Advances in Radiation Oncology (2024) 9, 101319

advances in radiation oncology

www.advancesradonc.org

Scientific Article

In Silico Analysis of Adjuvant Head and Neck Online Adaptive Radiation Therapy

Sean All, MD,[a] Xinran Zhong, PhD,[a] Byongsu Choi, MS,[a,b] Jin Sung Kim, PhD,[b] Tingliang Zhuang, PhD,[a] Vladimir Avkshtol, MD,[a] David Sher, MD, MPH,[a] Mu-Han Lin, PhD,[a] and Dominic H. Moon, MD[a,*]

[a]*Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, Texas; and* [b]*Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Received 6 February 2023; accepted 13 July 2023

Purpose: Recently developed online adaptive radiation therapy (OnART) systems enable frequent treatment plan adaptation, but data supporting a dosimetric benefit in postoperative head and neck radiation therapy (RT) are sparse. We performed an in silico dosimetric study to assess the potential benefits of a single versus weekly OnART in the treatment of patients with head and neck squamous cell carcinoma in the adjuvant setting.

Methods and Materials: Twelve patients receiving conventionally fractionated RT over 6 weeks and 12 patients receiving hypofractionated RT over 3 weeks on a clinical trial were analyzed. The OnART emulator was used to virtually adapt either once midtreatment or weekly based on the patient's routinely performed cone beam computed tomography. The planning target volume (PTV) coverage, dose heterogeneity, and cumulative dose to the organs at risk for these 2 adaptive approaches were compared with the nonadapted plan.

Results: In total, 13, 8, and 3 patients had oral cavity, oropharynx, and larynx primaries, respectively. In the conventionally fractionated RT cohort, weekly OnART led to a significant improvement in PTV V100% coverage (6.2%), hot spot (−1.2 Gy), and maximum cord dose (−3.1 Gy), whereas the mean ipsilateral parotid dose increased modestly (1.8 Gy) versus the nonadapted plan. When adapting once midtreatment, PTV coverage improved with a smaller magnitude (0.2%-2.5%), whereas dose increased to the ipsilateral parotid (1.0-1.1 Gy) and mandible (0.2-0.7 Gy). For the hypofractionated RT cohort, similar benefit was observed with weekly OnART, including significant improvement in PTV coverage, hot spot, and maximum cord dose, whereas no consistent dosimetric advantage was seen when adapting once midtreatment.

Conclusions: For head and neck squamous cell carcinoma adjuvant RT, there was a limited benefit of single OnART, but weekly adaptations meaningfully improved the dosimetric criteria, predominantly PTV coverage and dose heterogeneity. A prospective study is ongoing to determine the clinical benefit of OnART in this setting.

Introduction

The development of advanced technologies has greatly improved the delivery of radiation therapy (RT) for patients with head and neck squamous cell carcinoma (HNSCC). The coupling of intensity modulated RT (IMRT) with daily image guidance has been translated

Sources of support: This work had no specific funding.

All data generated and analyzed during this study are included in this published article. Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

*Corresponding author: Dominic H. Moon, MD; email: Dominic.Moon@UTSouthwestern.edu

https://doi.org/10.1016/j.adro.2023.101319

into enhanced dose conformality of targets and improved sparing of normal tissues such as major salivary glands, oral cavity, and pharyngeal constrictors.[1,2] Moreover, daily imaging has highlighted the potential extent of anatomic variations in tumor/organs-at-risk (OARs) contours during the treatment course,[3-6] which can result in unintended underdosing of targets and overdosing of OARs.[7-9] Adaptive RT (ART) has been introduced as a way to mitigate these risks by updating the treatment plan according to the anatomic changes and shifts seen during the treatment course.

Until recently, the technical and logistical challenges of performing ART made it a resource-intensive and almost prohibitive process for treatment of HNSCC. Patients would need resimulation, recontouring, and offline replanning.[10,11] Several papers have attempted to elucidate the optimal patient characteristics and frequency of replanning for definitive HNSCC ART, with no clear consensus.[10,12-15] Data on the role of ART in the adjuvant setting after surgical resection for HNSCC are particularly lacking. With gross tumor resected at the time of surgery, anatomic shifts are mainly driven by changes in the patient's weight and postoperative edema.[16] The magnitude of dosimetric changes, and thus the potential utility of adaptation, remains uncertain in the adjuvant setting.[17]

Recent technological innovations have lowered the barriers to performing routine ART. The Varian Ethos system (Varian Medical Systems, Palo Alto, CA) is an artificial intelligence/automation-powered treatment platform capable of online ART (OnART). It is designed to deliver reoptimized plans in real time based on cone beam computed tomography (CBCT) contours and automated reoptimization while the patient is on the treatment couch, which enables frequent adaptation.[18] Given the paucity of publications on the role of ART for postoperative HNSCC RT and the lack of data using OnART more specifically, the purpose of this study was to assess the dosimetry, plan quality, and optimal frequency of OnART in this setting.

Methods and Materials

Study data set

Twenty-four patients with HNSCC who underwent surgical resection and adjuvant RT between 2020 and 2021 at a single institution were analyzed for this study. Twelve patients were treated with hypofractionated RT (HFRT) on a prospective phase 1 clinical trial investigating the safety of HFRT in the adjuvant setting for HNSCC. Six patients received 46.5 Gy in 15 fractions, delivered 5 times a week, while 6 patients received 44.4 Gy in 12 fractions, delivered 4 times a week. Twelve consecutive patients receiving conventionally fractionated RT (CFRT) to 60 Gy in 30 fractions with the same eligibility criteria and time frame as the HFRT trial were also selected. All patients underwent standard CT simulation and planning before their radiation treatment without adaptive replanning. Institutional review board review was not required for this retrospective study of radiation dosimetry.

OnART workflow and treatment planning on Varian Ethos

The Varian Ethos system employs an intelligent optimization engine, which uses operator-specified planning directives in the preplanning phase to create adapted plans. For the purpose of this study, planning target volume (PTV) coverage was prioritized over OARs to ensure the robustness of target coverage against anatomic changes. The Ethos emulator, a nonclinical version of the Ethos treatment planning system (TPS), was used to reproduce adaptive treatments retrospectively. The initial pretreatment planning CT simulation along with the physician contoured target volumes and OARs were imported. Each patient's daily CBCT digital imaging and communications in medicine files were also imported to simulate the day-of CBCT acquisition of real-time Ethos OnART. To simulate a fraction of OnART treatment, the corresponding CBCT was acquired and automatically registered to the initial planning CT. Next, "influencer" structures including the mandible, parotid glands, spinal cord, and brain stem were auto-propagated by the Ethos TPS. These contours were then reviewed and adjusted as necessary by the radiation oncologist. Using the physician-approved influencers, the Ethos TPS further propagated the target and OAR contours onto the CBCT, which were again reviewed for accuracy and edited as appropriate by the physician. Upon approval, the TPS generated the new adapted plan based on the CBCT and its updated contours. Ethos TPS offers dose distributions for 2 plans for review: the scheduled plan is the preplan recalculated on the day-of CBCT consistent with image guided radiation therapy (IGRT), and the adapted (ADP) plan is the reoptimized plan using the day-of CBCT.

Data collection and analyzed parameters

The cumulative delivered dose was compared between treatment with the IGRT plan versus the different ADP plans (once midtreatment or weekly). Each radiation treatment plan underwent a simulated OnART at set fraction intervals. In the CFRT cohort, OnART was performed once during week 3 (fraction 11) versus once during week 4 (fraction 16) versus weekly (fractions 1, 6, 11, 16, 21, 26). In the HFRT cohort, OnART was performed once during week 2 (fraction 5 for the 12-fraction

regimen or fraction 6 for the 15-fraction regimen) versus once during week 3 (fraction 9 for the 12-fraction regimen or fraction 11 for the 15-fraction regimen) versus weekly (fractions 1, 5 or 6, 9 or 11). These dosimetric data points were collected from each OnART fraction: mean dose to the parotid gland (ipsilateral and contralateral), mean dose to the submandibular gland (contralateral), mean dose to the oral cavity (oral cavity minus PTV), point maximum dose to the mandible, point maximum dose to the spinal cord, PTV coverage of the standard and high risk volumes (PTVSR and PTVHR, respectively), and dose heterogeneity via measurement of hot spots. The PTVHR was defined as the primary surgical bed and dissected nodal level(s) with positive lymph nodes whereas the PTVSR was defined as the dissected and elective nodal levels.

To calculate the OAR and PTV values, dosimetric data points were recorded from both the IGRT and ADP plans with an updated CBCT on a weekly basis to approximate the anatomic change over time. For the IGRT plans used as the comparator, values were calculated by taking the dosimetry from the nonadapted IGRT plan each week (fractions 1, 6, 11, 16, 21, 26 for CFRT; fractions 1, 5 or 6, 9 or 11 for HFRT) to create the cumulative doses. For single midtreatment OnART, the nonadapted dose was calculated using the same method until the fraction of OnART, and the dosimetric data were calculated using the ADP plan applied to the appropriate CBCTs for each week thereafter. For example, if a single midtreatment OnART was performed on fraction 16 of 30 in the CFRT cohort, dosimetric values were calculated using the nonadapted IGRT plans for fractions 1 to 15 using the CBCTs for fraction 1, 6, and 11, and starting with the OnART plan that was calculated on fraction 16, dosimetric values were again calculated for fractions 16 to 30 but using the CBCTs from fractions 16, 21, and 26. The nonadapted IGRT dosimetric values from fractions 1 to 15 were then combined with the adapted dosimetric values from 16 to 30 to create the cumulative doses.

This same method was applied to calculate the dosimetric data for the once weekly OnART plans. For example, OnART was performed on fraction 1 with the corresponding CBCT with the ADP plan used to derive the doses for fractions 1 to 5. OnART was then performed on fraction 6 with the corresponding CBCT, and this new ADP plan was used to derive the doses for fractions 6 to 10. This process was repeated for each week at each predetermined fraction as previously described to calculate the cumulative doses. These values from the ADP plans (single midtreatment OnART and weekly OnART) were then compared with the IGRT (nonadapted) treatment plans to determine the dosimetric differences. A Wilcoxon signed rank test was used to evaluate for statistical significance of these dosimetric differences with $P < .05$ considered significant. All statistical analyses were performed using IBM SPSS software.

Results

Patient and treatment characteristics

In total, 13, 8, and 3 patients had oral cavity, oropharynx, and larynx primaries, respectively, with 11 of the 24 patients receiving ipsilateral neck RT (vs bilateral neck RT). The majority of patients had pT1-2 and node-positive disease (Table 1). The median absolute and percent weight changes for the entire group during treatment were −5 pounds (interquartile range [IQR], −9.3, −1.8) and −3% (IQR, −5.8, −0.9), respectively. Thirteen patients had a flap reconstruction, 3 patients had a tracheostomy in place throughout RT, and 1 patient with a Dobhoff tube in place at the initiation of RT had it removed during the treatment course. Further delineation of patient and treatment characteristics of the CFRT and HFRT cohorts is shown in Table 1.

Target coverage

Table 2 displays PTV V100% coverage for both dose/fractionation cohorts. In the CFRT cohort, the PTVHR coverage was improved with the greatest magnitude for weekly adaption (median [IQR]: 95.8% [95.4, 96.3]) versus IGRT (nonadapted) plan (89.6% [84.9, 92.6]). This trend was true for PTVSR coverage as well, with median V100% coverage with weekly adaption improving to 98.3% (IQR, 97.8, 98.7) from 95.3% (IQR, 92.8, 96.9) for IGRT. Table 2 also displays the absolute difference in median V100% coverage for each OnART schedule compared with IGRT. In the CFRT cohort, weekly OnART led to a statistically significant benefit in PTVHR and PTVSR percent coverage (6.2% and 3.0%, respectively) compared with IGRT. Single adaptation at week 3 had modest increase in PTVHR coverage (2.5%) compared with IGRT, whereas week 4 adaptation showed no significant improvement. When assessing PTV coverage using D95% (Gy), weekly OnART again demonstrated a statistically significant benefit in PTVHR and PTVSR (1.4 and 1.2 Gy, respectively) compared with IGRT.

In the HFRT cohort, weekly adaptation showed a similar benefit in target coverage compared with IGRT, with median PTVHR coverage increasing from 92.7% (IQR, 90.2, 94.4) to 95.7% (IQR, 95.4, 96.1) and PTVSR increasing from 96.4% (IQR, 94.7, 97.5) to 98.2% (IQR, 97.6, 98.7). This corresponded to an absolute improvement of median PTV coverages of 3.0% and 1.8%, respectively, versus IGRT. In this cohort, where patients finished treatment in just 3 weeks, single adaptation during week 2 or 3 resulted in no improvement in PTVHR or PTVSR coverages. When assessing PTV coverage using D95% (Gy), weekly OnART demonstrated a statistically significant benefit in PTVSR (0.7 Gy) but not PTVHR (0.3 Gy) compared with IGRT.

Table 1 Patient and treatment characteristics

Characteristic	CFRT No. (%)	HFRT No. (%)
Primary disease site		
- Oral cavity	7 (58)	6 (50)
- Oropharynx	3 (25)	5 (42)
- Larynx	2 (17)	1 (12)
Treatment field		
- Ipsilateral	6 (50)	5 (42)
- Bilateral	6 (50)	7 (58)
Submandibular gland status		
- Surgically absent	3 (25)	4 (33)
- Unilateral	4 (33)	1 (8)
- Bilateral	5 (42)	7 (58)
- Intact		
pT stage		
- pT1	1 (8)	2 (17)
- pT2	4 (33)	7 (58)
- pT3	4 (33)	0 (0)
- pT4a	3 (25)	3 (25)
pN stage		
- pN0	6 (50)	3 (25)
- pN1	5 (42)	7 (58)
- pN2	1 (8)	2 (17)
Dose/fractionation		
- 60 Gy/30 fx	12 (100)	0 (0)
- 46.5 Gy/15 fx	0 (0)	6 (50)
- 44.4 Gy/12 fx	0 (0)	6 (50)
Average weight change (median [IQR])		
- Absolute (lb)	−3 (−6, 0.5)	−8.5 (−10.8, −5)
- Percent	−2.1 (−3.1, 0.4)	−5.4 (−6.2, −3.1)
Flap reconstruction	8 (67)	5 (42)
Tracheostomy tube during RT	2 (17)	1 (8)
Dobhoff tube during RT	1 (8)	0 (0)

Abbreviations: CFRT = conventionally fractionated radiation therapy; fx = fractions; HFRT = hypofractionated radiation therapy; IQR = interquartile range; RT = radiation therapy.

Plan homogeneity

Maximum point dose (hot spot; defined as 0.035 cc dose) within the PTVHR for each plan was used as a metric to evaluate plan homogeneity (Table 2). In the CFRT cohort, weekly adaption improved plan homogeneity with a median hot spot of 64.1 Gy (IQR, 63.6, 64.6) compared with 65.3 Gy (IQR, 64.6, 66.0) for IGRT. On the other hand, the median hot spot was numerically higher with single adaptation versus IGRT. When comparing the absolute median difference in maximum dose, weekly adaption significantly decreased the absolute hot spot by 1.2 Gy over IGRT. Both week 3 and 4 single adaptation slightly but statistically significantly increased the absolute hot spot value over IGRT (0.4 and 0.2 Gy, respectively). There appeared to be no discernable trend between patient weight changes during treatment and improvements in plan homogeneity.

In the HFRT cohort, hot spot was improved slightly with weekly adaption compared with IGRT, with a

Table 2 PTV coverage and dose homogeneity of IGRT (no adaption), single adaption, and weekly adaption

	IGRT	Single ADP 1	Single ADP 2	Weekly ADP
CFRT				
PTVHR V100% coverage (%)	89.6 (84.9−92.6)	92.1 (85.4−94.2)	89.8 (85.8−92.6)	95.8 (95.4−96.3)
Single ADP 1 − IGRT		2.5*		
Single ADP 2 − IGRT		0.2		
Weekly ADP − IGRT		6.2*		
PTVSR V100% coverage (%)	95.3 (92.8−96.9)	95.5 (93.4−98.0)	95.5 (92.4−97.4)	98.3 (97.8−98.7)
Single ADP 1 − IGRT		0.2		
Single ADP 2 − IGRT		0.2		
Weekly ADP − IGRT		3.0*		
PTVHR max dose (Gy)	65.3 (64.6−66.0)	65.7 (65.1−66.7)	65.5 (64.8−66.7)	64.1 (63.6−64.6)
Single ADP 1 − IGRT		0.4*		
Single ADP 2 − IGRT		0.2*		
Weekly ADP − IGRT		−1.2*		
HFRT				
PTVHR V100% coverage (%)	92.7 (90.2−94.4)	93.8 (89.8−94.5)	93.8 (91.2−94.5)	95.7 (95.4−96.1)
Single ADP 1 − IGRT		1.1		
Single ADP 2 − IGRT		1.1		
Weekly ADP − IGRT		3.0*		
PTVSR V100% coverage (%)	96.4 (94.7−97.5)	95.5 (92.5−97.2)	96.1 (93.9−97.0)	98.2 (97.6−98.7)
Single ADP 1 − IGRT		−0.9*		
Single ADP 2 − IGRT		−0.3		
Weekly ADP − IGRT		1.8*		
PTVHR max dose (Gy)	47.7 (47.3−48.4)	48.8 (47.8−49.8)	48.3 (47.5−48.6)	47.3 (46.9−47.6)
Single ADP 1 − IGRT		1.1*		
Single ADP 2 − IGRT		0.6*		
Weekly ADP − IGRT		−0.4*		

Abbreviations: ADP = adapted plan; CFRT = conventionally fractionated radiation therapy; HFRT = hypofractionated radiation therapy; IGRT = image guided radiation therapy (nonadapted); IQR = interquartile range; PTV = planning target volume; PTVHR = high risk planning target volume; PTVSR = standard risk planning target volume.

*$P < .05$.

Data displayed as median (IQR). Difference in PTV coverage and dose homogeneity between IGRT (no adaption), single adaption, and weekly adaption displayed as absolute difference of median values.

median maximum dose of 47.3 Gy (IQR, 46.9, 47.6) versus 47.7 Gy (IQR, 47.3, 48.4) for IGRT. Similar to CFRT, single adaption in either week 2 or 3 increased plan heterogeneity and hot spot values compared with IGRT, by 1.1 and 0.6 Gy, respectively.

Figure 1 demonstrates the qualitative improvement in dose homogeneity with weekly OnART, which is not seen with single midtreatment OnART. Worsening of hot spot seen with single adaptation versus IGRT may be due to the limitations of the real-time OnART Ethos reoptimization algorithm at a single timepoint compared with the higher degrees of freedom (and time) afforded to the human planner. However, this limitation can be overcome by more frequent adaptation and optimization.

Cumulative dosimetric outcomes for OARs

Table 3 displays the cumulative dosimetric outcomes for each OAR of interest as a median (IQR) in both dose fractionation cohorts stratified by IGRT and adaption schedule. Absolute median differences between adapted plans and IGRT are shown in Table 3 as well.

In the CFRT cohort, weekly adaptation significantly improved the maximum dose to the spinal cord (−3.1 Gy) and mean dose to the oral cavity (−0.6 Gy), while increasing mean dose to the ipsilateral parotid (1.8 Gy). Single adaptation midtreatment resulted in a significant increase in the mean dose to the ipsilateral parotid (1.0-1.1 Gy) and maximum dose to the mandible (0.2-0.7 Gy)

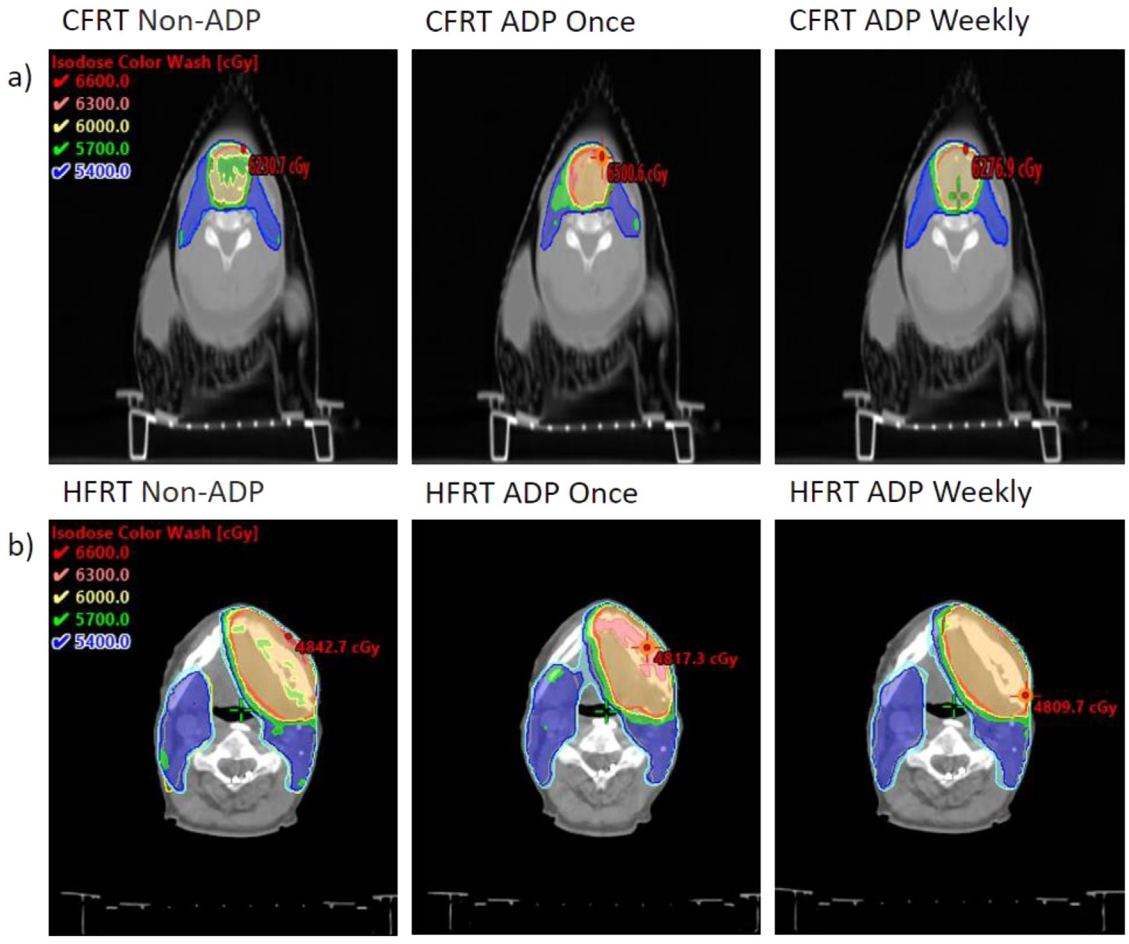

Figure 1 Visual dose homogeneity comparison between adapted and image guided RT (nonadapted) plans in the (a) CFRT cohort and (b) HFRT cohort. *Abbreviations:* ADP = adapted; CFRT = conventionally fractionated RT; HFRT = hypofractionated RT; RT = radiation therapy.

without an improvement in other OAR doses versus IGRT.

In the HFRT cohort, weekly adaptation led to a significant benefit in the maximum dose to the spinal cord (−1.6 Gy) and mean dose to the ipsilateral parotid (−0.8 Gy), while compromising mean dose to the contralateral parotid and submandibular glands, leading to an overall increase in mean dose to these OARs (0.9 and 1.2 Gy, respectively). Single adaptation midtreatment in week 2 had a small but significant improvement in mean dose to oral cavity (−0.4 Gy) compared with IGRT but led to an increase in mean dose to the contralateral parotid gland (1.2 Gy) and maximum dose to the mandible (1.0 Gy). Week 3 adaptation showed no significant improvement in OAR doses.

Given the limited benefit of a single adaptation in both the CFRT and HFRT cohorts, it was not feasible to determine the optimal week (week 3 vs 4 for CFRT and week 2 vs 3 for HFRT) to plan for a single midtreatment adaption in this setting.

Discussion

Our data suggest a significant dosimetric benefit with weekly adaptation, but not with a single midtreatment adaptation, for HNSCC postoperative RT. The PTV coverage and heterogeneity significantly improved in comparison with no adaptation. Our analysis shows a significant deterioration of PTV coverage over time with conventional, nonadapted, treatment that typically goes unnoticed in routine care. Dosimetric data on clinical target volume coverage was not collected in this analysis as it is not part of the standard clinical evaluation. The HFRT cohort, with treatments completed over just 3 weeks, saw a smaller magnitude of benefit for PTV coverage from weekly OnART compared with the CFRT cohort, presumably due to less time for the anatomic changes to alter the dosimetry of the initial plan.

We also observed a limited dosimetric advantage of adaptation for OARs overall, with some OARs receiving increased doses, because PTV coverage is prioritized in

Table 3 Cumulative dose to organs at risk of IGRT (no adaption), single adaption, and weekly adaption

	IGRT	Single ADP 1	Single ADP 2	Weekly ADP
CFRT				
Mean dose (Gy)				
Parotid IL (n = 12)	21.4 (17.1−25.0)	22.4 (18.0−26.3)	22.5 (17.7−24.6)	23.2 (19.0−24.6)
Single ADP 1 − IGRT		1.0*		
Single ADP 2 − IGRT		1.1*		
Weekly ADP − IGRT		1.8*		
Parotid CL (n = 12)	11.4 (6.5−15.7)	11.1 (6.3−18.4)	10.9 (6.18−17.6)	10.7 (5.6−18.8)
Single ADP 1 − IGRT		−0.3		
Single ADP 2 − IGRT		−0.5		
Weekly ADP − IGRT		−0.7		
Submandibular CL (n = 8)	10.6 (8.0.6-30.5)	11.7 (7.1−29.1)	10.6 (7.02−29.6)	11.2 (5.58−27.1)
Single ADP 1 − IGRT		1.1		
Single ADP 2 − IGRT		0.0		
Weekly ADP − IGRT		0.6		
Oral cavity (n = 12)	23.7 (21.6−26.7)	23.6 (19.0−26.2)	23.5 (20.5−25.1)	23.1 (17.7−24.6)
Single ADP 1 − IGRT		−0.1*		
Single ADP 2 − IGRT		−0.2		
Weekly ADP − IGRT		−0.6*		
Max dose (Gy)				
Spinal cord (n = 12)	34.6 (32.6−37.7)	35.0 (32.5−38.7)	35.6 (31.9−38.8)	31.5 (28.2−35.1)
Single ADP 1 − IGRT		0.4		
Single ADP 2 − IGRT		1.0		
Weekly ADP − IGRT		−3.1*		
Mandible (n = 12)	62.7 (56.5−63.3)	63.4 (59.3−65.0)	62.9 (61.1−65.1)	62.4 (58.9−63.2)
Single ADP 1 − IGRT		0.7*		
Single ADP 2 − IGRT		0.2*		
Weekly ADP − IGRT		−0.3		
HFRT				
Mean dose (Gy)				
Parotid IL (n = 12)	22.3 (18.3−26.0)	23.5 (19.1−25.6)	22.5 (18.3−25.8)	21.5 (18.3−25.4)
Single ADP 1 − IGRT		1.2		
Single ADP 2 − IGRT		0.2		
Weekly ADP − IGRT		−0.8*		
Parotid CL (n = 12)	11.1 (6.3−14.0)	11.5 (6.7−13.9)	11.9 (6.3−14.6)	12.0 (6.3−13.3)
Single ADP 1 − IGRT		0.4		
Single ADP 2 − IGRT		0.8*		
Weekly ADP − IGRT		0.9*		
Submandibular CL (n = 11)	27.3 (7.8−40.7)	28.5 (16.7−40.9)	27.4 (17.2−40.8)	28.5 (8.4−40.6)
Single ADP 1 − IGRT		1.2*		
Single ADP 2 − IGRT		0.1		
Weekly ADP − IGRT		1.2*		

(*continued on next page*)

Table 3 (*Continued*)

	IGRT	Single ADP 1	Single ADP 2	Weekly ADP
Oral cavity (n = 12)	17.7 (16.0−20.2)	17.3 (13.8−20.5)	17.7 (16.0−22.4)	16.9 (15.4−21.8)
Single ADP 1 − IGRT		−0.4*		
Single ADP 2 − IGRT		0.0		
Weekly ADP − IGRT		−0.8		
Max dose (Gy)				
Spinal cord (n = 12)	24.9 (23.3−27.5)	24.4 (22.7−26.8)	24.1 (23.2−27.5)	23.3 (20.2−24.8)
Single ADP 1 − IGRT		−0.5		
Single ADP 2 − IGRT		−0.8		
Weekly ADP − IGRT		−1.6*		
Mandible (n = 12)	46.7 (45.8−47.9)	47.7 (46.0−49.3)	47.3 (45.8−48.5)	46.9 (46.0−48.4)
Single ADP 1 − IGRT		1.0*		
Single ADP 2 − IGRT		0.6*		
Weekly ADP − IGRT		0.2		

Abbreviations: ADP = adapted plan; CFRT = conventionally fractionated radiation therapy; CL = contralateral; HFRT = hypofractionated radiation therapy; IGRT = image guided radiation therapy (nonadapted); IL = ipsilateral; IQR = interquartile range.
*$P < .05$.
Data displayed as median (IQR). Difference in dose to organs at risk between IGRT (no adaption), single adaption, and weekly adaption displayed as absolute difference of median values.

the Ethos TPS. For example, the ipsilateral and contralateral parotid gland received increased mean doses with weekly adaptation in the CFRT and HFRT groups, respectively, and this may be due to a decrease in parotid volume over time (1.6-2.9 cc in our study) as well as a relatively more medial position over time with weight loss. Weekly adaptive therapy appeared to minimize heterogeneity, but OAR sparing was not appreciably different. Although Ethos provides a streamlined OnART process, and the automatic reoptimization based on preplan objectives enhances the reproducibility of plan quality, it also limits the degree of freedom for users to adjust the plan during OnART. To our knowledge, the current study is the first analysis of simulated dosimetric outcomes of OnART in the adjuvant setting for HNSCC and the first study to clarify the optimal frequency of OnART in this population.

Our analysis demonstrated that weekly adaption is superior to a single midtreatment adaptation. Interestingly, some values were improved with weekly OnART compared with IGRT, but those same values would be worse with single midtreatment OnART compared with IGRT. For example, max dose to the spinal cord decreased by approximately 3 Gy in the CFRT cohort with weekly OnART but increased slightly with single OnART. The potential reasons for this finding are multifactorial, with the predominant explanation being that more frequent OnART invariably allows for more opportunities to adjust the treatment as patient anatomy changes throughout the course of treatment. For the single OnART scenarios, the anatomy captured by the CBCT on the day of planning represents only a single opportunity to improve plan metrics. If the planning directives are pushed to provide strict PTV coverage over OAR sparing, and the anatomy and contouring on the day of single OnART is such a way that OARs experience an increase in dose, this change could be propagated throughout the rest of the treatment course. Again, the Ethos platform does not allow for flexibility in planning directive priorities at the time of OnART, and the user is given the option to choose either the nonadapted (IGRT) or the adapted plan.

The literature suggests several potential dosimetric benefits of adaptation in the definitive setting, including improvement in target coverage, mean dose to the parotid, and maximum dose to the spinal cord, whereas potential clinical benefits include better locoregional control and patient-reported quality of life.[14,17] There are also limited reports on the use of adaptation in the postoperative setting for patients with HNSCC. Capelle et al[16] appears to be the first study that assessed the benefit of routine midtreatment replanning in a patient population that included both definitive and postoperative (35%) patients with HNSCC. Their results demonstrated significant benefits in the group of patients receiving definitive RT but found no significant benefit in the postoperative group with midtreatment adaptation. Chen et al[17] performed a similar analysis comparing a single midtreatment offline adaptation and found a locoregional control benefit favoring adaptation (88% vs 79%; $P = .01$). Their patient population included 138 postoperative patients

with HNSCC but only 12 underwent adaptation. Another study compared offline adaptive replanning at week 3 and 6 in a similar but smaller patient cohort of definitive and adjuvant patients with HNSCC (20 total).[19] They found a benefit to adaption in patients receiving definitive RT for bulky disease but found only a small percent of postoperative patients had significant enough changes at week 3 and/or 6 to trigger adaptation.

It is worth mentioning that the available literature pertains to hand-crafted plans by dosimetrists/physicists that allow for fine tuning of structures during replanning. In this study, automatic replanning of the Ethos TPS was used based on prespecified directives (eg, PTV V100% covering 95% as the highest goal, followed by contralateral parotid/submandibular gland mean dose constraints and then hot spot goals). Because the traditional replanning process requires resimulation, adaptation has been generally performed once during the treatment course in these published studies. The optimal timing of this single adaptation is uncertain, with some studies suggesting early replanning, around week 2, and others arguing for a later timepoint after week 3 to 4, with these differences likely because of the heterogeneity of patient population analyzed and the reasons prompting ART.[3,20] Manuscripts with small numbers have explored the question of ideal frequency of adaptation in the definitive setting, with 1 study showing 94% of the maximum dosimetric benefit obtained with 3 replans during the treatment course and another study suggesting no additional benefit of replanning more than weekly.[15,21] The calculus may be quite different with postoperative RT, as the tumor volumes do not change and delivered dose deviations may be more sensitive to weight and treatment-related edema. Our study confirms that weekly adaptation is beneficial versus a single adaptation in the adjuvant setting, although the question of adapting more frequently (eg, daily), remains unclear.

Given the dosimetric results of the current analysis, assessing the clinical significance and anticipated magnitude of benefit to OAR doses requires a review of the relevant literature. A prospective analysis of parotid gland dose-volume effects estimated loss of salivary function at a rate of 5%/1 Gy of mean dose.[22] Similarly, every 1 Gy reduction in mean dose to the submandibular gland reduced the probability of severe xerostomia by 2% to 2.5%.[23] Additional data support the importance of sparing the contralateral submandibular gland during head and neck IMRT with improvements in recovery of saliva output and lower grades of xerostomia,[24] which is particularly relevant in the postoperative setting where many patients have their ipsilateral submandibular gland removed during the neck dissection. For the mandible, dose response analyses suggest V50 and V60 Gy of the mandible correlate with rates of osteoradionecrosis,[25,26] and limiting D30% of the mandible to less than 35 Gy may reduce the risk of osteoradionecrosis to 5% or less.[27] Spinal cord dose parameters are well established,[28,29] and although both the scheduled and adaptive plans met conventional constraints, adaptive plans can improve the maximum dose, ensuring the principle of as low as reasonably achievable. This can become clinically relevant if patients were to require reirradiation.

Achieving adequate doses to the postoperative bed established by prospective data[30] and ensuring dose homogeneity of the target volume are fundamental aspects of head and neck treatment planning. More than half of the patients in this cohort had a surgical flap, and the flap can swell and contract during RT, resulting in changes to PTV coverage in a critical area of the postoperative field.[10,17] Adaptative RT allows adjustments to account for these inevitable changes to the target volume during the treatment course. One study found a locoregional control benefit with midtreatment adaptive replanning in patients with HNSCC receiving IMRT (88% vs 79%; $P = .01$).[17] The current study demonstrated a significant improvement in high-risk PTV coverage with weekly OnART (6.2% and 3.0%, respectively, for the CFRT and HFRT cohorts), and prospective studies will be needed to demonstrate whether such differences lead to meaningful gains in oncologic outcomes.

There are sparse data on OnART in general for HNSCC, mainly because of the relative novelty of online adaptive systems such as Varian Ethos. Yoon et al[31] performed a proof of concept retrospective simulation study in 5 patients receiving definitive RT for HNSCC using the Ethos TPS and concluded the feasibility of the workflow as well as the accuracy of the artificial-intelligence-driven contouring and plan optimization. The unsupervised adapted plans without human input appeared to spare OARs better than the original plans. Another small study of 2 patients examined OnART using Elekta Unity MR Linac (Stockholm, Sweden) and found it to be a practical workflow.[32] Although several options now exist for online adaptation capability, the early literature has focused on their feasibility. Additional studies are urgently needed to further delineate the dosimetric and clinical advantages of OnART.

The current study has several limitations that could have contributed to the reported results. Although this was a larger cohort of patients compared with other recent works, the sample size is still small, with 12 patients each receiving CFRT and HFRT. The patients had varied primary disease sites, type of surgery, and radiation treatment fields. For example, a meaningful number of patients underwent resection of the ipsilateral or bilateral submandibular glands as displayed in Table 1, so the dosimetric data for any given metric were based on fewer patients than the total sample size. Also, approximately half of the patients in each dose fractionation cohort were treated with ipsilateral versus bilateral neck fields, which can significantly affect the dosimetry to OARs and the level of challenge it poses for the Ethos TPS to meet dose

constraints. Although this adds heterogeneity to the data, it also reflects the range of patients receiving postoperative RT in the clinic. Finally, the Ethos system requires the operator to provide a list of planning parameters and its priority, which was kept uniform with PTV coverage as the highest priority. In reality, the parameters and priorities will be modified based on the specific patient and tumor characteristics when performed in clinic, and thus the results can be different for individual cases. In addition, this study does not provide direct insight into clinical or patient-reported outcomes with ART given its retrospective nature. Our department is currently conducting a prospective study of OnART in patients receiving postoperative RT for HNSCC to address these questions.

Conclusion

Patients receiving adjuvant RT for HNSCC may benefit from online ART when performed frequently, with an improvement in PTV coverage and heterogeneity, although there were minimal differences in OAR doses. Prospective studies are needed to determine the potential gains in clinical outcomes of OnART in this setting, and such a study is ongoing at our institution.

Disclosures

David Sher is principal investigator of the DART-BOARD study, funded by Varian. Research funding only.

Acknowledgments

We acknowledge the patients and their families for allowing us to take part in their care.

References

1. Puri DR, Chou W, Lee N. Intensity-modulated radiation therapy in head and neck cancers: Dosimetric advantages and update of clinical results. *Am J Clin Oncol*. 2005;28:415-423.
2. Schoenfeld GO, Amdur RJ, Morris CG, Li JG, Hinerman RW, Mendenhall WM. Patterns of failure and toxicity after intensity-modulated radiotherapy for head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2008;71:377-385.
3. Bhide SA, Davies M, Burke K, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: A prospective observational study. *Int J Radiat Oncol Biol Phys*. 2010;76:1360-1368.
4. Ghosh A, Gupta S, Johny D, Vidyadhar Bhosale V, Pal Singh Negi M. A study to assess the dosimetric impact of the anatomical changes occurring in the parotid glands and tumour volume during intensity modulated radiotherapy using simultaneous integrated boost (IMRT-SIB) in head and neck squamous cell cancers. *Cancer Med*. 2021;10:5175-5190.
5. Hou WH, Wang CW, Tsai CL, Hsu FM, Cheng JC. The ratio of weight loss to planning target volume significantly impacts setup errors in nasopharyngeal cancer patients undergoing helical tomotherapy with daily megavoltage computed tomography. *Radiol Oncol*. 2016;50:427-432.
6. Reali A, Anglesio SM, Mortellaro G, et al. Volumetric and positional changes of planning target volumes and organs at risk using computed tomography imaging during intensity-modulated radiation therapy for head-neck cancer: An "old" adaptive radiation therapy approach. *Radiol Med*. 2014;119:714-720.
7. Heukelom J, Kantor ME, Mohamed ASR, et al. Differences between planned and delivered dose for head and neck cancer, and their consequences for normal tissue complication probability and treatment adaptation. *Radiother Oncol*. 2020;142:100-106.
8. Noble DJ, Yeap PL, Seah SYK, et al. Anatomical change during radiotherapy for head and neck cancer, and its effect on delivered dose to the spinal cord. *Radiother Oncol*. 2019;130:32-38.
9. Stauch Z, Zoller W, Tedrick K, et al. An evaluation of adaptive planning by assessing the dosimetric impact of weight loss throughout the course of radiotherapy in bilateral treatment of head and neck cancer patients. *Med Dosim*. 2020;45:52-59.
10. Morgan HE, Sher DJ. Adaptive radiotherapy for head and neck cancer. *Cancer Head & Neck*. 2020;5:1.
11. Figen M, Çolpan Öksüz D, Duman E, et al. Radiotherapy for head and neck cancer: Evaluation of triggered adaptive replanning in routine practice. *Front Oncol*. 2020;10: 579917.
12. Avgousti R, Antypas C, Armpilia C, et al. Adaptive radiation therapy: When, how and what are the benefits that literature provides? *Cancer Radiother*. 2022;26:622-636.
13. Brouwer CL, Steenbakkers RJ, Langendijk JA, Sijtsema NM. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help? *Radiother Oncol*. 2015;115:285-294.
14. Castelli J, Simon A, Lafond C, et al. Adaptive radiotherapy for head and neck cancer. *Acta Oncol*. 2018;57:1284-1292.
15. Zhang P, Simon A, Rigaud B, et al. Optimal adaptive IMRT strategy to spare the parotid glands in oropharyngeal cancer. *Radiother Oncol*. 2016;120:41-47.
16. Capelle L, Mackenzie M, Field C, Parliament M, Ghosh S, Scrimger R. Adaptive radiotherapy using helical tomotherapy for head and neck cancer in definitive and postoperative settings: Initial results. *Clin Oncol*. 2012;24:208-215.
17. Chen AM, Daly ME, Cui J, Mathai M, Benedict S, Purdy JA. Clinical outcomes among patients with head and neck cancer treated by intensity-modulated radiotherapy with and without adaptive replanning. *Head Neck*. 2014;36:1541-1546.
18. Byrne M, Archibald-Heeren B, Hu Y, et al. Varian ethos online adaptive radiotherapy for prostate cancer: Early results of contouring accuracy, treatment plan quality, and treatment time. *J Appl Clin Med Phys*. 2022;23:e13479.
19. Mahmoud O, Reis IM, Samuels MM, et al. Prospective pilot study comparing the need for adaptive radiotherapy in unresected bulky disease and in postoperative patients with head and neck cancer. *Technol Cancer Res Treat*. 2017;16:1014-1021.
20. Barker Jr JL, Garden AS, Ang KK, et al. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys*. 2004;59:960-970.
21. Wu Q, Chi Y, Chen PY, Krauss DJ, Yan D, Martinez A. Adaptive replanning strategies accounting for shrinkage in head and neck IMRT. *Int J Radiat Oncol Biol Phys*. 2009;75:924-932.
22. Blanco AI, Chao KS, El Naqa I, et al. Dose-volume modeling of salivary function in patients with head-and-neck cancer receiving radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;62:1055-1069.

23. Murthy V, Lewis S, Kannan S, et al. Submandibular function recovery after IMRT in head and neck cancer: A prospective dose modelling study. *Radiother Oncol*. 2018;129:38-43.
24. Wang ZH, Yan C, Zhang ZY, et al. Impact of salivary gland dosimetry on post-IMRT recovery of saliva output and xerostomia grade for head-and-neck cancer patients treated with or without contralateral submandibular gland sparing: A longitudinal study. *Int J Radiat Oncol Biol Phys*. 2011;81:1479-1487.
25. Caparrotti F, Huang SH, Lu L, et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. *Cancer*. 2017;123:3691-3700.
26. Tsai CJ, Hofstede TM, Sturgis EM, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. *Int J Radiat Oncol Biol Phys*. 2013;85:415-420.
27. van Dijk LV, Abusaif AA, Rigert J, et al. Normal tissue complication probability (NTCP) prediction model for osteoradionecrosis of the mandible in patients with head and neck cancer after radiation therapy: Large-scale observational cohort. *Int J Radiat Oncol Biol Phys*. 2021;111:549-558.
28. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys*. 2010;76(3 Suppl):S42-S49.
29. Sahgal A, Chang JH, Ma L, et al. Spinal cord dose tolerance to stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys*. 2021;110:124-136.
30. Rosenthal DI, Mohamed ASR, Garden AS, et al. Final report of a prospective randomized trial to evaluate the dose-response relationship for postoperative radiation therapy and pathologic risk groups in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys*. 2017;98:1002-1011.
31. Yoon SW, Lin H, Alonso-Basanta M, et al. Initial evaluation of a novel cone-beam CT-based semi-automated online adaptive radiotherapy system for head and neck cancer treatment - a timing and automation quality study. *Cureus*. 2020;12:e9660.
32. Gupta A, Dunlop A, Mitchell A, et al. Online adaptive radiotherapy for head and neck cancers on the MR linear accelerator: Introducing a novel modified adapt-to-shape approach. *Clin Transl Radiat Oncol*. 2022;32:48-51.