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Evaluation and risk factors of volume and dose differences of selected structures in patients with head and neck cancer treated on Helical TomoTherapy by using Deformable Image Registration tool

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Abstract

Introduction: The aim of this study was the evaluation of volume and dose differences in selected structures in patients with head and neck cancer during treatment on Helical TomoTherapy (HT) using a commercially available deformable image registration (DIR) tool. We attempted to identify anatomical and clinical predictive factors for significant volume changes probability.

Material and methods: According to our institutional protocol, we retrospectively evaluated the group of 20 H&N cancer patients treated with HT who received Adaptive Radiotherapy (ART) due to soft tissue alterations spotted on daily MVCT. We compared volumes on initial computed tomography (iCT) and replanning computed tomography (rCT) for clinical target volumes (CTV) – CTV1 (the primary tumor) and CTV2 (metastatic lymph nodes), parotid glands (PG) and body contour (B-body). To estimate the planned and delivered dose discrepancy, the dose from the original plan was registered and deformed to create a simulation of dose distribution on rCT (DIR-rCT).

Results: The decision to replan was made at the 4th week of RT (N = 6; 30%). The average volume reduction in parotid right PG[R] and left PG[L] was 4.37 cc (18.9%) ($p < 0.001$) and 3.77 cc (16.8%) ($p = 0.004$), respectively. In N = 13/20 cases, the delivered dose was greater than the planned dose for PG[R] of mean 3 Gy ($p < 0.001$), and in N = 6/20 patients for PG[L] the mean of 3.6 Gy ($p = 0.031$). Multivariate regression analysis showed a very strong predictor explaining 88% ($R^2 = 0.88$) and 83% ($R^2 = 0.83$) of the variance based on the mean dose of iPG[R] and iPG[L] ($p < 0.001$), respectively. No statistically significant correlation between volume changes and risk factors was found.

Conclusions: Dosimetric changes to the target demonstrated the validity of replanning. A DIR tool can be successfully used for dose deformation and ART qualification, significantly reducing the workload of radiotherapy centers. In addition, the mean dose for PG was a significant predictor that may indicate the need for a replan.

Keywords: replanning; adaptive radiotherapy; head and neck cancer; Deformable Image Registration; Tomotherapy.

Introduction

Techniques used for treatment planning in modern radiotherapy (RT) are evolving. Intensity Modulated Radiation Therapy (IMRT) delivers highly conformal doses to irregular target areas while sparing surrounding organs at risk (OAR). Volumetric arc therapy (VMAT) or helical dose delivery techniques in Helical Tomotherapy (HT) are examples of the application of technological advances in radiotherapy. However, increasing accuracy also requires improvements in verifying anatomical changes that could occur during the 6–7-week Head and Neck cancer (HNC) treatment course.

The process of replanning based on response to treatment is defined as Adaptive Radiotherapy (ART). Image-guided radiotherapy (IGRT) as daily 3D imaging for all HNC patients is proposed as a standard protocol to enable faster and more accurate decisions about replanning and, further, ART.[1] Dose calculation and deformable image registration (DIR) based on

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Authors' contribution:
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article.

IGRT protocols are increasingly important in RT, from planning to toxicity prediction.[2-6] DIR routinely used can reduce the workload associated with contour propagation and treatment planning and streamline the ART procedure. It involves estimating the geometric transformation between two images to map them onto a standard coordinate system (CCS). This process is deformable or nonlinear because it includes deformations such as shrinkage or stretching in addition to the rigid transformation (i.e., translation or rotation).[7]

The purpose of this study was to evaluate the volume and dose differences in specified structures in patients with head and neck cancer, by comparing initial (iCT) and re-planning CT (rCT) and performing calculations using a commercially available deformable image registration (DIR) tool. Therefore, we have also demonstrated the validity of replanning at the time-point of replanning qualification according to our institutional B-ART (Best for - Adaptive Radiotherapy) protocol.[8] After achieving the first objective, we attempted to identify anatomical and clinical predictive factors for volume changes probability, such as age, gender, treatment scheme, or initial diagnosis.

Materials and Methods

Patient characteristics

A retrospective analysis of 20 patients who qualified for ART in the first 25 fractions of radiotherapy was done. All patients underwent helical TomoTherapy (Accuray Inc., Sunnyvale, CA, USA) IMRT for newly diagnosed, biopsy-proven head and neck squamous cell carcinoma (HNSCC), with (N = 16; 80%) or without (N = 4; 20%) concurrent chemotherapy (CHT) and (N = 7; 35%) patients had previously undergone surgery. **Table 1** shows the demographic and clinical characteristics of the sample. The median patients' age was 57 years (47–75 years). Most cases were at advanced clinical stage (T4; 70% and N2; 60%).

Treatment planning

All patients were immobilized with a 5-point (Civco Medical Solutions, Kalona, IA, USA) custom-fitted thermoplastic face and shoulder mask. Planning initial computed tomography (iCT) imaging was performed on a Siemens Definition AS scanner using 3-mm slice spacing. CT data were loaded into Aria – Eclipse ver. 13.6 software (Varian, Palo Alto, USA) for the contouring process. All treatment plans were optimized on a Hi-Art HT planning system. Gross tumor volume (GTV) was defined as the pathological mass shown in initial computed tomography (iCT) images fused with intravenous (IV) contrast CT. The clinical tumor volume (CTV1) was usually defined as the GTV with a margin of potential microscopic spread and (CTV2) as a high-risk area of lymph nodes. CTVs were expanded by 3 mm to respective planning target volumes (PTV). All organs at risk (OARs) were contoured according to DAHANCA, EORTC consensus guidelines.[9] For study purposes, a new parameter, B-body structure, covering the area from the apex of the skull to the sternum (suprasternal notch) at the T3 vertebra level was added for the analysis. Treatment plans were optimized to ensure that 98% of the PTV received 100% of the prescribed dose, with ≤ 2% of the PTV volume receiving 107% of the dose. The dose to the primary tumor ranged from 60–70 Gy. The median fraction dose was 2 Gy (range 1.8-2 Gy). N = 15/20 (75%) patients received 70 Gy/35 fx, N = 2/20 (10%) – 66 Gy/33 fx, N = 2/20 (10%) – 61.2 Gy/34 fx and N = 1/20 (5%) – 60 Gy/30 fx.

Re-plan management

All patients had daily mega-voltage computed tomography (MVCT) during the radiotherapy course and were evaluated with a weekly physical examination. According to our institutional B-ART protocol used for this study, the daily MVCT scanning area included the GTV and critical organs in its vicinity.[8] Once a week, the entire PTV area with all OARs included in the planning process was subjected to image verification. The correspondence evaluation was performed based on (I) bone structures and (II) soft tissue reconstruction. Our B-ART protocol considers changes > 3 mm on 3-4 consecutive scans at any point of the external contour as significant and as an indication for replanning. The whole ART workflow is detailed in **Figure 1**.

Table 1. Demographics and tumor characteristics of the patients. N = 20, median of age 57 years (range 47 – 75 years).

Characteristic		N	(%)
Gender	F	1	5%
	M	19	95%
Diagnosis	OPC	8	40%
	OCC	4	20%
	L	1	5%
	MS	3	15%
	HPC	1	5%
	NPC	2	10%
	NCC	1	5%
Stage (TNM)	T1	3	15%
	T2	1	5%
	T3	2	10%
	T4	14	70%
	N0	3	15%
	N1	4	20%
	N2	12	60%
	N3	1	5%
Treatment	RT (alone)	4	20%
	Post-operative	7	35%
	RTCHT	16	80%

Abbreviations; F = Female, M = Male, OPC = Oropharyngeal Cancers, Oral Cavity Cancers, OCC = Oral Cavity Cancers, NPC = Nasopharynx, L = Larynx, HPC = Hypopharynx, CUP = Cancer of unknown primary, NCC = Nasal Cavity Cancer, MS = Maxillary Sinus Cancer, RT = Radiotherapy, RTCHT = Radiochemotherapy

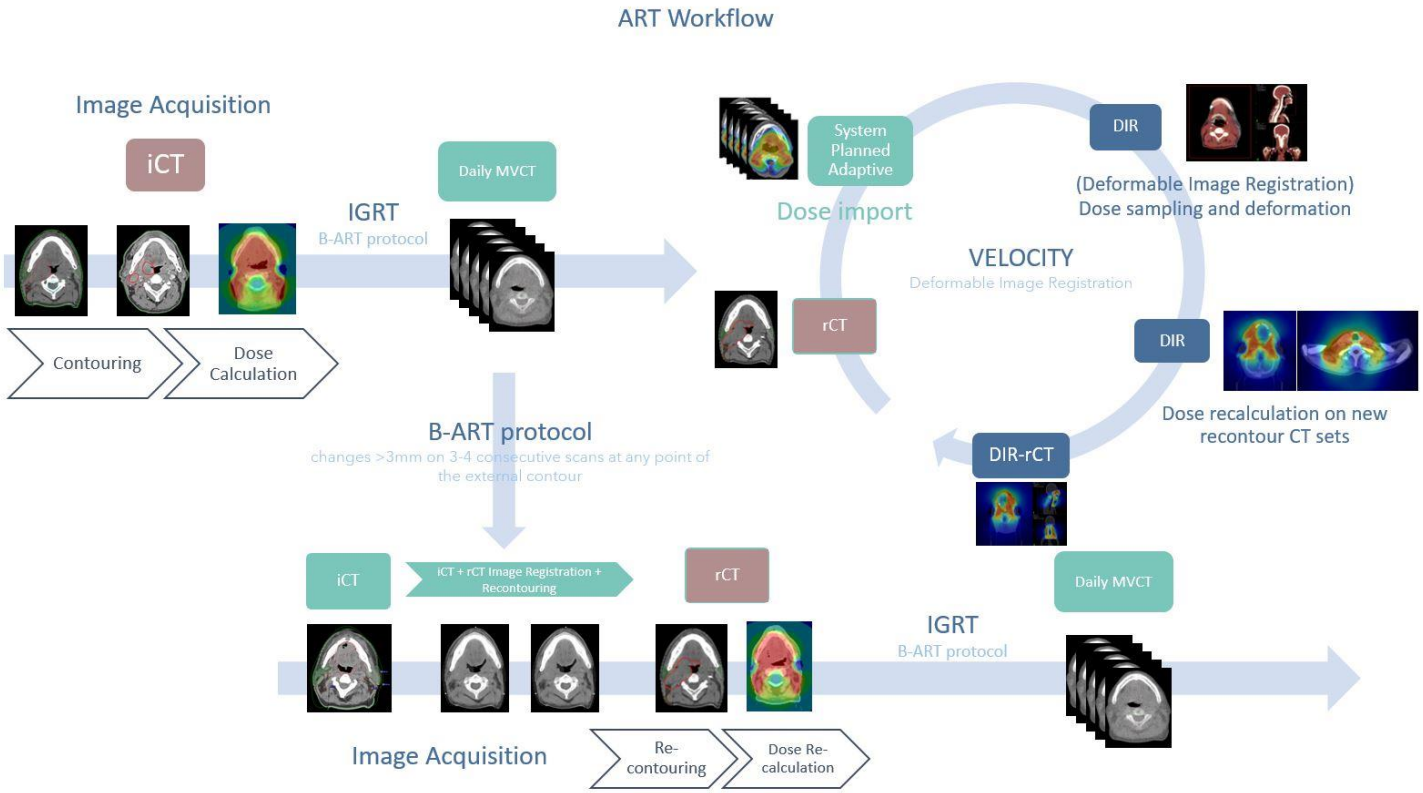


Figure 1. Workflow of our institutional Best Adaptive Radiotherapy protocol. Abbreviations; iCT = initial computed tomography, rCT= replan computed tomography, IGRT = Image-guided radiotherapy, DIR = deformable image registration, B-ART = Best for adaptive radiotherapy, ART = Adaptive radiotherapy.

The replanning CT (rCT) scans were acquired for all 20 patients according to the guidelines for replanning included in our B-ART protocol. GTVs and OARs were re-contoured as required on the rCT by the same radiation oncologist (RO). Attempts were made to maintain the original CTVs with the modification that adapt to the changes in patients' anatomy. Then new HT plans on replanning CT were generated for the remaining treatment fractions to achieve at least comparable target coverage and OAR doses to the original ones, and patients continued treatment. The associated dosimetric changes were also calculated to confirm the replanning decision's validity, which was based on observed anatomical (geometric) changes. The dose distribution was executed using the deformable image registration based on the B-spline algorithms (curvilinear registration) process available in the Velocity software ver. 3.2.0 (Varian Medical Systems, Palo Alto, USA). Velocity's validation process simulates the dose distribution from the initial treatment CT on new replanning CT (rCT) scans. The initial treatment plan was recalculated on the rCT scans to estimate the planned and delivered dose discrepancy. To achieve that, the dose from the original plan was registered and deformed using Velocity program to create a simulation of dose distribution on rCT (DIR-rCT).

Results

In the analyzed group of patients, the mean CTV1 (tumor) volume reduction was ΔVcc = 6.68 cc (-51.7–74.4cc), ΔV% = 4.6% (p = 0.243). The mean CTV2 (nodal) volume reduction was ΔVcc = 4.8cc (-37.7–40.6 cc), ΔV% = 6.6% (p < 0.236), and it was not statistically significant (**Table 2**). Parameter B-body differed in the neck region with a mean volume reduction of ΔVcc = 146.6 cc, ΔV% = 1.7% (p < 0.319) (**Table 2**). The average reduction in parotids' volume was statistically significant, and it was for PG[R] ΔVcc = 4.37 cc (-14.8–5.70 cc), ΔV% = 18.9% (p < 0.001), and for PG[L] ΔVcc = 3.77cc (-17.3–3.2 cc), ΔVcc = 16.8% (p = 0.004). The greatest absolute and percent volume reduction was noted for PTV: ΔVcc = 35.43 cc and ΔV% = 6% (p = 0.009) (**Table 2**).

There was no statistically significant correlation between ΔV of: PTV, CTV1 (tumor), CTV2 (nodal), PG and age, gender, primary diagnosis, or treatment scheme (RT/RCHT/Post-op) (**Table 4**).

Based on IGRT realized by the B-ART protocol, the average time at which significant changes were observed, and the decision to replan was made, was at the 16th fraction (6–22 fraction), corresponding to the beginning of the fourth week of treatment (N = 6, 30%). The average time for creating a new plan was three days.

Table 2. The volumes and the volumetric reduction (ΔVcc = ΔV(iCT/rCT), Δ% = (iCT - rCT)/ iCT × 100%) between images from initial CT (iCT) and re-planning CT (rCT) for primary tumor (CTV1), metastatic lymph nodes (CTV2), parotid glands (PG), planning target volume (PTV) and body contour (B-body). P-values resulting from dependent samples t-test(1) (for normally distributed continuous variables) and Wilcoxon- test(2) (for not normally distributed variables). P-values lower than 0.05, representing statistical significance, are in bold.

Volume	Mean [cc]	Median [cc]	SD [cc]	Volume	Mean Volume reduction		p-value
					[Δcc] / [SD]	[Δ%]	
iCTV1	145.9	138.3	79.1	iCTV1 / rCTV1	6.6 / 24.8	(4.6%)	0.243 (1)
rCTV1	139.2	134.2	75.0				
iCTV2	73.5	52	54.6	iCTV2 / rCTV2	4.8 / 17.3	(6.6%)	0.236 (1)
rCTV2	68.7	52.7	46.8				
iPTV	585.7	581.9	184.8	iPTV / rPTV	35.4 /54.6	(6%)	**0.009 (2)**
rPTV	550.3	555.8	169.3				
iPG [R]	23.1	21.9	8.1	iPG [R] / rPG [R]	4.3 / 5.07	(18.9%)	**< .001** (1)
rPG [R]	18.7	18.1	5.9				
iPG [L]	22.4	20.9	9.3	iPG [L] / rPG [L]	3.7 / 5.2	(16.8%)	**0.004** (1)
rPG [L]	18.6	18.4	7.1				
iB-body	8752.9	8702.6	1335.9	iB-body / rB-body	146.7 /641.6	(1.7%)	0.319 (1)
rB-body	8606.2	8675.5	1193.3				

Abbreviations; cc = cubic centimeter, iCT = initial computed tomography, rCT = replanning computed tomography, CTV = clinical target volume parotid glands right and left PG[R] = right parotid gland, PG[L] = left parotid gland planning target volume, PTV = planning target volume, B-body = body contour

Table 3. The dosimetric analysis parameters for selected structure for the H&N patients, p-values resulting from dependent samples t-test(1) (for normally distributed continuous variables) and Wilcoxon-test(2) (for not normally distributed variables). P-values lower than 0.05, representing statistical significance, are in bold.

Structure	Parameter	iCT (Mean)	DIRrCT (Mean)	Mean difference	SD	p-value
PTV	Dmean [Gy]	51.1	50.5	0.2	2.1	**0.002** (2)
	Dmax [Gy]	55.1	54.6	0.4	3.4	**0.016** (2)
	Dmin [Gy]	26.8	22.4	4.6	7.4	**0.024** (1)
	D95 [Gy]	49.6	48.2	1.1	1.2	**<.001** (2)
	V95 [%]	98.3	95.6	2.5	1.8	**<.001** (1)
	D5 [Gy]	51.8	51.6	0.2	2.4	**<.001** (2)
	D2 [Gy]	52.2	52	0.2	2.4	**<.001** (2)
PG [R]	Dmean [Gy]	17.8	19.1	1.0	5.02	0.108 (2)
	V30 [Gy]	23.5	26.1	3.5	13.8	**0.098** (2)
PG [L]	Dmean [Gy]	20.9	20.9	0.7	4.4	0.240 (2)
	V30 [Gy]	32.5	28.6	4	12.1	**0.004** (2)
SC	Dmax [Gy]	18.4	19	0.6	0.6	0.212 (2)
	D2 [Gy]	16.2	16.5	0.3	0.2	0.140 (2)

Abbreviations; D95 = near-minimum dose, V95 = near maximum dose, PTV = Planning Target Volume, PG = Parotid Gland, SC = Spinal Cord, iCT = initial computed tomography.

Table 4. Correlation test results between ΔV(iCT/rCT) for PTV, CTV1 (tumor), CTV2 (nodal) and PG for all the considered variables; age, gender, radiotherapy alone RT (yes/no), concomitant chemotherapy RCHT (yes/no), post-surgery post-op (yes/no), primary tumor site (nasopharynx, oropharynx, hypopharynx, larynx, other). PG = parotid gland, CTV = clinical tumor volume, PTV = planning target volume. P-Values resulting from independent samples t-test(1) (for normally distributed continuous variables), Mann-Whitney U test (2) (for continuous variables with skew distributions), and Kruskal-Wallis test(3). Statistically significant values are presented in bold.

ΔV(iCT/rCT)		PTV	CTV1	CTV 2	PG[R]	PG [L]
		p-value	p-value	p-value	p-value	p-value
Age		0.183 (2)	0.603 (2)	0.196 (2)	0.117 (2)	0.173 (2)
Gender		0.862 (2)	0.141 (2)	0.165 (2)	0.386 (2)	0.165 (2)
Primary tumor site		0.835 (1)	0.449 (1)	0.919 (1)	0.210 (1)	0.320 (1)
Staging	Stage T	0.924 (3)	0.069 (3)	0.098 (3)	0.149 (3)	0.100 (3)
	Stage N	0.738 (3)	0.057 (3)	0.094 (3)	0.402 (3)	0.328 (3)
RT Scheme	Radiotherapy	0.422 (2)	0.887 (2)	0.321 (2)	1.000 (2)	0.887 (2)
	RCHT	0.422 (2)	0.887 (2)	0.321 (2)	1.000 (2)	0.887 (2)
	post-surgery	0.250 (2)	0.142 (2)	0.905 (2)	0.663 (2)	0.322 (2)

Table 5. Multivariate regression analysis based on velocity replanned plans included analyses of 2 models: (1) DIR Dmean of replan parotid gland right (DIR-rPG [R] Dmean), and (2) DIR Dmean of replan parotid gland left (DIR-rPG[L] Dmean)

Model (1): DIR-Dmean rPG [R]

Model Fit Measures					
R	**R²**	**F**	**df1**	**df2**	**p**
0.940	**0.883**	16.35	6	13	**< .001**
Model Coefficients					
Predictor		**B**	**β**	**T**	**p**
Intercept		15.08		2.28	0.040
iPG [R] Dmean (Gy)		0.53	0.431	2.38	**0.033**
iPG [L] Dmean (Gy)		0.19	0.136	1.33	0.208
iPG [R] (cc)		-0.48	-0.625	-2.51	**0.026**
iPG [L] (cc)		0.42	0.628	2.49	**0.027**
iB-body (cc)		<0.01	-0.471	-2.95	**0.011**
iPTV (cc)		0.02	0.575	2.83	**0.014**

Model (2): DIR-Dmean rPG [L]

Model Fit Measures					
R	**R²**	**F**	**df1**	**df2**	**p**
0.912	**0.832**	10.80	6	13	**< .001**
Model Coefficients					
Predictor		**B**	**β**	**T**	**p**
Intercept		3.7320		0.552	0.590
iPG [R] Dmean (Gy)		0.13	0.123	0.567	0.580
iPG [L] Dmean (Gy)		1.002	0.840	6.845	**< .001**
iPG [R] (cc)		-0.468	-0.719	-2.412	**0.031**
iPG [L] (cc)		0.338	0.596	1.972	0.070
iB-body (cc)		-0.001	-0.171	-0.891	0.389
iPTV (cc)		0.005	0.182	0.747	0.468

Abbreviations; cc = cubic centimeter, PTV = Planning Target Volume, PG = Parotid Gland, SC = Spinal Cord, iPG = initial parotid gland, DIR = deformable image registration

Dosimetry validation – (Deformable image registration)

A significant difference was found between the median initial, original planned dose and a simulation of dose distribution on rCT (DIR-rCT) for the PTV Dmean ($p = 0.002$), PTV Dmax ($p = 0.016$), PTV Dmin ($p = 0.033$), PTV V95Gy ($p < 0.001$), PTV D5% and PTV D2% ($p < 0.001$). In N = 13/20 cases, predictive models based on DIR calculation showed that the delivered dose was greater than the planned dose on initial CT for PG[R] of mean 3 Gy (1.5–4.1 Gy, $p < 0.001$). For PG[L], the increased dose was found only in N = 6/20 patients of mean 3.6 Gy (0.48–6.7 Gy, $p = 0.031$). These changes were statistically significant. According to V30 PG[R], for 15 patients, we reported that the initial volume of the area receiving 30 Gy would increase by 5% (mean 3.5%) compared to the planned, and for PG[L], for three patients, by 6% (mean 4%). DIR's calculation showed the mean 0.6 Gy (0.32–2.7 Gy) higher dose in Dmax of spinal cord than in the initial plan. These changes were found to be statistically insignificant ($p = 0.212$).

Dosimetric predictive models

A multivariate regression analysis was performed based on DIR-rCT plans, including Dmean and V30 for PGs and Dmax and D2 for the spinal cord. After initial testing, results not statistically significant were removed from the model. A regression analysis was performed to determine which predictors correlated with increased PG dose. Two models were found to be statistically significant in predicting the need for replanning during treatment: DIR-rPG[R] D_{mean} and DIR-rPG[L] D_{mean} (**Table 5**). Based on multivariate regression analysis, the first model DIR-rPG[R] D_{mean} was a very strong predictor explaining 88% ($R^2 = 0.88$) ($p < 0.001$) of the variance. The strongest factors predicting the need for replanning were found in Dmean of initial iPG[R] ($p = 0.033$) and initial volume (iV) of iPG[R] ($p = 0.026$), iPG[L] ($p = 0.027$), iB-body ($p = 0.011$), and iPTV ($p = 0.014$). Only Dmean of iPG[L] was found to be statistically insignificant ($p = 0.208$). The second model explains 83% ($R^2 = 0.83$) ($p < 0.001$) predictors for Dir-rPG[L]Dmean. In this model, significant predicting factors were found in the initial mean dose of left PG (Dmean iPG[L], $p < 0.001$) and initial volume of right PG (iV-PG[R], $p = 0.031$).

Discussion

Adaptive radiotherapy has a leading role in the treatment of H&N cancer patients. The time and probability of replanning depend on many factors like larger nodal volumes, concurrent chemotherapy, weight loss or localization, and the size of the primary tumor.[3,11,12,15,18,21-30] In the past few years, several studies have shown clinically significant reductions in doses to the parotid glands [11,14,15,16,23,26,27,31] and spinal cord [17,32-34] with at least one re-planning during the RT course. Because offline adaptive replanning adds a significant workload to the departments and leads to an associated additional dose that the patient unnecessarily receives from imaging, many studies have focused on identifying anatomic and dosimetric guidelines to determine when the plan adaptation would be optimally effective.[10,12,14,15,17,19,26,28,29,32,33,35-38]

In our study (**Table 2**) the average reduction of the parotid glands (PG) volume was statistically significant, and it was 4.37 cc, 18.9% ($p < 0.001$) for PG[R], and 3.77 cc, 16.8% ($p = 0.004$) for PG[L]. Our previous study[1] marks the volumetric changes in the parotid glands, which is mostly shrinking, as one of the main factors determining the need for replanning. Based on a significant number of the reports, we estimate that during a typical radiotherapy course of H&N cancer, an average parotid gland volume reduction reaches even 26%.

Castelli et al.[16,36] estimated two scenarios: with or without replanning. Based on the analyzed data, around 60% of the PGs overdosed by 4 Gy, and weekly replanning decreased the mean dose in PGs by 5 Gy (28.3%), which corresponds to an average

decrease of 1.1 cc/week and therefore by 11% reduction in xerostomia risk. In another study, Ren. G et al.[37] examined the data from the 100 parotid glands of 50 nasopharyngeal cancer (NPC) patients treated with helical TomoTherapy. They found the parotid volume decreased, with an average volume reduction of 21.3–42% and an average reduction of 1.07%/day of the initial volume (0.4–1.4 %/day).

The first phase of the treatment is the most crucial regarding the ART decision.[33] In our previous study[1] for patients with locally advanced H&N cancer, a weekly replanning session or early replanning in the 2nd–4th week appears to be the optimal ART strategy especially recommended for patients with T3/T4 tumors, NPC/OPC, or treated with concurrent chemotherapy in terms of dose distribution to target volume or for sparing the parotid glands.

In this study, we present our initial experience of ART based on dose mapping using the deformable image registration tool for HNC patients treated on TomoTherapy. The dose propagation using the deformable image registration based on the B-spline algorithms process available in the Velocity software was used to verify patients' inclusion criteria based on our institutional image guidance protocol Best for Adaptive Radiotherapy (B-ART). The deformable registration algorithm was carefully tested worldwide. The results showed the reasonable accuracy potential to be used in clinical settings.[7,39-41]

Our B-ART criteria are very promising. Validation of the PG volume alterations, CTV, and PTV coverage was also supported by dose distribution information using the DIR algorithm implemented in the Velocity program to confirm our model (**Table 3**). In N = 13/20 patients, calculations showed that the delivered dose would be higher than the planned dose for PG by a 3 Gy – 3.6 Gy. According to V30 (volume receiving 30 Gy), even N = 15/20 patients would have received > 5 Gy extra dose than in the initial plan.

Also, in our previous review,[1] we found several potential parameters that could be used to identify patients who might benefit from ART. The dosimetric consequences of PG shrinkage varied widely, with an average PG dose increase of 2.2 ± 2.7 Gy and, in some studies, overdose can be as high as 4 Gy,[3,16,18,30,36,37,42,43] indicating the PG mean dose as significantly associated with PG volume loss,[12,16,30,36-38] suggesting its potential as a predictor of dose changes.

In the multivariable analysis of the current study, the direct relationship between the planned PG mean dose and deviations from the planned PG mean dose was confirmed: ($R^2 = 0.88$) ($p < 0.001$) and ($R^2 = 0.83$) ($p < 0.001$) for Dir-rPG[R]Dmean and Dir-rPG[L]Dmean, respectively.

Brouwer CHL in their study, et al.[44] developed a method to predict dose deviations from the planned PG mean dose. Based on two other studies, they assumed that the volume of the parotid gland does not significantly change after the last fraction of RT. That is why the endpoint as Dmean (replanning Dmean – initial Dmean) estimates the dose deviation between the treatment end and the treatment start. Our study based on several research papers [11,14-16,23,26,27,31] shows that the volume of PG significantly changes between the 2-4th week of treatment, which corresponds to the first 25 fractions. Therefore, based on the eligibility for the replan inclusion criteria according to our image-guided protocol, we decided that the best endpoint would be (rDmean), which is the moment when the decision for replanning was held. Therefore, we estimated the dose deviation between the moment of replanning and the moment of treatment start. Those assumptions confirmed that the decision to enroll patients for ART was clinically and dosimetrically justified. The decision about replanned in our study was made significantly faster than in the paper of Brouwer CHL. et al.[44] As we found (**Table 5**), our models based on multivariable analysis were characterized by 88% and 83% vs. 59% effectiveness in predicting dose deviations from the planned PG mean dose. Proper timing for ART is crucial; undertaken wisely allows to prevent the risk of xerostomia.[45-46] Moreover, in our model (1), initial parotid volume iPG[R] ($p = 0.026$), iPG[L] ($p = 0.027$), changes from initial body contour iB-body ($p = 0.011$), and initial planning target volume iPTV (0.014) were significantly associated with PG volume loss in multivariable analysis (**Table 5**). Model (2) explains 83% predictors for a mean dose of DIR-rPG[L] Dmean. Initiating by dose changes from iPG[L] Dmean and initial volume of iPG[R]. Those two models cause the salivary glands to receive a higher homogenous dose than initially calculated, which can be explained by (i) volume changes of the salivary glands, and (ii) parotids' shifting medially towards the nodal region (into the intermediate or high dose regions). Therefore, based on the multivariable analysis, we can assume that changes from the original planned dose of the initial PG Dmean by 0.5 Gy increased by 1 Gy Dmean at the moment of the qualification for replanned on average at week 4 of treatment (N = 6; 30%).

Worldwide, ART decisions are made in a two-way approach. The collected and analyzed images obtained during IGRT provide an optimal basis for decision-making and re-optimization of treatment plans. However, it is possible to autonomously calculate the actual dose distribution in OARs and target areas using dedicated deformable image registration tools or based on the cumulative dose from CBCT (Cone Beam Computed Tomography) or MVCT (Mega Voltage Computed Tomography). Therefore, adaptive radiotherapy is increasingly becoming non-randomized but ART in the true sense of the word.

Conclusions

In such a limited group of patients, as in our study, we showed statistically significant dose escalation in both parotid glands. That indicates the prevalence of the phenomenon and highlights the importance of proper timing for ART, which, if undertaken wisely, prevents the risk of xerostomia. A deformable image

registration tool can be successfully used for simulating the dose distribution on actual patients' anatomy during the treatment course and, therefore for ART qualification, significantly reducing the workload of radiotherapy centers.

Volumetric changes in the parotid glands, which are mostly shrinking, are one of the main factors determining the need for replanning in head and neck cancer patients. In addition, the mean dose for parotid glands was a significant predictor that may indicate the need for a replan. We demonstrated the validity of replanning at the time-point indicated by our institutional B-ART protocol, proving that it is appropriate to select patients for ART.

Our study found no statistically significant correlation between volume changes and selected risk factors (age, gender, primary diagnosis, or treatment scheme), but further exploration of the subject is justified in a larger group of patients.

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