Title:	Optimized Diffusion-Weighted Imaging for the Evaluation of Post-Treatment Squamous Cell Carcinoma in the Neck: Comparative study with FDG PET/CT
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Title: Optimized diffusion-weighted imaging for the evaluation of post-treatment squamous cell carcinoma in the neck: Comparative study with FDG PET/CT.

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Glossary of Abbreviations
ASNR= American Society of Neuroradiology
ADC= apparent diffusion coefficient
DWI= diffusion-weighted imaging
fMRI = functional MRI
MUSE= multiplexed sensitivity encoding algorithm
QIBA= Quantitative Imaging Biomarkers Alliance
SCC= squamous cell carcinoma
WIP= work in progress

Protocol Revisions History

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1.0 BACKGROUND AND RATIONALE

Head and neck tumors can be a significant imaging diagnostic challenge. Anatomic imaging alone is insufficient to differentiate between post-treatment change and recurrent tumor, as both demonstrate increased T2/FLAIR signal and enhancement. Diffusion-weighted sequences (DWI) is a more sensitive and specific sequence that can be used to evaluate this tumor, and that can more easily differentiate between residual/recurrent tumor and post-treatment change (Vandecaveye, 2007). Metabolic imaging with FDG PET/CT is impacted by false-positives in the setting of inflammation or post-radiation necrosis and thus, data must be acquired 8-12 weeks post-treatment to avoid this pitfall. Moreover, PET/CT imaging is less available compared to MRI or CT. MRI does not require ionizing radiation, which is an important factor in head and neck squamous cell cancer patients, as they have an increased risk of secondary tumors such as lung cancer.

MRI systems that include diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) measurements hold promise to facilitate differentiation of tumor recurrence from post-treatment changes and associated complications, since areas of tumor demonstrate restricted diffusion and post-treatment changes do not [Chawla, 2009; Friedrich, 2008; Hermans, 2010; Jansen 2010; King, 2010 and 2013; Maeda, 2008; Mudana, 2018; Perrone, 2011; Vandecaveye, 2007 and 2010]. However, there are multiple pitfalls associated with conventional DWI related to artifacts such as fat saturation, distortion, aliasing/ghosting and spatial resolution. These limit the utility of this technique.

We propose a longitudinal study evaluating post-treatment changes in patients with squamous cell carcinoma (SCC) of the neck using an **innovative optimized DWI pulse sequence to identify more accurately recurrent tumors as well as early non-responders to therapy.** Our optimized DWI pulse sequence includes a combination of new improvements in data acquisition—, specifically multiband echo planar imaging (MultiBand, Siemens Medical Solutions, Erlangen, Germany) and multi-segment K-space readout algorithm (RESOLVE, Siemens Medical Solutions, Erlangen, Germany), i.e. SMS/RESOLVE WIP 1051a. The multiplexed sensitivity encoding algorithm (the MUSE method pioneered by Dr. Nan-Kuei Chen of the University of Arizona, Figure 1) is applied at post processing. Our optimized DWI sequence **follows QIBA-recommended guidelines**. **We found that our DWI pulse sequence improved quantitative artifact parameters [Guzmán Pérez-Carrillo, 2019] which in turn should increase the diagnostic accuracy of our technique.**

We plan to enroll 60 biopsy-proven neck SCC patients after treatment with surgery, radiation or chemo-radiation. The Otolaryngology, Head and Neck Surgery physicians and their clinic staff will coordinate enrollment. The patients will undergo an optimized research neck DWI protocol up to 3 weeks post-treatment and then a standard-of-care 3-6 months post-treatment FDG PET/CT examination. The optimized research DWI images will be acquired on a dedicated research Siemens 3T Scanner belonging to Washington University's Center for Clinical Imaging Research. The standard-of-care FDG PET/CT will be acquired at one of the Siemens Biograph clinical **PET/CT units located throughout the Barnes-Jewish Hospital Systems that adhere to QIBA FDG PET/CT protocols**. We will compare the ADC values (ADCmin and ADCmean) from the optimized DWI pulse sequence to FDG PET SUVmax. We will follow patients for 1 year to assess their clinical outcomes, including histological results associated with re-biopsy or surgery.

2.0 OBJECTIVES

The Specific Aim of this application is as follows: To compare SUVmax and ADCmean/min values to assess the capability of the new DWI pulse sequence to differentiate post-treatment change from residual or early recurrent tumor.

Hypothesis: The optimized research DWI pulse sequence obtained up to3 weeks post treatment will accurately identify residual/recurrent tumor, as confirmed by the clinical FDG PET/CT obtained at 3-6 months. This would potentially result in a modification of imaging follow-up algorithms, increased cost-savings and eliminate radiation exposure to patients inherent in PET/CT. This would also result in earlier changes to treatment regimens and stratify patients into more or less aggressive tumor response to treatment. The gold-standard will be histological tissue where available and/or 1-year clinical and imaging outcomes, including imaging outcome measurements such as RECIST 1.1 [De Bree, 2017], PERCIST [Joo Hyun, 2016] and iRECIST [Persigehl, 2020].

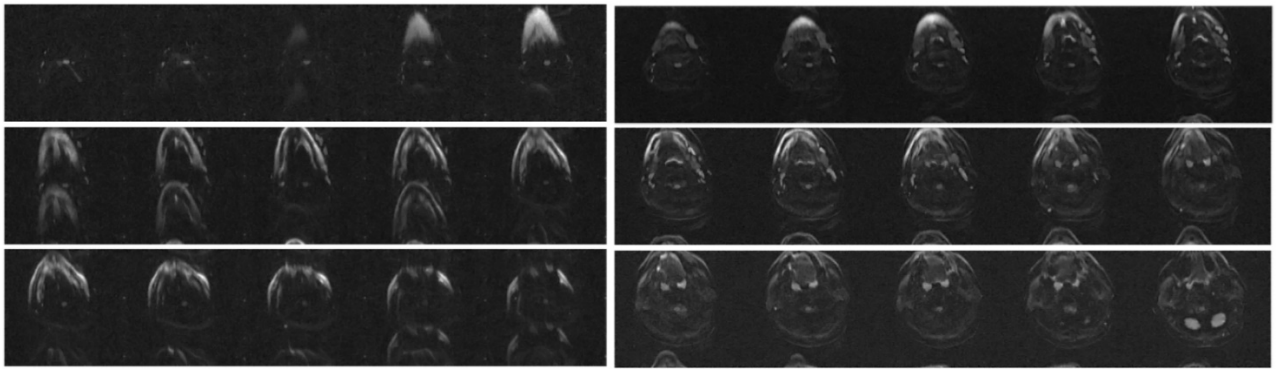

Figure 1: DWI data obtained from a healthy volunteer with a GE 3 Tesla system and eight-channel neurovascular array coil. Single-shot EPI-based DWI was obtained: matrix size = 128 × 128; parallel imaging acceleration factor = 2; field of view = 24 cm × 24 cm; b-value = 1000 s/mm^2. B, High-resolution DWI data obtained with four-shot interleaved EPI pulse sequence (matrix size = 256 × 256; field of view = 24 cm × 24 cm; b-value = 1000 s/mm^2) and reconstructed with our developed MUSE algorithm.

3.0 PARTICIPANT SELECTION

ELIGIBILITY CRITERIA

Inclusion Criteria:

1) Histologically-proven newly diagnosis or recurrence as indicated by tissue diagnosis of T3 or T4 squamous cell carcinoma of the head and neck
2) Must have had or be scheduled for standard-of-care surgical resection, radiation, and/or chemo-radiation of the diagnosed squamous cell carcinoma of the head and neck
3) At least 18 years of age
4) Patient must be able to understand and willing to sign a written informed consent document.

Exclusion Criteria:

1) Contraindications to MRI, including:
    a. MRI-incompatible implantable devices
    b. severe claustrophobia; and
2) Pregnant and/or breastfeeding, with women of childbearing potential having a negative urine or serum pregnancy test

Inclusion of Women and Minorities: Both male and female patients and members of all races and ethnic groups are eligible for this trial.

REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:
1) confirmation of patient eligibility;
2) registration of patient in the Siteman Cancer Center database;
3) assignment of unique patient number (UPN). The research coordinator(s), Robin Haverman and/or Rachel Reed will perform these tasks and obtain consent form the patients

Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the following information:
1) the patient's physician's name;
2) the patient's race, sex, and date of birth;
3) three letters (or two letters and a dash) for the patient's initials;
4) a copy of the signed consent form;
5) a completed eligibility checklist, signed and dated by a member of the study team;
6) a copy of the appropriate source documentation confirming the patient's eligibility. Robin Haverman and/or Rachel Reed will perform these tasks and obtain informed consent from the patients.

Both men and women and members of all races and ethnic groups are eligible for this trial.

Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.0 STUDY PROCEDURES

IMAGING PLAN

Overview: 60 biopsy-proven neck SCC patients after treatment with surgery, radiation or chemo-radiation will be enrolled for this trial. The Otolaryngology, Head and Neck Surgery physicians and their clinic staff will assist in coordinating enrollment. The patients will undergo an optimized research neck DWI MRI, up to 3 weeks post-treatment and then a standard-of-care 3-6 months post-treatment FDG PET/CT examination. (**Note: Patients who do not undergo SOC PET/CT at the 3-6 month time point will be considered inevaluable and will be replaced.) Patients who sign the consent form but do not have the MRI will not be considered accrued on this study. The optimized DWI images will be acquired on a dedicated research Siemens 3T Scanner belonging to Washington University's Center for Clinical Imaging Research. The standard-of-care FDG PET/CT mages will be acquired at one of the Siemens Biograph clinical PET/CT units located throughout the Barnes-Jewish Hospital Systems. We will compare the ADC values (ADCmin and ADCmean) to the optimized DWI sequence to FDG PET

SUVmax. For up to 1 year post-treatment, patients' medical records will be reviewed after scheduled SOC visits r to additionally assess for clinical outcomes.

	Baseline	up to 3 Weeks Post-Treatment	3-6 Months Post-Treatment	Follow up for up to 1 year post-treatment
Screening	X			
Enrollment	X			
Medical Record Review	X	X	X	X
DWI MRI		X		
FDG PET/CT			SOC	

Clinical Data to be Collected

The following clinical data points will be collected and recorded in REDCAP (Please see attached data sheet):

- **Age**
- **Birth Gender**
- Original Cancer Stage
- Date of original diagnosis
- Cancer Location
- Cancer Stage
- HPV Status
- Cancer Treatment (choice=Surgery)
- Cancer Treatment (choice=Chemotherapy)
- Cancer Treatment (choice=Radiation)
- Surgery Date
- Radiation Dosage
- Chemotherapy Type/Dosage
- Chemotherapy treatment range
- Date of Completion of Initial Treatment
- Smoking Pack Year History
- Date of Study MRI
- Why enrolled?
- MRI Imaging uploaded
- Biopsy Obtained
- Pathology confirms recurrence
- Date of recurrence diagnosis
- Length of time from MRI to clinical/radiographic progression
- Last clinical F/U
- Last imaging F/U
- Treatment after repeat biopsy/surgery

Duration of Imaging: MRI data to include anatomical MPRAGE volumetric T1, fat-saturated T2-weighted image (for anatomical localization and cystic/necrotic changes) and optimized research DWI sequence will be acquired in 30 minutes. If at any time the constraints of this protocol are considered detrimental to the patient's health and/or the patient no longer wishes to continue

imaging, the protocol should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Post-imaging: While there are no anticipated problems during the research imaging, continuous monitoring for any adverse events or abnormal events will occur during imaging. Once the research MRI is complete, the subject will be asked by a member of the study team how they are feeling prior to leaving the CCIR. If for any reason, the subjects is feeling abnormal, Dr. Gloria Guzmán or Dr. Matthew Parsons, the on-site neuroradiologist, will be notified and will address any adverse events.

Patient Compensation: Subject will receive $100 at the completion of their research DWI MRI imaging. Subjects will be provided compensation by check.

IMAGE ARCHIVING

Our image cloud computer system is the CNDA archive maintained at the Washington University School of Medicine, and it will serve as a central repository for all data collected as part of this project. Data will be securely transferred from the scanning facilities to CNDA. CNDA data are anonymized and can be accessed remotely.

MRI PROCESSING GUIDELINES

Overview: All MRI studies will be blindly evaluated by at least two experienced neuroradiologists (Drs. Guzmán and Parsons). If there is an urgent or emergent finding obtained by the research MRI study, this will be communicated by one of the neuroradiologists directly to the ENT physician for follow up who is caring for the patient, as per normal departmental protocol. In the case of this study, incidental findings are defined as anything not already noted in the medical record.

Methodology of MRI Evaluation: The research MRI study of the head and neck will be performed on a Siemens 3T MRI Scanner system located in the Center for Clinical Imaging Research (CCIR). Multiplanar / multisequence MRI data including the optimized research DWI sequence will be acquired. MRI subjects must complete an MRI screening evaluation form before entering MRI zone 3 or the scanning room. Images will be anonymized and sent to CNDA for archiving after diagnostic reports are complete. All anonymized MRI studies will then be blindly evaluated by at least two experienced neuroradiologists (Drs. Guzmán and Parsons). MUSE image processing will be applied post-acquisition.

Methodology of ADC Evaluation: The primary tumor, suspicious lesion, and/or area of post-treatment change will be first identified in the anatomical images and then outlined in the ADC sequence by experienced neuroradiologists (Drs. Guzmán and Parsons), excluding areas of cystic change and necrosis. If there are multiple lesions, only the dominant lesion with the lowest ADC will be utilized for analysis, akin to RECIST criteria. If there is geometric distortion, a region of interest will be placed in the undistorted region only. A histogram analysis method will be used to examine the distribution of ADC values within each region of interest (ROI). Only measurable disease defined as a primary tumor, a suspicious lesion, and/or an area of post-treatment change measuring at least 0.5 cm in two perpendicular dimensions will be used. Technically poor or non-diagnostic MR images will be excluded. ADCmean/min will be computed.

PET/CT IMAGING PROCESSING GUIDELINES

Overview: When the PET/CT is ordered as a clinical workup, a diagnostic report will be issued by the Nuclear Medicine Department faculty. Neither Dr. Guzmán nor Dr. Parsons will participate in the preparation or issuing of this report.

Methodology of SUV Evaluation: Anonymized FDG PET/CT data from CNDA will be uploaded into a MIM workstation (MIM Software Inc., Cleveland, Ohio). Fused MPRAGE/DWI images will be used. The region of interest chosen for the evaluation of ADC values will be copied onto the FDG CT/PET, and the SUVmax will be measured. While there is significant variability in SUV measurements [Kinehan, 2010], the reported literature suggest SUVmax > 9.0 -with interquartile range (IQR) 7.4–13.9 and range of 1.5-20.1 - is diagnostic of squamous cell carcinoma [Schwartz, 2004; Morand, 2018] for the primary mass and >4.5 for nodal tumor [Paidpally, 2012]. PET/CT studies are standard of care and are reported as clinical studies.

5.0 ADVERSE EVENT MONITORING AND REPORTING

5.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease related to this study protocol. For purposes of this research project, AEs associated with the MRI will be tracked.

Attribution (Relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website at: http://www.hhs.gov/ohrp/policy/advevntguid.html.

5.2 Unanticipated Problems

Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

5.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subject research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

5.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, and results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

5.5 Protocol Exceptions
Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation. Preapproval of all protocol exceptions must be obtained prior to the event.

5.6 Reporting to the Human Research Protection Office (HRPO)
Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

5.7 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University
The PI is required to notify the QASMC of any unanticipated problems involving risks to participants occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

5.8 Time Frame for Reporting Required Events
Any events that require reporting will be submitted per current IRB guidelines.

5.9 Incidental Findings
The research MRI scan is not a clinical MRI examination and is not conducted to diagnose brain abnormalities. However, some of the sequences are similar to clinical tests, and these images are reviewed for incidental findings by a board-certified radiologist. If there is an incidental observation from the testing which may be clinically significant, such as a suspected tumor or aneurysm, the Principal Investigator will communicate this information to the treating physician for review; this includes incidental finding of new tumor. If indicated, the Principal Investigator will contact the participant with this information. With your permission your doctor may also be contacted so that follow-up may occur as appropriate.*

6.0 DATA AND SAFETY MONITORING
In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician

- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Power analysis and/or interim analysis (if described in the protocol)
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

7.0 STATISTICAL CONSIDERATION

STATISTICAL ANALYSIS

Study Design and Endpoints: This is a pilot study designed as a paired, prospective, single-blinded study in which we compare the sensitivity and specificity of the optimized DWI sequence ADCmean/min versus FDG PET/CT SUVmax for the evaluation of recurrent SCC in post-treatment patients. The primary endpoints of sensitivity and specificity will evaluate the diagnostic accuracy of the optimized DWI sequence ADCmean/min versus the standard-of-care FDG PET/CT SUVmax. The secondary endpoint will evaluate if the enhanced DWI sequence can more expediently assess non-responders to treatment as compared to FDG PET/CT.

Aim 1: The 60 subject sample size for this pilot study was chosen for feasibility of recruitment based on the approximately 650 PET/CT exams performed for head and neck tumor in 2018. ROI will be used for statistical assessments of ADC measurements (see methodology of ADC measurement, above). FDG-PET SUVmax results will be used as the reference standard for tumor or non-tumor tissue. ADCmean, ADCmin and standard deviation will be used to describe distribution of ADC measurements (AADC) in tumor and non-tumor tissues and independent sample t-test will be used to compare ADC measurements between the two groups. Mean difference and 95% confidence interval around that will be used to interpret our results. For ROC analysis, the area under the curve (AUC) will be calculated and the Youden's J index will be used to identify the value of the predictor variable that optimized sensitivity and specificity. Youden's J index varies from 0-1. The threshold value that provides the value of the J index closer to 1 is the value with the best performance and discriminative power. PPV and NPV will also be evaluated. The logistic regression model allows for evaluating this impact after controlling for potential confounders. We will explore the linearity assumption of relationship of delta ADC with logit of outcome (response to treatment) and if the assumption is violated,

polynomial effects will be explored, and data transformation will be employed as needed. All statistical analysis will be carried out by Dorina Kallogjeri, a biostatistician in the ENT Department with extensive experience in head and neck cancer research. A 90% confidence interval will be calculated for the differences in sensitivity and specificity of the enhanced DWI sequence ADCmean/min as compared with the standard-of-care FDG PET/CT SUVmax. The positive and negative predictive values will also be evaluated. Since this is a pilot study, no existing data can be utilized to calculate a power analysis.

A binary logistic regression model will be utilized to evaluate the impact of the change in ADC in predicting early non-responders to treatment. A p-value will be calculated to evaluate if the enhanced DWI sequence can more expediently identify non-responders to treatment as compared to FDG PET/CT.

(**Note: Patients who do not undergo SOC PET/CT at the 3-6 month time point will be considered inevaluable and will be replaced.)

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