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STU 2020-1079
HYHOPE: Phase I study of de-intensified hypofractionated radiation therapy for human papilloma virus-associated oropharynx cancer

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Study Drug/Treatment: De-intensified hypofractionated intensity modulated radiation therapy with concurrent cisplatin

Funding Source: Gateway for Cancer Research

NCT Number: NCT04580446

Initial version: 1.0; 10/01/2020

Amended: 2.0; 06/16/2021
3.0; 10/20/2021
4.1; 11/01/2022
4.2; 01/30/2024

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Amendment/Version #_____Version 4.2_____

STU 2020-1079
HYHOPE: Phase I study of de-intensified hypofractionated radiotherapy for human papilloma virus-associated oropharynx cancer

Principal Investigator (PI) Name: **___Dominic Moon, MD_____**

PI Signature: _____

Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event
BED	Biological Effective Dose
CBCT	Cone Beam Computed Tomography
CR	Complete Response
CRO	Clinical Research Office
CMS	Centers for Medicare and Medicaid Services
CT	Computed Tomography
CTV	Clinical Target Volume
CTCAE	Common Terminology Criteria for Adverse Events
DM	Distant Metastasis
DOT	Disease Oriented Team
DSMC	Data Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
ENE	Extranodal Extension
EQ-5D-5L	EuroQol-5 Dimensions Questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
H&P	History & Physical Exam
HFRT	Hypofractionated Radiation Therapy
HNSCC	Head and Neck Squamous Cell Carcinoma
HRPP	Human Research Protections Program
HUD	Humanitarian Use Device
IMRT	Intensity-modulated Radiation Therapy
IRB	Institutional Review Board
IV	Intravenously
KPS	Karnofsky performance status
LRC	Locoregional Control
LRR	Locoregional Recurrence
LVI	Lymphovascular Invasion
MDADI	MD Anderson Dysphagia Inventory
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose/fractionation
NCI	National Cancer Institute
OAR	Organ at Risk
ORR	Overall Response Rate
OS	Overall Survival
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PNI	Perineural Invasion

PFS	Progression Free Survival
PR	Partial Response
PTV	Planning Target Volume
QOL	Quality of Life
RO-APM	Radiation Oncology-Alternative Payment Model
ROSAC	Radiation Oncology Safety Assurance Committee
RT	Radiation Therapy
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
UTSW	University of Texas Southwestern Medical Center
UW-QOL	University of Washington Quality of Life Questionnaire
VMAT	Volumetric Modulated Arc Therapy

STUDY SCHEMA

Patient registration:
T1-3 (≤6 cm), N0-2 (except T1-2N0)
p16 positive oropharyngeal squamous cell carcinoma
≤10 pack-year smoking history and no active smoking

↓

Treatment: Rolling 6 design
Hypofractionated radiotherapy with concurrent chemotherapy (weekly cisplatin 40 mg/m^2)

Level	Dose
~~1*~~	~~44.4 Gy in 12 fractions, 4 fractions/week~~
0	46.5 Gy in 15 fractions, 5 fractions/week
-1	52 Gy in 20 fractions, 5 fractions/week

*Level 1 has been eliminated in an amendment

↓

Assessment of primary endpoint:
Maximum tolerated dose/fractionation (MTD)
Dose limiting toxicity: Any CTCAE grade 4 acute toxicity or persistent grade 3 mucositis at 3 months post-treatment (per section 9.1)

↓

Dose expansion cohort
Enroll additional patients at the MTD to reach a total of 24 patients

↓

Assessment of clinical response:
Clinical and radiographic evaluation with PET/CT 12-14 weeks post-treatment
- Clinical complete response (cCR): routine surveillance
- <cCR of primary site: directed biopsy of suspected site(s); if positive, proceed with salvage transoral robotic surgery
- <cCR of nodes: proceed with neck dissection of suspected node level(s)

↓

Follow-up:
Assessment of endpoints at 6 and 12 months

STUDY SUMMARY

Title	HYHOPE: Phase I study of de-intensified hypofractionated radiation therapy for human papilloma virus-associated oropharynx cancer
Short Title	HYHOPE: De-intensified hypofractionated radiation therapy for HPV-associated oropharynx cancer
Protocol Number	STU 2020-1079
Phase	Phase I
Methodology	Rolling 6 dose finding cohort followed by dose expansion cohort
Study Duration	3 years to accrue, additional 1 year of follow-up
Study Center(s)	Single-center
Objectives	To assess the maximum tolerated dose/fractionation and signal for efficacy of de-intensified hypofractionated radiotherapy for favorable HPV-associated oropharynx cancer
Number of Subjects	24
Diagnosis and Main Inclusion Criteria	T1-3 (≤6 cm), N0-2 (except T1-2N0) p16 positive oropharyngeal squamous cell carcinoma with ≤10 pack-year smoking history
Study Product(s), Dose, Route, Regimen	Hypofractionated intensity modulated radiotherapy with concurrent chemotherapy (weekly cisplatin)
Duration of administration	3-4 weeks
Reference therapy	Conventionally fractionated radiotherapy (60-70 Gy) over 6-7 weeks with concurrent chemotherapy (historical control)
Statistical Methodology	Phase I: standard rolling 6 design to determine the maximum tolerated dose/fractionation. Additional patients will be enrolled to reach 24 patients to achieve 20 evaluable patients for the clinical response endpoint assuming a 15% attrition rate.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

The incidence of Human Papilloma Virus-associated oropharyngeal squamous cell carcinoma (HPVOPSCC) is increasing in the United States accounting for 70-80% of newly-diagnosed oropharyngeal cancers. With the recognition of HPVOPSCC as a distinct disease process from the smoking- or alcohol-related head and neck cancers and the associated favorable prognosis (1), investigations are ongoing to determine the best strategy to de-intensify therapy while maintaining good oncologic outcomes. Recently published results of reduced dose radiotherapy (RT) of 60 Gy with weekly cisplatin (30 mg/m^2) have shown excellent outcomes with 2- and 3-year progression free survival (PFS) of 86% and 85%, respectively, and 2- and 3-year overall survival (OS) of 95% (2). Preliminary results of NRG-HN002 was also recently presented at ASTRO 2019 with 2-year PFS of 90.5% in the 60 Gy RT plus weekly cisplatin (40 mg/m^2) arm while surpassing the pre-specified MD Anderson Dysphagia Inventory scale threshold (3). Although we do not have randomized data compared to the current standard of 70 Gy, 60 Gy with concurrent weekly chemotherapy is likely to become an important treatment strategy for favorable HPVOPSCC, perhaps representing the purest de-intensification paradigm without the addition of upfront surgery or induction chemotherapy.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Standard of care RT for head and neck squamous cell carcinoma (HNSCC) involves conventionally fractionated treatment of 2 Gy per fraction delivered over a course of 6-7 weeks, representing one of the longest RT courses among all cancers. In other disease sites including breast and prostate, moderately hypofractionated RT (HFRT) has been demonstrated to provide equivalent oncologic outcomes with similar toxicities (4, 5). However, concerns for potential increase in side effects have limited attempts of HFRT in HNSCC except in early stage glottic larynx cancer where treatment volumes are relatively small. In this disease subsite, moderately HFRT delivered in 2.25 Gy per fraction were shown to have superior local control with no significant increase in adverse reactions (6).

A small number of prospective trials using moderately HFRT in other HNSCC subsites have been reported. In a study of definitive chemoradiation delivering 55 Gy in 20 fractions (2.75 Gy/fraction) with concurrent carboplatin in 19 patients with HNSCC, all patients were able to complete RT with a complete response rate of 84% and 2-year local control of 75% (7). Acute grade 3 dermatitis and mucositis were seen in 26% and 84% of patients, respectively. In another small single arm trial, 20 patients were treated with 55 Gy in 20 fractions with concurrent weekly cisplatin (8). All patients were able to complete RT as prescribed with acute grade 3 dermatitis, grade 3 mucositis, and nasogastric tube rate of 30%, 40%, and 75%, respectively. Although the acute adverse reaction appeared to be comparable to conventionally fractionated RT, neither trial reported long term complication rates.

There are currently two ongoing multicenter randomized trials outside of the United States randomizing patients to HFRT vs conventionally fractionated RT in the definitive setting. In a trial sponsored by the International Atomic Energy Agency (IAEA-HYPNO), patients with stage I-IV HNSCC are being randomized to 55 Gy in 20 fractions 5 times a week vs 66 Gy in 33 fractions six times a week with primary endpoints of 3-year locoregional control and late toxicity. In another trial from the United Kingdom (COMPARE), patients with intermediate and high risk oropharyngeal cancers are being randomized to four different arms, two of which involve 64 Gy in 25 fractions (2.56 Gy/fraction) vs 70 Gy in 35 fractions with the primary endpoint of overall survival. Both trials are scheduled to complete accrual in 2021 with results likely reported in mid- to late-

2020s. There are no published or active trials assessing curative HFRT regimen with less than 20 fractions.

Study of HFRT is of particular interest as the health care system transitions to value-based care model. A change in the reimbursement model for radiation oncology in the Unites States will likely significantly affect the way RT is delivered in the near future. Centers for Medicare and Medicaid Services (CMS) have recently unveiled the radiation oncology alternative payment model (RO-APM), which is scheduled to take effect between now and 2022. Participation will be mandatory, and radiation oncology centers will receive a fixed payment for a 90-day episode of care in contrast to the current fee-for-service model where each visit and fraction is billed for and reimbursed (9). RO-APM is designed to incentivize cost-effective treatments while maintaining high quality. As a result of this change, the radiation oncology community will seek safe and effective strategies to decrease total costs per episode. A prospective study to assess HFRT with fewer number of fractions is thus timely and potentially paradigm changing for practices across the United States.

The current COVID-19 pandemic is highlighting the cost and risk to our society at large of a lack of viable alternatives to a 6-7 week daily RT course for patients with HNSCC. Patients and medical staff are exposed to increased risk of SARS-CoV-2 infection during a prolonged daily RT course. A well-validated HFRT regimen for HNSCC is urgently needed similar to other disease sites such as breast, prostate, rectum, and brain where safe and effective HFRT regimens have been established and are increasingly utilized.

1.3 Other Agents

The standard concurrent chemotherapy for the treatment of HNSCC consists of bolus cisplatin (100 mg/m^2) every 3 weeks for 2-3 cycles, which is associated with significant grade 3-4 toxicity (10, 11). As noted above, multi-institutional and national trials assessing low dose weekly cisplatin (30-40 mg/m^2) with RT for favorable HPVOPSCC have shown excellent oncologic results with a favorable toxicity profile (2, 3). The current trial will test HFRT with concurrent weekly cisplatin at 40 mg/m^2.

1.4 Rationale

1.4.1 Dose de-intensification

Analysis of multiple prospective trials have confirmed improved PFS and OS of patients with HPVOPSCC vs non-HPV associated cancers (12–14). Given the significant toxicity associated with standard chemoradiation of 70 Gy with concurrent cisplatin, it is imperative to identify optimal strategies to de-intensify therapy for favorable HPVOPSCC to achieve comparable outcomes to standard therapy while minimizing toxicity. Several Phase II studies have shown promising results using 60 Gy vs the current standard of 70 Gy (2, 3).

1.4.2 Volume de-escalation

Elective nodal volumes for head and neck cancer currently used for intensity-modulated RT (IMRT) is extrapolated from conventional RT fields. Assessment of patterns of failure following IMRT treatments have shown that regional recurrences almost always occur in the high-dose region and solitary failure in the elective volume/dose is rare (15–18). Trials assessing a reduction in the elective nodal volume following induction chemotherapy have shown no solitary elective volume failures (19, 20). More recently, a UT Southwestern Medical Center prospective study of volume de-escalation, where patients with oropharynx cancer received elective dose RT only to the involved and immediately adjacent cervical nodal levels, found no solitary nodal recurrences in

the treated or untreated elective neck volumes, with a minimum follow-up of nearly 2 years (21). Decreasing the volume of elective treatment can improve the toxicity profile of treatment and is currently being incorporated into the standard-of-care arm in large cooperative group trials such as NRG-HN005.

1.4.3 Hypofractionation

Cost of oncologic care has continued to increase with efforts in recent years to transition to a value-based care model. In this environment, especially with the implementation of the RO-APM described above, there is an economic rationale to elucidate ways to provide quality care while decreasing resource utilization. Also, there is a strong radiobiological rationale for HFRT in HNSCC to decrease the overall treatment time and thus minimize the effects of accelerated repopulation seen in this disease entity. Accelerated fractionation with its associated decrease in overall treatment time has been shown to improve local control and progression free survival compared to conventional fractionation in HNSCC (22). Effective and safe radiation treatment in a fraction of the time currently required will also improve patient quality of life by decreasing interruptions to their personal and professional lives. Moreover, reducing the overall treatment time may increase completion rates and compliance by reducing the time burden of the therapy. Shortened treatment time will lead to reduced number of weekly cisplatin cycles with concomitant decrease in total cumulative dose, which may also decrease potential chemotherapy side effects such as ototoxicity or nephrotoxicity.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the maximally tolerated dose/fractionation (MTD) of HFRT

2.2 Secondary Objectives

2.2.1 To assess physician-reported acute and late toxicities of HFRT

2.2.2 To assess the oncologic outcomes of HFRT

2.2.3 To assess patient-reported QOL of HFRT

2.2.4 To assess feeding tube dependence rate of HFRT

2.3 Endpoints

2.3.1 **Primary endpoint: MTD of HFRT**

2.3.2 Secondary endpoints:

- Physician-reported acute and late toxicities
  - Rate of ≥grade 3 acute toxicities during treatment, and at 1 and 3 months after treatment using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
  - Rate of ≥grade 3 late toxicities at 6 and 12 months after treatment using CTCAE v5.0
- Oncologic outcomes: locoregional control (LRC), progression-free survival (PFS), and overall survival (OS)

- Patient-reported QOL:
    - MDADI, University of Washington QOL questionnaire (UW-QOL) version 4, and EuroQol-5 dimensions (EQ-5D-5L) scores at baseline, 1, 3, 6, and 12 months after treatment. QOLs will be completed either on paper (included in Appendix C, D & E of the protocol) or electronically via MyChart.
- Feeding tube dependence rate at baseline, 1, 3, 6, and 12 months after treatment
    - Feeding tube dependence defined as daily use of the feeding tube with ≥2 nutritional supplements (e.g. Ensure, Boost, etc.) per day at the time of consultation.

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not recommended; however, if warranted, prior approvals are required per section 10.5.1. Subjects must meet all inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Once registered, a subject is still required to meet all inclusion and exclusion criteria on the first day of treatment, prior to treatment.

3.1 Inclusion Criteria

3.1.1 Pathologically-proven diagnosis of T1-3 (up to 6 cm), N0-2 (AJCC 8th edition) p16 positive squamous cell carcinoma of the oropharynx (except T1-2N0 as noted in the exclusion criteria)

3.1.2 ≤10 pack-year smoking history and not actively smoking

3.1.3 Age ≥18 years

3.1.4 ECOG performance status 0-2 or Karnofsky Performance Status of 50-100

3.1.5 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.5.1 A female of child-bearing potential is any woman (regardless of sexual orientation, marital status, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.6 Negative serum or urine pregnancy test within 2 weeks before registration for women of childbearing potential.

3.1.7 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Distant metastasis

3.2.2 T1-2N0 (AJCC 8th edition) p16 positive squamous cell carcinoma of the oropharynx (candidates for definitive RT alone or surgery alone)

3.2.3 Inability to receive concurrent weekly cisplatin due to comorbid conditions

3.2.4 Synchronous non-skin cancer primaries outside of the oropharynx, oral cavity, larynx, and hypopharynx except for low- and intermediate-risk prostate cancer and well-differentiated thyroid cancer. For prostate cancer, patient should not be receiving active treatment. For thyroid cancer, thyroid surgery may occur before or after radiation treatment, provided all other eligibility criteria are met.

3.2.5 Prior invasive malignancy with an expected disease-free interval of less than 3 years

3.2.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation fields

3.2.7 Subjects may not be receiving any other investigational agents for the treatment of the cancer under study.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to the chemotherapy agents in this study

3.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements

3.2.10 Subjects must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

3.2.11 History of severe immunosuppression, including HIV, organ or autologous or allogeneic stem cell transplant, or active immunosuppressive medication at the time of enrollment

4.0 TREATMENT PLAN

4.1 Radiation Treatment Dose and Administration

Patients will be enrolled on the trial in cohorts of up to 6 per the rolling 6 dose escalation design as outlined in section 9.1.1.

4.1.1 CT simulation

Patients will be simulated supine in a thermoplastic mask extending from the scalp through upper chest (e.g. “5 point mask”) or a thermoplastic mask covering the head in combination with shoulder retractors. IV contrast is recommended but not mandatory.

4.1.2 Dose and fractionation

Dose calculation for HFRT was based on the biologically effective dose (BED) model accounting for time/repopulation observed in HNSCC:

$$\mathrm{BED} = nd(1 + d/[\alpha/\beta]) - \log_e 2(T - T\mathrm{k})/\alpha T\mathrm{p}$$

n = number of fractions
d = dose per fraction
T = overall treatment time
Conventionally fractionated RT: 40 days (30 fractions)
Hypofractionated RT: 19 days (12-15 fractions), 26 days (20 fractions)
Tk = time delay of repopulation (21 days for tumor, 7 days for mucosa)
Tp = cell doubling time (3 days for tumor, 2.5 days for mucosa)
α/β = 3 for late complications, 10 for tumor/mucosa
α = 0.35 Gy^{-1}

Dose and fractionation were selected to satisfy two parameters (see Table):
- ≤ BED_3 vs conventional fractionation (60 Gy), i.e. late toxicity dose to normal tissue
- ≥ BED_{10} vs conventional fractionation (60 Gy), i.e. dose to tumor

Table. Total dose BED calculation for HFRT (vs comparison [conventional fractionation])

Level	**Dose**	**BED /w repopulation α/β = 10 (tumor)**	**BED /w repopulation α/β = 10 (acute mucosa)**	**BED α/β = 3 (late normal tissue)**
~~1*~~	~~44.4 Gy/12 fx (3.7 Gy/fx), 4 fx/week~~	~~61~~	~~52~~	~~99~~
0	46.5 Gy/15 fx (3.1 Gy/fx), 5 fx/week	61	51	95
-1	52 Gy/20 fx (2.6 Gy/fx), 5 fx/week	62	50	97
Comparison	60 Gy/30 fx (2 Gy/fx), 5 fx/week	59	46	100

Abbreviations: fx, fraction(s)
*Level 1 eliminated at time of amendment. See the end of the section for details.

Level 0 will test a 15-fraction HFRT regimen treated 5 times a week for 3 weeks. If successful, level 1 will test a 12-fraction HFRT regimen treated 4 times a week for 3 weeks. If level 1 is well-tolerated, this regimen will be considered maximally tolerated dose/fractionation (i.e. no further reduction in the number of fractions).

If Level 0 is deemed intolerable, patients will be enrolled on level -1, which will test a 20-fraction HFRT regimen treated 5 times a week for 4 weeks. Given published literature on 20-fraction regimens, we anticipate that a 20-fraction regimen will be tolerable.

The calculated BED for acute toxicity such as the normal mucosa may be slightly increased vs conventionally fractionated RT, but the dose ranges **are well below** the limits deemed tolerable (<59-63 Gy_{10}) based on analysis of toxicities associated with various head and neck cancer fractionation regimens published to date (23).

High risk (HR: regions of positive disease) and standard risk (SR: other regions at risk) volumes will receive doses as outlined below using dose painting intensity-modulated radiotherapy (IMRT):

Level 1:
- PTVHR: 370 cGy x 12 = 4440 cGy
- PTVSR: 330 cGy x 12 = 3960 cGy

Level 0:
- PTVHR: 310 cGy x 15 = 4650 cGy
- PTVSR: 270 cGy x 15 = 4050 cGy

Level -1:
- PTVHR: 260 cGy x 20 = 5200 cGy
- PTVSR: 230 cGy x 20 = 4600 cGy

Table. Standard risk dose BED calculation for HFRT (vs comparison)

Level	**Dose**	**BED /w repopulation α/β = 10 (tumor)**	**BED /w repopulation α/β = 10 (acute mucosa)**	**BED α/β = 3 (late normal tissue)**
~~1*~~	~~39.6 Gy/12 fx (3.3 Gy/fx)~~	~~53~~	~~43~~	~~83~~
0	40.5 Gy/15 fx (2.7 Gy/fx)	51	42	77
-1	46 Gy/20 fx (2.3 Gy/fx)	53	41	81
Comparison	54 Gy/30 fx (1.8 Gy/fx)	51	37	86

Abbreviations: fx, fraction(s)
*Level 1 eliminated at time of amendment. See the end of the section for details.

Elimination of Level 1
Upon a preliminary review of the toxicity profile of patients enrolled on a parallel Phase I trial in the post-operative setting with the same fractionation scheme, an apparent increase in acute grade 2 and grade 3 toxicities related to oral/pharyngeal mucositis and pain was observed on dose level 1 vs level 0. Although dose limiting toxicity is not expected at the conclusion of the evaluation period for patients on level 1 on that trial, the investigators have made a decision to forgo escalation to level 1 (i.e. eliminate level 1) for this current trial in light of potential increase in toxicity. As delineated in the tables above, the fractionation schemes of level 0 and 1 have the same biologically effective dose to the tumor and treatment length (3 weeks). The trial will proceed with the dose expansion phase once level 0 is confirmed to be without dose limiting toxicities.

4.1.3 Target volume delineation

4.1.3.1 Gross tumor volume (GTV)

The primary gross tumor volume (GTVp) will be contoured on the planning CT using radiographic and clinical information to define its extent. Image registration of staging scans including diagnostic CT, PET/CT, and/or MRI as available to aid delineation of GTVp is recommended, but not mandatory.

The nodal gross tumor volume (GTVn) will be contoured on the planning CT using radiographic and clinical information. Nodes meeting the criteria below will be considered positive and included in GTVn:

- Max SUV greater 3.0
- The short-axis diameter is ≥1.5 cm (level II), ≥1.0 cm (level I, III, IV, and V), or ≥0.8 cm (retropharyngeal)
- The node shows central necrosis

Suspicious nodes will be defined as those that do not meet the above criteria, but satisfy any of the criteria below:

- The combined diameter of the lymph node ≥ 17 mm on axial imaging
- FDG uptake greater than the adjacent blood pool
- Any size retropharyngeal node
- Heterogeneous enhancement or rounded appearance

At the discretion of the treating radiation oncologist, suspicious nodes can be included either as part of GTVn or included in CTVn as discussed below.

4.1.3.2 Clinical target volume (CTV)

CTVSR

GTVp will be expanded by 5 mm to create CTVp. CTVp may be expanded further to include surrounding anatomic structures at risk for microscopic spread such as the adjacent soft palate or glossotonsillar sulcus for tonsil cancers or the adjacent contralateral base of tongue for base of tongue cancers at the discretion of the treating radiation oncologist. CTVp should exclude structures that are a natural barrier to spread (e.g. bone).

CTVn will include the following:

-Bilateral level II

-Except in well-lateralized tonsil cancers (defined as having no invasion of the base of tongue and minimal invasion of the soft palate with >1 cm distance from the uvula), where the node negative contralateral level II may be omitted

-In the node positive neck, cranial extent of level II will be the base of skull

-In the node negative neck, cranial extent of level II will be the transverse process of C1 vertebrae or where the posterior belly of the digastric muscle crosses over the jugular vein

-Nodal level(s) with an involved node (i.e. GTVn)

-Nodal level(s) immediately adjacent to involved node (e.g. if level II has an involved node, levels III is included)

-Nodal level(s) with suspicious nodes

-Ipsilateral lateral retropharyngeal nodal region

-Level V is included if there are 2 or more involved nodal levels in the ipsilateral neck

-Level IB is included only if it harbors an involved or suspicious node

4.1.3.3 Planning target volume (PTV)

GTVp and GTVn will be expanded by 5 mm in all directions to create PTVHR.

CTVp will be expanded by 5 mm in all directions to create PTVp. CTVn will be expanded by 3 mm in all directions to create PTVn. PTVp and PTVn will be combined to create PTVSR.

4.1.4 Treatment planning

Radiotherapy must be delivered using IMRT. IMRT may be implemented using any delivery platform, including volumetric modulated arc therapy (VMAT), step and shoot IMRT, or helical tomotherapy.

4.1.4.1 Coverage constraints

Target volume	**Per protocol**	**Acceptable variation (Minor deviation)**	**Major deviation**
PTVHR	-At least 95% of the PTV should be covered by the prescription dose -At least 99% of the PTV should receive 93% of the prescription dose -Dose should not exceed 107% of prescription dose	-None -At least 97% of the PTV should receive 93% of the prescription dose -Dose should not exceed 110% of prescription dose	-<95% of the PTV is covered by the prescription dose -<97% of the PTV receives 93% of the prescription dose -Maximum dose is >110% of prescription dose
PTVSR	-At least 95% of the PTV should be covered by the prescription dose	-At least 93% of the PTV should be covered by the prescription dose	-<93% of the PTV is covered by the prescription dose

4.1.4.2 Organ at risk (OAR) constraints

12 fractions
Mandatory:

Organ	**Per protocol**	**Acceptable variation (Minor deviation)**	**Major deviation**
Spinal cord	Max < 34 Gy	None	Max ≥ 34 Gy
Spinal cord + 5 mm	Max < 38 Gy	Max < 41 Gy	Max ≥ 41 Gy
Brainstem	Max < 38 Gy	Max < 41 Gy	Max ≥ 41 Gy
Brainstem + 5 mm	Max < 44 Gy	None	Max ≥ 44 Gy
Mandible	Max < 46.6 Gy	Max < 48.8 Gy	Max ≥ 48.8 Gy

Recommended:
Contralateral parotid: mean < 16-21 Gy
Contralateral submandibular gland: mean < 22-27 Gy
Cochlea: maximum < 28-34 Gy, mean < 23-28 Gy
Oral cavity (excluding PTV): mean < 16-20 Gy
Constrictors: mean < 29-34 Gy
Post-arytenoid and cricoid space: mean < 19-24 Gy
Larynx: mean < 22-27 Gy
Cervical esophagus: mean < 16-20 Gy
Brachial plexus: max < 44-47 Gy
Brain: max < 44 Gy

15 fractions
Mandatory:

Organ	**Per protocol**	**Acceptable variation (Minor deviation)**	**Major deviation**
Spinal cord	Max < 37 Gy	None	Max ≥ 37 Gy
Spinal cord + 5 mm	Max < 43 Gy	Max < 44 Gy	Max ≥ 44 Gy
Brainstem	Max < 43 Gy	Max < 44 Gy	Max ≥ 44 Gy
Brainstem + 5 mm	Max < 48 Gy	None	Max ≥ 48 Gy
Mandible	Max < 48.9 Gy	Max < 51.5 Gy	Max ≥ 51.5 Gy

Recommended:
Contralateral parotid: mean < 17-22 Gy
Contralateral submandibular gland: mean < 23-29 Gy
Cochlea: maximum < 30-37 Gy, mean < 25-30 Gy
Oral cavity (excluding PTV): mean < 17-21 Gy
Constrictors: mean < 30-37 Gy
Post-arytenoid and cricoid space: mean < 20-25 Gy
Larynx: mean < 23-29 Gy
Cervical esophagus: mean < 17-21 Gy
Brachial plexus: max < 46-49 Gy
Brain: max < 46 Gy

20 fractions
Mandatory:

Organ	**Per protocol**	**Acceptable variation (Minor deviation)**	**Major deviation**
Spinal cord	Max < 40 Gy	None	Max ≥ 40 Gy
Spinal cord + 5 mm	Max < 46 Gy	Max < 49 Gy	Max ≥ 49 Gy
Brainstem	Max < 46 Gy	Max < 50 Gy	Max ≥ 50 Gy
Brainstem + 5 mm	Max < 52 Gy	None	Max ≥ 52 Gy
Mandible	Max < 54.6 Gy	Max < 57.2 Gy	Max ≥ 57.2 Gy

Recommended:
Contralateral parotid: mean < 19-23 Gy
Contralateral submandibular gland[+]: mean < 26-30 Gy
Cochlea: maximum < 33-40 Gy, mean < 27-32 Gy
Oral cavity (excluding PTV): mean < 19-22 Gy
Constrictors: mean < 33-40 Gy
Post-arytenoid and cricoid space: mean < 22-26 Gy
Larynx: mean < 26-30 Gy
Cervical esophagus: mean < 19-22 Gy
Brachial plexus: max < 52-54 Gy
Brain: max < 52 Gy

4.1.4.3 Treatment delivery
All patients will receive one fraction per day, 5 days per week (except at dose level 1, where patients will receive one fraction per day, 4 days per week). Patients who miss more than 1 planned treatment (or encounter more than 1 holiday during treatment) should attempt to make up the missed day(s) with a second daily fraction more than 6 hours apart. Daily cone-beam CT (CBCT) must be used for patient set-up (image-guided RT). Patients will preferentially start RT on a Monday, but this is not mandatory.

Total elapsed days

	Per protocol	**Acceptable variation (Minor deviation)**	**Major deviation**
12 fractions	18-20	21-25	>25
15 fractions	18-21	22-26	>26
20 fractions	26-28	29-33	>33
30 fractions	40-42	43-47	>47

4.1.4.4 Re-planning
If a patient loses a significant amount of weight on treatment, or the tumor contour changes substantially, repeat CT simulation and planning is allowed.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table in section 5.4. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.

The dose constraints for radiation therapy are described in sections 4.1.4.2. No alterations in treatment doses are allowable per protocol.

4.3 Concomitant Medications/Treatments

Supportive medications may be given at any point during the treatment course at the discretion of the treating physicians. These medications include:

- Anti-emetics
- Non-opiate and opiate pain medications
- Antidiarrheals
- Nutritional supplementation
- Anti-depressants

4.4 Other Modalities or Procedures

4.4.1 Concurrent systemic therapy

Concurrent systemic therapy will be administered using weekly cisplatin of 40 mg/m^2. Dose modifications should be performed per the standard of care at the treating facility. Patients are recommended to receive concurrent weekly cisplatin as long as it is tolerated as determined by the treating medical oncologist. Details of the systemic therapy can be found in section 8.0.

4.4.2 Gastric tubes

Gastrostomy tubes (feeding tubes) are optional for patients on this study. Physicians should attempt to avoid gastrostomy if patients are receiving ipsilateral radiotherapy. However, gastrostomy tubes are strongly recommended in the following scenarios:

- More than 10% body weight loss prior to diagnosis (prophylactic)
- Baseline BMI < 25 (prophylactic)
- More than 10% body weight loss on treatment (reactive)

The gastrostomy tube should be removed after patients maintain a stable or increasing weight for 1-2 weeks without enteral supplementation (or as clinically indicated).

4.4.3 Speech language pathology

Patients are strongly recommended to have evaluation and ongoing therapy as appropriate by a speech language pathologist before, during, and after radiation therapy.

4.5 Duration of Therapy

Duration of therapy will be per the treatment schedule as outlined in section 4.1.2 (3-4 weeks depending on the dose level).

Protocol therapy will end under the following conditions:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Subject decides to withdraw from the study, OR
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.5.1 Subject Withdrawal

In the event a subject chooses to withdraw from the study, document if the is withdrawing from treatment only (and willing to be included in follow-up data collection), or if they are withdrawing from all study participation. For subject safety, the subject should be encouraged to return for a follow-up visit per the Time and Events Table in section 5.4.

Notify the Principal Investigator/Sponsor-Investigator and document the reason for withdrawal from study and the date of discontinuation.

4.6 Duration of Follow Up

Patients will be followed for 1 year from the completion of treatment according to the Time and Events table in section 5.4.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in section 5.5 apply. Notify the Principal Investigator (or the co-Investigators if not available) and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.8 Subject Replacement

Subjects may be replaced in the study if they do not complete RT for reasons not related to toxicities associated with treatment. Because inadequate receipt of treatment may lead to a spuriously high rate of recurrence and/or inaccurate assessment of treatment side effects, these patients may be replaced. Patient replacement must be verified through review of the case by the Principal Investigator (or the co-Investigators if Principal Investigator is not available).

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration into the study unless otherwise stated. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Medical history

- Complete medical and surgical history

5.1.3 Demographics

- Age, gender, race

5.1.4 Review subject eligibility criteria

5.1.5 Review previous and concomitant medications

5.1.6 Physical exam including vital signs
- Temperature, pulse, blood pressure

5.1.7 Performance status
- ECOG Performance status (0-2) or Karnofsky Performance Status (50-100)

5.1.8 Adverse event assessment
- Baseline adverse events will be assessed pre-treatment using CTCAE v5.0. See section 7.2 for adverse event monitoring and reporting.

5.1.9 Pregnancy test (for females of child bearing potential)
- See section 3.1.5.1 for definition

5.1.10 Completion of PRO instruments (before start of radiation treatment)
- MDADI
- UW-QOL
- EQ-5D-5L

5.1.11 Feeding tube dependence assessment
- See section 2.3.2 for definition

5.1.12 Standard lab work including creatinine
- Assessment for cisplatin eligibility per medical oncologist

5.2 Procedures During Treatment

Dose escalation phase:
During each week of radiotherapy, following will be evaluated:
- Vital signs
- Physical exam
- ECOG performance status or Karnofsky performance status
- Adverse events assessment using CTCAE v5.0

Dose expansion phase:
Weekly visits will be conducted by the care team as per standard of care and not as part of trial procedures.

5.3 Follow-up Procedures

Patients will be assessed by a radiation oncologist and/or advanced practice provider at 1 month (+/- 1 week) and 3 months (+/- 2 weeks) from the completion of treatment per Time and Events Table (Section 5.4). More frequent visits are encouraged if the patient requires additional help with recovery and rehabilitation. Restaging PET/CT must be performed between 12-14 weeks from the completion of treatment.

Patients with a clinical complete response (cCR) based on history and physical exam and restaging PET/CT at 12-14 weeks as defined in Section 6.1.1 will undergo routine surveillance. Patients with less than cCR in the primary site will undergo directed biopsy of suspected site(s), and if positive, proceed with salvage transoral robotic surgery

(TORS). Patients with less than cCR in the neck will undergo neck dissection, with the extent of the neck dissection to be determined by surgeon discretion.

Patients with pathologically confirmed viable residual primary disease will be considered to have locoregional failure. Since the viability of residual nodal disease on pathology is often questionable at this time point (12-14 weeks post-treatment), and because adjuvant neck dissection is typically considered part of the original treatment package, residual nodal disease at neck dissection will not be considered a locoregional failure.

Patients will then be seen at 6 and 12 months (+/- 4 weeks) from the completion of treatment per Time and Events Table (Section 5.4). Patients with pathologically confirmed recurrent disease following assessment at these times points will be considered to have locoregional failure/recurrence. Subsequent and intervening follow-up visits will be made per physician preference.

5.4 Time and Events Table

Procedures/ Times	Pre-treatment	Weekly during treatment[a]	1[b], 3[c], 6[d], 12[d] months post treatment
History and PE	X[e]	X	X
Performance status (ECOG/ KPS)	X[e]	X	X
AE assessment	X[f]	X	X
DLT assessment (only during dose escalation phase)		X	X
Patient reported outcomes (MDADI, UW-QOL, EQ-5D-5L)	X[f]		X
Feeding tube dependence assessment	X[g]		X
Pregnancy test	X[h]		
Lab work (creatinine)	X		
Restaging PET/CT			X[i]

[a] Only during the dose escalation phase
[b] +/- 1 week
[c] +/- 2 weeks
[d] +/- 4 weeks
[e] ≤ 30 days prior to registration
[f] Prior to initiation of RT
[g] At the time of radiation oncology consultation
[h] Urine or serum in applicable female within 2 weeks of registration
[i] At 12-14 weeks post RT only

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from treatment (follow-up permitted)

5.5.2 Subject withdraws consent (termination of treatment and follow-up, see section 4.5.1)

5.5.3 Subject is unable to comply with protocol requirements

5.5.4 Subject demonstrates disease progression, however, continued treatment with study drug/treatment is permissible at the discretion of the investigator

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe

5.5.6 Treating physician determines continuation on the study would not be in the subject's best interest

5.5.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event)

5.5.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study

5.5.9 Lost to follow-up. If a research subject cannot be located to document survival after a period of one year, the subject may be considered "lost to follow-up." All attempts to contact the subject during the one year must be documented.

6.0 MEASUREMENT OF EFFECT

6.1 Antitumor Effect

6.1.1 Definitions

Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with radiotherapy.

Clinical complete response (cCR): Disappearance of all lesions on physical/clinical exam and negative PET/CT (12-14 weeks post-treatment), defined as no focal FDG avidity at the primary site (i.e. may have diffuse avidity consistent with post-radiation inflammation) and no focal FDG avidity above blood pool or liver of treated pathological lymph nodes per the Hopkins criteria (24). There can be no appearance of new lesions.

Locoregional recurrence (LRR): Biopsy-proven viable cancer originating from the primary tumor site (i.e. oropharynx) or a lymph node basin above the clavicles.

Locoregional control (LRC): Freedom from locoregional recurrence

Distant metastasis (DM): Recurrent cancer below the clavicles. Biopsy is strongly recommended but not mandated. If biopsy is not obtained, the initiation of anti-cancer therapy is assumed to indicate metastasis, with the date of scan prompting therapy serving as the date of metastasis.

Progression: locoregional recurrence or distant metastasis

Progression-free survival (PFS): Duration of time from start of treatment to time of progression or death.

Overall survival (OS): Duration of time from start of treatment to time of death.

6.1.2 Response Assessment

Patients who do not meet the cCR definition (section 6.1.1) during the evaluation at 12-14 weeks post-treatment will undergo pathologic evaluation as outlined in section 5.3.

6.1.3 Outcomes Assessment

Patients will be assessed for oncologic outcomes including LRC, PFS, and OS at 12-14 weeks post-treatment and at subsequent follow-ups at 6 and 12 months.

6.2 Safety/Tolerability

Analyses will be performed for all subjects having received at least one fraction of radiation. The study will use the CTCAE version 5.0 for reporting of adverse events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

6.3 Quality of life

6.3.1 UW-QOL

UW-QOL (Appendix C) is a concise patient-reported QOL survey with 12 domains including pain, appearance, activity level, recreation, swallowing, chewing, speech, shoulder function, taste, saliva, depression, and anxiety (25). A composite score can be derived for physical and social/emotional subscales. The most recent version, version 4, has incorporated mood and anxiety to capture the emotional QOL of patients with head and neck cancer (25).

6.3.2 MDADI

MDADI (Appendix D) is a validated self-assessment to specifically assess dysphagia's impact on the quality of life of patients with head and neck cancer (26). It is scored on a scale of 20 to 100 with higher score denoting better quality of life. MDADI is divided into subscales including functional, physical, emotional, and global domains with a combined composite score. A 10-point difference in score has been shown to be clinically meaningful (27).

6.3.3 EQ-5D-5L

EQ-5D-5L (Appendix E) is one of the most widely used assessment of health status and QOL internationally, composed of 5 items to address mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with an update in 2011 to expand each response to five levels (from three levels previously) (28).

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

Experimental therapy is de-intensified hypofractionated radiation therapy. Concurrent chemotherapy is considered standard of care.

7.1.1 Contraindications

There are no special contraindications for this study beyond typical contraindications to radiation therapy or chemotherapy.

7.1.2 Special Warnings and Precautions for Use

None

7.1.3 Interaction with other medications

None

7.1.4 Adverse Reactions

Head and neck radiotherapy and chemoradiotherapy are associated with potential acute and late toxicities.

- Acute adverse reactions:
  - Fatigue and weight loss
  - Loss of taste and appetite
  - Dysphagia and odynophagia
  - Mucositis
  - Dermatitis
- Late adverse reactions:
  - Dysphagia
  - Xerostomia
  - Altered taste
  - Lymphedema
  - Soft tissue damage (rare)
  - Osteoradionecrosis (rare)
  - Nerve or neurologic damage (rare)

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies. Adverse events are assessed in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.2.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 90 days post treatment will be considered acute adverse events. The protocol will separately define Dose Limiting Toxicity in section 9.1 as applicable.

Late Adverse Events

Adverse effects occurring in the time period from the end of acute monitoring, to 12 months post treatment, will be defined as late adverse events. The study team will review encounters in the following select specialty categories relevant to study endpoints: radiation oncology, medical oncology, and otolaryngology. The queried

encounters will be limited in scope based on categorization of events; namely, encounters that are related to any head and neck or gastrointestinal event or problem.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and potentially reported as SAEs.

[2]NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations

associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase “unanticipated problems involving risks to subjects or others” is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

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

AND

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

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up
All adverse events will be followed up according to good medical practices.

7.3 Steps to Characterize a Serious Adverse Event for Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to treatment must also be reported as indicated in the sections below.

Step 4: Determine the expectedness of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable);
- the drug package insert (if applicable);
- the current Investigator's Brochure (if applicable)
- the Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities section of this protocol

7.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. **All SAEs occurring during the protocol-specified monitoring period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s).** In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or other designee. Electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC.

UT Southwestern and affiliated will submit documentation via the SAE submission portal. All subsites participating in multi-center study may utilize the Serious Adverse Event Template and submit to the IIT Project Manager, or designee. The DSMC Coordinator will route the form to the DSMC Chair who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required via the same process. *(See Appendix V of the SCCC DSMC Plan for instructions on how to submit SAEs through the portal and for a template Serious Adverse Event Form which may be utilized by subsites on multi-center IIT studies).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chair reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chair determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Sarah Neufeld, Clinical Research Manager 214-648-1836
Written reports to: Department of Radiation Oncology Clinical Research Office The University of Texas Southwestern Medical Center Attention: Sarah Neufeld, Project Manager

2201 Inwood Road
Dallas, Texas 75390-9303
FAX #: 214-648-5923
Email: sarah.hardee@utsouthwestern.edu

UTSW SCCC Data Safety Monitoring Committee Coordinator
Email: SCCDSMC@utsouthwestern.edu
Fax: 214-648-5949 or deliver to BLB.306

UTSW Institutional Review Board (IRB)
Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of study team awareness.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/assets/policy_9.5reportable.pdf

7.4 Unblinding Procedures

Not applicable to current protocol.

7.5 Stopping Rules

The primary hypothesis of the phase 1 study is that de-intensified HFRT is safe and tolerable. The trial will terminate during the rolling 6 dose escalation phase if it has reached level -1 and 2 patients experience dose limiting toxicity (DLT) at this dose level.

The secondary hypothesis is that the crude 1-year LRC rate is at least 85% (based on historical controls). In other words, for the target of 20 evaluable patients at 1 year, up to 3

patients can have a LRR and satisfy the pre-specified hypothesis. Thus, if a 4th patient enrolled on the trial experiences LRR within 1 year of completing the study treatment, the trial will be terminated for futility.

8.0 DRUG/TREATMENT INFORMATION

8.1 Cisplatin

- Other names for the drug(s): Platinol
- Classification - type of agent: Cytotoxic chemotherapy
- Mode of action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. 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.
- Storage and stability: Please refer to the cisplatin prescribing information for storage and stability of the cisplatin commercial product
- Protocol dose: Weekly
- Preparation: Please refer to the cisplatin prescribing information for storage and stability of the cisplatin commercial product.
- Route of administration for this study: Intravenous
- Incompatibilities: Cisplatin may interact with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided. There is a total loss of cisplatin in 30 minutes at room temperature when mixed with metoclopramide and sodium metabisulphite in concentrations equivalent to those that would be found on mixing with a commercial formulation of metoclopramide. Cisplatin and sodium bisulphite have been known to react chemically. Such antioxidants might inactivate cisplatin before administration if they are present in intravenous fluids.
- Availability: Commercially available
- Side effects: Human toxicity includes nausea, vomiting, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretorytracts. Myelosuppression, often with delayed erythrosuppression, is expected. Please see the package insert for a comprehensive list of adverse events.
- Nursing implications: Not applicable

8.1.1 Return and Retention of Study Drug

Not applicable

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

9.1.1 Study design:

Phase I Rolling 6 design with dose expansion cohort
Study design will be a rolling 6 dose escalation study, a modification to the standard 3 + 3 design (29). In contrast to the 3 + 3 design where patients are enrolled in cohorts of 3, the rolling 6 design allows for continuous enrollment up to a total of 6 patients at the same dose level. The dose level assigned to a new patient is based on the number of patients currently enrolled and evaluable, and the number of patients experiencing a DLT. Once six patients have been enrolled at the current dose level, enrollment will stop until at least 5 of the 6 patients have completed evaluation for DLT. Escalation to the next dose level occurs if at time of enrollment 3/3, 4/4, 5/5, 5/6, or 6/6 patients at the dose level are evaluated for and without DLT. De-escalation occurs if at the time of enrollment, 2 or more patients have experienced a DLT at the dose level.

DLT definition:

- Any CTCAE grade 4 toxicity (generally described as life-threatening consequences with urgent intervention indicated) attributed to RT during and up to 3 months post-treatment
- Persistent CTCAE grade 3 mucositis at 3 months post-treatment
    - CTCAE definitions:
        - Oral mucositis: severe pain; interfering with oral intake
        - Pharyngeal mucositis: severe pain; unable to adequately aliment or hydrate orally; limiting self-care ADL
    - To decrease subjectivity of interpretation by each clinician, the definition for grade 3 mucositis was consolidated as below:
        - Severe pain defined as needing daily opioid use of >30 morphine equivalent dose during the past week for mucositis, AND
        - The pain interferes with oral intake or swallowing defined as tolerating a liquid only diet or requiring tube feeds (with the exception of patients who were on a liquid only diet at baseline prior to RT, in which case they would need to be feeding tube dependent to satisfy this definition).

MTD definition: highest dose/fractionation level among those listed in section 4.1.2 at which ≤1 of 6 patients have experienced a DLT.

During the dose expansion phase, patients will be enrolled at MTD to reach the total accrual goal of 24 patients.

9.1.2 Primary endpoint

- MTD of HFRT

9.1.3 Secondary endpoints

- Physician-reported acute and late toxicities
    - Rate of ≥grade 3 acute toxicities during treatment, and at 1 and 3 months after treatment using CTCAE v5.0
    - Rate of ≥grade 3 late toxicities at 6 and 12 months after treatment using CTCAE v5.0
- Oncologic outcomes: LRC, PFS, and OS from start of treatment
- Patient-reported QOL:

- MDADI, UW-QOL, and EQ-5D-5L scores at baseline, 1, 3, 6, and 12 months after treatment
- Feeding tube dependence rate at baseline, 1, 3, 6, and 12 months after treatment

9.2 Sample Size and Accrual

We anticipate 3-6 patients in each cohort with a maximum of 12 total patients (e.g. 6 in level 0, 6 in level 1 or -1) during the Rolling 6 dose escalation phase.

During the dose expansion phase, patients will be accrued until a total sample size of 24 is reached to ensure at least 20 evaluable patients at 1 year assuming an attrition rate of 15%. We anticipate accruing 3 patients per month for a total accrual period of approximately 3 years accounting for time to reach the primary endpoint at 3 months prior to enrolling on to the next cohort.

9.3 Data Analyses

9.3.1 Primary endpoint

9.3.1.1 MTD
Acute toxicity will be assessed weekly during treatment and 2 weeks, 1, 2, and 3 months post-treatment to assess for DLT to determine the MTD as outlined in Section 9.1.1.

9.3.2 Secondary endpoints

9.3.2.1 Locoregional control
LRC will be analyzed based on the definition in section 6.2 and estimated using cumulative incidence statistics, with death serving as a competing risk.

9.3.2.2 Progression free survival and overall survival
PFS and OS outcomes will be analyzed based on the definition in section 6.2 and estimated using the Kaplan-Meier method. Survival endpoints will be calculated from the initiation of RT.

9.3.2.3 Physician-reported toxicity
Only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. The rates of all Grade 3-5 adverse events will be characterized at each time point as outlined in section 5.4.

9.3.2.4 Patient-reported outcomes
The patient reported outcomes (MDADI, UW-QOL and EQ-5D-5L) will be collected as numeric scores at each time point as outlined in Section 5.4. Patients with disease recurrence will be excluded. The changes in these outcomes from baseline to the subsequent time points will be analyzed using generalized estimating equations.

9.3.2.5 Feeding tube dependence
The prevalence of feeding tube use will be described at each time point as outlined in section 5.4.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB of record will have the proper representation and function in accordance with federally mandated regulations. The IRB of record must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

10.3 Registration/Randomization Procedures

All patients will be registered electronically through Velos. All research data will be recorded and entered into Case Report Forms using REDCap (when applicable).

All subjects must be registered with the Research Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Research Office Study Coordinator.

New subjects will receive a number beginning with 01 upon study consent such that the first subject consented is numbered 01, the second subject consented receives the number 02, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 01 will become 01-101 upon enrollment. If subject 02 screen fails, and subject 03 is the next subject enrolled, subject 03 will become 03-102 and so-on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject consented as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

10.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project.

Trial monitoring will be conducted according to the study specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

Toxicity and dose escalation reviews will be performed at least annually and at time of dose escalation or de-escalation on this Phase I study. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the SCCC DSMC reviews all local and sub-site serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

10.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

Any deviation from the protocol requirements, whether pre-approved or unexpected, are to be recorded/logged as a protocol deviation and reported per institutional policy.

10.5.1 **Exceptions** (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- Intentional on part of the investigator; and/or
- In the investigator's control; and/or
- Not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)

  ➢ **Reporting requirement***: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if

your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

10.5.2 **Emergency Deviations:** include any departure from IRB-approved research that is necessary to:

- Avoid immediate apparent harm, and/or
- Protect the life or physical well-being of subjects or others

➢ **Reporting requirement***: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

10.5.3 **Serious Noncompliance** (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or
- Adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or
- Adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research**)**

➢ **Reporting requirement***: Serious Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

10.5.4 **Continuing Noncompliance:** includes a pattern of repeated noncompliance (in one or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

➢ **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

10.5.5 **Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:**

- Does not meet the definition of serious noncompliance or continuing noncompliance

➢ **Reporting requirement***: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure- whichever comes first.

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record

10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

10.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory & essential documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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12.0 APPENDICES

Appendix A: AJCC Staging, 8th Edition

1.0 Primary
1.1 Oropharynx (p16+)
T1: Tumor ≤2 cm
T2 Tumor >2 but ≤4 cm
T3: Tumor >4 cm or extension to lingual surface of epiglottis
T4: Tumor invades larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, mandible, or beyond

1.2 Oropharynx (p16-)
T1: Tumor ≤2 cm
T2 Tumor >2 but ≤4 cm
T3: Tumor >4 cm or extension to lingual surface of epiglottis
T4a: Tumor invades larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible

T4b: Tumor invades lateral pterygoid, pterygoid plates, lateral nasopharynx, skull base, or encasing carotid a.

2.0 Node
2.1 Oropharynx (p16+)
cN1: one or more ipsilateral lymph node(s) ≤6 cm
cN2: contralateral or bilateral lymph node(s) ≤6 cm
cN3: Lymph node >6 cm
pN1: <5 lymph nodes
pN2: ≥5 lymph nodes

2.2 Oropharynx (p16-)
c/pN1: single lymph node (≤3 cm) and no extranodal extension (ENE)
cN2a: single ipsilateral lymph node (>3 cm but ≤6 cm) and -ENE
pN2a: single ipsilateral lymph node (>3 cm but ≤6 cm) and -ENE OR single ipsilateral LN ≤3 cm and +ENE
c/pN2b: multiple ipsilateral lymph nodes (≤6 cm) and -ENE
c/pN2c: bilateral or contralateral lymph node (≤6 cm) and -ENE
c/pN3a: Lymph node >6 cm and -ENE
cN3b: clinically overt ENE
pN3b: lymph node >3 cm and +ENE

Appendix B: ECOG Performance Status / Karnofsky Performance Status
0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50- 60).

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).

4 Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).

5 Death (Karnofsky 0).

Appendix C: UW-QOL

University of Washington Quality of Life Questionnaire (UW-QOL)

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by checking one box for each question.

1. **Pain**. (Check one box: ☑)

   ☐ I have no pain.
   ☐ There is mild pain not needing medication.
   ☐ I have moderate pain - requires regular medication (codeine or nonnarcotic).
   ☐ I have severe pain controlled only by narcotics.
   ☐ I have severe pain, not controlled by medication.

2. **Appearance**. (Check one box: ☑)

   ☐ There is no change in my appearance.
   ☐ The change in my appearance is minor.
   ☐ My appearance bothers me but I remain active.
   ☐ I feel significantly disfigured and limit my activities due to my appearance.
   ☐ I cannot be with people due to my appearance.

3. **Activity**. (Check one box: ☑)

   ☐ I am as active as I have ever been.
   ☐ There are times when I can't keep up my old pace, but not often.
   ☐ I am often tired and have slowed down my activities although I still get out.
   ☐ I don't go out because I don't have the strength.
   ☐ I am usually in bed or chair and don't leave home.

4. **Recreation**. (Check one box: ☑)

   ☐ There are no limitations to recreation at home or away from home.
   ☐ There are a few things I can't do but I still get out and enjoy life.
   ☐ There are many times when I wish I could get out more, but I'm not up to it.
   ☐ There are severe limitations to what I can do, mostly I stay at home and watch TV.
   ☐ I can't do anything enjoyable.

5. **Swallowing**. (Check one box: ☑)

   ☐ I can swallow as well as ever.
   ☐ I cannot swallow certain solid foods.
   ☐ I can only swallow liquid food.
   ☐ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Check one box: ☑)

   ☐ I can chew as well as ever.
   ☐ I can eat soft solids but cannot chew some foods.
   ☐ I cannot even chew soft solids.

Patient ID: _____
Date: ____/____/____

v. 4

7. **Speech**. (Check one box: ☑)

- ☐ My speech is the same as always.
- ☐ I have difficulty saying some words but I can be understood over the phone.
- ☐ Only my family and friends can understand me.
- ☐ I cannot be understood.

8. **Shoulder**. (Check one box: ☑)

- ☐ I have no problem with my shoulder.
- ☐ My shoulder is stiff but it has not affected my activity or strength.
- ☐ Pain or weakness in my shoulder has caused me to change my work.
- ☐ I cannot work due to problems with my shoulder.

9. **Taste**. (Check one box: ☑)

- ☐ I can taste food normally.
- ☐ I can taste most foods normally.
- ☐ I can taste some foods.
- ☐ I cannot taste any foods.

10. **Saliva**. (Check one box: ☑)

- ☐ My saliva is of normal consistency.
- ☐ I have less saliva than normal, but it is enough.
- ☐ I have too little saliva.
- ☐ I have no saliva.

11. **Mood**. (Check one box: ☑)

- ☐ My mood is excellent and unaffected by my cancer.
- ☐ My mood is generally good and only occasionally affected by my cancer.
- ☐ I am neither in a good mood nor depressed about my cancer.
- ☐ I am somewhat depressed about my cancer.
- ☐ I am extremely depressed about my cancer.

12. **Anxiety**. (Check one box: ☑)

- ☐ I am not anxious about my cancer.
- ☐ I am a little anxious about my cancer.
- ☐ I am anxious about my cancer.
- ☐ I am very anxious about my cancer.

Which issues have been the most important to you during the past 7 days?
Check ☑ up to 3 boxes.

☐ Pain	☐ Swallowing	☐ Taste
☐ Appearance	☐ Chewing	☐ Saliva
☐ Activity	☐ Speech	☐ Mood
☐ Recreation	☐ Shoulder	☐ Anxiety

Patient ID: _____
Date: ____/____/____

v. 4

Appendix D: MDADI

The M.D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

Patient ID: _____
Date: ____/____/____

P3. People ask me, "Why can't you eat that?"

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

E6. I have low self-esteem because of my swallowing problems.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree	Agree	No Opinion	Disagree	Strongly Disagree

Patient ID: _____
Date: ____/____/____

Appendix E: EQ-5D-5L

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

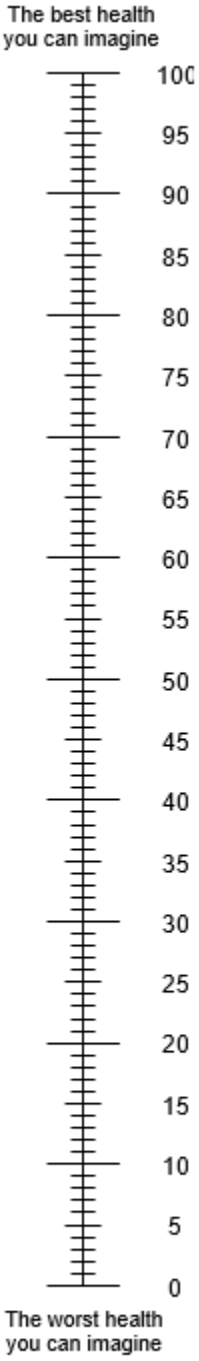
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Patient ID: _____
Date: ____/____/____

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Patient ID: _____
Date: ____/____/____