

ID: UMCC 2013.062

Randomized Phase II Study of DCE-MRI-based Dose Escalation for Poor-prognosis and Neck Cancer

NCT02031250

Randomized Phase II study of DCE-MRI-based dose escalation for poor-prognosis head and neck cancer

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Protocol version: 07-01-2020

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1.0 INTRODUCTION

HNC accounts for 3% of all new cancer sites and 2% of all cancer death in the United States, however it is the fifth most common malignancy worldwide. 37,000 new cases of HN cancer will be diagnosed and 11,000 will die due to this cancer in the US in 2003 [2]. The treatment of locally advanced cancer has traditionally been surgery followed with postoperative irradiation. In recent years, altered fractionated radiation and the addition of concurrent chemotherapy have yielded significant improvements in the rate of tumor control using non-surgical approaches [2]. However, specific patient groups still suffer poor prognosis following chemo-irradiation (chemo-RT), and their predominant mode of treatment failure is local-regional (LR). These groups include oropharyngeal cancers not associated with Human Papillomavirus Virus (HPV-negative tumors) or in heavy smokers, unresectable tumors (tumor stage 4b), and recurrent tumors treated with re-irradiation [3-7]. A major recent effort to improve outcome in locoregionally advanced, non-metastatic HNC has focused on the addition of induction chemotherapy or novel targeted agents such as EGFR or VEGFR blockers. Unfortunately, there is no evidence yet that these approaches are more effective than the use of concurrent chemo-irradiation with currently available cytotoxic agents. For instance, recent reports from the Dana-Farber and the Chicago groups showed no local-regional, disease-free survival, or overall survival gains with induction chemotherapy followed by chemo-irradiation compared with chemo-irradiation alone [8]. In addition, the recently reported large randomized RTOG 0522 study demonstrated no benefit for the addition of the EGFR inhibitor cetuximab to the combination of cisplatin-irradiation, compared with cisplatin-irradiation alone, in the treatment of locoregionally advanced advanced HNC [9]. New approaches are needed for improving LR disease control rates in poor-prognosis patients.

2.0 HYPOTHESIS, RATIONALE, AND PRELIMINARY STUDIES

Given that the predominant mode of failure in the poor-prognosis patient groups detailed above is LR, a substantial improvement in LR control rates is likely to translate into an improvement in overall survival. Based on our experience and that of others [10-14], the vast majority of LR failures in patients receiving intensity-modulated radiation therapy (IMRT) occur in-field, within the targets that received the full prescription dose. **Thus, to improve LR control rates, we propose using highly conformal radiotherapy (RT) to redistribute the doses within the tumor such that the dose to sub-volumes likely to be resistant to standard RT doses is increased, while standard doses to the rest of the tumor and surrounding normal tissues are maintained.** This approach depends on achieving two main requirements: (1) identifying relatively radioresistant tumor subvolumes that are spatially and temporally stable in order to allow their selective targeting for a radiotherapy boost, and (2) safely delivering higher doses to these subvolumes without exceeding normal tissue tolerance, in order to improve local-regional tumor control without increasing treatment-related complications.

This study aims to improve locoregional control of poor prognosis HNC patients by selectively escalating the radiotherapy dose to radioresistant subvolumes of tumor that demonstrate persistent hypoperfusion after 2 weeks of therapy. Dynamic contrast enhanced (DCE) CT or MRI can now be used to characterize key tumor vascular properties, including blood volumes, blood flow, vascular permeability, and mean transit time, as well as distribution volume and available interstitial space for the contrast agent [15]. This is important as newly synthesized tumor-related blood vessels, which exhibit poor functionality and manifest high permeability, tortuosity, and density heterogeneity, have

been shown to serve as a prognostic indicator of tumor aggressiveness [15]. Low pre-therapy tumor perfusion has been found to be correlated with local failure and poor response to therapy of head and neck cancer, independent of other known prognostic factors, in multiple studies [16-21]. While a significant inverse correlation exists between hypoxia and perfusion [22, 23], they do not measure the exact same physiological processes [15]. We have opted to use perfusion imaging in our studies, rather than hypoxia imaging, due to several factors. First, spatial and temporal stability of tumor sub-volumes identified by an imaging modality is essential to accurately and reproducibly determine the highest risk tumor sub-volumes for potential boosting. Longitudinal assessments of the spatial distributions of hypoxic subvolumes assessed by F-18-labeled fluoromisonidazole at Memorial Sloan Kettering Cancer Center showed variability in the spatial uptake between repeated images pre-therapy [24], which compromised the ability to specifically target hypoxic tumor volumes by dose-painting IMRT [25]. Furthermore, in almost all patients, hypoxia resolved completely at mid-therapy [26], similar to previous findings by Rischin et al [27]. **In contrast to the spatial and temporal variability of hypoxia-specific functional imaging studies, our data using DCE-MRI at 2 weeks after beginning chemoradiotherapy demonstrate that although reductions in hypoperfused sub-volumes were seen in some patients, the hypoperfused regions in all patients remained within the initial pre-therapy hypo-perfused subvolumes, suggesting relative spatial stability.** This issue will be assessed in detail by comparing the pre- and during-therapy hypoperfused subvolumes in protocol patients. Second, the spatial resolution of perfusion measurements using dynamic contrast enhanced MRI (DCE-MRI) is superior to that of current methods of hypoxia measurements using various PET tracers [22]. DCE-MRI may therefore be a better modality to define hypoperfused tumor subvolumes for boosting using IMRT.

In order to serve as an adequate target for dose redistribution, the imaging-based target needs to be the predominant site of LR failure following therapy, rather than just a general marker of high risk of failure. For example, some local-regional recurrences were found to be outside the boosted subvolumes defined by pre-therapy FDG-PET [28]. Our preliminary results suggest that the sites of LR failures are within the hypo-perfused subvolumes identified on DCE-MRI [1]. We conducted a preliminary evaluation of the spatial relationship between the subvolumes of the tumors with low blood volume (BV) and patterns of local failure. In two of the patients with LR recurrences for whom imaging early after recurrence was available, images were registered with the pre- and during-treatment DCE-MRI images. In both cases, the local recurrences occurred within sites corresponding to the tumor sub-volumes with low BV on pre-therapy and during therapy DCE-MRI. Additional supporting data is needed, however, and will be accumulated during the current study.

Pre-therapy tumor blood volume (BV) is a major prognostic factor measured by DCE-MRI [19]. Our preliminary results suggest that its change at 2 weeks after the beginning of therapy may provide an even better prognostic value than the pre-therapy value. We have evaluated DCE-MRI early during the course of chemo-RT, and found that patients demonstrating increased BV after 2 weeks compared with pre-therapy had significantly better outcome than those whose BV did not increase, a prediction that was more accurate than the extent of tumor shrinkage after 2 weeks [19]. As part of this study, 14 patients with unresectable HNC underwent DCE-MRI prior to and 2 weeks after the initiation of chemo-RT. Four patients experienced local failures. The BV in the primary tumors increased significantly from pretherapy to 2 weeks in the locally controlled patients compared with the locally failed patients ($p<0.03$), while no significant differences were noted in tumor shrinkage between failures and non-

failures [19]. This analysis used mean whole-tumor parameters. We have recently analyzed the predictive value of heterogeneous tumor perfusion in these patients. When sub-volumes of the tumors with low BV or blood flow (BF) before and during treatment were evaluated for their associations with local failure, we found that the sub-volumes of the tumors with low BV before and during treatment significantly differentiated local failure from local control ($p=0.02$ and 0.01 , respectively)[1]. The tumor sub-volumes with low BV before and during treatment had greater specificity for prediction of local failure, with a given sensitivity, than the pre-therapy total tumor volume, the percent change in tumor volume during therapy, or the change in mean tumor BV during therapy. Similar results have recently been reproduced by others [17]. BV at 2 weeks compared with pre-therapy promises to be a marker of the individual tumor response to therapy that can accurately predict treatment failure in areas of persistently low BV. In the current protocol we will target low-BV sub-volumes (which in almost all the cases in our previous study included a contiguous volume of tumor $>1\text{cc}$) for radiation dose intensification using highly conformal radiotherapy, in an effort to overcome the relative treatment resistance represented by these sub-volumes and improve LR tumor control rates.

In this study we propose to increase the nominal dose delivered to the hypoperfused tumor subvolumes to 80 Gy while other tumor subvolumes receive a standard dose of 70 Gy, all in 35 fractions, using IMRT.

Diffusion-weighted (DW) MRI has been studied extensively as a predictor of recurrences in brain tumors [29-33]. There are strong reasons to anticipate that a similar utility of diffusion MRI will be found in HNC, and preliminary studies both at our institution (36) and by others (Vandecaveye et al 2012) support this proposition. We will assess it in our proposed studies. The MRI studies performed in this protocol will also be used to obtain diffusion-related data which will supplement perfusion (DCE-MRI) data. Our preliminary results, as well as others', suggest that diffusion-weighted MRI can predict tumor response both on a global and on a local-spatial tumor level [34-37]. Changes in whole-tumor mean Apparent Diffusion Capacity (ADC) from pre-therapy to 1 week into therapy have been shown to correlate with clinical and pathologic response in HN cancer [36]. Recently, a voxel-wise approach to evaluate ADC changes within tumor has been developed at our institution as an early biomarker for quantifying the spatial heterogeneous response of tumor to therapy [29]. This approach (parametric response map, PRM, or functional diffusion map) uses registered baseline and early-treatment ADC maps to calculate regional responses that may be more sensitive to cellular changes than measurements of the mean change in ADC. We will analyze the diffusion MRI maps derived from the DW-MRI studies to determine their potential as a complementary modality to perfusion (DCE) MRI in defining the boosted tumor subvolumes. If it is found to provide complementary information, diffusion MRI will be integrated into the decision-making related to defining tumor subvolumes for boosting in the future. The addition of diffusion-weighted images to DCE-MRI will lengthen the MRI procedure by approximately 2 minutes.

While the MRIs performed pre-therapy and at week 2 of therapy will be used for decisions about treatment modification in the current protocol, we will also add an MRI (with both DCE and DW sequences) during the last week of therapy to assess its predictive value. This additional research MRI will be performed at the discretion of the treating physician, with consideration of the individual patient's tolerance of treatment and accompanying toxicities. If persistent hypoperfused subvolumes or

low apparent diffusion coefficient (see Vandecaveye et al 2012) at the end of therapy will be predictive of LR failure, future intervention such as a final boost will be contemplated.

Acute and late toxicity of chemo-RT for HNC are issues that need to be addressed when intensive chemo-RT is contemplated. Specifically, severe acute mucositis and consequential late dysphagia are the major factors limiting treatment intensification [38]. In a phase I dose escalation study from the Medical College of Virginia in which escalated doses were delivered to the entire gross tumor volume (GTV), severe acute mucositis was determined to be the dose limiting toxicity (DLT) at a dose of 73.8 Gy in 30 fractions (2.46 Gy per fractions), necessitating treatment breaks in the two patients treated at this dose level, and leading the investigators to define 70.8 Gy in 30 fractions of 2.36 Gy to the GTV as the maximum tolerable dose [39]. In contrast, a dose escalation study at Ghent University Hospital in which sub-volumes of the GTV were boosted based on pre-treatment and 2-week FDG-PET scans did not demonstrate any acute grade ≥ 4 toxicities during treatment, but did encounter excessive rates of unexpected late mucosal ulceration [40]. Specifically, at the highest dose level of 85.9 Gy in 32 fractions, 5 of out 14 patients (36%) developed late mucosal ulceration at a median 7 months follow-up (range 4-10 months), compared with only 1 out of 7 patients at the lower dose level of 80.9 Gy in 32 fractions, which the investigators determined to be the MTD for dose escalation to GTV sub-volumes. Of note, the use of concurrent chemotherapy in the Ghent study did not appear to increase the incidence of late mucosal ulceration. Given the apparent tolerability of dose escalation to tumor sub-volumes to 80.9 Gy in 32 fractions, we expect our proposed high dose arm delivering 80 Gy in 35 fractions to a sub-volume of the GTV, while limiting the dose to the mucosa to 70 Gy, to be similarly well tolerated. In light of the DLTs encountered by the MCV and Ghent dose escalation experiences, however, we will apply early stopping rules should either acute non-hematological grade 4 toxicities or late grade 4 toxicities exceed 15%.

Dysphagia after chemo-radiotherapy of HN cancer is a major late sequel of therapy. We have concentrated in recent years on reducing the dysphagia resulting from chemo-irradiation of HN cancer, having identified the anatomic structures whose damage causes dysphagia, established dose-effect relationships for these structures, and devised IMRT strategies to reduce their doses [41-46]. UMCC protocol 2-21 tested our ability to use IMRT to spare the swallowing structures, assessing whether swallowing function can be preserved while maintaining high rates of disease control. The long-term results show excellent tumor control rates (only 3 local-regional recurrences out of 73 patients with median follow-up 36 months), as well as excellent functional results related to dysphagia. We will use the treatment planning guidelines that yielded these excellent oncologic and functional results as the basis for the dosimetric constraints in the herein proposed protocol.

We have also recently modeled dose-response relationships for the parotid glands based on updated data from chemo-IMRT treated patients. These data suggest a continuous dose-response relationship without a threshold effect, with 26 Gy corresponding to a normal tissue complication probability (NTCP) of 25% and 39 Gy to a NTCP of 50% [43]. We have also established dose-response relationships for the submandibular glands (SMG) [41], which have guided us in sparing the contralateral SMGs in patients whose contralateral neck level I was not at risk. In a recent investigation into the correlates of xerostomia we have reported that beyond sparing the parotid glands, sparing of the SMGs and the non-involved oral cavity (within which minor glands are dispersed) reduces xerostomia significantly [42]. We

will incorporate these dose-response relationships into the treatment planning process to limit dose to the salivary glands and oral cavity in this new proposed protocol.

In order to assess our ability to safely increase the dose to hypoperfused subvolumes, we have re-optimized IMRT plans for 4 patients who underwent DCE MRI pre-therapy and again after 2 weeks of therapy. The optimization goal was to re-distribute the dose such that a total of 80 Gy will be delivered to the persistently hypoperfused tumor subvolumes after the initial 2 weeks of treatment. Optimization criteria were: Minimum 80 Gy, maximum 84 Gy within boost volume PTV, mean 70 Gy (maximum 75 Gy) elsewhere within the rest of the PTV, maximal mucosa dose 70 Gy, and to keep all other constraints used in previous protocols with regards to doses to swallowing structures, salivary glands (parotid, contralateral submandibular, minor glands within the oral cavity). We have achieved these dosimetric criteria within +/- 5%. Thus, in this protocol, we will limit mucosal and swallowing organ doses to tolerated levels, minimizing these major toxicities. In addition, early stopping rules are implemented in the protocol in case the rate of severe toxicities is estimated to exceed 15%.

Additionally, we have examined DCE-MRI in critical organs affected by chemo-RT, including the pharyngeal constrictor muscles whose dysfunction after chemo-RT is related to late dysphagia. We have recently analyzed whether changes in pharyngeal constrictor (PC) muscle perfusion early during chemo-irradiation could predict imaging findings after the completion of RT (unpublished data). In a prospective study, 15 patients with locally advanced HNC treated with chemo-IMRT, without intentional sparing of the PCs, underwent DCE-MRI prior to RT, after 2 weeks into RT, and 3 months after completion of RT. BV and BF were quantified for the PCs and for the sternocleidomastoid muscle ipsilateral to the primary tumor, which received a similar dose (59 ± 16 Gy) as the PCs (56 ± 15 Gy). Compared to pre-RT, BV increased in PC by 512% at 2 weeks and 620% at 3 months post RT, whereas little change in BV was seen in the sternocleidomastoid. Dose to the PCs was significantly correlated with the change in BV at both time points ($R^2 = 0.89$), and BV changes in PC during RT were significantly correlated with the changes at 3 months after RT ($R^2 = 0.87$). In the PCs, BV changes during RT, possibly reflecting inflammation, also significantly correlated with normalized T2 signal changes on MRI at 3 months after RT, possible representing therapy-induced edema. Truong et al., in studies using CT-perfusion imaging, have shown that the severity of dysphagia at 3 and 6 months after RT may be correlated with changes in BF and BV of the PCs after 2 weeks of RT [47]. However, neither our prior work nor the study by Truong et al. attempted to limit the dose to the PCs during IMRT planning, resulting in mean doses in excess of 50 Gy being delivered to the PCs. As the IMRT optimization goals in the presently proposed study will attempt to limit mean PC dose to 50 Gy, which produced excellent preservation of swallowing function and low rates of dysphagia in UMCC protocol 2002-021, we will investigate whether changes in PC perfusion after 2 weeks correlate with patient- and observer-rated dysphagia and objective video fluoroscopy swallowing assessments at 3 months post-RT, in protocol patients where treatment goal was sparing the PCs outside the targets.

Rationale for adding FDG-PET scan at 2 weeks after therapy started:

UMCC 2013.062 aims to assess whether higher-than-standard radiotherapy doses to resistant tumor sub-volumes improves the outcome compared with standard therapy in patients with locoregionally advanced, poor prognosis HNC. It relies on early changes in MRI-based hypo-perfusion (HP), associated with hypoxia, and restricted water diffusion (RWD), associated with local cellularity, and are identified using perfusion MRI and DCE-MRI, respectively. Both are associated with aggressive and less responsive

disease. Once these subvolumes are identified, the subvolumes which persist spatially from pre-therapy to 2 weeks into therapy, are planned for escalating radiation doses during the rest of the therapy course. Patients are randomized to escalation or standard therapy arms. Thus far 32 patients have been accrued and randomized out of planned 80 patients. Interim analyses showed that the HP and RWD are spatially distinct, prompted us to aim at both subvolumes for dose escalation, which was included in a previous amendment aimed to target both subvolumes. More recently we have assessed the pre-RT and during-RT spatial distributions of the MRI-based tumor subvolumes HP and RWD vs. pre-therapy FDG-PET-based metabolic tumor volumes (MTVs). We found a reduction by about 50% of the union between HP and RWD subvolumes at 2 weeks compared with pre-RT. This is similar to a 50% reduced total lesion glycolysis (TLG) defined as $(SUV_{avg}) \cdot (\text{tumor volume})$, with a threshold of 45% SUV_{max} in the volume of interest, reported in series of pre- vs during- treatment FDG-PET in head and neck cancer (Pollom WL Head neck 2016, Min M & Lin P, Eur J Nuc Med Mol Imag 2015). These series reported improved outcomes in patients whose TLG was reduced during therapy to below 50% pre-therapy levels, compared to patients whose TLG reduction was lower; the effect of the reduced PET parameters from pre to early during-treatment was more significant than the pre-therapy FDG-PET parameters in these studies (many previous papers reported prognostic importance of FDG-PET parameters in HNC). We hypothesize that FDG-PET during the second chemo-RT week will result in MTV that will be smaller than at pre-therapy, will be distinct spatially from HP and RWD, and that it will be possible to escalate dose to a limited volume combining all during-therapy 3 subvolumes, thus aiming at both MRI-based high-risk tumor subvolumes as well as the intra-treatment PET-based parts of the tumor that have survived the initial therapy, and are likely to be more resistant to therapy.

This amendment will examine two hypotheses in an exploratory pilot sub-study:

1. FDG-PET after 8-12 chemo-RT fractions will only partly overlap spatially with HP and RWD and its inclusion will be feasible in safe dose intensification in the future. Dice similarity coefficients will be used to assess overlap.
2. The extent of reduced FDG-PET parameters, MTV and TLG, compared with pre-RT, will be associated with tumor outcome. This will be tested by Cox regression models for DFS where predictors will be the changes in MTV and TLG, accounting for different treatments (boost vs standard RT) and assess whether including these changes improves our ability to predict DFS beyond other variables.

Rational for adding blood samples pre-, during, and after therapy to assess circulating tumor DNA (ctDNA).

“Liquid biopsy” consisting of ctDNA with specific mutations have proven to be a promising tool to determine early metastases or local-regional progression. At diagnosis, between 65% -86% of HNC patients have ctDNA detected in the serum (Bettewgoda C, Sci Transl Med 2014, Wang Y Sci Transl Med 2015). Their concentration pre-therapy is higher in patients with locoregionally advanced disease (Dahlstrom KR, Clin Ca Res 2015, Mazurek AM Oral oncol 2016) and in patients with shorter DFS or survival (Yanagita M Clin Ca Res 2016, Messaoudi SE Clin Cancer Res 2016), and their presence after therapy is associated with the risk of recurrence and metastases (Hamana K Br J Ca 2005, Ahn SM JAMA Otolaryngol HNSurg 2014). Also, those with a higher rate of genomic alterations in ctDNA had shorter survival (Schwaederle M Clin Ca Res 2016). Case studies in breast, colon and lung cancers suggest that ctDNA dynamics during therapy may provide an early indicator of tumor response (Ignatiadis M Clin Ca Res 2015). While tumor-specific mutations in cfDNA have been reported in pancreas, colorectal, and

lung carcinomas, very little has been published on HNC (Wang). Data related to potential prognostic implication of increase or decrease in cfDNA after therapy is conflicting (Cao H IJROBP 2012, Fakhry C Cancer Prev Res 2015), and there is no data at all regarding the implications of their levels at mid-therapy compared to pre- and end of therapy .

As protocol patients are at high risk for treatment failure, a non-invasive biomarker for response earlier in therapy is extremely important. The measurement of serum circulating tumor ctDNA as a biomarker for recurrence may be an important, noninvasive method to detect treatment responses. Dr Brenner's group at UM have identified HPV and mutant ctDNA in blood samples of patients with advanced or recurrent HNSCC, suggesting this noninvasive biomarker as a way to measure disease response to therapy. Using data generated from targeted next generation sequencing on tumor specimens, we can prioritize evaluable somatic mutations in ctDNA from blood of each patient for targeted sequencing studies as well as monitor for the occurrence of mutations common in tumors. Our goal is to collect longitudinal samples of serum as a part of our trial to determine if serum biomarkers can predict response to therapy and also identify emergence of resistant clones.

This amendment will examine in an exploratory pilot study whether the level and mutational profile of ctDNA pre, during, and after therapy is associated with tumor outcomes. Cox regression models will be done for DFS. Predictors will be cfDNA and boost arm and possibly interaction, then assess whether cfDNA is prognostic for DFS while accounting for different treatments (boost vs standard RT). Other baseline covariates will be added to the model to see if cfDNA improves our ability to predict outcome.

3.0 OBJECTIVES

3.1 Primary Objective:

Determine whether escalating the radiotherapy dose to resistant tumor subvolumes identified by persistent hypoperfusion on 2 week DCE-MRI (boost arm) and by persistent low apparent diffusion coefficients can improve disease-free survival compared to standard chemo-RT (control arm)

3.2 Secondary Objectives:

1. Compare local-regional control rates and overall survival between the two arms
2. Assess the site and timing of local recurrences as they relate spatially to the site and volume of the hypoperfused tumor sub-volume
3. Assess acute and late toxicities and functional outcomes
4. Correlate changes in perfusion of pharyngeal constrictor muscles and other normal tissues on 2 week DCE-MRI with dosimetric parameters and toxicity/functional outcomes
5. Assess the utility of diffusion-weighted MRI in predicting tumor and tumor sub-sites at high risk of local/regional recurrence

3.3 Exploratory Objectives:

1. Assess whether FDG-PET after 8-12 chemo-RT fractions overlaps spatially with the MRI-based high-risk tumor subvolumes and whether its inclusion will be feasible in safe dose intensification in the future.
2. Assess whether the extent of reduced FDG-PET parameters, MTV and TLG, during therapy compared with pre-RT, are associated with tumor outcome.
3. Correlate the level and mutational profile of ctDNA pre, during, and after therapy with tumor outcomes.

4.0 ELIGIBILITY CRITERIA

- 4.1 Patients must have pathologically-confirmed, non-metastatic locally/regionally advanced squamous cell carcinoma of the head and neck, stage III/IV, referred for definitive chemo-RT, and meet one of the following criteria:
 - 4.1.1 Primary tumor (T4) with or without metastatic lymph nodes. Tumor or nodes are: unresectable, resection is considered by the treating surgeon or patient to result in unacceptable functional or oncological results, patient refuses surgery, or surgery is not possible due to co-morbidities.
 - 4.1.2 HPV(-) or p16(-) locally/regionally advanced (T3-4 or N2-3) oropharyngeal cancer
 - 4.1.3 HPV(+) or p16(+) locally/regionally advanced (T4 or N3) oropharyngeal cancer
 - 4.1.4 T3 or T4 laryngeal or hypopharyngeal cancer that is locally advanced, bulky (>40 cc*), unresectable, or patient declines surgery
 - 4.1.5 Stage III/IV oral cavity or paranasal sinus cancers in patients who refuse surgery or are unfit for surgery
 - 4.1.6 Locally/regionally advanced (stage T3-4 and/or N3) nasopharyngeal cancer which is EBV (-) (Epstein-Barr Virus).
- 4.2 KPS \geq 70 (see Appendix A) within two weeks of enrollment
- 4.3 Pre-treatment laboratory criteria within four weeks of enrolment:
 - 4.3.1 WBC > 3500/ul, granulocyte > 1500/ul.
Platelet count > 100,000/ul.
Total Bilirubin < 1.5 X ULN.
AST and ALT < 2.5 X ULN.
Estimated Creatinine clearance >30cc/min
- 4.4 Patients must be able to receive protocol chemotherapy in the judgment of the treating Medical Oncologist
- 4.5 Patients are adults (Age \geq 18)
- 4.6 All patients must be informed of the investigational nature of this study and given written informed consent in accordance with institutional and federal guidelines.

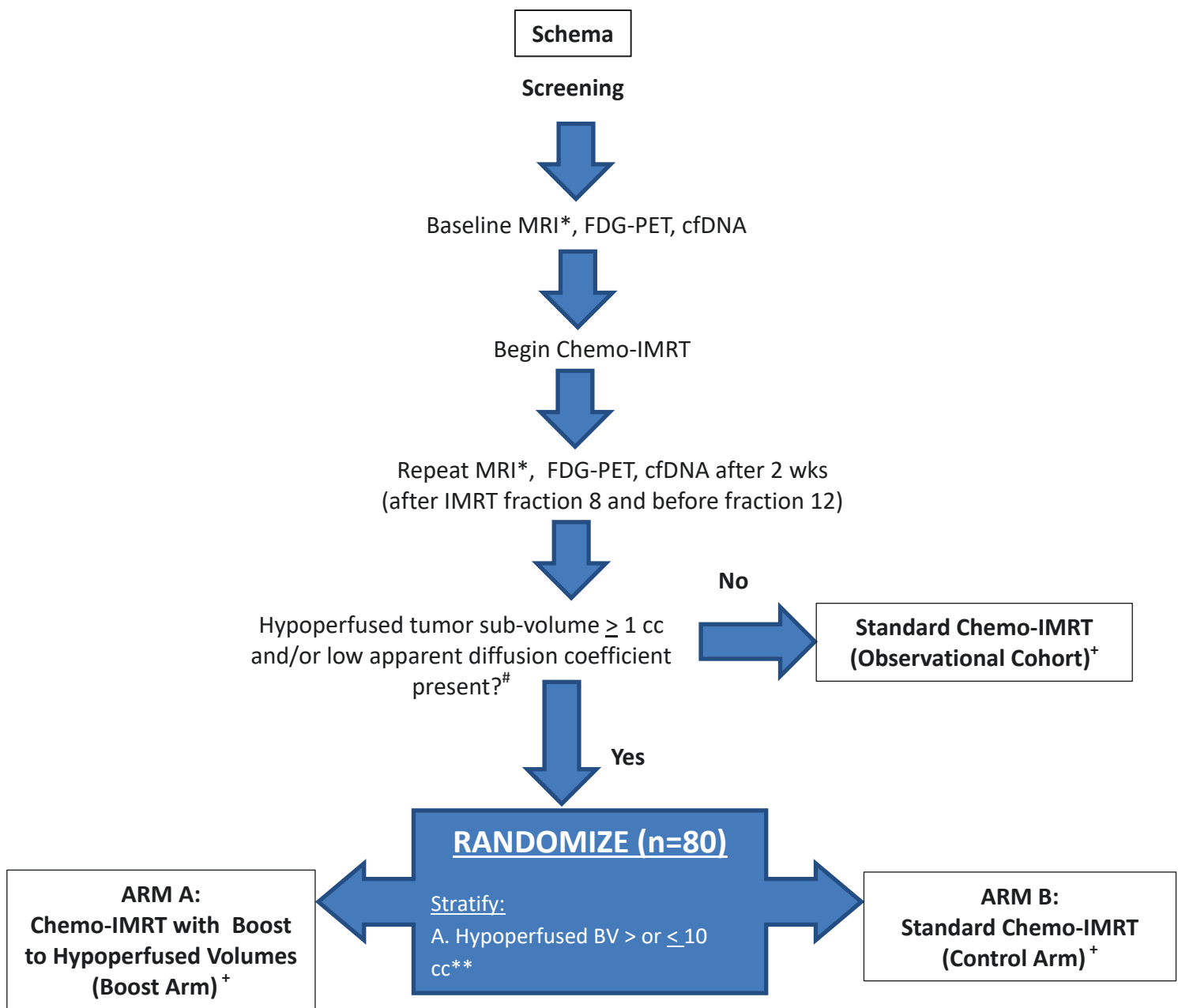
*Based on Mancuso A, Mukherji S, et al, JCO 1999;17:631-7

5.0 EXCLUSION CRITERIA

- 5.1 EBV (+) Nasopharyngeal Carcinoma in the protocol treated tumor.
- 5.2 Prior head and neck radiation.
- 5.3 Documented evidence of distant metastases.
- 5.4 Patients with active infection
- 5.5 Pregnant women

5.6 Patients should have no contraindications to having a contrast enhanced MRI scan. These contraindications will be assessed at the time of enrollment using the guidelines set up and in clinical use by the Institutional Standard Practice.

6.0 STUDY DESIGN



*MRI sequences include DCE (perfusion) and diffusion-weighted sequences

+ Patients on each study arm will have a research DCE and DW MRI in the last week of treatment, at the discretion of the treating physician.

#a threshold of 1 cc would have excluded 2 out of 13 patients in our previous DCE-MRI study (Cao et al)** 10 cc was the median hypoperfused BV in our previous MRI-DCE study (Cao et al)

6.1 Design Overview

Patients with HN cancer referred for definitive chemo-RT and are at high risk of local-regional failure as detailed in Eligibility Criteria will be eligible. After clinically required work-up (including a baseline DCE-MRI if clinically indicated for treatment planning), patients who meet eligibility criteria and provide informed consent will be enrolled. Enrolled patients will complete protocol-specific assessments of function (observer and patient-reported measures as well as objective swallowing evaluations) and undergo baseline DCE-MRI and diffusion MRI (if not previously done for clinical purposes), with documentation of hypo-perfused tumor subvolumes and subvolumes with low apparent diffusion coefficients. Patients will subsequently begin standard treatment, consisting of concurrent chemo-radiotherapy with cisplatin dosed at 40 mg/m² (or carboplatin AUC 2 weekly, per the prescribing physician's discretion in patients unfit to receive cisplatin - see Chemotherapy in section 10.0 for details) concurrent with IMRT, planned to deliver 70 Gy to gross tumor and 56-59 Gy to subclinical disease over 35 fractions, 5 days weekly, over 7 total weeks. No patient will receive 2 treatments daily. Holidays or missed treatments of one or two days will be accounted for by treatment on weekend or extending total treatment time.

DCE-MRI and diffusion-weighted MRI will be repeated at the end of 2 weeks of chemo-RT, between RT fractions 9 and 12. Patients with hypoperfused tumor subvolumes and/or low apparent diffusion coefficients (with contiguous volume ≥ 1 cc) that are spatially stable compared to the pre-treatment DCE-MRI and Diffusion-weighted MRI (overlapping spatially with part or all of the pre-therapy subvolumes) will be randomized to either (a) IMRT replanning, with an RT boost delivered to the persistently hypoperfused/low diffusion subvolumes beginning in week 4 (boost arm), or (b) continued standard chemo-RT (control arm). Patients with no persistently hypoperfused/low diffusion tumor subvolumes, contiguous hypoperfusion/low diffusion < 1 cc in volume, or hypoperfused/low diffusion volumes that do not overlap with the hypoperfused/low diffusion volume identified on pretreatment DCE-MRI and Diffusion-weighted MRI, respectively, (in which case hypoperfusion/low diffusion are assumed to not be stable in space), will be entered onto an observational cohort and continue to receive standard chemo-IMRT.

The radiotherapy boost in the boost arm will involve increasing the planned fraction dose to 2.5 Gy for the hypo-perfused and low-diffusion subvolumes while keeping the dose to the rest of the gross disease at 2 Gy/fraction. The maximal total dose to the mucosa, which is expected to be a major dose-limiting organ, will be limited to 70 Gy. Treatments according to the new plan will start at the start of week 4, such that 4 weeks (20 fractions of 2.5 Gy each) of boosted treatments will be delivered to the hypo-perfused sub-volumes, to a total of 80 Gy over 7 weeks (2Gy x 15 fractions in the initial 3 weeks, then 2.5 Gy x 20 fractions in the latter 4 weeks). This dose will be equivalent to approximately 87 Gy delivered at 2 Gy fractions to the tumor, and 85 Gy delivered at 2 Gy/fractions to late-responding tissue, using the linear-quadratic model.

The primary objective is to improve 3-year disease-free survival from an expected 50% in the control arm to 70% in the boost arm. Stopping rules are as detailed in section 24.4 and will be implemented in case of excess acute or late toxicities.

Follow-up will include observer-rated toxicities according to CTCAE version 4, patient-reported QOL (European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 and QLQ-H&N35 [48], and objective assessments of dysphagia (videofluoroscopy). Assessments of tumor response and disease status will be performed according to standard care.

7.0 INITIAL CLINICAL EVALUATION (WITHIN 4 WEEKS PRIOR TO ENROLLMENT)

- 7.1 Complete history and physical examination, multidisciplinary examination by Radiation Oncology, Medical Oncology and any department treating with head and neck surgery and/or maxillofacial surgery, with documentation of extent of primary tumor and regional disease.
- 7.2 Complete dental evaluation in dentulous patients.
- 7.3 Completion of laboratory studies: Comprehensive panel, CBC with platelets and differential, magnesium
- 7.4 Diagnostic CT scan or MRI of the head and neck and/or PET-CT.
- 7.5 Chest X-Ray or diagnostic CT of chest/thorax as determined by the treating physicians. (CT/PET may be used as an alternative to the diagnostic chest x-ray or CT).
- 7.6 Creatinine clearance, calculated or measured
- 7.7 Baseline toxicity evaluation.
- 7.8 Audiograms for patients with hearing complaints or hearing loss at the discretion of the prescribing physician.

8.0 RADIOTHERAPY

8.1 Immobilization, imaging and target definitions

All patients will undergo immobilization using thermoplastic mask as described previously [49] or another device providing similar or better immobilization. Targets will be defined on the planning CT images. Patients with tumors near the base of skull will undergo diagnostic MRI in addition to CT to aid in target delineation. The targets will consist of the primary tumor and lymph nodes containing metastases (gross tumor volume, GTVs), as well as lymph node groups at risk of metastases and the postoperative tumor bed, where applicable (clinical target volumes, CTVs). The GTVs will be expanded to yield the corresponding CTVs according to clinical assessment in each case. All CTVs will be expanded uniformly by 0.3 cm to yield the corresponding planning target volumes (PTVs). Organs at risk (OARs) that will be defined and contoured for each case for IMRT optimization will include the parotid and submandibular glands, lips, oral cavity (encompassing the oral surfaces of the lips, cheeks (buccinator muscle), hard and soft palate, tongue, base of tongue and floor of mouth), glottic larynx, pharyngeal constrictor muscles, upper esophagus, spinal cord, and mandible. The brain stem, eyes, optic nerve and optic chiasm will be contoured and specified if the target lies in vicinity to these structures. Additional OARs may be defined in specific cases as clinically indicated.

8.2 Initial Treatment planning

All targets will be treated in each treatment fraction. The planning objectives will be adequate target irradiation and achieving maximal sparing of OARs, as per the optimization goals described below. Adequate PTV coverage and relative dose homogeneity, however, will be constraints which will bear a higher weight in optimization and will usually override

noninvolved tissue sparing goals, with the exception of the constraints on the spinal cord and non-involved lips, for which the highest priority will be assigned due to prohibitive risks of late and acute toxicity, respectively, for these two OARs. Adequate target coverage of the non-involved lymph node CTVs will prioritize below the sparing constraints for the glottic larynx, inferior pharyngeal constrictor muscle, and upper esophagus, as per our routine clinical practice. Sparing of the remaining OARs will be prioritized below that of the CTVs.

8.3 Target Doses:

- 8.3.1 PTV1 (Gross tumor): 70 Gy in 35 fractions
- 8.3.2 PTV2 (High risk subclinical targets): 59 Gy in 35 fractions
- 8.3.3 PTV3 (Low risk subclinical targets): 56 Gy in 35 fractions

8.4 Optimization goals will be:

- 8.4.1 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.
- 8.4.2 The maximal dose to the spinal cord, expanded 0.5 cm, will be < 50 Gy, to the non-expanded cord < 45 Gy, to the optic pathways < 50 Gy and to the brainstem <54 Gy.
- 8.4.3 Mean dose to each parotid gland will be < 24 Gy
- 8.4.4 Mean dose to each submandibular gland will be < 30 Gy
- 8.4.5 Mean dose to the non-involved oral cavity will be < 30 Gy
- 8.4.6 Mean dose to the non-involved glottic larynx will be < 20 Gy
- 8.4.7 Mean dose to the non-involved upper and middle pharyngeal constrictors will be < 50 Gy
- 8.4.8 Mean dose to the non-involved lower pharyngeal constrictors and esophagus will be < 20 Gy
- 8.4.9 Maximal dose to the mandible will be <70 Gy or < 105% of the prescribed dose delivered to a volume of at least 0.5 cc, whichever is lower.
- 8.4.10 Mean dose to the lips will be < 30 Gy
- 8.4.11 Maximum dose to the eyes will be < 40 Gy
- 8.4.12 Maximal dose to the brachial plexus will be < 65 Gy
- 8.4.13 Maximal dose to each cochlea will be < 40 Gy

8.5 The planning process:

- 8.5.1 When target expansion to yield the PTV causes its extension beyond the skin contour, incorporation of zero dose (outside the tissue) should be avoided in the PTV dose calculations. This may be achieved by editing the PTV or by taking into account only the PTV residing within the external contour, in DVH calculations.

8.6 Planning of the adaptive boost doses (Boost arm only)

- 8.6.1 The IMRT boost plan will be identical to the original plan with the following modification: Hypo-perfused and low-diffusion sub-volumes (Hypo-GTVs) within

the gross tumor will be defined and delineated on the pre-therapy and the 2-week DCE-MRI and diffusion-weighted MRI. After registration of the pre-therapy and the 2-week MRI data sets, an overlapping hypoperfused and low diffusion sub-volumes will be defined. The overlapping hypoperfused and low-diffusion subvolume (=pre-therapy hypoperfused and low diffusion subvolume which did not become perfused or increased diffusion after 2 weeks of therapy, HypoGTV) will be transferred to the planning CT after registration. If there is no hypoperfused and/or low diffusion sub-volume at 2 weeks, no contiguous hypoperfused and /or low diffusion subvolume < 1 ml, or no overlap between the hypoperfused and/or low diffusion subvolumes from 2 weeks and pre-MRI, the patient will not be randomized and will be assigned to the observational cohort to continue standard chemo-RT.

- 8.6.2 The adaptive new plan will deliver 2.5 Gy per fraction to the HypoGTVs while the rest of the PTVs receive 2 Gy fractions, beginning week 4 (fraction 16) for the remaining 20 fractions. The planning of the boost will limit the mucosal fraction doses to ≤ 2 Gy, which will limit total mucosal dose to ≤ 70 Gy. Non-resectable lymph node GTVs will be planned in the same manner. For patients in whom delivery of the full boost dose of 2.5 Gy per fraction to the HypoGTVs will result in mucosal dose exceeding 2 Gy per fraction, the boost dose to portions of the HypoGTVs will be reduced as necessary such that the mucosal ≤ 2 Gy per fraction limit is not exceeded.

9.0 MRI

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.

9.1 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), [50] 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, [51]

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

(1)

is to be minimized. 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 , \bar{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 kernel, 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:

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

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, 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 discrete 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.

9.2 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 as follows:

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

where S is the DW image at b-values of $b_0=0$ and $b_1=800 \text{ s/mm}^2$.

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 ($\Delta ADC = \text{mid-treatment ADC} - \text{pre-treatment ADC}$) 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 [$= \times 10^{-5} \text{ mm}^2/\text{s}$] will be designated as significantly increased. Voxels whose ADC values significantly decreased by more than $25 \times 10^{-5} \text{ mm}^2/\text{s}$ (i.e. $\Delta ADC < -25 \times 10^{-5} \text{ mm}^2/\text{s}$) 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 ΔADC s (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.

9.3 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.

10.0 CHEMOTHERAPY (BOTH ARMS A AND B)

NOTE: Carboplatin may be substituted for cisplatin at any time if patients are not candidates for cisplatin or are not able to tolerate cisplatin secondary to toxicity, as deemed necessary by the patient's prescribing medical oncologist. Missed chemotherapy doses will not be made up at a later time.

- 10.1 Cisplatin 40 mg/m² administered as an IV infusion will be delivered prior to radiotherapy on day 1 of each week of chemoradiation, typically on Mondays, but other days are allowed if judged necessary by the treating medical oncologist. Chemotherapy schedule will not be affected if radiotherapy is held (as judged by the treating medical oncologist)
 - 10.1.1 Patients considered medically unfit to receive cisplatin as determined by the prescribing physician (i.e. due to creatinine clearance < 60 cc/min, hearing impairment < 30 decibels, or neuropathy > grade 1) will receive carboplatin (AUC 2) via IV infusion on day 1 of each week of chemoradiation
- 10.2 An aggressive antiemetic regimen is required before the administration of cisplatin, consisting of a neurokinin 1 antagonist, serotonin (5-HT₃) antagonist and a steroid (dexamethasone). Alternative antiemetic regimens may also be administered at the discretion of the prescribing physicians.
- 10.3 Pre-cisplatin hydration: normal saline plus 1 gram/L Magnesium Sulfate plus KCl 20 mEq/L i.v. infusion at 500 mL/hr x 3 hours before cisplatin. Alternative pre-hydration regimens may also be administered at the discretion of the prescribing physicians.
- 10.4 Mannitol 12.5 gm i.v. bolus may be given immediately prior to cisplatin, followed by 25 gm of mannitol in 500 mL of normal saline with cisplatin, as deemed necessary by the prescribing physician.
- 10.5 Post-cisplatin: Normal saline plus KCl 20 mEq/L plus MgSO₄ 1 gm/L at 500 mL/hr x 3 hours. Alternative post-hydration regimens may also be administered at the discretion of the prescribing physicians.

11.0 FDG-PET/CT

Patient Preparation

FDG-PET/CT will be performed prior to treatment initiation per clinical indications, and at approximately 8-12 days after commencement of chemo-radiation therapy (RT). In preparation for FDG PET/CT imaging at baseline (pre-treatment) and during EBRT, all patients will be fasted for >4-6 hours and have glucose levels <250 mg/dL at the time of FDG injection.

Imaging Acquisition

At least sixty minutes following intravenous administration of 300 MBq (8 mCi) of FDG, sequential CT and PET imaging will be performed from the vertex of the skull to the mid thigh on an integrated PET/CT scanner (Siemens Biograph T6; Siemens Medical Solutions, Hoffman Estates, IL, USA).

Per institutional protocol, helical CT from skull vertex to mid-thigh will be performed (CareDose 4D, reference mAs 50, kV 120, 5 mm collimation, pitch 1.0), followed by whole body PET with multiple overlapping bed positions from skull vertex to mid-thigh. Immediately thereafter, with the patient remaining still, 100 ml of non-ionic radioopaque contrast is administered intravenously and dedicated head and neck helical CT from skull base to thoracic inlet is performed (CareDose 4D, reference mAs 150, kV 120, 2 mm collimation, pitch 0.8).

Attenuation-corrected FDG-PET tomographic images are reconstructed (TrueD, iterative reconstruction 3 orders, 24 subsets, Gaussian filter 5.0, zoom 1.0) and co-registered to both the whole body and the contrast-enhanced head and neck CT. Co-registered non-contrast enhanced CT and attenuation corrected FDG PET images will be reviewed on a workstation using software with fusion capability (MedImage; MedView Pty, Canton, MI, USA) by a Nuclear Medicine Physician (KKW) providing a single read per study.

Imaging Interpretation and SUV Measurement

Objective quantification of FDG uptake in regions of interest (ROI) will be defined for each primary tumor and for cervical lymph nodes (LNs) displaying FDG uptake above background using the corresponding CT images for anatomic orientation. The maximum standardized uptake values (SUV_{max}) for the primary tumor and for the involved LN with the highest SUV_{max} on the pre-treatment and during PET/CT will be recorded. Additional parameters for investigation will include SUV_{peak} , total glycolytic volume (TGV).

Qualitative response during RT will be categorized into four bins according to metabolic response criteria primarily based on visual assessment: progressive disease (PD), stable disease (SD), partial response (PR), complete response (CR). The actual percentage decline of SUV_{max} and SUV_{peak} will be analyzed as a continuum.

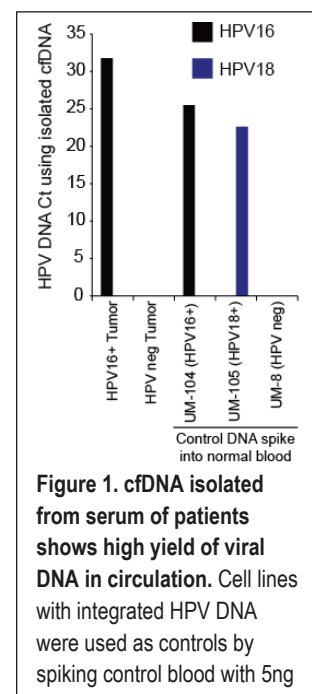
Liquid Biopsy: cfDNA: Experimental design: We will isolate ctDNA from blood samples of patients and perform integrative targeted sequencing.

12.0 CIRCULATING DNA LIQUID BIOPSY

Blood will be collected using BCT or PAXgene tubes at pre-defined intervals (pre-therapy, at 2 and 4 weeks after therapy started, at the end of therapy, and at 3, 6, 12 months post therapy) for each patient. At each blood draw, 6 ml of whole blood will be obtained in one 10 ml EDTA or PAXgene collection tube for the ctDNA analysis. We will then use the QIAamp Circulating Nucleic Acid Kit will be used to extract and purify DNA or RNA from cell-free plasma as in Fig 1 (which shows relative cfDNA analysis of HPV16 or control DNA content isolated from our index HPV16 positive patient at the time of surgery as compared to cfDNA of a stage matched HPV negative patient isolated at surgery, representative qPCR data shows detectable levels in circulation). Trizol solution combined with RNeasy Mini Kit (Qiagen) will be used to extract and purify total RNA from cfDNA fractions depending on the blood volume. At least 6mL blood per time point will be used for DNA/RNA extraction and protocols optimized by our group which has been used to isolate assayable DNA (median 25 ng) and RNA (median 20 ng) quantified using the Qubit fluorometer. As little as 2mL blood yields sufficient DNA and RNA for the studies proposed herein.

13.0 EVALUATION OF RESPONSE TO TREATMENT

- 13.1 Evaluation of tumor extent will be recorded for the primary tumor and regional nodes at each follow up interval. PET-CT scans will be performed 10 to 14 weeks after the completion of therapy to assess response and at 11 to 13 months following treatment.
- 13.2 A patient will be considered to have a complete response (CR) if there is no measurable or palpable tumor either on clinical or radiographic (CT-PET scan) examination assessed within 3 months after the completion of treatment. Complete response will be defined as complete disappearance of disease or residual radiographic abnormality that is not considered to be tumor.
- 13.3 Patients with any nodes who are PET-CT positive at 12 weeks (+/- 1 month) RT may be considered for neck dissection. Patients with palpable residual nodes at 3 months whose PET-CT shows a complete response (CR) may undergo clinical observation and periodic PET scans according to the judgment of the treating clinician
- 13.4 Clinical examinations will be performed as comparable to clinical practice: at approximately 1 month after the completion of therapy and then every 2 months during years 1 and 2, and at 3-month intervals during year 3, after which follow-up will be performed according to clinical practice. Allowable windows for these exams are +/- 1 month. Clinical examinations will be performed by medical oncology, radiation oncology, and/or surgical oncology. To meet the examination requirements, patients need to be seen by at least one discipline (but not all three) during the aforementioned time intervals.
- 13.5 Patients with tumor progression or recurrence will be followed as clinically indicated



14.0 DOSE DELAYS AND TREATMENT MODIFICATIONS

Non- Hematologic Toxicity	Action Taken
Abdominal Pain/Nausea/Vomiting	See Section 12.1 of the Protocol
<ul style="list-style-type: none"> Total bilirubin is > 2.5 x ULN AST and/or ALT is > 2.5 x ULN Alkaline phosphatase ≥ 2.5 x ULN and AST and 	<p>Step 1: Interrupt chemotherapy until the toxicity has resolved, up to 2 weeks (14 days). If not resolved at 14 days, then radiation will continue without chemotherapy.</p> <p>Step 2: Cisplatin should be</p>

ALT is > 2.5 x ULN	<p>reduced by 10 mg/m² and Carboplatin by an AUC 0.5.</p> <p>Monitor as clinically indicated.</p>
Hematologic Toxicity	
<ul style="list-style-type: none"> • Neutrophil count is < 1000 cells/ mm³ • Platelet count is < 75,000 cells/mm³ 	<p>Step 1: Interrupt chemotherapy until the toxicity has resolved to ≤ Grade 1 or pre-therapy baseline, up to 2 weeks (14 days). If not resolved at 14 days, then radiation will continue without chemotherapy.</p> <p>Step 2: Restart chemotherapy; monitor as clinically indicated.</p>
<ul style="list-style-type: none"> • Grade 4 neutropenia (< 500 cells/mm³) lasting 7 days or more • Grade 3 or 4 neutropenia with an oral temperature of at least 38.5°C 	<p>Step 1: Interrupt chemotherapy until resolved to ≤ Grade 1, up to 2 weeks (14 days). If not resolved at 14 days, then radiation will continue without chemotherapy.</p> <p>Step 2: At discretion of medical oncology provider, Cisplatin reduced by 10 mg/m² and carboplatin by AUC 0.5.</p> <p>Monitor as clinically indicated.</p>
Other Toxicities	
<ul style="list-style-type: none"> • Any Grade 1 	Continue chemotherapy

<ul style="list-style-type: none"> Any Grade 2 or 3, if clinically significant with the exception of toxicities expected from chemo-RT such as grade 2-3 mucositis, skin toxicity, transient nausea/vomiting, dysphagia/esophagitis, or other toxicities judged to be prevalent in standard clinical practice. 	<p>Step 1: Interrupt chemotherapy up to 2 weeks (14 days), until toxicity resolves to \leq Grade 1. If not resolved at 14 days, then radiation will continue without chemotherapy.</p> <p>Step 2: Cisplatin should be reduced by 10 mg/m² and Carboplatin by an AUC 0.5.</p> <p>Monitor as clinically indicated.</p>
<ul style="list-style-type: none"> Any recurrent Grade 2 or 3 after two (2) dose reductions, if clinically significant toxicities expected from chemo-RT such as grade 2-3 mucositis, skin toxicity, transient nausea/vomiting, dysphagia/esophagitis, or other toxicities judged to be prevalent in standard clinical practice (see above) 	<p>Discontinuation of chemotherapy and continue RT and follow-up per protocol.</p>
<ul style="list-style-type: none"> Any Grade 4 attributable to chemotherapy with the exception of grade 4 neutropenia 	<p>Discontinuation of chemotherapy and continue RT and follow-up per protocol.</p>
<p>NOTE: Carboplatin may be substituted for cisplatin at any time if patients not able to tolerate cisplatin secondary to toxicity, as deemed necessary by the patient's prescribing medical oncologist.</p>	
<p>See Section 13.1 for additional guidelines</p>	

14.1 Guidelines for Nausea, Vomiting or Abdominal Pain

- 14.1.1 If a patient has \geq Grade 2 nausea, \geq Grade 2 vomiting, or any abdominal pain that lasts for longer than 48 hours, chemotherapy should be held and the following actions are recommended:
- Physical examination, including the performance of vital signs
 - Screening abdominal radiography to include an abdominal series to exclude I
ileus, SBO, or pneumatosis intestinalis
 - Consideration for obtaining a CT scan with contrast of the abdomen should be

made based on clinical judgment

4. If ileus, SBO, or pneumatosis intestinalis are excluded, dosing of chemotherapy may be reinstated following the provisions in Section 8.0, Dose Delays and Dose Modifications for Toxicity. If a patient is determined to have ileus, SBO, or pneumatosis intestinalis, dosing of chemotherapy will be held and expectant management with supportive care is recommended, unless clinical signs or symptoms are present that suggest septicemia or abdominal catastrophe that warrants surgical management. No further chemotherapy can be administered following recovery from these events.

14.2 Radiation Dose Modification

14.2.2 No radiation dose modification or delay will be planned unless clinically necessary according to the judgement of the treating physician. Per Radiation Oncology department procedures, radiation is not given over holidays. Compensation for missed treatments (up to three days) will be determined by treating physician. Delays of treatment longer than three days will be considered deviations.

15.0 DRUG INFORMATION

15.1 Cisplatin

15.1.1 Biochemistry: cis-diamminedichloroplatinum (cis-DDP) is a heavy metal compound which a divalent platinum molecule binds two potential leaving groups, the chloride ions. Two NH₃ groups are bound in a firm covalent linkage in transposition to the chloride moieties. Both chloride ions undergo a slow displacement by water, generating a positively charged aquated complex, which is capable of interacting with a nucleophilic site on DNA, RNA, or protein.

15.1.2 Pharmacokinetics: The dominant action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25-49 minutes, and a secondary phase ranging from 58-73 hours. This prolonged phase is due to protein binding, which exceeds 90% of the activity in the second phase. Urinary excretion is incomplete with only 27-45% excreted in the first five days. Largely unchanged drugs are the initial fraction excreted. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

15.1.3 Pharmaceutical Data:

15.1.3.1 Formulation: Cisplatin (Platinol[®]) is available as an aqueous solution in a concentration of 1 mg/mL.

15.1.3.2 Storage and Stability: The aqueous solution is stored at room temperature protected from light. Cisplatin is stable in mannitol/NS/D5W mixtures for 48 to 72 hours at room temperature and up to 72 hours when refrigerated (per Trissel's Handbook on Injectable Drugs, 11th edition).

15.1.4 Human Toxicology: Human toxicity from cisplatin includes: nausea, vomiting, anorexia, loss of taste, renal toxicity (with an elevation of BUN, creatinine, and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss, which initially is in the high-frequency range, as well as tinnitus), peripheral

neuropathy, allergic reactions, and uricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white blood cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy.

- 15.1.5 Supplier: Cisplatin is commercially available, and should therefore be purchased by the third party.

15.2 Carboplatin

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

15.2.2 Pharmaceutical Data

15.2.2.1 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.

15.2.2.2 Formulation: Carboplatin is supplied as a sterile lyophilized powder in single-dose vials containing 150 mg and as 10mg/mL solution in 5, 15, 45, and 60mL vials. Each lyophilized powder vial contains equal parts by weight of carboplatin and mannitol. Immediately before use, the content of the 150 mg lyophilized powder vial must be reconstituted with 15 mL of either sterile water for injection, D5W, or normal saline to a concentration of 10 mg/mL. Carboplatin solution can be further diluted to concentrations as low as 0.5 mg/mL with D5W or normal saline injection.

15.2.2.3 Storage and Stability: Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at controlled room temperature (15-30oC), 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.

- 15.2.3 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.

15.2.4 Administration: Intravenous infusion.

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

16.0 EVALUATION OF TOXICITY AND QUALITY OF LIFE

- 16.1 Validated quality of life questionnaires: EORTC QLQ-C30 and EORTC QLQ-H&N35 (Appendix B) will be given to patients before and periodically after radiation (1, 3, 6, 12, 18, 24 and 36 months, with a +/- 1 month window for each). All Head and Neck Common Toxicity Criteria Adverse Events (CTCAE, v.4.0) observer related items will be gathered weekly during radiation and at every follow-up clinic visit through 3 years. As part of data collection related to the quality of life measures, pre and post-treatment employment status will also be recorded, as well as Performance Status Scale. Patients may be asked for this information during a clinic visit or contacted via phone. The study team will attempt to obtain this information from all enrolled patients.
- 16.2 Objective evaluation of swallowing will be performed by videofluoroscopy and esophagogram. A baseline study will be performed either before RT starts or on one of the first five days of RT. Three follow-up studies will be done: one study at 3 following RT completion (+/- 1 month), one study at 12 months following RT completion (+/- 1 month), and one study at 24 months following RT completion (with the acceptable window of 2 months prior or 6 months post). Each subject will be asked to swallow various food consistencies in varying amounts (5-15 ml). The consistencies included thin liquid barium (diluted with water) followed with non-diluted barium, followed with a puree, soft food (fruit mixed with barium) and a solid (shortbread cookie) coated with barium. The examinations will be recorded and analysis of the 3 phases of swallowing: oral, pharyngeal and esophageal will be made. Assessment will focus on bolus manipulation and control, bolus passage including cohesion, motility, and timing. The timing or duration of each swallowing phase will be determined. Also, the amount and incidence of aspiration and penetration, laryngeal sensation (response to penetrant/aspirate) and residue/pooling after the swallow will be recorded. Laryngeal sensation will be determined to be good, reduced or poor. Reduced sensation would be consistent with a cough reflex that is delayed or intermittent. Poor sensation is defined when subjects elicit no spontaneous cough reflex or throat clear. These subjects are considered to be "silent" aspirators.

17.0 Study Calendar

Assessment	Pre-Treatment	Day 10-16	Day 28 (+/- 3 days)	Weekly During RT	12-14 wks post chemo-RT (+/- 1 mo)	Follow Up ⁴
H&P/Physician assessment*	X			X	X	X
HPV or p16 Testing	X					
CT or diagnostic MRI of head and neck ¹	X					
PET-CT	X	X			X ²	X ²
CT Thorax or Chest X-Ray ³	X					
DCE&diffusionMRI	X ⁹	X ⁵		X ¹⁰		
Labs: Cbcpd, Comp, magnesium, calculated or measured CrCl	X			X		
Audiogram as deemed necessary	X					
Begin initial RT plan	X					
Begin boost RT plan (patients randomized to Arm A /Boost only)			X			
Dental Evaluation	X					
Toxicity ⁶ and QOL ⁷ Evaluation	X			X	X	X
Videofluoroscopy ⁸	X				X	X

Cisplatin (40 mg/m ²) or Carboplatin (AUC 2) Arms A and B				X		
cfDNA ¹¹	X ¹¹			X ¹¹		X ¹¹

*

H&P with PE required by otolaryngology, Radiation Oncology, and Medical Oncology pretreatment only. During follow up, clinic visits may be completed in person or virtually via phone or video visit, as per standard clinical practice.

¹ CT or MRI of Head and Neck are not required if a PET-CT was performed.

² Restaging PET-CT will be obtained at 10-14 weeks and at 11-13 months following treatment

³ CT Thorax or Chest X-Ray are not required if a PET-CT was performed.

⁴ Follow Up: Examinations will be performed as comparable to clinical practice: at 1 month after the completion of therapy and then approximately every 2 months during years 1 and 2 (+/- 6 weeks), and at approximately 3-month intervals during year 3 (+/- 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.

⁵ DCE and diffusion MRI after approximately 2 weeks to be performed after delivery of RT fraction 9 and before delivery of RT fraction 12

⁶ Toxicity evaluation will be collected at each visit.

⁷ Quality of Life Questionnaires will be given to patients at baseline and at follow-up visits at 1, 3, 6, 12, 18, 24 and 36 months. 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. QOLs may be mailed to the patient, or a study coordinator may call the patient to complete the questionnaire.

⁸ Pre treatment videofluoroscopy will be performed prior to treatment or during the first week of treatment. Follow-up videofluoroscopy will be done at 3 and 12 months after therapy, +/- 1 month, and at 24 months after therapy, with an allow windows of 22 to 30 months.

⁹ If a patient will have a clinical MRI scan for simulation, the patient is not required to have an additional MRI scan for this research study.

¹⁰ A third research DCE and DW MRI will be performed at the end of treatment, at the discretion of the treating physician.

¹¹ cfDNA will be checked pre, at 2 and 4 weeks of radiation therapy, end of radiation therapy, and at 3, 6, 12 months post radiation therapy. If the corresponding clinic visit is done virtually in lieu of an in-person visit, cfDNA may not be collected. Missing correlative blood draws due to virtual visits will not be reported as deviations.

18.0 CRITERIA FOR DISCONTINUATION OF TREATMENT

18.1 Unacceptable adverse event(s), intercurrent illness which prevents further administration of treatment, patient preference, progressive disease, life threatening or other unacceptable drug-related toxicity, changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigators

18.2 Stopping rules are specified in Statistics (section 24.4)

18.3 Off Study Conditions: Patients may be removed from study for the following conditions. Once off study, patients will no longer follow the study calendar and toxicities and adverse events will no longer be collected for these subjects:

- 18.3.1 Patient withdraws consent
- 18.3.2 Patient is unable or unwilling to comply with protocol requirements
- 18.3.3 Patient exhibits tumor progression (Note: unless patient specifies, data from these subjects may still be used for analysis, up to the point when tumor progression occurred).
- 18.3.4 Patient begins another therapy (outside of a surgical intervention to remove his/her disease).
- 18.3.5 Physician discretion.

19.0 OTHER THERAPY

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented as concomitant medication.

20.0 PATIENT SCREENING AND REGISTRATION

Patient registration for this trial will be centrally managed by the Coordinating Center of The University of Michigan Comprehensive 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 provided by the Coordinating Center.

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 Clinical Trials Office, either by fax or by email to CTSU-Oncology-Multisite@med.umich.edu.

A Multi-Site Coordinator of the Coordinating Center, 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 Section Two of the Eligibility Worksheet signed and dated by the registrar, will be faxed back or emailed 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.

21.0 MULTISITE DATA MANAGEMENT

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based Velos data management 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 Velos
 - Subject Status
 - Demographics
- During study participation
 - All data should be entered online within 10 business days of data acquisition.
[Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 21 of the protocol.]

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

22.0 REPORTING ADVERSE EVENTS

All Head and Neck toxicities, regardless of grade and attribution, will be collected in the study database from the initiation of treatment to the end of study. These include but are not limited to: dysphagia, mucositis, xerostomia, and salivary gland changes. All Non-Head and Neck toxicities grade 2 or greater will be collected from the initiation of treatment until 30 days following the last day of treatment. Abnormal laboratory findings will only be collected if they cause a change in treatment. Serious adverse events will continue to be followed until resolution or clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

22.1 Definitions: The definitions of adverse events (AEs) and serious adverse events (SAEs) are given below. The following definitions of terms are guided by the International Conference on Harmonization and the US Code of Federal Regulations and are included here verbatim. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

22.1.1 Adverse Events (AE) - An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (i.e. abnormal laboratory finding, symptom, or disease temporally associated with the use of a medicinal (investigational) product), whether or not related to the medicinal (investigational) product. Examples of an AE include:

- 22.1.1.1 Significant or unexpected worsening or exacerbation of the condition/indication under study.
 - 22.1.1.2 Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity (grade) of the condition.
 - 22.1.1.3 New conditions detected or diagnosed after investigational treatment delivery even though may have been present prior to the start of the study.
 - 22.1.1.4 Signs, symptoms, or the clinical sequelae associated with a suspected interaction of the investigational treatment with a concomitant medication.
 - 22.1.1.5 Any medical condition or laboratory abnormality with an onset date before initial treatment administration is considered to be pre-existing in nature.
 - 22.1.1.6 Any known pre-existing conditions that are ongoing at time of study entry, and any events of Grade 3 or 4 severity that occur up to 30 days before study entry (even if resolved prior to study entry) should be considered medical history and recorded in the appropriate section of the case report form.
 - 22.1.1.7 In addition to new events, any increase in the frequency or severity (i.e. toxicity grade) of a pre-existing condition that occurs after the patient begins chemo-radiation is also considered an adverse event.
- 22.1.2 Serious Adverse Events (SAE) - A serious adverse event is an AE which occurs after the initiation of chemo-RT, during treatment, or within 30 days of the last day of chemo-RT that fulfills one or more of the following criteria regardless of cause or assessed relationship to therapy. Any untoward medical occurrence that at any dose:
- 22.1.2.1 Results in death,
 - 22.1.2.2 Is life-threatening (NOTE: The term 'life-threatening' in the definition of 'serious' refers to any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.)
 - 22.1.2.3 Requires inpatient hospitalization or prolongation of hospitalization (NOTE: In general, hospitalization signifies that the patient or subject has been detained (usually involving at least an overnight stay) at the hospital for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE. Planned hospitalization for surgical procedures, either related or unrelated to the patients cancer is not considered a serious adverse event)

22.1.2.4 Results in persistent or significant disability/incapacity (NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions.

22.1.2.5 Is a congenital abnormality/birth defect.

Or

22.1.3 Important medical events

22.1.3.1 Events which may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

22.2 Adverse Event Reporting Requirements

22.2.1.1 *Serious Adverse Event Reporting*

Serious Adverse Events meeting the reporting guidelines in 20.2.1.2 will be reported to the IRB using the CTSU Oncology Serious Adverse Event Form. SAEs will also be reported to the multi-site coordinator and the Principal Investigator. AEs reported as Serious Adverse Events must also be reported in routine study data submissions including the Data and Safety Monitoring Report, in addition to the IRB.

22.2.1.2 *Serious Adverse Event Reporting Timeline*

The Principal Investigator must be notified within 10 business days of study team's knowledge of any event meeting the criteria and definition of a serious adverse event.

All Serious Adverse Events that are unexpected and possibly related (definite, probable or possible) to study treatment will be reported to the IRB using CTSU Oncology Serious Adverse Event form.

The following types of hospitalizations do not constitute SAEs:

20.2.1.2.1 Hospitalization or Emergency room visits secondary to expected cancer morbidity: Admission for palliative care or pain management

20.2.1.2.2 Planned hospitalizations for surgical procedures, either related or unrelated to the patient's cancer.

22.2.1.3 *Grading of Adverse Events*

22.2.1.3.1 The severity of all adverse events and laboratory abnormalities will be graded according to the US National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).

22.2.1.4 *Relationship to Chemo-RT Related Event*

Any adverse event that has a temporal relationship to the research intervention, follows a known or suspected pattern of response, and for which an alternative cause may not be present, is definitely, probably, or possibly associated with the research intervention. Investigator needs to judge relatedness and be prepared to justify the judgment.

- 22.2.1.4.1 Definitely Related: The adverse event is clearly related to the research intervention: the adverse event has a temporal relationship to the administration of the research intervention, follows a known pattern of response, and no alternative cause is present.
- 22.2.1.4.2 Possibly Related: There is a reasonable possibility that the event may have been caused by or is linked in a significant way to the research; the adverse event has a temporal relationship to the administration of the research intervention, follows a suspected pattern of response, but an alternative cause is present.
- 22.2.1.4.3 Probably Related: The adverse event is likely related to the investigational intervention: the adverse event has a temporal relationship to the administration of the research intervention, follows a known or suspected pattern of response, but an alternative cause may be present.
- 22.2.1.4.4 Unlikely to be related: The adverse event is doubtfully related to the investigational intervention: the adverse event has a temporal relationship to the administration of the research intervention, but follows no known or suspected pattern of response, and an alternative cause is present.
- 22.2.1.4.5 Unrelated (or Not Related): The adverse event is clearly NOT related to the investigational intervention: the adverse event has no temporal relationship to the administration of the investigational or research intervention, follows no known or suspected pattern of response, and an alternative cause is present.

23.0 DATA AND SAFETY MONITORING

The Data and Safety Monitoring Committee (DSMC) of The University of Michigan Comprehensive Cancer Center (UMCCC) is the DSMC for this study. This committee is responsible for the review and monitoring the study's scientific progress, accrual rate and any serious adverse events.

At each site the study team is required to meet quarterly to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or co-investigator. Each site is required to submit the completed DSMR to the Multi-Site Coordinator at the University of Michigan Coordinating Center on a quarterly basis together with other pertinent documents.

Similarly, protocol deviations are to be documented using the Notice of Protocol Deviation Form and requires the signatures of both the sites data manager or study coordinator and the site principal investigator or co-investigator. These reports are to be sent to the University of Michigan Coordinating Center within 7 calendar days of awareness of the event and on a quarterly/ basis with the Protocol Specific Data and Safety Monitoring Report.

The Coordinating Center is responsible for collating all the Data and Safety Monitoring Reports from all the participating sites, and providing the information to the Data and Safety Monitoring Committee.

24.0 CLINICAL MONITORING PROCEDURE

Clinical studies coordinated by The University of Michigan Comprehensive Cancer Center (UMCCC) 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 UMCCC. 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 UMCCC 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 first treatment cycle. 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 if all of the following apply:

- No patient has signed the Informed Consent Form and has enrolled into the study
- Investigational agent has not been dispensed
- All investigational agent and materials have been returned as defined for the study or destroyed and accounted for properly.

25.0 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.

26.0 STATISTICAL CONSIDERATIONS

26.1 General

This is a randomized phase II trial to assess whether the adaptive RT plan described in detail above, improves disease free survival, relative to standard treatment. Patients with hypoperfused and /or low-diffusion tumor subvolumes (with contiguous volume \geq 1 cc) that are spatially stable compared to the pre-treatment MRI (overlapping spatially with part or all of the pre-therapy hypoperfused subvolumes) will be randomized in a 1:1 ratio to either standard or adaptive treatment. Randomization will be stratified by

the volume of the hypoperfused and low-diffusion subvolumes (dichotomized as $>$ or $<$ 10 cc) and by pre-therapy tumor volume (dichotomized as $>$ or $<$ 56 cc, which is the median tumor size in our advanced disease population). Patients with small or non-spatially stable hypoperfused and/or low diffusion subvolumes will not be included in primary aim analysis but will still be enrolled in an observational cohort and followed for outcome. While the numbers of such patients is likely to be small, their data will be used in analyses addressing secondary objectives. A total of 40 evaluable patients will be randomized to each arm. Patients will be considered evaluable for the primary aim if they are able to complete study treatment regardless of reductions or modifications and also 1) complete at least 3 months of follow-up post-RT or 2) die or progress within 3 months of completing treatment. Non-evaluable patients may be included in toxicity analyses but will be replaced for the primary aim.

26.2 *Justification of Design*

Several recent studies of patients with locoregionally advanced, unresectable HNC have reported DFS at 3 years to be near 50% (Allen A et al). Thus, based on an assumed DFS rate at 3 years of 50% in the control arm, we calculate the power to detect an improvement in the adaptive RT arm, to 70% DFS at 3 years. Based on an expected enrollment period of 4 years, 2 additional years of FU, an exponential loss to FU function with 10% of patients lost to FU by 2 years, and a 1-sided .10 level test, 40 patients per arm will give 83% power. Based on our preliminary data we expect approximately 8-10 (10%) of all enrolled patients to be ineligible for the week 2 randomization. These patients will be used in addressing questions of the prognostic effect of hypoperfused volumes in the secondary objectives. Although the number of these patients will be small they will allow analyses designed to detect relationships between outcome and hypoperfused volumes in the absence of intervention.

26.3 *Analysis Plan:*

Here we describe the analyses for each of the protocol objectives.

Primary Objective:

26.3.1 *Determine whether escalating the radiotherapy dose to resistant tumor subvolumes identified by persistent hypoperfusion and low diffusion on 2 week DCE-MRI (boost arm) can improve disease-free survival compared to standard chemo-RT (control arm)*

Disease free survival (DFS) time is defined as the time to disease recurrence or death, whichever occurs first. Patients who are alive without evidence of disease at the end of follow-up will be censored at the date of their last clinical follow-up. Kaplan-Meier curves with point-wise 90% confidence intervals will be generated for each treatment arm, overall and by strata. Estimates with confidence intervals will be generated from these curves for the usual summary statistics, including median DFS times and DFS at 1, 2, and 3 years. The primary analysis for this aim will utilize a 1-sided .10 level stratified log-rank test to compare the two treatment arms with respect to disease free survival. There will be two strata corresponding to the strata used in randomization.

Secondary Objectives:

26.3.2 *Compare local-regional control rates and overall survival between the two arms*

Local-regional control is defined as the absence of local-regional progression. Subjects without documented progression at the time of analysis will be censored at the last visit in which imaging was performed to assess for progression. Analysis will otherwise mirror that described above for the primary aim of DFS.

26.3.3 *Assess the site and timing of local recurrences as they relate spatially to the site and volume of the hypoperfused tumor sub-volume*

The first part of this aim is to assess the spatial relation between the site of the hypoperfused sub-volume and the site of any local recurrence. Several approaches are possible here. In simple analyses, we will assess whether the hypoperfused subvolumes overlap with the recurrence volumes (rVOI) and calculate the proportion of patients for which this is the case. Of course this proportion could be made large by increasing the size of the sub-volumes and thus making overlap more likely. Thus more quantitative assessments utilizing diagnostic testing methods will also be used. For each patient we will compute the following quantities:

P1=Proportion of the imaging sub-volume overlapping with recurrence volume (rVOI)

P2=Proportion of the non-imaging sub-volume overlapping with rVOI

If $P1 > P2$, then there will be evidence that DCE-MRI is able to determine tumor sub-volumes at high risk of recurrence. Across the population of patients, we could test whether $E[P1] > E[P2]$ using a paired t-test. One confounding factor in these analyses is dose. In the adaptive arm, high dose will be confounded with hypoperfused sub-volume, by design. Thus primary analysis of this aim will be based on data from the randomized control arm. However, even in this arm, dose varies spatially. We will adjust for the impact of dose by including it as covariate in regression models or by stratifying above calculations by dose bins.

The second part of this aim involves an assessment whether, at the patient level, the volume of the hypoperfused sub-volumes is related to the time to local recurrence. To do this we will utilize a Cox proportional hazards regression model in which volume is included as a covariate. These analyses will include patients randomized to standard treatment and patients in the observational cohort (who also receive standard treatment).

An additional complication of the proposed analyses is that the recurrence volumes are not static over time. The more frequently imaging is performed, the smaller the rVOI will be when first visualized, and the cleaner the analysis will be. Fortunately however, in head and neck cancer, recurrences tend to be small when first visualized. In addition this factor should not result in any

systematic bias relative to above analysis, but will rather add noise to the measured quantities.

26.3.4 Assess acute and late toxicities and functional outcomes

Acute and late toxicities will be summarized descriptively by grade and type for each treatment group. The proportion of patients experiencing certain toxicity types will be calculated with score based confidence intervals. Chi-square tests will be used to test whether the proportion of patients with toxicity differs between treatment groups.

26.3.5 Correlate changes in perfusion of pharyngeal constrictor muscles and other normal tissues on 2 week DCE-MRI with dosimetric parameters and toxicity/functional outcomes

Two distinct questions are of interest. First whether dose is correlated with perfusion and second whether perfusion is correlated with toxicity/function outcomes. Perfusion and dose summary measures (likely mean) will be calculated at the level of a normal tissue for each patient. Pearson or Spearman rank based correlation between the continuous dose and perfusion summary measures will be calculated. Similarly the correlation between perfusion and continuous functional measures and ordinal toxicity grades will be calculated. AUC values will be calculated for binary toxicity outcomes to quantify the ability of week 2 perfusion to discriminate between patients who do and do not develop toxicity. Null hypotheses of no relation will be tested.

26.3.6 Assess the utility of diffusion-weighted MRI in predicting tumor and tumor sub-sites at high risk of local/regional recurrence.

Statistical approaches here will mirror those described above under the first part of secondary objective 26.3.2.

Exploratory Objectives:

26.3.7 FDG-PET-based MTV after 8-12 chemo-RT fractions spatial overlap with the MRI-based high risk subvolumes: Dice similarity coefficients will be used to assess overlap.

26.3.8 Assess whether the extent of reduced FDG-PET parameters, MTV and TLG, compared with pre-RT, will be associated with tumor outcome.

This will be tested by Cox regression models for DFS where predictors will be the changes in MTV and TLG, accounting for different treatments (boost vs standard RT) and assess whether including these changes improves our ability to predict DFS beyond other variables.

26.3.9 *Assess whether the level and mutational profile of ctDNA pre, during, and after therapy is associated with tumor outcomes.*

Cox regression models will be done for DFS. Predictors will be cfDNA and boost arm and possibly interaction, then assess whether cfDNA is prognostic for DFS while accounting for different treatments (boost vs standard RT). Other baseline covariates will be added to the model to see if cfDNA improves our ability to predict outcome.

26.4 *Stopping rules*

Stopping for the current protocol will be based upon the occurrence of excessive acute toxicity in patients randomized to the boost arm of the protocol. We will stop the trial and halt enrollment if we become reasonably confident that the rate of grade 4 acute non-hematologic toxicity (as scored by CTCAE version 4) exceeds 15%, as detailed in the table below. The stopping rule specifies that the trial will stop if the number of patients with toxicity is at least as great as the number in the second column. The operating characteristics of this rule, specifically the cumulative proportion of simulated trials that stopped early, are given in the table below. For example if the true probability of toxicity is .1, just 1% of trials would stop after 10 patients, and just 3% of trials would ever stop early. On the other hand if the true probability of toxicity is 35%, there is a 50% chance of stopping after just 10% patients and a nearly 80% chance of stopping by 20 patients.

Number of Patients Evaluable for Toxicity	Threshold for Stopping	True Probability of Toxicity			
		0.1	0.25	0.35	0.5
10	4	0.01	0.22	0.5	0.84
20	6	0.02	0.44	0.78	0.98
30	7	0.03	0.7	0.95	1

27.0 REFERENCES

1. Wang, P., et al., *An approach to identify, from DCE MRI, significant subvolumes of tumors related to outcomes in advanced head-and-neck cancer*. Med Phys, 2012. **39**(8): p. 5277-85.
2. Haddad, R.I. and D.M. Shin, *Recent advances in head and neck cancer*. N Engl J Med, 2008. **359**(11): p. 1143-54.
3. Allen, A.M., et al., *Acceleration of hyperfractionated chemoradiation regimen for advanced head and neck cancer*. Head Neck, 2007. **29**(2): p. 137-42.
4. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer*. N Engl J Med, 2010. **363**(1): p. 24-35.
5. Popovtzer, A., et al., *The pattern of failure after reirradiation of recurrent squamous cell head and neck cancer: implications for defining the targets*. Int J Radiat Oncol Biol Phys, 2009. **74**(5): p. 1342-7.
6. Salama, J.K., et al., *Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma*. Int J Radiat Oncol Biol Phys, 2006. **64**(2): p. 382-91.
7. Sulman, E.P., et al., *IMRT reirradiation of head and neck cancer-disease control and morbidity outcomes*. Int J Radiat Oncol Biol Phys, 2009. **73**(2): p. 399-409.
8. Haddad, R.I.R., Guilherme, et al., *The PARADIGM trial: A phase III study comparing sequential therapy (ST) to concurrent chemoradiotherapy (CRT) in locally advanced head and neck cancer (LANHC)*. J Clin Oncol, 2012. **Vol 30**(No 15_suppl): p. 5501.
9. Ang, K.K., et al., *A randomized phase III trial (RTOG 0522) of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III-IV head and neck squamous cell carcinomas (HNC)*. J Clin Oncol, 2011. **29**(No 15_supple): p. 5500.
10. Dawson, L.A., et al., *Patterns of local-regional recurrence following parotid-sparing conformal and segmental intensity-modulated radiotherapy for head and neck cancer*. Int J Radiat Oncol Biol Phys, 2000. **46**(5): p. 1117-26.
11. Eisbruch, A., et al., *Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing*. Int J Radiat Oncol Biol Phys, 2004. **59**(1): p. 28-42.
12. Studer, G., U.M. Luetolf, and C. Glanzmann, *Locoregional failure analysis in head-and-neck cancer patients treated with IMRT*. Strahlenther Onkol, 2007. **183**(8): p. 417-23; discussion 424-5.
13. Oksuz, D.C., et al., *Recurrence patterns of locally advanced head and neck squamous cell carcinoma after 3D conformal (chemo)-radiotherapy*. Radiat Oncol, 2011. **6**: p. 54.
14. Farrag, A., et al., *Pattern of failure after helical tomotherapy in head and neck cancer*. Strahlenther Onkol, 2010. **186**(9): p. 511-6.
15. Cao, Y., *The promise of dynamic contrast-enhanced imaging in radiation therapy*. Semin Radiat Oncol, 2011. **21**(2): p. 147-56.
16. Shukla-Dave, A., et al., *Dynamic contrast-enhanced magnetic resonance imaging as a predictor of outcome in head-and-neck squamous cell carcinoma patients with nodal metastases*. Int J Radiat Oncol Biol Phys, 2012. **82**(5): p. 1837-44.
17. Truong, M.T., et al., *Prediction of locoregional control in head and neck squamous cell carcinoma with serial CT perfusion during radiotherapy*. AJNR Am J Neuroradiol, 2011. **32**(7): p. 1195-201.
18. Chawla, S., et al., *Prediction of disease-free survival in patients with squamous cell carcinomas of the head and neck using dynamic contrast-enhanced MR imaging*. AJNR Am J Neuroradiol, 2011. **32**(4): p. 778-84.
19. Cao, Y., et al., *Early prediction of outcome in advanced head-and-neck cancer based on tumor blood volume alterations during therapy: a prospective study*. Int J Radiat Oncol Biol Phys, 2008. **72**(5): p. 1287-90.

20. Zima, A., et al., *Can pretreatment CT perfusion predict response of advanced squamous cell carcinoma of the upper aerodigestive tract treated with induction chemotherapy?* AJNR Am J Neuroradiol, 2007. **28**(2): p. 328-34.
21. Hermans, R., et al., *Tumor perfusion rate determined noninvasively by dynamic computed tomography predicts outcome in head-and-neck cancer after radiotherapy.* Int J Radiat Oncol Biol Phys, 2003. **57**(5): p. 1351-6.
22. Jansen, J.F., et al., *Noninvasive assessment of tumor microenvironment using dynamic contrast-enhanced magnetic resonance imaging and 18F-fluoromisonidazole positron emission tomography imaging in neck nodal metastases.* Int J Radiat Oncol Biol Phys, 2010. **77**(5): p. 1403-10.
23. Cho, H., et al., *Noninvasive multimodality imaging of the tumor microenvironment: registered dynamic magnetic resonance imaging and positron emission tomography studies of a preclinical tumor model of tumor hypoxia.* Neoplasia, 2009. **11**(3): p. 247-59, 2p following 259.
24. Nehmeh, S.A., et al., *Reproducibility of intratumor distribution of (18)F-fluoromisonidazole in head and neck cancer.* Int J Radiat Oncol Biol Phys, 2008. **70**(1): p. 235-42.
25. Lin, Z., et al., *The influence of changes in tumor hypoxia on dose-painting treatment plans based on 18F-FMISO positron emission tomography.* Int J Radiat Oncol Biol Phys, 2008. **70**(4): p. 1219-28.
26. Lee, N., et al., *Prospective trial incorporating pre-/mid-treatment [18F]-misonidazole positron emission tomography for head-and-neck cancer patients undergoing concurrent chemoradiotherapy.* Int J Radiat Oncol Biol Phys, 2009. **75**(1): p. 101-8.
27. Rischin, D., et al., *Phase I trial of concurrent tirapazamine, cisplatin, and radiotherapy in patients with advanced head and neck cancer.* J Clin Oncol, 2001. **19**(2): p. 535-42.
28. Olteanu, L.A., et al., *Evaluation of deformable image coregistration in adaptive dose painting by numbers for head-and-neck cancer.* Int J Radiat Oncol Biol Phys, 2012. **83**(2): p. 696-703.
29. Galban, C.J., et al., *Prospective analysis of parametric response map-derived MRI biomarkers: identification of early and distinct glioma response patterns not predicted by standard radiographic assessment.* Clin Cancer Res, 2011. **17**(14): p. 4751-60.
30. Ellingson, B.M., et al., *Volumetric analysis of functional diffusion maps is a predictive imaging biomarker for cytotoxic and anti-angiogenic treatments in malignant gliomas.* J Neurooncol, 2011. **102**(1): p. 95-103.
31. Barajas, R.F., Jr., et al., *Diffusion-weighted MR imaging derived apparent diffusion coefficient is predictive of clinical outcome in primary central nervous system lymphoma.* AJNR Am J Neuroradiol, 2010. **31**(1): p. 60-6.
32. Yamasaki, F., et al., *Glioblastoma treated with postoperative radio-chemotherapy: prognostic value of apparent diffusion coefficient at MR imaging.* Eur J Radiol, 2010. **73**(3): p. 532-7.
33. Ellingson, B.M., et al., *Graded functional diffusion map-defined characteristics of apparent diffusion coefficients predict overall survival in recurrent glioblastoma treated with bevacizumab.* Neuro Oncol, 2011. **13**(10): p. 1151-61.
34. Vandecasteele, V., et al., *Applications of diffusion-weighted magnetic resonance imaging in head and neck squamous cell carcinoma.* Neuroradiology, 2010. **52**(9): p. 773-84.
35. Srinivasan, A., et al., *Utility of pretreatment mean apparent diffusion coefficient and apparent diffusion coefficient histograms in prediction of outcome to chemoradiation in head and neck squamous cell carcinoma.* J Comput Assist Tomogr, 2012. **36**(1): p. 131-7.
36. Kim, S., et al., *Diffusion-weighted magnetic resonance imaging for predicting and detecting early response to chemoradiation therapy of squamous cell carcinomas of the head and neck.* Clin Cancer Res, 2009. **15**(3): p. 986-94.
37. Galban, C.J., et al., *A feasibility study of parametric response map analysis of diffusion-weighted magnetic resonance imaging scans of head and neck cancer patients for providing early detection of therapeutic efficacy.* Transl Oncol, 2009. **2**(3): p. 184-90.

38. Eisbruch, A., *Dysphagia and aspiration following chemo-irradiation of head and neck cancer: major obstacles to intensification of therapy*. Ann Oncol, 2004. **15**(3): p. 363-4.
39. Lauve, A., et al., *Simultaneous integrated boost intensity-modulated radiotherapy for locally advanced head-and-neck squamous cell carcinomas: II--clinical results*. Int J Radiat Oncol Biol Phys, 2004. **60**(2): p. 374-87.
40. Madani, I., et al., *Maximum tolerated dose in a phase I trial on adaptive dose painting by numbers for head and neck cancer*. Radiother Oncol, 2011. **101**(3): p. 351-5.
41. Murdoch-Kinch, C.A., et al., *Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy*. Int J Radiat Oncol Biol Phys, 2008. **72**(2): p. 373-82.
42. Little, M., et al., *Reducing xerostomia after chemo-IMRT for head-and-neck cancer: beyond sparing the parotid glands*. Int J Radiat Oncol Biol Phys, 2012. **83**(3): p. 1007-14.
43. Dijkema, T., et al., *Parotid gland function after radiotherapy: the combined michigan and utrecht experience*. Int J Radiat Oncol Biol Phys, 2010. **78**(2): p. 449-53.
44. Feng, F.Y., et al., *Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results*. J Clin Oncol, 2010. **28**(16): p. 2732-8.
45. Feng, F.Y., et al., *Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures*. Int J Radiat Oncol Biol Phys, 2007. **68**(5): p. 1289-98.
46. Eisbruch, A., et al., *Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: swallowing organs late complication probabilities and dosimetric correlates*. Int J Radiat Oncol Biol Phys, 2011. **81**(3): p. e93-9.
47. Truong, M.T., et al., *Correlating computed tomography perfusion changes in the pharyngeal constrictor muscles during head-and-neck radiotherapy to dysphagia outcome*. Int J Radiat Oncol Biol Phys, 2012. **82**(2): p. e119-27.
48. Bjordal, K., et al., *Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35*. J Clin Oncol, 1999. **17**(3): p. 1008-19.
49. Marsh, R., et al., *Design and analysis of an immobilization and repositioning system for treatment of neck malignancies*. Med Dosim, 1997. **22**(4): p. 293-7.
50. Wismuller, A., et al., *Cluster analysis of dynamic cerebral contrast-enhanced perfusion MRI time-series*. IEEE Trans. Med. Imag., 2006. **25**(1): p. 62-73.
51. Chen, S.C. and D.Q. Zhang, *Robust image segmentation using FCM with spatial constraints based on new kernel-induced distance measure*. IEEE Trans. Syst. Man Cybern. B Cybern., 2004. **34**(4): p. 1907-1916.

Appendix A: Karnofsky Performance Status Scale

Karnofsky performance status scale

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance, but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

Appendix B: EORTC Quality of Life Questionnaire (QLQ) C-30 and H&N35

EORTC QLQ – C30 and H&N35

Study UMCC: _____ Study ID#: _____ Date: _____

C30 (questions: 1-30): We are interested in some things about you and your health. Please answer all of the questions by circling the number that best applies to you. There are no “right” or “wrong” answers. The information you provide will remain strictly confidential.

		Not at all	A little	Quite a bit	Very much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
	During the past week:	Not at all	A little	Quite a bit	Very much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4

12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Study UMCC: _____ Study ID#: _____ Date: _____

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor			Excellent			

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor			Excellent			

H&N-35 (questions: 31-65)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experience these symptoms or problems during the past week.

	During the past week:	Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4

35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
Study UMCC: _____ Study ID#: _____		Date: _____			
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4

52.	Have you had trouble enjoying your meals?	1	2	3	4
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53.	Have you had trouble talking to other people?	1	2	3	4
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Study UMCC: _____ Study ID#: _____ Date: _____

54.	Have you had trouble talking on the telephone?	1	2	3	4
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55.	Have you had trouble having social contact with your family?	1	2	3	4
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56.	Have you had trouble having social contact with friends?	1	2	3	4
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57.	Have you had trouble going out in public?	1	2	3	4
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58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
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59.	Have you felt less interest in sex?	1	2	3	4
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60.	Have you felt less sexual enjoyment?	1	2	3	4
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		Yes	No		
61.	Have you used pain-killers?	1	2		

62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2		
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63.	Have you used a feeding tube?	1	2		
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64. Have you lost weight?

1

2

65. Have you gained weight?

1

2

Study UMCC: _____

Study ID#: _____

Date: _____