Original Research Article

Study of diffusion weighted MRI as a predictive biomarker of response during radiotherapy for high and intermediate risk squamous cell cancer of the oropharynx: The MeRInO study

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INTRODUCTION AND BACKGROUND

The incidence of oropharyngeal squamous cell cancer (OPSCC) has increased greatly in the developed world in recent years [1]. Radiotherapy (RT) or chemoradiotherapy (CRT) is an organ-preserving alternative to surgery with at least equivalent loco-regional control and disease-free survival (DFS) [2,3].

Smoking and alcohol are well established risk factors. The recent increase in incidence, however, is attributed to a rise in Human Papilloma Virus (HPV) driven OPSCC [4]. It has been shown that these HPV + OPSCC are more responsive to treatments and patients have better overall survival (OS) rates than their HPV negative counterparts [5–7]. However, it has also been demonstrated that smoking remains a significant factor in disease control with the risk of death increasing directly as a function of tobacco exposure in all OPSCC patients [8]. Ang et al. [7] suggested that the bio-

INTRODUCTION AND BACKGROUND:

A significant proportion of patients with intermediate and high risk squamous cell cancer of the oropharynx (OPSCC) continue to relapse locally despite radical chemoradiotherapy (CRT). The toxicity of the current combination of intensified dose per fraction radiotherapy and platinum based chemotherapy limits further uniform intensification. If a predictive biomarker for outcomes from CRT can be identified during treatment then individualised and adaptive treatment strategies may be employed.

METHODS/DESIGN: The MeRInO study is a prospective observational imaging study of patients with intermediate and high risk, locally advanced OPSCC receiving radical RT or concurrent CRT Patients undergo diffusion weighted MRI prior to treatment (MRI_1) and during the third week of RT (MRI_2). Apparent diffusion coefficient (ADC) measurements will be made on each scan for previously specified target lesions (primary and lymph nodes) and change in ADC calculated. Patients will be followed up and disease status for each target lesion noted. The primary aim of the MeRInO study is to determine the threshold change in ADC from baseline to week 3 of RT that may identify the sub-group of non-responders during treatment.

DISCUSSION: The use of DW-MRI as a predictive biomarker during RT for SCC H&N is in its infancy but studies to date have found that response to treatment may indeed be predicted by comparison of DW-MRI carried out before and during treatment. However, previous studies have included all sub-sites and biological sub-types. Establishing ADC thresholds that predict for local failure is an essential step towards using DW-MRI to improve the therapeutic ratio in treating SCC H&N. This would be done most robustly in a specific H&N sub-site and in sub-types with similar biological behaviour. The MeRInO study will help establish these thresholds in OPSCC.

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logical behaviour of HPV + OPSCC may be altered by tobacco use, rendering them less responsive to therapy. He proposed 3 ‘risk groups’ for OPSCC, using tumour stage, HPV status and smoking history to classify patients into low, intermediate or high risk of death, (Table 1). Current strategies in the low risk group focus on de-escalation of therapy and clinical trials are ongoing [9]. Conversely, intensification of treatment should be considered for the intermediate and high risk groups, which are the focus of the proposed study.

Patients with HPV-OPSCC tend to be older with significant smoking and/or alcohol history [10], resulting in more comorbidities than their HPV + OPSCC counterparts. Uniform treatment intensification of an already morbid treatment across this group is therefore unattractive. If, however, a predictive biomarker could be established to select patients who respond poorly to RT, an individualised treatment intensification strategy could be used for those who require it.

The role of imaging in early response detection for SCC H&N is currently ill-defined. Volumetric assessment during RT using CT or MRI based anatomical imaging has shown conflicting results [11–17]. PET-CT with FDG and other tracers continues to be investigated. There is some evidence that changes in FDG PET uptake early during the course of RT correlates with ultimate tumour response [18–21]. However, difficulties in delineating target volumes using PET-CT during treatment have been reported [22,23].

The use of DW-MRI as a predictive biomarker during RT for SCC H&N is in its infancy but studies have found that response to treatment may indeed be predicted by DW-MRI by acquiring images before and during treatment. It has been suggested that ‘for DW imaging to be of clinical value, ADC thresholds need to be established that can help predict local failure’ [28]. This is the primary aim of the MeRlnO study – to establish the threshold change in ADC from baseline to week 3 of RT that can differentiate responders from non-responders to treatment. This may then allow an individualised and adaptive approach to treatment based on the biological behaviour of a tumour during RT.

Methods/design

Study organisation/funding

The MeRlnO study was designed by a multi-disciplinary collaboration from The Beatson West of Scotland Cancer Centre, the Department of Clinical Physics and Bioengineering, NHS Greater Glasgow and Clyde, and the University of Glasgow. The study sponsor is NHS Greater Glasgow and Clyde (Sponsor reference number GN15ON249). The study received in-house approval by the Clinical Trials Executive Committee (CTEC) and National Research Ethics Committee approval (REC number 15/WS/0159). The study is registered on the publically accessible database Clinicaltrials.gov (NCT02497573).

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| Risk category | OS at 3 years | Demographics |
|---------------|--------------|--------------|
| Low risk      | 93%          | HPV+, <10 pack years |
| Intermediate risk | 70.8%        | HPV+, >10 pack years, N0-2a |
| High risk     | 46.2%        | HPV-, >10 pack years, N2b-3 |

Study design and patient population

The study is a prospective, longitudinal, single centre, observational imaging study of patients with intermediate and high risk, locally advanced OPSCC receiving primary radical RT or concurrent CRT.

Two DW-MRI scans will be carried out on participants in addition to all standard procedures. The information gained from the MRI scans will not be used to change standard treatment. The first DW-MRI (MRI_1) will be obtained on the same day RT commences. The second DW-MRI (MRI_2) will be carried out during the third week of RT treatment.

The DW-MRI scans will be used to measure ADC in each target lesion (primary and lymph nodes) and to calculate change in ADC between the 2 scans. After completion of RT, patients will attend for follow up visits at 3, 6, 12, 18 and 24 months post treatment. Fig. 1 shows this schematically.

Inclusion criteria:

- Histologically confirmed HPV negative OPSCC or HPV positive OPSCC and a significant smoking history (>10 pack years).
- Stage III or IVa or IVb disease.
- Scheduled to undergo radical RT or CRT as primary treatment.
- 18 years of age or older.
- HPV status: As defined by the Scottish HPV reference laboratory, multiplex assay on Luminex technology.
- Diagnosis and staging will be carried out as per standard regional guidelines [29].

Exclusion criteria:

- Sub sites other than oropharynx.
- Low risk OPSCC.
- Patients receiving cetuximab-RT.
- Confirmed distal metastatic disease (stage IVc).
- Patients who have undergone primary surgery for SCC H&N.
- Patients who have received induction chemotherapy.
- Patients with contra-indications to MRI scanning (cardiac pacemaker, surgery within 8 weeks, aneurysm clipped/treated, metal fragments in eye, previous cranial surgery, any ferrous metal in the body, pregnancy).

Study objectives and end-points

The primary objective of the MeRlnO study is to determine the threshold change in ADC from baseline to week 3 of RT that can differentiate responders from non-responders to treatment. This will be achieved by measuring ADC on MRI_1 and MRI_2 for all target lesions. Change in ADC (ΔADC) and % change in ADC (% ΔADC) will be calculated for each lesion and recorded.

Loco-regional failures at 24 months post-treatment will be recorded and pattern of relapse noted. Relapse status for each target lesion at 24 months post-treatment will be recorded. Progres-
sion free survival at 24 months will also be noted to account for distal metastases.

Secondary objectives are to assess
- feasibility of measuring ADC at baseline and week 3 of RT,
- time to relapse for each target lesion,
- correlation of ΔADC with pattern relapse.

Chemo-radiotherapy

Patients may receive concurrent CRT or RT alone as definitive primary treatment.

For RT planning and treatment patients are immobilised with a custom made thermoplastic mould with 5 point fixation (Klarity Medical Products, Newark, Ohio). A contrast enhanced planning scan is obtained on either a Discovery CT590 RT (GE Medical Systems, Amersham, UK) or a Philips Brilliance Big Bore (Philips Medical Systems B.V, The Netherlands).

Target delineation is carried out by the treating oncologist, using all available clinical and radiological information from diagnosis and staging and with reference to international guidelines [30]. Peer review and approval of the planning target volumes is mandatory and standard practice in our centre for all H&N cancers.

A treatment plan is created using the Eclipse™ planning system (Varian medical systems, Palo Alto, CA) and approved by the treating clinician.

All patients receive RT delivered on a Varian Clinac® 600 linear accelerator using Rapid Arc® (Varian medical systems, Palo Alto, CA) volumetric-modulated arc therapy (VMAT) with 6 MV photons. Gross tumour and the entirety of involved nodal levels receive 65 Gy/30# over 6 weeks. Prophylactic dose to areas considered at high risk of occult disease is 54 Gy/30# over 6 weeks.

Cisplatin is delivered at 100 mg/m² on days 1 and 22 of treatment for those receiving concurrent chemotherapy as per local protocols [31]. Concurrent cetuximab is not permitted, nor is

![Trial pathway](image-url)
induction chemotherapy to keep the cohort as homogeneous as possible.

**Diffusion weighted MRI**

All MRI images will be acquired on a Signa 1.5T HDxt (GE, Crawley, UK) scanner with patients in a supine position with neutral neck position. The decision to not employ immobilisation was taken to enable the use of the neurovascular coil and to facilitate recruitment and retention of patients to the study. A measurement from supra-ternal notch to mandible will ensure intra-subject consistency of head position at repeat scan. The position of the hard palate will also be checked on the sagittal localiser to verify axial alignment. A 16 channel neurovascular coil (HNS NV full, GE, 2012) provides coverage of the H&N area using the head coils, anterior and posterior neck coils and anterior chest coils.

MRI sequences will be acquired for anatomical identification of each target region. T1 weighted, T1 weighted fat sat, and T2 weighted fat sat and post-gadolinium contrast images will be obtained. The diffusion weighted images will be acquired using a single shot EPI sequence with several b-values between 0 and 1000 s/mm². The ADC map will be calculated automatically using inline post-processing (Optima Edition 23, GE, Milwaukee, 2012) from the acquired b value images using a mono-exponential fit.

All anatomical and DW images will be imported into the Eclipse™ treatment planning system (TPS) (Varian medical systems, Palo Alto, CA). Target lesions will be delineated on each axial slice of the ADC maps by expert clinical oncologist (CP) and radiologist (IMcC) with over 10 years experience. The anatomical MR sequences will be used to aid delineation generally and in particular identification and exclusion of necrotic areas on the ADC maps. Necrotic/cystic areas will be excluded from ADC analysis.

**Quality assurance (QA)**

To verify the accuracy of ADC measurement by the scanner software, a phantom will be scanned monthly. The phantom comprises four vials containing different concentrations of polyvinylpyrrolidone (PVP) solution and one vial of distilled water. The range of ADC values covered by the different concentrations of PVP encompasses the clinical range of interest [32]. The ADC measurements will be recorded using the scanner software and the Eclipse™ TPS (Varian medical systems, Palo Alto, CA).

Daily QA is performed on the MRI scanner to check fundamental parameters of the system.

RT treatment QA features throughout the process. Peer review of target volumes created by the treating clinician is required prior to planning. RT plans are produced and checked by two operators prior to treating clinician review and approval. Daily on-line KV-KV imaging is carried out prior to treatment to ensure accuracy of set-up. Our centre is an active participant in several UK multi-centre RT studies (e.g. recently NIMRAD [33], ART DECO [34]) and therefore subject to scrutiny by the NCRI RTQA group as well as meeting individual study QA requirements.

**Clinical follow up**

Following completion of RT, patients will attend for evaluation at 3, 6, 12, 18 and 24 months post treatment. At each visit, disease status will be recorded. This assessment will be based on clinical examination and any available imaging as per standard regional practice [35].

Local control is defined as:

- Static or reduction of residual mass during follow up (FU) ≥ 24 months.
- Histological confirmation of absence (based on surgical resection, not biopsy due to potential sampling error).

Local failure or relapse/recurrence is defined as:

- Biopsy proven recurrence.
- Development of new mass or serial increase in size of residual mass during FU ≥ 24 months.

**Statistical analysis**

**Sample size**

Around 80 OPSCC patients per year are treated in our centre with RT or CRT. Analysis of a local database found an overall relapse rate of 30% for intermediate and high risk OPSCC patients (unpublished work). This is consistent with previously published outcomes for locally advanced SCC H&N which had loco-regional failure of 26.7% in our centre [36].

We estimate that recruiting a sample of 80 patients will provide 24 patients who relapse and 56 patients who do not relapse assuming a 30% relapse rate. A sample of 24 relapsed patients will differentiate a test sensitivity of >80% from a sensitivity of <60% at 80% power and 10% 1-sided level of statistical significance. It is expected that there will be 56 patients who do not relapse. This number of patients will provide 94% power to distinguish a specificity of <60% from a specificity of >80% (assuming a 5% 1-sided level of statistical significance). We anticipate sensitivity and specificity of over 80% as reported by Kim et al. who found that the normalised ADC values after the first week of treatment had the highest accuracy to separate complete from partial responders, with a sensitivity of 86% and a specificity of 83% [37].

**Primary analysis**

The distribution of baseline demographic and clinical characteristics of patients will be described. We will report the percentage of patients with measurements of ADC at baseline and week 3 of RT. The proportion of patients experiencing loco-regional failure and progression free survival at the end of the study will be reported.

We will determine the sensitivity and specificity (with 95% CIs) for loco-regional failure of different cut-off values of the change in ADC from baseline to week 3. A receiver operator characteristic (ROC) curve will be used to illustrate the performance of change in ADC as its discrimination threshold is varied.

**Secondary analyses**

We will determine whether the association between change in ADC and relapse is different for primary and lymph node lesions. We will employ survival analysis techniques to determine whether associations between baseline characteristics (for example initial ADC value, age, or sex), change in ADC value and time to relapse exist. We will describe factors associated with drop out or discontinuation/interruption of treatment.

Analyses will use standard statistical significance level of 0.05.

**Interim data analysis**

The feasibility of measuring ADC at baseline and week 3 of RT will be assessed after the first 40 patients enter the study. The percentage of patients where it is feasible to measure ADC for at baseline and week 3 of RT will be calculated and the study will be discontinued if this is <50%.
Discussion

The need for a predictive biomarker

Historically, prognostic, rather than predictive, information in the form of the tumour, nodes, metastases (TNM) staging system has been used to inform therapeutic decision-making in the management of OPSCC. A standard approach to treatment of locally advanced disease has resulted in treatment failure in a significant proportion and perhaps unnecessary toxicity and functional impairment in others who may have achieved disease control with less intensive treatment [38]. The identification of a predictive biomarker is the first step towards an individualised cancer treatment approach and may allow an improved therapeutic ratio.

DW-MRI and ΔADC have been shown to correlate with response to treatment in prospective and retrospective studies in SCC H&N [6,14]. Kim et al. performed DW-MRI before 1 week into and approximately 2 weeks after CRT in 33 patients. They found that the normalised ADC values after the first week of treatment had the highest accuracy to separate complete from partial responders (sensitivity 86%, specificity 83%) [37]. In a similar study, Vandecaveye et al. found that the ΔADC values at week 2 and 4 of CRT were significantly correlated with 2-year LRC and DFS [29]. In patients with recurrence, the ΔADC at 2 and 4 weeks was significantly lower than in patients with a complete response in both adenopathies and primary tumour [28]. King et al. corroborated these results, reporting that changes in serial ADC values were associated with treatment response [39]. They calculated that a fall in ADC during treatment identified patients who developed treatment failure with 90% accuracy. A further study by King et al. [40] investigated ΔADC 2 weeks into CRT. Tumours that responded to treatment displayed a significantly higher percentage increase in ADC value at 2 weeks compared to those that failed treatment. These results suggest an insufficient rise in ADC during treatment correlates with a poor response to RT. Less evidence is available for a threshold rise in ADC that could be used to select non-responding tumours for treatment intensification with only 2 studies assessing this [28,40]. Vandecavey et al. [28] reported a threshold rise of 14% for primary lesions and 14.61% for lymph node metastases. The threshold rise to predict local control in primary lesions was identified as 15.5% in the study by King et al. [40].

These studies have included all H&N sub-sites with no differentiation between biological sub-types. Establishing a threshold rise in ADC to predict responders from non-responders would be done most robustly in a specific H&N sub-site and in sub-types with similar biological behaviour. This study will therefore validate the use of DW-MRI as a predictive biomarker specifically in the intermediate and high risk groups of OPSCC. If a discriminatory threshold rise in ADC can be identified early in treatment to discriminate non-responders an adaptive, dose-escalated radiotherapy treatment plan could be delivered for the remainder of the course in a safe but meaningful fashion. This would form the basis of subsequent clinical trials.

Potential future translational studies

All patients that are recruited for the MeRInO study will be given information about an exploratory biomarker study collecting blood samples of patients with malignant disease run by the Glasgow experimental cancer medicine centre [41]. Furthermore, histology samples taken at the time of diagnosis will be stored by the Greater Glasgow & Clyde Bio-repository. It is intended that the bank of clinical and radiological data that is acquired from the MeRInO study may be examined in conjunction with these blood and tissue samples in the future and potential biomarkers identified.

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