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Original Research Article

Robustness analysis of dynamic trajectory radiotherapy and volumetric modulated arc therapy plans for head and neck cancer

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ABSTRACT

Background and purpose: Dynamic trajectory radiotherapy (DTRT) has been shown to improve healthy tissue sparing compared to volumetric arc therapy (VMAT). This study aimed to assess and compare the robustness of DTRT and VMAT treatment-plans for head and neck (H&N) cancer to patient-setup (PS) and machine-positioning uncertainties.

Materials and methods: The robustness of DTRT and VMAT plans previously created for 46 H&N cases, prescribed 50–70 Gy to 95 % of the planning-target-volume, was assessed. For this purpose, dose distributions were recalculated using Monte Carlo, including uncertainties in PS (translation and rotation) and machine-positioning (gantry-, table-, collimator-rotation and multi-leaf collimator (MLC)). Plan robustness was evaluated by the uncertainties' impact on normal tissue complication probabilities (NTCP) for xerostomia and dysphagia and on dose-volume endpoints. Differences between DTRT and VMAT plan robustness were compared using Wilcoxon matched-pair signed-rank test ($\alpha = 5$ %).

Results: Average NTCP for moderate-to-severe xerostomia and grade $\geq$ II dysphagia was lower for DTRT than VMAT in the nominal scenario (0.5 %, $p = 0.01$; 2.1 %, $p < 0.01$) and for all investigated uncertainties, except MLC positioning, where the difference was not significant. Average differences compared to the nominal scenario were ≤ 3.5 Gy for rotational PS ($\leq 3°$) and machine-positioning ($\leq 2°$) uncertainties, <7 Gy for translational PS uncertainties (≤ 5 mm) and < 20 Gy for MLC-positioning uncertainties (≤ 5 mm).

Conclusions: DTRT and VMAT plan robustness to the investigated uncertainties depended on uncertainty direction and location of the structure-of-interest to the target. NTCP remained on average lower for DTRT than VMAT even when considering uncertainties.

1. Introduction

The treatment of loco-regionally advanced head and neck (H&N) cancer typically necessitates a multi-disciplinary approach involving chemotherapy, surgery, and radiation therapy (RT) [1]. This usually imposed toxicities such as xerostomia and dysphagia [2,3].

For this treatment site, intensity modulated RT (IMRT) improved dosimetric sparing for organ-at-risk (OAR) adjacent to the target compared to 3D conformal RT and reduced toxicities [4]. Volumetric modulated arc therapy (VMAT) improved delivery efficiency compared to IMRT, by dynamic gantry rotation during beam-on [5]. IMRT and VMAT are today's state-of-the-art techniques for H&N cancer [6]. Recent developments extended these techniques by incorporating additional degrees-of-freedom: The research technique dynamic trajectory radiotherapy (DTRT) [7,8] includes dynamic table and collimator rotation during beam-on. Compared to VMAT, DTRT has been shown to improve OAR sparing, while maintaining similar target coverage [9]. However, it was unclear if these dosimetric advantages persist amid

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uncertainties.

Uncertainties in patient-setup [10,11] or in the mechanical accuracy of the beam defining machine components (such as gantry, table, collimator or multi-leaf collimator, MLC) [12] influence the delivered dose distribution. Despite using patient immobilization devices or patient-setup techniques (e.g., laser alignment, image-guidance, or surface-monitoring), intrafraction motion and patient-setup uncertainties persevered [13–15]. Kanakavelu et al. reported, that 35.2 %, 38.6 % and 4.8 % of their H&N cancer patients had setup uncertainties $>$ 2 mm in lateral, longitudinal, and vertical direction, respectively [13]. Moreover, setup uncertainties $<$ 3 mm were typically not corrected with daily image guidance RT protocols [16]. On the machine side, logfile analysis has been employed to study machine delivery uncertainties [17,18]. Compared to patient-setup uncertainties, these were generally small (sub-degree, sub-mm). Studies showed similar logfile-reported delivery uncertainties for DTRT and VMAT, indicating maintained mechanical accuracy for DTRT [9,19,20]. However, logfiles are insensitive to miscalibrations [21].

Patient-setup or machine-related uncertainties are included in planning target volume (PTV) margin concepts, which are designed to ensure acceptable target coverage for a majority of the patients, even under uncertainties. Margin concepts were developed for IMRT/VMAT but their appropriateness for DTRT must be validated, considering the use of additional beam directions and dynamic machine axes compared to VMAT. The impact of patient-setup or machine miscalibration uncertainties on DTRT plan quality should be comprehensively evaluated.

Robustness analysis to determine the uncertainties' impact on the dose distribution is common in proton therapy [22]. Data from photon treatment techniques is more limited, generally only focusing on the impact of patient-setup uncertainties on target coverage [23,24]. However, uncertainties also impact OAR dose, frequently neglected in robustness studies [25]. Normal tissue complication probability (NTCP) models are based on OAR dose metrics and are clinically relevant, e.g. in the patient selection for proton- or photon-based treatments [26]. Uncertainties therefore impact also the NTCP. A previous large plan comparison for H&N cancer showed that DTRT improves OAR sparing for salivary glands and swallowing structures compared to VMAT, resulting in statistically significant lower NTCP for xerostomia and dysphagia [27]. However, the impact of patient- or machine-related uncertainties on the dosimetric plan quality was not investigated. Therefore, a comprehensive robustness assessment was needed to conclusively compare DTRT and VMAT and assess the potential clinical impact of uncertainties.

Consequently, the objective of this study was twofold: first, to conduct a comprehensive robustness assessment of DTRT and VMAT plans for H&N cancer cases, including the uncertainties' impact on the dose to target and OARs and on NTCP. Second, to compare the robustness of DTRT to VMAT plans, to identify the potential strengths and limitations of each technique in the presence of uncertainties.

2. Materials and methods

2.1. Patient cohort and treatment plans

This robustness study was based on DTRT and VMAT plans previously created for a treatment planning comparison for 46 patients with loco-regionally-advanced oropharyngeal carcinoma (Supplementary Table A.1) [27], enrolled in the UPFRONT-NECK trial (NCT02918955) between 12.2016 and 4.2022. The patients provided informed consent. The robustness study extended the analysis of the planning study by assessing the impact of uncertainties on the plan quality to compare the robustness DTRT and VMAT plans.

The prescription was 50 Gy in 2 Gy fractions to the elective nodal volume and up to 70 Gy in the sequential boost phases. The doses were calculated using the Anisotropic Analytical Algorithm (AAA). The clinical target volume (CTV) and all OARs (including those above the plane defined by the VMAT beam directions (VMAT beam-plane)) were delineated following international guidelines [28,29] and were included in the robustness assessment. Planning target volumes (PTVs) expanded the CTV by a 3 mm isotropic margin with a minimum 3 mm distance from the body contour. This PTV design aligned with international recommendations [28], accounting for our setup and IGRT technique (mask and CBCT) and considered setup uncertainties observed at our hospital and in literature [13,14,16]. Further beam set-up and planning details are available in the supplementary material 2. Fig. 1 shows the dynamic trajectory/arc setup for one of the 46 cases planned with DTRT/VMAT in three sequential phases.

2.2. Robustness analysis

For the present study, robustness analysis including patient-setup and machine miscalibration uncertainties was performed with a previously developed robustness tool [12] interfaced with the Swiss Monte Carlo Plan (SMCP) and using Monte Carlo (MC) for dose calculation [30,31] on a high-performance computing cluster. The dose was recalculated with MC for the nominal scenario (no uncertainty, without renormalization) and for each uncertainty scenario described below. The statistical uncertainty was $<$ 1.1 % for voxels with dose values higher than 50 % of the maximum dose.

The considered patient-setup uncertainty scenarios included a random component, to simulate intrafraction motion and inter-fraction setup uncertainties and different systematic components to simulate systematic setup uncertainties.

The random uncertainties were sampled from a Gaussian distribution with σ of 2 mm in anterior-posterior (AP), superior-inferior (SI) and left–right (LR) direction and σ of 0.5° in pitch, yaw and roll [23,24]. For each case and plan, one uncertainty scenario including only random setup uncertainties was evaluated. Additionally, uncertainty scenarios combining the random setup uncertainties with each of the following systematic uncertainties were considered: six systematic translational setup uncertainties (±2 mm, ±3 mm, ±5 mm) in SI, AP or LR direction (6*3 uncertainty scenarios) and eight systematic rotational setup uncertainties (±0.5°, ±1.0°, ±2.0°, ±3.0°) in pitch, yaw and roll (8*3 uncertainty scenarios).

The systematic uncertainties were based on literature but also included worst case scenarios [13,14,32]. This resulted in 43 uncertainty scenarios for random and systematic setup uncertainties per case and plan.

Furthermore, uncertainties in mechanical machine components were investigated. DTRT extends state-of-the-art treatment techniques by the combination of dynamic gantry, table and collimator rotation, along with MLC movement during delivery. The combined dynamic movement of these machine components increases the plan and delivery complexity compared to VMAT and makes it difficult to predict the impact of an uncertainty in the mechanical accuracy of these machine components on the dose distribution. It was therefore necessary to investigate these uncertainties before introducing DTRT into the clinics. The machine-related uncertainty scenarios included no random component, as previous machine logfile analysis found minimal delivery uncertainties [9,20] with negligible impact on the dose distribution [12]. Miscalibrations were simulated by systematic uncertainties [21,33–35]. Four systematic uncertainties (±1.0°, ±2.0°) in gantry, table and collimator angle (4*3 uncertainty scenarios) and twelve systematic uncertainties (±0.2 mm, ±0.5 mm, ±1.0 mm, ±2.0 mm, ±3.0 mm, ±5.0 mm) in MLC position (12*1 uncertainty scenarios) were investigated.

MLC uncertainties were simulated by opening (positive)/closing (negative) all leaves at all controlpoints of the treatment plan. Already closed leaves remained unaffected by a negative uncertainty. This resulted in 24 uncertainty scenarios for machine uncertainties per case and plan.

Over all cases, dose distributions for 6164 uncertainty scenarios were

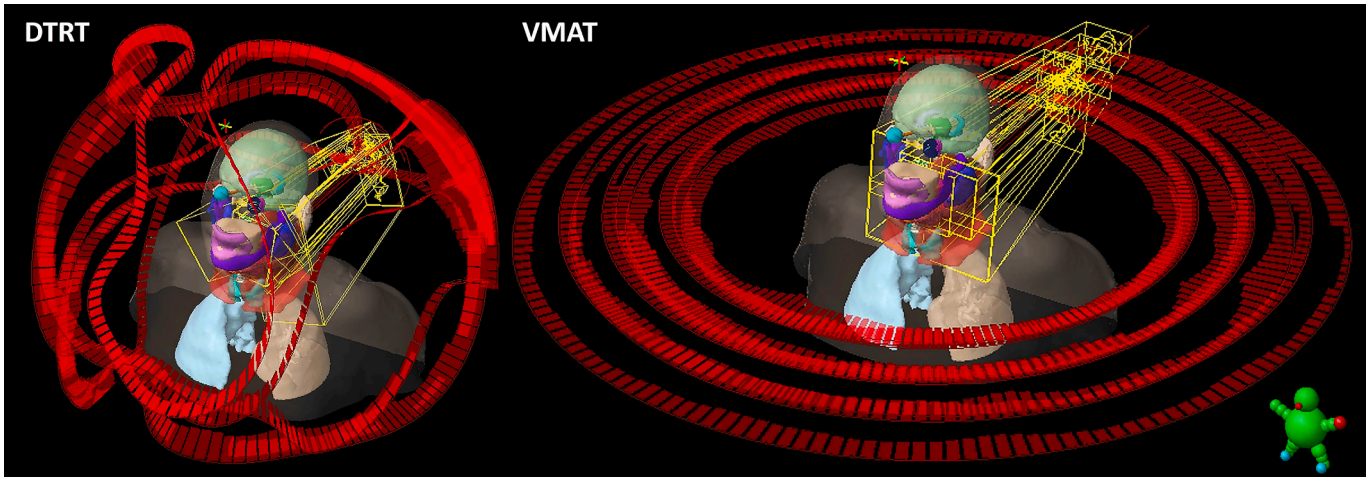

Fig. 1. Dynamic trajectories (left) and arcs (right) for a H&N cancer case, planned with three phases. The red bands indicated the dynamic trajectories of the DTRT plans and VMAT arcs. The PTVs are shown in red, the OARs in other colors.

calculated using approximately 140.000 CPU hours. The robustness of the DTRT and VMAT plans to the above-mentioned uncertainty scenarios was assessed and compared by quantifying the uncertainties' impact on the fulfillment of treatment planning-goals (supplementary table A.2) and the NTCP for xerostomia and dysphagia [36]. Additionally, a detailed robustness analysis of dose-volume endpoints for target and OARs was conducted.

Differences in DTRT and VMAT plan robustness were compared using Wilcoxon matched-pair signed rank test at 5 % significance level. Levene test with 5 % significance level was conducted to test for equal variances in endpoint differences. No correction for multiple testing was applied, exact p values were reported.

3. Results

3.1. Robustness of planning-goals

DTRT met more planning-goals for OARs in the VMAT beam-plane were in general better as compared to VMAT (Fig. 2 and Fig. A.1). Especially, when considering no or only random patient-setup uncertainties, DTRT plans fulfilled more planning-goals than VMAT plans. The difference was statistically significant for the oral cavity mean dose ($p = 0.05$): over all uncertainty scenarios and cases, the oral cavity mean-dose goal was respected for 2618 (DTRT) compared to 2352 (VMAT) uncertainty scenarios.

3.2. Robustness of NTCP

The DTRT plans had significantly lower NTCP for moderate-to-severe xerostomia and grade $\geq$ II dysphagia in both the nominal (0.5 and 2.1 percentage-points lower, respectively) and uncertainty scenarios, compared to VMAT (Fig. 3). Mean NTCP values for DTRT and VMAT plans were within 0.8 percentage-points of the nominal scenario values, except for uncertainty scenarios including MLC positions uncertainties, which deteriorated NTCP substantially more ($>$ 3.3 and $>$ 5.6 percentage-points for moderate-to-severe xerostomia and grade $\geq$ 2 dysphagia for DTRT and VMAT alike). The rainbow color-code indicates consistent NTCP order across cases, treatment technique and uncertainty scenarios. Similar trends were observed for severe xerostomia and dysphagia grade $\geq$ III (Fig. A.2).

3.3. Detailed robustness analysis

The MC dose recalculation led to an average [minimum, maximum] PTV underdosage of 1.9 Gy [-0.1, 5.4] for DTRT and 1.9 Gy [0.5, 5.6] for VMAT, compared to the AAA dose calculation of the nominal scenario ($D95\%_{PTV70}$, $p = 0.05$).

Degradation of $D98\%_{CTV70}$ due to random patient-setup uncertainties was not statistically significant ($p > 0.43$) for both DTRT and VMAT (Fig. 4). MLC miscalibration uncertainties resulted in the largest average differences, with an average 5 Gy increase of $D98\%_{CTV70}$ for a 1 mm opening for DTRT and VMAT. Statistically significant differences in robustness between DTRT and VMAT were observed for systematic uncertainties (e.g. a 3 mm uncertainty in superior-direction, $p < 0.01$).

OAR robustness to the investigated dose-volume endpoints was depended on the location of the OAR with respect to the VMAT beam plane (Fig. 5 and Fig. A.3). The differences in mean dose to OARs for the DTRT and VMAT plans in the VMAT beam-plane caused by random patient-setup uncertainties were within 0.8 Gy on the average. The difference between DTRT and VMAT was not statistically significant, except for the contralateral submandibular gland, $p < 0.01$ (Fig. 5 and Fig. A.3). For patient-setup uncertainties, the largest differences were observed in the SI direction: a 5 mm systematic uncertainty in inferior direction increases the ipsilateral parotid mean dose by 3.7 Gy [-5.2, 13.3] (DTRT) and 4.1 Gy [-5.7, 14.4] (VMAT, $p < 0.01$). The nominal dose to OARs above the VMAT beam-plane was close to zero for VMAT and significantly higher for DTRT: The mean dose to both eyes was on average 2.8 Gy ($p < 0.01$) higher and D0.03 cc to both optic nerves was on average 5.4 Gy ($p < 0.01$) higher. For all patient-setup uncertainty scenarios the dose difference to the nominal scenario for above-mentioned OARs remained below $<$ 0.9 Gy ($<$ 3.6 Gy) for VMAT (DTRT).

Gantry, table, and collimator angle uncertainties of $\pm$ 1° resulted in average differences of $<$ 0.7 Gy for all investigated OAR endpoints for both, DTRT and VMAT. MLC uncertainties resulted in substantially increased (opening) or decreased (closing of the leaves) dose.

For OARs in the VMAT beam-plane, the variance in robustness was not significantly different between DTRT and VMAT. For most OARs above the VMAT beam-plane, except for the brain, the dose difference to the nominal scenario varied for most uncertainty scenarios significantly ($p < 0.05$) between DTRT and VMAT.

Two example cases, case (A) and (B) with a CTV50 of 406 cm^3 and 59 cm^3, are analyzed in Fig. 6. For case (A), the DTRT plan met more planning-goals than VMAT for the investigated uncertainties. The opposite was true for case (B). The largest differences were observed for the oral cavity mean dose (case A, 2.9 Gy lower for DTRT) and hippocampus D40% (case B, 7.2 Gy lower for VMAT), indicated by white arrows.

For both cases, DTRT had lower NTCP values than VMAT. The largest differences were observed for moderate to severe dry mouth and grade $\geq$

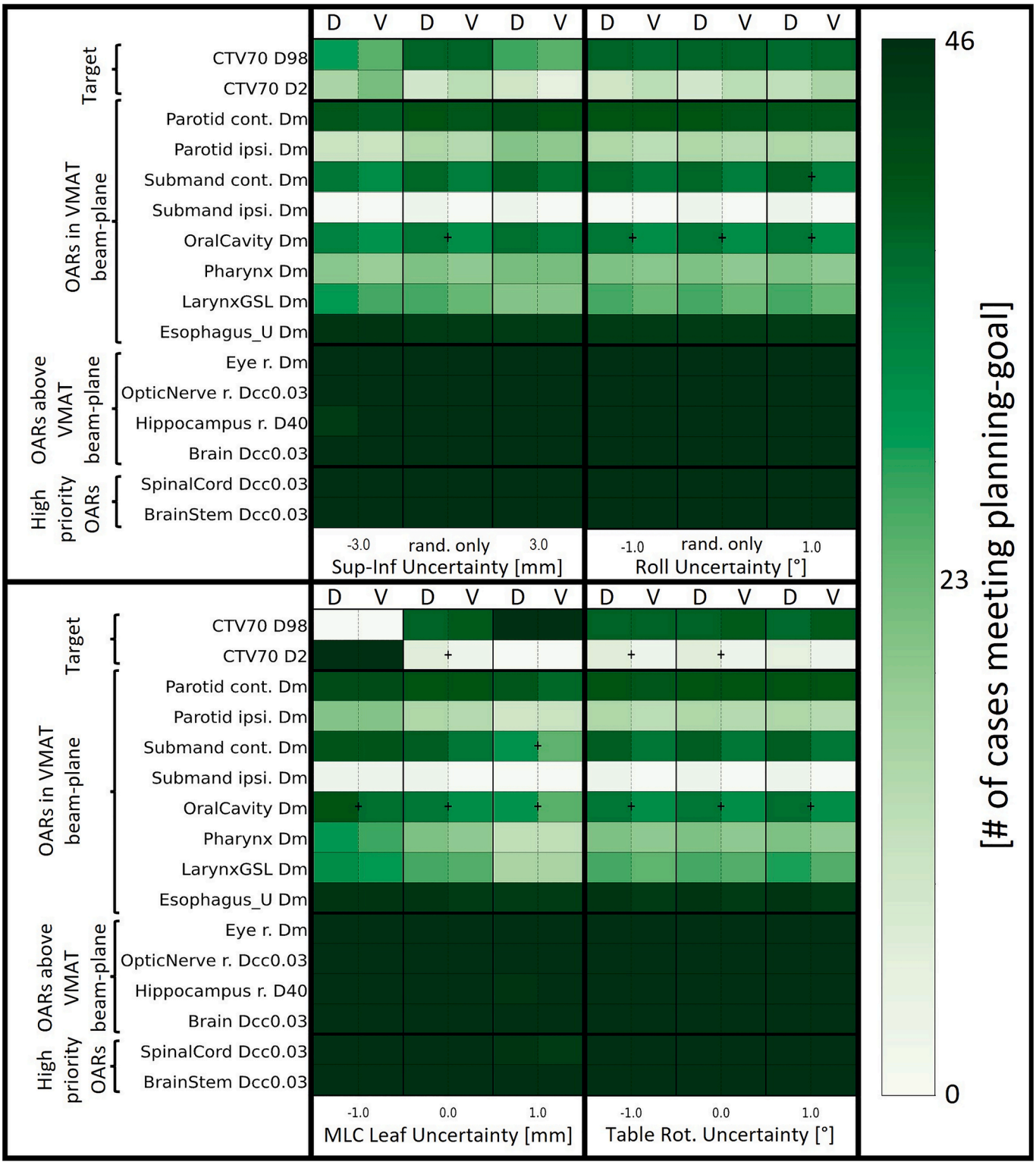

Fig. 2. Number of DTRT (left facet, D) and VMAT (right facet, V) plans fulfilling representative planning-goals for selected uncertainty scenarios related to superior-inferior and roll patient-setup (top) and MLC position and table rotation (bottom). Significant ($\alpha < 5$ %) differences are indicated with a "+" sign. (Dm, mean dose; D2 and D98, dose to 2 % or 98 % of the structure volume; Dcc0.03, near max dose with volume 0.03 cm^3).

II dysphagia, where the difference in NTCP was 1.7 and 3.5 percentage-points for case (A), and 3.4 and 0.7 percentage-points for case (B). The largest difference in NTCP robustness evaluated on all uncertainty scenarios was observed for grade $\geq$ II dysphagia and 1 mm MLC uncertainties, where the DTRT (VMAT) plans varied by 9.6 and 4.2 (9.3 and 3.7) percentage-points for case A and case B, respectively.

4. Discussion

The present robustness analysis was the first study to systematically analyze DTRT and VMAT plan robustness for a large cohort. Comparing their robustness enabled to assess if the dosimetric and NTCP benefits of DTRT persisted in the presence of uncertainties. The robustness analysis

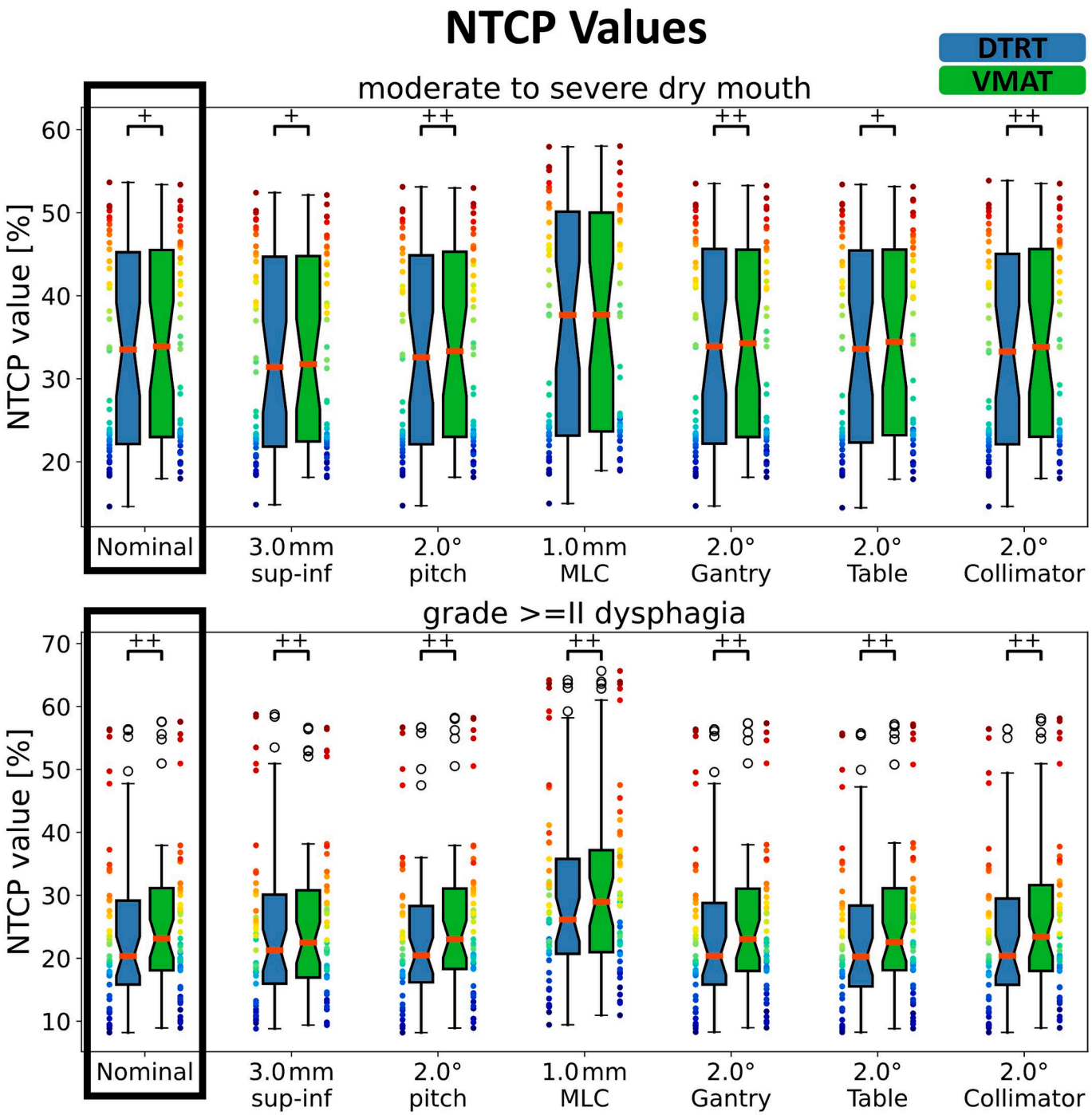

Fig. 3. NTCP values of the DTRT and VMAT plans for the nominal scenario and representative uncertainty scenarios. Significant differences between DTRT and VMAT are indicated by: $\alpha < 0.05$ "+" and $\alpha < 0.01$ "++". There is no significant difference in variance. Each of the rainbow colored dots corresponds to a datapoint of a single case. The color-code identifies the plans for the same case across the treatment techniques and uncertainty scenarios.

included three major novel aspects: *First*, clinical relevance was investigated by assessing the impact of uncertainties on planning-goals and NTCP for xerostomia and dysphagia. *Second,* next to target also OAR robustness was evaluated. *Third,* alongside patient-setup, machine-related uncertainties were investigated. This study substantially added to our treatment plan comparison [27] by extending the evaluation from the nominal to realistic uncertainty scenarios, recognizing robustness as an integral part of plan quality [37].

For 46H&N cases, DTRT and VMAT planning-goal robustness showed no significant difference, except for oral cavity mean dose (favoring DTRT) and hippocampus D40% (favoring VMAT). Generally, DTRT plans respected more planning-goals compared to VMAT across all uncertainty scenarios except for the CTV70 near max dose, brachial plexus and hippocampus. Planning-goal robustness further depended on the structures location with respect to the VMAT beam-plane: those above received only scattered dose with VMAT but could be in the primary beam path for DTRT. Thus, uncertainties were likely to induce greater absolute changes in dose in these regions for DTRT than for VMAT. Nonetheless, doses to optical and auditory structures remained well below planning-goals, even with uncertainties. This was not the case for the hippocampus; hence the use of planning organ at risk volumes (PRVs) for DTRT is recommended. Structures in the VMAT beam-

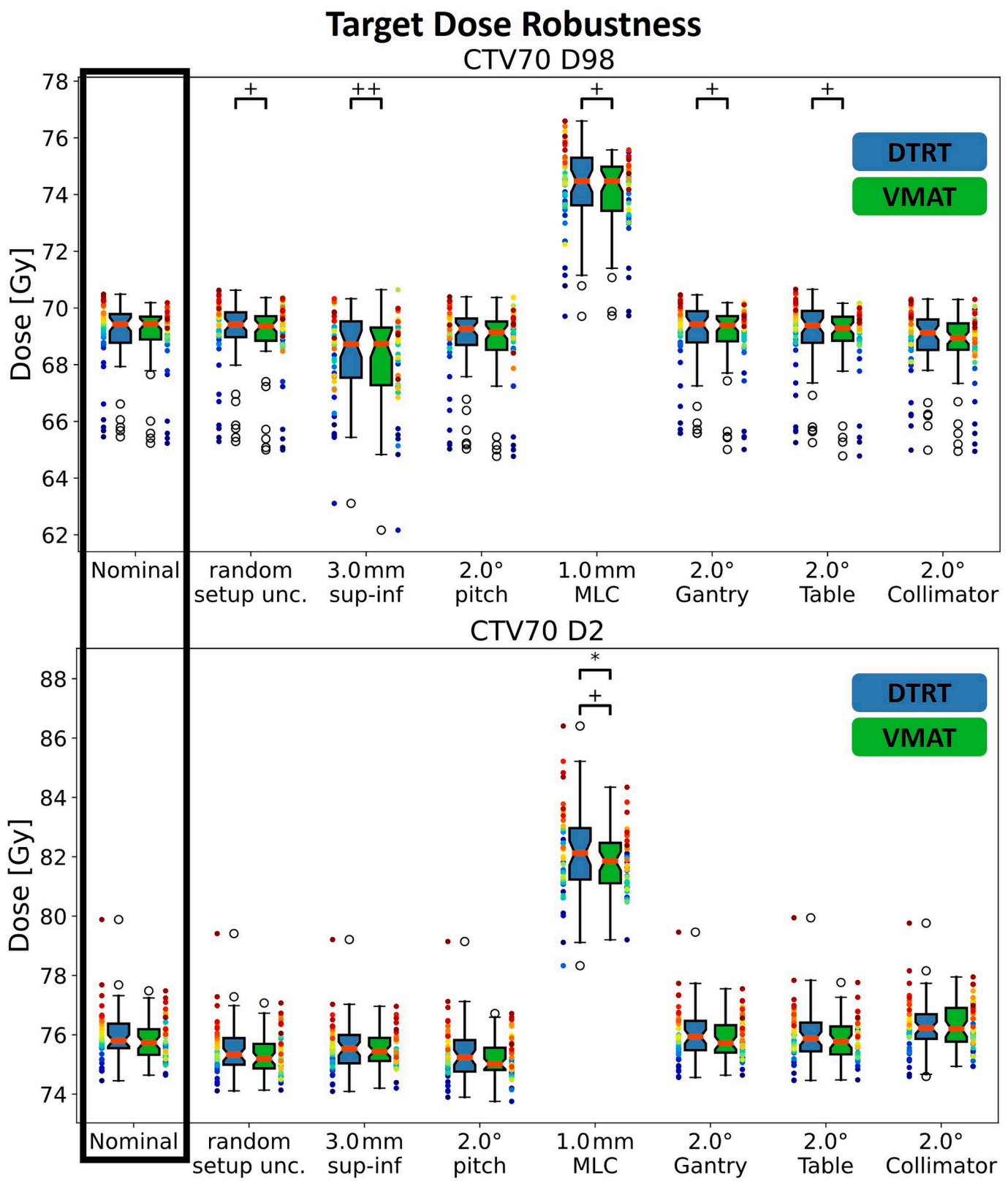

Fig. 4. Impact of representative uncertainty scenarios on CTV70 endpoints. Significant ($\alpha < 5$ %) differences in robustness and in the variance between DTRT and VMAT plans are indicated by "+" and "*" respectively. "++" indicates significance with$\alpha < 1$ %. Scenarios 3 mm sup-inf and 2.0° pitch also include random uncertainties. Each of the rainbow colored dots corresponds to a datapoint of a single case. The color-code identifies the plans for the same case across the treatment techniques and uncertainty scenarios.

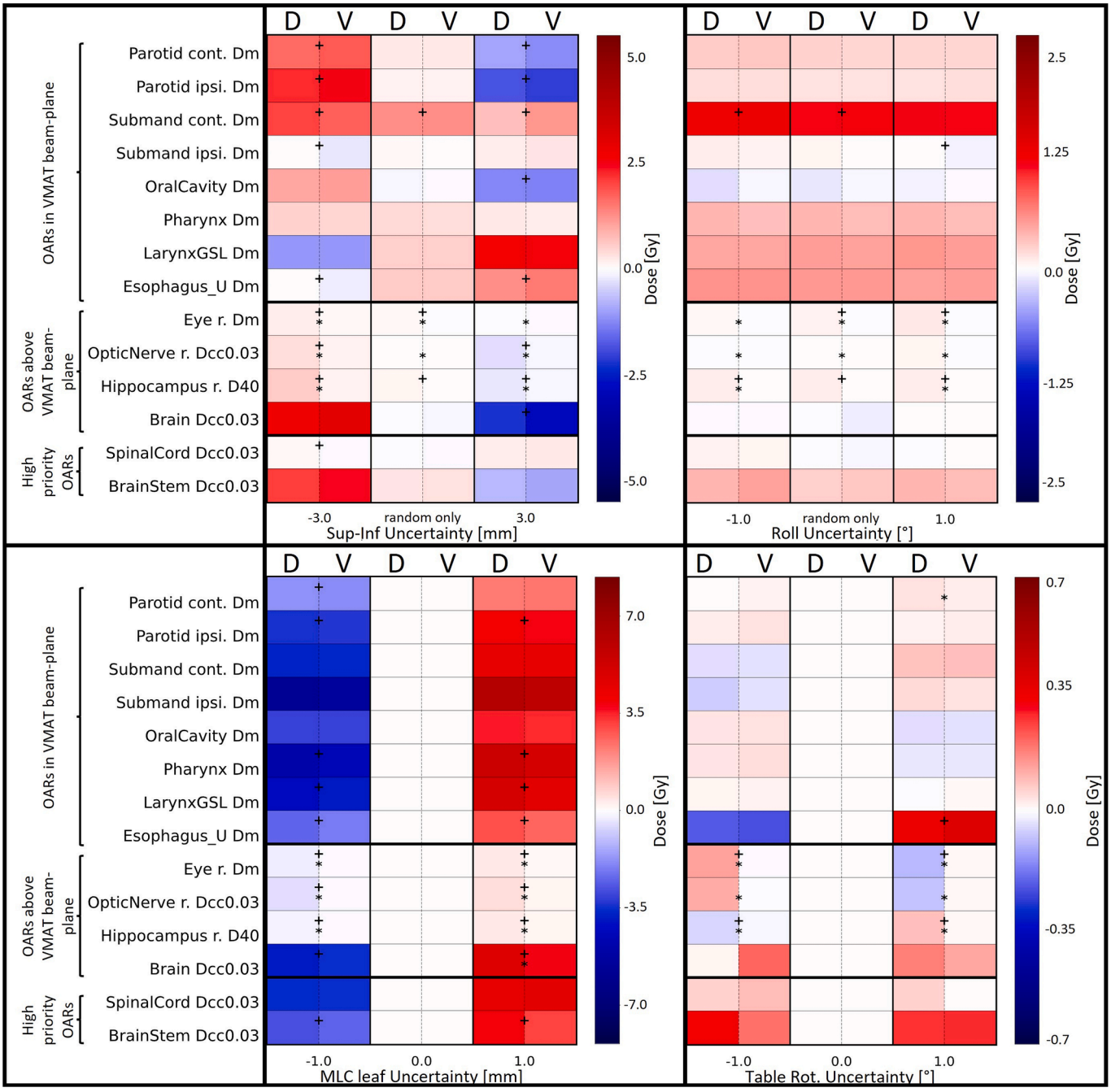

Fig. 5. Average difference with respect to the nominal scenario for DTRT (left facet, D) and VMAT (right facet, V) for patient-setup and machine position uncertainties. Depending on the uncertainty, different ranges for the differences are given, with the largest one for MLC uncertainties and the smallest one for table rotation uncertainties. Significant ($\alpha < 5$ %) differences in robustness of the dose-volume endpoints between DTRT and VMAT are indicated by a "+" sign; significant ($\alpha < 5$ %) differences in the variance of the DTRT and VMAT robustness are indicated by a "*". OARs in the VMAT beam-plane are shown in the upper part, followed by representative OARs above the VMAT beam-plane and the brain stem and spinal cord. (Dm, mean dose; D2 and D98, dose to 2 % or 98 % of the structure volume; Dcc0.03, near max dose with volume 0.03 cm^3).

plane (parotids, submandibular glands and oral cavity) benefited from improved sparing with DTRT, facilitating planning-goal fulfillment. It should be noted that cases meeting one planning-goal could differ from those meeting another. Furthermore, the OAR planning-goals vary in importance and should only serve as an initial evaluation point, while focusing on the "as low as reasonably achievable" (ALARA) principle [38].

While NTCP robustness has been mainly studied in the context of proton therapy [39,40], the present study confirmed and complemented these findings with patient-setup and machine-related uncertainties for state-of-the-art VMAT and novel DTRT photon-based treatments. Our results were in line with previous findings [39]: patient- and machine-related uncertainties (except MLC uncertainties) had little influence on the average NTCP (within 0.8 percentage-points on average) over all patients. Importantly, DTRT had on average, lower NTCP than VMAT for all considered uncertainty scenarios, except for MLC position uncertainties, where predicted xerostomia for DTRT was slightly higher than for VMAT. However, this difference was not statistically significant.

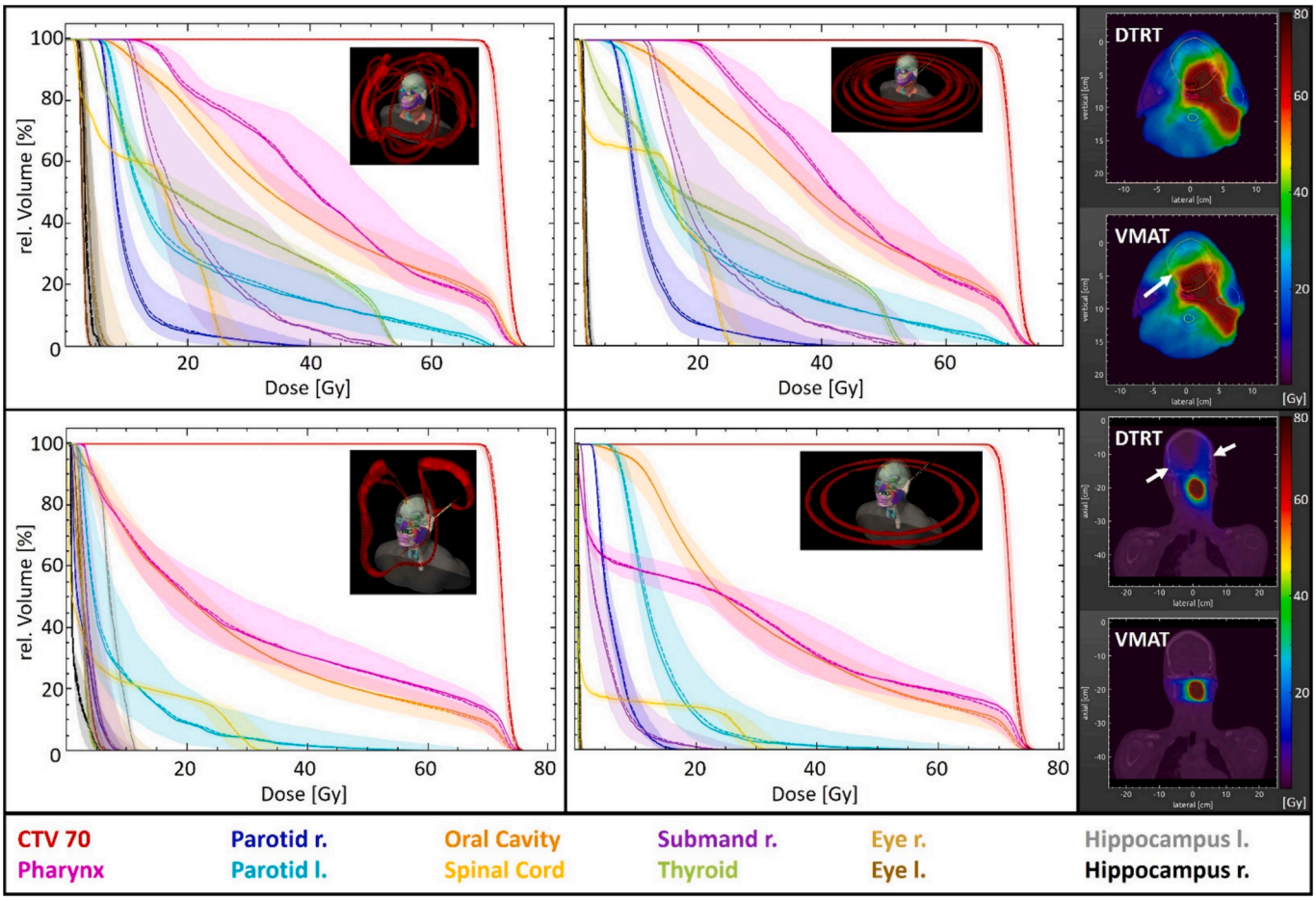

Fig. 6. DVH and nominal dose distribution comparison of the DTRT and VMAT plan for two example cases (A) and (B). Additionally, the dynamic trajectory/arc setup is shown by the red bands around the patient. The solid DVH lines represents the nominal scenario. The dashed line represents the uncertainty scenario with only random setup uncertainties, and the DVH bands include all random plus systematic patient-setup uncertainties. The arrows indicate the location of the greatest differences in the dose distribution between the DTRT and VMAT plan.

In the detailed investigation, we found that CTV coverage was lower when calculated with MC than with AAA. Target coverage robustness was similar between DTRT and VMAT, indicating that the PTV design was appropriate for DTRT. DTRT plans had steeper dose gradients in the VMAT beam-plane at the cost of increased dose to OARs above it. Furthermore, a directional trend, especially for non-central structures, was observed. For instance, contralateral parotid mean dose was more robust for DTRT with SI setup uncertainties but less for uncertainties in AP direction, partially due to VMAT's steeper dose gradients in the SI direction. The individual robustness analysis of the two cases highlighted the robustness tool's [12] applicability to evaluate plan robustness prior to delivery. Moreover, in the clinic, it could serve as an independent dose calculation for the generated plans. In such a case-by-case usage, also the combination of uncertainties could be evaluated, similar to previous studies [12,19]. In clinical practice, patient-setup and machine uncertainties can occur simultaneously. A comprehensive robustness assessment would therefore need to consider both uncertainty types in combination.

In the uncertainty scenario selection, we included random and systematic patient-setup uncertainties observed in clinical practice, as well as worst-case scenarios. The magnitudes of the patient-setup uncertainties were based on literature [13–16,23,24,32]. Machine uncertainties (e.g., MLC position uncertainty [21,35]) were selected according to tolerance limits [41,42], to investigate the effect of realistic miscalibrations. For investigative purposes, additional uncertainty scenarios beyond those limits that are commonly found in literature were assessed but should be considered extreme scenarios [21,33–35]. In a clinical delivery setting, routine QA checks, as well as patient-specific QA are performed [43], aiming to detect machine miscalibrations outside the tolerance limits. Regarding dosimetric impact, we observed that rotational patient-setup uncertainties ($\leq 3°$) had less impact than uncertainties in AP, SI or LR (≤ 5 mm) on the investigated endpoints. Similarly, uncertainties in the rotational machine components of up to $\pm 2°$ had less impact, than the investigated uncertainties in the MLC positions.

Apart from standard margins for the target, brainstem and spinal cord, no specific robustness measures were taken in this study, which could be seen as a limitation. While proton treatments are usually robustly optimized [44,45], robust optimization for photon-based treatments is not state-of-the-art yet. In future, patient- and machine-related uncertainties could be considered during robust optimization. Additionally, because DTRT paths were based on individual patient anatomy, robustness could be considered at the path-finding step of the treatment planning process.

In conclusion, this study thoroughly analyzed the robustness of DTRT and VMAT plans for 46 H&N cancer cases and a large range of uncertainty scenarios. Generally, no significant difference in planning-goal robustness between DTRT and VMAT was observed for the investigated uncertainties. DTRT had significantly lower NTCP for xerostomia and dysphagia than VMAT and this advantage generally remained for the investigated uncertainties.

CRediT authorship contribution statement

Hannes A. Loebner: Conceptualization, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. **Jenny Bertholet:** Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. **Paul-Henry Mackeprang:** Methodology, Writing – review & editing. **Werner Volken:** Methodology, Writing – review & editing. **Olgun Elicin:** Methodology, Writing – review & editing. **Silvan Mueller:** Methodology, Writing – review & editing. **Gian Guyer:** Methodology, Writing – review & editing. **Daniel M. Aebersold:** Methodology, Writing – review & editing. **Marco F.M. Stampanoni:** Supervision, Writing – review & editing. **Michael K. Fix:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing. **Peter Manser:** Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of competing interest

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.

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Data Statement

Research data are not available at this time.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100586.

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