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Research article

Feasibility of DW-MRI analysis of salivary glands during head and neck radiotherapy

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ABSTRACT

Introduction: With no effective treatment for xerostomia, there remains an unmet need to reduce radiation induced toxicity. Measuring physiological changes during RT in salivary glands using DW-MRI may predict which patients are most at risk of severe toxicity. This study evaluated the feasibility of measuring apparent diffusion coefficient (ADC) in the major salivary glands and describes the observed changes in volume and ADC during RT.

Methods: Scans were acquired at baseline (MR_base) and after 10 fractions (MR_rpt). Sequences included T1 post contrast fat saturated (T1PCFS) and DW-MRI (5b values, 0–1000 s/mm2). Ipsilateral and contralateral parotid (iPG/cPG), submandibular (iSMG/cSMG) and sublingual glands (iSLG/cSLG) were delineated on T1PCFS, modified on b0 and copied to the ADC map.

Results: 31 patients with intermediate/high risk squamous cell carcinoma (SCC) of the oropharynx were evaluated. On 124 scans, SMG and SLG delineations were successful on all; parotids were fully contoured in 90.7%. Baseline mean ADC were significantly different between each gland type ($p < 0.0001$). IPG and cPG volume decreased during treatment by 6.7% and 11.2%. ISMG, cSMG, iSLG and cSLG volume increased by 6.9, 0.9, 60.8 and 60.3% respectively. All structures showed an increase in mean_ADC values. For each gland the increase in ADC was statistically significant $p < 0.0001$. A smaller mean percentage increase in ADC was observed in the group experiencing a higher grade (2 or >) of toxicity.

Conclusion: It is feasible to measure volume and ADC of the salivary glands prior to and during RT for HNC. Early data suggests a lower rise in ADC during treatment is associated with more severe late xerostomia.

Introduction

Radiotherapy (RT) or chemo-radiotherapy (CRT) is a potentially curative standard of care for head and neck squamous cell cancer (HNSCC), delivering doses of up to 70 Gy, over 6–7 weeks. While technological advances such as parotid-sparing intensity-modulated radiotherapy (IMRT) have resulted in modest improvements in observer-rated and patient-reported xerostomia, [1] clinically significant xerostomia remains a problem for many patients [2,3]. Radiotherapy-induced xerostomia is the most commonly reported late and permanent side effect of RT to the head and neck (H&N) [4]. RT preferentially damages the fluid-secreting serous cells, rather than the mucin secreting cells, of the salivary glands, so patients experience a build-up of thick, sticky mucus and a dry mouth [5]. This can cause discomfort, taste alteration, speech and swallowing difficulties, accelerating dental caries [6].

The changing epidemiology of H&N cancer, mainly due to a rise in oropharyngeal cancer caused by human papilloma virus (HPV), means that patients are often younger with little comorbidity [7]. This group has a significantly improved response to treatment and overall survival [8–10] and will therefore live much longer with the consequences of treatment [11].

With no effective treatment for xerostomia, there remains an unmet clinical need to further reduce toxicity where possible. Functional imaging with serial quantification of tumour characteristics to predict treatment response is an area of much promise and may ultimately allow biologically adaptive RT strategies [12]. Likewise, there may be an

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opportunity to measure physiological changes during RT in salivary glands or other organs at risk (OARs), and use these parameters to predict which patients are most at risk of severe toxicity. Again, biologically adaptive strategies may allow modification of RT for those at highest risk of long term morbidity.

MRI is a non-invasive, non-ionising imaging method which gives superior soft tissue contrast and is the imaging modality of choice to accurately define tumour extent in several head and neck cancer subsites [13,14]. Diffusion weighted MRI (DW-MRI) is a form of functional MR imaging based upon measuring the random brownian motion of water molecules within tissue. Molecular movement is restricted by cellular structures in high-density tissue. DW-MRI measures the indirect value of cellularity by applying the same gradient at continuous short time intervals [15]. An apparent diffusion coefficient map (ADC) is created by acquiring multiple conventional DWI images with different amounts of DWI weighting (differing b values) and the change in signal is proportional to the rate of diffusion. Different rates of diffusion are seen as areas of high or low signal on the images acquired, this is also quantifiable using ADC to measure diffusion in a region of interest (ROI). By measuring change in ADC at intervals, changes in tissue characteristics can be identified.

Aim

The aim of this study was to evaluate the feasibility of measuring ADC in the major salivary glands and to describe the observed changes in volume and ADC following 2 weeks of radiotherapy.

Methods

Patient selection

Eligible patients were those with locally advanced intermediate or high risk oropharyngeal SCC [16] scheduled for radical primary RT or CRT. Patients had participated in the MeRInO study (study of diffusion weighted MRI as a predictive biomarker of response during radiotherapy for high and intermediate risk squamous cell cancer of the oropharynx) [17]. Staging was defined using the TNM classification of malignant tumours, 7th edition [18] and those selected for this substudy were participants with 12 months of follow up who had completed baseline (MR_base) and repeat MRI (MR_rpt) scans. Research ethics committee approval was gained for the primary study (reference 15/WS/0159) and written informed consent was obtained for each patient with, specific permission requested to use their scans for additional research beyond the primary study.

MRI scan acquisition

All scans were acquired on a dedicated scanner, GE Signa 1.5 T HDxt (GE, Crawley, UK) using a 16 channel neurovascular coil (HNS NV full, GE 2012). Sequences included T1 post contrast fat saturated (T1PCFS) followed by DW-MRI, using 5b values (0–1000 s/mm2). These were acquired using a single shot EPI sequence. To reduce distortion, parallel imaging was used. ADC maps were generated using a mono exponential fit. Scans were obtained immediately prior to treatment (MR_base) and after 10 fractions (MR_rpt) i.e. 2167 centigray (cGy) of radiotherapy. An individualised headrest and standard kneerest were used to ensure reproducibility of set-up, and to allow the use of the NV coil. A patient specific measurement i.e. distance from mental protuberance to sternal notch was recorded and verified to ensure consistency between scans. These were imported to Eclipse v 15.5 treatment planning system (Varian medical systems, Palo Alto).

Delineation and quantification of ROI on MR

Paired major salivary glands were delineated in full, this included ipsilateral (i) and contralateral (c) parotid (iPG/cPG), submandibular (iSMG/cSMG) and sublingual (iSLG/cSLG) glands as per guidelines [19]. Glands were contoured on all slices by a medical student and verified by a HN clinical oncologist on each MRI scan. Structures were initially contoured on the T1PCFS sequence and copied onto the b0 images. Modification of each structure was made to account for motion and artefact between the sequences. Final volumes on the b0 sequence were copied to the ADC map (without further adjustments) to be used as the ROI.

All measurements were made on the ADC map where mean (and standard deviation of the mean) ADC (mm^2/s) and volume (cm3) were obtained and recorded for each ROI. To verify whether the full structure was included in the imaging datasets, coverage of each SG was checked on the T1PCFS and ADC map on each baseline and repeat image. Any incomplete structures were recorded.

Chemo-radiotherapy

Patients were immobilised for RT with a 5-point thermoplastic head and shoulder mask (Klarity Medical Products, Newark, Ohio) and an individualised headrest. A planning CT (slice thickness 2 mm) was acquired on a Phillips Brilliance Big Bore scanner (Philips Medical Systems B.V, The Netherlands).

Gross tumour volume (GTV) was delineated for primary tumour and involved lymph nodes A 10–15 mm margin was added, then the outline further edited to exclude natural barriers to spread e.g. bone and air cavities, and extended to include the whole involved nodal level(s) to create the clinical target volume (CTV_65). CTV_54 included nodal areas considered at risk of containing microscopic disease as per international guidelines [20]. A 3–5 mm geometric expansion created planning target volumes (PTV_65 and PTV_54). A dose of 6500 cGy in 30 fractions over 6 weeks was prescribed to gross disease and 5400 cGy to elective areas.

The following planning criteria were applied D95% $\geq$ 95% to PTV_65. Critical organ at risk doses were maximum dose (Dmax) $\leq$ 4800 cGy, for planning risk volumes (PRV) PRV_spinal cord and

Dmax $<$ 5400 cGy for PRV_brainstem and were prioritized over PTV coverage. Ideally cPG, mean dose (Dmean) should be minimised to $<$ 2400 cGy but PTV coverage was not compromised to achieve this. Mean planned dose was recorded for cPG and iPG from routine planning parameters. Paired SMG and SLG were not routinely delineated at CT planning, hence dose was not available for these.

Treatment plans were created on Eclipse ™ treatment planning system (TPS) (Varian Medical System, Palo Alto, CA). These were optimised using the inverse planning Analytical Anisotropic Algorithm (AAA Version 13.6.23).

Treatment was delivered on a Truebeam® linear accelerator (Varian Medical System, Palo Alto, CA). Daily kV-kV images were acquired for verification with corrections based on bony matching applied before treatment. A planning CT was acquired at fraction 16 for volumetric and dosimetric assessment.

For eligible patients, cisplatin was delivered at 100 mg/m^2 on day 1 and 22.

Toxicity assessment

Toxicity was recorded using Radiation Therapy Oncology Group (RTOG) scoring criteria [21] to measure xerostomia at 12 months following treatment. Investigators were blinded to toxicity outcomes during ADC measurement and analysis.

MRI quality assurance (QA)

QA was carried out to ensure accuracy of ADC values and reliability of measurements. This was performed monthly by scanning a phantom comprising of four vials of polyvinylpyrrolidone (PVP) with different

concentrations and one containing distilled water [22]. Other routine parameters were checked as part of the daily scanner QA.

Statistical method

Patient characteristics were summarised as counts and percentages, or means with standard deviations (SD).

The percentage change in volume and in mean ADC for each gland was calculated after 2 weeks of treatment, differentiated by laterality to primary tumour. i.e. contralateral or ipsilateral.

At 12 months patients were categorised into two toxicity groups - those who had experienced grade 0–1 toxicity, and those with toxicity of grade 2 or higher.

The mean percentage change in volume and in mean ADC were compared between the two toxicity groups for the salivary glands, distinguished by treatment side. Two-sample t-tests were employed and a p-value < 0.025 was used as the threshold for statistical significance to minimise the chance of a type I error.

Results

The analytical sample consisted of 31 patients with intermediate or high risk squamous cell cancer of the oropharynx (OPSCC). Median age was 57 years (range 37 to 70 years). Disease characteristics are included in table 1.

Feasibility of outlining salivary glands

One hundred and twenty four scans were evaluated. Bilateral SMG and SLG delineations were successful on all 124 scans. PGs were not fully included on 8 baseline scans (3 on T1PCFS and 5 on ADC map) and PGs were incomplete on 15 repeat scans (8 on T1PCFS and 7 on ADC map). Of the 248 PGs on T1PCFS and ADC maps on MRI_base and MRI_rpt, 201 (90.7%) were fully visualised and contoured.

Salivary gland volumes, ADC at baseline

The largest volumes were recorded for PG, and smallest for SLG (table 2). Ipsilateral and contralateral were of similar volumes for each gland at baseline. The mean planned dose for the iPG and cPG was 3665 cGy and 2461 cGy repectively, dosimetric information was not available for the other glands. The highest mean_ADC values were observed in SLG, then SMG and the lowest in PG. Mean_ADC values in the SLG displayed the greatest variation between patients. The baseline mean ADC were significantly different between each gland type ($p < 0.0001$).

Change in measurements between scans

Parotid volume decreased during treatment by 6.7% and 11.2% for iPG and cPG respectively, with iSMG, cSMG, iSLG and cSLG volume increasing by 6.9, 0.9, 60.8 and 60.3% respectively (Table 3). All structures showed an increase in mean_ADC values at repeat scan. SMG showed the highest percentage change in ADC for all glands and least variation in measurements were seen in the PG. For each gland the increase in ADC was statistically significant $p < 0.0001$.

Table 1
Summary of disease characteristics.

Cancer stage		n	(%)
T stage	1–2	11	35.5
	3–4	20	64.5
N stage	0	5	(16.2)
	1	9	(29.0)
	2	1	(3.2)
	2a	1	(3.2)
	2b	12	(38.7)
	2c	2	(6.5)
	3	1	(3.2)
Stage group	III	7	(22.6)
	IVA	23	(74.2)
	IVB	1	(3.2)

Table 2
Summary of gland volumes (cm^3), mean_ADC (mm^2/s) at baseline.

		Mean (SD)			
Gland	**Side**	**Volume (cm^3)**		**Mean ADC (mm^2/s)**	
Parotid	contralateral	30.0	(10)	1224	(146)
	ipsilateral	29.7	(9)	1252	(140)
Submandibular	contralateral	9.1	(3)	1395	(196)
	ipsilateral	9.1	(3)	1404	(205)
Sublingual	contralateral	2.5	(1)	1522	(218)
	ipsilateral	2.7	(1)	1586	(247)

Toxicity groups

No statistically significant association was observed between toxicity groups and percent volume change (Table 4).

A smaller mean percentage increase in ADC was observed in the group experiencing a higher grade (2 or >) of toxicity (Table 4). This was the case for bilateral PG (Fig. 1), bilateral SMG and cSLG but was only statistically significant in the iPG.

Discussion

This is the largest DWI study of patients with a single sub-site of HNC to evaluate changes in salivary glands during RT. It is also the first to include assessment of SLG during RT. A review by Stieb et al, [23] identified a number of publications that evaluated salivary glands on serial MRI imaging, including baseline and mid treatment images. Of these studies, only 3 measured changes using DWI, and none assessed the SLG [24–26]. These studies included heterogeneous groups of patients with HNC. While differing disease characteristics may not directly impact assessment of changes in normal tissue with RT, it remains preferential to study a homogeneous group with similar characteristics and treatment. In this way we can ensure other variables that may confound results, e.g. dose received by salivary glands are minimised and results are robust.

We have demonstrated the feasibility of outlining the paired major salivary glands at baseline and during RT and measuring serial ADC on DW-MRI. On a small number of scans it was not possible to delineate full PG structures. This was due to the field of view being prioritised to include primary tumour and lymph nodes, meaning PG contours were incomplete. This should be borne in mind when considering our results, although < 10% of PGs were affected in this way.

We report there is a significant difference in volume and ADC between each paired gland at baseline. Our finding that ADC was higher in SMG than PG at baseline (table 2) was consistent with previous work [24,26–28]. The difference in ADC at baseline between each set of glands may indicate intrinsic differences in the micro structure and function of each. Alternatively it may be that measured ADC is simply affected by the volume of the gland under study as discussed below.

Volumetrically the glands behaved differently during RT, with PG and cSMG absolute volumes decreasing, and iSMG and both SLG increasing. When assessing the percent change in volume, both PG volumes decreased and all SMG and SLG increased. Although absolute mean volume decreases, the variation is showing an overall mean percentage increase in cSMG and iSMG. This is due to large variability in percentage change among patients with small volumes. PG volume decreasing during RT is consistent with the findings of other groups on MRI, although they reported higher volume decrease during

Table 3
Mean change in absolute volume (cm^3), mean ADC (mm^2/s) and percentage change (%) after 2 weeks of treatment, by gland type.

		Absolute change (SD)				Percent change (SD)			
Gland	**Side**	**Volume (cm^3)**		**Mean ADC (mm^2/s)**		**Volume (%)**		**Mean ADC (%)**	
Parotid	contralateral	−3.98	(7.22)	183.2	(134.0)	−11.2	(24.8)	15.8	(12.9)
	ipsilateral	−2.4	(8.87)	221.3	(137.5)	−6.7	(26.2)	18.3	(12.5)
Submandibular	contralateral	−0.46	(2.43)	237.1	(216.7)	0.9	(35.6)	18.6	(19.0)
	ipsilateral	0.27	(2.27)	282.1	(237.1)	6.9	(28.4)	21.9	(20.5)
Sublingual	contralateral	1.08	(1.28)	214.4	(242.7)	60.3	(75.0)	15.5	(17.8)
	ipsilateral	1.08	(1.52)	238.3	(312.8)	60.8	(84.7)	16.8	(21.7)

Table 4
Association with percent change in mean volume and percent change in ADC, with grade of toxicity (RTOG) at 12 months.

		Mean percent change (SD)								
		Volume percent change (SD)					Mean ADC percent change (SD)				
Gland	**Side**	**Grade 0–1**		**Grade 2+**		**p-value**	**Grade 0–1**		**Grade 2+**		**p-value**
Parotid	cPG	−13.0	(21)	−6.5	(31)	0.53	19.8	(14)	9.8	(11)	0.05
	iPG	−3.0	(26)	−8.3	(31)	0.64	23.5	(14)	10.9	(9)	0.013
Submandibular	cSMG	−9.5	(20)	14.9	(46)	0.08	22.1	(24)	15.5	(14)	0.41
	iSMG	−4.2	(23)	17.0	(29)	0.048	26.6	(27)	18.1	(14)	0.33
Sublingual	cSLG	39.8	(77)	98.3	(70)	0.06	16.6	(17)	14.8	(18)	0.8
	iSLG	43.3	(69)	94.9	(103)	0.14	11.3	(14)	19.6	(26)	0.31

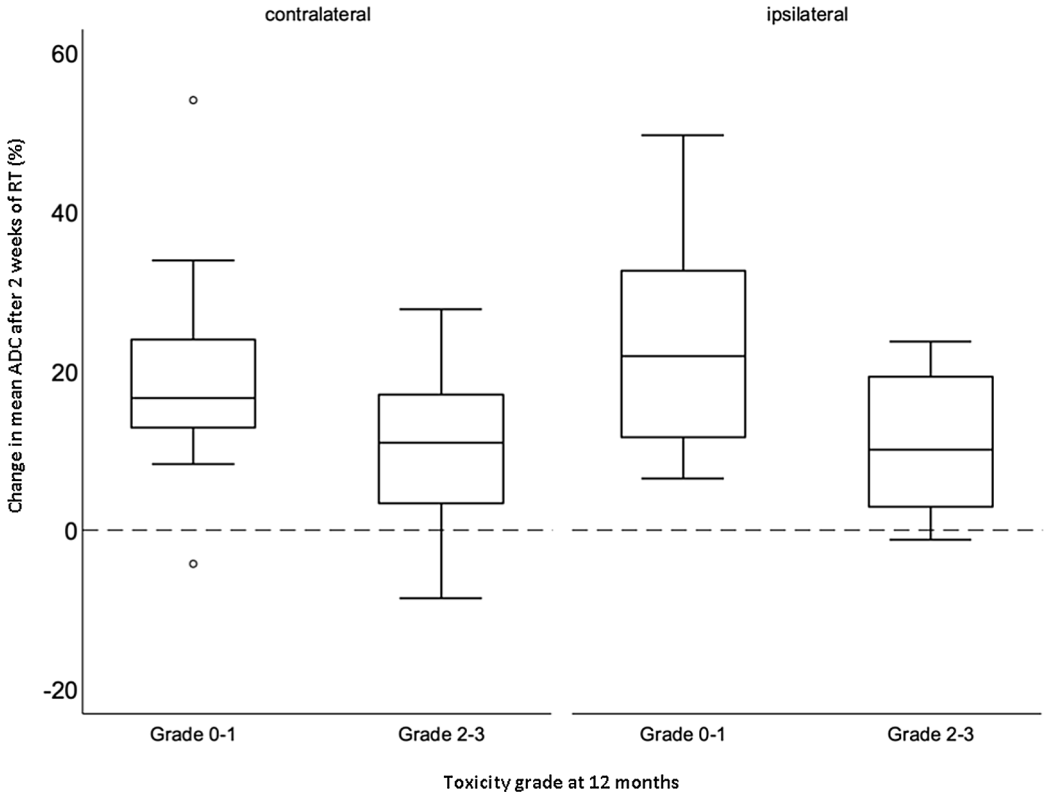

Fig. 1. Percent change in mean ADC of parotid glands after 2 weeks of treatment, when categorised by severity of toxicity (Grade 0–1 versus 2–3) at 12 months.

treatment, which continued following RT [25,29–31]. A direct comparison is challenging, where different methodologies, timings and sequences are reported. SMG decreased following completion of RT in one study [32], but no groups so far have assessed volume change of SMG and SLG during RT. The differential volume change between iPG and cPG during RT (smaller reduction in iPG than cPG) may demonstrate that dose received influences this parameter and will be analysed in future work.

The SLG measured smallest of all glands at baseline; showed the largest increase in percentage volume after 2 weeks of treatment; and had most variation in measurements. This could be attributed to the gland being small, where a very small absolute change in volume is equivalent to a high percentage. The variation in ADC might be a consequence of the challenges in defining small ROIs, where ADC may be affected by inclusion of a small volume/large percentage of normal tissue at the periphery of the structure. This could also explain why least variation was seen in the parotid glands.

All glands showed an increase in ADC after 2 weeks of treatment as

previously described [24–26]. This indicates a change in the cellularity, vascularity and function of salivary gland tissue during RT, not just a change in the anatomy or volume as is already well documented [23]. In this study, this increase in ADC could not be attributed to the dose received by the gland, as a similar change in ADC was seen in both ipsi- and contra- lateral PGs despite differences in planned dose to each. The influence of delivered dose on salivary gland characteristics (change in volume and ADC) is beyond the scope of this work but is worthy of future consideration. A correlation in mean dose and change in ADC has been previously reported in pre and post RT scans but this was not analysed using images captured during RT [28].

Results from this sample indicate an association with change in ADC and toxicity at 12 months. Patients with higher grades of toxicity (2 +) demonstrated a smaller percentage increase in ADC compared to those with lower toxicity grades. This was consistent across all glands except for the iSLG, the reason for this is unclear and may simply relate to the small volume of the SLG as described above.

Some authors reported a significantly higher change in ADC values during or post RT in patients who experienced xerostomia [26,28,33]. Zhang et al. [26], collected RTOG toxicity at 6 months and described that ADC increase in the PG were associated with the level of toxicity. This 6 month duration of follow up is too short to capture late toxicity and others also recognise their lack of clinical data as a limitation [25]. While our cohort benefits from 12 month follow up post-RT it is established that severity of xerostomia may continue to improve for up to 18 months post treatment [1]. A later time point for toxicity assessment may allow more robust evaluation of the relationship between changes in ADC and late toxicity outcomes.

Differences in techniques, hardware and software have always been a limitation when using MRI for quantitative evaluation [34,35]. These are further exasperated when repeated measurements are required. Here we have used a strict protocol to ensure reliable and valid results were obtained, mandating the same conditions throughout. Constants have included image acquisition on the same scanner, magnet strength, acquisition protocol (including high b values to reduce the effect of perfusion) and a protocolised methodology to define ROI. This ensures the process is reproducible. The reporting of percentage rather than absolute change in ADC also means results are more transferrable to other systems. A focus on standardising future work in a multi-centre setting should aim to define the optimal follow up and scanning protocol to capture meaningful data.

Delineation was performed with observers blinded to toxicity, this was to reduce bias. Use of immobilisation may have improved set-up reproducibility and image registration. The decision not to use a thermoplastic shell in these patients was to allow the use of the neurovascular coil and to facilitate recruitment and retention of patients to the study. All contours were redefined at each timepoint therefore, any discrepancies in position are unlikely to affect results.

This interim analysis of 31 patients is a small sample from a larger study to determine whether DW-MR can predict response to RT by defining a threshold change in ADC [17]. Further analysis of salivary glands and assessment of xerostomia at 24 months post RT will be undertaken for the full cohort to increase the robustness of our work and further explore the relationship between severity of late toxicity and change in ADC. As the primary study was not designed to predict salivary gland toxicity using ADC, we found our field of view was a limitation. Our priority to capture primary tumour and lymph nodes resulted in a small number of patients having the superior aspect of their PG excluded from the scan. This does add uncertainty to our volumetric and ADC analysis, however, we still identified a trend in decreasing volume and increasing ADC. This feasibility work has proven invaluable to identify these factors requiring optimisation where the primary question is OAR analysis.

Conclusions

It is feasible to measure volume and ADC of the major salivary glands prior to and during a course of radiotherapy for HNC. Image acquisition may need optimisation to ensure the field of view adequately allows tumour and OAR evaluation. Early data suggests that a lower rise in ADC during treatment is associated with more severe late xerostomia. Validation of these findings is required in a larger cohort with long term follow up.

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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