH-KBP plans. In this cross-institutional library sharing, a generic factor ($1.27$) was used to scale-down the doses from JHU library to match RUMC protocol. However, a smaller factor could be applied to cord dose scaling if the increased oral cavity dose is a concern.

Table 2 shows that the dose constraints for the parotids, larynx, oral cavity and submandibular glands were not achieved in the majority of the plans, but the constraints for the cord, brainstem and target coverage were largely achieved. The reason is that in both RUMC and JHU planning practice [2], the targets/OARs constraints were divided into three groups with different priorities: cord and brainstem constraints have the highest priority that must be achieved; target coverage has the medium priority, which cannot compromise the highest priority constraints; sparing of the parotids, larynx, oral cavity and submandibular glands has the lowest priority: the doses to those OARs should be as low as possible without compromising the constraints in the medium and highest priorities. The conflicting demands between target coverage and OAR sparing put limitations on the satisfaction for all constraints. Consequently, in many cases, OAR sparing with the lowest priority was compromised to ensure satisfaction of target coverage, which was reflected in the results of Table 2.

Our study has the following limitations: (1) the scaling in JHU library to match RUMC’s protocol could potentially introduce sub-optimal performance in the OVH-KBP approach; a focused planning comparison study of APE vs. OVH-KBP under the same protocol would be of interest and may lead to slightly different results. However, even with such a possibility, OVH-KBP with cross-institutional library sharing still produced non-inferior dosimetric results with respect to APE; (2) the primary focus of the study is to compare OVH-KBP and APE plans, which has perhaps diverted somewhat from an aggressive comparison between those plans and clinically-delivered plans [1–3,17,18], consistent with our findings in Table 2; (3) the observed comparable dosimetric results between OVH-KBP and APE are influenced by the quality of the JHU’s library in KBP generation. Use of other institutions’ libraries of different quality may lead to different conclusions; (4) the observed comparable results between OVH-KBP and APE are specific to the KBP methodology employed here and may not be applicable to other KBP approaches e.g., RapidPlan.

**Conclusions**

The comparable results obtained with OVH-KBP and APE suggest that either method may be used to generate plans for treatment planning, as supported by publications demonstrating the quality comparability between OVH-KBP (or APE) and clinically-delivered plans [2,17,18]. However, the “automation” as implied in the auto-planning process should not be taken literally, as both approaches still require certain skilled manual inputs to achieve acceptable results, e.g., the planning parameters determined in training cycles. In addition, this study was focused on oropharynx cancer only and whether the results will hold for other disease sites needs further investigation. Nevertheless, the auto-planning applications discussed here and by other authors offer useful avenues to shorten treatment planning time and reduce plan quality variation, as evidenced in the commercial application of RapidPlan in Eclipse TPS and APE in Pinnacle TPS.

**Conflict of interest**

Binbin Wu and Todd McNutt are the co-inventors of a patent associated with the proposed KBP approach, which was licensed to Varian Medical Systems in 2015.

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**Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2017.01.012.
References


