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Online adaptive radiotherapy for head and neck cancers on the MR linear Accelerator: Introducing a novel modified Adapt-to-Shape approach

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ABSTRACT

Introduction: The Elekta Unity MR-Linac (MRL) has enabled adaptive radiotherapy (ART) for patients with head and neck cancers (HNC). Adapt-To-Shape-Lite (ATS-Lite) is a novel Adapt-to-Shape strategy that provides ART without requiring daily clinician presence to perform online target and organ at risk (OAR) delineation. In this study we compared the performance of our clinically-delivered ATS-Lite strategy against three Adapt-To-Position (ATP) variants: Adapt Segments (ATP-AS), Optimise Weights (ATP-OW), and Optimise Shapes (ATP-OS).

Methods: Two patients with HNC received radical-dose radiotherapy on the MRL. For each fraction, an ATS-Lite plan was generated online and delivered and additional plans were generated offline for each ATP variant. To assess the clinical acceptability of a plan for every fraction, twenty clinical goals for targets and OARs were assessed for all four plans.

Results: 53 fractions were analysed. ATS-Lite passed 99.9% of mandatory dose constraints. ATP-AS and ATP-OW each failed 7.6% of mandatory dose constraints. The Planning Target Volumes for 54 Gy (D95% and D98%) were the most frequently failing dose constraint targets for ATP. ATS-Lite median fraction times for Patient 1 and 2 were 40 mins 9 s (range 28 mins 16 s – 47 mins 20 s) and 32 mins 14 s (range 25 mins 33 s – 44 mins 27 s), respectively.

Conclusions: Our early data show that the novel ATS-Lite strategy produced plans that fulfilled 99.9% of clinical dose constraints in a time frame that is tolerable for patients and comparable to ATP workflows. Therefore, ATS-Lite, which bridges the gap between ATP and full ATS, will be further utilised and developed within our institute and it is a workflow that should be considered for treating patients with HNC on the MRL.

Introduction

MR-guided radiotherapy (MRgRT) is capable of fulfilling the objectives of online or offline adaptive radiotherapy (ART) that are beyond the capabilities of conventional C-arm linacs. The Elekta AB. (Stockholm, Sweden) Unity MR-Linac (MRL) provides the ability to perform daily MR imaging with the on-board 1.5 T MRI scanner. The Elekta-Unity based treatment strategies include Adapt-To-Position (ATP) and Adapt-To-Shape (ATS), described in detail by Winkel *et al* [1].

Preliminary work at our institute explored the ATP-based approach to treat HNC on the MRL [2]. It was not possible to reproduce clinically acceptable dose distributions when ATP workflows based on patient offsets >2 mm were simulated. For an ATS workflow, daily online delineation of target structures in head and neck cancers (HNC) is time-consuming due to the complex anatomy. With the patient immobilised in a radiotherapy shell, treatment sessions should be as short as practically possible. Therefore, we ruled out full ATS as a feasible strategy for our practice and a simplified ATS workflow (ATS-Lite) was developed and clinically commissioned at our institute to treat patients with HNC.

The aim of this study was to analyse the first two patients with HNC treated on the MRL, comparing the dosimetry for clinically delivered plans generated using ATS-Lite against what would have been generated using ATP.

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Materials and Methods:

Patient characteristics and study protocol:

Two patients with locally-advanced, (T3-4a/ N2c/ M0), p16-positive base-of-tongue squamous cell carcinomas received radical radiotherapy within the PERMIT study (NCT03727698). Primary tumour and involved nodes received 65 Gy and nodal regions at risk of harbouring microscopic disease received 54 Gy in 30 fractions over six weeks [3]. Targets were delineated according to primary CTV consensus delineation guidelines as described by Gregoire *et al* [4]. A 3 mm CTV to PTV expansion margin was used as per institutional protocol. Concurrent Cisplatin (100 mg/m^2) on days 1 and 29 was prescribed for one patient.

Radiotherapy workflow and planning:

Bulk-Density Assignment:

It has previously been shown that bulk-density override (BDO) techniques can provide sufficient accuracy and the radiotherapy dose calculations using the algorithm in the Raystation treatment planning system (TPS) accurately agree with those using the ground truth look-up-table (LUT) approach [5]. A minimum of eight BDOs were required for sufficient dosimetry when using the Monaco (Elekta AB, Stockholm, Sweden, V5.40.01) TPS (Supplementary Section A).

Adapt-to-Shape-Lite:

Patients had a contrast-enhanced planning CT and an Elekta-approved T2-weighted 3D MRI sequence on the MRL, in a 5-point thermoplastic head shell. Reference plans were generated using a 15-field beam arrangement in the Monaco TPS according to local departmental clinical goals (Table 1).

Dose was calculated to medium using a 0.3 cm isotropic dose grid and 1% statistical uncertainty per plan. Ten segment shape optimisation (SSO) loops were used with a maximum of 100 segments, minimum segment area of 4 cm^2 and minimum of 6 monitor units per segment allowed. After optimisation, the monitor units were re-scaled so that the primary PTV D50% was 65 Gy. For clinically delivered treatments using ATS-Lite, dose calculation on MR was facilitated by locally implemented bulk-density assignment approach. A LUT check was performed as part of the standard reference planning procedure (Supplementary Section A).

For daily treatments, deformable propagation of external contours from the reference CT image to the daily MRI accounts for interfraction external contour changes. The integrity of this propagation is reviewed online by the attending physicist and any errors manually corrected if necessary. Rigid propagation of other contours absolves the clinician from having to be present on a daily basis to perform online contouring. To assess gross regions of interest (ROI) propagation errors, online reviews at the time of image registrations are performed by members of the physics team on a daily basis. In addition, offline reviews are performed by clinicians once weekly, where any target or organ displacements and incorrect ROI placements are rectified by performing a repeat set-up, head-shell and planning CT.

Region of Interest Propagation:

The potential for rigidly-propagated superficial structures (e.g. parotid glands or CTV) appearing outside the external contour in the event of weight loss was previously evaluated. Parotid ROIs are constrained to regions intersecting with the external contour only. It is well known that parotid glands may migrate medially over the course of radiotherapy [6], so the medial border of the parotids is reviewed in a weekly clinicians' offline review to ensure the ROIs still accurately represent the location of parotid glands.

Adapt-to-Position:

ATP requires an initial reference treatment plan to be generated on a reference image (CT or MR). The daily MR image is registered with the reference image and the Multi-Leaf Collimator (MLC) leaves are adapted to the new target position according to the translations-only rigid registration. The ATP plan can either be recalculated with the adapted MLCs (Adapt Segments, AS), or undergo optimisation following MLC adaptation to better recreate the dose of the reference plan. This optimisation may either be segment weights alone (Optimise Weights, OW)

Table 1

Structure sets and dose constraints passed: percentage pass rates are reported for the total number of fractions that achieved the mandatory/ optimal dose constraints for each planning modality (maximum 53 fractions per constraint). *Numbers in brackets denote the percentage of fractions that also passed optimal clinical goals. Clinical goals for the parotid glands required dose to be as low as possible, with optimal constraints only. A summary of the total dose constraints achieved is presented at the bottom. A total of 1060 dose constraints per planning method are counted. Pass refers to both optimal and mandatory passes. Optimal and mandatory failures are presented separately. PRV – Planning Risk Volume (3 mm expansion); AS – Adapt Segments; OW – Optimise Weights; OS – Optimise Shapes.

Structure	Dose Constraint (Gy)		ATP Mandatory Pass (Optimal Pass), (%)			ATS-Lite Mandatory Pass (Optimal Pass), (%)
	Mandatory	Optimal	AS	OW	OS	
PTV 65.00 Gy	D95% >61.75	–	75.5	92.5	100	100
	D98% >60.45	D98% >61.75	94.3 (20.8)*	98.1 (37.7)*	100 (52.8)*	100 (86.8)*
	D99% >58.50	–	100	100	100	100
	D2% <71.50	D2% <69.55	100 (90.6)*	100 (100)*	100 (98.1)*	100 (100)*
	D5% <69.55	D5% <68.25	100 (67.9)*	100 (90.6)*	100 (84.9)*	100 (92.5)*
PTV 54.00 Gy	D95% >51.30	–	45.3	34	37.7	98.1
	D98% >50.22	D98% >51.30	52.8 (1.9)*	49.1 (0)*	56.6 (1.9)*	100 (49.1)*
	D99% >48.60	–	84.9	73.6	88.7	100
	D2% <59.40	D2% <57.78	100 (15.1)*	100 (22.6)*	100 (34)*	100 (81.1)*
	D5% <57.78	D5% <56.70	94.3 (13.2)*	100 (24.5)*	100 (39.6)*	100 (90.6)*
Spinal Cord	D0.1 cm^3 < 44.50	–	100	100	100	100
Spinal Cord (PRV)	D0.1 cm^3 < 46.50	–	100	100	100	100
Brainstem	D0.1 cm^3 < 52.50	–	100	100	100	100
Brainstem (PRV)	D0.1 cm^3 < 54.50	–	100	100	100	100
Left Lens	D_{mean} < 6.00	–	100	100	100	100
Right Lens	D_{mean} < 6.00	–	100	100	100	100
Left Orbit	D0.1 cm^3 < 43.50	–	100	100	100	100
Right Orbit	D0.1 cm^3 < 43.50	–	100	100	100	100
Left Parotid	–	D_{mean} < 24.00	(43.4)*	(43.4)*	(37.7)*	(3.8)*
Right Parotid	–	D_{mean} < 24.00	(56.6)*	(56.6)*	(58.5)*	(56.6)*

SUMMARY	AS	OW	OS	ATS-Lite
PASS (%)	70.8	73.8	76.7	88
OPTIMAL CONSTRAINT FAIL (%)	21.6	18.6	17.5	12
MANDATORY CONSTRAINT FAIL (%)	7.6	7.6	5.8	0.1

or segment shapes and weights (Optimise Shapes, OS). The ATP dose is calculated on the reference image and, therefore, does not explicitly account for variations in daily anatomy compared to that at the time of the reference image acquisition.

For this study's assessments, simulated online plans for each ATP variant were retrospectively calculated (AS) or optimised (OW or OS) using the default Monaco TPS optimisation parameters for every fraction. ATS-Lite uses the standard Monaco TPS inverse planning optimiser, whereas ATP utilises a simplified optimisation algorithm specifically developed for this planning strategy [7]. Daily plans were calculated to 30 fractions to allow the use of local standard clinical goals to assess plan acceptability.

Data Analysis:

Passes and failures of mandatory and optimal dose constraints were recorded for twelve organs-at-risk (OARs) and twenty targets (Table 1). To assess for any differences in the pass rates between the four planning methods, a Chi squared test with six degrees of freedom was used. Correlations between maximum set-up shifts in three dimensions (left–right, superior-inferior and anterior-posterior) and the rate of dose constraint pass or failures for each patient at every fraction were determined using the Pearson correlation coefficient. A p-value of < 0.05 was considered statistically significant. Other data were presented as absolute values or differences. Statistical analyses were performed using Microsoft Excel (version 16.45, 2021).

Results:

'Patient 1' completed 23 fractions on the MRL and 7 fractions on conventional C-arm linac due to non-radiotherapy associated complications. 'Patient 2' received 30 fractions on the MRL. Therefore, a total of 53 fractions treated on the MRL were evaluable. During radiotherapy, 'Patients 1 and 2' lost 12.5 and 6.5 kg mass during the course of treatment with a maximum of 11 and 14 mm external contour changes within the treatment fields, respectively. Neither patient required a new mask to be made or required any amendments to the contours as a consequence. The parotid ROIs remained clinically acceptable.

A breakdown of clinical goal pass rates is displayed in Table 1 with a summary of dose constraint pass rates to highlight differences between optimal and mandatory constraint passes. Dose re-scaling after optimisation was $< 1\%$ in all cases. ATS-Lite was the superior planning modality with the greatest pass rate for mandatory constraints (99.9%; $p < 0.01$). There was only a single mandatory dose constraint failure. OS was the best-performing ATP planning modality, with the fewest mandatory dose constraint failures ($n = 62$, 5.8%). ATP-AS and ATP-OW performed inferiorly and produced the greatest numbers of mandatory dose constraint failures ($n = 81$, 7.6% each). An example dose-volume histogram is provided in Supplementary Section B. A significant moderate correlation was noted between the degrees of patient set-up errors and dose constraint failures (Table 2).

PTV 54 Gy D95% and D98% mandatory dose constraints failed most frequently. Mean dose deficits were greatest for ATP-OW (0.51 Gy (standard deviation (SD) 0.28 Gy) and 0.70 Gy (SD 0.46 Gy)) and least for ATP-OS (0.27 Gy (SD 0.19 Gy) and 0.44 Gy (SD 0.25 Gy)) for PTV 54 Gy D95% and D98% respectively. Failures occurred throughout treatment and were not skewed towards any time-point during radiotherapy. 'Patient 1' experienced 70% of all ATP related failures. Further information on degree of dose deficits are provided in Table 3.

For ATS-Lite, median online plan optimisation times for 'Patient 1' and 'Patient 2' were 11 mins 29 s (range 3 mins 18 s – 13 mins 26 s) and 6 mins 4 s (range 3 mins 15 s – 8 mins 8 s), respectively. Median treatment session durations (defined as total time on treatment couch) for 'Patient 1' and 'Patient 2' were 40 mins 9 s (range 28 mins 16 s – 47 mins 20 s) and 32 mins 14 s (range 25 mins 33 s – 44 mins 27 s), respectively.

Table 2
Patient set-up shifts compared against dose constraint failures: absolute setup displacement was compared against the degree of dose constraint pass or failures. Pearson correlation coefficients are reported for each ATP planning modality for the two most frequently failing targets (PTV 54.00 Gy, D95% and D98%). Direct isocentre shift distances were calculated from setup shifts in 3 coordinates using Pythagoras theory methods. The greatest shifts occurred in the superior-inferior direction.* p-value < 0.05 in all cases. AS – Adapt Segments; OW – Optimise Weights; OS – Optimise Shapes.

Dose Constraint		ATP Variant	Patient 1	Patient 2
PTV 54 Gy	**D95% >51.30 Gy**	**AS**	*0.35 (-0.07–0.67)	*0.4 (0.05–0.67)
		OW	*0.54 (0.17–0.78)	*0.57 (0.26–0.77)
		OS	*0.52 (0.14–0.77)	*0.41 (0.06–0.67)
	D98% >50.22 Gy	**AS**	*0.46 (0.05–0.73)	*0.48 (0.15–0.72)
		OW	*0.57 (0.21–0.80)	*0.58 (0.28–0.78)
		OS	*0.56 (0.2–0.79)	*0.44 (0.09–0.69)
		Mean setup shift (SD, mm)		
		Right-Left	-1.63 (1.94)	1.18 (1.56)
		Anterior-Posterior	-1.78 (1.44)	-0.20 (1.43)
		Superior-Inferior	3.29 (1.95)	3.31 (1.87)

Discussion:

Our data show that the novel ATS-Lite approach was the most robust online treatment planning method, satisfying 99.9% of mandatory dose constraints. ATS-Lite was designed as a means of providing adapted dose delivery for HNC on the MRL, avoiding the need for daily presence of a clinician as is required for ATS-based approaches.

We concluded that ATP performance was not consistent enough to warrant its use over conventional C-arm linac-based treatments, as we deem it similar to daily IGRT-based treatment on a C-arm linac, but with MLC adaptation rather than couch movements. This was reflected in our preliminary assessments, where all ATP modalities could not generate adequate plans when simulating shifts above 2 mm or when less complex reference plans were used (9 beams and sequence parameters adjusted to generate plans with fewer overall segments). In contrast, our ATS-Lite planning solution has demonstrated robustness to such degrees of patient alignment shifts and anatomical changes over the course of treatment, making the decision process to determine online plan acceptability more straightforward.

McDonald *et al* evaluated the workflow and performance of their ATP approach for HNC [8]. Their tolerance for set-up shifts is < 5 mm in any one direction, with any greater shifts triggering an offline ATS re-plan. Although per fraction dose statistics were not reported, 40% of patients had combination ATP and single offline ATS plans as a result of excessive soft-tissue deformation. Their median ATP fraction time was 46 mins (range 31–85 mins). Longer treatment times were attributed to patient repositioning or unacceptable plans being generated due to anatomical changes. In the event of recurrent dose constraint failures despite repositioning, their protocol warrants consultation with a clinician and potential triggering of an offline ATS re-plan.

Improvements in treatment experience resulted in progressively shortened planning and treatment times in subsequent fractions for 'Patient 1,' eventually matching treatment times for 'Patient 2.' ATS-Lite is also more robust to large shifts, which resulted in fewer dose constraint failures and no need to re-position or re-plan our patients, contributing to the relatively shorter treatment times. Although the parameters for defining treatment times are not standardised, our times are on par with ATP-based treatment deliveries reported for other

Table 3
Dose deficits for ATP fractions failing mandatory dose constraints: the table below displays the mean dose deficit compared to the reference plan for each ATP modality, for Patients "1" and "2." For comparisons, ATS-Lite data is also shown to demonstrate the mean amount of dose by which constraints were passed. PTV 54 Gy target was the most frequently failing target. Patient 2 did not fail 'PTV 54 Gy D99%' target.

Structure	Dose Constraint (Gy)	Mean Degree of Dose Failure (SD, Gy)							
		ATP-AS		ATP-OW		ATP-OS		ATS-Lite	
	Mandatory	1	2	1	2	1	2	1	2
PTV 54.00 Gy	D95% >51.30	−0.5 (0.25)	−0.21 (0.14)	−0.67 (0.22)	−0.34 (0.24)	−0.34 (0.17)	−0.16 (0.17)	0.4 (0.17)	0.64 (0.15)
	D98% >50.22	−0.69 (0.31)	−1.32 (0.17)	−0.82 (0.51)	−1.54 (0.21)	−0.49 (0.24)	−1.31 (0.21)	0.78 (0.25)	1.19 (0.18)
	D99% >48.60	−1.96 (0.13)	–	−2.09 (0.18)	–	−1.86 (0.26)	–	1.87 (0.3)	2.42 (0.21)

tumour sites [9–11].

Our current ATS-Lite treatment workflow provides a sound basis for the delivery of MRgART using the Elekta Unity MRL. However, although the deformable external contour algorithms provide a means for correction for body contour and weight loss, rigid OAR and target contour propagation does not account for evolving target changes. This study is an initial analysis of our novel approach and we acknowledge the limited number of patients in this study. However, by comparing ATS-Lite and ATP performance on a per fraction basis, we feel that 53 planning events provide sufficient quality assurance to continue using and building confidence in ATS-Lite for all locally-advanced HNC on the MRL.

Further development of treatments for HNC that include exploration of deformable contour propagation strategies to mitigate organ positional shifts or volume changes would pave the way towards full ATS workflow. Auto-segmentation tools under development could be implemented to assist accuracy and allow adapted contours with minimal or no clinician input [12]. Optimisation of functional MRI sequences are also in progress, within the PRIMER (NCT02973828) and MOMENTUM (NCT04075305) studies, and we aspire to translate biologically-guided ART strategies currently being investigated on diagnostic MRI machines and C-arm linacs onto the MRL [13].

Conclusion:

To generate clinically acceptable HNC treatment plans for the MRL in a tolerable timeframe, the novel ATS-Lite workflow is preferred. ATS-Lite produced optimised plans with negligible clinical goal failure rates, whereas ATP could not reliably reproduce clinically acceptable dose distributions. ATS-Lite bridges the gap between ATP and ATS and is a step towards full online plan adaptation to perform daily anatomical and biological ART.

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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Conflicts of interests

KH reports personal fees for serving as an advisory board member from MSD, AstraZeneca, Amgen, Boehringer Ingelheim, Merck Serono, Mersana, Oncolys, Pfizer, Replimmune, and Vyriad; personal fees for serving as a speaker from MSD, AstraZeneca, Amgen, Merck Serono; and honoraria from MSD, AstraZeneca, Amgen, Boehringer Ingelheim, Merck Serono, Pfizer, Replimmune, and Vyriad. All other authors declare they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2021.11.001.

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