Review Article

Knowledge-based planning in nasopharyngeal carcinoma

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Abstract: Radiotherapy planning for treatment of nasopharyngeal carcinoma (NPC) could be challenging and tedious. Both planning quality and time are vastly operator dependent and a high level of skill and experience is required to yield an optimal plan. Various knowledge-based planning (KBP) systems have been developed lately to automate planning based on past treatment plan data, with the aims of improving the planning efficiency and consistency. In this article, we will briefly review the various types of KBP systems, their clinical uses and performances in the nasopharynx site. To give a more concrete example to how KBP can be implemented in practice, we will demonstrate the application of RapidPlan™ (RP)—a knowledge-based optimization toolbox available in the Eclipse treatment planning system—to generate high quality intensity-modulated radiation therapy (IMRT) plans for NPC planning. Training, fine-tuning and validation of the RP model were described. Uses of KBP for head and neck cancers in general, uses of KBP for purposes other than planning as well as possible future development of KBP will also be discussed.

Keywords: Nasopharyngeal carcinoma (NPC); intensity-modulated radiation therapy (IMRT); knowledge-based algorithm; RapidPlan (RP)

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Introduction

Radiation therapy is a widely adopted and effective treatment in nasopharyngeal carcinoma (NPC).

With the complicated disease nature, intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) are the key treatment techniques for maximizing cancer control while minimizing toxicity to normal organs (1-3). Inverse planning techniques which optimize the doses to both the planning target volumes (PTVs) and organ-at-risks (OARs) are required for the planning of IMRT and VMAT (4). Universal planning goals can be used to judge whether the plan can meet the acceptance standards, whether the plan could be further improved is dependent on the patient's anatomy and thus differs from case-to-case. This relies on the planner's ability to observe and pinpoint particular areas for further improvements and ultimately guide the optimization to obtain better results (5-7). To explore various possibilities of achieving a better plan, some trial-and errors processes are inevitable. Simply knowing what to try and when to stop could largely reduce the time spent on unnecessary trials. Thus not only the quality of the treatment plan but also the planning time are highly dependent to the knowledge and experience of the planners (8,9).

As early as 1980s, automatic planning systems have been experimented to aid the design of computerized radiation treatment plans (10). Those systems mainly translate the knowledge and experience to rules and algorithms that help to automate the tedious and repetitive manual manipulations

in the planning process. With the improvement of computer power and speed, these systems have further advanced and in recent years, some of them were developed as commercially available solutions. One example is AutoPlanning™ within Philips Pinnacle TPS (11). Similar to the steps that a human planner would take in planning, the software optimizes the plan iteratively by creating additional ROI and optimization constraints based on transient dose distribution using a fix set of proprietary rules. These systems are typically efficient in generating clinically acceptable plans, however, they offer limited control on the trade-off between target coverage and OAR sparing. To tackle this limitation, multi-criteria optimization (MCO)—another type of auto-planning algorithm—has emerged. As of year 2020, various MCO planning tools are available commercially including Eclipse (Varian) (12), Raystation (RaySearch Laboratories) (13), Erasmus-iCycle (Erasmus MC, Rotterdam) (14), etc. MCO automatically generates a series of Pareto-optimized plans (plans of which no objective quantity can be improved without impairing at least one another) with a variety of trade-offs and the clinician can choose from the pool the one that best suits the patient. Choosing an optimal trade-off could be challenging and requires good clinical knowledge and experiences. As clinical experiences with IMRT/VMAT accumulates over the past two decades, a new data-driven method, known as knowledge-based planning (KBP), has been developed to extract the best clinical judgement and knowledge from prior good cases and apply them to generate new plans automatically (15-24). In the big data era, such approach allows the sharing of knowledge between different oncology centers and shows great promise in the development of fully automated planning with improving planning quality and efficiency.

General overview of KBP

KBP engines are generally comprised of three components: (I) an input library/database consisting of ensembles of prior clinical data, (II) extraction of knowledge from the database and conversion into optimization parameters, (III) an optimization algorithm that uses the optimization parameters determined to guide the creation of a deliverable plan.

Input library/database

The input data may include the planning CT images, delineated structures, planning parameters, dose volumes, patient demographic characteristics, etc. Usually the inputs are restricted to only a particular anatomical site, sometimes even disease type and protocol. These variations could also affect the minimum amount of input plans required for a good KBP system. One would normally expect a larger number of plans required for KBP in head and neck cancers due to the sophisticated and diversification natures of the diseases (many PTVs/OARs, various dose levels, large variation in PTV shapes and locations).

Extraction of knowledge from database

There are two main ways of extracting key knowledge from past data—atlas-based and model-based.

In atlas-based KBP, the reference patient(s) in the database best matching the subject patient to be treated is first identified from whose plans the knowledge is extracted. Various methods have been explored to pick out the best matched patient. A popular approach is to look for maximal similarities between patients in terms of the relative spatial locations of targets and OARs [e.g., overlapping area of the overlap volume histograms (OVH) (25)] which are most critical factors affecting the attainable target coverage and normal tissue sparing. Among the reference patients that are sufficiently similar to the subject patient, one might also want to choose the one with the best plan quality, for instance, choose a plan with minimum OAR dose, but with sufficient target coverage (26).

Model-based KBP, on the other hand, instead of extracting knowledge from only the best matched reference patient(s), incorporates the essence of knowledge and experience of all reference plans in the database into a single prediction model. The model fits upon features and patterns available in the reference plans and output the estimation of the best geometrical configuration for planning or the best dosimetric outcome that should be achievable in the new plan. A large variety of prediction model exist, majority of them are based on Machine learning methods such as regression, random forest, support vector machine, etc. Deep learning, a particular type of machine learning based on artificial neural network, has also been applied in KBP (27) and is starting to gain increasing popularity and has shown significant promise as the next generation of auto-planning algorithm.

Generating optimization parameters

The knowledge extracted in the atlas-based KBP or predictions from model-based KBP are used to generate optimization parameters for optimization of new plans.

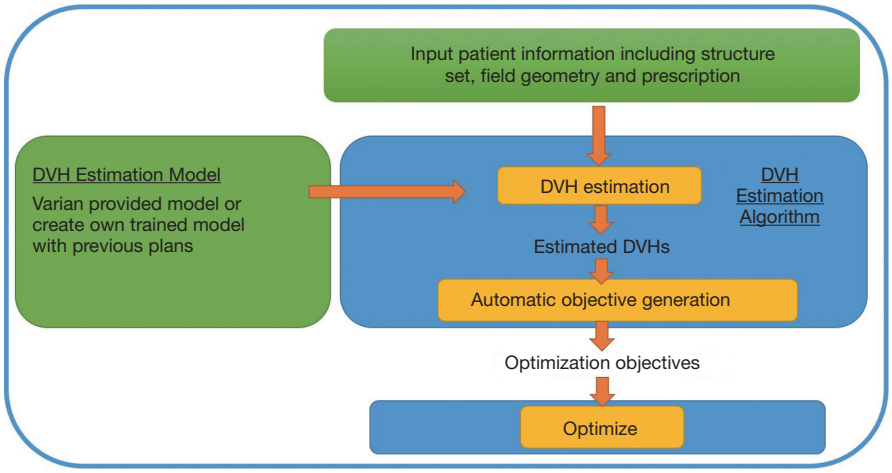


Figure 1 Workflow of RapidPlan™ (RP). DVH, dose-volume histogram.

For instance, the fluence map of the new plan can be obtained by deformation registration of the fluence map of the best matched patient plans in an atlas-based KBP system, dose-volume histogram (DVH) prediction from a model-based KBP can be fed to inverse optimization algorithm to generate new plan. Other examples of knowledge transferred/optimization parameters include beam parameters (e.g., gantry/collimator/couch angles, jaw settings), voxel dose distribution, objective function weights, etc. DVH estimates are by far the most commonly used. However, one potential pitfall in the DVH approach is that DVH contains no geometrical information, as such the plan produced might fulfil all the DVH criteria but still presented with an inferior 3D dose distribution (e.g., slow fall-off). This provokes new research and developments in voxel-based planning. For instance, Chen *et al.* has recently implemented a convolutional neural network, ResNet, a specialized architecture for imaging and vision purposes, for 3D dose distribution prediction for simultaneous integrated boost (SIB) radiotherapy in NPC (28).

Creation of deliverable plans

The prediction or knowledge transferred can only be used as a guide for further optimization since (I) every patient is inevitably different, no matter how similar with one another; (II) the plan needs to be deliverable, i.e., ones that are physically possible with the modality of interest, e.g., linac, Cyberknife, etc.). Examples of optimization engines include DVH guided inverse-planning algorithms (the most commonly used), voxel-based dose mimicking algorithms [McIntosh *et al.* (29)/Raystation], etc.

Example of KBP (RapidPlan) applied to NPC IMRT planning

To demonstrate how actually KBP is implemented, we will look at a specific example of using RapidPlan™ (RP) in NPC IMRT planning. This is the custom NPC model that was employed in the study of Chang *et al.* (30). It had been commissioned and used clinically in our oncology center to assist NPC planning since 2016.

RP in a nutshell

RP is a knowledge-based optimization application that is provided as an integrated option in the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, USA) since release 13.5.

The RP model is first trained using prior high quality plans to establish the relationship between geometry (both anatomy and field arrangement) and dosimetry. The model can be used to estimate the OARs' DVH in a new plan when given the patient information (structure sets, prescription, field geometry). The DVH estimation (*Figure 1*) and the automatically generated priorities are then fed into inverse optimizer to generate a deliverable plan (*Figure 2*).

RP DVH Estimation algorithm (31)

Volume sub-division

Each OAR is sub-divided into four regions (*Figure 3*): out of

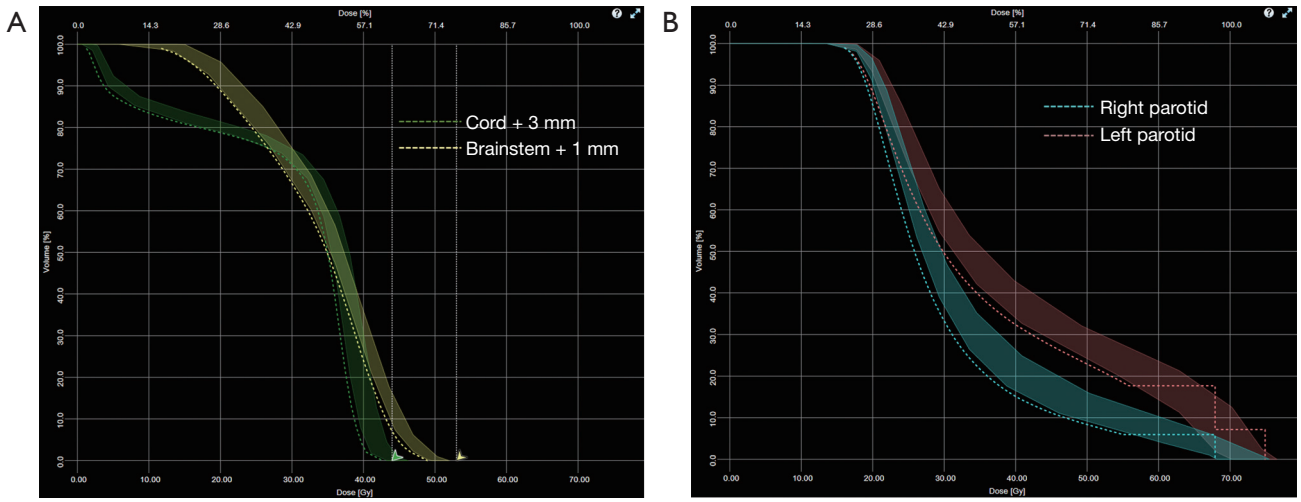


Figure 2 Examples of DVH predictions and optimization objectives created using the RapidPlan model. (A) Predicted ranges of DVHs (shaded regions) for cord + 3 mm and brainstem + 1 mm. Line objectives are placed along the inferior boundary of the predicted DVHs (dotted lines). The arrow represents the fixed optimization objective at maximum dose; (B) predicted ranges of DVHs (shaded regions) for left and right parotid. Line objectives are placed along the inferior boundary of the predicted DVHs (dotted lines). Since PTV takes priority at the overlapping region between the PTV and the parotid, the line objective appears to be "stair like" near maximum dose. DVH, dose-volume histogram; PTV, planning target volume.

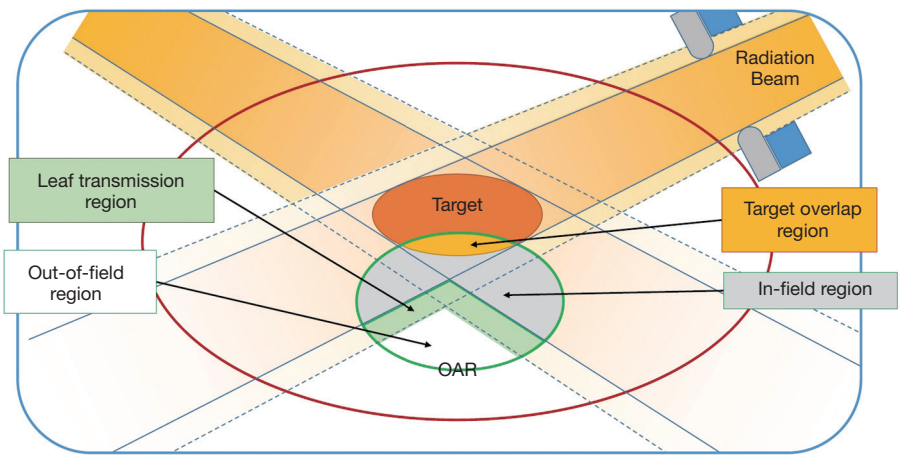


Figure 3 The four functional regions of an OAR. OAR, organ-at-risk.

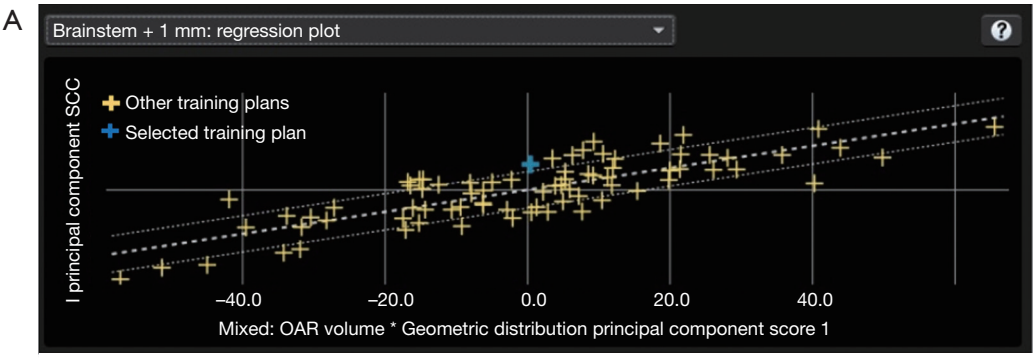
field, in-field, leaf transmission, overlapping region. DVH of the in-field region could be highly variable depending on how the plan is optimized, and will be modelled with the help of prior data. Variations of DVH in other regions are limited and are estimated using relatively crude models.

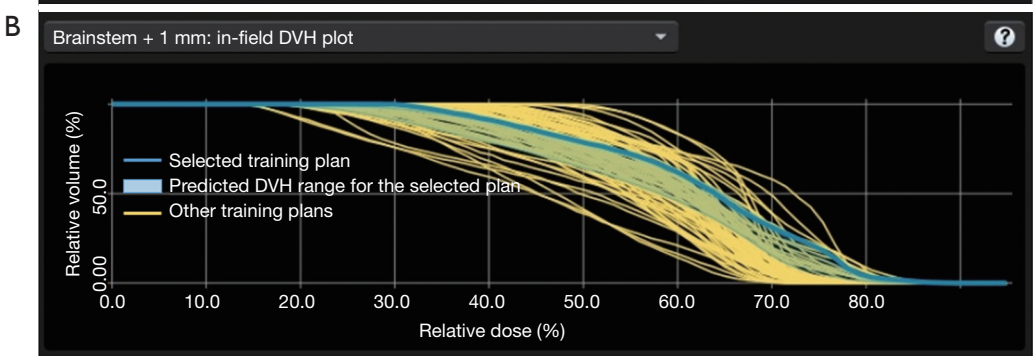
Evaluation of geometry

The geometry is represented through the construction of the geometry-based expected DVH (GBDVH). Details of GBDVH construction is beyond the scope of this article, more detail can be found in reference (31).

Principle component analysis (PCA)

PCA is performed to both the GBDVH and the in-field DVH to extract principle components (PCs) that maximizes the variance of the DVHs in the training set. PC score





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Model goodness statistics:

Estimation model statistics for structure Brainstem + 1 mm:

Model goodness of fit

DVH's principal components average fit 0.999508 out of 1.0

GED's principal components average fit 0.99939 out of 1.0.

Regression model parameters' coefficient of determination 0.656278 out of 1.0

Regression model's parameters average chi-square 1.05709

Whole estimation model's fit 0.655555 out of 1.0

Whole estimation model's average MSE 39.5196

Model goodness of estimation

Mean squared error between original and estimate 0.00396297

Statistics outside boundaries:

Proportion of histogram bins outside boundaries 33.6028

Train model: while training the estimation model for structure 'Brainstem + 1 mm' the following plans' structures were identified as possible outliers: Structure ID Brainstem + 1 mm in plan 22.

Reason:

Significant Cook's distance found for one or more dependent parameters: 5.04375 (reporting threshold 4).

Structure ID Brainstem + 1 mm in plan 27.

Reason:

Significant studentized residual value found for one or more dependent parameters: 3.56162 (reporting threshold 3).

Significant Cook's distance found for one or more dependent parameters: 14.0851 (reporting threshold 4).

Structure ID Brainstem + 1 mm in plan 46.

Figure 4 Statistics of the trained RapidPlan model. (A) Regression plot; (B) in-field DVH plot; (C) training log. DVH, dose-volume histogram.

(PCS)/coefficient of each plan for each OAR is calculated.

Regression

For each OAR, stepwise-regression is performed to correlate the PCS of GBDVH and PCS of in-field DVH across all plans in the training set.

DVH estimation of new plan

PCS of GBDVH for the new plan is calculated. Using coefficients obtained in the regression, PCS of the in-field DVH can be determined which are in turn used to generate the in-field DVH estimates. By combining DVH estimates from the other OAR sub-volume, DVHs of the OARs can be estimated. Line objectives for OARs are then created along the lower DVH estimation boundaries for inverse optimization along with other fixed objectives manually chosen for PTV (and OAR) structures. The priority of the line objective can also be automatically generated.

Input library for the NPC RP model

In order for the model to be applicable in most clinical cases, the input library should contain enough samples that can represent the majority of the NPC population. In our model, plans of 79 NPC patients, with no differentiation made regarding the stage of disease, were included for training. These NPC patients were given SIB treatments in 35 fractions to three prescription dose levels (70, 63, 56 Gy) using IMRT technique (six MV photon). VMAT was not included in the model because our Institute only used IMRT for NPC treatment and no previous knowledge of using VMAT was available for the KBP model.

PTVs of different dose levels were individually cropped, and were made to separate from each other by 3 mm margins. OARs of left and right side were grouped together (for instance, left and right parotid as "parotid" in the model). Altogether, nine OAR structures that were included in the model. They were Brainstem + 1 mm, Cochlea, Cord + 3 mm, Eye, Lens_PRV, Op_Chiasm + 1 mm, Optic Nerve, Parotid and Temporal Lobe.

Training and refinement of RP model

The DVH Estimation model of each OAR is trained using the plans imported in the library. The statistics of the trained model are summarized in the geometry plot (containing statistics of OAR/target volume, percentage overlapping of OAR to target, PCSs of the GBDVH), regression/residual plots as well as in-field DVH/overall DVH. By analyzing these statistics together with the training log (*Figure 4*), possible geometric/dosimetric outliers that can impact the reliability of the model can be detected [more information can be found in the manual (31,32)]. Metrics such as regression coefficient of determination, studentized residuals and Cook's distance in the training log help to pinpoint particular outlier plans that should be removed from the model. To further improve the reliability and precision of DVH estimation, the model was re-trained iteratively and recursively (33), i.e., the model was used to re-plan cases if the estimated DVHs of OARs outperform that of the input plans. The input plans were then replaced by these re-optimized plans and re-training was performed. Finally, all cases were re-planned with the re-trained model and all the new data were imported to train and create a new RP model. As illustrated by the example shown in *Figure 4A*, a strong correlation is found between the geometry and dosimetric PCS, indicating that the model is well-configured. The model performance could probably be further enhanced by adding more quality plans into the input library.

Performance and validation of the NPC RP model

The performance of the RP model was evaluated against manual planning for a set of twenty NPC patients that are independent of the training set (30). In general, the target coverage for both the manual and RP plans (plans generated using line constraints and priorities suggested by the RP model) were similar. The mean doses of OARs were generally reduced with the help of DVH line constraints. However, control on the maximum OAR dose was inferior to the manual plans with about half of the plans not fulfilling the acceptance criteria of the top priority serial OAR structures [the summary of the target and normal tissue constraints are described as in the article (30)]. Nevertheless, the difference was very small and all these plans could be made acceptable with minimal manual adjustments. The planning time using RP plan followed by manual adjustments is still significantly less than the time required for full manual plans: 64 *vs.* 295 minutes. These results demonstrated the current status and feasibility of RP employed in IMRT planning of NPC. RP does not limit the application of VMAT planning even though the model is configured using IMRT plans only, however, the result concerning the IMRT KBP model might not be applicable to VMAT plans and the reader should interpret these results with cautions.

Use of KBP in head and neck cancers

Previous reports on KBP are based on two main types of validation studies comparing KBP-predicted dose metrics, or KBP-produced dose distribution with those of manual clinical plans. General findings suggest that KBP methods are capable of achieving clinically acceptable target volume coverage with improvements in OAR sparing. Universally, planning time was found to be significantly reduced, especially for complex cases. In head and neck cases, various studies have shown sparing to parotids, submandibular glands, oral cavity, and swallowing muscles (such as pharyngeal constrictor muscles); a study by Tol *et al.* (21) showed that significant improvement in mean parotid dose (more than 4 Gy) can be achieved with RP when compared with the original plans from an older series, reflecting most benefit for inexperienced centers. It is also noted that

plan quality is less consistent for some "outlier" cases. In building the model, anatomical features of PTV and OAR and their spatial relationships are important parameters, such as median OAR and PTV distance, proportion of OAR volume within a specific distance range or overlapping with PTV etc. (34-36). It is controversial as to the number of cases required to train a model as it is expected that head and neck cancers contain higher complexity and likely require more training cases, compared with other tumor types such as prostate cancer with fewer OAR's to consider.

Automated treatment planning has also been adopted in the context of clinical trials. The Radiation Therapy Oncology Group (RTOG) 0920 and 3501 utilized a model which incorporated data from head and neck cancer patients who had previously received helical tomotherapy or VMAT, to re-plan VMAT patients who were recruited into these clinical trials. Model plans were shown to improve OAR sparing compared with manual plans with maintenance of clinically acceptable dose uniformity. A clear advantage is significantly improved planning efficiency (37-39).

Other applications on KBP

Patient selection for different modality

The predictive power of KBP in dosimetric outcome can also be exploited for patient selection purposes. Due to the limited availability and high cost of proton therapy, as well as the capability of modern IMRT techniques, there is always a need to select the right patients who can benefit most from proton therapy. Usually treatment plans of these two modalities need to be produced, optimized and compared, which is time and labor intensive. Delaney *et al.* (40) demonstrated the idea of patient selection by KBP-predicted mean OAR doses for 10 head and neck cancer patients. The mean doses of parotid glands, contralateral submandibular gland and swallowing muscles were predicted for both intensity-modulated proton therapy (IMPT) and IMRT plans and then compared. Using 6 Gy as the threshold mean dose difference for selection, the method identified four out of five eligible patients (out of a total of ten) for IMPT, and four out of five that would not qualify. The study was subject to the limited capability of applying the KBP model on proton therapy as the KBP algorithm was not yet designed to handle proton beam characteristics, it did however clearly demonstrate the potential of KBP in patient selection to receive the most appropriate treatment modality.

Quality control of IMRT planning

A study by Zhou *et al.* utilizes knowledge library of reference plans for the quality control of IMRT planning (25). New measures derived from OVH and DVH were used as additional parameters to control IMRT plan quality. Twenty-eight NPC IMRT plans were included and compared against one another according to these new measures; and those for which a better "reference" plan could be found were re-optimized using reference plan DVHs as additional objectives. Significant improvement could be achieved for these plans; in particular, the parotid median dose was reduced by 3.4 Gy on average. The method successfully identified the sub-optimal plans and provided an easy mean for improvement.

IMRT plan quality check is also an important issue in a multi-center clinical trial setting. As sub-optimal plans that still achieve the minimum plan acceptance criteria are usually not considered in trial's stratification, they can introduce bias and affect final trial outcomes. To demonstrate the use of KBP for planning quality assurance (QA), Tol *et al.* (41) produced KBP plans for 100 head and neck cases submitted by thirteen different institutes participating in the EORTC-1219-DAHANCA-29 trial, and compared the difference in the mean OAR doses. Only the dose to parotid/submandibular glands and swallowing muscles were compared as the serial OARs constraints must be met for plan submission. They found that the mean dose could be improved by more than 3 Gy for 293/570 OARs. In fact, the mean OAR doses predicted by the knowledge-based model are found to be sufficiently close to that can be achieved in the optimized KBP-plan so that the predicted doses can be used directly for QA purposes without needing to produce a KBP plan at all. Using DVH prediction alone identified 60 submitted plans that the OAR mean dose can be potentially reduced by more than 3 Gy. The KBP prediction provides a quick means for plan QA and the predicted DVH can also be passed to the institutes for plan re-optimization if needed.

Evaluation of dosimetric consequences due to contouring inconsistencies

A study utilized automatically generated treatment plans to evaluate the impact on contour variation was reported by Lim *et al.* (42). Twenty-two residents contoured the clinical target volumes of different dose levels (54.12, 59.4 and 69.96 Gy), both parotids and cochleae for a T1N1

NPC patient and the contours were compared with the "gold standard" contours created by two expert oncologists. Sixty-seven VMAT plans with four full coplanar arcs were generated with KBP model for four different combinations of resident-drawn and gold-standard PTV and OAR contours. Analysis of the dosimetric indices (PTV D_{98} and OAR D_{mean}) provided clinically meaningful conclusion on the consequence of contouring discrepancy, and the inadequacy of the commonly-used geometric indices for contour evaluation (poor correlation between geometric and dosimetric indices with R^2 <0.2 for 61 % of the correlations studied). The authors of this study recommended using KBP-produced plans for future contour evaluation studies.

Limitations and future developments

As suggested by the name, KBP approach draws from the experience of previous high quality plans. The KBP performance will suffer if poor quality plans have been used to construct the model library. Usually individual institutions construct their own library based on their own treatment protocols with specific prescription dose levels, fractionations, OAR constraints, contouring convention, etc. The KBP plans thus produced would be limited by the institute's previous planning capability, and the models may not be transferrable to another institute using different protocols. Panettieri *et al.* (43) demonstrated the feasibility of constructing a universal KBP model for prostate cancer trained with 110 treatment plans contributed from five centers employing different treatment protocols, and then distributed and revalidated by eight centers. A standardized OAR constraint was developed in the process and the KBP model was able to produce quality plans with general improvement in OAR sparing despite the variations in target dose prescription and fractionation scheme. We believe future KBP algorithm will be developed to accommodate a large diversity of treatment schemes, dose constraints, modalities, and even with tuning features; so that with sufficient number and variety of training plans, the resultant model will be sufficiently flexible and easily transferrable to a large number of users with different planning aims.

Conclusions

KBP could improve the efficiency of IMRT planning for NPC patients and produce less planner dependent treatment plan with good quality, although some manual touch-up was occasionally needed for the KBP plans to meet the clinical acceptance criteria. The performance of the model could be further improved by adding more quality data and tuning of the model, potentially removing the need of manual touch-up. With the help of auto-contouring (44) and scripting, fully automated planning might become plausible. Such potentials would be worthy for further exploration. The benefit of improved planning quality and efficiency can also be enjoyed by a large number of patients with the construction of universal KBP models that are highly flexible and transferable to different radiotherapy centers with limited resources.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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