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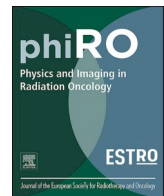
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Original Research Article

Estimation of accumulated dose to organs at risk in head and neck cancer patients treated with scheduled replanning and dose painting in the ARTFORCE trial



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ABSTRACT

Background and purpose: This study investigated whether scheduled adaptive radiotherapy (ART) improved delivered dose to organs at risk (OAR) in patients with locally advanced head and neck cancer treated with dose painting (DP).

Materials and methods: Delivered doses were estimated for 81 patients who were prospectively treated with DP + ART using deformable image registration between CBCT and the planning CT's. Three simulations were conducted, evaluating (1) a scenario without replanning (Sim_{noART}), (2) a scenario with ART at fraction 12 (Sim_{ART}), and (3) the clinical practice with ad hoc replanning (Sim_{delivered}). It was further evaluated whether selecting patients for ART using accumulated dose in the first 10 fractions (Df10) to the parotid glands and larynx would improve ART efficacy.

Results: In Sim_{noART}, 41% of patients had delivered dose deviations ≥ 3 Gy compared to the planned dose in any OAR, primarily in the parotid glands and larynx. No significant differences were seen between Sim_{noART}, Sim_{ART} and Sim_{delivered} ($P \geq 0.10$). Df10 predicted relevant changes upon completing treatment with AUC ≥ 0.95 . By selecting patients for ART using Df10, delivered dose significantly improved for the larynx ($P \leq 0.01$).

Conclusions: Although relevant dose differences between planned and delivered doses were seen in almost half of the patients without ART, minimal improvements in delivered doses were seen introducing ART. Nonetheless, Df10 was prognostic for relevant changes upon completing treatment and selecting patients for ART significantly

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improved larynx dose. Incorporating accumulated dose into patient selection for ART could help avoid unforeseen increases in delivered dose.

1. Introduction

Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) are the standard of care in radiotherapy as they allow for dose conformity while sparing surrounding organs at risk (OAR). The high degree of modulation achievable with IMRT or VMAT plans has offered opportunities for redistributing dose within the tumor volume depending on tumor aggressiveness while maintaining OAR dose constraints, a strategy called dose painting (DP), with the aim of improving disease control [1].

A challenge in highly conformal radiotherapy is that its accuracy can be compromised by anatomical variations and changes. During a 6–7 week treatment course for head and neck squamous cell carcinoma (HNSCC), significant weight loss, tumor volume changes, edema and inflammation may occur [2–5]. These changes alter tumor and organs at risk (OAR) geometry causing dose levels to deviate from the planned dose. Heukelom et al. reported that in conventional radiotherapy, without altering treatment plans, clinically relevant dose increases were observed in 17% of patients, leading to an increased risk of toxicities [6]. To ensure that the delivered dose will closely resemble the intended planned dose, ad hoc replanning for clear anatomical changes has been reported in a wide range (9–67%) of patients across cohort studies, reflecting differences in institutional practices [7–14]. Still, there are currently no standardized criteria for initiating ad hoc replanning, and detected anatomical changes correlate poorly with clinically relevant dose changes to OAR [6]. Also, the unanticipated nature results in disruptions of the clinical workflow which may burden or even rush clinical staff, possibly hampering treatment quality or safety.

Small prospective studies suggest that scheduling adaptive radiotherapy (ART) improves the management of anatomical changes and limit unforeseen OAR dose increases [15–21]. In DP strategies, escalating dose in tumor subvolumes may increase the risk of overdosing OAR when patient geometry changes. The ARTFORCE trial is a prospective multicenter study investigating 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)-guided DP, with locoregional control as a primary endpoint [22]. In this trial, scheduled ART was implemented based on the hypothesis that scheduling ART in DP will result in reduced exposure of OAR and is a necessary step to ensure acceptable dose to OAR during dose escalation. While DP and scheduled ART have both been explored independently, their combined impact on accumulated OAR dose has not been evaluated. The aim of this in silico study was to assess whether scheduled ART improved accumulated OAR dose in HNSCC patients treated with DP + ART using prospective multicenter data collected within the ARTFORCE trial. While not fully generalizable to standard IMRT/VMAT, this study offers insight into the impact of scheduled ART on delivered dose, and could be used for future ART and DP implementations.

2. Methods

2.1. Patient selection and data collection

This study is a secondary analysis of prospectively collected data from patients enrolled in the multicenter, randomized controlled ARTFORCE trial (NCT01504815) trial between 2012 and 2019 [22]. In summary, patients with stage III–IV, T3–4, N0–3, M0 (6th edition AJCC) HNSCC were randomized (1:1) in nine participating institutes to receive conventional radiotherapy or DP combined with scheduled ART. In DP, an FDG-PET-guided dose range between 64–84 Gy was delivered to planning target volume of the primary tumor (PTVp) in contrast to the 70 Gy homogeneous dose in conventional radiotherapy (Supplementary

Fig. S1).

In the DP arm, scheduled ART was performed after the second week of treatment in all patients independently from observed changes. In this ART strategy, original PTVs were only adjusted for obvious anatomical changes within clear borders, such as bone and air. Reduction of planning target volumes (PTV), due to weight loss and nodal mass shrinkage, was anticipated to result in decreased doses to OAR. Additional ad hoc replanning was allowed based on institutional practice.

For this in silico study, patients from the DP + ART arm were included when they completed all 35 fractions and underwent scheduled replanning within the third or fourth week of treatment (fraction 11–20). As scheduled ART is not standard practice, it was not performed in the control arm and its effects could therefore not be evaluated for conventional radiotherapy. Patients with missing planning data or missing (CB)CTs for two or more weeks were excluded from this analysis. Dose distributions for fractions with missing CBCTs were imputed by taking a weekly weighted mean of the two preceding and two succeeding distributions, with double weight assigned to distribution immediately before and after the missing CBCT.

2.2. Dose accumulation and simulations

Planned dose was derived from the baseline treatment plan (Plan_0), scheduled ART in the third week of treatment (Plan_{ART}) and ad hoc replanning ($\text{Plan}_{\text{ad hoc}}$) using the corresponding planning CTs. Three dose accumulation simulations were conducted to evaluate the impact of Plan_{ART} and $\text{Plan}_{\text{ad hoc}}$. In the first simulation, accumulated dose was simulated as if Plan_0 was used for the complete treatment course without interventions ($\text{Sim}_{\text{noART}}$). In the second simulation, to minimize the impact of the observed variability in scheduled replanning timing, Plan_0 doses were accumulated until the 12th fraction, after which the Plan_{ART} dose was accumulated (Sim_{ART}). Finally, the true scenario ($\text{Sim}_{\text{delivered}}$) was accumulated by incorporating the actual fraction at which Plan_{ART} was performed, along with any additional $\text{Plan}_{\text{ad hoc}}$.

Couch correction shifts of replanning and daily (CB)CTs to Plan_0 CT were performed by rigid registration of bony anatomy in a region of interest using a clip box surrounding the tumor, lymph node(s) and elective fields. Deformation vector fields between Plan_0 CT and replanning or daily (CB)CTs were calculated with ADMIRE (research version 3.48.4, Elekta AB). These deformation fields were used to map Plan_0 , Plan_{ART} or $\text{Plan}_{\text{ad hoc}}$ physical dose to the Plan_0 CT for accumulation. This dose accumulation approach assumes shift dose invariance, which has been demonstrated to resemble recalculated dose [23,24]. However, it may introduce errors at the patient skin surface. Therefore, doses were expanded to fit the patients' anatomy.

2.3. Statistical analyses

The impact of ART on OAR overdosing was evaluated by comparing the three simulations ($\text{Sim}_{\text{noART}}$, Sim_{ART} and $\text{Sim}_{\text{delivered}}$) using the Friedman test. Dose differences between simulations were assessed using the maximum dose ($D_{1\%}$) for the mandible and mean dose (D_{mean}) for the other OARs. Clinically relevant dose increases were summarized using descriptive statistics and defined as $D_{1\%}/D_{\text{mean}} \geq 3$ Gy over the full treatment course (35 fractions) or ≥ 2 Gy after replanning (23 fractions). These model-independent thresholds, previously shown to correlate with toxicity and implemented in other studies, were used for clarity and to limit bias in this multicenter cohort [25,26]. Wilcoxon matched-pairs signed-rank test was used to evaluate differences in nodal (PTVn), tumor (PTVp) PTV and elective fields (PTVelec) between the Plan_0 and Plan_{ART} to determine whether ART resulted in significant PTV adjustments.

Exploratory analyses examined strategies for selecting patients for scheduled ART focussing on the three most commonly affected OAR. Receiver operating characteristic (ROC) curves were generated to evaluate whether accumulated dose could predict clinically relevant dose increases. Prognostic value was quantified using the area under the ROC curve (AUC) and 95% confidence intervals were obtained by bootstrapping (100 samples). For each OAR, ART benefit was evaluated in subgroups defined by accumulated doses at fraction 10 with ART simulated at fraction 12 to reflect time required for ART implementation and quality assurance. Selection thresholds were derived using the Youden index J and dose differences between $\text{Sim}_{\text{noART}}$ and Sim_{ART} assessed with the Wilcoxon signed-rank test. Analyses were two-sided with p-values < 0.05 considered significant and performed in R (v4.4.1).

3. Results

Of all 109 patients allocated to the DP + ART arm, 81 patients were included in this study. Sixteen patients were excluded due to incomplete imaging data, scheduled ART was not performed in ten patients and two patients prematurely ended treatment. Baseline characteristics were not significantly different between patients who were in- or excluded from this study (Supplementary Table S1).

Evaluation of $\text{Sim}_{\text{noART}}$ showed that 41% of patients had one or more OAR with ≥ 3 Gy accumulated dose increase. The most frequently affected OAR were the ipsi- and contralateral parotids (23 and 14%, respectively) and larynx (9%, Supplementary Fig. S2). These dose increases were observed across the full dose range, including around established dose constraints (Supplementary Fig. S3). In Sim_{ART} , the dose to OAR improved in 9% of patients compared to $\text{Sim}_{\text{noART}}$. However, this represented a minority (approximately 1/5th) of patients with relevant dose changes in $\text{Sim}_{\text{noART}}$. Also, 17% of patients had increased OAR dose in the Sim_{ART} when comparing to $\text{Sim}_{\text{noART}}$. These patients are depicted in Field A of Fig. 1. An additional $\text{Plan}_{\text{adhoc}}$ was made in 20% of patients. Within those patients, $\text{Sim}_{\text{delivered}}$ led to decreased dose to the

OAR in 25% of patients and in 10% of patients increased dose was observed when comparing $\text{Sim}_{\text{delivered}}$ to Sim_{ART} . When comparing $\text{Sim}_{\text{noART}}$ to Sim_{ART} and $\text{Sim}_{\text{delivered}}$, no significant differences were observed ($P \geq 0.10$, Table 1).

In Plan_{ART} , the PTVp (Fig. 2), PTVn and PTVelet (Supplementary Fig. S4), were adapted for regression in 56%, 74%, and 64% of patients, respectively. However, minimal PTV changes were observed between Plan_0 and Plan_{ART} as only 15% and 14% of patients had more than 10 cm^3 volume reduction of their PTVp (median -2.7 cm^3 , min-max -61.3 – 24.1 cm^3) and PTVn volumes (-1.1 cm^3 – -23.2 – 59.1 cm^3), respectively. Larger changes were seen for elective fields, with 28% of patients having more than 20 cm^3 PTVelec decrease (-5.5 cm^3 – -139.3 – 79.6 cm^3). In 5% and 6% of patients PTVn and PTVp volumes, respectively, increased beyond 10 cm^3 in Plan_{ART} . 10% of patients had more than 20 cm^3 increase of their PTVelec.

Fig. 3 shows that the predictive performance of accumulated dose increased for both Plan_0 as Plan_{ART} as more fractions were delivered, but was already in the first week of treatment. At fraction 10, the AUC for the larynx, ipsi- and contralateral parotids were 0.988, 0.960 and 0.953, respectively (Supplementary Fig. S6). By selecting patients based on the accumulated dose to the parotid glands or larynx at fraction 10 for scheduled ART, only doses to the larynx significantly improved ($P \leq 0.01$) in 6% of patients with a median of -1.6 Gy (min-max -13.6 – 0.1). Selecting patients for scheduled ART did not significantly reduce dose to the ipsi- (-0.7 Gy (-2.5 – 4.6), $P = 0.22$) or contralateral parotid (-0.8 Gy (-5.9 – 2.9), $P = 0.09$).

4. Discussion

In this in silico study we estimated delivered doses to OAR to evaluate the clinical impact of scheduled ART on delivered dose in DP. Although significant increases in delivered dose were observed for almost half of the patients, a minority (9%) of patients had delivered dose improvements with ART. Using accumulated dose to select patients

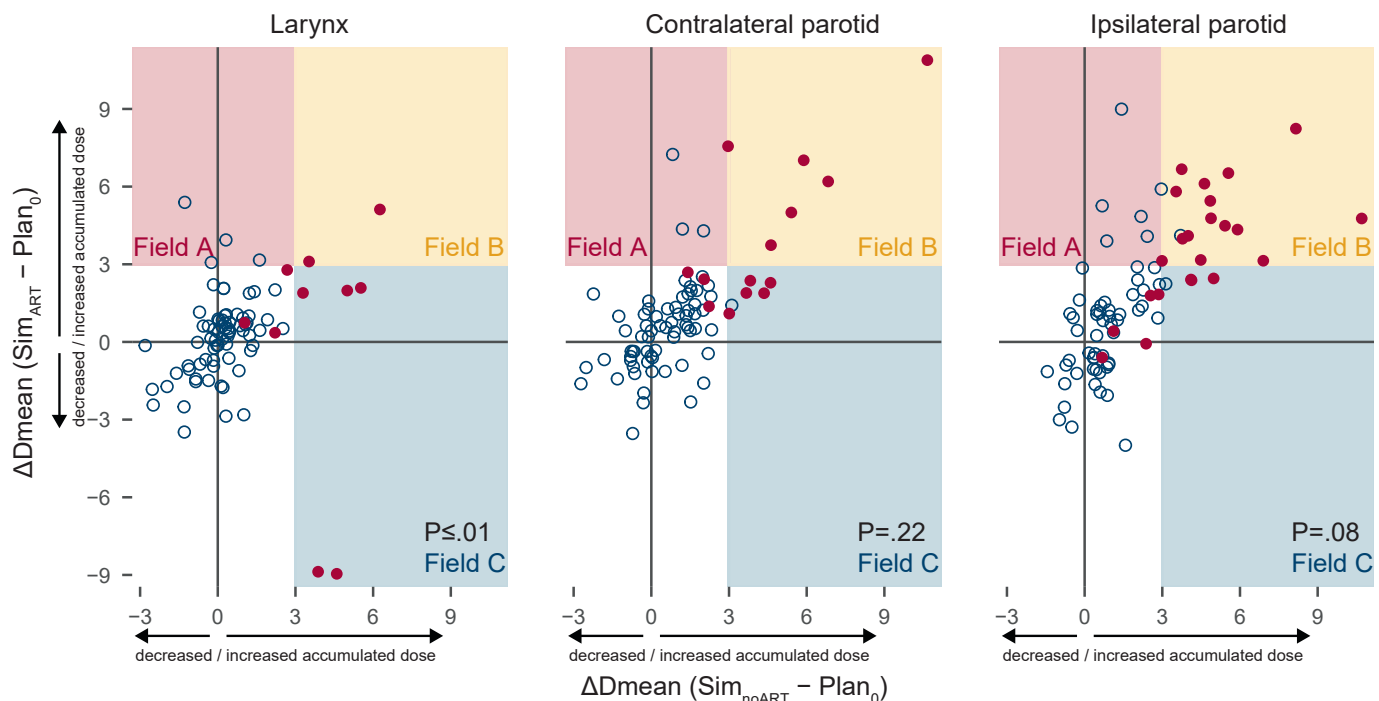


Fig. 1. Differences between planned dose (Plan_0) and accumulated dose simulations without ($\text{Sim}_{\text{noART}}$, x-axis) or with (Sim_{ART} , y-axis) replanning. Minimal differences ($<3 \text{ Gy}$) were observed in both simulations for the majority of patients (o). While some patients with relevant increases ($\geq 3 \text{ Gy}$) in $\text{Sim}_{\text{noART}}$ had improved doses to the OAR (Field C) with Sim_{ART} , others had increased doses in Sim_{ART} (Field A). Lastly, patients with increased accumulated dose despite replanning are plotted in Field B. P-values (Wilcoxon match pair tests) represent the significance level of OAR dose decrease after selecting patients for scheduled replanning (●) based on the accumulated dose to that OAR at 10 fractions.

Table 1

Differences in $D_{1\%}$ for mandible and D_{mean} for all other organs at risk between the baseline treatment plan (Plan_0) and the accumulated dose of the three simulations: (1) without any replanning ($\text{Sim}_{\text{noART}}$), (2) scheduled replanning at the 12th fraction (Sim_{ART}), and (3) scheduled and ad hoc replanning as the patient was treated ($\text{Sim}_{\text{delivered}}$).

Organ at risk	Plan_0 (Gy)	Dose difference (Gy, $\text{Sim}_{\text{noART}} - \text{Plan}_0$) Median (min–max)	Dose difference (Gy, $\text{Sim}_{\text{ART}} - \text{Plan}_0$) Median (min–max)	Dose difference (Gy, $\text{Sim}_{\text{delivered}} - \text{Plan}_0$) Median (min–max)	P-value
Contralateral parotid (D_{mean})	23.5 (9.4–47.4)	1.1 (–2.7–10.7)	1.0 (–3.5–10.9)	0.7 (–3.3–10.9)	0.64
Ipsilateral parotid (D_{mean})	31.4 (13.1–67.7)	1.1 (–1.4–10.7)	1.2 (–4.0–9.0)	1.2 (–3.8–8.3)	0.10
Ipsilateral submandibular gland (D_{mean})	67.9 (26.1–75.9)	0.4 (–4.3–3.6)	0.6 (–4.0–4.0)	0.6 (–4.1–4.0)	0.11
Contralateral submandibular gland (D_{mean})	54.8 (23.5–70.1)	0.3 (–4.6–3.4)	0.5 (–5.7–7.1)	0.4 (–5.1–6.6)	0.63
Oral cavity (D_{mean})	47.7 (5.1–69.8)	0.3 (–3.3–3.3)	0.5 (–3.5–3.5)	0.6 (–3.9–3.3)	0.99
Larynx (D_{mean})	48.9 (29.4–71.4)	0.3 (–2.8–6.3)	0.4 (–9.0–5.4)	0.4 (–9.2–5.1)	0.54
Base of tongue (D_{mean})	65.6 (27.8–77.2)	0.2 (–3.3–3.9)	0.2 (–4.3–8.9)	0.2 (–3.6–8.2)	0.85
Mandible (D_1)	69.7 (40.3–83.2)	–0.2 (–3.1–2.2)	–0.3 (–15.4–2.4)	–0.2 (–13.7–2.4)	0.70
Constrictor muscle (D_{mean})	55.8 (38.7–75.1)	0.0 (–2.6–2.8)	0.1 (–2.8–6.9)	0.1 (–2.6–6.5)	0.92

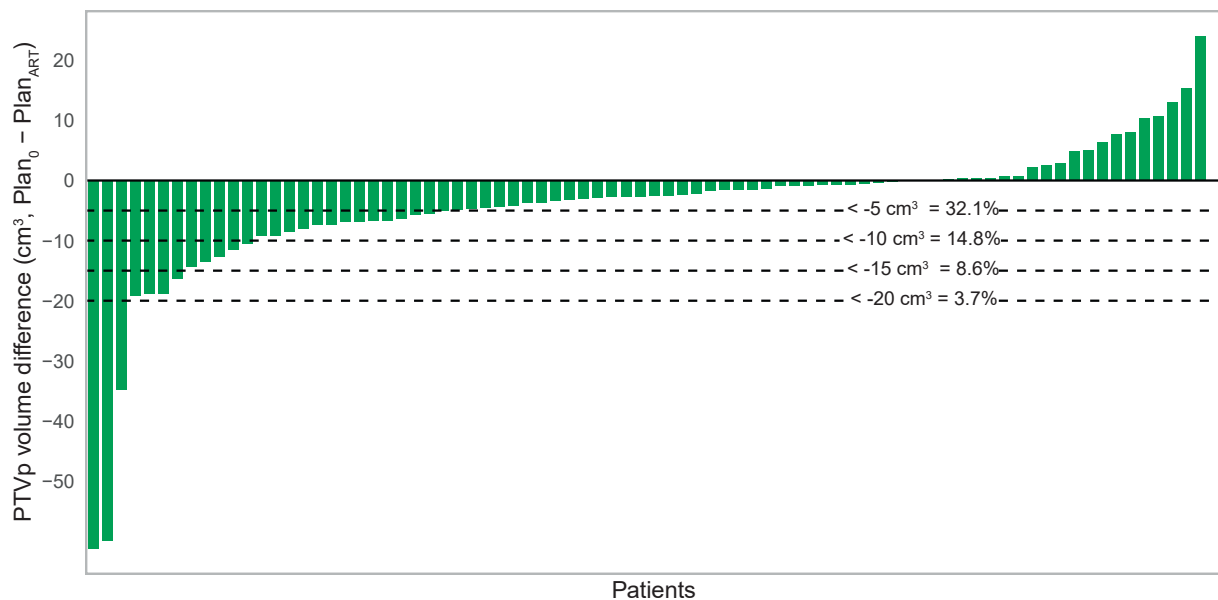


Fig. 2. Volume changes between baseline (Plan_0) and replanning (Plan_{ART}) planning target volumes of the primary tumor (PTVp). Values below zero indicate a volume reduction in Plan_{ART} compared to Plan_0 . Cut-off points are highlighted with dotted lines, indicating the portion of patients having greater volume reductions than the highlighted value.

for ART appeared highly prognostic for all organs at risk, but selective replanning based on accumulated dose only significantly improved the delivered dose to the larynx. These findings suggest that although relevant unforeseen increases in delivered dose can be detected early in treatment, applying scheduled ART to all patients without selection did not prevent unforeseen delivered dose increases to OAR.

The parotid glands are particularly prone to increased delivered dose due to parotid shrinkage and apparent migration [27], which may increase risk for xerostomia and affect quality of life [28]. Multiple studies with overall small cohort sizes (≤ 36 patients) have prospectively investigated the impact of ART on delivered dose and reported a mean 0.6–15.9 Gy reduction to the parotid glands with ART [15–20,29–32]. Castelli et al. observed a 3.6 Gy (0–12.2) mean dose reduction to the parotid glands in 15 patients when weekly ART was performed, which would have corresponded to a 11% xerostomia risk reduction [19]. In contrast, we did not observe a significant improvement in parotid dose with ART, possibly due to the multi-center design and our use of accumulated dose incorporating daily anatomical changes throughout treatment rather than solely comparing treatment plans. In the ARTIX trial, Castelli et al. randomized 132 patients to either weekly ART or no ART with the aim of detecting a 25% improvement in xerostomia outcomes [33]. Despite the initial promising delivered dose improvements, minor (7%) improvements were seen in the parotid gland excretory

function without a significant reduction in xerostomia. As the dosimetric data from this trial have not yet been published, it remains uncertain which dose changes lead to clinically meaningful outcomes.

The limited OAR dose improvement with ART may reflect minimal anatomical changes as ART was limited to clear target volume regression, resulting in small adjustments in most patients. Also, the potential impact of ART might be (partly) masked by planning variation caused by balancing dose between OAR on Pareto fronts and the absence of dosimetric guidelines for replanning. Castelli et al [19] investigated weekly replanning with the primary focus of reducing dose to the parotid glands. No such instructions for planning were given in our trial other than meeting the original constraints, meaning that significant variation could still occur [34–36]. Future studies on ART should include clear prioritization strategies and integrate previous plans to ensure that potential delivered dose improvements are not lost due to planning variation. Automated replanning might be another instrument to minimize planning variation [37]. It is also worth noting that although ART itself did not significantly reduce delivered dose, it might facilitate margin reduction that could lead to substantially lower OAR dose. This was demonstrated by Van Kranen et al [38], who showed that every millimeter of margin reduction resulted in a 1 Gy reduction in mean dose to OAR.

Although ART was performed after the second week of treatment,

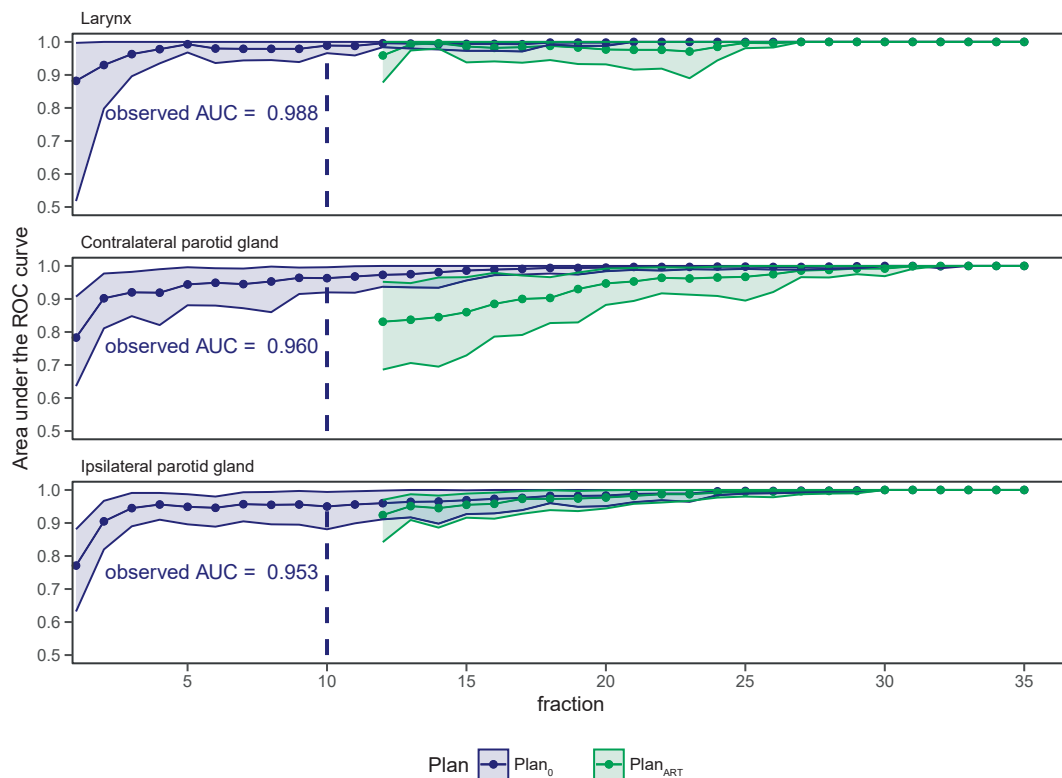


Fig. 3. Area under the ROC-curve (AUC) values and 95% confidence interval of accumulated dose for every fraction. The AUC values are calculated for the baseline plan (Plan₀, blue) and scheduled replanning (Plan_{ART}, green). As the replan was only used from fraction 12 onwards, no values are given for the replan in the first 11 fractions. Highlighted is the AUC at fraction 10, as it corresponds to the timing of scheduled replanning in this study. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

accumulated dose within the first week of treatment was already highly prognostic for identifying patients at risk of unforeseen OAR dose increases. The larynx showed a consistent and systematic deviation from the planned dose throughout treatment eventually leading to increases in delivered dose. These findings might be explained by that, similar to daily CBCTs, the original planning CT represents a single snapshot of an anatomy that is continuously changing. Similar early deviations were observed for the parotid glands. However, in the parotid glands, progressive differences between planned and delivered dose were observed throughout treatment, likely due to gradual anatomical changes and proximity to the PTVp. These distinct deviation patterns (systematic for the larynx and progressive for the parotids) may be another explanation for why selective replanning improved the delivered dose to the larynx but had limited impact on the parotids.

Although this *in silico* study was based on data from a prospective ART trial [22], simulations were used to control for variability in ART timing and unplanned ad hoc replanning. Anatomical changes were assumed independent of the number of delivered fractions, which may have led to overestimation of ART effects when plans were generated later in treatment. Secondly, delivered doses were not recalculated, but instead a shift invariance approach was used focusing primarily on geometry-induced dose deviations. This was necessary due to differences in treatment planning systems across institutions, which made dose recalculation not feasible, and is considered to be a good approximation of delivered dose [24]. However, uncertainties remain regarding registration algorithm, dose mapping and dose-volume histogram calculation in multi-institutional studies and limited soft tissue contrast of CBCT may have affected image registration accuracy. MR-linacs may improve anatomical visualization and thereby the accuracy of image registration in future studies [24].

Another challenge in planning studies is identifying clinically relevant dose differences. We used the 3 Gy threshold for its clarity,

reproducibility, and correlation with clinical outcomes [25,26]. While other studies have used NTCP models or dose constraints, the binary nature of all these methods doesn't fully reflect the complex dose-toxicity relationship. Lastly, scheduled replanning was limited to the experimental DP arm where doses at the target volume borders were lower compared to conventional radiotherapy. In conventional radiotherapy, especially when OARs are close to the tumor, delivered dose increases may occur more rapidly, potentially increasing ART impact.

In conclusion, our findings suggest that scheduling ART for all patients with LAHNSCC treated with DP is unlikely to improve OAR sparing. Nonetheless, ART remains a promising technique when applied with more intention. Our results suggest that using accumulated dose to the larynx to guide ART patient selection could potentially lead to reduced unforeseen increases in larynx dose. Systematic deviations seem early detectable in treatment and the impact of planning variation should be considered when designing ART strategies. Future studies on ART should aim to reduce planning variation through, for example, automated planning, adjustable dose constraints and clear ART guidelines.

CRediT authorship contribution statement

Anna Liza M.P. de Leeuw: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Simon R. van Kranen:** Writing – review & editing, Supervision, Resources, Methodology, Investigation, Data curation, Conceptualization. **Jordi Giral:** Writing – review & editing, Resources. **Yungan Tao:** Writing – review & editing, Resources. **Sergi Benavente:** Writing – review & editing, Resources. **Thanh-Vân F. Nguyen:** Writing – review & editing, Resources. **Frank J.P. Hoebbers:** Writing – review & editing, Resources. **Ann Hoeben:** Writing – review & editing, Resources. **Chris H.J. Terhaard:** Writing – review & editing, Resources. **Lip Wai**

Lee: Writing – review & editing, Resources. **Signe Friesland:** Writing – review & editing, Resources. **Roel J.H.M. Steenbakkers:** Writing – review & editing, Resources. **Harry Bartelink:** Writing – review & editing, Supervision, Resources. **Coen R.N. Rasch:** Writing – review & editing, Supervision, Resources. **Jan-Jakob Sonke:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Olga Hamming-Vrieze:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The Netherlands Cancer Institute has research collaborations with Elekta Oncology AB and licences software for CBCT-guided radiotherapy to Elekta AB.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2026.100957>.

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