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Technical Note

Organs-at-risk dose and normal tissue complication probability with dynamic trajectory radiotherapy (DTRT) for head and neck cancer

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ABSTRACT

We compared dynamic trajectory radiotherapy (DTRT) to state-of-the-art volumetric modulated arc therapy (VMAT) for 46 head and neck cancer cases. DTRT had lower dose to salivary glands and swallowing structure, resulting in lower predicted xerostomia and dysphagia compared to VMAT. DTRT is deliverable on C-arm linacs with high dosimetric accuracy.

Introduction

Loco-regionally advanced head and neck cancer (HNC) treatment generally involves a combination of surgery, radiation therapy (RT) and chemotherapy imposing toxicities with a high impact on quality of life (QoL) [1–3]. Intensity modulated RT (IMRT) has enabled improved dosimetric organs-at-risks (OARs) sparing, significantly lowering toxicity compared to 3D conformal RT [4], while volumetric modulated arc therapy (VMAT), using also dynamic gantry rotation and dose rate modulation [5] has become a standard of care [6]. Nevertheless, toxicities remain prevalent [1–3].

Non-coplanar dynamic techniques using multiple arcs at different static table angles [7–10], or dynamic trajectory radiotherapy (DTRT) using simultaneous gantry and table rotation with [11–13] or without [14,15] dynamic collimator rotation during beam-on have been developed to further improve dosimetric plan quality [16,17]. Most studies focused on intracranial or small nasopharyngeal targets with a large collision-free space [7,12,17–19]. Recently, Pokhrel et al. applied class-solution non-coplanar VMAT for re-irradiation of more caudally located HNC targets with small planning target volumes (PTVs) [8]. Dosimetric benefit was also found for larger targets including elective nodal volumes with class-solution non-coplanar VMAT compared to VMAT [9,10], or with intensity modulated non-coplanar arc RT using dynamic table rotation compared to IMRT [15]. Relatively conservative planner-defined gantry and table parameters with generic collision models were used in these planning studies.

DTRT has shown promising results for multiple treatment sites where treatment plans were created in a research version of a clinical treatment planning system (TPS) [11]. Specific gantry-table-collimator path-finding strategies for common HNC cases were recently developed and successfully delivered on an anthropomorphic phantom [20]. This proof-of-concept provided a promising treatment planning approach for loco-regionally advanced HNC with large target volumes but it was limited to a small and intentionally heterogeneous set of cases on a phantom.

Here we applied this novel DTRT planning approach to 46 loco-regionally advanced HNC cases to quantify the potential benefit of DTRT using case-specific dynamic gantry, table, and, collimator paths, and collision models to reduce OAR dose and normal tissue complication probability (NTCP) for xerostomia and dysphagia compared to VMAT.

Methods and materials

The full materials and methods are available in supplementary material.

Forty-six patients with loco-regionally advanced HNC enrolled in the UPFRONT-NECK trial (NCT02918955) between 12.2016 and 4.2022, were included in this retrospective planning study (Supplementary Table 1). OARs (including optical and auditory structure) and clinical target volume (CTV) delineation followed international guidelines [21–23]. The bilateral hippocampus was delineated [24] and subject to a mandatory dose limit of $D_{40\%} \leq 7.3$ Gy [25]. PTVs extended CTVs by a

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3 mm isotropic margin, trimmed 3 mm from the body contour. Treatment plans were created for 2 Gy fractions with 50 Gy to the elective nodal volume and sequential boost plans to 66 Gy for any post-operative positive margin and nodal levels with extracapsular extension and 70 Gy for non-operated primary tumor and involved lymph nodes [26–29]. Plan normalization was D95%(PTV) = 100% of the prescribed dose. Details of the planning goals can be found in supplementary material.

DTRT and VMAT plans were created in Eclipse (Research version, Varian Medical Systems) for a 6 MV-flattened beam on a TrueBeam linac (Varian) equipped with a 120-leaf Millennium multi-leaf collimator (MLC) and a PerfectPitch 6-degree-of-freedom table. Treatment planning for DTRT followed the procedure of [20] for the oropharyngeal cases with case-specific collision model [30] as described in supplementary material.

DTRT and VMAT were compared based on dosimetric endpoints and predicted xerostomia and dysphagia using the validated NTCP model of [31,32], described in the supplementary material. Differences between DTRT and VMAT were compared using Wilcoxon matched-pair signed-rank test with an alpha of 5% and Bonferroni correction for multiple testing.

One verification plan was created for a Polymethyl methacrylate (PMMA) cubic phantom with two interleaved EBT3 films (Ashland Advanced Materials, Bridgewater, NJ) [33], exported in extended markup language (xml) format and delivered on a TrueBeam using Developer Mode for dosimetric validation as described in supplementary material [34–38].

Results

All individual plans had acceptable and similar near-max target doses, conformity and homogeneity indices (Supplementary Table 2). Target coverage and OAR dose for the combined plans are reported in Supplementary Tables S3 and S4. Target coverage was acceptable and mandatory OAR limits were respected for all plans.

Salivary and swallowing structures had significantly lower mean doses with DTRT compared to VMAT except for the ipsilateral parotid gland and submandibular glands and the larynx where the differences were not significant (Supplementary Table 2). Fig. 1 (top) shows the distribution of the difference between DTRT and VMAT as boxplots.

Optical and auditory structures had significantly higher doses with DTRT than with VMAT but remained well within the clinical goals (Supplementary Table 4.). Both hippocampi and the thyroid gland had significantly higher doses with DTRT than VMAT; the opposite was true for the lips (Supplementary Table 3). The near-max dose to the brain was significantly higher for DTRT than for VMAT however it remained well below the clinical goal for both techniques. $D_{10\%}$ to the contralateral carotid artery (11 cases) was significantly lower with DTRT than with VMAT. Other endpoints were not significantly different between the two techniques.

DTRT had significantly higher integral dose than VMAT (Supplementary Table 3). However, although the volumes receiving doses of 7 Gy or less are larger for DTRT than VMAT, the opposite is true for the volumes receiving intermediate dose levels between 15 and 40 Gy. For 50 Gy or higher, the two techniques were equivalent (Supplementary

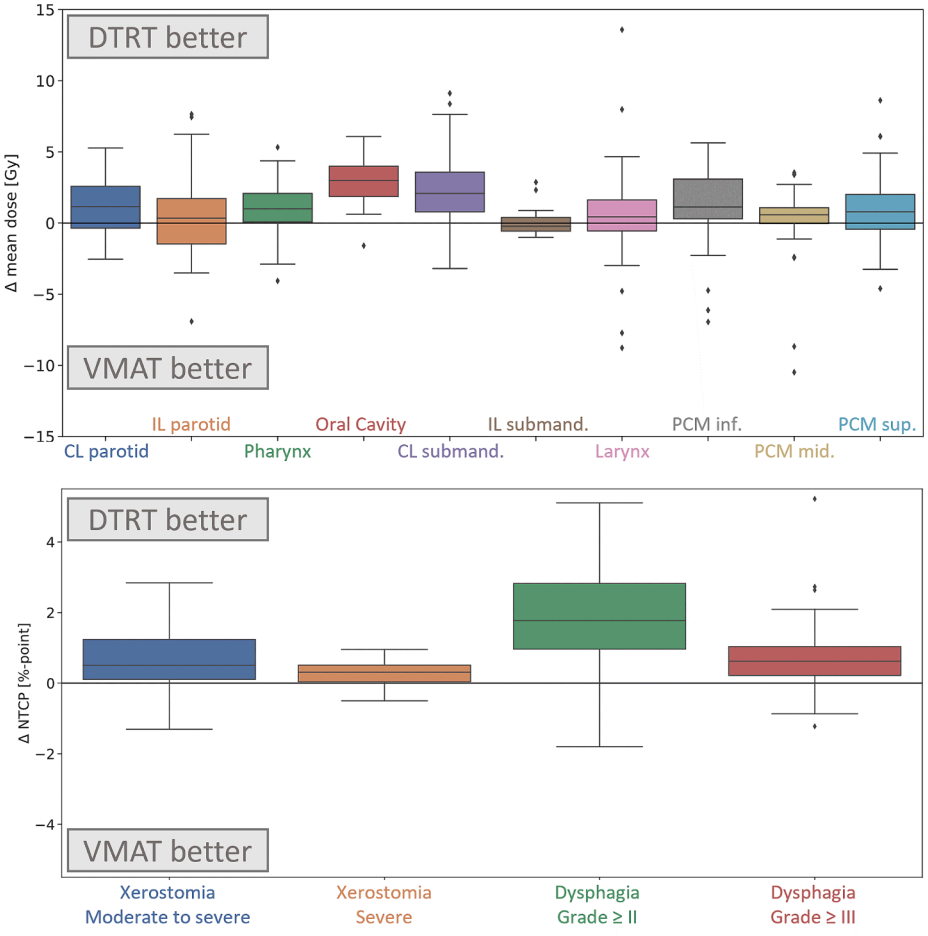

Fig. 1. Distribution of the difference between DTRT and VMAT for the main OAR endpoints (top) and the NTCP values (bottom). The line indicates the median, the box extends to the quartile range and the whisker to the last data point except for outliers shown with diamonds. Abbrev: CL = contralateral, IL = ipsilateral, submand. = submandibular (gland), inf. = inferior, mid. = middle, sup. = superior, PCM = pharyngeal constrictor muscles.

Fig. 2).

Supplementary Figs. 3 and 4 show the dose volume histograms, dose distributions and 3D views of the DTRT trajectories for two representative cases.

All xerostomia and dysphagia NTCP endpoints were significantly lower for DTRT than for VMAT (Fig. 1 and Table 1). The xerostomia model was invalid for four patients because both submandibular glands and, in one case, also the ipsilateral parotid were resected.

For the 42 patients where the xerostomia model was applicable, both grades of NTCP were higher with DTRT than VMAT for 10 cases (24%) but it was lower by at least 2 percentage-points for 3 cases (7%) for the moderate to severe grade. For the dysphagia model, NTCP for grade $\geq$ II and $\geq$ III was higher for DTRT than VMAT for 4 (9%) and 6 cases (13%) respectively. Conversely, it was lower by at least 3 percentage-points with DTRT compared to VMAT for 9 (21%) and 1 case (2%) for grade $\geq$ II and $\geq$ III respectively. Nearly half the cases, 21 (46%), had a decrease in dysphagia grade $\geq$ II with DTRT compared to VMAT of at least 2 percentage-points.

The plan for the 50 Gy dose level of the case shown in Supplementary Fig. 3 was successfully delivered with high dosimetric accuracy (see supplementary material).

The overall RATING score was 98% (supplementary material) [39].

Discussion

In this planning study of 46 loco-regionally advanced HNC cases, DTRT improved OAR sparing, associated with a reduction in predicted xerostomia and dysphagia, compared to VMAT while maintaining target coverage, homogeneity, and conformity. The differences were statistically significant, also after stringent Bonferroni correction for multiple testing. This represents the first large planning study systematically comparing DTRT with state-of-the-art VMAT for this patient population.

Non-coplanar beam arrangements have generally been associated with improved contralateral sparing [11,17,18], as found also in this study with an average reduction in mean dose to the contralateral salivary glands of 1.2 and 2.2 Gy for DTRT compared to VMAT. The greatest improvement was observed for the oral cavity and the lips (average reduction in mean dose of 3.0 and 2.7 Gy respectively), located anteriorly to the target volume. The NTCP reduction was statistically significant for xerostomia and dysphagia of all grades. Nevertheless, 10 cases had worse predicted xerostomia with DTRT than VMAT. The maximum increase was 1.3 percentage-points for moderate to severe xerostomia in one case. However, the decrease achieved with DTRT over VMAT reached 2 percentage-points or more for 3 cases (7%) with a maximum of 2.8 percentage-points. For dysphagia, the predicted benefit of DTRT was greater with a decrease for grade $\geq$ II of 2 percentage-points or more for nearly half the cases and 3 percentage-points for 21% of cases. The maximum decrease was greater than 5 percentage-points (both grades) in one patient. It should be noted that 47.8% of the patients had neck dissection but were treated in the primary setting with 70 Gy to the primary tumor. There is, to our knowledge, no validated NTCP model for this setting and we used the postoperative model, hence results for this group should be interpreted with caution. Nevertheless, the main contributor to toxicity is primary tumor site which was correctly attributed. In addition to NTCP reduction, DTRT also showed better dosimetric sparing for the contralateral carotid planning at risk volume, and the lips.

Increased salivary and swallowing structures sparing came at the cost of higher integral dose and higher doses to structures situated above the VMAT beam-plane. Other authors have also observed higher brain dose and integral dose; however, without reporting optical and auditory structure doses [9,10,15]. Here, dose to the brain and optical and auditory structures were well below the clinical goals. Due to the possible beam incidences through the apex of the head with DTRT, the bilateral hippocampus was contoured and subject to a mandatory limit of $D_{40\%} \leq 7.3$ Gy [25]. The hippocampus was not considered in other studies that have investigated (dynamic) non-coplanar techniques for HN [7–9,15]. Yet, in our experience, this structure should be considered at the path-finding stage and during intensity modulation optimization to avoid introducing a risk for neurocognitive impairment [25]. In future studies, dose to the cerebellum and posterior fossa should also be considered as it may be related to acute fatigue [40,41]. An increase in integral dose could potentially increase the risk of secondary cancer. However, for the considered patient population (median age of 62 years in this cohort), the actual risk remains low, whereas reducing xerostomia and dysphagia is paramount for QoL [1–3]. The higher integral dose is caused by low dose bath but the volume of normal tissue receiving intermediate doses were higher for VMAT than DTRT, echoing previous observations made when introducing VMAT in the clinic [42].

With 46 cases, this is the largest planning comparison between dynamic non-coplanar delivery techniques and VMAT, considering OAR sparing and NTCP, for HNC patients with bilateral elective nodal irradiation. In a study of ten patients, Krayenbuehl et al. found lower mean dose to the parotid glands and oral mucosa similar to the present study for non-coplanar arcs compared to 5-field IMRT [15]. For 22 patients, Gayen et al. found better shoulder sparing for non-coplanar VMAT compared to coplanar VMAT [10]. For 25 patients, Subramanian et al. observed a reduction in mean dose to the parotids, larynx, oral cavity and pharynx of 3–5 Gy for non-coplanar VMAT with multiple isocenters compared to coplanar VMAT; however, the non-coplanar plans had up to 3 times more arcs than the coplanar ones offering substantially more freedom to the intensity modulation optimizer [9]. With the increasing adoption of ring-gantry systems, a large number of coplanar arcs can be delivered in a short time, potentially reducing the advantage of non-coplanar techniques over coplanar delivery for similar treatment times. However, these systems often restrict set-up correction to translation only. In addition, C-arm linacs remain the most widely available treatment machine making DTRT an attractive option for high plan quality on standard equipment with 6-degree-of-freedom table correction option [43].

Our DTRT treatment planning process imposes only minimal modifications to the standard workflow with the collision model and path-finding software integrated into Eclipse through scripting [11,20,30]. This results in deliverable plans (in Developer Mode) with high dosimetric accuracy as demonstrated here and in previous studies [11,20,44,45]. Deliverability, dosimetric robustness, and modulation

Table 1
Population mean NTCP in % for xerostomia and dysphagia endpoints. Statistically significant differences are indicated in bold for the Bonferroni adjusted $\alpha = 0.0013$, with the best one between DTRT and VMAT underlined.

NTCP endpoint	DTRT		VMAT		p	$NTCP_{VMAT} - NTCP_{DTRT} < 0$	$NTCP_{VMAT} - NTCP_{DTRT} > 2$
	Mean ± SD	95 %CI	Mean ± SD	95 %CI		N	N
Xerostomia (n = 42)							
Moderate to severe	**<u>30.4</u> ± <u>10.1</u>**	[28.3–34.6]	**32.0 ± 9.8**	[29.0–35.1]	**<0.001**	10	3
Severe	**<u>7.8</u> ± <u>4.0</u>**	[6.5–9.0]	**8.1 ± 3.8**	[6.9–9.2]	**<0.001**	10	0
Dysphagia (n = 46)							
Grade $\geq$ II	**<u>25.4</u> ± <u>13.1</u>**	[21.5–29.3]	**27.3 ± 13.3**	[23.4–31.3]	**<0.001**	4	21
Grade $\geq$ III	**<u>9.1</u> ± <u>4.5</u>**	[7.7–10.4]	**9.8 ± 4.8**	[8.4–11.2]	**<0.001**	6	4

complexity were reported to be on par with VMAT in a previous study [45].

Finally, while this study focused on loco-regionally advanced HNC, DTRT is applicable to any treatment site with potential benefits shown for other types of HNC [20], brain, prostate, lung and esophagus [11], with further developments including dynamic table translations [46,47], or mixed photon-electron modalities [48].

Conclusions

We showed that DTRT significantly improves OAR sparing, resulting in NTCP reduction for xerostomia and dysphagia for patients with loco-regionally advanced HNC compared to state-of-the-art VMAT. The proposed technique is applicable on conventional linacs with minimal changes to the standard workflow, providing deliverable plans on standard linacs. High dosimetric accuracy was demonstrated in an end-to-end test.

CRediT authorship contribution statement

Jenny Bertholet: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Paul-Henry Mackeprang:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Hannes A. Loebner:** Writing – review & editing, Methodology, Data curation. **Silvan Mueller:** Writing – review & editing, Methodology. **Gian Guyer:** Writing – review & editing, Methodology. **Daniel Frei:** Writing – review & editing, Software. **Werner Volken:** Writing – review & editing, Software. **Olgun Elicin:** Writing – review & editing, Data curation. **Daniel M. Aebersold:** Writing – review & editing, Funding acquisition. **Michael K. Fix:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Peter Manser:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This work was supported by Varian, a Siemens Healthineers Company. JB, GG, SM, PM, MF declare funding from Grant 200021_185366 of the Swiss National Science Foundation outside of the submitted work.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110237.

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