Novel methodology to quantify dehydration in head and neck cancer radiotherapy using DIXON MRI

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Keywords
Head and Neck < Clinical Site, Magnetic Resonance Imaging < Discipline, Radiotherapy (Radiation Therapy) < Discipline

Abstract

Introduction: Head and neck cancer (HNC) patients are at risk of weight change, due to inadequate nutrition intake or dehydration, when receiving radiotherapy (RT). This study aimed to develop methodology to measure water content changes on magnetic resonance imaging (MRI) scans of the head and neck region over the course of RT. Methods: Retrospective datasets of 54 patients were analysed. Eligible patients had been treated for HNC with cisplatin chemoradiation (CRT) or RT alone and underwent a minimum of 2 MRI scans from weeks 0, 3 and 6 of their treatment. Anatomical regions consisting of ≥90% water, on T2-weighted DIXON MRI sequences, were contoured. Water volume changes of all patients were evaluated, within an anatomically standardised external volume, by comparing the absolute water fraction volume (cc) (VEx90WF) and relative water fraction volume (%) (RelVEx90WF) at weeks 0 and 6 of RT. Results: There was a statistically significant difference between the RelVEx90WF at weeks 0 and 6 (P = 0.005). However, no statistically significant difference was identified between weeks 0 and 6 VEx90WF (P = 0.064). There were no statistically significant differences identified between patients who received CRT versus RT alone. Conclusion: This study developed a novel method for measuring changes in water fraction volumes over time, using T2-weighted DIXON MRIs. The methodology created in this study requires further validation through phantom imaging, with known fat and water values.

Introduction

It is estimated that 5168 Australians were diagnosed with mucosal head and neck cancer (HNC) in 2020 with approximately 1151 deaths.1 Primary treatment modalities for HNC include surgery, radiotherapy (RT) and chemotherapy, as single modality treatments or in combination. Primary RT is often given with concurrent chemotherapy, as an organ preservation treatment technique.2

Head and neck cancer RT side effects, along with other pre-existing factors common in some HNC patients, including poor dentition, alcohol consumption, smoking and poor dietary habits, can contribute to poor oral
intake resulting in malnutrition and dehydration.³ Malnutrition is characterised by the reduction in body composition measures, such as weight and skeletal muscle, due to reduced food intake and metabolic abnormalities.⁴ HNC patients are also known to experience unintentional weight loss resulting in decreased rates of overall survival.⁵ Approximately 70% of the weight loss is characterised by loss of lean body mass.⁶ Significant weight loss and skeletal muscle loss in HNC patients are predictors for a poor prognosis after treatment.⁷ Early and intensive dietitian interventions during RT for HNC are essential to help patients maintain or achieve adequate nutrition intake to minimise loss of weight and muscle mass.⁸,⁹

Altered body composition can result in decreased precision of RT due to anatomical changes affecting the dose delivered to the tumour and surrounding organs.⁸,¹⁰ These changes can be due to a combination of weight loss, dehydration, tumour shrinkage, inflammation, muscle atrophy or radiation impacts on normal tissue.⁸ External changes greater than 1 cm can shift the 95% and 93% isodose lines up to 4 mm.¹⁰ This impact on delivered dose can result in unintended overdosage to nearby organs, associated with worsened toxicity, or underdosage to tumour sites, associated with decreased local control.⁸

Anatomical changes are observed daily throughout RT via cone-beam computed tomography (CBCT) scans. One limitation to CBCT is the difficulty in differentiating between soft tissue. This has led to the increased use in MRI in HNC RT due to its unparalleled tissue contrast and sequences which allow for evaluation of the complex head and neck anatomy.¹¹ Water and fat protons display different signal intensities on magnetic resonance imaging (MRI), which can assist in delineating body composition such as the T2-weighted DIXON is a turbo spin echo chemical shift imaging sequence.¹¹ The DIXON sequence produces 4 images: water only, fat only, in-phase and out-of-phase. These sequences may be utilised to evaluate and quantify changes in body composition, since intensification of the water and fat signals allows for accurate assessment of their changes throughout treatment. Whilst a methodology has been developed for measuring fat content utilising T2-weighted DIXON MRIs,¹²,¹³ it has not been evaluated in terms of water volume. Clinical observations in the cancer care centre where this study was conducted demonstrated that, following chemotherapy appointments, HNC patients’ external changes were not as apparent on CBCT. Therefore, it was hypothesised that rehydration, via intravenous (IV) fluid administration, may have the potential to prevent these external changes and decrease the risks associated with dosimetric changes. Whilst there is literature which focusses on how malnutrition affects HNC patient anatomy during RT, a gap in the published literature exists regarding the effects of dehydration alone on body composition changes and its’ dosimetric effects. This study is novel research which investigates the changes in water content of tissues using DIXON water MRI sequences, to address a current gap in the literature and potential role in assessing changes in body composition and dehydration during treatment. These changes may guide future interventions which may subsequently improve patient quality of life and treatment outcomes.

The primary aim of this study was to develop methodology to measure water volume changes on head and neck MRIs over the course of treatment. The secondary aim was to determine any differences in water volumes throughout treatment between patients who received chemoradiation (CRT) versus RT alone, as well as the correlation between water changes and weight loss. This study hypothesised that patients who receive RT alone will experience greater water volume changes throughout treatment compared with those who received CRT (with hydration). This is a novel investigation, and methodology developed in this investigation may be utilised in future studies to guide the most appropriate nutritional intervention for the patient and potentially improve RT accuracy.

**Methods**

**Study materials**

**Retrospective data sources**

Following South Western Sydney Local Health District Human Research Ethics Committee approval, 54 retrospective HNC MRI imaging datasets of patients who had previously participated in two clinical trials (n = 28 and n = 26) were obtained. Patients were treated between May 2014 and December 2020 and were diagnosed with primary mucosal HNC (non-metastatic). All patients underwent MRIs with 2-point DIXON sequences in weeks 0, 2, 3, 5 and 6 of RT, as well as 1- and 3-month post-RT. All MRI scans were performed on a wide bore 3.0-T scanner (MAGNETOM® Skyra; Siemens Healthcare, Germany) with no post-processing used and images reconstructed in the sequence. The locally developed RT head and neck MRI protocol, as shown in Table 1, was followed. Initially, patients were scanned using two four-channel surface coils placed over the thermoplastic mask in treatment positions. Due to poor tolerance by patients, later scans were performed using a dedicated 16-channel head and neck coil without the use of thermoplastic masks. Details of these studies including imaging protocol
and inclusion/exclusion criteria have been reported previously.14,15

Study methodology

Participant selection

Of the 54 patients, 23 were excluded as they either received less than 2 of the MRI scans scheduled in weeks 0, 3 or 6, which had scan levels inclusive of vertebral levels C2 to C7; received a chemotherapy regimen other than Cisplatin; or did not complete the prescribed chemotherapy treatment. The remaining 31 eligible patients were analysed based on whether they received cisplatin CRT and therefore received weekly IV fluid hydration (Arm A, \(n = 24\)), or if they received RT alone (Arm B, \(n = 7\)).

Arm A patients received daily RT and weekly cisplatin (40 mg/m²) with pre- and post-hydration. In total, each patient received 3 L of saline at each chemotherapy appointment.16 Patients allocated to Arm B received RT alone and therefore received no additional hydration.

Analysis

Records of patient weight at weeks 0, 3 and 6 of RT were collected. On each available MRI, a contour of patient external anatomy was created on the T2-weighted DIXON water sequences. It was limited within the anatomical boundaries of 2nd and 7th cervical vertebrae in the superior and inferior directions, and mid clavicles in each lateral direction.

Fat and water images generated with T2-weighted DIXON sequences were utilised. Using MIM Software (v6.9.5; MIM Software Inc., Cleveland, OH, USA), water fraction images were created from these sequences, determined by:13

\[
\text{Fat Fraction}(\%) = \frac{\text{fat signal only image}}{\text{water only + fat only images}} \times 100
\]

\[
\text{Water Fraction}(\%) = \frac{\text{water signal only image}}{\text{fat only + water only images}} \times 100
\]

Optimal thresholds for average water fraction for such methods are unknown. However, based on previous literature concluding that adipose tissue is made up of approximately 10% water,17 for this study, the water fraction was evaluated by assessing all regions, which are made up of 90% or more of water. An automatic threshold tool was utilised to create a region of interest (ROI) consisting of ≥90% water as per the water fraction formula (90WF). The absolute volume of VEx90WF was created using:

\[
\text{Relative Volume of } V\text{Ex}90\text{WF}(\text{RelVEx90WF})(\%) = \frac{\text{VEx90WF cc}}{\text{Extrnal Volume (cc)}} \times 100
\]

The fat fraction was evaluated using the same method but evaluating the 80% threshold. This threshold was chosen based on initial visual assessment of the MRI datasets.

To further explore differences between water fraction volumes in the two arms, the left Splenius Capitis (SpCap) muscle was contoured on T2-weighted in-phase DIXON MRIs within the anatomical boundaries of the 2nd and 5th cervical vertebrae using a reference MRI atlas of cervical spine musculature.18 This muscle was chosen due to its’ distance from HNC treatment high dose volumes thus reducing the direct effect of radiation-induced inflammation. Two HNC Radiation Oncologists randomly audited 10% of the SpCap contours, including those that were identified as more complex than others, to ensure accuracy and consistency. Using the automatic threshold tool, an absolute volume (cubic centimetres) of the 90WF within SpCap (VSp90WF) and relative volume of VSp90WF (RelVSp90WF) (%) was created.

Weight changes were evaluated for the patient cohort between weeks 0 and 6 using ANOVA with repeated measures test. Changes in weight were assessed between Arm A and Arm B using a paired t-test. Changes in RelVEx90WF and VEx90WF at weeks 0 and 6 were evaluated across the entire patient cohort using a paired t-test and exact sign test. A scatterplot was used to visualise the changes between changes in RelVEx90WF and weight between weeks 0 and 6. Comparisons of

| Parameter | T2-w TSE DIXON Sequence |
|-----------|-------------------------|
| Sequence name | Turbo spin echo |
| Repetition Time | 14,590 ms |
| Echo Time | 85 ms |
| Slice Thickness | 3 mm |
| Slice Spacing | 0 mm |
| Field of View | 250 mm |
| In-plane resolution | 1 × 1 mm² |
| Matrix | 256 × 205 |
| Averages | 1 |
| Echo Train Length | 12 |
| Flip Angle | 140° |
| Parallel Imaging (Acceleration factor) | 2 |

Table 1. Liverpool and MacArthur cancer therapy centre magnetic resonance imaging head and neck protocol.
RelVEx90WF and RelVSp90WF between Arm A and Arm B were assessed at weeks 0, 3 and 6 of RT with a one-way ANOVA utilising the Welch test. The mean difference between the VEx90WF and VSp90WF was assessed using The independent samples t-test and Mann–Whitney U-test. Clinically, significant differences between Arm A and Arm B would confirm our secondary aim hypothesis. Differences of $P \leq 0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics (Version 25).

**Results**

Table 2 summarises the patient characteristics of Arm A and Arm B.

### Water volume changes

Figure 1A and B demonstrate the changes in RelVEx90WF and VEx90WF of the entire patient cohort from weeks 0 and 6. The mean RelVEx90WF at weeks 0 and 6 were 14.53% and 17.18%, respectively. A paired samples t-test revealed significant differences between weeks 0 and 6 RelVEx90WF ($t^{18} = -3.167, P = 0.005$). The means of absolute volumes of VEx90WF at weeks 0 and 6 were 404.49 cc and 419.72 cc, with no statistically significant difference identified ($P = 0.064$).

### Water volume changes between Arms throughout the standardised external patient volume

Figure 2A demonstrates the changes in RelVEx90WF throughout treatment time points (pre-treatment week 0, week 3 and week 6) for both arms. Welch–Satterthwaite method was used to correct for unequal variances in the one-way ANOVA test. Table 3 reports the mean RelVEx90WF at weeks 0, 3 and 6 for Arms A and B. There were no significant differences at each time point. The mean change in VEx90WF between week 0 and week 6 was 10.91 cc for Arm A and 75.12 cc for Arm B. An independent t-test found that there was no significant difference between these volumes ($P = 0.139$).

### Water volume changes between Arms throughout the left splenius capitis muscle

The mean volume of the splenius capitis muscle at week 0 and week 6 was 13.68 cc and 11.62 cc, respectively. Changes in RelVSp90WF were evaluated at weeks 0, 3 and 6 using a one-way ANOVA test. Figure 2B demonstrates the changes in these volumes for both arms. No significant differences were found for RelVSp90WF between the two patient arms (Table 3). The mean changes in VSp90WF for Arms A and B were 0.58 cc and 1.08 cc, respectively. A Mann–Whitney U-test reported there was no statistically significant difference between Arm A and B’s change in VSp90WF ($U = 20.0, P = 0.317$).

### Weight changes

Overall, the entire patient cohort weight (kg) declined throughout treatment (Table 2). The mean weight change

| Variable | Arm A ($n = 24$) | Arm B ($n = 7$) |
|----------|-----------------|----------------|
| Gender   |                 |                |
| Male     | 23              | 7              |
| Female   | 1               |                |
| Age, years |           |                |
| 40–49    | 4               |                |
| 50–59    | 9               | 2              |
| 60–69    | 6               | 3              |
| 70–79    | 5               | 1              |
| 80+      | 1               |                |
| Primary Tumour Site |       |                |
| Larynx   | 4               | 4              |
| Tonsil   | 7               | 2              |
| Oropharynx | 2            | 1              |
| Base of Tongue | 5       |                |
| Nasopharynx | 2            |                |
| Hypopharynx | 3            |                |
| Vallecula | 1               |                |
| Smoking History |       |                |
| Yes      | 20              | 6              |
| No       | 4               | 1              |
| Treatment Technique |        |                |
| IMRT Only | 2             |                |
| VMAT Only | 3             | 2              |
| Tomotherapy | 14            | 5              |
| Tomotherapy and IMRT | 4     |                |
| Tomotherapy and VMAT | 1       |                |
| Feeding Tube |            |                |
| PEG Tube  | 14              | 1              |
| NG Tube   | 6               |                |
| No feeding tube used | 4 | 6 |
| Weight (kg) |            |                |
| Week 0 (mean, range) | 81.8, 53–109.8 | 76.9, 46.8–100.5 |
| Week 3 (mean, range) | 75.3, 52.4–102 | 75.1, 51–96.7 |
| Week 6 (mean, range) | 76.5, 52–99    | 68.4, 51.5–96.7 |
| Mean Weight change (%) | −8.3%         | −5.2%          |
| Number of MRIs evaluated (amount, %) |     |                |
| Week 0 | 24 (100%) | 7 (100%) |
| Week 3 | 20 (83.3%) | 7 (100%) |
| Week 6 | 15 (62.5%) | 4 (57.1%) |

*Abbreviations: IMRT, intensity-modulated radiation therapy; NG, nasogastric; PEG, percutaneous endoscopic gastrostomy; VMAT, volumetric-modulated arc therapy.*
for the entire patient cohort was 7.6% loss, and the weight changes for each arm are reported in Table 2. The mean scores for weight changes were significantly different (ANOVA $F = 52.233, P < 0.001$). The average weight loss for Arm A and Arm B was 7.0 kg and 4.7 kg, respectively ($P = 0.412$). The relationship between the

| Timepoint | Arm | RelVEx90WF Mean (%) | One-way ANOVA | RelVSp90WF Mean (%) | One-way ANOVA |
|-----------|-----|---------------------|---------------|---------------------|---------------|
| Week 0    | A   | 15.75               | $F(1,29) = 0.289, P = 0.546$ | 22.67               | $F(1,29) = 0.006, P = 0.940$ |
|           | B   | 14.81               |               | 23.18               |               |
| Week 3    | A   | 18.26               | $F(1,25) = 1.987, P = 0.061$ | 31.16               | $F(1,25) = 0.741, P = 0.235$ |
|           | B   | 15.19               |               | 24.00               |               |
| Week 6    | A   | 16.61               | $F^A(1,17) = 0.560, P = 0.289$ | 24.07               | $F^A(1,17) = 2.564, P = 0.239$ |
|           | B   | 19.31               |               | 39.04               |               |

Figure 1. (a) Relative percentage of $\geq 90\%$ water volume within this external contour (RelVEx90WF) (%) changes of all patients from week 0 to week 6 (b) Changes of absolute volume (cubic centimetres) of the $\geq 90\%$ water regions within external contour (Vex90WF) from weeks 0 and 6.

Figure 2. (a) Changes relative percentage of $\geq 90\%$ water volume within this external contour (RelVEx90WF) (%) for both arms at weeks 0, 3 and 6 (b) Changes in relative percentage of $\geq 90\%$ water volume within splenius capitis (SpCap) (RelVSp90WF) (%) for both arms at weeks 0, 3 and 6.
weight changes and RelVEx90WF is shown in Figure 3. Since there is no relationship between these measures, no correlation could be tested.

**Fat volume changes**

The mean percentage of fat loss within the external volume between weeks 0 and 6 was 4.28% (week 0 average = 34.28%, week 6 average = 30%) for the entire cohort. Arm B fat volume loss was greater than Arm B, 6.8% vs 3.91%.

**Discussion**

The primary aim of this study sought to develop a methodology to measure the water fraction volume changes on head and neck region MRIs during RT. It is a novel investigation based on previous fat fraction evaluation methodology which had been developed. Water fraction was used as a surrogate to determine water volumes within the specified ROI. This study has developed a methodology to measure water content changes; however, further exploration is needed to validate, using phantom imaging, where values of fat and water are known. Also, due to the small sample size of our study, it is not possible to come to strong conclusions based on our results alone.

The change in RelVEx90WF appeared to increase for the entire patient cohort; however, the VEx90WF measurement showed no significant change. This apparent increase in RelVEx90WF could be affected by discrepancies in external body contours due to the change in imaging protocol described earlier (removal of thermoplastic mask for imaging) or impacts of treatment-related oedema within the irradiated volume. Therefore, patient position would have most likely have differed from week to week. Differing external volumes could have affected the relative volume measure. Grimm et al. reported that long-term (13 weeks) repeatability errors was significantly larger than short-term errors on DIXON MRI sequences. This study also recognised that physiological changes occurring between scans could not be accounted for. Since the present study is retrospective, data regarding patients’ physiological changes and fluid intake have not been accounted for when assessing the RelVEx90WF changes. Furthermore, this study has only evaluated one threshold value (90WF). By evaluating more threshold values, a greater understanding could be obtained of which threshold value best demonstrates significant decrease in water fraction and patients’ potential hydration status.

Changes in RelVEx90WF and RelVSp90WF were not significantly different between patients who received CRT or RT alone. Differences in time between the MRI and chemotherapy appointments for Arm A (mean = 3.5 days) and the different sample sizes between the two arms could have potentially affected this. CBCT data could alternatively be used to evaluate volume changes pre- and post-chemotherapy and IV fluid administration. Retrospective CBCT data with a large field of view were not available for this study and would not provide functional information. However, this could be a tool which is used in a prospective study with a larger field of view to evaluate volumetric changes. Wallace et al. found that the proportion of HNC patients experiencing dehydration throughout their

![Figure 3. Relationship between changes in relative percentage of ≥90% water volume within external (RelEx90WF) (%) and changes in weight (%) from weight 0 to 6.](image-url)
treatment course was significantly higher in patients who received CRT versus those who received RT alone (44.4% vs 8.5%). This study also reported that these patients were more likely to suffer from significant weight loss (>5% in 8 weeks) (71.4% vs 42.7%)6; this supported our findings where Arm A average weight loss was greater than Arm B. Gastrointestinal side effects, as a result of CRT, may be intensified, often resulting in a decrease in the patients’ ability to tolerate adequate oral nutrition or fluid intake.5 Similarly, a systematic literature review7 reported that patients receiving CRT had higher hospitalisations rates for dehydration than those receiving RT alone or RT following surgery. However, these studies included patients receiving a range of chemotherapy regimens; therefore, hydration protocols could have differed to this study. Since this study demonstrated no change in VEx90WF, our methodology may not be a reliable clinical method to measure hydration status. Cisplatin is known to be associated with nephrotoxicity and renal cell death which can cause dehydration.16 This drug is also classified as a highly emetogenic drug, meaning there is a >90% risk of chemotherapy-induced nausea and vomiting without the use of antiemetics.20 Vomiting is a common cause of dehydration; therefore, a patients’ antiemetic regimen could have affected hydration levels.16

The growing use of MRI in RT, due to its superior soft tissue and tumour visualisation,11 makes this study extremely relevant. The use of T2-weighted DIXON MRI sequences strengthens the methodology developed in this study. The head and neck region is susceptible to movement artefacts; therefore, a scan with short acquisition times is important. DIXON MRI sequences are advantageous due to their rapid acquisition times as well as being highly repeatable and accurate.21 Assessing the images with a consistent method also strengthens the methodology developed as it can be replicated easily in future studies.

Malnutrition can affect over 70% of HNC patients undergoing RT, as shown in this study’s’s finding of significant weight loss22 and is a contributing factor to survival as well as causing undesirable interruptions in patient treatment.6,22,23 Our study found that muscle mass and fat volume decreased throughout RT from weeks 0 to 6 with no significant changes to water volumes. Increased doses to healthy tissues as a result of a change in body composition can lead to more severe side effects as well as other complications such as a potential need for replans, treatment breaks or discontinuation of treatment.15 Increased toxicities also significantly contribute to substantial nutritional deficit, reduced physical activity and muscle catabolism leading to sarcopenia24; known to be associated with poorer prognostic outcome and overall survival.23 Since muscle mass did show decrease on MRI, this shows potential for MRI to be used as an imaging device which does not increase patient radiation dose to predict sarcopenia.

Increasing treatment toxicity significantly contributes to substantial nutritional deficit, reduced physical activity and muscle catabolism.24 This has led to increasing research in body composition evaluation.23 Nutritional interventions can improve/maintain nutritional status and reduce treatment breaks and unplanned hospital admissions.7 If the methodology in this study is validated, further investigations can be conducted to evaluate muscle changes during RT, which may be used to optimise interventions and improve outcomes.

The present study must be viewed within its limitations. Potential selection bias may have occurred in terms of enrolling patients of favourable age, tumour site and stage, comorbidities and ECOG status. Selection bias within this study could exist, as only patients who received 2 of the weeks 0, 3 and 6 MRIs were chosen and may therefore be fitter or more compliant with nutrition/intake of water during treatment. Excluded patients could have experienced the most impactful side effects, explaining their incomplete participation in the previous studies. Furthermore, only one muscle was contoured within the head and neck region and only one threshold value analysed. The small sample size of Arm B, that is patients who received RT alone, is also a limitation and potentially could have affected the outcome of the paired t-test used to evaluate the average weight loss between Arm A and Arm B. The inconsistency of weight measurements (differing scales, time of day and clothing), due to data being retrospective, is also a limitation. Moving forward, if this methodology is validated on phantom studies, it could be utilised in a prospective study without the limitations noted above. Additionally, by delineating subregions within the head and neck (e.g. vasculature, muscle, soft tissue, fat and tumour site) and evaluating their water content, there is potential to highlight the regions most affected by dehydration. Having the ability to determine if hydration status is changing the position of surrounding tissues is important in cases where tighter margins exist.

**Conclusion**

This study has developed novel methodology for measuring changes in water fraction volumes with time using T2-weighted DIXON MRIs and identified changes in the relative volume of regions consisting of ≥90% water within the external region, across the entire cohort. However, no differences were detected between patients who received CRT vs RT alone. Further analysis and
confirmation of the methodology is needed through phantom imaging where values of fat and water are known.

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