Title: A Prospective, Multi-centre trial of Multi-parametric MRI as a Biomarker in Anal Carcinoma

Author names and affiliations:

Michael Jones (corresponding author)

- Email: Michael.Jone@ths.tas.gov.au
- Postal: WP Holman Clinic, Royal Hobart Hospital, 48 Liverpool Street, Hobart, Tasmania, Australia
- The University of Newcastle, Callaghan, New South Wales, Australia
- The Royal Hobart Hospital, Hobart, Tasmania, Australia

George Hruby

- Department of Radiation Oncology, Royal North Shore Hospital, St Leonards, New South Wales, Australia

Catherine Coolens

- Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Brandon Driscoll

- Princess Margaret Cancer Centre, Toronto, Ontario, Canada

Peter Stanwell

- The University of Newcastle, Callaghan, New South Wales, Australia

Mahesh Kumar

- Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, New South Wales, Australia

Anne Capp

- Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, New South Wales, Australia

Swetha Sridharan

- Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, New South Wales, Australia

Jameen Arm

- Calvary Mater Newcastle, Waratah, New South Wales, Australia

Sarah Gallagher

- Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, New South Wales, Australia

Carl Holder

- Hunter Medical Research Unit, New Lambton Heights, New South Wales, Australia

Christopher Oldmeadow

- Hunter Medical Research Unit, New Lambton Heights, New South Wales, Australia

Jarad Martin

- The University of Newcastle, Callaghan, New South Wales, Australia
- Department of Radiation Oncology, Calvary Mater Newcastle, Waratah, New South Wales, Australia

ABSTRACT

Background and purpose: To investigate the role of multi-parametric magnetic resonance imaging (MP-MRI) as a biomarker for squamous cell carcinoma of the anal canal (AC).

Materials and methods: From January 2013 to January 2017, 25 patients with non-metastatic AC were enrolled on a multi-centre prospective clinical trial, of whom 20 completed protocol treatment. MP-MRIs, incorporating diffusion weighted (DW) and dynamic contrast enhanced (DCE) sequences, were performed before (baseline), during the second and fourth weeks of chemo-radiotherapy (CRT), and 8 weeks following treatment completion. Histogram analysis of multi-parametric maps generated maximum, mean, median, minimum, skewness, kurtosis and standard deviation metrics. Exact logistic regression and ROC AUC analyses were performed for each metric at every timepoint. An elastic net LASSO logistic regression was also performed using all measures at each timepoint.

Results: With a median follow up of 17.1 months, 3/20 patients had a local recurrence, and 5/20 had any recurrence. Several apparent diffusion coefficient (ADC) metrics extracted from DW-MRI correlated with local recurrence and demonstrated excellent discrimination: baseline skewness (p=0.04, ROC AUC 0.90) and standard deviation (SD) (p=0.02, ROC AUC 0.90), week 2 skewness (p=0.02, ROC AUC 0.91) and SD (p=0.01, ROC AUC 0.94), week 4 kurtosis (p=0.01, AUC 0.92) and SD (p=0.01, ROC AUC 0.96). Changes in minimum ADC between baseline and week 2 (p=0.02, ROC AUC 0.94) and baseline and week 4 (p=0.02, ROC AUC 0.94) were prognostic for local recurrence. For prediction of any recurrence, ADC minimum (p=0.02, ROC AUC 0.87) and SD (p=0.01. AUC 0.85) at baseline and ADC maximum (p=0.03, ROC AUC 0.77) and SD (p=0.02, ROC AUC 0.81) at week 4 were significant. On LASSO logistic regression, ADC minimum and SD at baseline were retained for any recurrence. The only significant finding for DCE-MRI was a correlation of k-trans min at the second follow-up with local recurrence (p=0.05, AUC 0.84).

Conclusion: Several ADC parameters at various time points correlate with recurrence suggesting DW-MRI requires further validation as a potential biomarker for anal cancer.

Keywords
Anal cancer; chemo-radiotherapy; multi-parametric MRI

Introduction

Squamous cell carcinoma of the anal canal (AC) is an uncommon malignancy with an increasing incidence [1]. Definitive chemo-radiotherapy (CRT) allows for organ preservation but carries significant acute and late toxicity [2] even with contemporary modulated RT techniques [3]. Recurrence rates also remain high for locally advanced disease [4].

With the aim of optimising radiotherapy (RT) dose, the PersonaLising Anal cancer radioTherapydOse (PLATO) trials are using tumour stage to tailor treatment [5]. Intermediate risk disease will receive a lower RT dose and locally advanced disease will be dose escalated. This approach, however, potentially overlooks the heterogeneity of response to CRT within stage groupings.

Standard morphological MRI is recommended for AC staging [6] and post-CRT MRI may help identify candidates for salvage abdomino-perineal resection but it has not proven predictive of outcome [7,8]. Alternatively, changes on multi-parametric magnetic resonance imaging (MP-MRI) performed during CRT have been correlated with outcome in rectal, head and neck, cervical, and oesophageal cancers [9-14].

Response assessments performed during treatment also present opportunities for treatment adaptation allowing clinicians to refine treatments and enhance the therapeutic window [15]. With the emergence of MRI-linear accelerators, this approach could be incorporated into a standard radiotherapy workflow [16].

To explore MP-MRI as a biomarker for response in AC, and therefore its potential as a tool for treatment adaptation, we undertook a multi-centre prospective clinical trial.

Materials and methods

Study population

Patients with histologically confirmed non-metastatic squamous carcinoma of the anal canal were enrolled on a prospective study at three Australian centres. The study protocol has been previously published [17]. Patients were staged according to the AJCC cancer staging manual, seventh edition (2010). P16 testing as a surrogate for Human Papilloma Virus (HPV) infection was performed on all tumours. The study was approved by the Hunter New England Human Research Ethics Committee (reference: HREC/12/HNE/408) and prospectively registered (ACTRN12614001219673).

Chemo-radiotherapy

Patients were treated with Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT). Prescription dose, contouring, and radiotherapy planning were performed according to the Australasian Gastrointestinal Trials Group (AGITG) guidelines [18]. Radiotherapy doses ranged from 50.4-54Gy, depending on the tumour stage. Continuous infusional 5-Fluorouracil (5-FU) was delivered during the first and fourth weeks of RT at a dose of 800-1000mg/m2/day over 5 days. Mitomycin-C at 10mg/kg was delivered on day one only.

Image acquisition

MP-MRI of the pelvis was performed at time of staging (baseline), during the second and fourth weeks of CRT, and 8-weeks post completion of treatment. Both structural and physiologic imaging were performed on 3 tesla (T) MRI scanners (MAGNETOM Skyra or Vida, Siemens AG, Germany). Structural imaging consisted of axial and coronal T2-weighted and axial T1-weighted imaging pre-contrast, and axial fat-saturated T1-weighted post-contrast. Physiologic scans included axial diffusion-weighted imaging (DW-MRI) and dynamic contrast-enhanced (DCE-MRI) imaging acquired orthogonal to the rectum and anal canal. DW-MRI was acquired using a 2D echo planar imaging (EPI) sequence with four b-values of 0, 400, 800, and 1200s/mm^2 (TE/TR=90/6200ms, matrix=170×170, FOV=230× 230mm^2, slice thickness=3.5mm). DCE-MRI was acquired using a three-dimensional (3D) time-resolved contrast-enhanced MRA (TWIST) (echo time/repetition time [TE/TR]=1.86/4.82ms, flip angle [FA]=12º, matrix=192×192, field of view [FOV]= 270×270mm, slice thickness=3.5mm) with a temporal resolution of 5.8s. Sequential images were obtained from 40s before administration of intravenous (IV) contrast medium to 7.5min after contrast injection. DCE-MRI images were acquired following the injection of Magnevist (0.2ml/kg) at a rate of 2.5mL/s using a power injector followed by a 20mL saline chase at the same injection rate. Pre-contrast images were also acquired in the same slice location as the DCE-MRI imaging with different FAs of 4º and 21º to facilitate T1 mapping for use in kinetic modelling. Patients were immobilised using a knee cushion and ankle stocks. No rectal coil was used. All patients had a single IV bolus of hyoscine butylbromide (20mg/ml) immediately preceding the first sequence.

Image analysis

MP-MRI images were analysed using validated Temporal Dynamic Analysis (TDA) software on a voxel-by-voxel basis hosted by the QIPCM Imaging Core Lab (http://qipcm.technainstitute.com/) [19,20]. The T1- and T2-weighted images were fused with the DW-MRI and DCE-MRI sequences, then all primary tumours at each time point were manually contoured as a volume of interest (VOI) by the lead author. Areas of necrosis within the primary tumour were not excluded. Involved lymph nodes were not contoured. Histogram analysis of DW-MRI (apparent diffusion coefficient) and DCE-MRI (ktrans, kep) maps was performed to extract the following metrics: maximum, mean, median, minimum, skewness, kurtosis, standard deviation (SD). DCE-MRI analysis was performed using a population-based vascular input function. Individual endogenous T_1 (T10) maps were used where available. For patients who did not have individual T10 maps, an assumed T10 value of 1600 milliseconds was used.

Statistical analysis

MP-MRI parameters at baseline, first follow-up and second follow-up, as well as the change in parameters between scans, were analysed and correlated with local and any recurrence. Change was assessed as a continuous variable. Exact logistic regression and receiver operating characteristic (ROC) area under the curve (AUC) analyses were performed for each metric at each time point. An AUC between 0.6-0.7, 0.7-0.8, 0.8-0.9, and 0.9-1.0, was considered to have poor, fair, good, and excellent discrimination performance, respectively. An elastic net LASSO logistic regression was performed for all measures at every time point, as well as for the change between time points. While our original protocol stated a complete response would be defined at 26 weeks, the subjective nature of this endpoint and its variability between clinicians and methods (e.g. digital rectal exam versus examination under

anaesthetic) meant we switched to local progression as a more robust measure of tumour response.

Results

Between January 2013 and January 2017, 25 patients were enrolled from three Australian centres. Five patients withdrew from the study. The reasons for withdrawal are listed in Table 1. The characteristics of the remaining 20 patients are detailed in Table 2. All tumours were P16 positive. To ensure primary tumours were of sufficient size to perform a meaningful quantitative analysis, the inclusion criteria stipulated minimum T2 tumours. One patient with a T1N2 (1.9cm primary) was permitted to enrol as it was felt the primary tumour size was adequate to allow ADC and DCE map analysis.

Median follow-up was 17.1 months (range: 8.2-54.3). Three patients (15.0%) developed a local recurrence. Two had persistent disease at 26 weeks (original stage T2N2 and T3N0) and one recurred 16 months post-CRT (original stage T4N2). Two patients developed distant metastatic disease without local failure for a total of 5 patients (25.0%) with any recurrence. At last follow-up, one patient had died of disease.

The average median apparent diffusion coefficient (ADC) at baseline, week 2, and week 4 was 0.8, 0.9 and 1.0 x10^-3 mm2/s. Several ADC parameters were significant predictors of local recurrence (Table 3). ADC skewness and SD were significant at baseline and week 2. Kurtosis and SD were significant at week 4. Change in minimum ADC was significant between baseline and week 2, and baseline and week 4. On LASSO regression, ADC skewness and SD were retained at both week 2 and week 4.

Baseline ADC minimum and SD, and week 4 maximum and SD, were significant for predicting any recurrence (Table 4). The LASSO regression models only retained the ADC minimum and SD at baseline. The sole significant finding for DCE-MRI was a correlation between k-trans min and local recurrence at week 4 (p=0.05, AUC 0.84).

Discussion

This is the first study to prospectively investigate the role of MP-MRI as a biomarker in AC. Patients were treated uniformly on a multi-centre prospective trial. MP-MRIs were performed before, during, and following CRT according to a common protocol and MP-MRI parameters were correlated with recurrence.

ADC values extracted from the DW-MRI sequences proved the most promising with a number of parameters demonstrating a significant correlation with recurrence and excellent discrimination values. These results suggest that DW-MRI may be a potential biomarker in AC.

Standard morphological MRI and positron emission tomography/computed tomography (PET/CT) are complimentary imaging modalities recommended for AC staging [6,21]. While clinical examination is the mainstay of response assessment, emerging evidence indicates MRI and PET/CT performed following CRT may also help identify patients at increased risk of treatment failure [7,8,22].

The unique value of imaging performed during CRT is the prospect of using that information to inform treatment adaptation. Presently, radiotherapy dose selection is based on the tumour stage [5,18]. Once validated, MP-MRI performed during treatment may allow further refining of the radiotherapy dose according to treatment response.

Several studies have investigated DW-MRI performed during CRT in other tumour sites [10-13]. In general, they showed a greater increase in ADC during CRT predicted a favourable response. However, these studies assessed only the mean or median ADC within the VOI. This approach overlooks the spatial heterogeneity within a tumour and may be missing important changes during treatment [23].

In addition to assessing mean and median parameter values, we performed a texture-based analysis of ADC histograms. This provides metrics that describe the distribution of ADC values within the VOI: skewness, kurtosis, and standard deviation [24]. These parameters can be considered a quantitative surrogate of tumour heterogeneity [25].

Tumours with high intra-tumoural heterogeneity are associated with a poorer prognosis [26-28] and decreasing heterogeneity during treatment appears to portend a good response [29]. Markers of ADC heterogeneity, specifically skewness and kurtosis, have been correlated with response to CRT in head and neck and cervical cancer [30-32], and we also found a correlation between these metrics and recurrence. Interestingly, two recent retrospective analyses correlated heterogeneity metrics on staging MRI with recurrence in AC [33,34] indicating this deserves further investigation, perhaps incorporating a radiomics approach [35,36].

While one DCE-MRI metric, k-trans min, was significant and several DCE-MRI metrics approached significance, the relationship between DCE-MRI parameters and recurrence was less apparent than ADC. There may be a number of reasons for this. Our small sample size may have lacked sufficient statistical power. There was variability in T10 map acquisition between centres. Despite the use of hyoscine butylbromide, a small amount of spatial motion remained evident on DCE sequences. Considering the sparse temporal resolution of the DCE acquisition, this can reduce the parameter estimation accuracy [37]. Nevertheless, DCE has shown promise as a biomarker for radiation treatment response in a number of tumour sites [38] and now AC can be added to that list.

Previous studies have tended to perform MP-MRIs at a single time point during CRT, usually week 3 [9-14]. Changes in ADC as early as week 1 can predict treatment response [10] and earlier assessments present greater opportunity for treatment adaptation. With this in mind, and with a view to examine the importance of timing, we elected to perform MP-MRIs at two time points – weeks 2 and 4. Our results did not show a significant difference between the time points suggesting the timing of MP-MRIs may not be critical.

Achieving consistent image acquisition across multiple centres can be challenging. Fortunately, all centres in our study had the same make of MRI (3T MAGNETOM Skyra or Vida, Siemens AG). This allowed sequences to be easily standardised using an electronic protocol (EDX file). We also used power injectors to deliver IV contrast at a fixed rate when acquiring the DCE sequences.

While performing the image analysis, some limitations to the process became apparent. Firstly, manual delineation of the VOI is a subjective process open to significant inter-, and even intra-observer variability. Semi-automated methods using threshold ADC values have been proposed [39,40] to improve the objectivity of the delineation process. Indeed, one may imagine a time when automated extraction and radiomic analysis of MP-MRI metrics from MRI linear accelerators will allow monitoring of radiotherapy response and inform treatment adaptation.

Secondly, as other authors have noted [10], delineation became increasingly difficult as the tumour regressed. This was a particular challenge for smaller tumours. By the 8-week post-CRT timepoint, tumour regression rendered only the largest tumours amenable to meaningful quantitative analysis. As such, analysis of the post treatment MRI images was not completed. Imaging earlier during the course of CRT could avoid these challenges and also lends itself to an adaptive approach, allowing time for the clinician to enact treatment changes.

The principle limitations of this study are the small sample size, low event rate, and short follow-up. AC is an uncommon tumour which poses recruitment challenges, and this was intended as a pilot study only. Despite the low event rate, we had several statistically significant findings, and our median follow-up of 17.1 months seems acceptable considering local recurrence in AC occurs at a median of 16 months post-CRT [41].

We acknowledge that our analysis generated a large amount of data which increased the likelihood of finding statistically significant results. This was a preliminary study; such an exploratory analysis is useful for identifying signals which warrant further investigation in larger patient cohorts.

As described above, we found several ADC parameters correlate with recurrence, suggesting that DW-MRI is a potential biomarker in AC.

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Figures

Figure 1 caption: Apparent diffusion coefficient maps from pre-treatment (a), week 2 (b) and week 4 (c) of chemo-radiotherapy of a patient who did not experience a local recurrence. Apparent diffusion coefficient maps from pre-treatment (d), week 2 (e) and week 4 (f) of chemo-radiotherapy of a patient who subsequently experienced a local recurrence.