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A Phase I Study of Hypofractionated Adjuvant Radiotherapy for Resected Head and Neck Cancers (HART-HN)

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HART-HN Study

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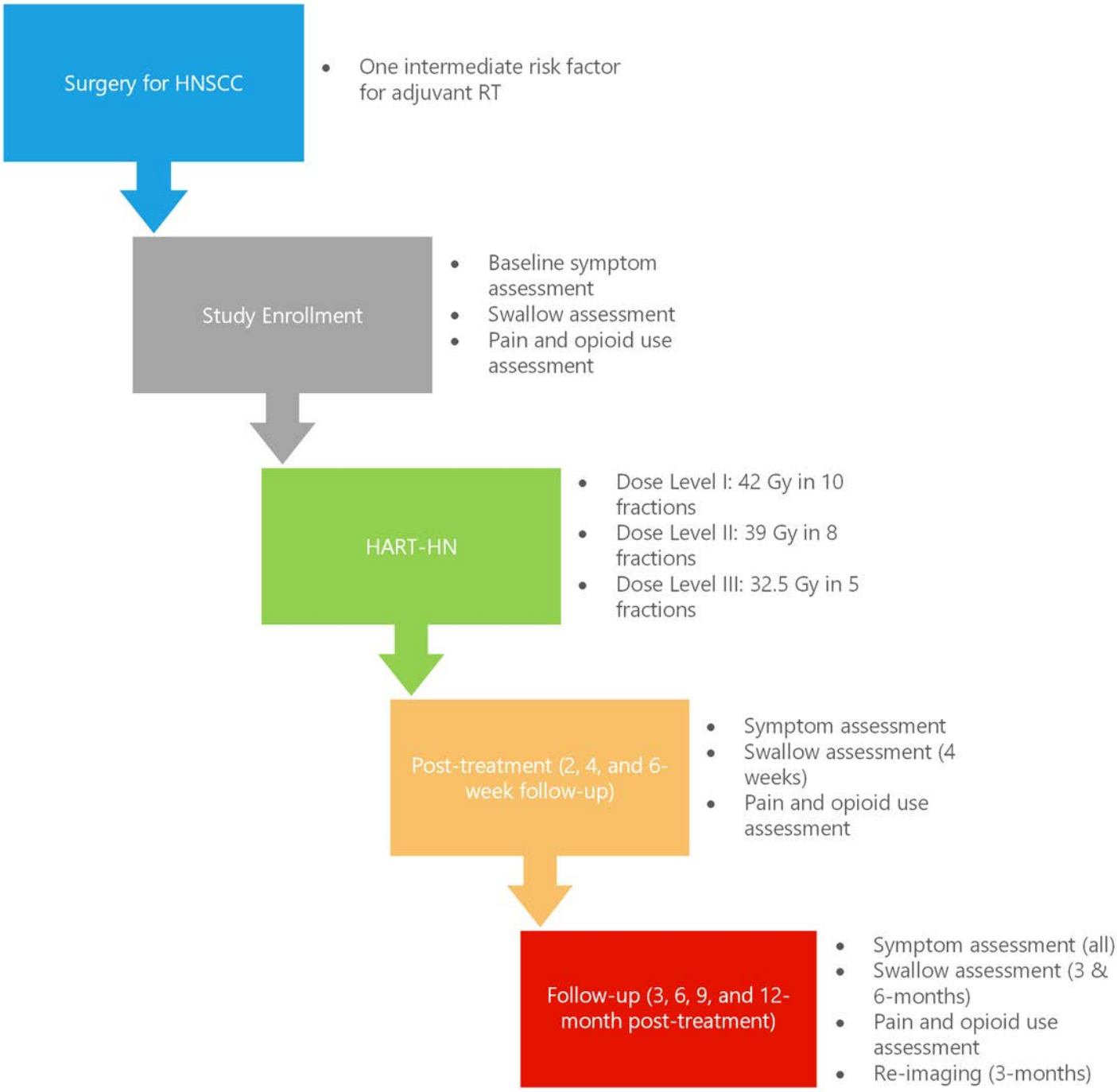
PROTOCOL SUMMARY

Title	A Phase I Study of Hypofractionated Adjuvant Radiotherapy for Resected Head and Neck Cancers (HART-HN)
IND Sponsor	NA - Investigator-Sponsor
Principal Investigator	Musaddiq Awan, MD and Joseph Zenga, MD
Clinical Trial Phase	Phase I
Study Population	Patients with Intermediate-Risk Resected Head and Neck Cancers
Primary Objectives	To determine the safe reduction of the treatment fractions to 10, 8, or 5, that may be delivered safely in resected HNSCC patients with intermediate pathologic risk features.
Secondary Objectives	1. To evaluate the efficacy of the HART-HN regimen at the minimum number of safe fractions at 1-year as measured by locoregional control and overall survival 2. To assess patient quality of life during and after the HART-HN regimen at the minimum number of safe fractions as measured by a battery of patient quality of life and functional metrics.
Study Design	We propose a pilot Phase I study using a Time-to-Event Continuous Reassessment Methodology (TITE-CRM) to estimate the minimum number of fractions of the HART-HN regimen that may be delivered safely. Patients with resected head and neck cancers found to have intermediate pathologic features warranting adjuvant radiation with no prior history of head and neck radiation and a life expectancy of at least 12 months will be enrolled. Baseline symptom evaluation will be obtained using validated surveys of head and neck cancer patients: the Functional Assessment of Cancer Therapy for the Head and Neck (FACT-HN) and the MD Anderson Dysphagia Inventory for Head and Neck (MDADI-HN). Patients will then undergo treatment using HART-HN and will then be followed for up to 1 year.

Number of Subjects	18
Estimated Time to Complete Enrollment:	Approximately 2 years

STUDY SCHEMA



STUDY CALENDAR

Study Assessment	Screening	Pre-Intervention*	Intervention**					Follow-up (until 12-months post RT)***			
Procedures	**Day -30 to Enrollment**	**Simulation & Evaluations**	**RT 1**	**RT 2-4**	**RT 5**	**RT 6-completion**	**Final Fraction of RT (+/- 48 hours)**	**2, 4, and 6 wk Post-RT Follow-Up (+/- 7 days)**	**3 mo Post-RT Follow-Up (+/- 14 days)**	**6 mo Post-RT Follow-Up (+/- 14 days)**	**9 and 12 mo Post-RT Follow-up (+/- 14 days)**
Informed Consent	X										
Physical Exam (Radiation Oncologist)[1]	X		X (One visit no later than 24 hours after fraction 5)			X (One visit to be completed no later than 24 hours after final RT fraction)		X	X	X	X
Physical Exam (Surgical Oncologist)[1]	X								X	X	X
Performance Status	X		X (One visit no later than 24 hours after fraction 5)			X (One visit to be completed no later than 24 hours after final RT fraction)		X	X	X	X
Medical History	X										
Concomitant Medications	X		X (One visit no later than 24 hours after fraction 5)			X (One visit to be completed no later than 24 hours after final RT fraction)		X	X	X	X
AE Assessment	Recorded until completion of the 12-month follow-up period										
Basic Metabolic Panel[2]	X										
Magnesium (Mg)[3]	X										
Fasting glucose[4]	X										
Pregnancy Test[5]	X										
CT/MR Simulation		X									
Radiotherapy[6]			X	X	X	X	X				
Radiation Planning		X									
SLP Evaluation		X						X	X	X	X
VFSS Study[7]		X							X	X	
DIGEST Grade		X							X	X	
FACT- HN Survey		X					X	X	X	X	X
MDADI Survey		X					X	X	X	X	X

Study Assessment	Screening	Pre-Intervention*	Intervention**					Follow-up (until 12-months post RT)***			
Procedures	**Day -30 to Enrollment**	**Simulation & Evaluations**	**RT 1**	**RT 2-4**	**RT 5**	**RT 6-completion**	**Final Fraction of RT (+/- 48 hours)**	**2, 4, and 6 wk Post-RT Follow-Up (+/- 7 days)**	**3 mo Post-RT Follow-Up (+/- 14 days)**	**6 mo Post-RT Follow-Up (+/- 14 days)**	**9 and 12 mo Post-RT Follow-up (+/- 14 days)**
Total opioid intake		X					X	X	X	X	X
Visual analog pain scale		X					X	X	X	X	X
Neck CT or MRI and Chest CT or PET/CT of chest[8]	X								X		

* Should be completed before starting radiation treatment

** Scheduled as per institutional guidelines and study protocol

*** If a subject has disease progression/relapse or subject withdrawal, then they will be followed as per follow-up requirements.

[1] Physical exam to include patient height on screening visit only. Weight, temperature, HR, RR, BP, and O_2 sats as per institutional standards at all other timepoints.

[2] Laborotory work must be completed within 14 days of study registration to assess normal ranges for eligibility: Sodium > 130 mmol/L or < 155 mmol/L; Potassium > 3.5 mmol/L or < 6 mmol/L; Serum calcium (ionized or adjusted for albumin) > 7 mg/dl or < 12.5 mg/dl.

[3] Laborotory work must be completed within 14 days of study registration to assess magnesium levels are within normal range; defined as Magnesium > 0.9 mg/dl or < 3 mg/dl.

[4] Fasting glucose should fall within normal range, > 40 mg/dl or < 400 mg/dl and be completed within 14 das of study registration.

[5]For women of childbearing potential. A negative pregnancy test (serum) must be obtained within 30 days prior to the first study intervention

[6]Radiotherapy given as per protocol and assigned dose level. Patients taking known radiosansitizers (e.g. methotrexate) are recommended to hold such medications during protocol treatment.

[7] Speech-language pathologist evaluation will include an eating assessment (EAT-10) score, the Functional Oral Intake (FOIS) score, and DIGEST grade, following the VFSS study.

[8] Neck CT (with or without contrast) or MRI of the Neck and Chest CT or PET/CT of chest (with or without contrast) must be available at screening (within 30 days prior to study enrollment) and repeated for surveillance at 3 months (+/- 2 weeks) as per institutional standard of care, based on NCCN guidelines. A Head and Neck CT may be ordered at any time, if clinically indicated. The same imaging modality and technique should be used for surveillance scans at the specified follow-up timepoints above.

LIST OF ABBREVIATIONS

AE	Adverse Event
CRC	Clinical Research Coordinator
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTO	Clinical Trials Office
DFS	Disease-Free Survival
DIGEST	Dynamic Imaging Grade of Swallowing Toxicity
DLT	Dose-Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FACT-HN	Functional Assessment of Cancer Therapy for the Head and Neck
GCP	Good Clinical Practice
HART-HN	Hypofraction Adjuvant Radiation Therapy for Resected Head and Neck Cancers
HNSCCs	Head and neck squamous cell carcinomas
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
MCWCC	Medical College of Wisconsin Cancer Center
MDADI	MD Anderson Dysphagia Inventory for Head and Neck
MRgRT	MR-guided radiation therapy
MTD	Maximum-Tolerated Dose
NCI	National Cancer Institute
NSCLCs	Non-small cell lung cancers
RT	Radiation therapy
SAE	Serious Adverse Event
SBRT	Stereotactic body radiation therapy
SD	Standard Deviation
SLP	Speen and Language Pathologist
SRC	Scientific Review Committee
TITE-CRM	Time-to Event Continuous Reassessment Methodology
ULN	Upper Limit of Normal

UP	Unanticipated Problem
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
VLSS	Videofluoroscopic Swallow Studies

1 BACKGROUND

1.1 Introduction

Mucosal head and neck squamous cell carcinomas (HNSCCs), including tumors of the oral cavity, pharynx, and larynx, are the ninth leading cause of cancer-related mortality worldwide, with an estimated 65,000 cases and 13,000 deaths in the United States in 2019 alone.[1] Two-thirds of cases present with advanced stage disease requiring multi-modality therapy. Upfront surgical resection remains a principal management strategy for HNSCCs.[2] Because recurrence rates after resection are high in the setting of adverse pathologic features, adjuvant post-operative radiation is frequently given to improve outcomes.[3,4]

Conventional post-operative radiation is a long and grueling treatment course: radiation is delivered five days per week for six weeks in 30 low-dose fractions. For HNSCC patients, this means that while recovering from major oral or pharyngeal surgery, they are forced to experience months of additional toxicities including diminished salivary flow, difficulty swallowing, and painful ulcerations of the mouth and throat (mucositis).[5] Patients may find the prospect of undergoing a six-week course of radiation after surgery overwhelming and many refuse adjuvant therapy despite the very high risk of disease relapse.[6] Even among patients who undergo post-operative radiation, excessive toxicities frequently cause breaks in therapy resulting in a prolonged treatment package time (time from surgery to completion of radiation), a feature associated with increased risk of both cancer recurrence and decreased survival.[7] Even worse, such toxicities may prohibit completion of the full treatment course.[8] ***Shortening the duration of therapy*** would increase the number of HNSCCs patients who receive the full course of indicated post-operative radiation on time and without interruption.

Hypofractionation, a strategy that takes advantage of recent advances in radiation planning and delivery to reduce the duration of radiation therapy, delivers fewer fractions of radiation at a higher dose-per-fraction.[9] Post-operative hypofractionated radiation has proven safe and effective for other disease sites including skin, breast, and prostate cancer.[10-12] Hypofractionation has also demonstrated feasibility in recurrent and unresectable HNSCC, in which target volumes are limited.[13] Based on both the difficulty of recovery after HNSCC surgery and the timeframe for radiation toxicity, condensing post-operative radiation therapy into five fractions delivered over one week would improve compliance and treatment completion rates. However, ***application of a five-fraction hypofractionated radiation regimen to the large treatment volumes required for post-operative radiotherapy in untreated mucosal HNSCCs represents a significant modification of current treatment.***

The optimal radiation dose for this novel regimen is unknown, and will require a step-wise approach to transition from current standard of care to a 5-fraction regimen. We, therefore, propose a Phase 1 clinical trial testing the safety of progressively shorter post-operative radiation regimens. ***We hypothesize that condensing post-operative radiation will reduce the duration of treatment toxicities while maintaining oncologic efficacy.*** This less onerous regimen will lead to fewer refusals and breaks in radiation, thus improving HNSCC cure.

1.2 Study Significance and Rationale

Post-operative hypofractionated radiation is well-established in many malignancies, yielding benefits in compliance, access to care, convenience, and cost savings. In several solid tumor types, short-course high dose-per-fraction (hypofractionated) post-operative radiation has shown excellent tolerability, reduced healthcare costs, improved compliance, and at least equivalent cancer control compared to conventional post-operative radiation (long course, low dose-per-fraction).[10-12] Despite advances in other malignancies, hypofractionated post-operative radiation is not used in previously untreated mucosal HNSCCs, for which an extended course of conventional post-operative radiation (usually 60 Gy in 2 Gy fractions delivered over six weeks) remains the standard. Hypofractionation has been stymied in the post-operative setting for HNSCCs primarily due to concerns of toxicity in treating a large mucosal field and an inability to spare critical structures such as the brain and spinal cord. These concerns were well-founded in the 1970s during the era of 2-dimensional radiotherapy when conventional HNSCC radiotherapy regimens were developed.[3] ***But because radiotherapy can be delivered far more precisely using intensity modulated radiation therapy (IMRT), we***

hypothesize that post-operative radiation for HNSCCs can now be delivered safely in only five fractions delivered over one week.[12,14,15] We anticipate that this condensed post-operative regimen will yield similar benefits to those seen in other malignancies: convenience, decreased costs and improved compliance and outcomes. **Specifically, we propose a clinical trial of hypofractionated post-operative radiation in intermediate risk HNSCC with three successively more condensed regimens (42 Gy in 10 fractions, 39 Gy in 8 fractions, and 32.5 Gy in 5 fractions) for three reasons:**

1) The proposed regimens can be delivered in only **two weeks or less**, increasing compliance and tolerance for HNSCC patients and decreasing omission, delays or breaks in post-operative radiation, which represent major causes of disease relapse.[6,8,16] Since substantial radiation toxicities do not typically begin until the third week of treatment, delivering post-operative radiation in only two weeks or less should lead to high compliance rates without treatment breaks. Further, HNSCC patients' ability to receive consistent post-operative radiation can be limited by travel distance and transportation challenges often related to social determinants of health including socioeconomic status, rural setting, and race.[17-19] Patients of black race, Hispanic ethnicity, or with Medicaid insurance are significantly less likely to travel long distances for treatment. As such, these groups are less likely to receive care at academic and high-volume centers, more likely to have treatment breaks, and have worse survival outcomes.[20] By condensing therapy from six weeks to two or less, this regimen will lessen the financial and psychosocial burden of radiotherapy and may reduce disparities in treatment and outcomes by facilitating greater access to care. Further, we have shown that in interviews of a subset of our patient population who refused adjuvant radiotherapy, 75% would have undergone radiation if it were completed in two weeks or less, leading us to select regimens that could be delivered in this time frame (10, 8 and 5 fractions).[21]

2) These three regimens target a biologically effective dose (BED) will of ~100 Gy for an α/β=3 for all dose levels. An important risk of hypofractionated regimens is late toxicity to normal tissues. The design of these three proposed dose levels, however, maintains an acceptable BED to late-responding tissues that is consistent with the BED3 (100 Gy) of conventional postoperative radiation of 60 Gy in 30 fractions:

Total dose(Gy)/number of fractions	Dose per fraction (Gy)	a/b 10 (Gy)	a/b 3 (Gy)
42/10	4.2	59.64	100.8
39/8	4.875	58.01	102.3
32.5/5	6.5	53.6	102.9

3) Similar hypofractionated regimens have demonstrated both safety and efficacy in multiple malignancies including skin, intracranial, and breast cancers.[12,14,15] In particular, comparable regimens such as 40 Gy delivered in ten fractions[22,23] and 30 Gy delivered in five fractions[13] have demonstrated high tumor response rates and good tolerability for HNSCCs when used in the upfront and recurrent setting for unresectable disease. Using the linear-quadratic model to compare RT dose regimens,[24] the 2 Gy per fraction equivalent dose (EQD2) of the proposed dose levels range from 44.7 Gy to 49.7 Gy. However, for very low dose-per-fraction radiotherapy, the linear-quadratic model is limited and it does not account for the potentially increased efficacy of hypofractionation due to shorter overall treatment time and reduced tumor repopulation. As such, we hypothesize these dose levels to be both safe and effective in an intermediate risk post-operative population.

Potential benefits of HART-HN: Easier access to care will lead to increased compliance with radiation and improved cancer control rates. It is well-established that patients with advanced stage HNSCCs have improved LRC and survival with the addition of post-operative radiation as compared to surgery alone.[25-28] However, while the critical importance of post-operative radiation has been known for decades, a large percentage of patients with advanced HNSCCs forego this life-saving therapy. In a preliminary study, our group analyzed the National Cancer Database (NCDB) from 2004-2015 and found that of 7,271 patients with surgically resected pathological stage III-IV oral cancer, **32% did not receive any post-operative radiotherapy and a further 14% did not finish the full course of radiotherapy** (<60Gy conventional radiation). These advanced oral cancer patients who did not receive indicated post-operative radiation therapy (PORT) or could not complete the full course of therapy had **significantly worse survival outcomes** (**Figure 1**). Omission or inability to complete radiation is frequently related to the long duration and extended toxicities of conventional therapy: six weeks of radiation is an immense physical, psychosocial, and financial commitment for patients to make immediately after a major operation. We hypothesize that if patients were offered HART-HN over two weeks or less instead of the conventional six-week course, a higher proportion would receive the full radiation treatment course, with critical implications for disease recurrence and survival. Six of the last eight HNSCCs patients at our institution who refused recommended post-operative radiation, indicated that they may have pursued treatment if offered over a shorter course.[29] This is further supported by data from breast cancer showing adoption of hypofractionation has increased radiotherapy utilization,[30] decreased wait times, and improved access to care.[31]

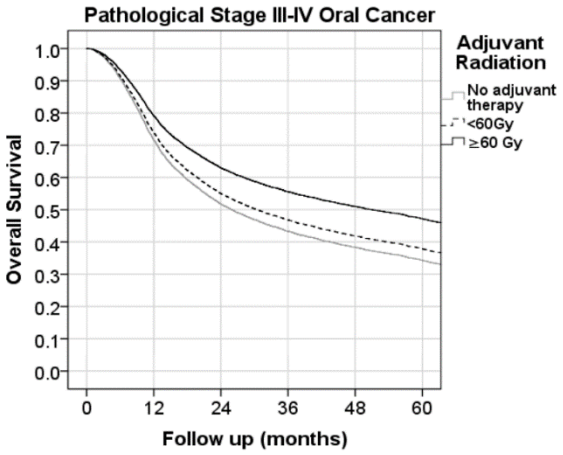


Figure 1. Association of Survival with PORT for advanced stage oral cancer. Overall survival of 7,271 patients from the NCDB with pathological stage III-IV oral cancer stratified by adjuvant radiation dose and adjusted for covariates.

Potential benefits of HART-HN: Shorter duration of treatment-related pain and less long-term opioid dependence. The addition of conventional post-operative radiation to surgery for HNSCC is a consistent risk factor for long-term opioid use.[32,33] Opioids are a cornerstone of radiation-related pain management and a necessary therapeutic tool to treat severe discomfort resulting from oral and pharyngeal mucositis. The typical duration of opioid use in patients receiving conventional post-operative head and neck radiation is over three weeks and up to one-third may continue to require opioids three months after treatment.[32-37] Both dose and duration of opioid use predicts long-term dependence.[38] We hypothesize that shortening the course of radiation through HART-HN will limit the duration of mucositis-related pain, leading to both less short-term and long-term opioid use (**Figure 2**).

Potential benefits of HART-HN: Healthcare cost reduction. Since hypofractionation involves fewer radiation treatments over a shorter duration compared to conventional therapy, it substantially reduces both healthcare and societal costs. In prostate and breast cancer, hypofractionated regimens consistently demonstrate greater than 30% direct healthcare savings over conventional therapy,[39-41] in addition to reducing transportation expenses and lost productivity from longer treatment schedules.[40,42]

Potential risks of HART-HN: Increased Acute or Late Toxicity or Decreased Efficacy. Since hypofractionation compresses radiation into a shorter time frame, there may be potential risks compared to conventional radiation. Hypofractionation may result in increased acute toxicity that may may result in an inability to complete radiation treatment or increased late toxicity that may result in chronic complications such as need of a tracheostomy unrelated to tumor progression, soft tissue necrosis, osteoradionecrosis. Further though aforementioned data suggests otherwise, a trial of hypofractionation must still be conducted as hypofractionated radiation may have decreased cancer control efficacy compared to conventional radiation.

1.3 Study Innovation

Several aspects of the HART-HN framework **(Figure 2)** for delivering post-operative radiation to patients with mucosal HNSCCs are innovative.

a. Compressed Time Frame: Unlike conventional post-operative radiation, which is delivered to a total dose of 60 Gy in 30 fractions over six weeks, HART-HN would be delivered to a total cumulative dose of 32.5-42 Gy in five to ten fractions over one to two weeks. Though the cumulative radiation dose for HART-HN is lower than for conventional post-operative radiation, we predict HART-HN to be at least as efficacious as conventional post-operative radiation for HNSCCs based on both empiric principles and analogous data from other malignancies. Accelerated repopulation of tumor cells after surgery and during radiotherapy is a principle mechanism of treatment failure in HNSCCs. From tumor line models, the estimated kickoff time for such repopulation is estimated at 21-35 days after initiation of therapy.[43] As post-operative radiation is usually initiated as soon as three to four weeks after surgery, patients receiving HART-HN will complete surgery and radiation therapy within 30-45 days, before tumors begin to rapidly repopulate, thus reducing the risk of failure. Given the short treatment time-course we also anticipate that breaks in radiotherapy will be unlikely. Additionally, radiation regimens similar to HART-HN have long been used in post-operative treatment of resected melanomas with excellent LRC upwards of 90%.[12]

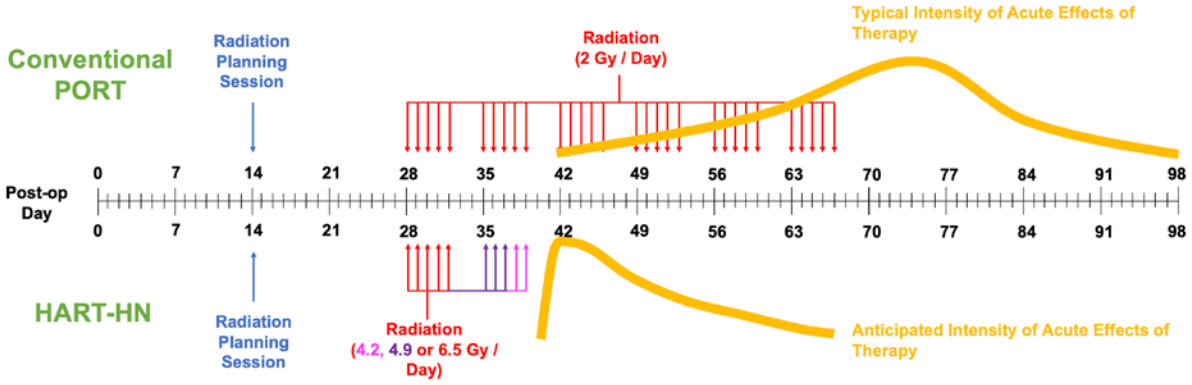


Figure 2. Comparison of conventional post-operative radiation (PORT) and HART-HN. HART-HN reduces the overall treatment time compared to conventional therapy allowing patients to initiate and complete adjuvant radiation prior to developing acute effects of therapy and reducing overall treatment package time. Patients receiving HART-HN may have a shorter total duration of acute effects of therapy (yellow) and therefore tolerate it better than conventional therapy.

Until now, the safety and efficacy of the radiotherapy dosing regimen proposed for HART-HN has not been evaluated for mucosal HNSCCs. This is because delivering such high doses per fraction was previously unfeasible due to limited image guidance capabilities and an inability to delivery precisely targeted (conformal) radiotherapy, resulting in undue toxicities to the sensitive mucosal structures of the head and neck. With the development of IMRT, it should be feasible to safely deliver this regimen post-operatively for mucosal HNSCCs while protecting critical structures including the spinal cord and brainstem.

b. Improved QOL: HART-HN is innovative in its promise to reduce the duration of acute toxicity in patients receiving treatment for HNSCCs. As depicted in Figure 2, acute radiation toxicities usually begin about 2 weeks after the initiation of radiation. These toxicities continue to escalate in intensity, reaching a maximum about 1 week after completion of treatment and resolving about one month after treatment. This delayed response occurs since acute toxicity is reflective of radiation effects on rapidly dividing tissues such as the epithelium of the skin and oral mucosa. Radiation preferentially kills rapidly dividing cells and toxicity manifests when these epithelial regions are not sufficiently repopulating, leaving a denuded epithelium. As new stem cells repopulate the area (when radiation completes), toxicity resolves. Prior to the epithelium being denuded, there is no acute toxicity.
With HART-HN, we anticipate a similar onset of symptoms about one week after treatment, as the epithelium likely will not denude until completion of treatment. Thus, patients will complete their adjuvant

treatment with HART-HN prior to developing significant acute effects, reducing the risk of treatment breaks or early discontinuation of therapy. Assuming that the acute effects of HART-HN persist for a similar duration after completion of therapy as they do for conventional post-operative radiation due to similar speed of stem cell repopulation, patients will recover from acute effects of HART-HN before patients would have even completed conventional post-operativeradiation. This should reduce patient pain and the duration of opioid therapy, ultimately improving QOL.

c. HART-HN Differs From Other Trials: Motivated by the potential benefits of hypofractionation, two clinical trials are actively investigating post-operative hypofractionation in previously untreated HNSCCs, but have important distinctions from our study.[44,45] In NCT04403620,[44] hypofractionated radiation is delivered over three or more weeks, offering limited temporal benefit over conventional therapy and therefore continued risk of treatment breaks or refusal. NCT03401840,[45] in which hypofractionated radiation is delivered in 6 fractions to 36 Gy, may not be widely applicable to all HNSCCs because it includes only a very limited subset of early stage HNSCC and omits elective nodal radiation.

2 HYPOTHESIS, OBJECTIVES, AND ENDPOINTS

We hypothesize that hypofractionated adjuvant radiation therapy for resected head and neck cancers (HART-HN) may be safely delivered in as few as 5 fractions after surgery in intermediate-risk HNSCC patients. To test this, we propose a Phase I radiation hypofractionation trial in patients with resected head and neck cancers who would require adjuvant radiation for intermediate risk factors (detailed below). This allows us to establish the safety of this regimen in patients for whom locoregional therapy is critical. If HART-HN is shown to be safe and demonstrates a signal of efficacy, this Phase I trial will serve as a foundation for future trials comparing HART-HN with conventional six-week adjuvant radiation therapy.

2.1 Primary Objectives

To determine the safe reduction of the number of fractions (10, 8, or 5), that may be delivered safely in resected HNSCC patients with intermediate pathologic risk features.

2.2 Secondary Objectives

1. To evaluate the efficacy of the HART-HN regimen at the minimum number of safe fractions at 1-year as measured by locoregional control and overall survival
2. To assess patient quality of life during and after the HART-HN regimen at the minimum number of safe fractions as measured by a battery of patient quality of life and functional metrics.

2.3 Primary Endpoint

The primary endpoint of the study is to find the maximum tolerated dose density for radiation regimens with a BED3 = 100 Gy, that may be safely delivered for the HART-HN regimen in patients with resected HNSCC with intermediate pathologic risk features.

2.4 Secondary Endpoint(s)

1. 1-year locoregional control of patients receiving HART-HN (efficacy objective)
2. 1-year overall survival of patients receiving HART-HN (efficacy objective)
3. Temporal changes in the CTCAE version 5.0 scores (quality of life objective)
4. Temporal changes in composite FACT-HN scores, composite MDADI scores, opioid use, EAT-10 questionnaire scores, Functional Oral Intake (FOIS) scores and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) grading (quality of life objective)

3 STUDY DESIGN

3.1 General Description

We propose a pilot Phase I study using a Time-to-Event Continuous Reassessment Methodology (TITE-CRM) design to estimate the minimum number of safe fractions. Patients with resected head and neck squamous cell carcinomas and no evidence of measurable disease with indications for adjuvant radiation alone and a life expectancy of at least 12 months will be enrolled. Patients with extracapsular extension and/or positive margins will be excluded due to data from multiple randomized trials suggesting a benefit for concurrent chemotherapy in this population.[4] Baseline symptom evaluation will be obtained using validated surveys of head and neck cancer patients: the Functional Assessment of Cancer Therapy for the Head and Neck (FACT-HN)[46] and the MD Anderson Dysphagia Inventory for Head and Neck (MDADI-HN).[47] Patients will then undergo treatment using HART-HN and will subsequently be followed for up to 1 year.

Adjuvant radiation is the experimental therapy in this study, which will be the subject of fraction reduction while maintaining a BED_3 of approximately 100 Gy. The minimum number of safe fractions will be determined as the radiation dose fractionation scheme with the least number of fractions at which there is no more than a 33% rate of dose-limiting toxicity (DLT) up to one year after treatment (to allow for the development of late toxicities from radiation).

All patients will receive a course of radiation therapy to the operative bed and regional elective using image-guided intensity modulated radiation therapy as detailed in section 5.1.

Patients will undergo standard consultation to receive adjuvant head and neck radiotherapy for HNSCC and will be determined to be eligible for the clinical trial. If eligible, patients will receive informed consent about the risks and benefits of the trial and if they accept, will sign confirming their enrollment. Patients will then undergo standard radiotherapy simulation including CT simulation with and without IV contrast and/or MRI simulation with and without Gadolinium contrast. Patients will complete baseline FACT-HN and MDADI surveys. Patients will also be followed with a speech and language pathologist (SLP) and undergo videofluoroscopic swallow studies (VFSS) prior to treatment, 3 months after treatment and 6 months after treatment, as is standard of care in the treatment of HNSCCs and will be graded by the Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scale.

A radiation treatment plan will be developed as per the details in Section 5.1 with two target volumes: the PTV_High (defined as the operative bed plus a 3 mm margin) will receive the experimental dose over the experimental number of fractions (BED3 of ~100, the BED3 of 60 Gy in 30 fractions) and the PTV_Low (elective lymph node regions plus 3 mm setup margin) will receive a subclinical dose over the experimental number of fractions (BED3 of ~86.4, the BED3 of 54 Gy in 30 fractions).

Patients will then undergo daily image-guided radiotherapy on a Monday-Friday basis for the total number of experimental fractions. During treatment, all patients will be evaluated for acute toxicities at least once every five fractions with a physician visit. Additionally, patients will complete repeat FACT-HN and MDADI surveys on the day of treatment review.

After completion of the HART-HN, patients will be seen in follow-up at the following time points after completion of radiotherapy: bi-weekly for the first 6 weeks, at 3 months, 6 months, 9 months and 12 months. Patients will complete repeat FACT-HN and MDADI surveys to assess for quality of life outcomes at each follow-up. Repeat imaging including a PET/CT or Chest CT (with or without contrast) and a diagnostic CT (with or without contrast) or MRI of the neck will be ordered at the 3-month (+/- 2 weeks) follow-up timepoint. A head and neck CT or MRI may be ordered at any time, if clinically indicated.

To assess efficacy of the HART-HN regimen assessment of locoregional control and overall survival will be made by the treating radiation oncologist or surgeon at each follow-up, by clinical examination of the head and neck as per the standard of care. Standard post-treatment imaging including a neck CT (with or without contrast) or MRI and a chest CT (with or without contrast) or PET/CT (with or without contrast) will be obtained at 3 months post-treatment (+/- 2 weeks), as per standard of care. Additional surveillance imaging in the follow-up setting has not shown any benefit in 3-year disease-free survival as compared to ongoing clinical surveillance.[48] Therefore, patients will be clinically followed for disease control until locoregional progression, completion of the 12-month follow-up period, patient refusal, or death.

In order to understand the acute and long-term toxicities of the HART-HN regimen patients will be followed clinically by the treating radiation oncologist, undergo routine FACT-HN and MDADI surveys, and undergo scheduled SLP visits including VFSS and DIGEST grading as detailed in the prior section. For the purposes of this study, acute toxicity will be deemed any toxicity that occurs within 90 days of completion of radiation therapy, and late toxicity will be deemed any toxicity that occurs more than 90 days after completion of radiation therapy. During each weekly treatment review and each post-treatment follow-up, the treating physician will record a pain score (scale 1-10) and use the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) to record toxicity scores for dysphagia, oral mucositis, dehydration and weight loss. The treating physician will also record tracheostomy tube dependence and feeding tube dependence at each visit.

3.2 Study Completion

The study will reach study completion approximately 24 months from the time the study opens to accrual.

4 SUBJECT PARTICIPATION, DISCONTINUATION, AND WITHDRAWAL

MCW must follow all MCW IRB requirements and policies regarding subject participation, found here:
https://www.mcw.edu/HRPP/Policies-Procedures.htm

This study protocol will be available at the Clement J. Zablocki Veterans Affairs Medical Center (CJZVAMC) where local VA IRB requirements and policies will also be followed:
https://www.research.va.gov/resources/policies/human_research.cfm

4.1 Subject Status

Subject statuses throughout the trial are defined as follows:

- Prescreening: preconsent (subject considering trial or study staff considering patient for the trial per institutional recruitment methods).
- Screening: period after consent, but prior to eligibility confirmation.
- Consented: consented, prior to eligibility confirmation.
- Eligible: the local investigator confirms all eligibly criteria apply.
- On study/enrolled: date eligibility is confirmed.
- On arm: date of enrollment.
- On treatment: first day treatment was given to the last day treatment was given.
- Off treatment: the last day treatment was given.
- On follow-up: from last day of treatment to the end of follow-up period.
- Off study: follow-up period completed, with no additional data gathered.
- Withdrawn: subject fully withdraws consent (i.e., refuses ALL follow-up, even survival) or is taken off study by the local principal investigator.

4.2 Prescreening and Screening Log

The MCW study principal investigator regularly reviews screen failure reasons to understand barriers to accrual and consider amending eligibility criteria. Screen failures are defined as participants who were considered for the trial to participate in the clinical trial with or without consent, but are not subsequently assigned to the study intervention or enrolled in the study. This study will follow our departmental and institutional SOPs regarding prescreening and screening tracking.

4.3 Consent

Investigators or their appropriate designees will identify potentially eligible subjects from their clinics, subject self-referrals, referrals from other clinicians, and/or other IRB-approved recruitment methods. No study conduct, including subject prescreening, can occur until after IRB approval.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record (per local IRB policies and SOPs). The original will be kept on file with the study records.

4.4 Screening Procedures

Refer to study calendar of events.

Visit procedures that were performed as standard of care prior to consent (without the specific intent to make the subject eligible for the trial), may count toward screening tests and eligibility if they are within the screening window.

4.5 Registration Procedures

Study staff must adhere to MCWCC CTO SOPs regarding eligibility review/confirmation.

No waivers of protocol eligibility will be granted. When clinical factors relating to an eligibility item are unclear or questionable, the MCW PI can only provide guidance or clarification on eligibility. Any eligibility questions should be directed to Musaddiq Awan, MD (mawan@mcw.edu) or Joseph Zenga, MD (jyzenga@mcw.edu).

4.6 Eligibility Confirmation

Subject Initials: _____ Subject Study ID: _____

Inclusion Criteria

1. Patients 18 years or older with gross totally resected (R0 resection) HPV-negative squamous cell carcinoma of the head and neck (squamous cell carcinoma of the larynx, hypopharynx, oropharynx, oral cavity, nasal cavity, paranasal sinuses or carcinoma of unknown head/neck primary) who have at least 1 of the following intermediate risk factors for adjuvant radiation:
    a) **Pathologic Node Positive Disease**
    b) **Perineural Invasion**
    c) **Oral cavity cancer with depth of invasion of at least 5 mm**
    d) **Lymphovascular Space Invasion**
    e) **Pathologic T3 or T4 disease**
2. Zubrod performance status 0-2.
3. Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.
4. Inclusion of Covid-19 positive patients will be based on standard institutional protocol.
5. Female patients must meet one of the following:
    - Postmenopausal for at least one year before the screening visit, or
    - Surgically sterile (i.e. undergone a hysterectomy or bilateral oophorectomy), or
    - If subject is of childbearing potential (defined as not satisfying either of the above two criteria), agree to practice two acceptable methods of contraception (combination methods requires use of two of the following: diaphragm with spermicide, cervical cap with spermicide, contraceptive sponge, male or female condom, hormonal contraceptive) from the time of signing of the informed consent form through 90 days after the last dose of study agent, AND
        - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptom-thermal, post ovulation methods] and withdrawal are not acceptable contraception methods).
6. Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to one of the following:
    - Practice effective barrier contraception during the entire study period and through 60 calendar days after the last dose of study agent, OR
    - Must also adhere to the guidelines of any study-specific pregnancy prevention program, if applicable, OR
        - Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptom-thermal, post ovulation methods] and withdrawal are not acceptable methods of contraception.)
7. Ability to understand a written informed consent document, and the willingness to sign it.

Exclusion Criteria

A potential subject who meets any of the following exclusion criteria is ineligible to participate in the study.

1. Pathologic evidence of extranodal extension.
2. Pathologic evidence of a final positive margin (R1 resection) or gross residual disease (R2 resection).
3. HPV-positive squamous cell carcinoma.
4. Prior invasive malignancy within the past 3 years (except for non-melanomatous skin cancer, and early stage treated prostate cancer).
5. Life expectancy less than 12 months.

6. Performance status Zubrod ≥ 3.
7. Patients with prior radiation therapy to the head and neck Note: Prior external beam radiotherapy is excluded, but Iodine 131 is allowed.
8. Prior systemic therapy, including cytotoxic chemotherapy, biologic/targeted therapy, or immune therapy for the study cancer.
9. Body weight ≤ 30 kg.
10. Any of the following severe laboratory abnormalities within 14 days of registration, unless corrected prior to it: Sodium < 130 mmol/L or > 155 mmol/L; Potassium < 3.5 mmol/L or > 6 mmol/L; Fasting glucose < 40 mg/dl or > 400 mg/dl; Serum calcium (ionized or adjusted for albumin) < 7 mg/dl or > 12.5 mg/dl; Magnesium < 0.9 mg/dl or > 3 mg/dl.
11. Unstable angina and/or congestive heart failure requiring hospitalization within 3 months prior to Step 1 registration.
12. Transmural myocardial infarction within 3 months prior to Step 1 registration.
13. Medical or psychiatric illness which would compromise the patient's ability to tolerate treatment or limit compliance with study requirements.
14. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception during treatment and for 6 months after radiation, this exclusion is necessary because the treatment involved in this study may be significantly teratogenic. Women who are breastfeeding are also excluded.

“I have reviewed all inclusion and exclusion criteria and confirm the subject is eligible.”

_____ _____

(CRC Name and Initials) **(Date)**

_____ _____

(Investigator Signature) **(Date)**

4.7 Discontinuation of Study Treatment, Withdrawal, and Compliance

Discontinuation from the study treatment does not mean discontinuation from the study. Subject will be considered in follow-up, study procedures should still be completed as indicated by the study protocol, and AEs/SAEs will continue to be reported according to this protocol.

In the absence of treatment delays due to adverse events, study treatment/intervention may continue until:

- Disease progression.
- General or specific changes in the subject's condition renders the subject unacceptable for further treatment in the investigator's judgment.
- Inter-current illness that prevents further treatment administration.
- Subject decides to withdraw from the study.
- The subject has significant noncompliance with the protocol (see below).
- Unacceptable adverse event(s) and/or dose level reduction beyond requirements as detailed in this protocol.
- Study stopping rules are met.

Subjects who sign the informed consent form, enroll and receive the study intervention, but subsequently withdraw, or are withdrawn or discontinued from the study will not be replaced.

Consent Withdrawal

A subject may decide to withdraw from the study at any time. MCW IRB of record's SOPs regarding consent withdrawal will be followed. If a subject intends on withdrawing consent, staff should confirm which of the following options the subject chooses and document the discussion:

- Full consent withdrawal, with no study follow-up.
- Selective consent withdrawal from interventional portion of the study but agree to continued follow-up of associated clinical outcome information.

Investigator-initiated Withdrawal

The investigator will withdraw a subject whenever continued participation is no longer in the subject's best interests. Reasons for withdrawing a subject include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a subject's request to end participation, a subject's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. The reason for study withdrawal and the date the subject was removed from the study must be documented.

4.8 Lost to Follow-Up

The following actions must be taken if a participant fails to return to the clinic for a required study visit and/or is unable to be reached for follow-up:

- The investigator or designee must make every effort to regain contact and/or reschedule a missed visit with the participant.
- A participant is deemed lost to follow-up if his/her status cannot be obtained after *all* of the following occurs at two consecutive scheduled protocol calendar timepoints:
    - Three telephone calls (at least one day apart) from the study team are unanswered,
      AND

    - A letter (Appendix 2) to the participant's last known mailing address goes unanswered, **AND**
    - These contact attempts must be documented in the participant's medical record or study file.
- Update OnCore®/REDCap (Follow-Up tab and eCRF) when a participant is officially considered lost to follow-up.
- If a subject is considered lost to follow-up, but subsequently contacts the study team, the subject should be considered in follow-up again.

4.9 Accrual Suspension and Closure

The MCW PI facilitates the suspension and closing of accrual in the following manner:

- OnCore® and REDCAP track accrual throughout the study.
- If the study must be suspended, OnCore® and REDCap are updated to a 'suspended' status.
- When the accrual number is reached, OnCore® and REDCapnotifies staff of study closure.

4.10 End of Study Definition

A participant is considered to have completed the study if he or she completed all phases of the study, including the last visit or the last scheduled procedure shown in the calendar of events or has been discontinued.

4.11 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause (as determined by the MCW study PI, DSMC, sponsor, and/or IRB). Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the MCW principal investigator (PI) will promptly inform the MCW Institutional Review Board (IRB), and the sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes.

5 TREATMENT PLAN

5.1 Radiation Therapy

Radiation therapy will be delivered using intensity modulated radiation therapy with daily cone-beam CT.

5.1.1 Simulation, Localization and Treatment Planning Requirements

Patients must be immobilized using a thermoplastic head mask extending to include neck and shoulder immobilization.
Treatment planning CT and/or images will be required for target volume delineation including gross tumor volume (GTVs), clinical target volumes (CTVs) and planning target volumes (PTVs). CT will be used for dose calculation. All tissues to be irradiated should be included in the CT scan. CT slice thickness should be 2 mm or less. MR simulation is optional.
Daily Cone-Beam CT is required.

5.1.2 Target Volumes

CT images will be segmented by the attending radiation oncologist to define the target volumes detailed below:

GTVp: The initial GTVp is defined as the pre-operative extent of all known gross primary disease determined from clinical information, endoscopic examination, MRI and PET images.
GTVn: The GTVn is defined as the pre-operative extent of all known pathologically-involved lymph nodes as determined from clinical information, CT, MRI, PET images and pathology reports.
CTV_High: The high-dose CTV will be the entire post-operative bed including dissected lymph node levels regardless of whether there is pathologic evidence of lymph nodes.
CTV_Low: The low-dose CTV will include any elective treatment areas including areas at risk near the primary site including at least a 1 cm anatomically-confied margin around the operative bed (i.e. the contralateral tongue or adjacent floor of mouth) and/or undissected lymph node beds at risk for disease involvement based upon the guidelines outlined in Biau et al. (Biau Green Journal 2019).
Planning Target Volumes: A margin no larger than 3 mm will be added to the CTV_High and CTV _Low to define the PTV_High and PTV_Low, respectively for daily changes in setup motion.

5.1.3 Critical Normal Tissues

Required critical normal tissues to be segmented (recommended labeling in italics) include unless those tissues were resected at the time of surgery (i.e. the Supraglottic and glottic larynx in a total laryngectomy patient):

- Brainstem (Brainstem)
- Spinal Cord (SpinalCord)
- Brainstem PRV 5 mm (Brainstem_PRV03)
- Spinal Cord PRV 5 mm (SpinalCord_PRV05)
- Left (OpticNrv_L) and right (OpticNrv_R) optic nerves
- Optic chiasm (OpticChiasm)
- Mandible (Bone_Mandible)
- Left (Parotid_L) and right (Parotid_R) parotid glands
- Left (Glnd_Submand_L) and right (Glnd_Submand_R) submandibular glands
- Oral cavity (Oral_Cavity)
- Lips (Lips)
- Supraglottic and glottic larynx (LarynxGSL)
- Pharyngeal constrictors (Pharynx)
- Trachea (Trachea)
- Esophagus on Slices with the PTV (Esophagus_S)
- Left (BrachialPlexus_L) and right (BrachialPlexus_R) brachial plexus
- Patient (External)

5.1.4 Radiation Treatment Planning

The treatment plan will be based on the analysis of the volumetric dose, including dose volume histogram analyses of the PTVs and critical normal tissues. IMRT planning is mandatory.

5.1.4.1 Dose Fractionation

Once daily radiation will be delivered as per the enrolled dose level of the patient:

	Target	Dose Level 1	Dose Level 2	Dose Level 3
D_{PTV_High}	PTV_High	42 Gy in 10 fx	39 Gy in 8 fx	32.5 Gy in 5 fx
D_{PTV_Low}	PTV_Low	38 Gy in 10 fx	34 Gy in 8 fx	29 Gy in 5 fx

5.1.4.2 Dose Specification

The prescribed dose for each PTV volume should cover at least 95% of the volume. Additionally, 98% of the prescribed dose for each PTV volume should cover at least 98% of the volume.
As an acceptable deviation, 95% of the prescribed dose for each PTV volume should cover at least 95% of the volume. Additionally, 93% of the prescribe dose for each PTV volume should cover at least 98% of the volume.

5.1.4.3 Dose Constraints

Required

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
PTV_High	$D_{95\%}$ $D_{98\%}$	D_{PTV_High} 98% of D_{PTV_High}	95% of D_{PTV_High} 93% of D_{PTV_High}
PTV_Low	$D_{95\%}$ $D_{98\%}$	D_{PTV_Low} 98% of D_{PTV_Low}	95% of D_{PTV_Low} 93% of D_{PTV_Low}
Patient	$D_{0.03cc}$	106% D_{PTV_High}	110% D_{PTV_High}

Dose Level 1 (42 Gy in 10 fractions)

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Spinal Cord	$D_{0.03cc}$	20 Gy	30 Gy
Brainstem	$D_{0.03cc}$	20 Gy	30 Gy
SpinalCord_PRV05	$D_{0.03cc}$	20 Gy	30 Gy
Brainstem_PRV03	$D_{0.03cc}$	20 Gy	30 Gy
OpticNrv_L or OpticNr	$D_{0.03cc}$	20 Gy	30 Gy
OpticChiasm	$D_{0.03cc}$	20 Gy	30 Gy
Mandible	$D_{0.03cc}$	30 Gy	108% D_{PTV_High}
Esophagus	$D_{0.03cc}$	30 Gy	108% D_{PTV_High}
Trachea	$D_{0.03cc}$	30 Gy	108% D_{PTV_High}
BrachialPlexus_L or BrachialPlexus_R	$D_{0.03cc}$	30 Gy	105% D_{PTV_High}

Dose Level 2 (39 Gy in 8 fractions)

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Spinal Cord	$D_{0.03cc}$	17.5 Gy	24 Gy
Brainstem	$D_{0.03cc}$	17.5 Gy	24 Gy
SpinalCord_PRV05	$D_{0.03cc}$	17.5 Gy	24 Gy
Brainstem_PRV03	$D_{0.03cc}$	17.5 Gy	24 Gy
OpticNrv_L or OpticNr	$D_{0.03cc}$	17.5 Gy	24 Gy
OpticChiasm	$D_{0.03cc}$	17.5 Gy	24 Gy
Mandible	$D_{0.03cc}$	24 Gy	108% D_{PTV_High}
Esophagus	$D_{0.03cc}$	24 Gy	108% D_{PTV_High}
Trachea	$D_{0.03cc}$	24 Gy	108% D_{PTV_High}
BrachialPlexus_L or BrachialPlexus_R	$D_{0.03cc}$	24 Gy	105% D_{PTV_High}

Dose Level 3 (32.5 Gy in 5 fractions)

Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Spinal Cord	$D_{0.03cc}$	15 Gy	20 Gy
Brainstem	$D_{0.03cc}$	15 Gy	20 Gy
SpinalCord_PRV05	$D_{0.03cc}$	15 Gy	20 Gy
Brainstem_PRV03	$D_{0.03cc}$	15 Gy	20 Gy
OpticNrv_L or OpticNr	$D_{0.03cc}$	15 Gy	20 Gy
OpticChiasm	$D_{0.03cc}$	15 Gy	20 Gy
Mandible	$D_{0.03cc}$	20 Gy	108% D_{PTV_High}
Esophagus	$D_{0.03cc}$	20 Gy	108% D_{PTV_High}
Trachea	$D_{0.03cc}$	20 Gy	108% D_{PTV_High}
BrachialPlexus_L or BrachialPlexus_R	$D_{0.03cc}$	20 Gy	105% D_{PTV_High}

Recommended

Dose Level 1 (42 Gy in 10 fractions)

Structure	Dosimetric Parameter	Recommended Constraint
Mandible	$V_{20\ Gy}$ $V_{25\ Gy}$	< 50% < 33%
Parotid_L or Parotid_R	D_{mean}	18 Gy
Glnd_Submand_L or Glnd_Submand_R	D_{mean}	27 Gy
Pharynx	D_{mean}	30 Gy
LarynxGSL	D_{mean}	30 Gy
Lips	$D_{0.03cc}$	20 Gy
Oral Cavity	D_{mean}	20 Gy
Esophagus	D_{mean}	20 Gy

Dose Level 2 (39 Gy in 8 fractions)

Structure	Dosimetric Parameter	Recommended Constraint
Mandible	$V_{20\ Gy}$ $V_{25\ Gy}$	< 50% < 33%
Parotid_L or Parotid_R	D_{mean}	17 Gy
Glnd_Submand_L or Glnd_Submand_R	D_{mean}	25 Gy
Pharynx	D_{mean}	29 Gy
LarynxGSL	D_{mean}	29 Gy
Lips	$D_{0.03cc}$	19 Gy
Oral Cavity	D_{mean}	19 Gy
Esophagus	D_{mean}	19 Gy

Dose Level 3 (32.5 Gy in 5 fractions)

Structure	Dosimetric Parameter	Recommended Constraint
Mandible	$V_{15\ Gy}$ $V_{20\ Gy}$	< 50% < 33%
Parotid_L or Parotid_R	D_{mean}	13 Gy
Glnd_Submand_L or Glnd_Submand_R	D_{mean}	20 Gy
Pharynx	D_{mean}	22 Gy
LarynxGSL	D_{mean}	22 Gy
Lips	$D_{0.03cc}$	15 Gy
Oral Cavity	D_{mean}	15 Gy
Esophagus	D_{mean}	15 Gy

5.1.5 Treatment Verification

Daily CBCT is required for treatment setup

6 ADVERSE EVENTS: DEFINITIONS, COLLECTION, AND REPORTING REQUIREMENTS

6.1 Definitions

6.1.1 Adverse Event (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. (International Conference on Harmonisation [ICH], E2A, E6).

This includes the following:

- Adverse events not previously observed in the subject that emerge during the protocol-specified adverse event reporting period, including signs or symptoms associated with head and neck cancer that were not present prior to the adverse event reporting period.

- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)

- If applicable, adverse events that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified adverse event reporting period.

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, located on the CTEP web site:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures.

6.1.2 Serious Adverse Event (SAE)

Serious Adverse Event (SAE) means any untoward medical occurrence that results in any of the following outcomes:

- **Death.** Results in death.
- **Life threatening**. Is life threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- **Hospitalization**. Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
- **Disability/incapacity**. Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- **Pregnancy**
- **Congenital anomaly/birth defect:** Results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- **Medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

6.1.3 Assessment of Severeity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. The below table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated

2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated
5	Death related to adverse event

Notes:

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event.

d. Grade 4 and 5 events must be reported as serious adverse events.

6.1.4 Attribution of an Adverse Event

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to study intervention (see following guidance), and actions taken.

An assessment of the relationship between the adverse event and the medical intervention, using the following categories:

Definitely Related: *The AE is clearly related to the intervention*. There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

Probably Related: *The AE is likely related to the intervention.* There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

Possibly Related: *The AE may be related to the intervention.* There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial intervention). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events).

Unlikely: *The AE is doubtfully related to the intervention.* A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).

Unrelated: *The AE is clearly NOT related to the intervention.* The AE is completely independent of study intervention, and/or evidence exists that the event is definitely related to another etiology.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes: Related (definitely, probably, possibly, unlikely)

There is a plausible temporal relationship between the onset of the AE and administration of the radiotherapy and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug or with similar treatments; and/or the AE abates or resolves upon discontinuation of the radiation therapy or dose reduction and, if applicable, reappears upon re- challenge.

No: Not Related (unrelated)

Evidence exists that the AE has an etiology other than the radiation therapy (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to radiotherapy administration (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

6.1.5 Expectedness of an Adverse Event

Study Investigator or treating Physician will be responsible for determining whether an AE is expected or unexpected as indicated in the protocol, informed consent form and/or drug information brochure. Expected adverse events of study intervention are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B), when applicable.

Unexpected adverse events of study intervention are those not listed in the P.I or current I.B or not identified that are not attributable to radiotherapy. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis. An AE will be considered unexpected if the nature, severity, or frequency of the event is NOT consistent with the risk information previously described for the study intervention (radiotherapy).

6.2 Collection and Reporting Requirements for Adverse Events and Serious Adverse Events

6.2.1 Collection of Adverse Events

All AEs (including SAEs) must be recorded in OnCore® and REDCap (as applicable) and/or an Adverse event log. All AEs required to be collected must be graded according to the CTCAE v5. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Investigator's or Treating physician's assessment of AE attributions must also be documented.

AEs will be collected from the time the subject signs the consent form through completion of the entire 12-month follow-up period. After this period, investigators should only report SAEs that are attributed to prior study treatment. AEs will be tracked and followed until resolution, subject withdraws consent, or is lost to follow-up (including subjects who discontinue early). All adverse events collected per the protocol will be followed with appropriate medical management until they are resolved, if they are related to the study treatment, or until the investigator deems the event to be chronic.
Please see section 6.2.2 and table 2 to identify the adverse events that need to be reported.

6.2.2. Procedures for eliciting, recording, and reporting adverse events

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- ❑ "How have you felt since your last clinical visit?"
- ❑ "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

6.2.2.1 Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

6.2.2.2 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

6.2.2.3 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

6.2.2.4 Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

6.2.3 Reporting of Adverse Events and Serious Adverse Events

Sponsor-Investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports, other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the investigational product

Please refer to table 2 below to identify adverse events that meet reporting requirements.

All serious adverse events (SAEs) must also be documented in OnCore® and REDCap.

Table 2

<table>
<tr><td rowspan="3">Attribution</td><td colspan="4">SAE</td><td colspan="3">AE</td></tr>
<tr><td colspan="2">Grade 1, 2 & 3</td><td colspan="2">Grade 4 and 5</td><td>Grade 3</td><td colspan="2">Grade 4</td></tr>
<tr><td>Expected</td><td>Unexpected</td><td>Expected</td><td>Unexpected</td><td>Unexpected</td><td>Expected</td><td>Unexpected</td></tr>
<tr><td>Unrelated
Unlikely</td><td rowspan="2">IRB[1] and DSMC-Routine Review[2]</td><td>IRB[1] and DSMC-Routine Review[2]</td><td rowspan="2">IRB[1]-Routine Review[2]

DSMC[3]-Within 5 calendar days</td><td>IRB[1]-Routine Review[2]

DSMC[3]-Within 5 calendar days</td><td rowspan="2">DSMC[2]-Routine Review</td><td rowspan="2">DSMC[3]-Within 5 calendar days</td><td rowspan="2">DSMC[3]-Within 5 calendar days</td></tr>
<tr><td>Possible
Probable
Definite</td><td>IRB[1] and DSMC[3]-Within 5 calendar days</td><td>IRB[1] and DSMC[3]-Within 5 calendar days</td></tr>
</table>

[1]Guidance on Adverse Event Reporting to the IRB is available online at MCW IRB Policies and Procedures.

[2]For routine reporting, the events will be reported to IRB as part of the annual continuing progress report, and the DSMC will review events entered in OnCore® at the time of scheduled monitoring.

[3]For expedited DSMC reporting, study coordinator/research nurse must notify the DSMC via email. For AEs, include the subject ID, date of event, grade, relatedness, expectedness, and a short narrative. For SAEs, DSMC will review the SAE report entered into OnCore®.

6.2.4 Reporting Instructions

- **Reporting to Regulatory Authorities, Ethics Committees and Investigators**

  Sponsor Investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial

approval, in compliance with local regulations.

Sponsor Investigator, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

Sponsor Investigator will be responsible for the expedited reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

Sponsor Investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

6.3 Unanticipated Problem Involving Risk to Subject or Other (UPIRSO)

The investigator and his or her team will follow the Medical College of Wisconsin policies related to unanticipated problems involving risks to subjects or others. This information may be found on the Human Research Protection Program website.

6.4 Subject Complaints

If a complaint is received by anyone on the study staff, it will be discussed with the study staff and will be addressed on a case-by-case basis. The PI will be notified of any complaints. Complaints will be reported to the IRB if indicated.

If the subject has questions about his or her rights as a study subject, wants to report any problems or complaints, obtain information about the study or offer input, the subject can call the Medical College of Wisconsin/Froedtert Hospital research subject advocate at 414-955-8844. This information is provided to the subject in their consent.

Further, if VA subjects have questions about their rights as study participants, they may contact the local VA IRB research subject advocate at 414-384-2000, ext 41430. This information is provided to the subject in their consent form.

7 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is a Phase I dose-hypofractionation trial of radiation dose using a novel radiation treatment regimen called HART-HN. The primary objective of the study is determine the safe reduction of the number of fractions (10, 8, or 5), of the HART-HN regimen, that may be delivered safely in resected HNSCC patients with intermediate pathologic risk features, using the Time-to-Event Continuous Reassessment Methodology design. This will be determined as the radiation dose with the minimum number of fractions at which there is no more than a 33% rate of dose-limiting toxicity (DLT) up to 12 months after completion of radiation treatment (to allow for the development of late toxicities from radiation treatment). There will be three radiation dose levels (all with a BED_3 of approximately 100 Gy) evaluated to the operative bed: 42 Gy in 10 fractions (Dose Level 1), 39 Gy in 8 fractions (Dose Level 2) and 32.5 Gy in 5 fractions (Dose Level 3). The total sample size for this study is 18 patients to be recruited over 12 months.

TITE-CRM is an adaptive Phase I trial design methodology which allows for MTD-finding by weighting the follow-up contribution of previously enrolled patients to the selection of the dose level for each newly enrolled patient. If a patient dies of disease progression without evidence of radiation-related toxicity, they will be censored for

toxicity at the time point of last follow-up. Thus, TITE-CRM allows for dose modification even if patients have not completed the entire follow-up period. At the enrollment of each new patient, beyond the three initial patients who will receive the lowest dose of 42 Gy), all available follow-up for all patients already on study will be used to determine the dose level for the newly enrolled patient based on the TITE-CRM methodology. For example, if three patients are enrolled every two months, by month seven, the first patient (who enrolled in month 1) provides up to 6 months of follow-up whereas the ninth patient (who enrolled in month 6) provides only about 1 month of follow-up. All available follow-up data from the first nine patients will be used by the TITE-CRM model to make a decision on the dose for the tenth patient. Unlike a standard 3+3 design, the TITE-CRM model may maintain the current dose level, increase the dose level or decrease the dose level based on all available follow-up data at the time of enrollment of the tenth patient.

To implement the TITE-CRM model, we will be using the titecrm function from the R package dfcrm. An unconstrained TITE-CRM model potentially allows for rapid early dose escalation from Dose Level 1 to 3. To prevent this overly aggressive dose escalation we will require at least 3 sequential patients at each dose level, pior to escalating dose. Further, in the case of rapid enrollment of 3 sequential patients at a new dose level, enrollment will be paused until one of these patients experiences a DLT or a minimum of 3 months elapses from the initiation of radiation treatment for these 3 patients.

7.2 Objectives and Analysis Plans

7.2.1 Primary Objective and Analysis Plan

The primary objective of the study is to determine the safe reduction of the number of fractions (10, 8, or 5), that may be delivered safely in resected HNSCC patients with intermediate pathologic risk features.

The minimum number of safe fractions will be determined as the radiation dose at which there is no more than a 33% rate of dose-limiting toxicity (DLT) up to 12 months after completion of radiation treatment (to allow for the development of late toxicities from radiation treatment) using the TITE-CRM design.

A DLT will be defined for the purposes of this protocol as an inability to complete radiation treatment within 30 days of the start of radiotherapy not deemed to be related to disease progression or unrelated death, unacceptable toxicity within one year of treatment (Grade 4+ toxicity) probably or definitely related to radiation treatment as deemed by the treating physician, or a death within one year of treatment deemed probably or definitely related to treatment. Expected Grade 3 acute toxicities typical of head and neck radiation that resolve within 90 days of treatment, including acute dermatitis, acute mucositis, feeding tube placement, electrolyte abnormalities, pain requiring narcotic medication and dehydration requiring IV hydration will **NOT** be considered DLTs. Grade 4+ late toxicities that may be considered a DLT of radiation include but are not limited to:

- Chondronecrosis of the laryngeal cartilages
- Laryngeal edema requiring tracheostomy
- Carotid blowout syndrome or other life-threatening vascular bleed
- Aspiration pneumonia requiring ICU admission not related to tumor progression
- Chronic non-healing wound or soft tissue necrosis requiring flap reconstruction
- Brainstem necrosis
- Radiation myelopathy

Death deemed unrelated to radiation (such as death due to malignancy or other comorbidity) will not be considered a DLT.

All patients who initiate radiation therapy will be evaluable for the primary endpoint as long as they initiate radiation therapy.

7.2.2 Secondary Objectives

1. To evaluate the efficacy of the HART-HN regimen at the minimum number of safe fractions at 1-year as measured by locoregional control and overall survival

    a. To estimate 1-year locoregional recurrence, patients will be followed for locoregional recurrence during the 12-month follow-up period with death as a competing risk using the methodology of Fine and Gray. Cumulative incidence curve will be plotted to describe dynamics of locoregional recurrence over time.

    b. To estimate 1-year overall survival, the Kaplan-Meier methodology will be used.

2. To assess patient quality of life during and after the HART-HN regimen at the minimum number of safe fractions as measured by a battery of quality of life and functional metrics.

    a. Quality of life changes will be determined by measuring the following quality of life/toxicity scores at the time points specified in the study calendar: CTCAE version 5.0 scores, composite FACT-HN scores, composite MDADI scores, opioid use, EAT-10 questionnaire scores, Functional Oral Intake (FOIS) scores and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) grading. QOL measures will be summarized by descriptive statistics; no inferential statistics or hypothesis testing will be performed. The proportion of missing responses will be reported on QOL and functional measures.

    b. To determine changes in quality of life and toxicity scores, longitudinal plots of these scores will be used to determine whether these return to baseline or improve after treatment.

7.3 Sample Size Justification

The projected sample size will be 18, and we estimate an accrual rate of 3 patients every 2 months for a total estimated accrual time of 12 months. Patients will be recruited for the study based on whether they are unsuitable candidates for full course definitive chemoradiation either due to inability to tolerate cisplatin, locoregionally recurrent disease after surgery, or de novo metastatic disease. Based on our tumor board presentations, we typically have 6 patients who meet these criteria every month, so the proposed study of 18 patients can be easily accomplished within 12 months of opening if we are able to enroll 25% of eligible patients on this trial. We estimate an accrual of 3 study patients every 2 months (1.5 patients per month)

A review of patients treated at our institution with conventional post-operative radiotherapy from 2017-2019 had a one-year Grade 4+ toxicity rate of 9.5% with a one-year overall survival of 75%. As hypofractionated radiation has similar toxicity rates to conventional fractionation and non-inferior disease control in other malignancies,[15] it is reasonable to expect that the HART-HN regimen may have a similar rate of late toxicity (9.5%) and at least similar survival outcomes to our patient population. In order to demonstrate the feasibility of detecting the correct MTD of the HART-HN regimen with a sample size of 18 patients, we performed Monte-Carlo simulation studies (1000 resamples each) with various *a priori* estimates of toxicity at the three doses (Table 1). For these simulations the following assumptions were made: (1) a constant hazard of observing DLT through the 12-month follow-up period; (2) a one-year survival of 75.4% (constant hazards as well); (3) a study accrual rate of three patients every two months; (4) toxicity as a function of dose level is modeled empirically; and (5) enrollment suspension prior to dose escalation as detailed at the end of section 7.1.

Table. Results of Monte Carlo Simulation Studies Across Different Assumed Dose-Toxicity Profiles (Bolded Numbers Reflect Values for the MTD Based on the Assumed Toxicity Profile)

Assumed 1-year toxicity rates at 42 Gy in 10 fractions, 38 Gy in 8 fractions and 32.5 Gy in 5 fractions	Probability that MTD is declared at 30, 32.5 or 35 Gy and the probability that the stopping rule is invoked
5%, 15%, **30%**	15.9%, 28.2%, **55.9%,** 0.0%
10%, 15%, **25%**	24.4%, 25.2%, **50.3%,** 0.1%
10%, **30%,** 50%	51.0%, **27.8%,** 21.1%, 0.1%
30%, 45%, 60%	**86.0%,** 6.2%, 1.1%, 6.7%

The probability of correctly identifying the MTD depends on the assumed toxicity at each dose level. However, using a wide variety of assumed toxicities at each dose level and a sample size of 18, results in a good probability of detecting the MTD for the majority of *a priori* estimates. Further, the chance of incorrectly selecting a dose level higher than the true MTD is reasonable (~20% or less at each assumed toxicity level).

No confidence intervals will be constructed due to the small sample size of our study.

7.4 Study Monitoring, Interim Analyses, and Early Stopping Rules

This is a Phase I clinical trial. Patients will receive continued follow-up during and after treatment up to 12 months after completion of the HART-HN regimen. All side effects will be reported and any adverse events will be reported to the IRB as per national and local clinical trial requirements. The project is monitored at all times by the Principal Investigators and/or co-investigators. A physician is present at all exams. The Institutional IRB reviews each project yearly. If at any time during the study, there is a greater than 95% probability that the 12-month of Dose Level 1 exceeds 33%, accrual will be suspended temporarily. Accrual will only resume, if, after further follow-up, this probability is less than 95%.

Adverse Event Reporting: Any adverse event such as unanticipated or severe toxicity from radiation would be reported to the IRB under the guidelines as required by our Institution. Any DLT will be reported to the MCW DSMC within 5 calendar days of the study staff's knowledge of such an event.

Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

Study Discontinuation by PI

The PI has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients. Patient enrollment is unsatisfactory.

8 DATA AND SAFETY MONITORING PLAN (DSMP)

8.1 Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with safety and progress reports submitted to the DSMC.

The DSMP for this study will involve the following entities:

8.2 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist, and the study biostatistician. While subjects are on study, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings including attendance are documented.

8.3 Quality Assurance

The MCW Radiation Oncology ROCKET program and CCCTO will provide ongoing quality assurance audits. This protocol was classified as high risk and will be reviewed internally by the MCW Cancer Center Clinical Trials Office Quality Assurance Staff according to the MCWCC Data and Safety Monitoring Plan and current version SOP, 6.5.2 Internal Quality Assurance Reviews.

8.4 Clinical Trials Office

The MCW Radiation Oncology ROCKET program will provide administrative assistance and support to the DSMC.

8.5 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website (Data and Safety Monitoring Plan).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension, or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

9 REGULATORY COMPLIANCE, ETHICS, AND STUDY MANAGEMENT

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

9.1 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Pre-study Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

Prior to implementing this protocol at CJZVAMC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the VAMC IRB.

9.3 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g., advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the subject (and Legally Authorized Representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, hospital staff was present for consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients that require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. We will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to Health Information Management (HIM) a copy of the signed consent to be scanned into EPIC, the legal medical record.

VA Cancer Clinical Trial Office consent policy will apply to VA subjects. The original consent will be kept in the subject's study file.

9.4 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the principal investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that additional people will handle the subject's personal health information. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked Clinical Research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the Case Report Forms contain the study identifiers, subject initials, date of birth and date of service.

The principal investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor/s or other authorized representatives of the principal investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

9.5 Protection of Human Subjects

9.5.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

9.5.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

9.5.3 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review, and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

9.6 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

10 DATA HANDLING AND RECORD KEEPING

10.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss, or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians, and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

10.2 Data Management Responsibilities

Principal Investigator
The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication, and investigational product(s), measurements, exams, evaluations, and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

Research Coordinator
A research coordinator creates, collects, and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

Research Nurse/Medical Staff

The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events, and compliance to study procedures.

Biostatistician
The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

10.3 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file.

All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

10.4 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document outcomes. All study data will be entered into OnCore® and REDCap via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The Clinical Research Coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC DSMC and regulatory agencies.

10.5 Study Record Retention

The principal investigator is required to maintain adequate records.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation.

Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory 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.

APPENDIX 1. PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity Fully active, able to carry on all predisease performance without restriction	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	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
2	In bed < 50% of the time Ambulatory and capable of all self-care, but unable to carry out any work activities Up and about more than 50% of waking hours	60	Requires occasional assistance, but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2. LOST TO FOLLOW-UP LETTER

Date: _____

Dear _____,

The research study team has been unable to contact you regarding the clinical trial (A Phase I Study of Hypofractionated Adjuvant Radiotherapy for Resected Head and Neck Cancers (HART-HN)) you participated in.

We would like to discuss how you are doing and if we may continue contacting you.

Please contact us at _____

Sincerely,

_____

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