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Scientific Article

Development and Validation of Single-Optimization Knowledge-Based Volumetric Modulated Arc Therapy Model Plan in Nasopharyngeal Carcinomas

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Purpose: Knowledge-based planning (KBP) has evolved to standardize and expedite the complex process of radiation therapy planning for nasopharyngeal cancer (NPC). Herein, we aim to develop and validate the suitability of a single-optimization KBP for NPC.

Methods and Materials: Volumetric modulated arc therapy plans of 103 patients with NPC treated between 2016 and 2020 were reviewed and used to generate a KBP model. A validation set of 15 patients was employed to compare the quality of single optimization KBP and clinical plans using the paired *t* test and the Wilcoxon signed rank test. The time required for either planning was also analyzed.

Results: Most patients (86.7%) were of locally advanced stage (III/IV). The median dose received by 95% of the high-risk planning target volume was significantly higher for the KBP (97.1% vs 96.4%; $P = .017$). The median homogeneity (0.09 vs 0.1) and conformity (0.98 vs 0.97) indices for high-risk planning target volume and sparing of the normal tissues like optic structures, spinal cord, and uninvolved dysphagia and aspiration-related structures were better with the KBP ($P < .05$). In the blinded evaluation, the physician preferred the KBP plan in 13 out of 15 patients. The median time required to generate the KBP and manual plans was 53 and 77 minutes, respectively.

Conclusions: KBP with a single optimization is an efficient and time saving alternative for manual planning in NPC.

Introduction

Nasopharyngeal cancers (NPC) are one of the most challenging sites for radiation therapy planning for medical physicists/dosimetrists. The reasons include relatively

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large and complex target volumes requiring high doses (~70 Gy) with several critical organs at risk (OARs), such as the spinal cord, brain stem, optic structures, and parotid glands, lying in close vicinity.[1] Furthermore, specific anatomic configurations of tumor like abutments around the optic structures or brain stem and intracranial extension complicate the planning process.[2]

Intensity modulated radiation therapy (IMRT) and related techniques are now widely acknowledged as the standard of care for radiation treatment of NPC.[3] IMRT uses an inverse treatment planning model wherein optimization uses an iterative approach to achieve the treatment planning goals.[4,5] It is a complex process with the aim of achieving pareto optimal plans, defined as a planning solution where another solution does not exist that is better in at least 1 objective while being no worse in every other objective.[6] Nevertheless, it is a trial and error procedure that consumes significant time because medical physicists/dosimetrists must predetermine the baseline optimization objectives and manually adjust them during optimization to achieve the desired dose distribution. The quality of the IMRT plans also depends immensely on the planner's experience and expertise.[5,7-14,16]

Knowledge-based planning (KBP) has been introduced to expedite planning and standardize plan quality among different planners. KBP simplifies the IMRT optimization process by using prior plans to predict an achievable dose for a new patient or derive a better starting point for optimization by a planner.[16] KBP methods are generally formulated as 2-stage processes. In most cases, the first stage is a machine learning method that predicts the dose distribution or dose-volume histogram (DVH) that should be delivered to a patient based on contours done on computed tomography images. The second stage is an optimization model that generates a treatment plan based on the predicted dose distribution.[17,18]

RapidPlan (Varian Medical Systems, Palo, Alto, CA), a commercial KBP tool, is integrated into the Eclipse treatment planning system (TPS) version 16.1 and is an machine learning tool that uses best practices from previous treatment plans to create knowledge-based models for the treatment of new patients.

This study was undertaken as an institutional guide to validate the suitability and efficiency of single-optimization knowledge-based plans compared with manual plans in NPC.

Methods and Materials

This was a dosimetric noninterventional study undertaken at a tertiary cancer institute in India. Institutional review board approval was waived as no patient intervention was planned.

Patient selection

A collection of consecutive 103 histologically proven cases of stage II-IV nasopharyngeal carcinoma treated with volumetric modulated arc therapy (VMAT) with the Eclipse TPS between the years 2016 and 2020 was used for the training of the KBP model. All patients were staged according to the 7th edition of the American Joint Committee on Cancer tumor-node-metastases system.[19] The decision to treat after 2 to 3 cycles of neo-adjuvant chemotherapy was made in a multidisciplinary joint clinic, per prevailing institutional protocol.

Immobilization and contouring

Patients were immobilized in the supine position with a neutral neck in a customized 4-clamp thermoplastic mask. Axial planning computed tomography scan with intravenous contrast was acquired from the vertex to the carina using a 2.5-mm slice thickness. The target volumes and OARs were delineated according to the preneoadjuvant chemotherapy volumes (if applicable) and per the international consensus guidelines.[20] Elective nodal clinical target volume included uninvolved, bilateral retropharyngeal, retrostyloid, and levels II-V (including level Ib, if indicated based on clinic-radiologic features). An isotropic margin of 5 mm was applied to the clinical target volume to generate the planning target volume (PTV) based on institutional protocol along with requisite anatomic correction and editing of the part extending outside the body contour. The brain stem, eyes, optic nerves, optic chiasm, pituitary gland, thyroid, mandible, oral cavity, spinal cord, and parotid glands were included as OARs. A uniform 3-mm margin was added to the spinal cord and brain stem as a planning OAR volume.

Radiation therapy dose and treatment planning

IMRT plans were generated using VMAT and simultaneous integrated boost techniques to deliver a dose of 66 to 70 Gy to the gross disease and 54 to 56 Gy to the microscopic disease in 30 to 35 fractions, using daily image guidance. Planning objectives were based on the International Commission on Radiation Units and Measurements (ICRU) 83 and Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) [21,22] guidelines for target volumes and OARs. Patients with adequate renal function also received concurrent weekly or 3 weekly cisplatin. The goals and acceptance criteria for the DVH parameters are summarized in Table 1. All the VMAT plans were generated using 2 full arcs bilaterally according to the location of the tumor. The collimator

Table 1 Acceptance criteria for evaluating overall plan quality based on ICRU-83 and QUANTEC guidelines

Biologic equivalent dose at 2 Gy fraction	Acceptable	Minor deviation	Major deviation
Priority 1 parameters			
Brain stem	D0.03cc* ≤ 54 Gy	54 Gy < D0.03cc* ≤ 60 Gy	D0.03cc* > 60 Gy
Spinal cord	D0.03cc* ≤ 45 Gy	45 Gy < D0.03cc* ≤ 50 Gy	D0.03cc* > 50 Gy
Optic chiasm	D0.03cc* ≤ 54 Gy	54 Gy < D0.03cc* ≤ 60 Gy	D0.03cc* > 60 Gy
Both optic nerves	D0.03cc* ≤ 54 Gy	54 Gy < D0.03cc* ≤ 60 Gy	D0.03cc* > 60 Gy
Both eyes	D0.03cc* ≤ 54 Gy	54 Gy < D0.03cc* ≤ 60 Gy	D0.03cc* > 60 Gy
GTVp and GTVn	100% of GTV ≥95% of prescription dose	100% of GTV ≥93% to <95% of prescription dose	100% of GTV <93% of prescription dose
PTV-HR: D_{min}	95% of PTV ≥95% of prescription dose	95% of PTV ≥93% to <95% of prescription dose	95% of PTV <93% of prescription dose
Priority 2 parameters			
PTV-HR: D_{max}	<107% outside PTV	≥107% to <110% outside PTV	Maximum ≥110% outside PTV
PTV-LR: D_{min}	95% of PTV ≥95% of prescription dose	95% of PTV ≥93% to <95% of prescription dose	95% of PTV <93% of prescription dose
One optic nerve	D0.03cc* ≤ 54 Gy	54 Gy < D0.03cc* ≤ 60 Gy	D0.03cc* > 60 Gy
Temporal lobe	D1cc < 65 Gy	D0.03cc* < 72 Gy	D0.03cc* > 72 Gy
Priority 3 parameters			
Parotid and submandibular salivary glands	D_{mean} < 26 Gy	D_{mean} < 30 Gy	D_{mean} < 36 Gy
Uninvolved DARS	D_{mean} ≤ 50 Gy		
Oral cavity	D_{mean} ≤ 50 Gy		
Both lenses	D_{max} < 7 Gy	D_{max} < 10 Gy	
Mandible	D_{max} < 70 Gy	D_{max} < 75 Gy	
Both cochleae	D_{mean} ≤ 45 Gy	D_{mean} < 60 Gy	

Abbreviations: DARS = dysphagia and aspiration-related structures; GTVn = gross tumor volume node; GTVp = gross tumor volume primary; ICRU = International Commission on Radiation Units and Measurements; PTV-HR = high-risk planning target volume; PTV-LR = low-risk planning target volume; QUANTEC = Quantitative Analyses of Normal Tissue Effects in the Clinic.
*Both D0.03cc and D_{max} are acceptable.

angles were kept between 5° to 10° to reduce the multileaf-transmission. The photon optimizer (version 16.1.0) was used for the VMAT optimization, and dose calculation was done with the help of Acuros XB Algorithm (version 16.1.0) with a 2.5- mm grid calculation size. The selected plans had uniform contours, dose prescription, and beam and collimator arrangements and were thus chosen for the training data set for the model generation.

Model configuration and DVH estimation

Model configuration consists of data extraction and model training phases. In the data extraction phase, volumetric and spatial information related to the selected OARs, like the structure set, dose, and field geometry, was converted into a few characteristic curves and parameter values. Data extraction was performed for each case to be included in the training set of the given model. Information from the selected OARs was extracted by dividing them into different regions: out-of-field region, leaf-transmission region, in-field region, and the overlap region. In the subsequent phase of model training, DVH estimation models were created for each OAR with the help of the DVH estimation algorithm and the extracted data. This was achieved by 3 possible models available for OAR regions in the RapidPlan module of the Eclipse TPS.[23] Various geometric and dosimetric outliers were excluded or replanned.[25] All these models were combined for different areas in each OAR to obtain a single model for each OAR selected for training.

The DVH estimation component of the DVH estimation algorithm has 2 phases − the estimation generation and objective generation phase. It uses the structure set, filed geometry, and dose level of targets to generate an estimated DVH range and optimization objectives for each OAR. The various regression scatter plots with upper and lower bounds of OARs along with plans of the DVH estimation model for high-risk PTV (PTV-HR) and low-risk PTV used for our model generation are depicted in Fig. E1.

Configuration for the KBP model

A model named "KBP_NPX_Final" was created in the RapidPlan module of the Eclipse TPS. The target structures and the associated OARs were added to the model. Considering that only the same structure codes could be automatically matched between the model and the clinical planning structures, it was ascertained that the codes and nomenclature of the structures remained the same. For controlling the low-dose spill and achieving dose constraints for OARs, physics structures were created with the nomenclature as "Z_OAR Name," and these structures were cropped from the target volumes by a 2- to 3-mm margin and also from the body contour by a 2-mm margin. The plans of the training data set were extracted and incorporated into the model, and the structures were matched respectively to the model structures.

Outliers and model training

The KBP model creates regression models between geometric and dosimetric components, which can detect outliers that help improve the model's predictive capability.[24] Once the training data set was extracted and matched and the outliers defined, the model training began. The model was fine-tuned, and optimization objectives for the target volumes and OARs were generated and optimized iteratively until a good model result was obtained. The final optimization objectives and priorities established using both clinical experience and model estimation are given in Table 2. Upper and lower objectives were given for target volumes, whereas upper objectives were given for the OARs. Line objective preferring target was generated for most of the OARs. The model did not use optimization rings to control the dose spillage outside the PTV. However, it was controlled employing the normal tissue objective.

Model validation and evaluation

The validation set consisted of 15 patients with NPC who were not a part of the training set. All 15 patients were already treated with clinical plans (CP) before the initiation of the study, and KBPs were thereafter generated for comparison. On an average, 2 to 3 reruns of manual optimization were required for achieving an optimal CP. For all validation plans, the same arc geometry and beam configuration were used as the clinical plans. These KBPs were generated in a single optimization run, without any manual intervention during optimization. The plan evaluation by the head and neck radiation oncologists was blinded, and all plans were evaluated for target volume coverage and OAR constraints per the ICRU-83 and QUANTEC recommendations. Various dose-volume parameters for target volumes, including conformity index (CI), homogeneity index, and OARs (mean and maximum dose), were used for comparing the CP and KBP. Quantitative comparisons between the 2 plans were established using the standard 2-tailed paired t test (for normally distributed data) and Wilcoxon signed rank test (for non-normal data) using the Statistical Package for Social Sciences software (version 26 and Rstudio version 4.2.).

Results

The KBP model was trained using VMAT plans of 103 patients with nasopharyngeal carcinoma. After the model

Table 2 Optimization objectives and priorities for various model structures

Model structure	Objective	Volume (%)	Dose (% or Gy)	Priority
PTV-HR	Upper	0	102%	125
	Lower	100	100%	123
PTV-LR	Upper	0	102%	95
	Lower	100	99%	100
Brain stem	Upper	0	54 Gy	90
	Line	Generated	Generated	45
Eyes	Line	Generated	Generated	50
Mandible	Upper	0	63 Gy	40
	Line	Generated	Generated	30
Uninvolved DARS	Upper	0	50 Gy	70
	Upper	Generated	26 Gy	60
	Line	Generated	Generated	55
Optic chiasm	Upper	0	50 Gy	55
	Line	Generated	Generated	40
Optic nerves	Upper	0	52 Gy	120
	Line	Generated	Generated	Generated
Parotids	Mean		Generated	Generated
	Line	Generated	Generated	Generated
PRV_BS	Upper	0	54 Gy	75
	Line	Generated	Generated	30
PRV_SC	Upper	0	45 Gy	85
	Line	Generated	Generated	30
Spinal cord	Upper	0	32 Gy	55
	Line	Generated	Generated	30
Temporal lobes	Line	Generated	Generated	Generated

Abbreviations: DARS = dysphagia and aspiration-related structures; PRV_BS = planning organ-at-risk volume brain stem; PRV_SC = planning organ-at-risk volume spinal cord; PTV-HR = high-risk planning target volume; PTV-LR = low-risk planning target volume.

configuration, a validation set of 15 cases was used to generate both clinical and knowledge-based plans. The patient and tumor characteristics of the training and validation sets, including age, sex, and American Joint Committee on Cancer stage, are summarized in Table 3.

The median dose received by 95% (D95%) of the PTV-HR was significantly higher for the KBP (97.1% vs 96.4%; $P = .017$). The median homogeneity (0.09 vs 0.10; $P = .019$) and CIs (0.98 vs 0.97; $P = .018$) were also significantly better for the KBP than CP. However, for the low-risk PTV, the D95%, homogeneity index, and CI were similar for both plans (Fig. 1).

In terms of OAR doses, there was significantly better ($P < .05$) sparing of most of the normal surrounding organs, like optic nerves, optic chiasm, spinal cord, and uninvolved dysphagia and aspiration-related structures, in the KBP than the CP, as depicted in Fig. 2.

On evaluating both the clinical and model plans by a blinded head and neck radiation oncologist, the KBP plan was preferred over CP in 13 (86.7%) of the 15 patients. The remaining 2 plans had significant overlap with the optic neural structures like the optic nerves and/or the optic chiasm, and therefore were not accepted in KBP and required further manual optimization in clinical plans to achieve the OAR dose constraints. Figure 3 compares the dose color wash between KBP and CP for a given patient. Neither plan had a significant difference in the 95% dose coverage. Moreover, there was better sparing of critical structures like the spinal cord and parotid glands in the KBP, as depicted in the 50% dose spillage.

The mean time required to achieve clinically acceptable dose distributions with KBP was 53 minutes (range, 30-80 minutes), which was nearly 30% less than CP, which was 77 minutes (range, 52-109 minutes).

Table 3 Characteristics of patients with nasopharyngeal carcinoma included in the training and validation set for model generation

Characteristic	Training set (n = 103)	Validation set (n = 15)
Age (y), median (range)	44 (17-72)	47 (19-74)
Sex		
Male	72 (69.9%)	7 (46.7%)
Female	31 (30.1%)	8 (53.3%)
T stage		
T1	21 (20.4%)	4 (26.7%)
T2	23 (22.3%)	3 (20%)
T3	36 (35%)	5 (33.3%)
T4	23 (22.3%)	3 (20%)
N stage		
N0	12 (11.7%)	2 (13.3%)
N1	14 (13.6%)	2 (13.3%)
N2	40 (38.8%)	6 (40%)
N3	37 (35.9%)	5 (33.3%)
AJCC stage grouping		
Stage I	1 (1%)	0 (0.0%)
Stage II	9 (8.7%)	2 (13.3%)
Stage III	36 (35%)	5 (33.3%)
Stage IV	57 (55.3%)	8 (53.3%)
NACT		
Yes	100 (97%)	14 (93.3%)
No	3 (3%)	1 (6.7%)

Abbreviations: AJCC = American Joint Committee on Cancer; NACT = neoadjuvant chemotherapy.

Discussion

In this study, we developed a single optimization knowledge-based model for VMAT planning in NPC to achieve equal or superior results compared with clinically optimized plans in a shorter time. KBPs, which were optimized only once, improved the acceptability and consistency of VMAT plans for most patients, except in those where optic structures were involved, which required manual optimization. The most noticeable differences were in doses received by PTV-HR and OARs like the spinal cord, optic structures, and uninvolved dysphagia and aspiration-related structures.

A Dutch study has shown RapidPlan KBP to be comparable to CP if the patient's OAR-PTV geometry was within the range of those included in the models.[12] Another study has shown that RapidPlan could produce clinically acceptable plans for 9 of the 20 patients; manual touch-ups increased the number of acceptable plans to 19.[15] In our results, the proportion of patients who required manual touch-up of the KBP plans was significantly less (13 out of 15). The likely reason for this is the selected patients' favorable target and OAR anatomy, wherein there was minimal or no overlap between the target volume and optic structures.

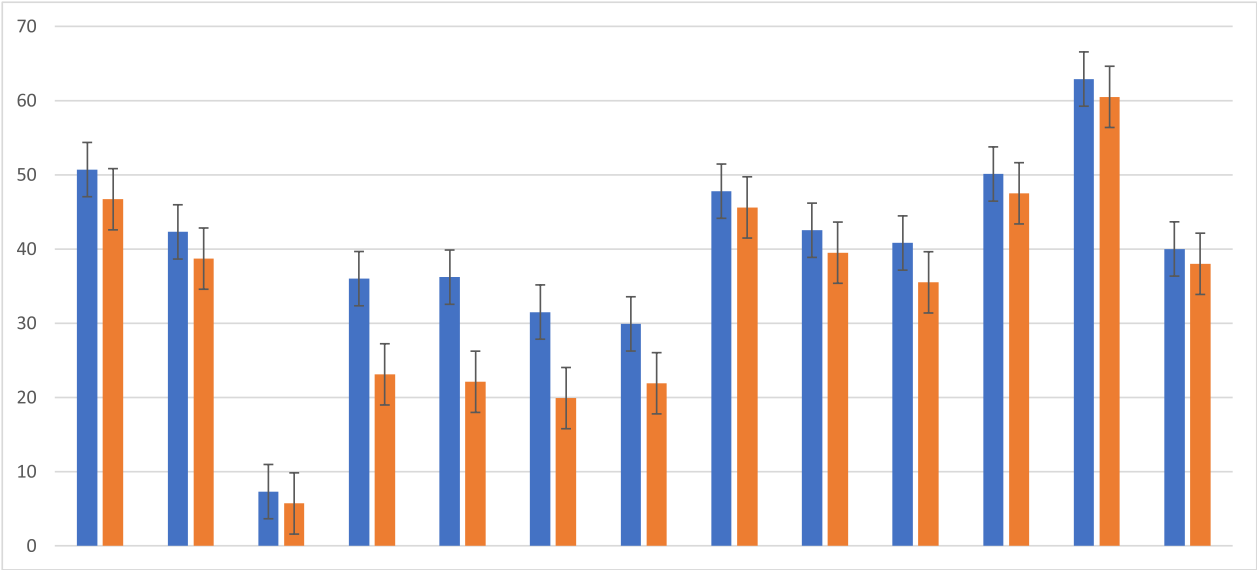
Our results are also comparable with another study from Japan, which showed that KBPs from a single optimization with manual addition of objective constraints to PTV and OARs were comparable to or better than clinical manual optimized plans in 87% of patients.[25] In a different study that included patients from multiple disease sites including rectum and prostate, it was suggested that the RapidPlan model could generate treatment plans independent of the type of treatment machine.[26]

The NRG-HN001 QA KBP model, using RapidPlan, showed that a relative improvement of at least 5% can be achieved in the dose parameters of many OARs without sacrificing the dose parameters of the PTVs. Hence, it can be a very helpful tool for improving the quality and efficiency of treatment planning in patients enrolled in clinical trials.[27]

Figure 1 Comparison of high-risk and low-risk planning target volumes for D95% (A, B), homogeneity index (C, D), and conformity index (E, F) between a clinical plan and a knowledge-based plan for the 15 patients used for model validation. *Abbreviations:* CP = clinical plan; KBP = knowledge-based plan; PTV-HR = planning target volume (high risk); PTV-LR = planning target volume (low risk).

Our study also demonstrated that KBP required less time to generate a plan than CP (53 vs 77 minutes). Another similar study revealed that the total planning time for KBP was significantly less than that for manual plans (64 vs 295 minutes; $P < .001$).[5] Another Chinese experience showed that the average time required to generate an acceptable plan decreased with the increase of work experience of the planners, and significantly reduced planning time with KBP, nearly 30 minutes compared with 55 to 85 minutes with manual planning.[16] Using the KBP model for NPC takes care of the limitation of the lengthy process of IMRT plan optimization. It provides a good starting point with adequate time for the planner for fine tuning. It also reduces the dependence on the planners' experience, helping less-experienced planners to produce good-quality plans.[16,17,28]

The major strength of our study was that the KBP model generation on a single output with no additional



	Brain stem (Dmax)	Spinal Cord (Dmax)	Optic Chiasm (Dmax)	L_Optic Nerve (Dmax)	R_Optic Nerve (Dmax)	L_Eye (Dmax)	R_Eye (Dmax)	L_Parotid (Dmean)	R_Parotid (Dmean)	Uninvolved DARS (Dmean)	Oral Cavity (Dmean)	IL_Cochlea (Dmean)	CL_Cochlea (Dmean)
CP	50.7	42.3	22.6	36	36.2	31.5	29.9	47.8	42.5	40.8	50.1	62.9	40
95% CI	48.4-53	41.2-43.4	12-33.2	25.7-46.3	26.3-46.1	24.4-38.6	23.5-36.3	40.7-54.9	35.2-49.8	35.2-46.4	45.1-55.1	58.1-67.7	36.8-43.2
KBP	46.7	38.7	21.1	23.1	22.1	19.9	21.9	45.6	39.5	35.5	47.5	60.5	38
95% CI	44.8-48.6	38-39.4	10.2-32	12.5-33.7	11.5-32.7	10.8-28.9	14.4-29.4	40.1-54.7	38.2-53.4	29.5-41.5	43.2-51.8	56.2-64.8	34.7-41.3
p-value	0.086	**0.001**	**0.046**	**0.034**	0.055	0.323	0.405	0.660	0.104	**0.001**	0.996	0.540	0.776

Figure 2 Comparison of the mean and maximum dose received by various organs at risk between clinical plan and knowledge-based plan for the 15 patients used for model validation. Doses to the spinal cord, optic nerves, chiasm, and uninvolved dysphagia and aspiration-related structures are significantly less in the knowledge-based plans. *Abbreviations:* CP = clinical plan; DARS = dysphagia and aspiration-related structures; Dmax = maximum dose; KBP = knowledge-based plan.

manual optimization was effective in most patients. In the 2 patients where the KBP was found to be suboptimal, there was a significant overlap of the optic apparatus and the PTV. In such patients, further manual optimizations are essential to achieve an acceptable plan as per the physician's discretion.

Limitations

One of the major caveats of the study remains the small number of patients in the validation set, which may not have been representative of the entire cohort of NPC in the real world. There were only 2 patients with

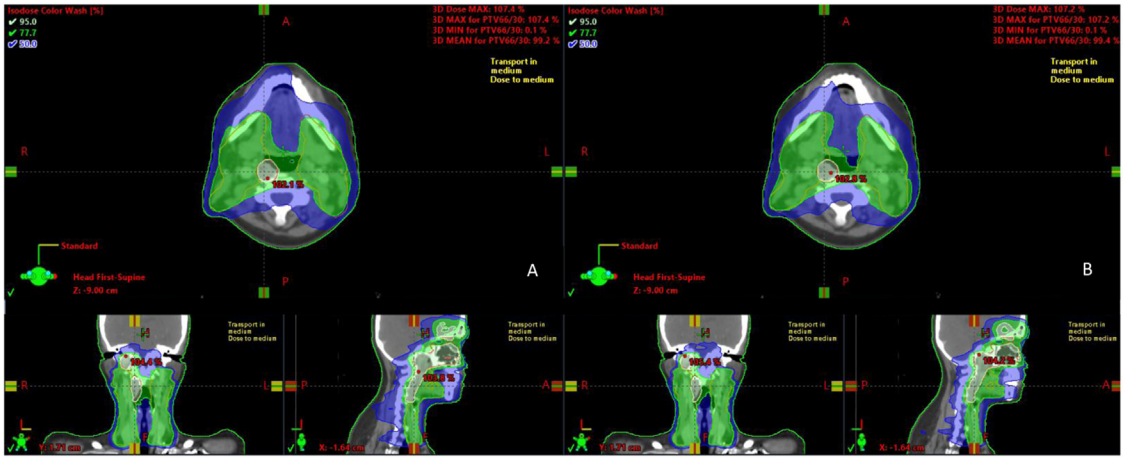


Figure 3 Difference in dose distribution between clinical plan (A) and knowledge-based plan (B) in terms of better conformality of both high-risk and low-risk target volumes as well as reduced low-dose spill to normal surrounding tissues with the knowledge-based plan.

unfavorable anatomy, which may have underrepresented the actual prevalence of such cases. The use of larger (5 mm) PTV margin (as per the institutional protocol) in the face and neck regions might have had an effect on the higher OAR doses. Finally, the efficacy of KBP with an intermediate-risk PTV remains to be investigated.

Furthermore, patients with complex target volume −OAR anatomy should be incorporated either in the original model or in a separate model reserved for patients with complex disease anatomy. We plan to test these 2 approaches in the future and validate both of these models in larger prospective cohorts.

Conclusion

Knowledge-based plans with single optimization were found to be comparable with or better than clinical manual plans for the majority of patients with NPC. The plan quality could be further improved with a manual optimization using appropriate objective constraints while greatly reducing the time required compared with clinical plans. They have the potential to more efficiently benefit a significant number of patients in high-volume and resource-constrained settings.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101311.

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