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Individualized Adaptive De-escalated Radiotherapy for HPV-related Oropharynx Cancer

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A MULTI-CENTER PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE DE-ESCALATED RADIOTHERAPY USING PRE and MID-TREATMENT FDG-PET/CT FOR HPV-RELATED OROPHARYNX CANCER

Principal Investigator:
Michelle Mierzwa

Coordinating Center:
University of Michigan

Biostatistics:
Matt Schipper

Otolaryngology lab:
Chad Brenner

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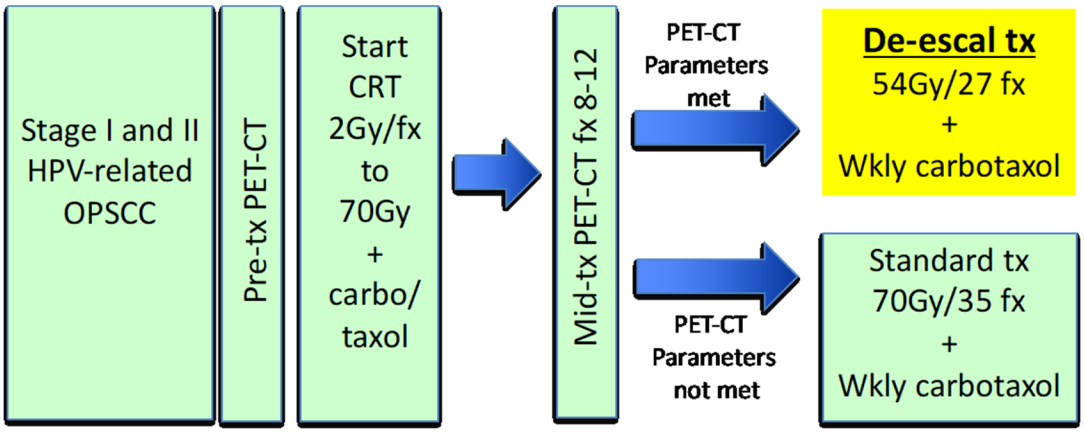
DEFINITIONS

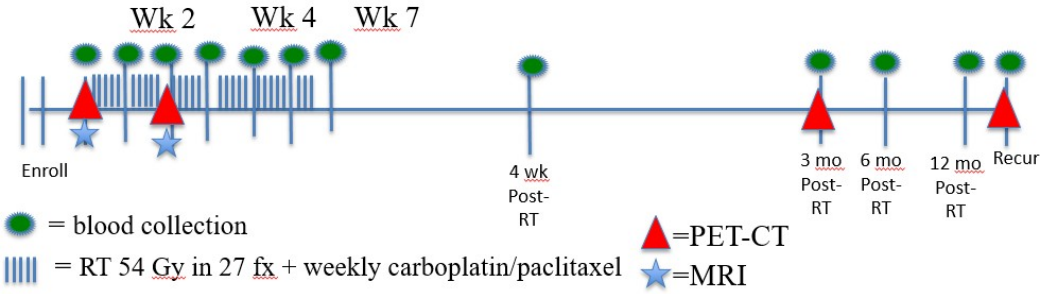
AIDS: Acquired Immune Deficiency Syndrome
ASTRO: American Society for Therapeutic Radiation Oncology ANC: Absolute neutrophil count
AUC: Area under the concentration curve (chemotherapy) or area under the curve (statistics)
BED: Biologic equivalent dose
CMR: Complete metabolic response
CR: Complete response
CTV: Clinical target volume
ECG or EKG: Electrocardiogram
ED: Effective dose
FDG: 18F-Florodeoxyglucose, a PET/CT imaging agent
GTV: Gross tumor volume
Gy: Gray
HIV: Human immunodeficiency virus
HPV: human papilloma virus
IGRT: Image-guided radiation therapy
IMRT: Intensity modulated radiation therapy
iPET: midtreatment PET/CT
IV: Intravenous
LRC: Local-regional control
LRR: Local-regional recurrence
LRPF: Freedom from local-regional progression
MTV: Metabolic tumor volume
NRG: NRG Oncology
OARs: Organs at risk
OPSCC: squamous cell carcinoma of the oropharynx
OS: Overall survival
pPET: pre-treatment PET/CT
PD: Progressive disease
PFS: Progression-free survival
PMR: Partial metabolic response
PR: Partial response
PTV: Planning target volume
RT: Radiation therapy or radiation treatment RTOG: Radiation Therapy Oncology Group SD: Stable disease
SMD: Stable metabolic disease
SUV: Standardized uptake value
SUVmax: The SUV of the most intense voxel within a tumor
SUVpeak: The average SUV within a 1.2-cm diameter sphere centered on the most metabolically active region of the tumor
3D-CRT: Three dimensional-conformal radiation therapy

SCHEMA



All patients will undergo FDG PET/CT at baseline for staging and RT planning and during RT for treatment response assessment and adaptive planning. This baseline scan should be performed within 4 weeks prior to registration, while the during-RT scan should be performed between fractions 8 and 12 for both arms.

If PET-CT parameters for de-escalation met:



If PET-CT parameters for de-escalation NOT met:

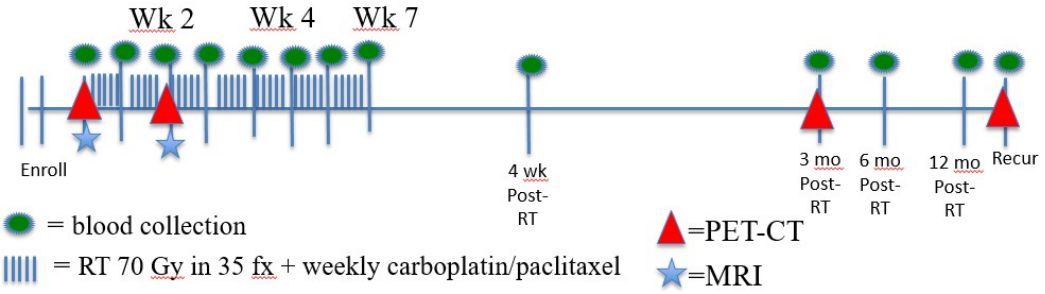


Figure 1 parameters for de-escalation

1.0 INTRODUCTION

Oropharyngeal Carcinoma

Over the past three decades, there has been an increase in the incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) with good overall prognosis and high rates of loco-regional control *(d'souza 2007, Gillison, 2000, Fahkry, 2008, Ang 2010).* Current standard of care therapy includes definitive chemoradiation as well as resection followed by adjuvant radiation or chemoradiation. Due to the good prognosis and relatively good health of most patients with HPV-related OPSCC, there has been widespread interest in treatment de-intensification strategies including decreased doses of radiotherapy and chemotherapy. Ideally, pre- or mid-treatment biomarkers of response would be used to adapt therapy. However, no proven clinical or radiographic biomarkers exist to monitor response during therapy.

Post-treatment PET-CT obtained 12 weeks after therapy has been shown to be a reliable predictor of treatment response and has been widely adopted. A recently published prospective, randomized control trial studying PET surveillance at 12 weeks post-treatment found PET-CT surveillance was not inferior to planned neck dissection for advanced (N2/N3) SCC of the head and neck *(Mehenna et al., NEJM 2016).* While PET-CT surveillance at this interval was non-inferior in terms of survival benefit, this group resulted in fewer neck dissections overall, no difference in complication rate, and similar 2-year survival rate. Furthermore, PET-CT was more cost effective, saving about $2000 per patient over the trial duration in decreased number of operations *(Mehenna et al NEJM 2016)*.

Prospective trials have demonstrated value of pre- treatment PET-CT (pPET) and mid-treatment interval PET-CT (iPET) as a potential radiographic biomarker to predict loco-regional control (LRC), disease-free survival (DFS) and distant metastasis free survival (DMFS). For example, Pollom, et al. studied iPET at median radiation dose of 33.5Gy in OPSCC where 88% of patients were p16 positive and 40% were "smokers". They found that pre-treatment $MTV_{50\%}$ and iPET $MTV_{2.0}$ were correlated with PFS (p=0.015), where MTV_x was defined as the metabolic tumor volume above a threshold "x". Additionally, they found that nodal total lesion glycolysis (TLG) of > 5% per week correlated with PFS (p=0.03).

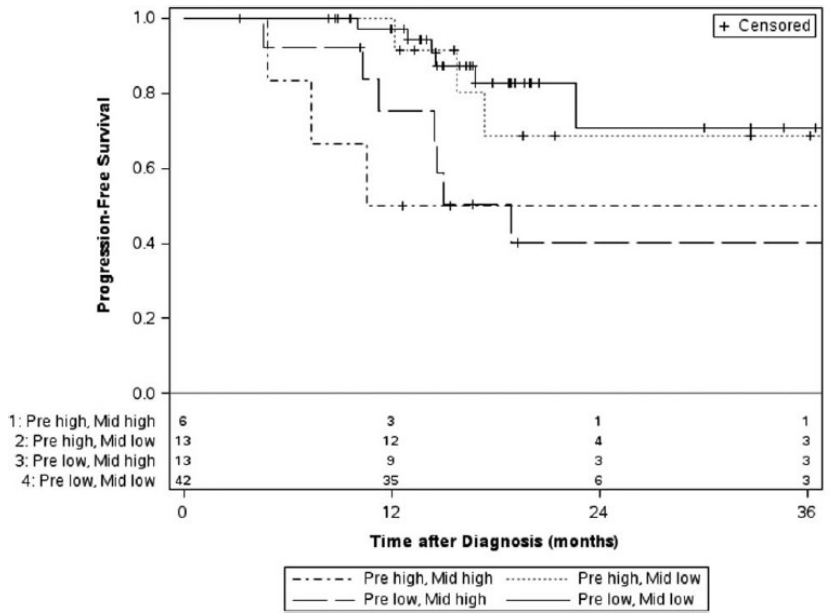


FIGURE 2. Kaplan—Meier progression free survival curves for risk groups based on pretreatment metabolic tumor volume $(MTV)_{50\%}$ ("pre") and midtreatment $MTV_{2.0}$ ("mid"), logrank $p = .015$. "High" is upper quartile, whereas "low" is lower 3 quartiles for both pretreatment $MTV_{50\%}$ and midtreatment $MTV_{2.0}$. $MTV_{50\%}$ is MTV using threshold of 50% standardized uptake value (SUV) maximum. $MTV_{2.0}$ is MTV using a threshold of SUV 2.0.

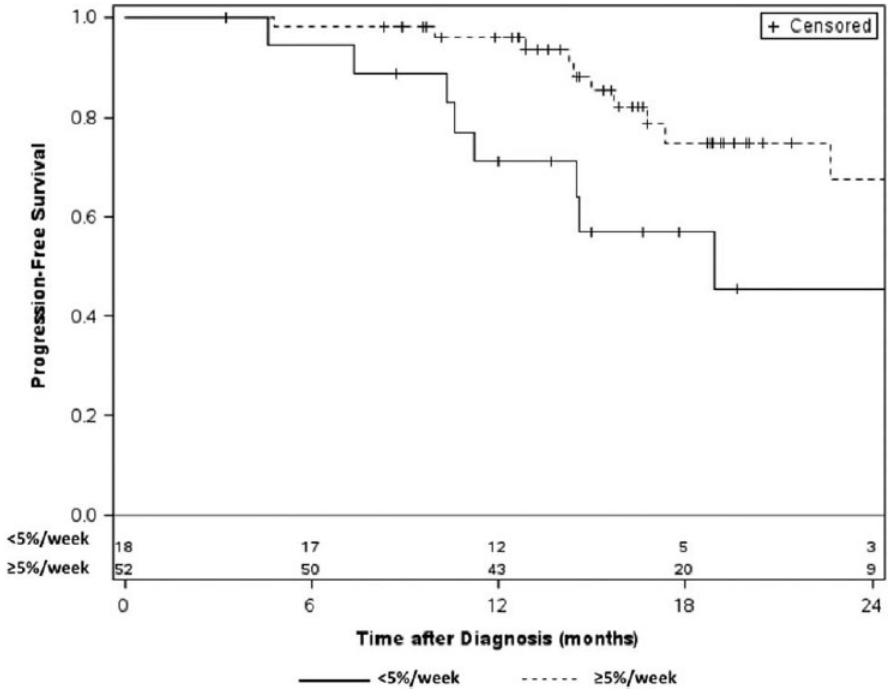


FIGURE 3. Nodal total lesion glycolysis (TLG) velocity (stratified by lower quartile or 5% decrease in nodal TLG/week) is associated with progression-free survival (PFS) in all patients, logrank $p = .03$. Those with $\geq$5% decrease in nodal TLG/week had improved PFS.

Schwartz, et al. performed a retrospective analysis of pPET in 74 patients treated on RTOG 0522 patients. They found that the SUV_{max} and SUV_{mean} were non-prognostic, but that $MTV_{40\%}$ of the primary tumor as well as the total MTV (primary tumor + involved lymph nodes) higher than cohort mean correlated with worse PFS (HR 2.34, 95% CI [1.02, 5.37], p=0.05) and LRC (HP 4.01, CI [1.28,12.52], p=0.02). Primary MTV remained prognostic in the 56 patients of this study who had p16+ OPSCC.

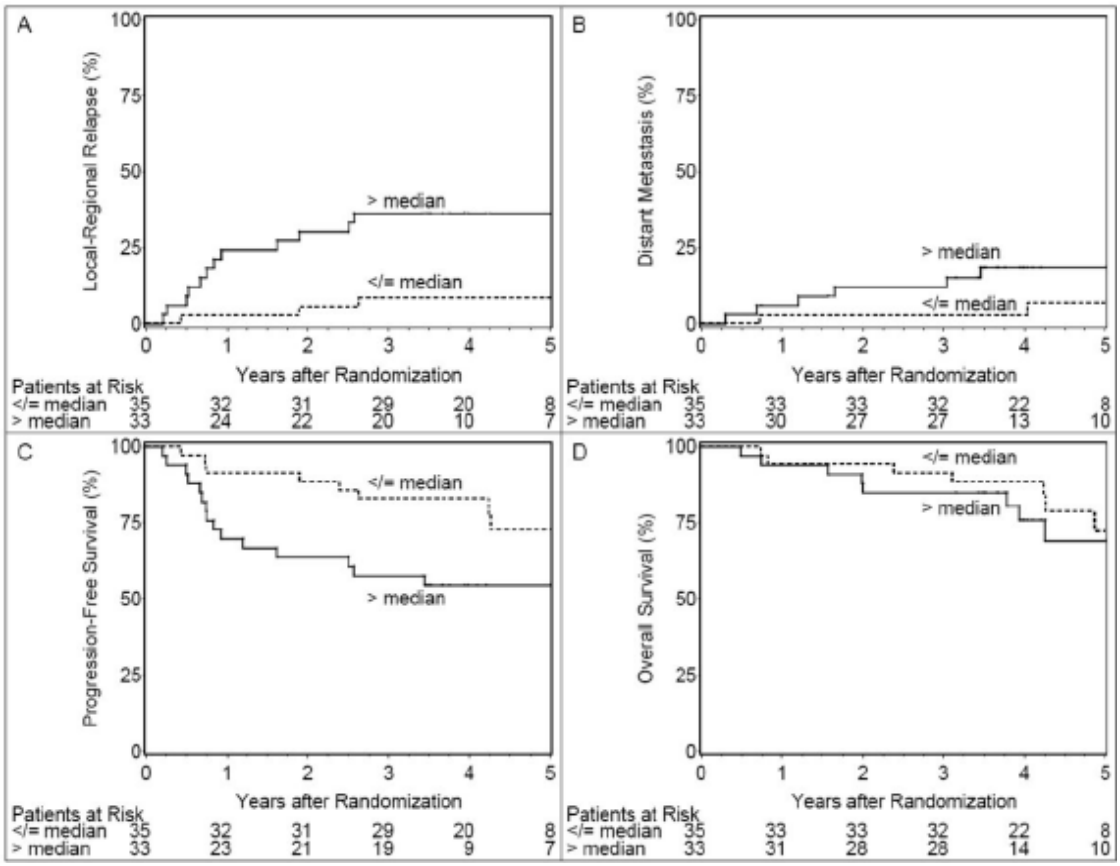


Figure 4. Schwartz, et al. Cumulative incidence estimates of local-regional relapse (Panel A) and distant metastasis (Panel B) and Kaplan-Meier estimates of progression-free survival (Panel C) and OS (Panel D) for patients with baseline primary MTV ≤ median or > median. Two-year local-regional relapse rates were 5.7% (95% CI: 0, 13.5) for patients with MTV ≤ median and 30.3% (95% CI: 14.3, 46.3) for patients with MTV > median. Two-year distant metastases rates were 2.9% (95% CI: 0, 8.5) for patients with MTV ≤ median and 12.1% (95% CI: 0.8, 23.4) for patients with MTV > median. Two-year progression-free survival rates were 88.6% (95% CI: 78.0, 99.1) for patients with MTV ≤ median and 63.6% (95% CI: 47.2, 80.0) for patients with MTV > median. Two-year overall survival rates were 94.3% (95% CI: 86.6, 100) for patients with MTV ≤ median and 84.9% (95% CI: 72.6, 97.1) for patients with MTV > median.

An Australian study of pPET and iPET in 75 patients by Lin, et al. evaluated all head and neck mucosal sites of cancer. They performed iPET at a mean of 18.5 days from the start of RT, and evaluated SUV_{max}, SUV_{mean}, MTV and TLG in both primary tumor and lymph nodes. They found that the pPET parameters were not predictive of treatment response. However, multi-variate analysis demonstrated iPET reduction of total node MTV by 50% from baseline to correlate with loco-regional failure -free survival (FFS), DFS and OS (p=0.026, 0.003, and 0.014, respectively). iPET reduction of nodal TLG by > 50% from baseline was predictive of FFS, DFS and OS in multi-variate analysis (p=0.01, 0.01, 0.014).

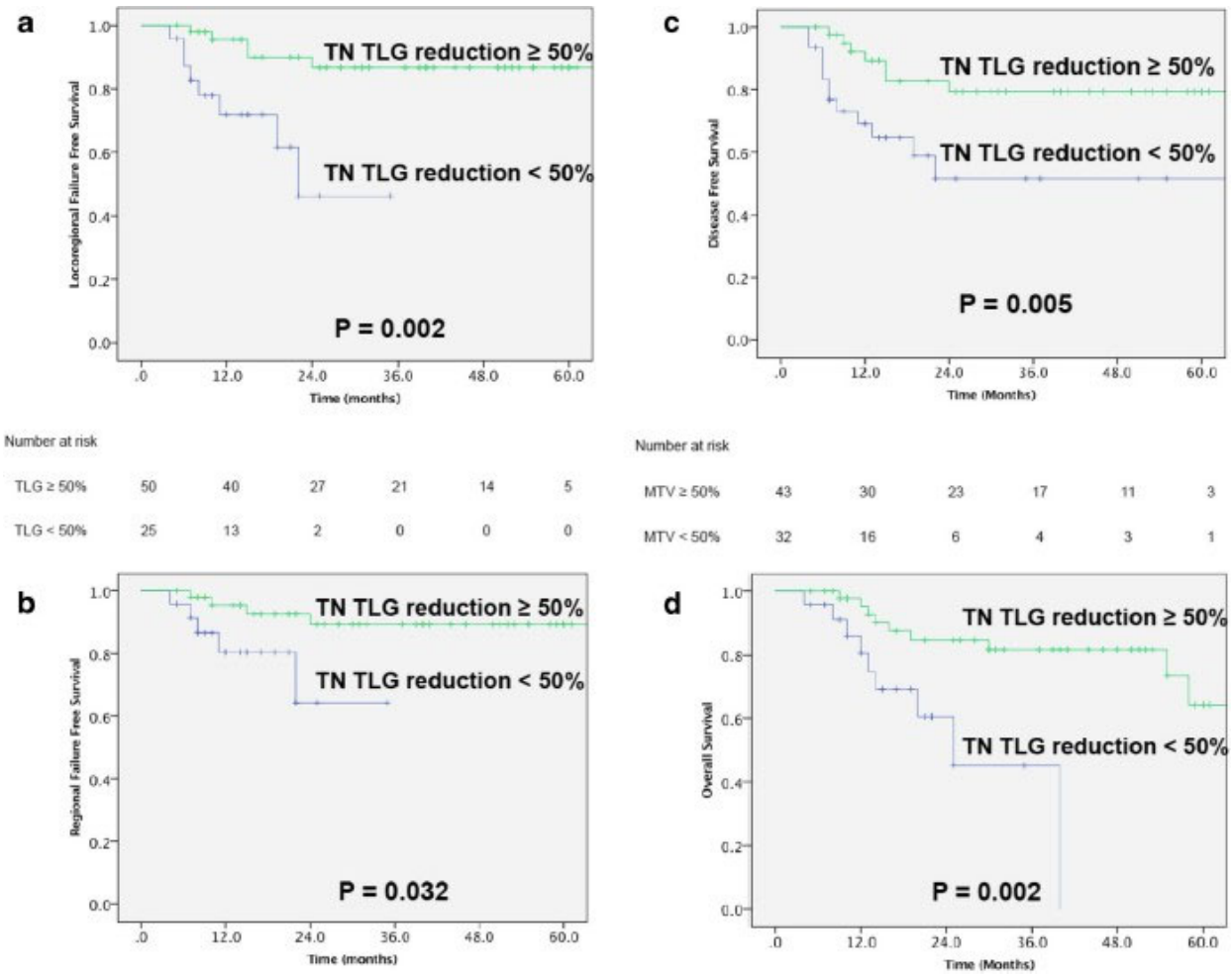


Figure 5. Kaplan-Meier survival rates in relation to the optimum total node TLG cut-off value of 50 % on iPET for locoregional failure-free survival (LRFFS), b regional failure-free survival (RFFS), c disease-free survival (DFS) and d overall survival (OS).

In non-small cell lung cancer (NSCLC), the University of Michigan has conducted 2 consecutive prospective dose escalation trials to test a hypothesis that radiation dose can be escalated safely above 74 Gy when the radiation dose prescription is individualized at the beginning (UMCC 2003-073) and adapted to the reduced MTV on during-RT FDG-PET/CT (UMCC 2007-123). The prescription dose of the first trial was individually set to correspond to a 15% risk of RT-induced lung toxicity (RILT) according to a NTCP model at the baseline. RT dose was further escalated in the second trial by adapting dose individually to the residual metabolic volume on FDG-PET/CT obtained during RT, so the residual metabolic volume would receive the maximal dose that would maintain a tolerable risk of RILT while the pre-RT CTV on CT was not compromised (would receive at least 60 Gy). On the first trial, patients treated to a higher dose had significantly better survival (p=0.02). The median survival on the second trial has not yet been reached.

This prospective study aims to utilize pre- and mid-treatment PET-CT to guide de-escalation of radiation therapy in HPV-related squamous cell carcinoma of the oropharynx. Early timing of mid-treatment PET-CT between fractions 8-12 has been planned to minimize risk of mucositis induced false positivity.

University of Michigan experience with definitive chemoradiation treatment of 515 patients with HPV+ oropharyngeal cancer, AJCC 8th edition, stage 1 and 2 patients had 88 % LRC at 2 years and 2 year progression free survival (PFS) of 80%. These patients were treated with IMRT to 70Gy as well as concurrent carboplatin and paclitaxel.

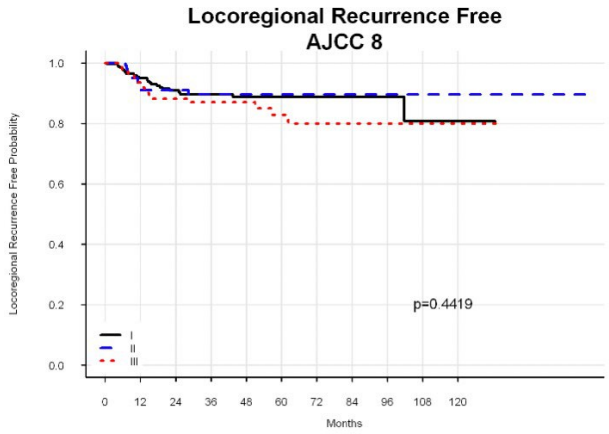


Figure 6. Kaplan- Meier loco-regional control curve for HPV+ OPSCC treated with definitive chemoradiation at UM 2003-2015 staged according to AJCC 8.

Furthermore, we have explored the association of smoking with loco-regional control and overall survival. On multivariate analysis, any 1+ pack year smoking history correlated with OS (HR 1.98, 95%CI 1.2-3.2, p<0.01) but not LRRFS or DRFS as seen in Table 1 below.

Table 1. Multivariate analysis, accounting for group stage (per AJCC 8th Ed.), correlating smoking history and age with OS, LRRFS, and DRFS.

	OS		**LRRFS**		**DRFS**	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Any smoking	1.98 (1.2 – 3.2)	<0.01	1.27 (0.7 – 2.2)	0.42	1.32 (0.8 – 2.3)	0.33
10+ pack years	1.52 (1.0 – 2.3)	0.05	1.26 (0.7 – 2.2)	0.41	1.0 (0.6 – 1.7)	0.95
20+ pack years	1.22 (0.8 – 1.9)	0.38	1.03 (0.6 – 1.8)	0.93	1.0 (0.6 – 1.8)	0.98
Current smoking	1.09 (0.7 – 1.8)	0.72	0.77 (0.4 – 1.5)	0.43	1.05 (0.6 – 1.9)	0.88
Age (per year increase)	1.04 (1.0 – 1.1)	<0.01	1.03 (1.0 – 1.1)	0.03	1.02 (1.0 - 1.1)	0.14

Each row represents a separate Cox model. HR = hazard ratio. CI = confidence interval.

AJCC 8th edition staging begins clinical use in January 2018 and our 8th ed stage 1 and 2 patients have high rates of LRC without effect from smoking status. These patients are thus candidates for de-escalation of local therapy and are included in the present trial.

Exploratory Potential BioMarkers Predictive of Treatment Response and Long-Term Outcome

Circulating tumor DNA (ctDNA)

An additional exploratory aim of this study is to study circulating tumor DNA in the blood of patients undergoing therapy on this study. Based on review of our previous experience at UM, we estimate the 2 year LRC of our study population to be 88% in patients with less than 20 pack year history of cigarette smoking and 82% in patients with greater than 20 pack year history. Furthermore, 15-20% of HPV-related oropharynx cancer patients will go on to develop distant metastases. We hypothesize that additional biomarkers will aid in personalized care with potential selective treatment de-intensification for our patients.

One promising non-invasive biomarker is quantification of circulating tumor DNA (ctDNA). It is known that tumor cell division and death causes release of cell free fragmented DNA into circulation. ctDNA is composed of small fragments of nucleic acid that are not associated with cells. ctDNA is currently being explored in many cancers in early stage and metastatic settings to evaluate response (Schwarzebach, et al, Tie, et al). Circulating tumor DNA has been detected in 70-100% at diagnosis in a cohort of 640 patients with multiple types of advanced stage cancers (Bettegowda, et al). This study included 14 head and neck cancer patients of all stages and found 73% were positive for detectable ctDNA.

The concept of ctDNA is not new to head and neck cancer. In EBV (Ebstein Barr virus)-related endemic nasopharynx cancer, multiple publications have demonstrated detectable serum EBV (Ebstein Barr virus) DNA in > 80% patients with pre-treatment levels correlated to tumor stage (Le 2005, Chan 2002). Furthermore, clearance of EBV DNA after definitive chemoradiation is associated with improved PFS (Wang, 2012, Lin 2004).

Serum detection of ctDNA has been largely unexplored in other head and neck cancers. Two small studies have been published that explored serum detection of HPV DNA. Sturgis, et al, evaluated pre-treatment HPV DNA in blood and found no significant correlation with response in a small number of patients. To date, no group has attempted to detect ctDNA in head and neck cancer through somatic mutations. Dr. Brenner's lab has the technical ability to detect HPV DNA as well as the capability to detect the most commonly mutated oropharynx cancer genes through a next generation sequencing approach to ctDNA cell fragments. In this trial, we plan to collect 6ml of EDTA blood at several time points correlated with clinical blood draw times in order to explore correlation with ctDNA and treatment response as well and potential early detection of recurrence.

DCE-MRI

Several physiological and metabolic imaging modalities, most in isolation, have been investigated for prediction of treatment failure in head and neck cancer. Fludeoxyglucose (FDG) positron emission tomography (PET), a marker for glucose metabolism, has shown high FDG uptake associated with poorer prognosis, whereas rapid metabolic response on PET/CT has been associated with high LRC. Hypoxic PET, and perfusion CT/MRI and diffusion MRI have shown to be biomarkers for outcomes in HNSCC. Persisting poorly perfused tumors during the early course of RT is associated with high risk for local and regional failure. Diffusion imaging, a measure of water mobility in tissue and sensitive to cellularity, has shown that an increase in apparent diffusion coefficient (ADC) of the HNSCC during RT is associated with positive therapy response. Most clinical trials currently underway use a single imaging modality to guide radiation escalation or de-escalation and single imaging modalities are limited to image only one aspect of tumor biology. The spatial relationship between imaging risk-factor parameters in HNSCC are largely unknown.

One exploratory aim of this study is to investigate whether FDG uptake, low blood volume, and low diffusion coefficient in HPV-related oropharynx cancer have any spatial correspondence and their early responses to RT to determine the implication of this overlap or lack thereof for adaptive boosting strategy.

2.0 OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether tumor dose can be de-escalated with equivalent/non-inferior loco-regional control as compared to historical standard when an individualized adaptive radiation treatment (RT) plan is applied by the use of a FDG-PET/CT scan acquired during the course of fractionated RT in patients with HPV-related squamous cell carcinoma of the oropharynx.

2.1.2 To determine whether the relative change in $MTV_{2.5}$ of 50% from the baseline to the mid- treatment FDG-PET/CT is a prognostic biomarker for local regional tumor control.

2.2 Secondary Objectives

2.2.1 To determine patterns of failure (locoregional relapse versus distant) and survival (overall and progression-free) at 3 months and 2 years;

2.2.2 To determine acute toxicity profiles at the end of radiation therapy and at 3 and 6 months;

2.2.3 To determine late toxicity profiles at 1 and 2 years;

2.2.4 In patients with detectable ctDNA pre-treatment, to determine the fraction of patients ctDNA in the blood at week 4 of RT

2.3 Exploratory Correlative Science Objectives

2.3.1 To quantify the fraction of patients in whom ctDNA is detectable pre-treatment and to characterize detectable ctDNA in those patients during RT, post-treatment and at recurrence

2.3.2 To quantify circulating tumor DNA in the blood pre-, mid- and post-treatment.

2.3.3 To quantify the low blood volume and apparent diffusion coefficient in DCE-MRI of HPV-related oropharynx cancer

2.3.4 To determine patient-reported quality of life at 3, 6 months and 1 year using FACTHN, U Washington QOL, CTCAE PRO as well as xerostomia questionnaire;

2.3.5 To determine swallowing outcomes using barium swallow pre-treatment as well as 3- and 12- months post treatment

2.3.6 To correlate physician and patient reported CTCAE scores during and after therapy

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Patients must have FDG-avid (maximum SUV ≥ 4.0) (from PET scan of any date, any scanner) and histologically or cytologically proven squamous cell carcinoma of the oropharynx (tonsil, base of tongue, oropharyngeal wall, soft palate) that is p16 positive by immunohistochemistry or HPV positive by in situ hybridization

3.1.2 Clinical stage: stage I-II AJCC 8^{th} edition staging

3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

- History/physical examination, including documentation of weight within 4 weeks prior to registration;
- FDG-PET/CT scan for staging and RT plan within 4 weeks prior to registration;
- Zubrod Performance Status 0-1 within 4 weeks prior to registration;
- Age ≥ 18;

- Able to tolerate PET/CT imaging required to be performed

3.1.4 CBC/differential obtained within 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dL

3.1.5 Serum creatinine within normal institutional limits or a creatinine clearance ≥ 45 ml/min within 4 weeks prior to registration;

3.1.6 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study.

3.1.7 The patient must provide study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 cT4, cN3 or cM1 disease (also explained as AJCC 8th ed staging Stage 3 or 4 disease)

3.2.2 "Matted nodes" as determined by review with Neuroradiology

3.2.3 Gross total excision of both primary and nodal disease with curative intent; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease. In other words, to participate in this protocol, the patient must have clinically or radiographically evident gross disease for which disease response can be assessed.

3.2.4 Carcinoma of the neck of unknown primary site origin (even if p16 positive);

3.2.5 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.6 Any prior therapy for the study cancer; note that prior chemotherapy for a different cancer is allowable if > 3 years prior to study;

3.2.7 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.8 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Transmural myocardial infarction within the last 3 months;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition. Note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.2.9 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.10 Poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite 2 attempts to improve glucose control by fasting duration and adjustment of medications. Patients with diabetes will preferably be scheduled in the morning and instructions for fasting and use of medications will be provided in consultation with the patients' primary physicians;

4.0 REGISTRATION PROCEDURES

Patient registration for this trial will be centrally managed by the Coordinating Center of The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the **completed** Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Coordinator, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar, will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

4.1 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists required baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1.1 A complete panel of electrolytes within 4 weeks prior to treatment

4.1.2 Quantification of patients smoking history including number of pack years (# packs per day x # years) and whether they have smoked more than 5 packs within last 365 days

4.1.3 Pre-treatment DCE-MRI protocol completed in UM Department of Radiation Oncology; unless contraindicated or patient refusal

4.1.4 Pre-treatment blood draw collected for ctDNA, if the local lab is available for processing

4.1.5 Pre-treatment patient reported quality of life questionnaire. Patients have the option to complete these remotely and mail, fax, or send through the patient portal to the study clinic.

4.1.6 Pre-treatment barium swallow videofluoroscopy examination should be performed prior or during the first week of chemo-radiation. When staff is not available to complete the videofluoroscopy tests, these will be skipped and listed as protocol deviations.

4.1.7 A nutritional assessment (virtual or in-person) by MD, should be performed within 6 weeks prior to start of treatment. The assessment should include an evaluation of the need for prophylactic gastrostomy tube placement.

4.1.8 Tumor biopsy submission to coordinating center for tumor sequencing analysis. If core sample is not available, contact the Study PI.

5.0 TREATMENT PLAN

5.1 OVERALL TREATMENT PLAN:

All patients will undergo a pre-treatment study PET-CT (pPET-CT) within 4 weeks of registration, and then proceed with standard chemoradiation including RT prescribed to 70Gy in 35 fractions to gross disease and weekly carboplatin/paclitaxel for 7 weeks. PET scans from outside institutions may be acceptable and this will be evaluated by PI (Michelle Mierzwa) and physicist (Ben Rosen) on an individual basis. All patients will then undergo amid-treatment PET-CT (iPET) between fractions 8 and 12 and the following parameters will be calculated

on primary tumor and each pathologic lymph node of the pPET and iPET: MTV50%, MTV2.5, TLG, SUV_{max} and SUV_{mean}. Patients who meet criteria for treatment de-escalation will have chemoradiation plans decreased as follows: radiation prescription will be changed to 54Gy total dose and only 6 doses of concurrent carboplatin/paclitaxel will be given.

5.2 RADIATION THERAPY

Simulation and Treatment Planning

Patients should undergo simulation to include 5-point aquaplast masking and CT scan with IV contrast unless contraindicated in the Department of Radiation Oncology at the University of Michigan. The treatment planning CT scan should be obtained in the immobilization device and in the treatment position with a slice thickness of 3 mm or less. After mask is made, patient will undergo PET-CT in the Department of Nuclear Medicine on flat tabletop with mask in place. This PET-CT will be defined as the pre-treatment PET-CT (pPET-CT).

Adequate image registration between FDG-PET and the CT from the PET/CT scanner and the CT of the PET/CT with a simulating CT is required. Deformable registration is not permitted.

Dose Specifications

GTVp is gross primary tumor volume. GTVn is gross nodal tumor volume.
CTV1 is gross clinical volume with tight (typically 0.5 cm) margins around the GTV.
CTV2 includes areas containing sub-clinical at-risk around the gross disease and at areas at risk of lymph node metastases.
PTV1 and PTV2 consist of uniform 3 mm expansions of the CTV1 and 2 respectively.

Patients will initially receive a single prescription of 70 Gy to PTV1 in 35 fractions with RT given once daily, 5 days a week along with weekly carboplatin/paclitaxel (standard therapy). All fields must be treated daily. On days when chemotherapy is given, it will be administered prior to RT. Prescription to high risk PTV will be 70Gy in 35 fractions and to PTV2 will be 56Gy in 35 fractions.

Patients who meet the following pPET-CT and iPET-CT parameters are candidates for de-escalation: pre-treatment MTV50% $\leq$ 22cc, $iMTV_{2.5}$ is decreased $\geq$50% from baseline. Two independent physicians will review all PET-CTs for de-escalation (this will likely be a Nuclear Medicine physician and a Radiation Oncology physician). Review of scans and decision for de-escalation will be made by fraction 20. **PET-CTs will be standardly reviewed by 2 treating physicians: Dr. Wong (Nuclear Medicine) and Dr. Mierzwa (Radiation Oncology) independently. Treating physicians from Otolaryngology and or Radiation Oncology will serve as a surrogate if either Drs. Wong or Mierzwa are unavailable. In reference to timing of evaluation: the mid-treatment PET-CT is performed between fractions 8-12 of RT and the decision to de-escalate therapy will not be necessary until fraction 20 (2 weeks later), so it extremely unlikely that these 3 physicians will be unavailable for scan review.**

Drs. Wong, Mierzwa or alternate will use UM software for analysis where the initial volumes and parameters (primary tumor as well as individual lymph nodes/nodal conglomerate masses) will be defined by physician. The MTV is then autogenerated by UM software and values will be recorded on a common Excel spreadsheet. Any disagreement regarding treatment de-escalation will be resolved through direct communication between physicians and a 3rd physician tie-breaker when necessary. TLG for primary tumor and each lymph node conglomerate will also be collected for analysis.

These patients will proceed to de-escalation as follows: prescription and plan will be amended to deliver a total dose of 54Gy to high risk PTV and 43.2Gy to low risk PTV all in 27 fractions.

Patients who do not meet pPET-CT and iPET-CT parameters for de-escalation will proceed with original prescription to 70Gy.

Optimization goals:

The primary PTV dose will be 99% + 7% of the prescribed dose and to sub- clinical PTVs within +/- 5% of the prescribed dose. The maximal "hot spot" within a PTV will be <115% of the prescribed dose to that target delivered to a volume of at least 0.5 cc. The maximal dose outside the targets will be <105% of the prescribed dose delivered to at least 0.5 cc. volume. The maximal dose to the spinal cord, expanded by 0.5 cm, will be < 50 Gy, to the non-expanded cord < 45 Gy, and where applicable, to the optic pathways < 50 Gy and to the brainstem <54 Gy. Other normal tissue optimization are per institutional standards.

Treatment Interruptions: It is expected that the entire treatment for definitive irradiation will be completed in approximately 7.5 weeks. Treatment interruptions due to symptomatic mucositis or skin reactions should be minimal. In the case of severe mucositis impairing oral intake, a gastric tube will be inserted and radiation will continue uninterrupted at the discretion of the treating physician. Weight will be recorded weekly in the Radiation Oncology Chart. If the patient's unintentional weight loss exceeds 10% of the initial weight or if the patient is malnourished before radiation, a feeding tube will be considered.

5.3 Chemotherapy

All patients will undergo radiation therapy in combination with weekly Carboplatin and paclitaxel.

6.0 PET-CT scans

Serial FDG-PET/CT scans of the same patient must be done on the same scanner for this study.

The PET/CT scanner calibrations should be routinely verified according to manufacturer recommendations. The scanner should be assessed regularly for quantitative integrity and stability by scanning a standard quality control phantom with the same acquisition and reconstruction protocols used for study participants. The SUV verification measurements must include the dose calibrator used to measure the doses of study participants to ensure that the dose calibrator and PET scanner are properly cross calibrated, i.e. the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images.

A quality control (QC) check must be performed at the beginning of the day for the dose calibrator and well counter, in accordance with the manufacturer recommendations. If any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled and the problem rectified before scanning any patients.

FDG-PET/CT will be performed in all patients at baseline for staging RT planning and tumor activity assessment. Patients who have already undergone staging FDG-PET/CT at the time of registration may need to repeat the FDG- PET/CT in a treatment planning position due to time lapse or image quality issues. PI and physicist will make a determination if outside institution PET scans are acceptable on an individual basis.

If the baseline FDG-PET/CT is not performed on a flat palette in treatment planning position, it can still be used as the baseline scan only if all of the following conditions are met:

- done within 4 weeks prior to registration
- acceptable imaging parameters: 4 hour fast, blood glucose < 200 mg/dl, 8-20 mCi F-18 FDG dose, injection to scan interval 50-70 minutes
- conducted on UM PET-CT scanner OR outside PET-CTs reviewed by Nuclear Medicine and deemed to be of good quality for study purposes
- can be acceptably registered to the simulation CT; the simulation CT must also be submitted as a reference scan for registration

Pre-FDG-PET/CT Patient Preparation:
- Prior to injection, the patient must fast for at least 4 hours;
- Patients are encouraged to be well hydrated prior to the scan;
- Blood glucose measurement is required (ideally within one hour of FDG administration) before the injection of FDG and must be < 200mg/dL;
- If the serum glucose concentration is found to be greater than 200 mg/dL, the study should be rescheduled. The referring physician or primary physician of the patient will be contacted to optimize blood glucose control;
- The patient's height and weight must be measured using calibrated and medically approved devices (not verbally relayed by the patient);

Injection of FDG:
- An IV catheter access lines (18 or 20 gauge is preferred) are placed in one arm (ideally contralateral to the side of the primary tumor) for the FDG injection;
- The dose of FDG will be 296-740 MBq (8-20 mCi) depending on institutional procedure and in accordance with manufacturer recommendations;
- A saline flush of at least 10 mL should follow the FDG injection;
- The exact time of calibration of the dose should be recorded using a global time piece consistently used throughout the study for time recording. The exact time of injection should be noted and recorded to permit correction of the administered dose for radioactive decay. In addition, any of the dose remaining in the tubing or syringe, or that was spilled during injection, should be recorded. The injection should be performed through an IV catheter and 3-way stopcock.

FDG-PET/CT Imaging:
- All PET exams should contain 3 trans-axial whole body series, attenuated and non-attenuated, corrected PET and CT images;
- The emission PET scan will begin 60 +/- 10 minutes after injection;
- The patient will empty his/her bladder immediately before the acquisition of images;
- The patient will be positioned on the flat table imaging couch in treatment planning position.
- The transmission scan should be a low-dose CT scan without IV contrast (oral contrast is permitted per institutional procedure) for the PET/CT, done before the emission imaging. The transmission scan type, length, etc., should exactly match that used in the calibration and qualification procedure.
- An emission scan from the skull base to thighs will be performed. The number of bed positions will be determined by the patient's height. The acquisition time per bed position will be 2 minutes. Typical parameters are 6-8 bed positions, leading to an emission scan time of 12-16 minutes.

Minimum Acceptable Tumor FDG Uptake:
If the FDG uptake of the tumor tissue is too low for quantitative analysis (maximum SUV < 4.0) the patient will be removed from participation.

In patients whose measurable tumor has an absolute baseline SUVmax of less than 4.0, a 25% decrease

of tumor FDG uptake would result in a decrease in SUV of ≤ 1 to the tumor. Data on the test/retest reproducibility of FDG-PET/CT suggest that in an individual patient such a small absolute change in tumor FDG uptake cannot be reliably identified by PET/CT imaging given background uptake in the liver/blood is an SUV of 1.5. Therefore, a baseline absolute SUVmax of at least 4.0 is required for the present study. We expect that the tumor absolute SUVmax will be less than 4.0 in fewer than 5% of patients. This estimate is based on data on FDG uptake of untreated, advanced SCCOP were patients normally have absolute SUVmax in the low teens.

6.1 Calculations and Criteria for de-escalation

To be a candidate for de-escalation, patients must meet ALL criteria listed below:
1)pPET MTV50% (largest GTV) ≤ 22cc
2)iPET $MTV_{2.5}$ decrease by >50% in primary tumor OR largest pathologic lymph nodes

Pre-treatment PET/CT: The Suvmax, SUVmean, MTV50%, and TLG will be calculated for each research scan on primary tumor and the largest pathologic lymph nodes. MTV(total)= MTVprimary + MTVnodes. For the purpose of de-escalation, each separate geographic area of gross tumor will be considered separately on the iPET. For example, if patient meets criteria for de-escalation in the primary tumor but not lymph nodes, the primary tumor will receive 54Gy and the lymph nodes that did not meet criteria will receive 70Gy.

6.2 Expected Adverse Events Related to FDG-PET Imaging

Adverse events (AEs) from FDG-PET/CT are exceedingly rare. If an AE from functional imaging is to occur, it would most likely be related to the intravenous catheter infusion site, consisting of erythema and discomfort from the IV. An allergic reaction to the FDG is possible as well. The most expected AEs from a PET scan include discomfort and claustrophobia.

Expected Adverse Events from the FDG Injection:
- Bruising;
- Bleeding;
- Phlebitis;
- Infection at the site of injection;
- Allergic-type or other adverse reaction to FDG.

Expected Adverse Events from the PET Scan:
- Discomfort;
- Claustrophobia.

Expected Adverse Events from the CT Scan:
- Discomfort;
- Claustrophobia;
- Malfunction of implanted electronic medical devices, e.g., pacemakers, neurostimulators, insulin pumps.

Estimation of Radiation Doses Due to FDG-PET/CT
Reports of radiation doses from PET/CT scanning have varied in the literature. These differences can be attributed to different methods of attenuation correction, the timing of the scan, the area of the body being evaluated, and the radiopharmaceutical being investigated. This research study involves radiation exposure from 2 FDG-PET/CT scans for patients. The radiation exposure from each FDG-PET/CT scan is

equal to a uniform whole-body exposure of approximately 14 mSv, with approximately 11 mSv from the injected radioactive FDG and 3 mSv from the CT component.

7.0 Drug Information

Carboplatin

Dose: AUC=1 weekly during RT

Chemistry: Carboplatin (CBDCA) is a hydrophilic platinum coordination compound and is an analog of cisplatin, producing intrastrand DNA cross- links.

Human Toxicology: Side effects of CBDCA include: myelosuppression, nausea, vomiting, abdominal pain, diarrhea, and constipation. Other toxicities include: allergic reactions (including hypersensitivity, i.e. rash, urticaria, erythema, pruritis, bronchospasm, and profound hypotension), peripheral neuropathy, paresthesias, loss of hair, hearing loss, visual disturbances, and change in taste. Serum creatinine elevations and blood urea elevations have occurred as well as abnormal liver function tests and decreased serum electrolyte values. Although rare, pain asthenia, cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in some patients. Cancer-associated hemolytic uremic syndrome has been reported rarely carboplatin may cause fetal harm; therefore, women of childbearing potential should be advised to avoid becoming pregnant. The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or to other platinum-containing compounds or mannitol. This drug should not be used in patients with severe bone marrow depression or significant bleeding. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pharmaceutical Data
Kinetics: The differences in potencies of carboplatin as cisplatin are due to differences in equation rates. The initial half-life of carboplatin is 1.1-
2.0 hours and the post-distributional half-life is 2.5-5.0 hours. Sixty-five percent of the dose is excreted into the urine within twelve hours. Carboplatin is not bound to plasma proteins.

Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous injection. Each vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, D5W, or normal saline injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

These dilutions all produce a carboplatin concentration of 10 mg/mL. Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with D5W or normal saline injection, USP.

Storage and Stability: Unopened vials of carboplatin for injection are stable for the life indicated on the

package when stored at controlled room temperature (15-30^{O}C), and protected from light. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for eight hours at room temperature (25 oC). Like cisplatin, this drug should not be given through aluminum needles. Caution: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after dilution.

Administration: Intravenous infusion.

Supplier: Carboplatin is commercially available and should be purchased by a third party.

Paclitaxel

Dose: 30mg/m2 weekly during RT

Chemistry: Paclitaxel is a semi-synthetic antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes

microtubules by preventing depolymerization hence producing abnormal bundles of microtubules throughout the cell cycle. As a result, paclitaxel inhibits interphase and cellular function.

Human Toxicology: Side effects of paclitaxel include: hypersensitivity reaction, myelosuppression, alopecia, peripheral neuropathy, nausea/vomiting, mucositis, alkaline phosphatase elevation, abnormal EKG, myalgia/arthlagia, asthenia, and hypotension. The development of severe hypersensitivity reactions is rare and documented in 1% of patients overall.

Pharmaceutical Data

Kinetics: Following IV administration, plasma concentrations decline in a biphasic manner due initially to distribution and later due to slow efflux of the drug from the peripheral compartment. Pharmacokinetic studies have demonstrated extensive extravascular distribution and/or tissue binding of paclitaxel. In addition, paclitaxel has been demonstrated to be highly protein bound (89-98% of infused sample). The drug is extensively non-renally cleared with 71% excreted via GI tract and 14% via renal clearance. It has been demonstrated to be metabolized primarily by CYP450 2C8 and to a lesser extent 3A4. As a result, the pharmacokinetics of paclitaxel may be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4

Formulation: Paclitaxel is a clear, colorless slightly yellow viscous solution intended for dilution prior to intravenous infusion. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor, and 49.7% dehydrated alcohol:

Storage and Stability: Unopened vials of paclitaxel for injection are stable for the life indicated on the package when stored at controlled room temperature (20-25^{O}C), and protected from light. Neither freezing nor refrigeration adversely affects the stability of the product. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for up to 27 hours at room temperature (25 ^{O}C).

Administration: Intravenous infusion.

Supplier: Paclitaxel is commercially available and should be purchased by a third party.

	Pre-Therapy	Between fraction 8 and 12	Weekly during CRT[6]	+ 1 Month[7]	+ 3 month[7]	+ 6 month[7]	+ 12 month[7]	+ 24 month[7]
Rad Onc eval[7]	X		X	X	X	X	X	X
CBC with diff [8]	X							
CMP, Mg [8]	X		X					
PET/CT[3]	X	X			X			
DCE-MRI[10]	X	X						
Toxicity Evaluation[4]	X		X	X	X	X	X	X
Nutritional assessment by MD	X							
QOL Questionnaire[5]	X		X	X	X	X	X	
Videofluoroscopy[1]	X				X		X	
Dental Evaluation[2]	X							
Carboplatin/paclitaxel			X					
Blood for correlatives[9]	X		X	X	X	X	X	
Primary tumor specimen for correlatives[11]	X							

1) Videofluoroscopy to be completed prior to or during the first week of chemoradiation, 3 mo post RT and 12 mo post-RT per standard of care. When staff is not available to complete the videofluoroscopy tests, these will be skipped and listed as deviations.
2) Pre-therapy dental evaluation is encouraged but not required for all patients due to insurance issues
3) PET-CT to be completed at baseline within 4 wks of registration, mid-treatment (fx 8-12) and 3 mo post-RT (+/- 3 weeks)
4) Toxicity evaluation per CTCAE v 5.0
5) QOL suggested but not required. Patients have the option to complete these remotely and mail, fax, or send through the patient portal to the study clinic. Financial toxicity will only be given at one-time point 3 months post RT. All other questionnaires given pre-therapy and all follow-ups through 1 year. The CTCAE PRO will be given weekly during RT (this will be the only questionnaire administered during RT).
6) Weekly during CRT: Virtual monitoring visits will be allowed at the discretion of the provider.
7) Follow Up: Examinations will be performed as comparable to clinical practice: at 1 month (+/- 2 weeks) after the completion of therapy and then approximately every 3 months (+/- 1 month) for 2 years (+/- 2 months). This follow up schedule will adhere to standard of care clinical follow up. Therefore, missed visits and visits that diverge from this regimen will not be considered protocol deviations. RadOnc evaluation must be completed at baseline, but follow-up visits may be completed by RadOnc, Oto, or MedOnc. Virtual monitoring visits will be allowed at the discretion of the provider.
8) Within 4 weeks of registration
9) Serum samples will be obtained if the local lab is available for processing pre-therapy, weekly during chemoradiation, 1 month and every 3 months post therapy and at recurrence. Subjects who do not provide some samples, miss time-points or decline any or all of the sample collections will not be reported as protocol deviations.
10) DCE-MRI is not required if contraindicated or patient refuses
11) Contact the PI if sample is not available

8.0 Evaluation of Response to Therapy

Toxicities related to treatment will be evaluated using the Common Toxicity Criteria Adverse Events (CTCAE, version 5.0) weekly during treatment and at every follow-up visit for 2 years.

Quality of Life Questionnaires (U Washington QOL, xerostomia questionnaire (XQ), FACT HN, CTCAE PRO, financial toxicity) will be given to patients at follow-up research visits after completion of definitive therapy through 1 year. *As patients can be seen in a variety of clinics, and occasionally do not follow a standard clinic schedule, missed QOLs will not be reported as a protocol deviation. Patients have the option to complete these remotely and mail, fax, or send through the patient portal to the study clinic.*

PET/CT will be obtained at 3 months (+/- 2 weeks) post definitive therapy.

Repeat videofluoroscopy will be performed at approximately 3 and 12 months (+/- 1 month) after completion of radiotherapy to correlate with clinical follow-up. When staff is not available to complete the videofluoroscopy tests, these will be skipped and listed as protocol deviations.

Blood/plasma draws for correlative studies will be collected at each follow up visit through 1 year. These will only be collected if the local lab is available for processing.

Response Assessment Criteria

Response will be captured by standard clinical and radiological documentation. The designations will be: (1) NED; (2) failure primary tumor; (3) failure regional node; (4) distant metastasis. Any notation of failure at the primary tumor or regional node is considered local-regional progression. Initial staging imaging will be obtained at registration; then routine imaging will be obtained at 3 months (+/- 1 month) from completion of definitive therapy. Imaging will be combined to make as few visits and encounters as possible for the patient.

Decision to obtain further imaging will be left to the provider (i.e. if on clinical exam there are signs concerning for disease recurrence).

If there is clinical or radiologic evidence concerning for recurrent malignancy, confirmatory biopsy will be required before designating the patient to have recurrent disease.

9.0 Criteria for Discontinuation of Treatment

- Unacceptable adverse event(s).
- Intercurrent illness, which prevents further administration of treatment.
- Patient preference.
- Progressive disease.
- Life threatening or other unacceptable drug-related toxicity.
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator(s).

Duration of Follow-Up

Patients will be followed for 2 years after removal from treatment or until death, whichever occurs first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Examinations (virtual or in-person) will be performed as comparable to clinical practice: at 1 month after the completion of therapy and then approximately every 3 months for 2 years (+/- 2 months). This follow up schedule will adhere to standard of care clinical follow up. Therefore, missed visits and visits that diverge from this regimen will not be considered protocol deviations.

Off Study Criteria

- Patient withdraws consent (termination of treatment and follow-up);
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
- Patient is unable to comply with protocol requirements;
- Treating physician judges continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
- If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented;
- Termination of the study by The University of Michigan;
- Patient completes protocol treatment and follow-up criteria.

10.0 Adverse Event Reporting

An adverse event is any new, undesirable medical experience or change of an existing condition which occurs during or after treatment, whether or not considered product-related.

A serious adverse event is any untoward medical occurrence that suggests significant hazard or side effect that:

1. is fatal or life-threatening
2. required or prolonged hospitalization
3. results in persistent or significant disability/incapacity
4. constitutes a congenital anomaly or a birth defect
5. is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The definition of serious adverse event (experience) also includes important medical events. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Attribution: Definitions of relationship to study are as follows:

UNRELATED: The AE is clearly ***NOT*** related to the intervention/investigational agent.
UNLIKELY: The AE *is* ***doubtfully related*** to the intervention/investigational agent.
POSSIBLY: The AE ***may be related*** to the intervention/investigational agent.
PROBABLY: The AE ***is likely related*** to the intervention/investigational agent.
DEFINITELY: The AE ***is clearly related*** to the intervention/investigational agent.

Adverse events attributable to the chemotherapy will be reported if the adverse events are at an intensity that is more severe than previously documented or considered significant by the investigator. The definition of "related" is that there is a reasonable possibility that the drug caused the adverse experience.

If required on the adverse event case report forms, the investigator will use the following definitions of severity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report.

GRADE	Clinical Description of Severity
0	no change from normal or reference range
1	mild adverse event
2	moderate adverse event
3	severe adverse event
4	life-threatening or disabling adverse event
5	death related to adverse event

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial. If it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.
- Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.
- Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study treatment discontinuation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

Instructions for rapid notification of serious adverse events

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study treatments, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center SAE form as available in the study. A copy of the Coordinating Center SAE form as available in the study database should be sent to the Coordinating Center via fax at 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

Contact information for Principal Investigator SAE Reporting:
Name: Michelle Mierzwa, MD
Email: mmierzwa@med.umich.edu

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per local site's current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study treatment(s).

All adverse events will be noted in the case report forms

11.0 Data and Safety Monitoring

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety

Monitoring Committee (DSMC).

The Sponsor Investigator (S-I)/Study Principle Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Sponsor Investigator (S-I)/Study Principle Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per defined quarterly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a quarterly basis for independent review.

12.0 Data Handling and Record Keeping

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration

- Subject entry into EDC
    - Subject Status
    - Demographics
- During study participation
- All data should be entered online within 10 business days of data acquisition. [Information on dose limiting toxicity events must be entered within one business day.] Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 10 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to the Coordinating Center's Standard Practice Guidelines.

13.0 Statistical Considerations and Justification of Sample Size

Description and Justification of Design

This is a two arm, non-randomized, phase II study. A total of 85 evaluable patients will be enrolled and treated. Subjects will be considered evaluable for the primary endpoint after completing the baseline PET-CT scan, beginning protocol treatment, and completing the mid-treatment PET-CT scan. Patients that do not meet evaluability criteria will be replaced.

All patients will initially receive the same treatment. Based on the mid-treatment PET scan, patients who meet the criteria described in section 6.1 will receive de-escalated treatment (54 Gy) while patients not meeting all of these criteria will receive standard treatment (70 Gy). Both the de-escalation criteria and the de-escalated treatment (RT) will be applied separately to the primary tumor and the lymphnodes. Arm 1 will be all patients who did not qualify for de-escalation in either the primary tumor or lymph nodes; Arm 2 will include all patients who qualified for de-escalation in either the primary tumor or the lymph nodes.

The overall goal is to reduce dose of RT and thus toxicity in patients with very favorable prognosis with minimal reduction in tumor control. The sample size is justified with respect to the primary aim of estimating the risk of local-regional recurrence (LRR) within 2 years of treatment for all patients treated on this protocol. The estimated proportion of patients with LRR at 2 years was 12% in a retrospective analysis of 515 previously treated patients at UM or VA who were treated with standard treatment (ChemoRT with Radiation Dose of 70Gy) and would have been eligible for this study. By selectively lowering radiation doses, we cannot decrease LRR rates. However, we would like high power to demonstrate that the true overall LRR at 2 years is less than 25%. The null hypothesis to be tested in this non-inferiority analysis is H0: LRR > 25% and the alternative hypothesis is HA: LRR < 25%. When the true LRR is 15% (slightly higher thanthe historical control rate of 12%), a sample size of 68 patients provides 80% power at a significance level of .10 based on a one sample binomial test with a normal approximation. Based on the retrospective analysis of prior patients, we expect few deaths without prior LRR (< 5%) and few patients in this population to be lost to follow-up during the 2 years following treatment. However, to allow for 10% of patients lost to follow-up prior to 2 years, we will enroll 85 evaluable patients. If more patients are lost to follow-up than weexpect, we will estimate the risk of LRR at 2 years as 1 – the Kaplan-Meier estimate of local regional controland compare the upper 1-sided 90% confidence limit to 25%. Based on previous experience, a combined 60-80

eligible patients per year will be seen in Radiation Oncology at UM and AAVA. Assuming successful enrollment of 1/2 of these patients we expect to enroll 85 evaluable patients in approximately 3-4 years.

Preliminary analysis focused on toxicity presented at the ASTRO multi-disciplinary oral plenary session in February 2022 (Allen, et al, 2022) showed that 50% of the first 50 patients were able to be de-escalated and showed significantly improved objective measures of toxicity in the patients who were able to be de-escalated to 54Gy. Additionally, while the study has not yet met its primary endpoint, we have performed a preliminary LRC analysis in February 2022 for the primary endpoint with a median follow-up of 20 months in the first 65 patients showing LRC is >95% with only 1 patient having loco-regional failure. Our data to date suggest that patients have favorable LRC compared to historic control and favorable toxicity on this trial and increasing the enrollment to 85 evaluable patients will improve our power to show LRC non-inferiority of our approach.

Interim Analysis

We will conduct one interim analysis after 30 evaluable patients have completed their 6-month follow-up. Based on an expected accrual rate of 30 patients per year this will likely occur about 18 months after trial initiation or when 45 total patients have been enrolled. The goal of the interim analysis will be to halt the trial if there is sufficient evidence that the true LRR rate in these patients exceeds 20%. Specifically, if more than 6 of the first 30 patients experience LRR, the trial will be halted. If the true LRR is 25 or 30%, the probability of the trial stopping early is 65% and 85%, while if the true LRR rate is 10%, the probability of stopping early is only 3%.

The interim analysis was completed and results indicated no safety issues and no changes needed to the protocol, including the study's de-escalation criteria.

Analysis Plan

The primary study endpoint will be the binary occurrence of LRR within 2 years of treatment. We expect very few patients to be lost to follow-up or die within the first 2 years and so expect to observe this endpoint in nearly all patients. LRR rates over time will also be estimated as a survival type endpoint using the Kaplan-Meier method in which patients with no observed LRR are censored at the last date they were assessed for LRR. The cumulative incidence of LRR will also be estimated treating death prior to LRR and distant failure as competing risks. The primary study analysis will be based on comparing a 1-sided upper 90% confidence limit for the 2 year LRR rate to 25%. An upper bound below 25% will be interpreted as evidence that the true rate of LRR is less than 25% which is the goal of the study. In the primary analysis, all patients will be analyzed together as the goal of the study is to estimate risk of LRR in this patient population treated with this individualized de-escalation strategy in which some patients continue to receive standard therapy while others are de-escalated. Results will also be estimated and reported separately for patients receiving standard or de-escalated therapy but recognizing that these two groups of patients differ in an important prognostic variable (mid-treatment PET) as well as treatment. The second primary aim involves the use of an early imaging variable to predict future risk of LRR. Specifically, the change in $MTV_{50\%}$ at the mid-treatment timepoint will be calculated as percent change from baseline and used as a continuous variable in a Cox model for an outcome of time to LRR. We will also evaluate more non-parametrically, the relation between hazard of LRR and mid-treatment $MTV_{50\%}$ using a kernel estimator in a Cox model.

Secondary aims include estimation of toxicity, efficacy and other outcomes. The key toxicity outcomes are the patient reported XQ score (capturing Xerostomia) and HNQOL eating domain. Both variables are assessed longitudinally with primary interest on the 3 month values. Due to lack of xerostomia at baseline, we will work with the absolute scores over time while for HNQOL we will work with change from baseline

(pre-treatment). To characterize patterns of failure we will summarize at fixed timepoints, the proportion of patients who progressed in any location and whether the first progression was local, regional or distant or in multiple locations. Overall survival will be estimated using the Kaplan-Meier methods with associated 90% confidence intervals. Toxicity outcomes will be estimated as proportions of patients with available toxicity data at 3, 6 12 and 24 months. They will also be estimated as the proportion of all treated patients through cumulative incidence estimates with death treated as a competing risk and censoring for patients lost to FU. Quality of Life (QOL) outcomes and swallowing study results will be summarized descriptively by timepoint. If there is substantial missingness in the QOL outcomes we will assess for informative missingness by comparing earlier QOL scores and change in earlier QOL scores between patients missing QOL at later timepoints (e.g. 1 or 2 years).

Another secondary endpoint includes determination of the fraction of patients in whom we lose the ability to detect ctDNA during the fourth week of RT. Based on a recent abstract reporting similar data (Chera, ASTRO 2017), we expect approximately 90% of patients to have detectable ctDNA at baseline and about 33% of these to have no detectable ctDNA at the 4 week mid-treatment timepoint. Thus we expect that about 30% of all enrolled patients will fall into the category of ctDNA detectable at baseline but not 4 weeks. A sample size of 85 evaluable patients will provide at least 85% power to rule out proportions of 15% or less when the true proportion is 30%. The ctDNA data will be analyzed in several ways. First, the proportion ofpatients in whom ctDNA is detectable will be summarized as a binomial proportion at each timepoint. Patients with detectable ctDNA at baseline that disappears during treatment are potential targets for treatment de-escalation and are of particular interest. One of the goals of this analysis will be to estimate what proportion of trial patients fall into this category. Additionally, the relation between ctDNA presence or other characteristics and patient outcomes including time to local or distant progression will be assessed by including ctDNA as a covariate in Cox models for local or distant control.

Exploratory endpoints include cell free DNA (cfDNA) characterization of ADC and low blood volumes from DCE-MRIADC values and low blood volumes will also be summarized descriptively.

14.0 Justification of the Correlative Science

Hypothesis: Recurrent cancer in HPV positive OPSCC can be detected in serum biospecimens collected at routine interval time points and will identify tumor recurrence earlier than clinical exam.

Correlative Justification

Patients enrolling in deintensification trials for HPV+ OPSCC are at risk for treatment failure, thus careful monitoring in the post-treatment period is of extreme importance. The measurement of serum circulating free (cf)DNA and antitumor antibodies as a biomarker for recurrence may be an important, noninvasive method to detect treatment failures. We have previously examined serum antitumor antibodies (E6 and E7) in a longitudinal sample of patients who were treated under UMCC 2002-0221. Ourpreliminary data indicate that patients who have decreased clearance of E6/E7 antibody from their baseline measurement are at risk for disease recurrence. Finally, we have funding to perform targeted next generation sequencing on the primary tumor specimens from all patients enrolling in this trial, which can be used to prioritize evaluable somatic mutations in cfDNA from the blood of each patient for targeted sequencing studies (Hypothesis 1). Therefore, our goal is to collect longitudinal samples of serum as a partof our trial to determine if serum biomarkers can predict recurrence in HPV+ OPSCC. Our hypothesis is that *serum biospecimens collected at routine interval time points will identify tumor recurrence earlier thanclinical exam.*

ctDNA Sample Collection

We plan to collect and bank serial serum samples if the local lab is available for processing until 36 months from diagnosis. These samples are obtained at baseline, weekly during chemoradiation, 1 month and every 3 months post-therapy and at recurrence (see Study Calendar). Samples will be banked for planned analysis in the Brenner lab.

Blood Samples
Patient's blood will be drawn if the local lab is available for processing at baseline, during treatment, and at 4 wks, 3 mo, 6 mo, and 12 months post-therapy as part of their routine follow up appointments.

- Two heparinized green top 6 mL tubes and two Paxgene tubes at baseline only.
- Subsequent draws will include two Paxgene tubes only. Sample tubes will be provided by Brenner Lab.
- We will extract measure cfDNA from serum samples using the QIAamp Circulating Nucleic Acid Kit according to manufacturer instructions, cfDNA will be sequenced according to standard protocol in the Brenner lab and we will use our previous technique with an ELISA assay to determine E6 and E7 antibody levels.

Sample Transportation
Whenever as specimen has been obtained (i.e. after a blood draw), the study coordinator will transport the sample directly to the Brenner laboratory.

DCE-MRI

Hypothesis: Changes in BV and apparent ADC seen on DCE-MRI between pre-treatment and mid-therapy will be significantly inversely correlated with changes in MTV50%.

Methods:
The MRI scan will be performed in the exact patient position used for the simulation CT, including the same head rest and mask used for simulation. The MRI scanner installed recently at the UM Department of Radiation Oncology will be used for imaging. It has a large bore which facilitates imaging using these devices. Images will include FLAIR T2-weighted imaging, pre contrast T1-weighted imaging, diffusion weighted imaging, T1-weighted dynamic contrast enhancement imaging with single-bolus intravenous injection of Gd-DTPA, and post Gd-DTPA T1-weighted imaging. All images will be obtained with multiple-slices or 3D to cover the whole tumor volume. The scan time will be estimated to be one hour.

Identification of Subvolumes of the Tumor
Global-initiated regularized local fuzzy clustering (GIRLFC) is a method that is designed to first globally initiate training to identify fuzzy clusters of the physiological imaging parameters in the feature space, and then classify each tumor volume with local regularization to subvolumes according to the global feature clusters. This method is designed not only to identify the subvolumes of individual tumors based upon the heterogeneous distributions of physiological imaging parameters but also to be able to compare the classified subvolumes of the tumors across patients and over multiple time points. The fuzzy clustering method, specifically fuzzy C- means clustering (FCM), chosen in the GIRLFC method aims to deal with (1) intrinsic variations of the physiological parameters in the tumors, (2) partial volume effects due to the limited resolution of imaging sources, and (3) uncertainty due to noise.

Fuzzy C-Means clustering is a method of unsupervised learning to assign a set of observations to belong to subsets (clusters) with probability memberships. To partition a set of observations [x_k], e.g., image voxels, into c clusters, an objective function with local spatial regularization is to be minimized.

$$(1) \quad J_m = \sum_{i=1}^{c}\sum_{k=1}^{N} u_{ik}^{m}\left\|x_k - v_i\right\|^2 + \alpha\sum_{i=1}^{c}\sum_{k=1}^{N} u_{ik}^{m}\left\|\bar{x}_k - v_i\right\|^2$$

In Eq [1], the first term is a standard FCM cost function and the second term provides a spatial constraint to overcome the effect of image noise and to improve spatial connectivity. Here u_{ik} is a probabilistic (fuzzy) membership of observation x_k belonging to class i v_i is a prototype vector of class i, x_k is a mean or median value of neighbors of voxel k, m defines fuzziness of the membership, and α is a weighting factor of spatial constraints. A 2D or 3D kennel, depending upon image resolution, can be used to define neighbors of each voxel for spatial constraint. Solutions that minimize the objective function of Eq [1] are given by:

which are solved iteratively until reaching a stopping criterion. The values for m and α are usually determined empirically. The analysis can be applied to either single- or multiple- component parameters.

In order to evaluate longitudinal changes in physiological imaging parameters of interest in the tumor,

$$u_{ik} = \frac{\left(\left\|x_k - v_i\right\|^2 + \alpha\left\|\bar{x}_k - v_i\right\|^2\right)^{\frac{1}{(m-1)}}}{\sum_{j=1}^{c}\left(\left\|x_k - v_j\right\|^2 + \alpha\left\|\bar{x}_k - v_j\right\|^2\right)^{\frac{1}{(m-1)}}} \quad \text{and} \quad v_i = \frac{\sum_{k=1}^{n} u_{ik}^m (x_k + \alpha\bar{x}_k)}{(1+\alpha)\sum_{k=1}^{n} u_{ik}^m} \tag{2}$$

first a set of data is used as training data to determine definitions of clusters (prototype vectors and relationships between fuzzy memberships and observations), and then the remaining sets of data are partitioned according to the class definitions of training data. To avoid a bias from large tumors in training data, each of the tumor volumes is up-sampled or down-sampled to have an equal number of voxels contributing to the training data while maintaining the initial distribution of the physiological imaging parameters from the original into the re-sampled tumor. To do so, a histogram of the physiological imaging parameters of each tumor is generated, and re-sampled to create a new tumor volume with the same size. The re- created tumor volume, while preserving the original distribution (histogram) of the imaging parameters, cannot maintain the original spatial relationship between voxels, which is not critical for training data to determine prototype vectors of global clusters. To partition individual tumors in the second data set, fuzzy membership of each voxel of each tumor is classified using the prototype vectors found in analysis of the training data by Eq [2], where spatial constraint is used to improve spatial continuity. Finally, the highest probability of fuzzy membership of each voxel is used to assign the voxel to a discreet class. As a result, the tumor is partitioned into spatial subvolumes based upon the similarity of the physiological parameters of interest. The temporal changes in partitioned subvolumes of the tumor are evaluated for their association with outcomes.

To evaluate this method to identify significant subvolumes of the tumor related to outcomes, we will apply the method to BV and BF images derived from DCE MRI of patients with advanced head and neck cancer.

Diffusion-weighted MRI

A diffusion weighted, single shot, spin-echo, echo planar imaging (EPI) series with diffusion sensitization will be constructed along three orthogonal directions, with the diffusion-weighted images (DWI) contributing approximately two minutes of scan time to the MRI. The product of the three orthogonal DW images exhibits strong sensitivity to diffusion but without sensitivity to the structural directionality of the tissues. This isotropic feature is crucial to follow serial changes in water diffusion without confounding effects due to tissue orientation. ADC maps will be calculated from the DW images

$$ADC = \ln\left[\frac{S_{b_0}}{S_{b_1}}\right] \Big/ (b_1 - b_0) \qquad (1)$$

as follows:
where S is the DW image at b-values of b_0=0 and b_1=800 s/mm^2.

Subsequent to image registration, contours will be manually drawn over tumors as delineated on T_2-weighted, T_1-weighted or contrast-enhanced images. From the volume-of-interest (VOI) tumor volume and mean ADC will be assessed pre- and 2 weeks post-treatment initiation. Subsequent to contouring the tumors, a geometric warping interpolant, i.e. thin plate spline, algorithm will be used to map (warp) the tumor volumes from interval exams onto the tumor volumes from pre-therapy b_0 DW images (reference dataset). The Parametric Response Map of ADC (PRM_{ADC}) will be determined by first calculating the difference between the ADC values (ΔADC = mid-treatment ADC – pre-treatment ADC) for each voxel within the tumor pre- treatment and at week 2 post-treatment initiation. Voxels yielding ΔADC greater than a predetermined threshold set to 25 ADC units [= x 10^{-5} mm^2/s] will be designated as significantly increased. Voxels whose ADC values significantly decreased by more than 25 x 10^{-5} mm^2/s(i.e. ΔADC < -25 x 10^{-5} mm^2/s) will be designated as significantly increased, and the rest of the voxels as non-changed. The volume fractions within the tumor as determined by PRM_{ADC} will be denoted by PRM_{ADC+} (increased ADC), PRM_{ADC-} (decreased ADC), and PRM_{ADC0} (unchanged ADC). PRM thresholds of significant change will be empirically assessed over a range of ΔADCs (0 to 70). PRM_{ADC+} with a threshold of ±25 ADC units provided the best correlation with tumor control in our previous study (Galban et al) and will be tested in the current study.

Risks in MRI

Our MRI protocol has risks and discomforts similar to clinical MRI with intravenous injection of a contrast agent. Subjects run the risk of claustrophobia when they are lying inside the MRI scanner. They may also feel uncomfortable because of the loud noises made by the machines and the physical sensations they may feel during the process. Subjects are also exposed to some risk because of the injected contrast agent, gadolinium-DTPA, which may cause headache, nausea, and local burning. Because of the use of the contract agent, all female subjects of child- bearing potential will be required to use adequate birth control. Patients who have implanted or internalized metallic objects cannot participate in this research. Recent FDA guideline indicates there is an association between exposure to gadolinium and the development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF)) in 3-5% of the patients with advanced renal failure. We will follow the Institutional Standard

Practice guidelines, which is based upon the FDA guideline, to screen the patients with renal disease, dysfunction, and dialysis for this study.

15.0 Quality Assurance and Audits

The Data and Safety Monitoring Committee can request a 'for cause' quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

16.0 Clinical Monitoring Procedure

Clinical studies coordinated by The University of Michigan Rogel Cancer Center must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the University of Michigan Rogel Cancer Center. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate Coordinating Center personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes treatment. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected

- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

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