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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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ABSTRACT

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.

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 chemo-radiotherapy (CRT) is an organ-preserving alternative to surgery with at least equivalent locoregional 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-

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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 co-morbidities 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].

DW-MRI enables us to detect the Brownian motion of water molecules in biological tissues [24]. The apparent diffusion coefficient (ADC) value is the parameter that is used to quantify DW-MRI, estimating the diffusion rate of water molecules in tissue. [25].

MRI is attractive as an imaging biomarker as it is non-invasive and does not involve additional radiation exposure. It has better tissue contrast resolution when compared to CT and is the imaging modality of choice to accurately define the extent of OPSCC [3,26,27].

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 MeRInO 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 MeRInO 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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Table 1
Risk of death in OPSCCs, Ang et al. [7].

Risk category	OS at 3 years	Demographics
Low risk	93%	HPV+, <10 pack years HPV+, >10 pack years, N0-2a
Intermediate risk	70.8%	HPV+, >10 pack years, N2b-3 HPV−, <10 pack years
High risk	46.2%	HPV−, >10 pack years HPV−, <10 pack years, T4

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 MeRInO 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-