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ORIGINAL ARTICLE

Assessing the impact of magnetic resonance treatment simulation (MRSIM) on target volume delineation and dose to organs at risk for oropharyngeal radiotherapy

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Abstract

Introduction: Assessing the use of a radiation therapy (RT) planning MRI performed in the treatment position (pMRI) on target volume delineation and effect on organ at risk dose for oropharyngeal cancer patients planned with diagnostic MRI (dMRI) and CT scan. **Methods:** Diagnostic MRI scans were acquired for 26 patients in a neutral patient position using a 3T scanner (dMRI). Subsequent pMRI scans were acquired on the same scanner with a flat couch top and the patient in their immobilisation mask. Each series was rigidly registered to the patients planning CT scan and volumes were first completed with the CT/dMRI. The pMRI was then made available for volume modification. For the group with revised volumes, two IMRT plans were developed to demonstrate the impact of the modification. Image and registration quality was also evaluated. **Results:** The pMRI registration led to the modification of target volumes for 19 of 26 participants. The pMRI target volumes were larger in absolute volume resulting in reduced capacity for organ sparing. Predominantly, modifications occurred for the primary gross tumour volume (GTVp) with a mean Dice Similarity Coefficient (DSC) of 0.7 and the resulting high risk planning target volume, a mean DSC of 0.89. Both MRIs scored similarly for image quality, with the pMRI demonstrating improved registration quality and efficiency. **Conclusions:** A pMRI provides improvement in registration efficiency, quality and a higher degree of oncologist confidence in target delineation. These results have led to a practice change within our department, where a pMRI is acquired for all eligible oropharyngeal cancer patients.

Introduction

Magnetic resonance imaging (MRI) is widely used as a complementary imaging modality in target volume delineation for oropharyngeal radiation therapy (RT).[1,2] While the gold standard of CT provides the required electron density information for accurate RT dose calculation, it does not compete with MRI for image quality in terms of enhanced soft tissue contrast and high resolution imaging.[1,2] As current RT techniques including intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), permit dose escalation to asymmetrical volumes and steep dose gradients, confident and accurate delineation of target structures is crucial.[1] This shift has resulted in a heightened interest in the use of MRI and a need for the

continuing evaluation of the introduction of MRI into RT planning.[3]

There are certain challenges and limitations in applying MRI for a purpose other than its diagnostic intent. MRI images acquired using head and neck coils for the purpose of diagnostic imaging present functional restrictions when they are to be co-registered to an RT planning CT, acquired in the patient's RT treatment position with custom immobilisation.[4,5] The likelihood of disagreement in head, neck, chin and shoulder rotation when using rigid registration to fuse the two datasets together can significantly impact the useability and accuracy of scans, potentially resulting in geometric error.[1]

Diagnostic MRI images are routinely used in prostate and brain RT treatment planning. The benefit of which is to provide enhanced soft tissue contrast and visualisation of critical structures.[6] As these anatomical locations may be scanned in a similar anatomical positions, they are less affected by positional differences and can be corrected within the rigid registration process.

Traditionally our departmental diagnostic MRI (dMRI) images would be acquired without any reference to the planning CT position. The scans would be registered as a 'best fit' through the region of gross disease or viewed on a separate screen and compared using anatomical landmarks. This could contribute to random and systematic errors in the definition of target volumes or surrounding structures which has the potential to result in geometric errors in volume definition.[7]

The aim of this project was to determine for what proportion of patients three radiation oncologists (RO) would modify their target volumes and anatomical structures defined using CT and a diagnostic MRI scan (dMRI) when presented with a dedicated radiotherapy planning MRI (pMRI) performed in the treatment position for oropharyngeal cancer patients.

Methods and Materials

Patient selection

A cohort of twenty-six (26) patients were accrued to this single arm, single centre clinical pilot study. The National Ethics Application Form (NEAF), study protocol and governance submission were approved by the local Human Research Ethics Committee, Hunter New England (HNE HREC), New South Wales, Australia. Written and informed consent was obtained from each of the 26 participants. Eligible patients were to be over 18 years of age and have histopathologically confirmed squamous cell carcinoma (SCC) of the oropharynx; tonsil, soft palate, posterior pharynx, or base of tongue. They were to be prescribed radiation therapy plus or minus concurrent chemotherapy, not to have had surgical resection or neo-adjuvant chemotherapy and have no contraindication to undergo MRI. Of the 26 participants, there was a reasonable dissemination of primary sites within the oropharynx, laterality and disease staging as listed in Table 1.

CT and MRI patient data collection

All patients underwent standard radiotherapy simulation using a Toshiba Aquilion CT scanner (Toshiba Medical Systems Corporation, Otawara, Japan) or GE Lightspeed CT scanner (General Electric Healthcare, Little Chalfont, United Kingdom). A 120 kV and 2 mm or 2.5 mm slice thickness scan protocol was used for all patients. Intravenous contrast (Ultravist®, Bayer Germany) was

Table 1. Participant characteristics

		Revised from pMRI		
Variable		Revised (n = 19)	Not Revised (n = 7)	Total (N = 26)
Age	Mean (SD)	58.9 (9.38)	56.9 (7.58)	58.4 (8.83)
	Median (min, max)	59.0 (44.0, 83.0)	58.0 (41.0, 63.0)	58.5 (41.0, 83.0)
Gender	Male	18 (75%)	6 (25%)	24 (92%)
	Female	1 (50%)	1 (50%)	2 (7.7%)
Site	Tonsil	12 (80%)	3 (20%)	15 (58%)
	Base of tongue (BOT)	3 (60%)	2 (40%)	5 (19%)
	Soft plate	1 (100%)		1 (3.8%)
	Tonsil and BOT	3 (60%)	2 (40%)	5 (19%)
Laterality	Left	7 (64%)	4 (36%)	11 (42%)
	Right	11 (79%)	3 (21%)	14 (54%)
	Bilateral	1 (100%)		1 (3.8%)
Tumour Staging	T1	5 (71%)	2 (29%)	7 (27%)
	T2	10 (83%)	2 (17%)	12 (46%)
	T3	2 (50%)	2 (50%)	4 (15%)
	T4a	2 (67%)	1 (33%)	3 (12%)
Nodal Staging	N0	1 (100%)		1 (3.8%)
	N1	1 (100%)		1 (3.8%)
	N2a	1 (100%)		1 (3.8%)
	N2b	14 (74%)	5 (26%)	19 (73%)
	N2c	1 (100%)		1 (3.8%)
	N3	1 (33%)	2 (67%)	3 (12%)
HPV 16 +/− status	P16+ve	19 (79%)	5 (21%)	24 (92%)
	P16−ve		2 (100%)	2 (7.7%)

administered to each patient and the CT images were acquired with the patient supine, head first to gantry, immobilised with a head rest (Alcare Co. Ltd., Sumida-ku, Japan), thermoplastic mask (CIVCO Medical Solutions, Iowa, USA) and a CIVCO cushion under knees. The anatomical scan parameters were from the vertex superiorly to carina inferiorly.

Within two weeks of their CT simulation appointment, all patients underwent both dMRI and pMRI sessions with intravenous contrast (Gadovist® Bayer, Germany) and were all scanned using the same Siemens Skyra 3-Tesla scanner, with 70cm open bore (Siemens Healthineers, Erlangen, Germany). For the dMRI session, the patient was positioned by the MRI radiographers with no radiation therapy input. A 20 channel head and neck diagnostic MR coil and soft couch top with 32-channel spine array were used to acquire the dMRI sequences as listed in Table 2.

For the pMRI, the attending radiation therapist and MRI radiographers positioned the patient using custom radiotherapy immobilisation on a flat CIVCO couch top (CIVCO Medical Solutions, Iowa, USA) as shown in Fig. 1. A LAP Dorado MR3T laser bridge (LAP GmbH Laser Applikationen, Lueneburg, Germany) was used to ensure that the neck flexion and chin extension were suitably reproduced from simulation. One 18 channel body surface coil was overlaid on a thermoplastic bridge to ensure that adequate signal could be received superiorly from the supraorbital margins to the head of clavicles inferiorly. To acquire signal posteriorly, a 32-channel spine coil was used.

Image registration

Both MRI series were imported to the treatment planning system; Varian Eclipse v 11.0.31 (Varian Medical Systems, Palo Alto, United States) by a senior radiation therapist or the investigating radiation therapist.

One registration was completed per the dMRI and pMRI series. Both were manually registered to the radiation therapy planning CT through the volume of interest and the first and second cervical vertebrae were used as a secondary point of anatomical reference. The spinal canal was also used as an ancillary measure of best fit to gauge registration quality. The process was timed by the investigating radiation therapist using a stop watch, commencing from the point of beginning the rigid registration and ending when a satisfactory result was achieved.

Each RO qualitatively categorised their impression of the standalone image quality and registration of both MRI series using an adapted image quality scoring rubric

Table 2. dMRI and pMRI sequence parameters acquired

dMRI	TE (ms)	TR (ms)	2D	Axis	FOV (mm^2)	Bandwidth (Hz)	Resolution (mm)	Slice thickness (mm)	Time (min)	Slices
T1 DIXON pre-contrast	10	656	2D	AXIAL	250	305	256	3 mm	4 min	70
T1 DIXON pre-contrast	10	718	2D	COR	250	305	256	3 mm	3.04 min	33
T1 DIXON post-contrast	10	610	2D	AXIAL	250	305	256	3 mm	3.4 min	70
T1 DIXON post-contrast	10	809	2D	COR	250	305	256	3 mm	4.14 min	33
T2 DIXON	81	3810	2D	AXIAL	250	305	256	3 mm	3.1 min	70
T2 DIXON	85	4360	2D	COR	240	300	320	3 mm	3 min	33
pMRI	TE (ms)	TR (ms)	2D	Axis	FOV (mm^2)	Bandwidth (Hz)	Resolution (mm)	Slice thickness (mm)	Time (min)	Slices
T1 DIXON pre-contrast	10	531	2D	AXIAL	250	305	256	3 mm	3.5 min	70
T1 DIXON pre-contrast	10	701	2D	COR	250	305	256	3 mm	3 min	33
T1 DIXON post-contrast	10	531	2D	AXIAL	250	305	256	3 mm	3.1 min	70
T1 DIXON post-contrast	10	717	2D	COR	250	305	256	3 mm	4.04 min	33
T2 DIXON	81	3810	2D	AXIAL	250	305	256	3 mm	3.3 min	70
T2 DIXON	85	4309	2D	COR	250	300	256	3 mm	3.1 min	33

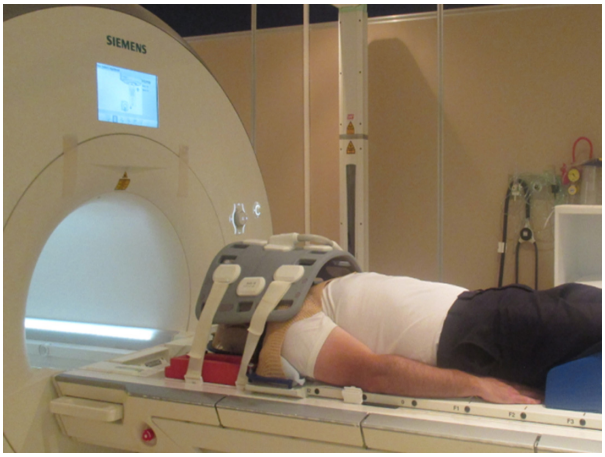

Figure 1. pMRI patient positioning and flexible body coil arrangement

(IQSR). This visual qualitative methodology has been validated by Hunold et al.[8] The marking style was linear with a value of *1* referring to the image being clinically acceptable, to *4* referring to being clinically unacceptable. A score was awarded for; artefact, image noise and overall image quality. This same scale applied to an image registration scoring rubric (IRSR) that was also completed for each patient. The subjective nature of the rubrics introduces an inherent level of variation and to mitigate this, operational definitions were provided. Noise was defined as the undesired grainy appearance that is seen in images to a varying degree, originating from several sources including the scanning protocol, coil configuration and patient positioning. (Fig. 1)[9] Artefact was defined as unwanted signal in the image as result of patient motion such as swallowing and respiration or hardware interference.[10] More recent publications, (Daisne et al[11]; Chuter et al[4]) have acknowledged that visual, qualitative interrogation of images is reproducible with multiple observers.

Target structure voluming and modification

Departmental guidelines based on the DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines (Grégoire et al, 2003 [12]; 2013[13])[10,11] were used for contouring visible disease and organs at risk.

The two registered datasets were made available in a staged interval and contoured by the treating RO only. The RO's were firstly provided with the simulation CT / dMRI images and followed their standard contouring practice in preparation for radiotherapy planning. The target volumes to be contoured were specified as the gross target volumes (primary and nodal GTVp, GTVn), clinical target volumes and elective nodes and the respective low, intermediate and high risk planning target volumes (i.e. PTV 54 or56, PTV 63, PTV 70). The organs at risk (OAR) structures to be contoured were brainstem, bilateral cochleae, bilateral parotid glands, bilateral submandibular glands, mandible, oesophagus, oral cavity, lips, spinal cord, pharyngeal constrictors, larynx, optic nerves, chiasm, lens and orbits and the brachial plexus where appropriate. With these contours completed, CT/pMRI registration was then made available to the RO for contour revision. The maximum period between the provision of datasets was fourteen days. If changes were required to the original dMRI/CT contours after viewing the pMRI, these volumes were duplicated for editing. For each patient, the RO completed a workbook to record which structures were modified and the rationale i.e. the structure was more clearly defined for outlining on the pMRI; structure incorrectly outlined previously or changes not related to improved anatomical information on pMRI. All final contours and plans were peer reviewed by another RO.

RT planning

All patients were treated with an infield boost IMRT technique to 70 Gy in 35 fractions.

Where a change was made to the target volume as a result of using the pMRI, two IMRT plans were developed to assess the impact of the modification. Dose to the GTV and PTV structures were recorded to demonstrate comparable plan quality and adherence to the plan prescription as per ICRU reporting guidelines for IMRT (ICRU 50, 62, 83). The doses to OARs were recorded at the points of maximum and mean dose as we would in standard practice.

Statistics

The statistical tests for this study were performed using SAS v9.4 (SAS Institute, Cary, North Carolina, USA). A Dice Similarity Co-efficient (DSC)[14] was calculated for each target structure to demonstrate the comparability of spatial overlap. For the difference in contour volume and dose, a Wilcoxon signed rank test was used. Registration time was compared using a paired t-test. A Wilcoxon signed rank test was used to test for any significant difference between MRI groups for each image quality category. A binomial exact (Clopper-Pearson) 95% confidence interval was used to test that the proportion of patients in the modified group was greater than 20%. P-values less than 0.05 were considered statistically significant.

Results

Of the 26 participants, 19 of these had revised volumes due to the pMRI image and 7 were unchanged from the dMRI/CT. For analysis, the participants were categorised as having revised volumes if a modification had been made to any of the following target volumes, p GTVp, p GTVn, p PTV 56, pPTV 63, p PTV 70, $n = 19$. The proportion of revised volumes was 0.73 with 95% confidence interval (0.52, 0.88) which is more than the hypothesized 20%.

All of the modified target structures showed a difference in the change of volume between those contoured using the CT/dMRI and the pMRI. The pMRI volumes were on average larger than the dMRI volumes as visually demonstrated in Fig. 2. The extension to which they were visually different in terms of larger medially, laterally, superiorly and so on was varied across the sample.

The largest differences in contour modification were for the GTVp with a mean DSC of 0.7 and the PTV70 with a mean DSC of 0.89. The primary gross nodal volume and low and intermediate risk planning volumes (PTV54, 56 and 63) had mean DSC scores of 0.91, 0.97, 0.96 and 0.93 respectively. It should be noted that normal tissue and anatomical structures were not modified as a result of using either MRI registration. The RO's recorded that they were confident in their first iteration and that these contours did not require revision.

As stated in the Methods, for those patients where the RO modified their volumes using the pMRI scan, two IMRT plans were generated to assess the effect of the revision on target coverage and OAR doses. The volumes included in Fig. 3 demonstrate the potential under coverage of targets in one patient that was representative of the group. The figure shows that the final pMRI contour would have only been covered by 90% (6300cGy) of the prescribed 7000cGy rather than the prescribed 6650 Gy to cover 95% of the volume. This particular image embodies the possible miss of disease that may have occurred if the volume was not revised using the pMRI. Resultingly, with the increase in physical volume to the target structures, there was an increase in the dose to salvageable areas of both serial and parallel organs surrounding the target volumes. The oral, auditory and optical structures recorded the largest changes in mean and max doses overall (Fig. 4) while midline structures such as the larynx and oesophagus showed a reduction in mean dose but not maximum dose.

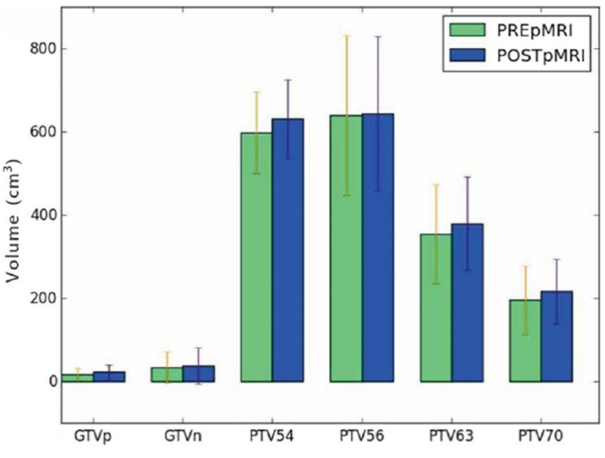

Figure 2. Difference in target volume (cm3) pre and post pMRI

To compare the difference in efficiency, each image registration was timed and recorded. A small group of experienced radiation therapists completed the registrations as would be the case clinically, in preparation for RO contouring. The mean time to register CT and dMRI was 6.24 ± 1.32 min (mean ± 1 SD), for CT to pMRI the mean was 3.82 ± 0.96 min. The differences in registration time were statistically significant ($P < 0.001$) between the MRI groups. There is a notable efficiency gain in registering the two matching positional datasets and the registration scores also show a statistically significant difference in favour of the CT/pMRI($P < 0.001$).

Fig. 5 demonstrates the lowest scoring RO rating for dMRI/CT registration quality against the well rated pMRI/CT for the same patient. This image is representative of several registrations included in the study and justifiably illustrates the increased time taken to reconcile two scans acquired in separate positions.

There is not enough evidence ($P = 1$, 1 and 0.18 for artefact, noise and overall image quality) to reject the hypothesis that the image quality for these categories are equivalent between pMRI and the d MRI.

Discussion

This study has shown that using a pMRI results in a higher degree of RO confidence in target delineation compared to dMRI registration and has led to a change of practice within our department. It has also demonstrated improvement in registration efficiency and visual registration quality. At the time of undertaking this project, it was the department protocol to complete image registrations through the volume of interest. The authors acknowledge two or more registrations for the dMRI may have resulted in better image agreement, that is through the volumes of interest and a second through the neck however this was not evaluated.

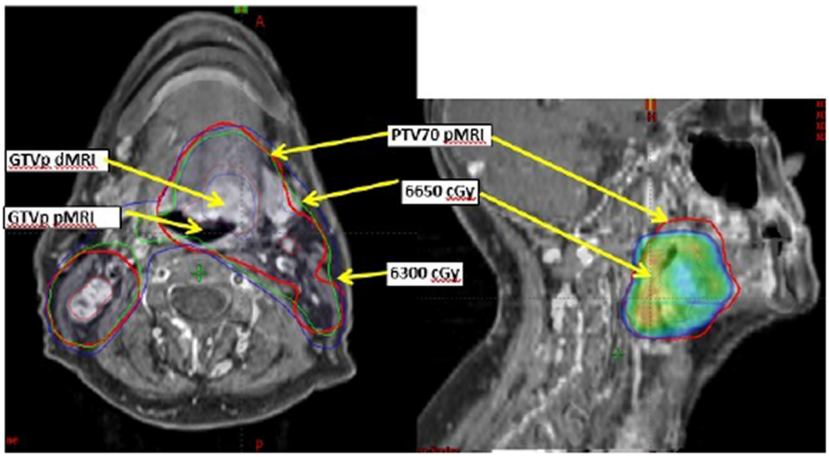

Figure 3. Potential miss of high risk disease without pMRI volume revision

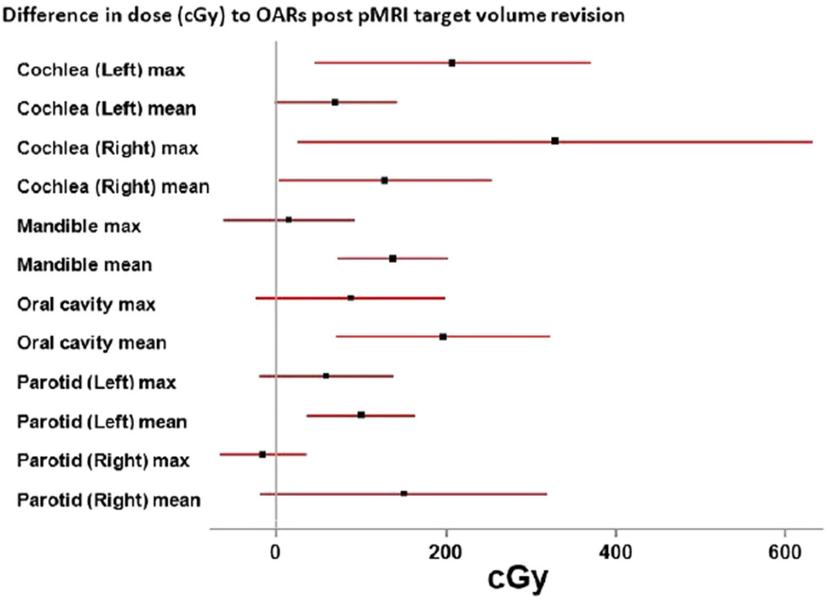

Figure 4. Difference in dose (cGy) to OARs post pMRI target volume revision

Deformable registration was not available for clinical use in the department and was not investigated as part of this work.

The use of PET/CT was not assessed as they were not available for all patients participating at the time of undertaking the study. If the study were to be conducted in the present clinical environment, this would have been incorporated as they are now completed routinely for staging.

The seminal paper by Peters, et al[15] demonstrated the importance of accurate target delineation for achieving high cure rates. This is a recurring citation in the context of previously published works regarding the introduction of MRI to RT planning and the influence of scan position on image quality, registration and accuracy. Hanvey et al[1] and Ahmed et al[2] have previously assessed the effect of patient positioning for oropharyngeal MRI registration quality and the impact for GTV contouring. They both found improvements in registration and target definition, similar to the results of this paper. Chuter et al[4] and Fortunati et al[5] have also evaluated MRI positioning and the use of deformable registration where access to a dedicated RT is not feasible. However, a gap remains in the evidence to quantify the utility of the additional scan procedure and whether it may be used for other structures. The use of a validated tool for visual assessment is also unique to this study.

The authors acknowledge that contouring can be inherently subjective and may lead to implicit bias in a

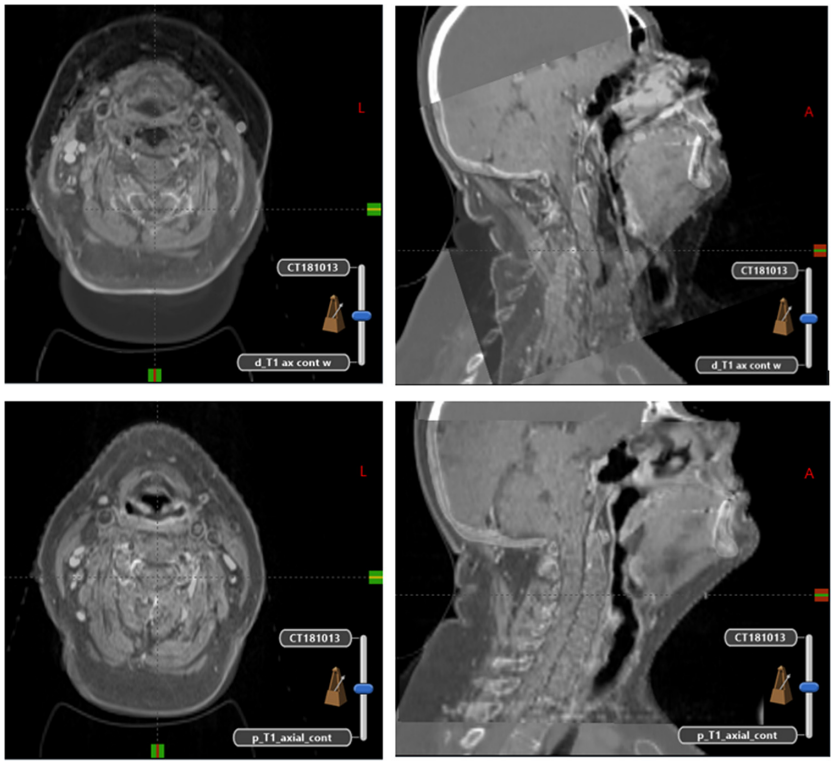

Figure 5. dMRI / CT registration (A) versus pMRI/CT registration (B)

study such as this. Without the clinical time available to blind the contouring in real time, it may be useful in future to assess the same patients in a blinded fashion. Previously, this team of Oncologist's had participated in an in house benchmarking study and we reference this as justification that their contouring is comparably similar in nature. Additionally, the RO's have also completed externally validated clinical trial benchmarking using international consensus guidelines.

It is well recognised that inter-observer variability can affect the validation of study data relative to dosimetric and clinical outcomes.[16] Bird et al[17] and Daisne[11] both found however that while the use of different modalities produces different GTV volumes, the use of MRI reduced the overall inter-oberver variability. Gordon et al[18] analysed intraobserver variability in the MRI delineation of pharyngeal SCC and also found across a sample of seventeen[17] patients that the MRI imaging based volumes contoured by a neuroradiologist were reliably reproducible.

It should be noted that radiologist consultation was sought when necessary to confirm scan anomalies or probable disease extension. This input was sought for two (2) cases resulting in muscular and perineural invasion being identified having not been previously visualized on the CT and Dmri contours. To characterise the impact of contouring variability for these structures, the authors considered the findings of Feng et al[19] in that while reasonable variations may be present, that the IMRT planning optimiser is relatively insensitive to these discrepancies for the final dose distribution.

In collaboration with a team of MRI radiographers, numerous coil arrangements and sequence parameters were trialled to acquire images of a satisfactory quality with respect to reducing image distortion and reducing the potential for geometric inaccuracies. There were inherent challenges in adapting this modality for a purpose contrary to its original designed intent. In undertaking this project, we experienced limitations with custom immobilisation equipment and compatibility issues such as adequate inputs for coil cables and limited commercially available coil extensions before reaching the solution used for this study. In the time elapsed since undertaking this study, MRI vendors now offer standard radiotherapy solutions and particular image sequences which address the challenges we faced in adapting this technology.

There were a limited number of confounding variables that were not able to be assessed within the scope of this study. The differences in split field IMRT (n = 12) versus whole field IMRT (n = 7) plans for dose differences to midline structures were not considered in the final

analysis and in the overall comparison of increased OAR doses, the laterality of the primary disease was not considered in the calculation of the descriptive statistics.

A further challenge to undertaking this study with continually evolving practice, was the time to prospectively recruit participants. A total of sixty-three (63) patients eligible by diagnosis were screened between April 2013 and May 2015. There were twenty (20) eligible patients who declined participation in the study, commonly citing limited transport to attend and no interest in participating in clinical research if it would not directly benefit them. A further seventeen (17) were ineligible including but not limited to claustrophobia, contra-indicated for MRI, unable to receive IV contrast or were indicated for neoadjuvant chemotherapy.

Conclusion

The oropharynx is a challenging site for target delineation due to the reduced soft tissue discrimination by CT scan. While the pMRI was an additional requirement for patients, the procedure was well tolerated by the participants. The further resource utilization is justified, as this study has demonstrated an improvement in target visualization which could potentially lead to an improvement in the planned tumour coverage.

These results have led to a practice change within our department and a pMRI is recommended for all oropharyngeal squamous cell cancer patients undergoing definitive radiotherapy or chemo-irradiation with no recognised contraindications. The data and experience from undertaking this project and others supported the case for a dedicated MRI scanner within our radiation oncology department, and this has now been clinical since 2018. It is used for multiple anatomical areas including the head and neck and provides confidence in the clinical management of these patients.

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Conflicts of Interest

The authors declare no competing conflicts of interest.

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