

Real-time interactive planning for radiotherapy of head and neck cancer with volumetric modulated arc therapy



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ABSTRACT

Background and purpose: Planning complex radiotherapy treatments can be inefficient, with large variation in plan quality. In this study we evaluated plan quality and planning efficiency using real-time interactive planning (RTIP) for head and neck (HN) volumetric modulated arc therapy (VMAT).

Materials and methods: RTIP allows manipulation of dose volume histograms (DVHs) in real-time to assess achievable planning target volume (PTV) coverage and organ at risk (OAR) sparing. For 20 HN patients previously treated with VMAT, RTIP was used to minimize OAR dose while maintaining PTV coverage. RTIP DVHs were used to guide VMAT optimization. Dosimetric differences between RTIP-assisted plans and original clinical plans were assessed. Five blinded radiation oncologists indicated their preference for each PTV, OAR and overall plan. To assess efficiency, ten patients were planned *de novo* by experienced and novice planners and a RTIP user.

Results: The average planning time with RTIP was < 20 min, and most plans required only one optimization. All 20 RTIP plans were preferred by a majority of oncologists due to improvements in OAR sparing. The average maximum dose to the spinal cord was reduced by 10.5 Gy (from 49.5 to 39.0 Gy), and the average mean doses for the oral cavity, laryngopharynx, contralateral parotid and submandibular glands were reduced by 3.5 Gy (39.1–35.7 Gy), 6.8 Gy (42.5–35.7 Gy), 1.7 Gy (17.0–15.3 Gy) and 3.3 Gy (22.9–19.5 Gy), respectively.

Conclusions: Incorporating RTIP into clinical workflows may increase both planning efficiency and OAR sparing.

1. Introduction

Planning complex treatments such as head and neck (HN) volumetric modulated arc therapy (VMAT) can be very inefficient, with varying results in terms of plan quality. In recent years many studies have explored the clinical benefits of knowledge based planning (KBP) to address these challenges, and reported time savings [1–3] and increased efficiencies [4–6] with KBP. Variation in plan quality has been explored by Nelms et al. [7] who proposed that the variation in plan quality may be due to individual planner skill level. Previous research [1–3,5,8–12] has shown that KBP can consistently produce high quality

plans and reduce variability in plan quality, while reducing number of optimizations and planning time [8].

KBP relies on a model library of previously developed plans for a given site to guide the optimization of a new plan [1]. The minimum number of plans required for an adequate model depends on the treatment site, and complex sites such as HN, which have greater variation between patients, may require a larger number of plans to create a robust model [13]. Plans produced using KBP models are sensitive to the quality of the plans in the model library [11,14]. Improvements in plan quality using KBP are dependent on the quality of sub-optimal plans in the library being improved prior to using the KBP models [15],

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and dosimetric outliers in KBP models may deteriorate plan quality for complex sites such as HN [16]. In addition, consistent contouring is required in order to create reliable KBP models [14].

More recently, techniques exploiting multicriteria optimization (MCO) to explore trade-offs between different treatment planning goals [17–19] and beam geometries (e.g., Erasmus-iCycle [20–22]) have been investigated, with reported improvements in both plan quality and planning efficiency. Although very promising, with some MCO approaches discrepancies have been reported between desired Pareto-optimal plans and final deliverable plans [23], potentially compromising clinical decisions made during trade-off exploration.

Recently, Otto [24] has developed a novel approach termed real-time interactive planning (RTIP). RTIP employs rapid 3D dose calculations (~2–20 ms) and a graphics interface that allows users to manipulate DVHs and other dose metrics in real-time in order to quickly estimate what is achievable for a given patient. An advantage of RTIP compared to KBP is that there is no requirement for a model plan library. As such, RTIP is ideally suited to explore dosimetric trade-offs that are specific to an individual patient's anatomy and contours. A potential advantage of RTIP compared to MCO-based techniques is there is no requirement to pre-compute a set of Pareto-optimal plans from a limited set of planning goals and constraints. With RTIP, patient-specific goals and constraints can be added and removed in an interactive fashion, and trade-offs explored immediately in “real-time” [24].

Our study investigates the use of RTIP to guide the optimization of HN VMAT plans. The efficiency of RTIP for HN VMAT planning is explored by tracking planning time and number of optimizations required compared to conventional planning methods, and RTIP plan quality is investigated via dosimetric comparisons between plans generated using RTIP and plans created using conventional methods that were approved and treated in our institution (“clinical” plans). The quality of RTIP-assisted plans versus clinical plans is also investigated via blinded plan review by five HN radiation oncologists (ROs) with VMAT experience. We hypothesize that using RTIP will produce treatment plans that are of equivalent or higher quality than clinical plans, with improvements in planning efficiency.

2. Material and methods

2.1. Patient and plan information

After institutional research ethics board approval, 20 HN patients previously planned with VMAT (Varian, Eclipse v11) at our institution between March 2014 and April 2015 were included and anonymized for this retrospective study. Patients were excluded if they had received prior radiotherapy to the HN region or if planning target volume (PTV) or organ-at-risk (OAR) contours varied from our standard local HN protocol. The patient cohort included various HN primary sites (oral cavity, larynx, oropharynx and hypopharynx) at various disease stages, and included both ipsilateral and bilateral targets. All patients with multiple dose levels were planned with a simultaneous integrated boost (SIB) technique. Twelve patients were planned to a total dose of 70 Gy in 35 fractions, two to 66 Gy in 33 fractions, five to 60 Gy in 30 fractions and one to 60 Gy in 25 fractions. Seven patients had three PTV dose levels, ten had two PTV dose levels and three had a single PTV dose level. VMAT plans used either two or three full or partial arcs as required. Gantry rotation limits, collimator angles, jaw sizes, isocentre placement, and bolus were matched to the original clinical plan for all new plans created.

2.2. RTIP process

Patient CT images, structure sets (including any digitized bolus), and clinical plan parameters for isocentre placement and arc geometry were exported from the Eclipse treatment planning system and imported into the RTIP system. No optimization structures (e.g.,

avoidance structures or cropped OARs) were used. A standardized template with predefined planning goals for each PTV and OAR, set by our local HN protocol, was loaded into RTIP, and an automated goal matching algorithm was used to modify the initial unconstrained RTIP dose distribution (a conformal distribution that covers the target volume with a uniform dose [24]) to meet as many planning goals as possible, in order of priority defined by our local protocol. First, target coverage and homogeneity goals were automatically met and constrained, followed by automated reduction of OAR doses to meet standard planning goals. Goals achieved were automatically converted to either dose-volume histogram (DVH) or mean dose constraints, which cannot be violated during subsequent RTIP dose modifications. For OAR planning goals that were not achieved by the RTIP system automatically, constraints were placed at the lowest corresponding dose achieved for that OAR volume. Once automated goal matching was completed, the RTIP dose distribution was manually adjusted to further minimize doses to all OARs, while maintaining PTV coverage and homogeneity. Once manual adjustments were complete, DVH and mean dose constraints for OARs were automatically placed at the minimum dose levels (at OAR volumes defined by our local protocol for DVH constraints) achieved in the RTIP system. These OAR constraints were exported from the RTIP system and used as OAR planning goals for VMAT optimization in Eclipse. In this study, for RTIP-guided VMAT optimization in Eclipse, an in-house recipe was used for PTV goals and priorities, OAR priorities, and normal tissue objective (NTO) parameters and priorities (see Supplemental Material S1). Subsequent re-optimization with adjusted constraints or priorities was only performed if the planner deemed the plan clinically unacceptable. The final RTIP-assisted plan was considered clinically acceptable if it achieved all required goals for coverage and homogeneity for all target volumes, yielded OAR doses comparable to those predicted by RTIP, and achieved good dose conformity to all targets as judged by the planner.

2.3. Dosimetric assessment of RTIP-assisted vs. clinical plans

PTV and OAR doses were compared using DVH and mean dose metrics corresponding to the planning goals defined by our local HN protocol. For comparing dose homogeneity and conformity for the primary PTV, homogeneity index (HI) was calculated using the ICRU 83 [25] definition ($HI = (D_{2\%} - D_{98\%})/D_{50\%}$), and conformity index (CI) was calculated using the Knöös definition [26], as $V_{PTV}/V_{95\%}$ for high dose CI ($CI_{95\%}$) and $V_{PTV}/V_{50\%}$ for low dose CI ($CI_{50\%}$). Total plan monitor units (MU) were compared to assess differences in plan modulation.

2.4. Blinded radiation oncologist assessment of RTIP-assisted vs. clinical plans

Five ROs, across three regional centres, with expertise in HN VMAT planning agreed to review the 20 sets of plans. The same 20 sets of clinical and RTIP plans as used in the dosimetric assessment were randomly assigned as plan A or B. Plan review order was randomized and specific to each RO who reviewed the cases according to a standardized evaluation form (see Supplemental Material S2) for each of the 20 patients. ROs were asked to select which plan (A or B) was clinically superior, or equivalent, in terms of each PTV dose level and each OAR structure. If a contour did not exist for a given patient then “N/A” would be selected. The ROs also indicated their preferred plan overall or indicated no preference between the plans. A free text comment section was included for the RO if they wished to provide any comments to explain their decisions.

2.5. Plan deliverability

Both anonymized clinical and RTIP plans were delivered to an ArcCheck phantom (Sun Nuclear) using high resolution mode for

measurements. The acquired data for each plan was compared to the predicted measurement (SNC Patient v6.7.2) using absolute dose mode and clinically appropriate gamma index pass rates defined by a 3%/2 mm distance to agreement with a 50% dose threshold [27].

2.6. Timing and efficiency

Ten of the same anonymized plans used for the dosimetric and blinded RO assessments were planned *de novo* by three treatment planners. One planner (“RTIP planner”) created the plans using the RTIP software to guide Eclipse optimization, as described above. The other two planners created the plans using conventional inverse planning approaches; one planner (“experienced planner”) had four years’ experience planning HN VMAT treatments while the other planner (“novice planner”) was experienced with planning VMAT treatments but had no experience with the HN site. To define a consistent stopping criterion for planning, all three planners were provided with a list of PTV and OAR dose constraints with qualitative stopping criteria for each PTV and OAR that indicated which constraints must be met, which may not be met but should be kept as low as reasonably achievable (ALARA), and which could be ignored during optimization.

Each planner recorded the time they took to create an acceptable plan. The timing was broken into three categories: (1) “preparation time” was defined as the time spent creating any optimization structures (not required, and were not used by RTIP planner) and inputting the optimization objectives and priorities into the optimization program, (2) “optimization adjustment time” included the time spent adjusting priorities or optimization objectives in the optimizer before letting it run to completion, and (3) “plan evaluation time” was the time spent assessing the dose distribution and DVHs to determine if the plan was acceptable. The computation time required to optimize and calculate the plan without any planner interaction was not included. Each planner also recorded the total number of optimizations required to generate a clinically acceptable plan according to the stopping criteria provided.

2.7. Statistical analysis

Statistical analysis was performed for the dosimetric assessment and timing portions of the study. *P*-values were calculated from two-tailed paired *t*-tests (Microsoft Excel 2010) for data satisfying a Shapiro-Wilk normality test (MATLAB, The Mathworks Inc.), and from a Wilcoxon signed-rank test (MATLAB) otherwise. A *P*-value of ≤ 0.05 was considered statistically significant.

3. Results

3.1. RTIP timing and efficiency

For all 20 plans created with RTIP guidance, the average time spent using the RTIP system was 4.9 ± 0.9 min (range 3.5–7.0 min). Using RTIP guidance, average planning time in Eclipse was 18.0 ± 6.0 min (range 8.5–28.5 min), and a clinically acceptable treatment plan (as defined above) was achieved on the first optimization for 13 of the 20 plans. Six RTIP-guided plans required a second optimization and one required a third optimization to achieve a clinically acceptable plan.

3.2. Timing and efficiency: RTIP vs. conventional planning

For the ten plans used for the timing and efficiency study, there were statistically significant differences in the planning time in Eclipse for the RTIP planner (median 17.8 min [range 8.5–28.5 min]) versus experienced planner (median 10.3 min [range 5–23.5 min]) versus novice planner (median 27.8 min [range 16.5–81 min]) to achieve an acceptable treatment plan (Fig. 1A). No significant differences were observed in the number of optimizations required to create the plans

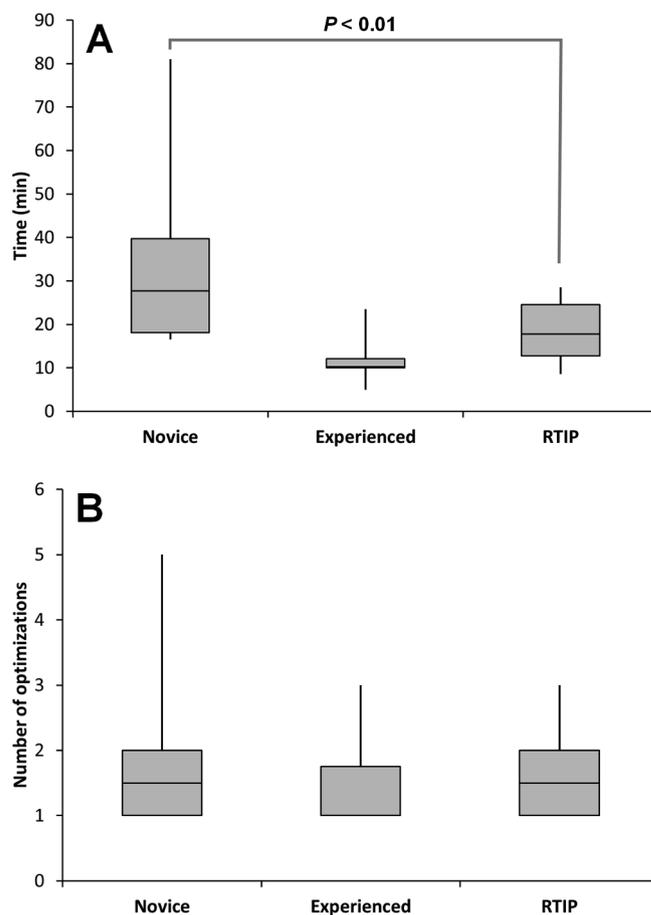


Fig. 1. (A) Total planning time in Eclipse per plan and (B) number of optimizations per plan required, based on both planner experience and software used.

(Fig. 1B), although the novice planner required the most optimizations (total = 19, median = 1.5, range = 1–5), versus the experienced planner (total = 14, median = 1.0, range = 1–3) and RTIP planner (total = 16, median = 1.5, range = 1–3).

3.3. Dosimetric assessment: RTIP-assisted vs. clinical plans

All clinical and RTIP plans achieved the desired PTV coverage for all PTV dose levels and no significant differences were observed between the planning methods, with the exception that RTIP yielded slightly improved coverage of intermediate dose PTVs ($P = 0.04$, $N = 7$) (Table 1). RTIP was often able to achieve lower doses to OARs (Table 1). The brainstem and spinal cord PRVs exhibited significant max dose reductions with RTIP. The mean dose to both the ipsilateral and contralateral parotid glands and the contralateral submandibular gland were significantly reduced with RTIP planning. The mean dose to the oral cavity and laryngopharynx was significantly lower for the RTIP plans, as was the laryngopharynx V_{50Gy} and mandible V_{70Gy} . No OARs exhibited significant increases in any dose parameter for RTIP plans (Table 1).

The average target dose homogeneity was improved ($P < 0.01$) for RTIP plans (Table 1). For dose conformity, average $CI_{95\%}$ was slightly improved ($P = 0.04$) in the clinical plans versus RTIP plans whereas average $CI_{50\%}$ was improved ($P = 0.01$) in the RTIP plans versus clinical plans (Table 1).

The average total number of MU increased from 504 ± 118 MU for clinical plans to 591 ± 81 MU for RTIP plans ($P < 0.01$), but this did not degrade plan deliverability as all RTIP and clinical plans delivered to an ArcCheck phantom achieved greater than 95% gamma pass rate.

Table 1
Dosimetric comparison of clinical and RTIP plans.

Structure	Parameter	Clinical: mean \pm SD (min, max) [‡]	RTIP: mean \pm SD (min, max) [‡]	Clinical – RTIP: mean \pm SD (min, max) [†]	P-value	N
PTVhd	V95% (%)	99.0 \pm 0.7 (98.1, 100)	99.2 \pm 0.7 (98.0, 100)	–0.2 \pm 0.7 (–1.2, 1.4)	0.30	20
	Dmax (%)	107.0 \pm 1.5 (103.6, 109.3)	106.6 \pm 1.7 (102.8, 109.8)	0.4 \pm 1.2 (–1.8, 2.8)	0.19	
	HI	0.08 \pm 0.01 (0.06, 0.10)	0.07 \pm 0.01 (0.04, 0.10)	0.01 \pm 0.01 (–0.02, 0.04)	< 0.01	
	CI _{95%}	0.90 \pm 0.07 (0.66, 0.97)	0.87 \pm 0.08 (0.63, 0.98)	0.03 \pm 0.05 (–0.05, 0.17)	0.04	
	CI _{50%}	0.18 \pm 0.13 (0.01, 0.44)	0.19 \pm 0.14 (0.01, 0.44)	–0.01 \pm 0.01 (–0.04, 0.01)	0.01	
PTVid	V95% (%)	98.7 \pm 0.9 (97.9, 99.9)	99.2 \pm 0.7 (98.1, 100)	–0.4 \pm 0.4 (–1.1, 0.0)	0.04	7
PTVed	V95% (%)	98.7 \pm 0.7 (97.5, 99.9)	98.8 \pm 0.6 (98.0, 99.7)	–0.1 \pm 0.6 (–1.2, 1.2)	0.44	16
Spinal Cord PRV [†]	Dmax (Gy)	49.5 \pm 4.8 (39.2, 55.1)	39.0 \pm 6.4 (24.3, 51.3)	10.5 \pm 4.8 (1.4, 20.8)	< 0.01	20
	V45Gy (%) [‡]	2.7 \pm 2.2 (0.0, 7.6)	0.2 \pm 0.7 (0.0, 3.0)	2.5 \pm 1.9 (0.0, 6.6)	< 0.01	
Brainstem PRV [†]	Dmax (Gy)	29.1 \pm 18.9 (2.5, 55.3)	23.2 \pm 14.8 (2.6, 49.7)	5.9 \pm 6.8 (–2.3, 21.5)	< 0.01	19
Parotid Ipsi.	Dmean (Gy)	28.1 \pm 11.3 (13.8, 57.1)	26.1 \pm 11.3 (10.3, 48.0)	2.0 \pm 3.5 (–2.6, 10.0)	0.02	19
Parotid Contra.	Dmean (Gy)	17.0 \pm 7.9 (5.1, 26.7)	15.3 \pm 9.7 (2.9, 30.4)	1.7 \pm 3.3 (–6.5, 7.0)	0.03	20
Submand. Contra.	Dmean (Gy)	22.9 \pm 9.9 (13.7, 46.6)	19.5 \pm 13.6 (6.8, 52.5)	3.3 \pm 5.3 (–5.9, 10.2)	0.03	14
Laryngopharynx	Dmean (Gy)	42.5 \pm 7.6 (27.4, 62.2)	35.7 \pm 12.5 (15.1, 63.3)	6.8 \pm 6.3 (–1.1, 18.6)	< 0.01	16
	V50Gy (%) [‡]	32.3 \pm 24.1 (0.3, 87.4)	27.4 \pm 23.9 (0.3, 90.1)	4.9 \pm 8.0 (–2.7, 29.2)	0.03	
Oral Cavity	Dmean (Gy)	39.1 \pm 6.4 (25.7, 47.3)	35.7 \pm 6.7 (20.4, 46.7)	3.5 \pm 3.1 (–0.6, 11.1)	< 0.01	15
	V60Gy (%) [‡]	15.9 \pm 13.0 (0.0, 34.6)	15.8 \pm 13.7 (0.0, 39.0)	0.1 \pm 2.1 (–5.6, 2.6)	0.57	
Mandible	V50Gy (%) [‡]	26.6 \pm 13.8 (7.5, 58.1)	28.4 \pm 15.3 (6.3, 59.6)	–1.8 \pm 4.5 (–12.1, 3.4)	0.23	20
	V70Gy (cc) [‡]	0.8 \pm 1.4 (0.0, 4.7)	0.5 \pm 0.8 (0.0, 2.4)	0.3 \pm 0.6 (–0.1, 2.3)	0.01	

Abbreviations: SD = standard deviation, PTVhd = high dose PTV, PTVid = intermediate dose PTV, PTVed = elective dose PTV, Ipsi. = Ipsilateral, Contra. = Contralateral, Submand. = submandibular gland, PRV = planning organ-at-risk volume, Dmax = maximum dose, Dmean = mean dose, V95% = % volume of target structure receiving 95% of prescription dose for that target, HI = homogeneity index $((D_{2\%} - D_{98\%})/D_{50\%})$, CI = conformity index $(CI_{95\%} = V_{PTV}/V_{95\%}, CI_{50\%} = V_{PTV}/V_{50\%})$.

Mean values are the averages of the respective parameters for the 20 patients, with the total number of available structures indicated (N). Bolded values indicate statistically significant differences.

[‡] (min, max) indicates the minimum and maximum observed values for the parameter (for Clinical or RTIP) or the minimum and maximum difference between clinical and RTIP values for the parameter (for Clinical – RTIP). All difference results are clinical minus RTIP.

[†] PRVs are 5 mm radial expansions from the true OAR structure.

* Absolute doses indicated are for 35 fractions, and are BED adjusted for < 35 fractions.

3.4. Blinded RO assessment: RTIP-assisted vs. clinical plans

All plans reviewed (RTIP and clinical plans) were deemed clinically acceptable by all reviewing ROs. For the 20 pairs of plans, a total of 215 structures were reviewed, of which 212 structures had a majority response (at least 3 of 5 ROs) indicating preference for either the clinical plan or the RTIP plan, or equivalent, for each structure. The three structures without a majority response by ROs were excluded from the analysis.

The doses to each PTV were reported as equivalent between the clinical and RTIP plans by a majority of ROs for 92.5% of all PTVs contoured (Fig. 2A).

Fig. 2B shows the distribution of plan preference by a majority of ROs for each OAR structure. ROs more frequently preferred dose to OAR structures from RTIP plans than clinical plans, most commonly for spinal cord, brainstem, parotids, contralateral submandibular, oral cavity, and laryngopharynx. Majority preference for any OAR from a clinical plan was infrequent, and only ever occurred for three

structures: contralateral parotid, contralateral submandibular, and mandible. For uncounted other normal tissues, both RTIP and clinical plans were equivalent in 100% of cases.

Including responses from all ROs (not by majority analysis), RTIP plans were preferred overall in 86% of cases (Fig. 2C). However, under majority analysis, ROs preferred the RTIP plan in 100% of cases (Fig. 2D). The most common reason indicated by ROs for RTIP plan preference was clinically significant reductions in OAR dose (as per Fig. 2B), while maintaining clinically acceptable target coverage, homogeneity, and conformity.

4. Discussion

This study demonstrated that RTIP is capable of producing high quality HN plans in a short amount of time, with a small number of optimizations. Dosimetric analysis and blinded RO evaluation demonstrated that RTIP-guided VMAT optimization created plans that were preferable to plans created through conventional methods. In our study,

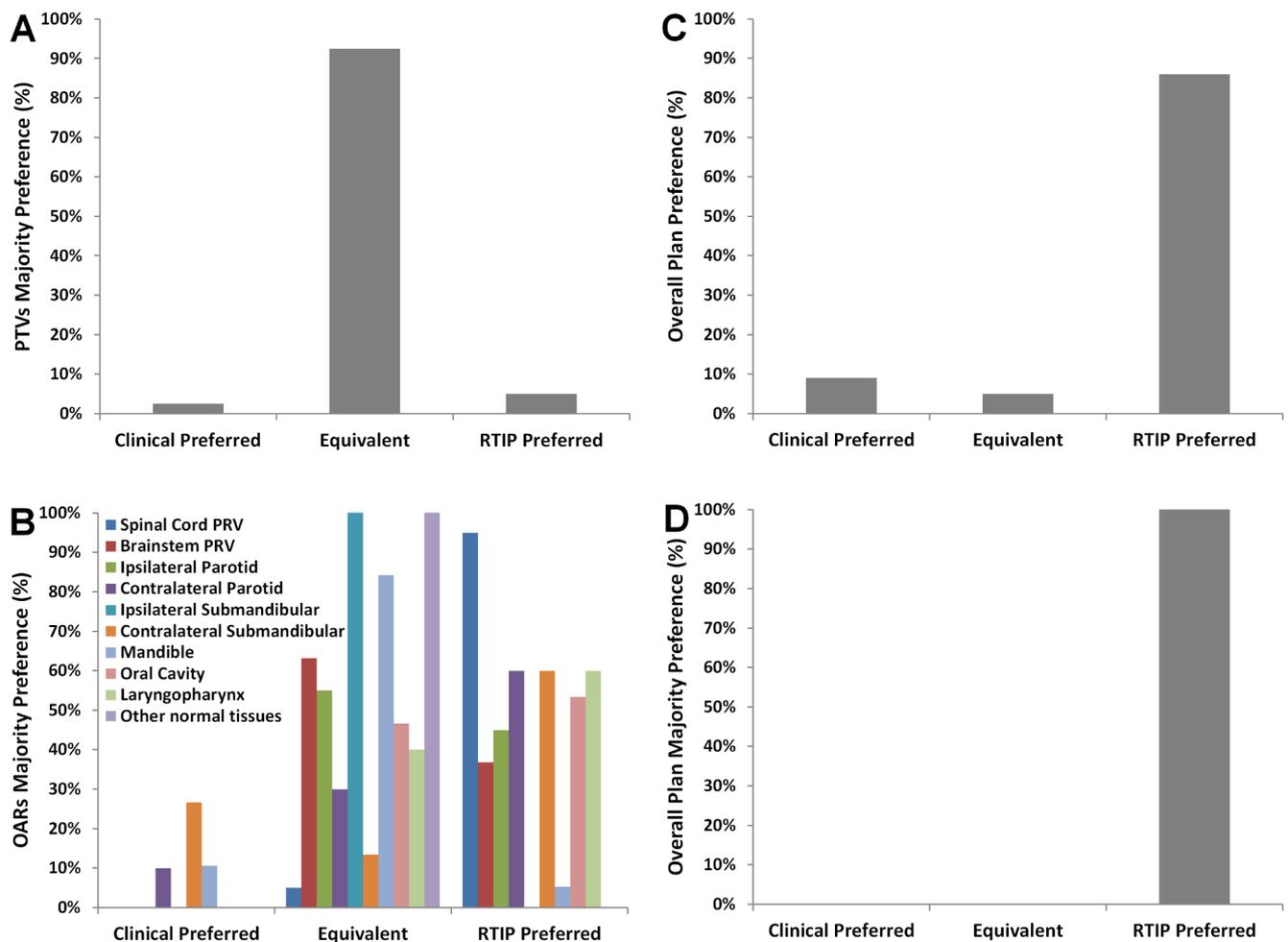


Fig. 2. Radiation Oncologist (RO) Plan Evaluation: (A) RO majority preference for all PTV dose levels, (B) RO majority preference for OARs and other normal tissues, (C) RO preferred plan overall (all responses) and (D) RO preferred plan overall by majority analysis.

RTIP plans were preferred over clinical plans 100% of the time by a majority of ROs, primarily due to reductions in OAR dose.

This study also confirms that the RTIP algorithm is sufficiently accurate for guiding VMAT optimization of HN plans, as initially demonstrated by Otto for a single representative HN case [24]. Due to the intrinsic limitations of the RTIP algorithm, further study is required to determine the suitability of RTIP for guiding optimization for highly heterogeneous treatment sites (e.g., lung), and to compare dose distributions between the final RTIP predictions and the final RTIP-assisted plans for various sites.

One limitation of this study is in the comparison of planning times. All three planners were provided a list of what PTV coverage and OAR constraints must be met, which OAR doses were to be kept “ALARA”, and which OARs could be ignored for planning. This approach resulted in “planning times” that are likely much shorter than clinical reality. In conventional planning, most planners aim to meet all PTV goals and abide by the ALARA principle for all OARs, which would typically require more than one or two optimizations. Future work could compare RTIP and conventional planning where planners are not given pre-defined stopping criteria.

Another limitation of this work is RTIP user variability. Despite the standardized and prescriptive RTIP process (described in Section 2.2) there is still potential for user variability in the manual portion of the RTIP process, and any optimization adjustments in Eclipse. Quantifying RTIP user variability vs. clinical planner variability is a subject for further study.

Several alternative approaches to increasing planning efficiency and

plan quality using inverse planning without requiring a plan library have been recently investigated, using techniques such as feasibility DVHs [28], AutoPlanning by Pinnacle³ [29], and interactive dose shaping [30,31]. Currently, interactive dose shaping is the most similar approach to RTIP that has been reported, but it is currently only applicable to static-gantry IMRT (not VMAT) [30], and to our knowledge only a limited proof-of-concept clinical investigation has been performed to date [31]. Many future investigations will be required to compare all the various strategies (including KBP and MCO) that will be available to clinicians and treatment planners in the future.

We have demonstrated that RTIP is a highly effective tool for creating high quality HN VMAT plans that may be preferable to plans created with conventional methods. Plans created with RTIP guidance can be completed in a short overall time frame compared to conventional methods, which may be especially beneficial for novice HN VMAT planners.

Conflict of interest

Dr. Olson reports grants from Varian Medical Systems, outside the submitted work.

Dr. Otto reports other from Varian Medical Systems Inc., during the conduct of the study; personal fees from Varian Medical Systems Inc., outside the submitted work; In addition, Dr. Otto has a patent on the software system used in this research issued to Varian Medical Systems Inc.

Source of financial support/funding statement

None related to the submitted work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2019.03.002>.

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