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Scientific Article

Knowledge-Based RapidPlan Volumetric Modulated Arc Therapy Model in Nasopharyngeal Carcinoma

Szu-Huai Lu, MS,[a] Chun-Wei Wang, MD, PhD,[a,b,c] Hsiang-Kuang Liang, MD, PhD,[a,d] Chih-Kai Chang, MS,[a] Hao-Ting Lan, MS,[a] Shih-Fan Lai, MD,[a,d] Bing-Shen Huang, MD, PhD,[e] and Wan- Yu Chen, MD, PhD[a,d,f,*]

[a]Division of Radiation Oncology, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan; [b]Cancer Research Center, National Taiwan University College of Medicine, Taipei, Taiwan; [c]Department of Radiology, College of Medicine, National Taiwan University, Taipei, Taiwan; [d]Department of Radiation Oncology, National Taiwan University Cancer Center, Taipei, Taiwan; [e]Department of Radiation Oncology, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan; and [f]Institute of Oncology, College of Medicine, National Taiwan University, Taipei, Taiwan

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Purpose: RapidPlan™ (RP) Eclipse®, a commercial knowledge-based planning software, predicts radiation doses, enhancing treatment planning efficiency and quality. This study developed a nasopharyngeal carcinoma (NPC) volumetric modulated arc therapy RP model and assessed its quality and efficiency against manual plans.

Methods and Materials: The existing plans for 160 patients with NPC constituted the RP model training cohort. An additional 33 patients formed a testing cohort to compare RP and manual plans based on dose-volume histograms, isodose curves, physician plan scores, and selection.

Results: The RP plan could be completed within 1 hour. RP plans demonstrated superior conformity compared with manual plans in planning target volume 70. RP plans outperformed manual plans in reducing organs-at-risks (OARs) doses. For advanced T3/4 tumors, chiasma and optic nerve doses remained similar to manual plans. RP plans had higher physician-rated scores in dose-volume histograms of targets, OARs, isodose curves, and holistic scores. Clinical plan acceptance rates of RP plans reached 100%. Physicians chose RP plans over manual plans for 31, 30, and 28 patients for doctors A, B, and C, mainly because of superior OAR sparing and higher conformity.

Conclusions: The RP plan efficiently generates high-quality NPC volumetric modulated arc therapy plans. Further applications of RP Eclipse in single-institutional clinical flows and multi-institutional collaborations or clinical trials are warranted.

Introduction

Nasopharyngeal carcinoma (NPC) has a distinct geographic distribution, mainly in southern China, Southeast Asia, and North Africa, with incidence rates ranging from

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*Corresponding author: Wan-Yu Chen, MD, PhD; Email: b89401088@ntu.edu.tw

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4 to 25 cases per 100,000 individuals in endemic areas, which is 50 to 100 times higher than in nonendemic regions.[1]

Radiation therapy is essential for NPC treatment, with advanced techniques such as fixed-angle intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) providing better target coverage and organs-at-risks (OARs) protection.[2] Because of the complex nature of NPC radiation planning, VMAT planning is time-consuming, and quality can vary among planners. Although experienced planners may require only hours to complete the planning process, inexperienced planners may require several days. Even experienced planners typically require between 1.5 and 5 hours to complete a manual plan for NPC.[3-5]

Knowledge-based planning (KBP) aims to predict radiation doses, enhancing treatment planning efficiency and quality. Varian Medical Systems' commercial software, RapidPlan™ (RP) Eclipse@, uses existing plans to create a statistical model (RP model) based on volumetric and spatial data. It incorporates the minimum distance from a voxel to the planning target volume (PTV) surface (distance-to-target histogram). The distance-to-target histogram and dose-volume histogram (DVH) undergo principal component analysis, and anatomical and dosimetric features are quantified using 1 to 4 principal components. Multivariate regression is then used to select significant variables for individual OARs. Support vector regression is used to build a mathematical model.[5] The final RP model can be used to predict DVH and dosimetric constraints for new cases.

In this study, we developed an NPC RP model using training cohorts and evaluated its quality and efficiency against manual plans.

Methods and Materials

Study schema

This study received approval from our institutional review board (institutional review board number 202308079RINC). Figure 1 illustrates the study schema. A total of 193 consecutive patients with NPC underwent definitive concurrent chemoradiation therapy (CCRT) using TrueBeam@ (Varian Medical Systems) at National Taiwan University Hospital between April 2014 and August 2022. Among them, we randomly selected 160 patients to comprise the RP model development training cohort, whereas the remaining 33 formed a testing cohort for comparing RP and manual plans based on DVHs, isodose curves, physician plan scores, and selection. At the time this study was initiated, the optimal number of patient plans required to train an NPC RP model was unknown. Our institutional database contained a total of 193 NPC patient cases for use in this study. To perform a statistically sound *t* test according to the central limit theorem, a minimum sample size of 30 is recommended.[6] Therefore, we decided to allocate 160 patients to the training cohort and 33 patients to the testing cohort, balancing the need to maximize training data with the statistical robustness of the testing cohort. Allocation was done through randomization to minimize selection bias. Table E1 provides a summary of the clinical characteristics of both cohorts.

Development of the RP model

The targets and dose were as follows: (1) PTV 70 Gy: covering the gross tumor and lymph nodes; (2) PTV 60 Gy: targeting the tumor with margin, skull base foramina (pterygopalatine fossa, pterygoid plate, foramen rotundum, foramen ovale, and foramen lacerum), parapharyngeal space, paranasal sinuses/nasal cavity, and retropharyngeal/level II/III/V lymphatics; and (3) PTV 54 Gy: level IV/V lymphatics. Treatment was 1 fraction per day, 5 days per week, with a total of 33 fractions administered using simultaneous integrated boost.

The existing plans for the 160 patients with NPC in the training cohort were generated using the Eclipse treatment planning system v.16.1. We employed VMAT with a 6 MV photon beam and used 2 full coplanar arcs with an angled collimator (10°) for each arc. When the targets were close to serial organs (eg, brainstem, spinal cord, optic nerves, etc), we used 3 full arcs for better beam control. Prior to commencing inverse planning optimization (RapidArc, Varian Medical Systems), we selected the y-jaws to achieve effective coverage of the largest PTV area, with a 1 cm margin throughout gantry rotation. To overcome the limitations of the leaf span, we split the x-jaw positions by using an x-jaw field size of <15 cm for each arc. Dose calculation was performed using the anisotropic analytical algorithm with a dose grid resolution of 2.5 mm. The OARs training in the RP model and the dose constraints were adopted and modified from the Radiation Therapy Oncology Group (RTOG) 0615 protocol.[7] Table 1 outlines the planning objectives for both PTVs and OARs.

When developing the RP model, Eclipse allowed a mix of prespecified fixed constraints and generated constraints. We used a combination of prespecified constraints modified from RTOG 0615 and generated constraints. Table E2 shows the parameters for RP model development. In this stage of RP model development, the "Generated*" in the table indicates the data input into RP that is extracted from the training cohort to create the

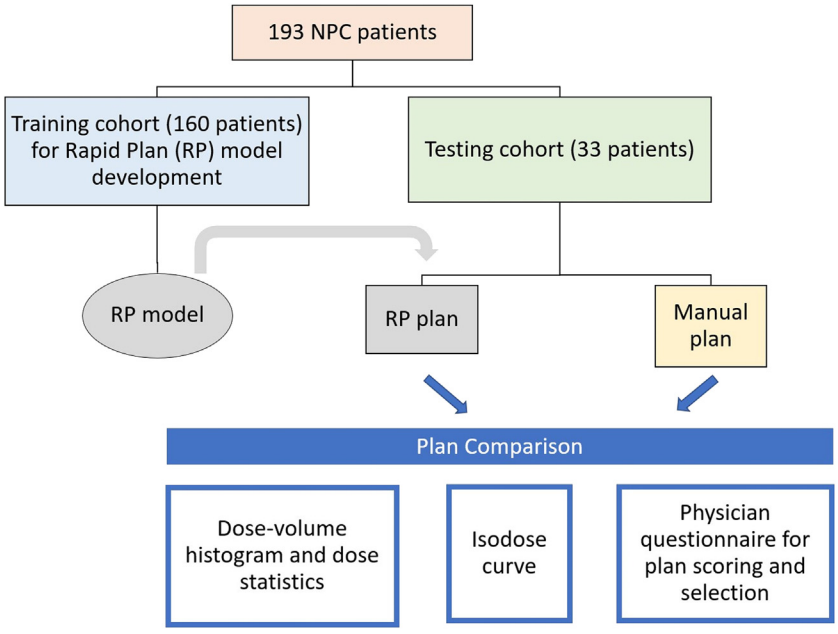

Figure 1 Study schema.
Abbreviations: NPC = nasopharyngeal carcinoma; RP = RapidPlan.

model. An RP model was then built after entering data from all 160 patients.

Using a testing cohort to compare the RP model-generated plan and manual plan

After developing the RP model using the training cohort, an additional 33 patients were enrolled in the testing cohort. Each patient in the testing cohort was created with both a manual treatment plan and an RP plan. The manual plan was designed using the aforementioned procedures.

Generation of the RP plan

The RP model was built using all 160 patients without excluding outliers or fine-tuning. We directly used this model for the testing cohort. To create an RP plan for a testing cohort during the first optimization, we used parameters identical to those used in RP model development (Table E2). However, in this stage, the "Generated*" in the table indicates the numbers determined by our built RP model estimation. After the first optimization, if second or third optimizations were needed, we fine-tuned the parameters, mainly focusing on dose and priority adjustments. Expert planners reviewed the initial optimization plan to determine if a second or third optimization was necessary. If the first optimization plan was considered sufficient, no further optimization was performed, and this plan was used for comparison. However, if additional optimizations were conducted, only the final optimized plan was used for comparison with the manual plans.

All 33 RP plans required further fine-tuning after the first optimization. Five plans underwent a second optimization, whereas 28 required a third optimization. The dosimetric criteria for plan approval were based on the RTOG 0615 and NRG HN-001 protocols, as summarized in Table 1.

The flowchart of the RP plan generation is presented in Fig. E1. Eclipse Script Application Planning Interface (ESAPI; Varian Medical Systems) was used to create pseudostructures for planning. We used our established RP model to estimate DVHs and dose constraints. Following initial optimization using these model-based constraints, we manually fine-tuned them in a second optimization. If the plan met the approval of medical physicists, no further changes were made. Otherwise, a third optimization was conducted with additional fine-tuning constraints. If the third optimization plan was considered acceptable by the medical physicists, then the plan was finalized. If not, we then stopped optimization, recorded the dose statistics, and presented the RP plan to the physicians for further plan comparison. The total amount of time from application programming interface scripting to plan finalization was limited to 1 hour.

Manual plan versus RP plan comparison

After the RP and manual plans for each patient were obtained, they were compared in terms of DVHs, isodose curves, and physician plan scores and selection. Homogeneity indexes (HIs) and new conformity indexes (nCIs)

Table 1 Dose statistics for targets and organs at risk

Types	Index	Criteria	Manual plan		RP plan		*P* value
			Average	SD	Average	SD	
Body	D_{MAX} (Gy)	<115% prescribed dose	76.60	0.47	76.32	0.54	.032
PTV70	V_{70Gy} (%)	≧93	95.82	2.98	96.25	1.45	.389
	D_{mean} (Gy)	N/A	72.89	0.42	72.68	0.28	.027
	nCI	N/A	1.20	0.05	1.15	0.03	<.001
	HI	N/A	1.06	0.02	1.06	0.01	.483
PTV60	V_{60Gy} (%)	≧93	96.03	1.21	95.83	0.61	.346
PTV54	V_{54Gy} (%)	≧93	97.74	1.17	97.84	1.23	.719
Brainstem	D_{MAX} (Gy)	<54	42.61	10.54	39.50	9.27	.006
	D_{mean} (Gy)	N/A	24.29	10.09	21.87	7.34	.007
Spinal cord	D_{MAX} (Gy)	<45	31.47	4.63	27.14	4.42	<0.001
	D_{mean} (Gy)	N/A	20.17	5.82	17.53	4.42	<.001
Parotid-L	V_{30Gy} (%)	<50	40.42	9.27	34.68	12.88	<.001
	D_{mean} (Gy)	<26	31.61	4.59	29.06	5.90	<.001
Parotid-R	V_{30Gy} (%)	<50	37.85	9.12	31.80	10.26	<.001
	D_{mean} (Gy)	<26	30.45	4.41	27.92	4.87	<.001
Ear-L	D_{mean} (Gy)	<45	37.21	6.45	37.20	7.12	.996
Ear-R	D_{mean} (Gy)	<45	37.35	8.27	34.28	7.15	<.001
Oral (exclude PTV)	D_{mean} (Gy)	<40-45	41.40	3.48	39.80	2.87	<.001
Pharyngeal constrictor	D_{mean} (Gy)	<50-55	60.15	3.86	59.56	3.91	.007
Larynx	D_{mean} (Gy)	<45	41.69	3.20	40.73	2.50	.023
Lens-L	D_{MAX} (Gy)	<10	5.44	2.11	5.23	2.26	.698
Lens-R	D_{MAX} (Gy)	<10	5.41	2.14	5.06	2.09	.496
Eye-L	D_{MAX} (Gy)	<50	19.90	12.05	15.71	9.87	<.001
	D_{mean} (Gy)	N/A	6.75	4.04	6.03	3.73	.002
Eye-R	D_{MAX} (Gy)	<50	19.28	10.07	16.42	9.36	<.001
	D_{mean} (Gy)	N/A	6.32	3.44	5.80	3.29	.001
Chiasm	D_{MAX} (Gy)	<54	23.27	17.75	20.97	18.09	.002
Optic nerve-L	D_{MAX} (Gy)	<54	24.97	17.56	23.60	17.90	.019
	D_{mean} (Gy)	N/A	16.47	14.63	14.33	13.06	<.001
Optic nerve-R	D_{MAX} (Gy)	<54	24.20	17.47	22.59	18.25	.003
	D_{mean} (Gy)	N/A	15.56	13.82	13.56	12.74	<.001
Esophagus	$V_{55Gy}\_cm^3$	N/A	0.29	0.48	0.27	0.43	.293
Mandible	$V_{72Gy}\_cm^3$	<1	0.52	0.96	0.47	0.78	.456
Brain	D_{mean} (Gy)	N/A	8.62	3.06	8.15	2.90	<.001
	D_{1cc} (Gy)	<72.1	67.18	6.27	66.07	6.28	<.001
Temporal lobe-L	D_{MAX} (Gy)	<70	68.44	7.38	66.96	7.79	<.001
Temporal lobe-R	D_{MAX} (Gy)	<70	68.23	5.40	66.91	5.39	<.001
Brachial plexus-L	D_{MAX} (Gy)	<66	65.97	5.41	65.59	5.79	.087
Brachial plexus-R	D_{MAX} (Gy)	<66	65.50	4.62	64.92	4.82	.007

Abbreviations: D_{MAX} = maximum dose; D_{mean} = mean dose; Dx% = dose covering x% of the volume; HI = homogeneity index; L = left; N/A = not available; nCI = conformity index; PTV = planning target volume; R = right; RP = RapidPlan; VxGy = volume covered by the x-Gy isodose.

were calculated and compared. The HI and nCI formulas are as follows:

1. HI: measurement of how evenly the radiation dose is distributed in the PTV

$$\mathrm{HI} = \frac{D5\%}{D95\%}$$

D5%: The dose received by the hottest 5% of the target volume (i.e., the minimum dose within the top 5% of the dose distribution). D95%: The dose received by at least 95% of the target volume (i.e., the minimum dose covering 95% of the structure). A higher HI indicates poorer homogeneity.

2. nCI: measurement of dose distribution conformity throughout the target volume

$$\mathrm{CI} = \mathrm{VPTV} \times \frac{\mathrm{VTV}}{\mathrm{TVPV}^2}$$

whereV_{TV} is the volume of the actual prescribed dose, V_{PTV} is the volume of PTV, and TV_{PV} is the volume of V_{PTV} within the V_{TV}.

A higher nCI indicates lower dose conformity in the PTV.

Regarding physician plan scores and selection, an example of the questionnaire the physicians completed for plan scoring and selection is presented in Fig. 2A. Each patient with 1 RP plan and 1 manual plan was evaluated by 3 radiation oncologists specializing in NPC treatment. The radiation oncologists were blinded to the patients' information and completed the questionnaires independently.

Statistical analysis

A paired *t* test was used to assess dosimetric differences in the manual and RP plans. A *P* value of <.05 indicated significance.

Results

Comparison of DVHs and dose statistics in manual and RP plans

All plans were reviewed by qualified medical physicists who checked parameters such as total dose, fractionation, OAR limits, machine settings, and energy, following guidelines from the American Association of Physicists in Medicine (AAPM) Task Group 275 report.[8] No specific concerns were raised during the review process for any of the 33 testing cohort plans.

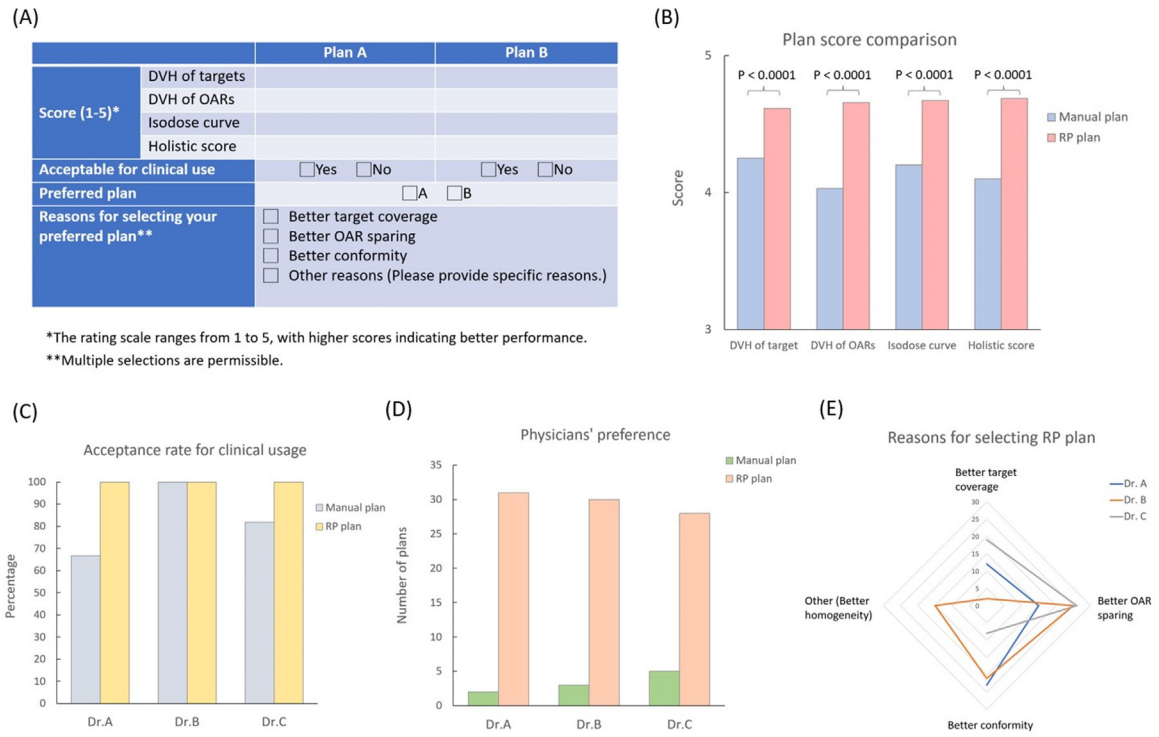

Figure 2 Comparison of physician plan scores and selection outcomes. (A) Questionnaire for physician plan scoring and selection, (B) plan score comparison, (C) acceptance rate for clinical use, (D) physicians' preferred plans, and (E) reasons for RapidPlan (RP) plan selection.

Abbreviations: DVH = dose-volume histogram; OAR = organ at risk.

To confirm the deliverability of these 33 plans, we conducted dose verification using Varian's portal dose image prediction.[9] The dose verification result for a representative patient is shown in Fig. E2. For all 33 patients in the testing cohort, the γ criteria (3%/3 mm, $\gamma \leq 1\%$) pass rates were >90%, with mean ± SD values of 99.23% ± 1.3% for the RP plan and 99.13% ± 1.3% for the manual plan, in compliance with AAPM Task Group 119 standards for deliverability.[10]

Table 1 provides a comparison of dose statistics for the testing cohort's manual and RP plans. Regarding the targets, RP plans demonstrated superior conformity compared with manual plans (nCI: manual 1.20 ± 0.05 vs RP 1.15 ± 0.03, $P < .001$) in PTV70. However, target coverage did not differ significantly between the manual and RP plans (Fig. 3A). RP plans outperformed manual plans in reducing OAR doses. The RP plans had significantly lower brainstem D_{MAX} (maximum dose) (42.61 ± 10.54 vs 39.50 ± 9.27 Gy, $P = .006$), spinal cord D_{MAX} (31.47 ± 4.63 vs 27.14 ± 4.42 Gy, $P < .001$), and larynx D_{mean} (mean dose) (41.69 ± 3.20 vs 40.73 ± 2.50 Gy, $P = .023$; Fig. 3B and Fig. E3A, B, G). Although the mandible doses of the 2 plans did not differ, the RP plans had significantly lower parotid gland doses than the manual plans (left parotid V_{30Gy} [%] 40.42 ± 9.27 vs 34.68 ± 12.88, $P < .001$; right parotid V_{30Gy} (volume covered by the 30Gy isodose) [%] 37.85 ± 9.12 vs 31.80 ± 10.26, $P < .001$; Fig. 3C and Fig. E3E). RP plans also demonstrated significantly lower eye and optic nerve doses than manual plans. The D_{MAX} for the left eye, right eye, left optic nerve, and right optic nerve for the manual plans and the RP plans was 19.90 ± 12.05 versus 15.71 ± 9.87 Gy ($P < .001$), 19.28 ± 10.07 versus 16.42 ± 9.36 Gy ($P < .001$), 24.97 ± 17.56 versus 23.60 ± 17.90 Gy ($P = .019$), and 24.20 ± 17.47 versus 22.59 ± 18.25 Gy ($P = .003$), respectively (Fig. 3D and Fig. E3C, D). Additionally, RP plans had lower pharyngeal constrictor D_{mean} values (60.15 ± 3.86 vs 59.56 ± 3.91 Gy, $P = .007$) and lower oral cavity D_{mean} values (41.40 ± 3.48 vs 39.80 ± 2.87 Gy, $P < .001$; Fig. 3E and Fig. E3F). Finally, the RP plans had lower chiasma D_{mean} values (23.27 ± 17.75 vs 20.97 ± 18.09 Gy, $P = .002$) and right ear D_{mean} values (37.35 ± 8.27 vs 34.28 ± 7.15 Gy, $P < .001$; Fig. 3F and Fig. E3H). The brain D_{mean} and D_{1cc} (dose received by the hottest 1 cubic centimeter) were significantly lower in the RP plans than the manual plans (brain D_{mean}: 8.62 ± 3.06 vs 8.15 ± 2.90 Gy, $P < .001$; D_{1cc}: 67.18 ± 6.27 vs 66.07 ± 6.28 Gy, $P < .001$) (Fig. E4A). Similarly, doses to the bilateral temporal lobes were both lower in the RP plans (D_{MAX} temporal lobe-left: 68.44 ± 7.38 vs 66.96 ± 7.79 Gy, $P < .001$; D_{MAX} temporal lobe-right: 68.23 ± 5.40 vs 66.91 ± 5.39 Gy, $P < .001$) (Fig. E4A). For the brachial plexus, there was no significant difference in dose to the left side, whereas the RP plans achieved lower doses to the right side (brachial plexus-right D_{MAX}: 65.50 ± 4.62 vs 64.92 ± 4.82 Gy, $P = .007$) (Fig. E4B).

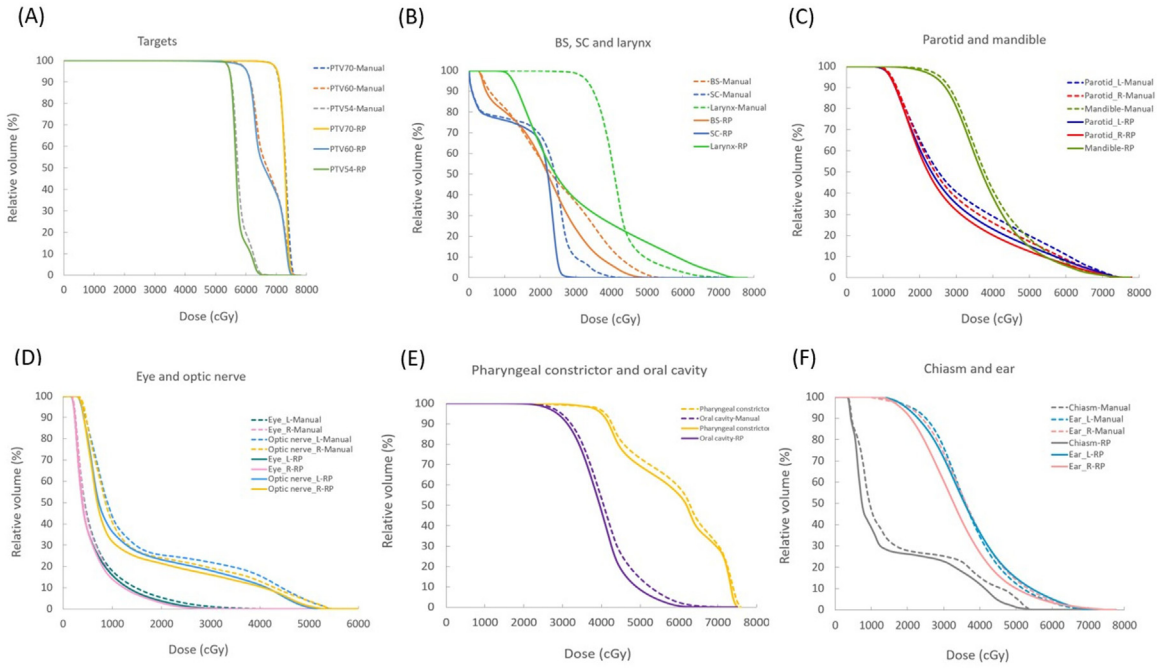

Figure 3 Dose-volume histogram comparison for the manual plan and RapidPlan (RP) plan. (A) Targets; (B) brainstem (BS), spinal cord (SC), and larynx; (C) parotid gland and mandible; (D) eye and optic nerve; (E) pharyngeal constrictor and oral cavity; and (F) optic chiasma and ear.

Abbreviations: L = left; PTV = planning target volume; R = right.

NPC radiation planning can be especially challenging for advanced tumors. We analyzed the effectiveness of RP plans in reducing OAR doses for T1/2 or T3/4 tumors separately (Table 2). For T3/4 tumors, the RP plans significantly reduced doses to the brainstem (D_{MAX} [Gy] Δ [RP − manual] = −4.05, P = .003) and the spinal cord (D_{MAX} [Gy] Δ [RP − manual] = −6.01, P < .001) than the manual plans. Parotid gland dose reductions were observed, with a greater effect in T1/2 tumors. Left parotid V_{30Gy} (%) Δ (RP − manual) for T1/2 and T3/4 tumors was −6.13 (P = .004) and −0.05 (P = .024), respectively. Right parotid V_{30Gy} (%) Δ (RP − manual) for T1/2 and T3/4 tumors was −5.92 (P < .001) and −0.06 (P < .001), respectively. RP plans also showed reduced oral cavity, pharyngeal constrictor, and eye doses for T3/4 tumors compared with manual plans. Oral cavity D_{mean} (Gy) Δ (RP − manual) for T1/2 and T3/4 tumors was −0.97 (P = .034) and −2.35 (P = .002), respectively. Pharyngeal constrictor D_{mean} (Gy) Δ (RP − manual) for T1/2 and T3/4 tumors was −0.48 (P = .125) and −0.71 (P = .022), respectively. Left eye D_{MAX} (Gy) Δ (RP − manual) for T1/2 and T3/4 tumors was −2.72 (P = .002) and −5.94 (P < .001), respectively. Right eye D_{MAX} (Gy) Δ (RP − manual) for T1/2 and T3/4 tumors was −2.54 (P = .003) and −3.23 (P = .017), respectively. The RP plans did not have lower doses to the chiasma or

Table 2 RapidPlan plan organs-at-risk dose reduction for T1/2 and T3/4 tumors

OARs	Index	T1, 2			T3, 4		
		Δ (RP − manual)	SD	*P* value	Δ (RP − manual)	SD	*P* value
Brainstem	D_{MAX} (Gy)	−2.34	2.05	.190	−4.05	0.04	.003
	D_{mean} (Gy)	−0.66	2.58	.563	−4.54	1.83	.001
Spinal cord	D_{MAX} (Gy)	−2.92	2.05	<.001	−6.01	3.85	<.001
	D_{mean} (Gy)	−1.68	0.73	<.001	−3.81	1.55	<.001
Parotid-L	V_{30Gy} (%)	−6.13	2.63	.004	−0.05	0.05	.024
	D_{mean} (Gy)	−2.74	0.65	<.001	−2.32	1.91	.017
Parotid-R	V_{30Gy} (%)	−5.92	2.25	<.001	−0.06	0.00	<.001
	D_{mean} (Gy)	−2.43	0.81	.002	−2.66	0.01	<.001
Ear-L	D_{mean} (Gy)	−0.10	0.15	.942	0.11	1.79	.908
Ear-R	D_{mean} (Gy)	−2.90	1.91	.030	−3.26	0.45	.008
Oral (exclude PTV)	D_{mean} (Gy)	−0.97	0.10	.034	−2.35	1.05	.002
Pharyngeal constrictor	D_{mean} (Gy)	−0.48	0.14	.125	−0.71	0.01	.022
Larynx	D_{mean} (Gy)	−0.86	0.61	.190	−1.07	0.91	.042
Eye-L	D_{MAX} (Gy)	−2.72	0.63	.002	−5.94	2.25	<.001
	D_{mean} (Gy)	−0.67	0.63	.008	−0.77	0.23	.075
Eye-R	D_{MAX} (Gy)	−2.54	0.79	.003	−3.23	0.53	.017
	D_{mean} (Gy)	−0.50	0.41	.006	−0.54	0.06	.056
Chiasm	D_{MAX} (Gy)	−2.64	0.61	.005	−1.89	0.65	.119
Optic nerve-L	D_{MAX} (Gy)	−1.48	0.05	.087	−1.24	0.52	.125
	D_{mean} (Gy)	−1.38	1.06	<.001	−3.06	1.75	.006
Optic nerve-R	D_{MAX} (Gy)	−1.93	0.14	.010	−1.23	1.08	.127
	D_{mean} (Gy)	−1.49	1.06	<.001	−2.62	1.17	<.001
Brain	D_{mean} (Gy)	−0.17	0.16	.266	−0.80	−1.03	.028
	D_{1cc} (Gy)	−1.18	0.56	.003	0.28	0.46	.011
Temporal lobe-L	D_{MAX} (Gy)	−1.31	0.31	.025	−1.92	1.36	.011
Temporal lobe-R	D_{MAX} (Gy)	−1.61	0.22	.005	−0.98	0.06	.018
Brachial plexus-L	D_{MAX} (Gy)	−0.72	0.36	.066	−0.12	0.34	.751
Brachial plexus-R	D_{MAX} (Gy)	−0.70	0.00	.013	−0.45	0.51	.133

Abbreviations: Δ = dose differences; D_{MAX} = maximum dose; D_{mean} = mean dose; Dx% = dose covering x% of the volume; L = left; OAR = organ at risk; PTV = planning target volume; R = right; RP = RapidPlan; VxGy = volume covered by the x-Gy isodose.

optic nerves for T3/T4 tumors than the manual plans. D_{MAX} (Gy) Δ (RP − manual) for chiasma, left optic nerve, and right optic nerve for T1/2 versus T3/4 tumors was −2.64 (P = .005) versus −1.89 (P = .119), −1.48 (P = .087) versus −1.24 (P = .125), and −1.93 (P = .010) versus −1.23 (P = .127), respectively.

Isodose comparison of manual and RP plans

An isodose comparison of the manual and RP plans is displayed in Fig. 4 clinical target volume (CTV) 70 is in red, PTV70 is in green, CTV60 and PTV60 are in blue and yellow, respectively, and CTV54 and PTV54 are in magenta and cyan, respectively. For a T1N1M0 NPC patient (Fig. 4A), RP offers better brain stem, parotid gland, and oral cavity outcomes than the manual plan. For a T4N2M0 NPC patient (Fig. 4B), RP excels in sparing the temporal lobe, oral cavity, and pharyngeal constrictors.

Comparison of physicians' plan scores and selection outcomes

A comparison of the physicians' plan scores and the selection outcomes is presented in Fig. 2. Figure 2A displays the physicians' questionnaire for plan scoring and selection. Figure 2B displays the results of plan score comparisons. RP plans outperformed manual plans in DVHs of targets (4.25 vs 4.61, $P < .0001$), OARs (4.03 vs 4.66, $P < .0001$), isodose curves (4.20 vs 4.67, $P < .0001$), and holistic scores (4.10 vs 4.68, $P < .0001$). Figure 2C presents clinical plan acceptance rates, with RP plans at 100% and manual plans at 66.7%, 100%, and 81.8% for doctors A, B, and C, respectively. Figure 2D shows physicians' preferred plans, with RP plans preferred for 31, 30, and 28 patients for doctors A, B, and C, respectively, mainly because of superior OAR sparing and higher conformity (Fig. 2E).

Discussion

Our study developed an efficient RP model for patients with NPC, generating plans within an hour. RP plans achieved lower OAR doses and maintained target coverage. Physicians rated the RP plans more highly in terms of the DVHs of the targets, DVHs of the OARs, isodose curves, and holistic scores. The RP plans were selected over the manual plans for clinical use for >80% of the patients.

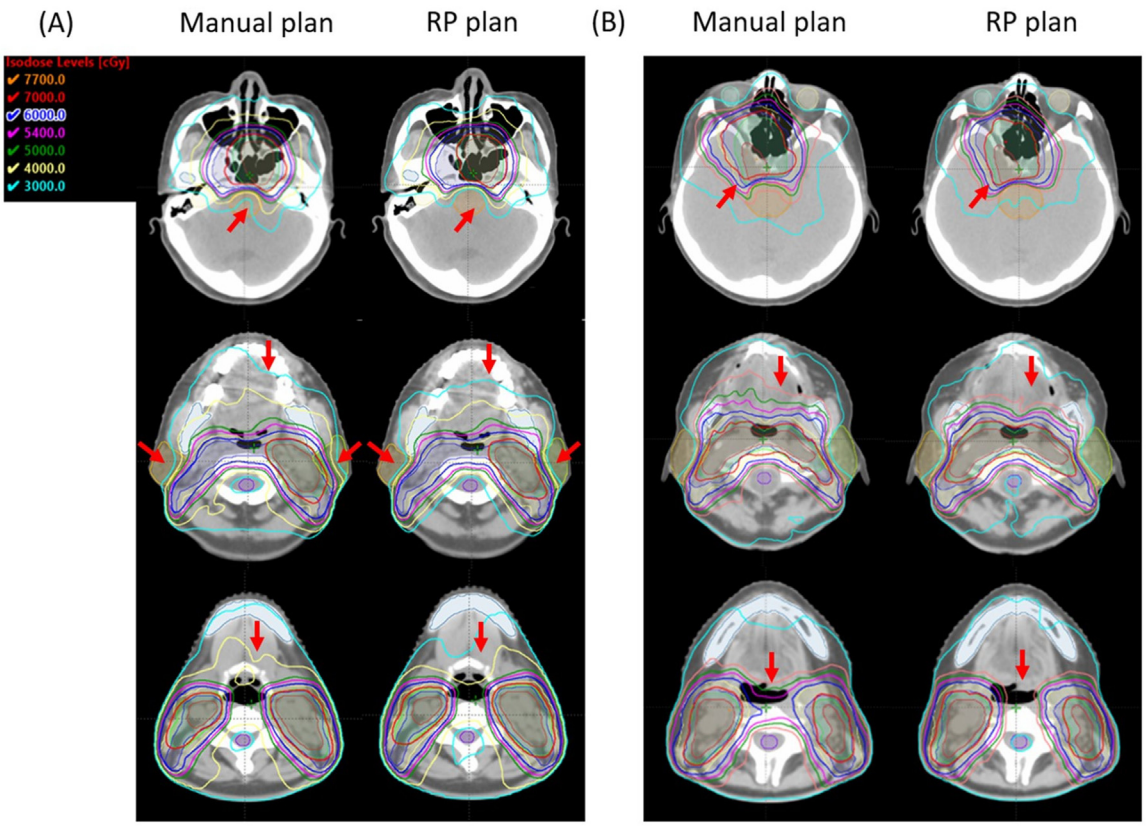

Figure 4 Isodose comparison for the manual plan and RapidPlan (RP) plan. (A) Clinical patient with T1N1M0 nasopharyngeal carcinoma. (B) Clinical patient with T4N2M0 nasopharyngeal carcinoma.

To quantify plan comparison studies, several dosimetric scoring systems have been developed. For instance, in prostate cancer, the Plan Quality Metric score is often used to compare different plans.[11,12] For a broader range of disease sites, commercially available software, such as PlanIQ (Sun Nuclear Corporation)[13] or the PlanScore-Card ESAPI tool,[14-16] can be used for quantitative dosimetric scoring.

However, a practical clinical dilemma arises in cases where a physician is presented with multiple plans—potentially with minor, statistically significant differences in dosimetric results—and still must select a single plan for treatment. This selection process is inherently subjective and resembles a qualitative study, because it reflects the physician's judgment on the clinical relevance of each plan beyond dosimetric scores alone. Currently, no validated consensus exists on a standardized questionnaire to capture qualitative plan preferences. Nevertheless, we designed our questionnaire based on published studies to incorporate essential qualitative items that also correlate with quantitative metrics.

In our questionnaire, we applied a classic 5-point Likert scale to measure physician satisfaction on key items, including DVHs of targets, DVHs of OARs, isodose curves, and an overall holistic score.[17] These items were selected because previous research indicates they are major considerations for physicians during plan selection.[18] Studies have also shown that qualitative physician scores correlate with quantitative plan scores.[19] Additionally, given that the clinical benefit of RP lies in generating clinically acceptable plans, our questionnaire asked physicians to assess plan acceptability for clinical use and to indicate their preferred plan. This element of plan selection is commonly included in planning studies.

Our RP model was developed based on existing plans for 160 patients with NPC without removing any outliers. Most previous studies on NPC RP models had training cohorts of 79[3]to 99[5] patients. In head and neck cancer studies, patient numbers varied from 30,[20,21] 50,[22] 60,[21] 70,[23] 83,[24] to 90.[25,26] The optimal number of patient plans for training an NPC RP model remains unknown. Tol et al[21] demonstrated that models based on 30 plans were similar to those using 60 plans. Plan libraries and patient characteristics are vital for RP models, and excluding outliers has minimal impact.[27] Our study included 160 diverse patients with NPC, enhancing clinical reliability.

For RP plans in NPC, additional manual intervention may be necessary alongside RP model-generated constraints. For partial breast irradiation,[28] prostate cancer treatment,[29] and stereotactic body radiation therapy of centrally located lung tumors,[30] RP plans without manual adjustments perform comparably or better than manual plans. However, radiation planning for NPC is challenging because of the complex target shape and proximity to critical organs. Chang et al[3] used the lower limit of the RP DVH estimation range as an initial optimization objective and demonstrated that RP could be used to produce clinically acceptable plans for 9 of 20 patients; manual adjustments increased this number to 19. Hu et al[5] used RP to estimate mean values as initial optimization objectives for adjacent OARs in T3 to T4 cases. After single optimization without human intervention, 15 of the 17 RP plans (88.24%) were clinically acceptable. In similar NPC studies with knowledge-based automatic planning (Pinnacle[3], Philips Medical Systems), up to 3 manual interventions were allowed when necessary.[31-33] Research shows that single-iteration automatic planning for NPC plans does not fully address dose inhomogeneity.[34] Zhang et al[33] found that even with up to 3 post optimizations or minimal manual intervention in NPC Auto-Planning in Pinnacle[3], not all plans met PTV and OAR dose objectives, especially in patients with T4 cancer. When the anatomic distance is <5 mm, automatic VMAT plan quality may be equal to or worse than manual VMAT plans. In our RP plans, brainstem or optic nerve doses for T3/T4 tumors remained unsatisfactory after the first optimization. Manual adjustments during the second optimization typically yielded satisfactory plans within 40 minutes. Advanced T3/T4 tumor plans may require a third optimization, which results in a total planning time of <60 minutes.

Table E3 provides a detailed comparison with existing literature, focusing on studies that have employed similar KBP approaches for various cancer types or treatment modalities. This included several major disease sites (NPC, head and neck, lung, breast, and prostate) and various treatment modalities (intensity modulated radiation therapy, VMAT, stereotactic body radiation therapy, and breast tangential fields).

RP plans offer 2 key advantages: reduced planning time and comparable or superior quality with manual plans. To expedite planning, we used ESAPI to generate pseudostructures, enhancing conformity and reducing OAR doses. Kamima et al[35] also achieved time savings with an RP model using 2 pseudostructures for VMAT plans in postoperative uterine cervical cancer. In our study, ESAPI-generated pseudostructures to RP Eclipse DVH estimation took just 5 to 7 minutes, resulting in total planning times <60 minutes. Our model and approach yielded RP plans with higher physician ratings and 100% clinical acceptance, demonstrating their utility in busy institutions or for frequent adaptive planning needs. We acknowledge that the lack of recorded actual time required to create manual plans is a limitation of our study. However, published studies indicate that even experienced planners typically need between 1.5 and 5 hours to complete a manual plan for NPC.

There are several key clinical implications associated with the use of rapidly generated high-quality NPC VMAT plans. For institutions with high patient volumes or limited resources, these plans can be efficiently generated with limited manpower without compromising quality. In urgent adaptive planning scenarios, RP plans can

expedite replanning for new treatment.[30] Moreover, RP plans are useful for basic needs such as generating plans for insurance purposes or for training new planners.[36] Additionally, transferring or combining RP models between institutions is feasible,[21,37] which can standardize interinstitutional plans and improve the quality of radiation therapy clinical trials.[38]

RP plans, although beneficial, have limitations. They excel at reducing OAR doses without jeopardizing target coverage,[24,39] but their effectiveness diminishes when the target or OAR proximity is small.[33] In our study, RP plans significantly reduced doses to the brainstem, spinal cord, oral cavity, pharyngeal constrictor, and eyes for advanced T3/4 tumors but not to the chiasma and optic nerves, which remained similar to manual plans. Additionally, our RP plans relied on a model trained with previous plans and used RP Eclipse for DVH estimation and objective generation. However, in cases involving unique patient conditions or unusual DVH constraints not covered by the model, manual planning is necessary and cannot be substituted by RP plans.

There are anticipated challenges in implementing RP plans into routine clinical practice. First, there are software compatibility issues because RP Eclipse is a commercial software that requires purchase by institutions. This acquisition process can be complex, requiring department leaders to consider budgets, departmental goals, and machine and software specifications. Second, planners need to undergo training to familiarize themselves with the concept, software interface, and utilization process of RP. Third, there are preparatory steps involving model creation and evaluation before formal clinical implementation. Departments must decide whether to train their own models or use those from other institutions, determine the disease site for which to develop the model, evaluate obtained RP models, and redesign relevant clinical workflows accordingly. A single institution can establish its own RP library. Additionally, published data have shown that cross-institutional library sharing to form a "broad model" can address challenges related to institutional protocol differences and promote planning harmonization.[40-43] RP plans rely on predicted DVHs, making it essential to consider the planning goals and contour definitions of component libraries. Even with a "broad model," attention to these factors is crucial for adaptability and effectiveness.[44,45]

In addition to traditional KBP Auto-Planning using Pinnacle^3 (Philips Medical Systems) or RP Eclipse, deep learning (DL)-based KBP methods such as DL-based dose prediction, DL-based fluence map prediction, and DL-based virtual treatment planning are emerging.[46] However, although DL-based dose estimation may provide dosimetrically attractive dose estimates, these doses may not be physically achievable. Inverse treatment planning through manual intervention is required for post−DL-based dose prediction. Accurately determining the deliverability of plans is crucial, and plans must account for various mechanical, physical, and algorithmic constraints.[47] It is worth noting that DL-based fluence map predictions may face the same challenges. One of the key features of Eclipse RP is its ability to generate predictive DVHs. Planners are still required to perform optimization based on these DVHs, with or without additional fine-tuning. However, the optimization process incorporates physical machine parameters, ensuring that RP plans are physically deliverable. Furthermore, published data support the full deliverability of RP plans.[30,48]

Currently, mature, commercially available KBP Auto-Planning using Pinnacle^3 (Philips Medical Systems) or RP Eclipse remains the primary clinical planning method. Further applications of RP Eclipse in single-institutional clinical flows and multi-institutional collaborations or clinical trials[22,38,43,49,50] are warranted.

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.2025.101716.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68:394-424.
2. Lu SH, Cheng JC, Kuo SH, et al. Volumetric modulated arc therapy for nasopharyngeal carcinoma: a dosimetric comparison with TomoTherapy and step-and-shoot IMRT. *Radiother Oncol*. 2012;104:324-330.
3. Chang ATY, Hung AWM, Cheung FWK, et al. Comparison of planning quality and efficiency between conventional and knowledge-based algorithms in nasopharyngeal cancer patients using intensity modulated radiation therapy. *Int J Radiat Oncol Biol Phys*. 2016;95:981-990.
4. Sinha S, Kumar A, Maheshwari G, et al. Development and validation of single-optimization knowledge-based volumetric modulated arc therapy model plan in nasopharyngeal carcinomas. *Adv Radiat Oncol*. 2024;9:101311.
5. Hu J, Liu B, Xie W, et al. Quantitative comparison of knowledge-based and manual intensity modulated radiation therapy planning for nasopharyngeal carcinoma. *Front Oncol*. 2020;10:551763.
6. Mishra P, Singh U, Pandey CM, Mishra P, Pandey G. Application of student's t-test, analysis of variance, and covariance. *Ann Card Anaesth*. 2019;22:407-411.

7. Lee NY, Zhang Q, Pfister DG, et al. Addition of bevacizumab to standard chemoradiation for locoregionally advanced nasopharyngeal carcinoma (RTOG 0615): a phase 2 multi-institutional trial. *Lancet Oncol*. 2012;13:172-180.
8. Ford E, Conroy L, Dong L, et al. Strategies for effective physics plan and chart review in radiation therapy: report of AAPM Task Group 275. *Med Phys*. 2020;47:e236-e272.
9. Van Esch A, Huyskens DP, Hirschi L, Baltes C. Optimized Varian aSi portal dosimetry: development of datasets for collective use. *J Appl Clin Med Phys*. 2013;14:4286.
10. Ezzell GA, Burmeister JW, Dogan N, et al. IMRT commissioning: multiple institution planning and dosimetry comparisons, a report from AAPM Task Group 119. *Med Phys*. 2009;36:5359-5373.
11. Nelms BE, Robinson G, Markham J, et al. Variation in external beam treatment plan quality: an inter-institutional study of planners and planning systems. *Pract Radiat Oncol*. 2012;2:296-305.
12. Kubo K, Monzen H, Ishii K, et al. Inter-planner variation in treatment-plan quality of plans created with a knowledge-based treatment planning system. *Phys Med*. 2019;67:132-140.
13. Olch AJ, Gopalakrishnan M, Murphy ES, MacDonald SM, Hua CH. Toward systematic assessment and improvement of radiation therapy plan quality of cooperative group trial submissions: a report from the Children's Oncology Group. *Pract Radiat Oncol*. 2023;13:e374-e382.
14. Rayn K, Magliari A, Clark R, Rana O, Moore K, Ray X. Using scorecards to tune ethos directive templates: an adaptive radiation therapy individualized approach-cervix dosimetric planning study. *Adv Radiat Oncol*. 2024;9:101550.
15. Rayn K, Clark R, Magliari A, et al. Scorecards: quantifying dosimetric plan quality in pancreatic ductal adenocarcinoma stereotactic body radiation therapy. *Adv Radiat Oncol*. 2023;8:101295.
16. Magliari A, Clark R, Rosa L, Beriwal S. HN-SIB-BPI: a single click, sub-site specific, dosimetric scorecard tuned RapidPlan model created from a foundation model for treating head and neck with bilateral neck. *Med Dosim*. 2024. https://doi.org/10.1016/j.meddos.2024.08.002. Published online September 13.
17. Pogue JA, Cardenas CE, Harms J, et al. Benchmarking automated machine learning-enhanced planning with ethos against manual and knowledge-based planning for locally advanced lung cancer. *Adv Radiat Oncol*. 2023;8:101292.
18. Cornell M, Kaderka R, Hild SJ, et al. Noninferiority study of automated knowledge-based planning versus human-driven optimization across multiple disease sites. *Int J Radiat Oncol Biol Phys*. 2020;106:430-439.
19. Leone AO, Mohamed ASR, Fuller CD, et al. A visualization and radiation treatment plan quality scoring method for triage in a population-based context. *Adv Radiat Oncol*. 2024;9:101533.
20. Delaney AR, Dahele M, Tol JP, Kuijper IT, Slotman BJ, Verbakel WFAR. Using a knowledge-based planning solution to select patients for proton therapy. *Radiother Oncol*. 2017;124:263-270.
21. Tol JP, Delaney AR, Dahele M, Slotman BJ, Verbakel WFAR. Evaluation of a knowledge-based planning solution for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2015;91:612-620.
22. Giaddui T, Geng H, Chen Q, et al. Offline quality assurance for intensity modulated radiation therapy treatment plans for NRG-HN001 head and neck clinical trial using knowledge-based planning. *Adv Radiat Oncol*. 2020;5:1342-1349.
23. Delaney AR, Tol JP, Dahele M, Cuijpers J, Slotman BJ, Verbakel WFAR. Effect of dosimetric outliers on the performance of a commercial knowledge-based planning solution. *Int J Radiat Oncol Biol Phys*. 2016;94:469-477.
24. Fogliata A, Reggiori G, Stravato A, et al. RapidPlan head and neck model: the objectives and possible clinical benefit. *Radiat Oncol*. 2017;12:73.
25. Tol JP, Dahele M, Delaney AR, Slotman BJ, Verbakel WFAR. Can knowledge-based DVH predictions be used for automated, individualized quality assurance of radiotherapy treatment plans? *Radiat Oncol*. 2015;10:234.
26. Liu H, Sintay B, Wiant D. A two-step treatment planning strategy incorporating knowledge-based planning for head-and-neck radiotherapy. *J Appl Clin Med Phys*. 2023;24:e13939.
27. Hussein M, South CP, Barry MA, et al. Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy. *Radiother Oncol*. 2016;120:473-479.
28. Frederick A, Roumeliotis M, Grendarova P, Quirk S. Performance of a knowledge-based planning model for optimizing intensity-modulated radiotherapy plans for partial breast irradiation. *J Appl Clin Med Phys*. 2022;23:e13506.
29. Panettieri V, Ball D, Chapman A, et al. Development of a multicentre automated model to reduce planning variability in radiotherapy of prostate cancer. *Phys Imaging Radiat Oncol*. 2019;11:34-40.
30. Visak J, McGarry RC, Randall ME, Pokhrel D. Development and clinical validation of a robust knowledge-based planning model for stereotactic body radiotherapy treatment of centrally located lung tumors. *J Appl Clin Med Phys*. 2021;22:146-155.
31. Jihong C, Kaiqiang C, Yitao D, Xiuchun Z, Yanyu C, Penggang B. Evaluation of auto-planning in VMAT for locally advanced nasopharyngeal carcinoma. *Sci Rep*. 2022;12:4167.
32. Zhang Q, Peng Y, Song X, Yu H, Wang L, Zhang S. Dosimetric evaluation of automatic and manual plans for early nasopharyngeal carcinoma to radiotherapy. *Med Dosim*. 2020;45:e13-e20.
33. Zhang Q, Ou L, Peng Y, Yu H, Wang L, Zhang S. Evaluation of automatic VMAT plans in locally advanced nasopharyngeal carcinoma. *Strahlenther Onkol*. 2021;197:177-187.
34. Bai P, Weng X, Quan K, et al. A knowledge-based intensity-modulated radiation therapy treatment planning technique for locally advanced nasopharyngeal carcinoma radiotherapy. *Radiat Oncol*. 2020;15:188.
35. Kamima T, Ueda Y, Fukunaga JI, et al. Knowledge-based planning using pseudo-structures for volumetric modulated arc therapy (VMAT) of postoperative uterine cervical cancer: a multi-institutional study. *Rep Pract Oncol Radiother*. 2021;26:849-860.
36. Wang J, Hu W, Yang Z, et al. Is it possible for knowledge-based planning to improve intensity modulated radiation therapy plan quality for planners with different planning experiences in left-sided breast cancer patients? *Radiat Oncol*. 2017;12:85.
37. Tudda A, Castriconi R, Benecchi G, et al. Knowledge-based multi-institution plan prediction of whole breast irradiation with tangential fields. *Radiother Oncol*. 2022;175:10-16.
38. Kavanaugh JA, Holler S, DeWees TA, et al. Multi-institutional validation of a knowledge-based planning model for patients enrolled in RTOG 0617: implications for plan quality controls in cooperative group trials. *Pract Radiat Oncol*. 2019;9:e218-e227.
39. Hansen CR, Bertelsen A, Hazell I, et al. Automatic treatment planning improves the clinical quality of head and neck cancer treatment plans. *Clin Transl Radiat Oncol*. 2016;1:2-8.
40. Wu B, Kusters M, Kunze-Busch M, et al. Cross-institutional knowledge-based planning (KBP) implementation and its performance comparison to Auto-Planning Engine (APE). *Radiother Oncol*. 2017;123:57-62.
41. Ueda Y, Fukunaga JI, Kamima T, et al. Standardization of knowledge-based volumetric modulated arc therapy planning with a multi-institution model (broad model) to improve prostate cancer treatment quality. *Phys Eng Sci Med*. 2023;46:1091-1100.
42. Fukunaga JI, Tamura M, Ueda Y, et al. Multi-institution model (big model) versus single-institution model of knowledge-based volumetric modulated arc therapy (VMAT) planning for prostate cancer. *Sci Rep*. 2022;12:15282.
43. Matrosic CK, Dess K, Boike T, et al. Knowledge-based quality assurance and model maintenance in lung cancer radiation therapy in a statewide quality consortium of academic and community practice centers. *Pract Radiat Oncol*. 2023;13:e200-e208.

44. Claridge Mackonis E, Sykes J, Hardcastle N, et al. A comparison of in-house and shared RapidPlan models for prostate radiation therapy planning. *Phys Eng Sci Med*. 2022;45:1029-1041.
45. Ray X, Kaderka R, Hild S, Cornell M, Moore KL. Framework for evaluation of automated knowledge-based planning systems using multiple publicly available prostate routines. *Pract Radiat Oncol*. 2020;10:112-124.
46. Fu Y, Zhang H, Morris ED, et al. Artificial intelligence in radiation therapy. *IEEE Trans Radiat Plasma Med Sci*. 2022;6:158-181.
47. Momin S, Fu Y, Lei Y, et al. Knowledge-based radiation treatment planning: a data-driven method survey. *J Appl Clin Med Phys*. 2021;22:16-44.
48. Fanou AM, Patatoukas G, Chalkia M, et al. Implementation, dosimetric assessment, and treatment validation of knowledge-based planning (KBP) models in VMAT head and neck radiation oncology. *Biomedicines*. 2023;11:762.
49. Younge KC, Marsh RB, Owen D, et al. Improving quality and consistency in NRG Oncology Radiation Therapy Oncology Group 0631 for spine radiosurgery via knowledge-based planning. *Int J Radiat Oncol Biol Phys*. 2018;100:1067-1074.
50. Li N, Carmona R, Sirak I, et al. Highly efficient training, refinement, and validation of a knowledge-based planning quality-control system for radiation therapy clinical trials. *Int J Radiat Oncol Biol Phys*. 2017;97:164-172.