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NCI Comprehensive Cancer Center
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STUDY NUMBER: CASE 4318

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Version Date: 5/8/2020

STUDY TITLE: Feasibility Study of Temporally Feathered Radiation Therapy (TFRT) for Head and Neck Squamous Cell Carcinoma: Means of Toxicity Reduction

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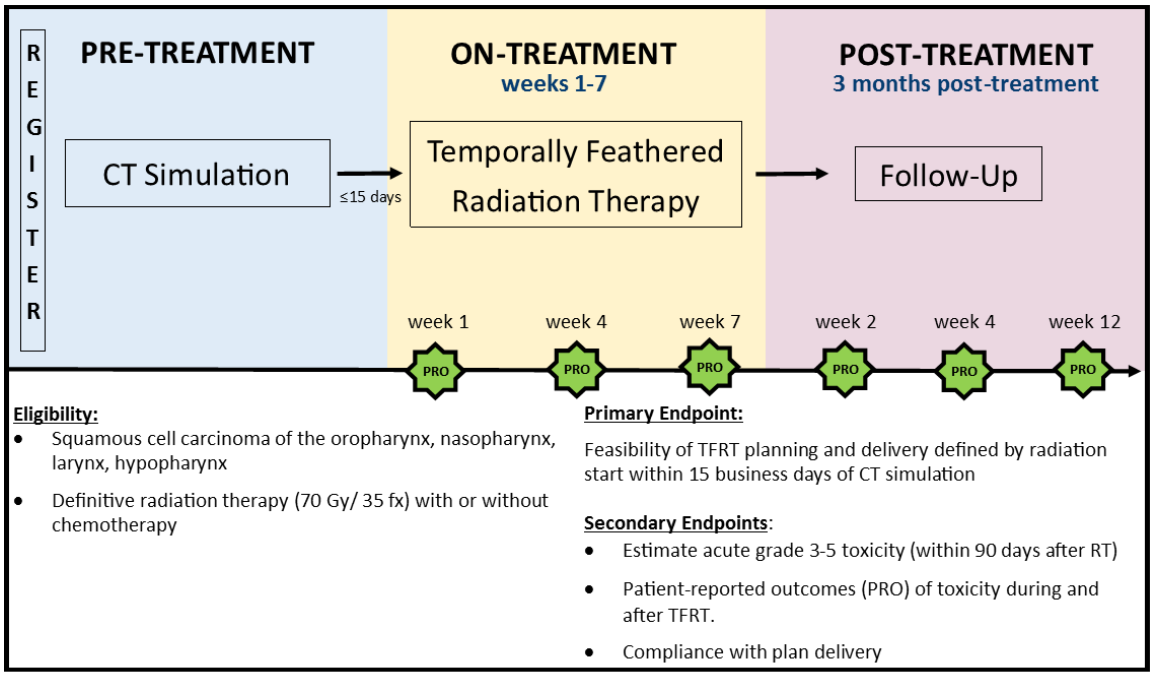
SUMMARY OF CHANGES

Protocol Date	Section	Change
10/10/18	6.5.1	Target Volumes updated to include extra CTV_and PTV_6300
	6.8	Compliance criteria table updated to include PTV_6300
	11.0	List of Patient Reported Outcomes Questionnaires updated
	Appendix III	Treatment subplan updated from days Mon-Fri to treatments A-E
12/7/18	Title Page	Clinicaltrials.gov NCT number added
	Title Page	Protocol date updated
	Title Page	Shireen Parsai changed from Study Coordinator to Co-Investigator
	Title Page	Study Coordinator last name and email change
	4.1.1	"Oral cavity" removed from eligibility criteria
	6.6.2	Clarification of treatment plan documents required in Mosaiq
	9.2	"Height" removed from required assessments in study calendar
	Appendix II	"Missed fractions should NOT be added to the end of the treatment schedule" removed
12/28/18	Footer	Version date change to reflect previous amendment
4/10/19	Title Page	Study coordinator name and contact info changed.
4/10/19	7.1.3	Clarification on AE's that are to be reported in the database.
5/8/20	Title Page, 7.3.1	PI changed from Dr. Joshi to Dr. Koyfman, additional study staff updated

STUDY SCHEMA



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PROTOCOL SUMMARY

Protocol Number/Title	CASE4318 Feasibility Study of Temporally Feathered Radiation Therapy (TFRT) for Head and Neck Squamous Cell Carcinoma: Means of Toxicity Reduction
Study Phase	Feasibility
Brief Background/Rationale	Intensity-modulated radiation therapy (IMRT) has allowed for optimization of three-dimensional spatial radiation dose distributions permitting target coverage while reducing normal tissue toxicity. However, acute and late radiation-induced normal tissue toxicity is a major contributor to patients' quality of life and often a dose-limiting factor in the definitive treatment of cancer with radiation therapy. We propose the next logical step in the evolution of IMRT incorporates canonical radiobiological principles, optimizing the temporal dimension through which radiation therapy is delivered to further reduce radiation-induced toxicity by increased time for normal tissue recovery. This new technique of radiation planning and delivery is termed Temporally Feathered Radiation Therapy (TFRT). TFRT has been previously modeled *in silico* and has demonstrated potential to reduce normal tissue toxicity. Given that TFRT is dependent on normal tissue recovery, a dynamic normal tissue complication probability (NTCP) model is used to ascertain the potential benefits of TFRT as compared to conventional IMRT planning. In this study, we will examine the feasibility of generating and delivering TFRT plans in the modern clinical workflow. Importantly, the radiation dose to the target volume is not altered and therefore this technique of radiation planning only examines techniques to reduce toxicity. All radiation prescription doses used in this study are determined as per current standards of care.
Primary Objective	Primary Endpoints Feasibility of TFRT planning and delivery defined as patient starting radiation within 15 days of CT simulation.
Secondary Objective(s)	Secondary Endpoints (1) Estimate acute grade 3-5 toxicity (within 90 days after RT) (2) Patient-reported outcomes of toxicity during and after TFRT. (3) Compliance with plan delivery
Exploratory Objective(s)	Exploratory Endpoints (s) • Compare doses to organs at risk delivered by TFRT compared to conventional IMRT plans on a per patient basis

Correlative Objective(s)	Correlative Endpoint(s) N/A
Sample Size	5 patients Patients age >18 years, male and female
Disease sites/Conditions with ICD 10 codes	C01 Base of Tongue C05 Palate (soft) C09 Tonsil C10 Oropharynx C10 Epiglottis C11 Nasopharynx C11 Pharyngeal Wall C12-C13 Hypopharynx C13 AE Fold C14 Pharynx (NOS) C32 True Vocal Cord C32 Glottis C32 Larynx C32 Supraglottic C44 Squamous Cell Cancer
Interventions	Temporally Feathered Radiation Therapy (TFRT)

ABBREVIATIONS

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals
TFRT	Temporally Feathered Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
OAR	Organ At Risk
d_S	Standard fractional dose
d_L	Low fractional dose
d_H	High fractional dose
NTCP	Normal tissue complication probability

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1.0 Introduction

1.1 Background of Study Disease

In 2017, the incidence of new cases of head and malignancies, including the oral cavity and pharynx was estimated to be about 1.7 million with about 600,000 deaths worldwide.[1] These cancers have been historically treated with a surgical approach; however given the morbidity of surgery, the standard has shifted to definitive non-surgical organ sparing approaches including radiotherapy with or without concurrent chemotherapy.[2] Conventional techniques of radiotherapy and chemotherapy resulted in high rates of late effects, such as dysphagia, radionecrosis, and xerostomia. With the advancement of radiotherapy techniques through the years, specifically the adoption of intensity-modulated radiotherapy (IMRT) coupled with image guidance, the practitioner now has greater control over the physical distribution of dose over the target volume and nearby surrounding structures. This has led to decreased late toxicity rates. In a recent study of patients receiving definitive radiotherapy with or without chemotherapy for HPV-related oropharynx cancer, the cumulative incidence of severe late toxicity at 2-years after completing treatment was 2.3%, whereas 42% of patients experienced grade 3 or higher acute toxicity.[2] The most common grade 3 or greater acute toxicity was dysphagia (24%), followed by mucositis (17%), and dermatitis (8%). For those who required feeding tube placement, the median duration of acute feeding tube use was 1.7 months. Of the patients followed greater than one year without local failure, 24% experienced grade 2 xerostomia. Notably, in historic trials, higher rates of toxicity have also been recorded with concurrent chemotherapy and radiotherapy.[3-7] Quality of life also declines following therapy. Though most patients recover global quality of life by 12 months, deterioration in physical functioning, fatigue, xerostomia, and sticky saliva persist beyond 12 months in head and neck cancer survivors.[8,9] In this study we aim to further decrease acute and late toxicities associated with radiotherapy. We examine a new technique termed temporally feathered radiation therapy (TFRT), through which the dose delivered to the target volume remains unchanged while the fractional dose delivered to the surrounding organs at risk is altered.

The biologic basis of dose and fractionation arises from the four pillars of radiobiology: (i) repair of sub-lethal damage, (ii) reassortment of cells within the cell cycle, (iii) repopulation, and (iv) reoxygenation.[10] Recovery from radiation-induced toxicity is primarily dependent on sub-lethal damage repair and repopulation. For this reason, fractionated radiotherapy still predominates in the clinic. As a low fractional dose of radiation is delivered daily, consistent insult is delivered to tumor cells while allowing time for normal tissue recovery between fractions. Despite this, as discussed above, toxicity still manifests mid-way or toward the end of most treatment courses acutely and late toxicities remain dose-limiting. Attention has been turned to techniques to widen the therapeutic ratio between tumor control probability (TCP) and normal tissue complication probability (NTCP). This had been achieved previously by pharmaceuticals such as radiosenstizers and radioprotectants, until the advent of intensity modulated radiation therapy (IMRT), which now is one of the greatest contributors to reduced toxicity associated with radiotherapy.[2,11,12] The implementation of IMRT into clinical practice

took nearly 50 years from when Dr. Birkhoff solved the inverse problem of IMRT in the 1940s, until Dr. Brahme illustrated the IMRT principles in 1988, and ultimately when the Peacock planning system was used to treat the first patient with IMRT in the mid-1990s.[13-17]

As an extension of IMRT, other researchers namely Dr. Unkelbach have examined the role of altering both the fractional dose delivered to the target as well as the organs at risk to continue to widen the therapeutic ratio.[18-22] Temporally feathered radiation therapy takes a different approach to reducing toxicity, without altering target volume coverage or dosing. Temporally feathered radiation therapy optimizes not only the physical distributions of dose, but also the time through which radiation therapy is delivered with the goal of allowing increased time for normal tissue recovery between fractional doses. Preclinical data demonstrating the potential benefit of TFRT are discussed below (section 1.2.1).[23]

1.2 Temporally Feathered Radiation Therapy

1.2.1 Preclinical Data

Temporally feathered radiation therapy is designed for targets within close proximity to multiple organs at risk. The foundation of this planning technique is the rotation of radiation dose to the nearby organs at risk on a daily basis, and hence the term "feathering". Radiation dose feathering is a technique that has been long used for creating a uniform distribution of dose across radiation field junctions at which hot or cold spots may occur. In TFRT planning, the physical dose is deliberately feathered among the neighboring organs at risk unevenly. Temporally feathered radiation plans are composed of 5 isocurative *subplans* which are scheduled to be delivered once per week as illustrated in Figure 1. Each of these subplans delivers a therapeutic dose of radiation therapy to the target, however one organ at risk is chosen to be deprioritized per subplan and therefore receive a slightly higher fractional dose (d_H) as compared to the standard fractional dose (d_S) delivered by conventional planning. dH is defined as a measure of dose distributed over a deprioritized organ. The following is true: $d_H > d_S > d_L$. Resultantly, each OAR which received a slightly higher fractional dose once weekly, followed by slightly lower fractional dose the remaining four fractions of that week as reflected in the other four subplans. The hypothesis is that if d_H is delivered to an organ at risk once weekly followed by four d_L (lower fractional dose), there is increased time for normal tissue recovery.

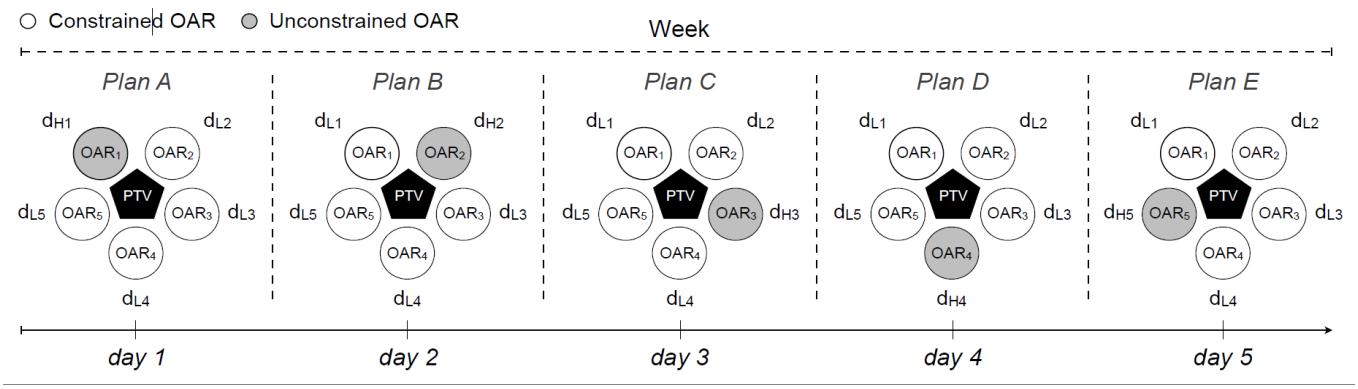

Figure 1. Schematic representation of Temporally Feathered Radiation Therapy. The target volume (*black pentagon*) is surrounded by 5 organs at risk (*circles*). Five individual radiation plans are created for each day of the week whereby a higher fractional dose, $d_{H,}$ is delivered to the OAR of interest (grey) and the remaining four OARs receive a lower fractional dose, d_L.

In silico simulations, TFRT demonstrated potential for reduced normal tissue toxicity compared to conventionally planned IMRT as demonstrated in Figure 2.[23] The sequencing of high and low fractional doses delivered to OARs by TFRT plans suggested increased normal tissue recovery, and hence less overall radiation-induced toxicity compared to conventionally planned IMRT. The simulations were conducted using the following dynamic normal tissue complication probability model (equation 1) which accounts for normal tissue recovery in response to radiation therapy.[23]

$$\frac{dN}{dt} = \mu N(t)\big(1 - N(t)\big) - \delta(t_i)\, RT(d)\, N(t)\big(1 - N(t)\big), \qquad (1)$$

The organ-specific parameter $\mu > 0$ represents the recovery rate of radiation-induced damage. $N(t) < N(0)$ represents the level of normal tissue damage by radiotherapy, considering that normal tissue at homeostasis with a 1% turnover rate would be denoted as $N(0) = 0.99$. Small values of N(t) relate to severe damage. The effect of radiation is included by the loss term $\delta(t_i)\ RT(d)\ N(t)(1\text{-}N(t))$ where $\delta(t_i)$ is a characteristic function equal to 1 at the time of irradiation t_i, and zero in other case. The magnitude of toxicity reduction by TFRT planning was found to depend on corresponding standard fractional dose of IMRT and organ-specific recovery rate of sub-lethal radiation-induced damage.

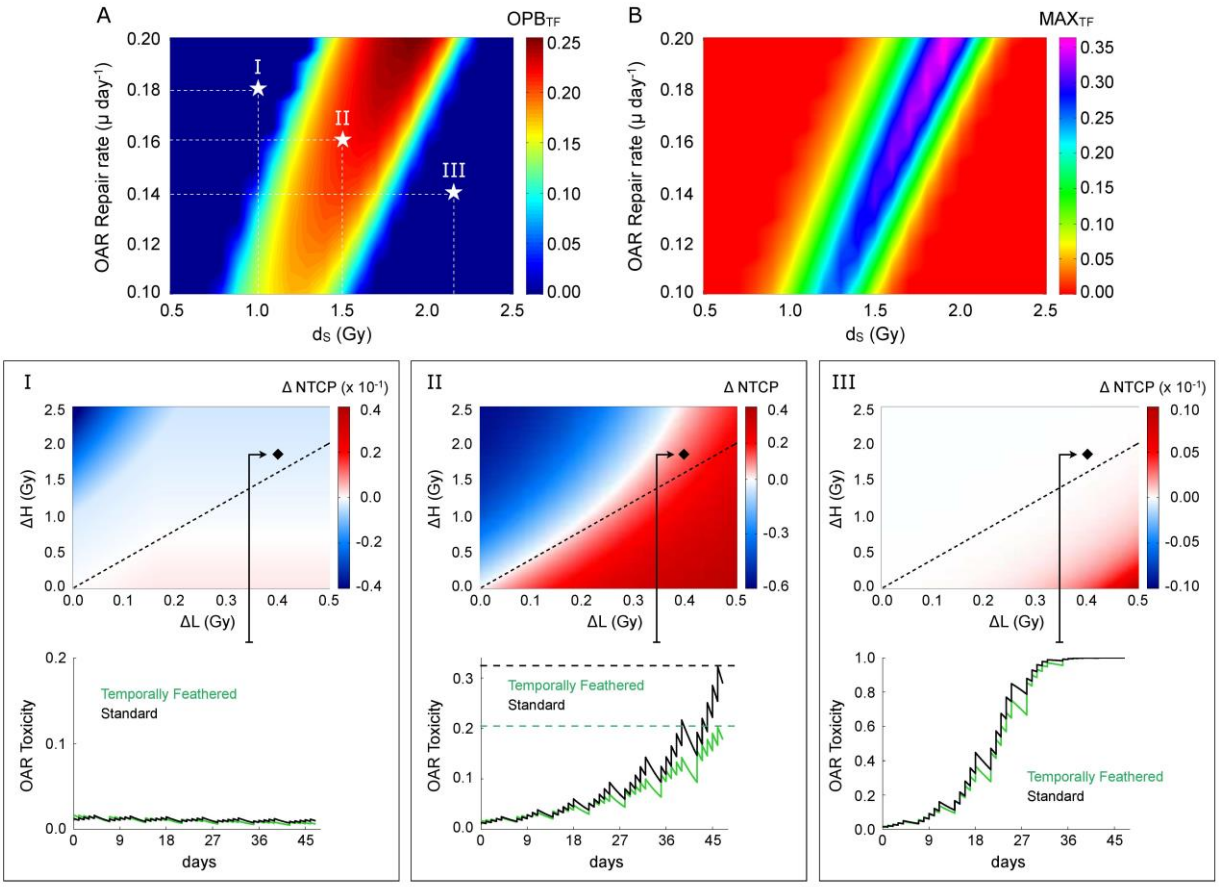

Figure 2. Comparison of conventionally fractionated IMRT and TFRT with respect to the standard fractional dose (d_S) and organ-specific recovery rate (μ). (a) Overall potential benefit (OBP_{TF}) and (b) maximum potential benefit (MAX_{TF}) of TFRT over conventional planned IMRT. (I-III) Top panels represent the single cases marked by stars in (a). The x- and y-axes represent $\Delta L = d_S - d_L$ and $\Delta H = d_H - d_S$, respectively. Bottom panels show time-evolution of OAR toxicity included by the IMRT and TFRT plans corresponding to the location marked by diamonds in the top panels.

Further dosimetric evaluations were conducted with IMRT head and neck cases that were replanned with TFRT technique. As illustrated in figure 3, the TFRT plans were achievable while maintaining the dose delivered the planning target volume.

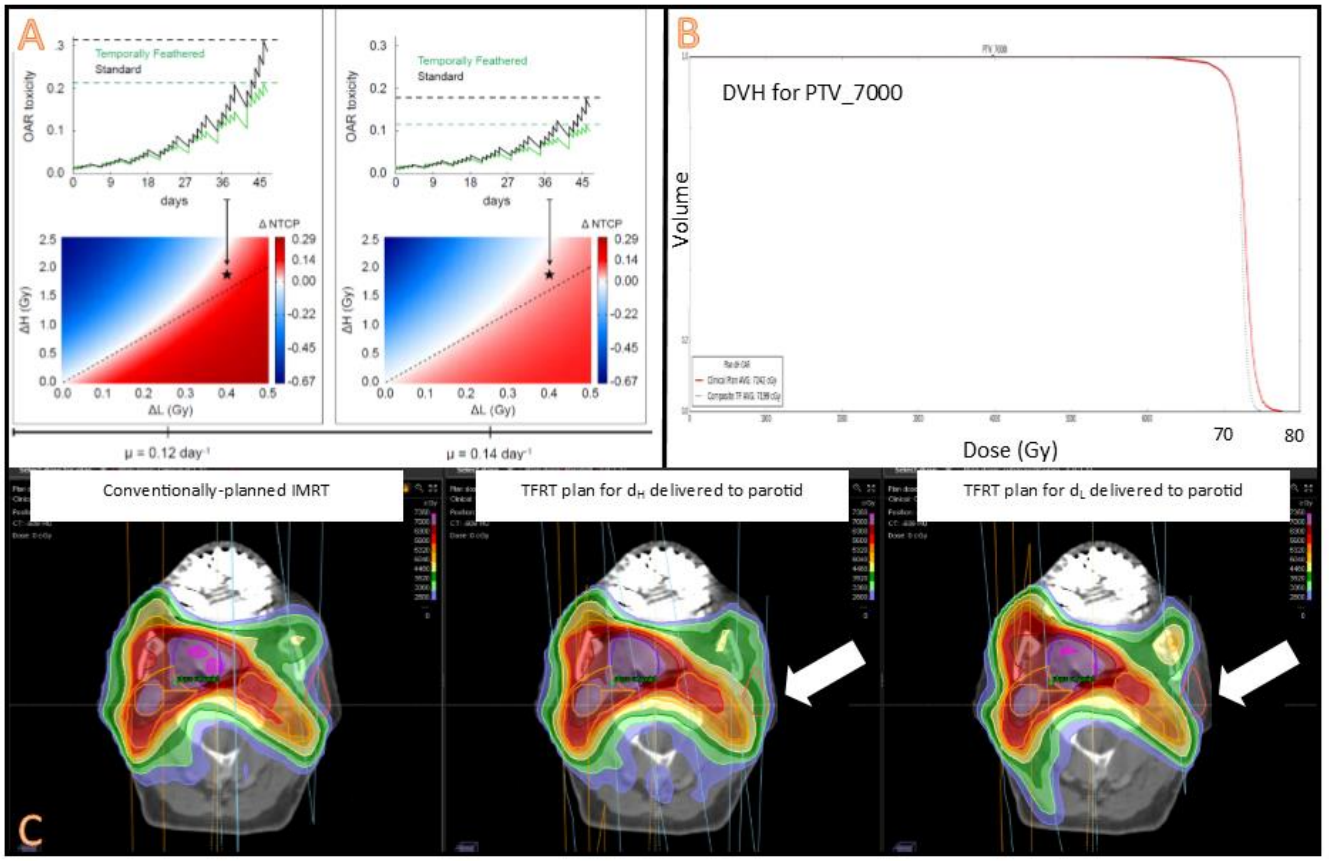

Figure 3. Proof of principle of Temporally Feathered Radiation Therapy. Panel A illustrates changes in OAR toxicity and NTCP over time for varying OAR recovery rates. Panel B demonstrates a dose volume histogram for the target in a TFRT plan (*red*) compared to conventionally planned IMRT (*black*). Panel C demonstrates axial images of a head and neck plan with superimposed isodose lines for conventionally planned IMRT, a TFRT plan with d_H delivered to the OAR, and a TFRT plan with d_L delivered to the OAR (*left to right*).

1.2.2 Clinical Data

There are no available clinical research data to date on temporally feathered radiation therapy.

1.3 Rationale

Given prior preclinical data suggesting the potential for reduced normal tissue toxicity with TFRT, we will now evaluate the feasibility of treatment planning and delivery in current clinical workflow. Subsequent studies will be powered for toxicity outcomes. Patients with head and neck malignancies were chosen, as the current standard of care requires conventionally fractionated radiation therapy over 7 weeks. Due to the anatomy

of the region, the target volume often is surrounded by multiple organs at risk. Therefore, head and neck malignancies are a prime example in which temporally feathered radiation therapy may decrease normal tissue toxicity.

2.0 Objectives

2.1 Primary Objective

To determine feasibility of TFRT planning and delivery for head and neck squamous cell carcinoma defined as patient starting radiation within 15 days of simulation.

2.2 Secondary Objective(s)

(1) Estimate grade 3-5 acute toxicity (within 90 days after RT)
(2) Patient-reported outcomes (PRO) of toxicity during and after TFRT.
(3) Compliance with plan delivery

3.0 Study Design

3.1 Study design including dose escalation / cohorts

This study is planned as a single arm feasibility trial to demonstrate clinical delivery of TFRT plans. Five patients will be accrued as a single cohort.

3.2 Number of Subjects

Five patients will be enrolled in this trial.

3.3 Replacement of Subjects

Subjects who come off of study for reasons unrelated to treatment course may be replaced.

3.4 Expected Duration of Treatment and Subject Participation

Treatment will last for a duration of 7 weeks and patients will be followed for a total of 3 months following treatment completion.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Eligibility criteria must be met to confirm a subject's eligibility.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

___ 4.1.1 Subjects must have histologically or cytologically confirmed squamous cell carcinoma arising from a primary head and neck site (oropharynx, larynx/ hypopharynx, nasopharynx). TX-4, NX-3, MX-0 stages are permitted.

___ 4.1.2 Subjects must be eligible for definitive radiation therapy (70Gy in 35 fractions) with or without chemotherapy.

___ 4.1.3 Age ≥18 years.

___ 4.1.4 Karnofsky Performance status ≥80 [See Appendix 1].

___ 4.1.5 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

___ 4.2.1 Subjects receiving any other investigational agents.

___ 4.2.2 Postoperative radiotherapy is not permitted.

___ 4.2.3 History of prior head and neck radiation therapy.

___ 4.2.4 Subjects with uncontrolled inter-current illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

___ 4.2.5 Pregnant or breastfeeding women are excluded from this study because radiation therapy has the potential for teratogenic or abortifacient effects. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with radiation therapy, breastfeeding should be discontinued if the mother is treated with radiation therapy. These potential risks may also apply to other agents used in this study.

___ 4.2.6 The patient cannot have distant metastatic disease (or M1 disease by AJCC 8th edition).

4.3 Inclusion of Women and Minorities

Men, women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore® Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through Cleveland Clinic and will be provided a study number by contacting the study coordinator listed on the cover page.

6.0 Radiation Treatment Plan

6.1 Radiation Treatment Regimen Overview

Protocol treatment must begin within 15 days after simulation.

Patients will receive temporally feathered radiation therapy as part of their definitive course of radiation therapy with indications as per standard of care for patients with head and neck malignancies.

No investigational agents or investigational therapies may be administered with the intent to treat the subject's malignancy.

6.2 Dose Specifications

6.2.1 Dose Fractionation

Patients must be eligible to receive 70 Gy in 35 fractions to the primary target (PTV_7000) and to receive 56 Gy in 35 fractions to the elective volume (PTV_5600). The doses are prescribed at the edge of the PTV. Treatment will be delivered once daily from Monday to Friday over 7 weeks. Missed treatments can be compensated for by treating on the Saturday or Sunday of that week, or adding to the end of treatment.

6.3 Technical Factors

6.3.1 Treatment Planning and Delivery

The IMRT plan can be delivered with step-and-shoot, sliding window, or volumetric modulated arc therapy (VMAT) techniques on a linear accelerator with equipped with multileaf collimator (MLC). Any MV photon beam energies will be allowed.

6.3.2 Image Guidance for IGRT

Daily image guidance should be achieved using kilovoltage (KV) cone-beam CT (CBCT) images.

6.4 Localization, Simulation, and Immobilization

6.4.1 Patients must have an immobilization device (Aquaplast mask) at the time of CT simulation. It is strongly encouraged that the immobilization device should limit motion in the head and neck region as well as the shoulders. Bite blocks may be used for maintaining tongue position.

6.4.2 IV contrast should be used with the treatment planning CT unless the patient has a contraindication. The treatment planning CT will be acquired in the treatment position with the immobilization device. CT slice thickness should be ≤ 0.3 cm.

6.5 Target Volumes

6.5.1 Definition of Target Volumes
In addition to the planning CT, additional imaging (e.g. PET/CT, MRI) can be fused with the planning CT to guide target delineation. Standard volume definitions were borrowed from consensus from RTOG 1016 protocol

Gross Tumor Volume (GTV): The GTV represents the clinical or radiographic areas grossly involved with tumor and will be designated as GTV_7000. Involved nodes must be included in the GTV and are defined as those greater than 1 cm in short axis, nodes with central necrosis or those with PET avidity deemed to be positive.

Clinical Target Volume (CTV): The CTV represents the area at risk for microscopic disease spread, respecting natural barriers of disease spread. Two CTVs must be created. CTV_7000 will encompass possible local subclinical infiltration at the primary site. CTV_7000 is created by a 0.25-0.5 cm expansion of GTV_7000. CTV_5600 will encompass the clinically uninvolved nodal regions considered to be at high risk for microscopic spread. An optional CTV_6300 may be designated at the physician's discretion in regions felt to be at especially high risk for recurrence.

Planning Target Volumes (PTV): The PTV represents the volume to which radiation dose will be prescribed, delivered, and evaluated. The PTV accounts for interfraction set-up variability. Two PTVs will be generated. A PTV_7000 will be created from the CTV_7000 and a PTV_5600 will be created from the CTV_5600. An option PTV_6300 may also be designated as above. The PTV is created by an isotropic expansion of 0.25cm-0.5 cm on the CTV. The PTV should not extend beyond the skin surface. If the skin is considered to be at high risk, bolus material should be placed over this portion of the PTV.

6.5.2 Definition of Normal Tissues/ Organs at Risk (OARs): All normal tissues are evaluated as the regions not overlapping with the PTV and are summarized in Table 1.
Spinal cord: The cranial border of the spinal cord is at the craniocervical junction (the top of C1 vertebral body). The inferior border is at approximately T3-T4 (i.e., just below the lowest slice that has PTV on it). A Planning Risk Volume (PRV) of the cord should be created by expanding the cord with a uniform margin of 5 mm.

Brainstem: The cranial border of the brainstem is approximately at the level of the top of the posterior clinoid. The inferior border is at the craniocervical junction. The brainstem and spinal cord are contiguous structures. A PRV of 3 mm should be delineated around the brainstem also as a separate structure.

Lips and Oral Cavity: Delineation of lips is self-explanatory. The oral cavity is delineated as the anterior ½-2/3 of the oral tongue/ floor of mouth, buccal mucosa, and palate.

Parotid Glands: Each parotid gland is drawn as an individual structure based on CT anatomy. The superficial and deep lobes should be included.

Submandibular Glands: Each submandibular gland is drawn as an individual structure based on CT anatomy.

OARpharynx: This structure encompasses the posterior pharyngeal wall and adjacent constrictor muscles, extending cranially from the level of the pterygoid plates to the level of the esophagus.

Esophagus: The cervical esophagus is defined on CT anatomy. The superior border is at the bottom of the pharynx (cricopharyngeal inlet) and the inferior border is at the thoracic inlet.

Supraglottis: The supraglottis is drawn separate from the larynx, cranially including the epiglottis. This structure is contiguous with the glottic larynx caudally.

Larynx: The larynx only encompasses the glottic larynx.

Glottic/Supraglottic Larynx (GSL): The GSL includes a fusion of the supraglottic larynx and the glottic larynx.

Table 1: Normal Tissues/Organs at Risk to be Delineated

OAR Standard Name	Description
SPINAL_CORD	Spinal cord
SPINAL_CORD_PRV5	Planning risk volume of 5 mm around spinal cord
BRAINSTEM	Brainstem
BRAINSTEM_PRV3	Planning risk volume of 3 mm around brainstem
LIPS	Lips
ORAL_CAVITY	Oral cavity
PAROTID_R	Right parotid gland
PAROTID_R_PTV	Right parotid gland, nonoverlapping with PTV

PAROTID_L	Left parotid gland
PAROTID_L_PTV	Left parotid gland, nonoverlapping with PTV
SUBMANDIBULAR_R	Right submandibular gland
SUBMANDIBULAR_L	Left submandibular gland
OAR_PHARYNX	OAR pharynx
OAR_PHARYNX_PTV	OAR pharynx, nonoverlapping with PTV
ESOPHAGUS	Esophagus
SUPRAGLOTTIS	Supraglottis
LARYNX	Glottic larynx
GSL	Supraglottic and glottic larynx

6.5.3 In cases of anatomical changes (i.e. due to weight loss), an adaptive replan is permitted with repeat CT simulation at the discretion of the treating physician in order to recreate an immobilization mask and adjust the planning volumes.

6.5.4 Any OAR involved by tumor will not need to be deliberately avoided. However, they should still be contoured.

6.6 Treatment Planning, Assessment and Delivery

6.6.1 Planning Temporally Feathered Radiation Therapy: The treating physician will designate up to 5 organs at risk (OARs) to be feathered based on proximity to target, prior to treatment planning. As shown in Figure 1, 5 *subplans* (designated as plan A, plan B, plan C, plan D, and plan E) will be generated, with each deprioritizing one of the 5 OARs. The **plans are considered to be isocurative** based on meeting standard guidelines for PTV coverage as described in 6.2.2.

- For each of these subplans, a single OAR is deprioritized such that it receives a higher dose (d_H) while the remaining 4 OARs receive a lower dose (d_L) than the standard fractional dose (d_S) delivered in a conventional IMRT plan.
- The daily dose delivered to the PTV is still 2 Gy.
- The OARs that may be feathered include, but are not limited to, the following: oral cavity, each submandibular gland, each parotid gland, OARpharynx, supraglottis, larynx, and esophagus.
- A standard IMRT plan must also be generated. If the patient cannot be started on the TFRT plan within 15 days of simluation, the standard IMRT plan should be delivered instead.
- **Note**: If the patient's start date for radiation therapy is delayed for medical reasons (eg dental extractions) not related to the timing of TFRT planning, TFRT planning can still be continued as planned. Delays in radiation start date must be designated whether directly attributable to TFRT planning.

Refer to appendix III on correct procedures for resumption of treatment schedule after a missed fraction.

6.6.2 Assessing Temporally Feathered Radiation Therapy: The treatment plan documents signed by the physician will be stored in Mosaiq. The treatment plan documents must include the treatment fields, the isodose lines, and DVH composite plan (labeled as COMPOSITE). Appendix III lists all of the components necessary in the approved treatment plan document.

Each subplan must be assessed individually in addition to the composite plan.

1. *Assessment of the composite plan*: The composite plan and DVH must be generated from the cumulative dose delivered by each of the 5 temporally feathered subplans. The composite plan must meet the compliance criteria as in 6.8.
2. *Assessment of each subplan*: d_H is defined as a measure of dose distributed over a deprioritized organ. The max point dose for d_H must comply with:0.03 cc of the deprioritized organ cannot exceed >10% of the prescription dose. The dose delivered to each PTV must meet the compliance criteria as in 6.8.

6.6.3 Delivery of Temporally Feathered Radiation Therapy: The patient should start radiation treatment within 15 days of CT simulation. If the patient is unable to be started on TFRT treatment plan within 15 days of the date of CT simulation, the patient must start radiation therapy using the standard IMRT plan previously created (and not TFRT plan) so as not to delay treatment schedule.

The treatment plan can be started on any day of the week, as long as at least 2 consecutive fractions are delivered before the weekend.

Specific IMRT QA should be performed for each subplan to ensure plan integrity.

Two therapists must be present for the delivery of TFRT. The therapists should continue with standard time out procedures with an additional verification that the correct subplan is selected for treatment according to the day of the week as in Appendix II. It is strongly encouraged that the attending physician or physicist to be present at the first 5 fractions of TFRT delivery.

6.7 Doses to critical structures for the composite plan

All dose constraints to critical structures include the volume of the critical structure outside of the planning target volume. Standard dose constraints were adapted from RTOG 1016 protocol (NCT01302834).

Spinal cord: 0.03 cc of the PRV should not exceed ≥50 Gy. 0.03 cc of the spinal cord should not exceed ≥45 Gy.

Brainstem: 0.03 cc of the brainstem should not exceed 60 Gy. 0.03 cc of the PRV brainstem should not exceed 63 Gy.

Lips: Reduce dose as much as possible, with goal of mean dose <20 Gy.

Oral Cavity: Reduce dose as much as possible, with goal of mean dose <30 Gy for the uninvolved oral cavity. Hot spots >60 Gy should be avoided as possible within the uninvolved oral cavity.

Parotid Glands: Each parotid gland should be optimized separately, with a goal of mean dose <26 Gy.

Contralateral Submandibular Glands: If contralateral nodal level IB is not targeted, goal is to reduce mean contralateral submandibular to <39 Gy.

OARpharynx: Reduce the dose as much as possible with goal mean dose <45 Gy.

Esophagus: Reduce the dose as much as possible, with goal mean dose <30 Gy.

Supraglottis: Reduce the dose as much as possible, with goal mean dose <45 Gy.

Larynx: Reduce the dose as much as possible, with goal mean dose <45 Gy.

GSL: Reduce the dose as much as possible, with goal mean dose <45 Gy.

6.8 Compliance Criteria

Treatment breaks and reasons must be indicated in the treatment record. Treatment breaks should not exceed 5 consecutive treatment days or 10 days total.

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Total RT dose to PTV_7000 (to 95% of the PTV)	70 Gy	None	none
Minimum dose ("cold spot" within PTV_7000, not including portion near (<8 mm skin)	66.5 Gy (equals 95% prescribed dose)	<66.5 but >63 Gy	≤63 Gy

defined for a point that is 0.03 cc in size			
Maximum dose ("hot spot" >1 cc) within PTV_7000	≤77 Gy	>77 Gy but ≤82 Gy	>82 Gy
Total RT dose to PTV_5600 (to 95% of the PTV)	56 Gy	≥45 but <56 Gy	<45 Gy
Total RT dose to PTV_6300 (to 95% of the PTV)	63 Gy **Required when applicable**	≥52 but <63 Gy	<52 Gy
Total RT dose to spinal cord PRV (0.03 cc)	≤50 Gy	≥50 Gy but ≤52 Gy	>52 Gy

6.9 Radiation Therapy Adverse Event Reporting

Adverse event reporting will occur according to section 7.

6.10 General Concomitant Medications and Supportive Care Guidelines

Subjects should receive full supportive care, including transfusions of blood and blood products, cytokines, antibiotics, antiemetics, etc when appropriate.

6.11 Criteria for Removal from Study

In the absence of treatment delays due to adverse events, treatment will continue until completion of treatment or one of the following criteria applies:

• Disease progression,

• Inter-current illness that prevents further administration of treatment,

• The investigator considers it, for safety reasons, to be in the best interest of the subject.

• Subject decision to withdraw from treatment (partial consent) or from the study (full consent),

• Pregnancy during the course of the study for a child-bearing participant

6.12 Duration of Follow Up

Subjects will be followed for toxicity for 3 months after treatment has been completed/ discontinued or until death, whichever occurs first.

7.0 Adverse Events and Potential Risks

Note: Only serious adverse events as defined above will be reported. Standard head and neck radiotherapy engenders significant acute toxicity and may be associated with grade 3-5 acute toxicity. These may be associated with pain, dysphagia, mucositis, weight loss, feeding tube use, narcotic use, hospitalizations, dehydration, infections, dermatitis, laryngeal edema. These are routine expected side effects from radiation and should not be affected by the method of planning used in this study.

7.1 Definitions

7.1.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

7.1.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

7.1.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

For the purposes of data collection, only non-serious adverse events that are possibly, probably or definitely related to protocol treatment will be reported in the database. Serious adverse events of any attribution will be reported in the database.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the treatment- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes,

dose interrupted, reduced, discontinued, etc. or action taken with regard to the event
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the prescribed course of radiotherapy. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the prescribed course of radiotherapy.
- Probable – The AE is likely related to the prescribe course of radiotherapy.
- Possible – The AE may be related to the prescribed course of radiotherapy.
- Unlikely – The AE is doubtfully related to the prescribed course of radiotherapy.
- Unrelated – The AE is clearly NOT related to the prescribed course of radiotherapy.

There is no attrition allowed for the prescribed course of radiotherapy depending on response to therapy.

7.2 SAE Report Form

SAE's related to radiation therapy only will be recorded into OnCore and reported to IRB according to local IRB policies and procedures.

SAEs related to agent therapy will be recorded on the Radiation Oncology SAE Report Form [Appendix V].

7.3 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur from the day of registration through 90 days after the completion of the prescribed course of therapy. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

7.3.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - Lead Site PI: Shlomo Koyfman, koyfmas@ccf.org Fax: 216-445-1068. Protocol coordinator can be contacted if applicable.
- The Lead Site Principal Investigator will review the SAE and report the event to IRB as applicable.
- It is the Principal Investigator's responsibility to ensure that ALL serious adverse events that occur on the study are reported to the Data Safety Toxicity Committee.

Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

7.4 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

7.5 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

7.6 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

8.0 EXPLORATORY ENDPOINTS

8.1 Dosimetric Comparison of TFRT and Conventional IMRT

Dosimetric parameters including the mean dose, maximum dose, and minimum dose to the organs at risk will be analyzed among the subplans, composite TFRT plan, and conventional IMRT plan.

8.1.1 Background

Using the dynamic NTCP model, the greatest difference between d_H and d_L theoretically will create the biggest reduction in normal tissue complication probability. To further

understand the appropriate prioritization parameters dosimetric endpoints will be compared.

8.1.2 Rationale for Analysis

The dosimetric parameters will be reported in a descriptive pattern to detail the planning parameters used to optimize temporally feathered radiation therapy plans.

9.0 STUDY PARAMETERS AND CALENDAR

9.1 Study Parameters

9.1.1 Screening Evaluation

Evaluations including that needed to establish diagnosis, will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed < 40 days prior to administration of protocol therapy.

9.1.2 Treatment Period

Patients will be evaluated in consultation, at which time information will be gathered regarding trial eligibility. Subsequently, patients will undergo CT simulation, initiation of radiation delivery, and weekly on-treatment visits. Follow-up visits will occur 2 weeks, 4 weeks, and 3 months post completion of treatment. At the indicated visits below, toxicity will be assessed by way of CTCAE criteria and patient-reported quality of life questionnaires.

9.2 Calendar

At the scheduled visits below the patients will undergo evaluation of toxicity with physician-assigned grade as per CTCAE V4 as well as patient reported outcome measures using EORTC QLQ-C30, EORTC QLQ-HN35 and Xerostomia Questionnaire (XQ) as demonstrated in Appendix IV.

A visit window of +/- 4 days is allowed for the visits while the patient is undergoing treatment. A visit window of +/- 7 days is allowed for the visits 2 and 4 weeks after completing treatment. A visit window of +/- 28 days is allowed for the 3 month post-treatment.

Study Days	Wk 1 of RT (+/- 4 days)	Wk 4 of RT (+/- 4 days)	Wk 7 of RT (+/- 4 days)	2 Wks post-RT (+/- 7 days)	4 wks post RT (+/- 7 days)	3 mos post RT (+/- 28 days)
REQUIRED ASSESSMENTS						
Weight	X	X	X	X	X	X
Vitals (*blood pressure, pulse, respiratory rate, and temperature)*	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X
PRO Assessment	X	X	X	X	X	X

Karnofsky PS	X	X	X	X	X	X

10.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

10.1 Data Reporting

The Overture Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. Overture is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. Access to data through Overture is restricted by user accounts and assigned roles. Once logged into the Overture system with a user ID and password, Overture defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the Overture Administrator at OnCore-registration@case.edu.

Overture is designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the Overture database. A calendar of events and required forms are available in Overture

10.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

10.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

10.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

10.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

10.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

11.0 STATISTICAL CONSIDERATIONS

This study is designed as a feasibility study, with the goal of accruing 5 patients over the course of one year from trial opening. The primary objective is to determine the feasibility of TFRT planning and delivery in a modern clinical workflow. Feasibility is defined as a patient starting radiotherapy within 15 days of simulation. The TFRT technique will be deemed feasible if 3/5 patients meet the above criteria.

Descriptive statistics will be applied. Secondary endpoints include estimates of (1) acute grade 3-5 toxicity as per CTCAE version 4, (2) estimates of patient-reported outcomes during and after TFRT delivery using EORTC QLQ-H&N35, EORTC QLQ-C30, and Xerostomia Questionnaire (XO) and (3) compliance with plan delivery.

The patient-reported outcomes (PROs) from the above questionnaires will be collected at week 1 (baseline), week 4, and week 7 of treatment, as well as 2 weeks, 4 weeks, and 3 months post completion of treatment radiation. Descriptive associations between PROs and CTCAE toxicity criteria will be reported.

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APPENDIX I

KARNOFSKY PERFORMANCE STATUS CRITERIA

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead

APPENDIX II

Therapist Treatment Delivery Timeout

Two therapists must be present for the treatment timeout.

1. Current practices of verifying patient and treatment site must occur.

2. The treatment navigator in Mosaiq must be used to confirm the treatment plan fraction delivered the day before and determine the next appropriate fraction. Fractions will be delivered in a pattern of Plan A – Plan B – Plan C – Plan D – Plan E. For example, if plan B was delivered the day prior (i.e. on a Wednesday) then plan C must be delivered next for the next fraction (i.e. Thursday). In this example, Plan D would be delivered on Friday and Plan E would be delivered on Monday.
    - In the event the patient misses a planned treatment fraction, the therapist must notify Eric Murray, CMD, Peng Qi, PhD, and Shlomo Koyfman, MD. The determination can then be made in how to update the patient data in Mosaiq. Treatments should be resumed as soon as possible. The patient should resume therapy following the same pattern previously used A-B-C-D-E. Two fractions can never be delivered in the same day.
    - No overrides are allowed to occur without the presence of a physicist.

APPENDIX III

Safety Summary Tables for Treatment Plan Documentation

The following tables must be completed and printed in the treatment plan.

Treatment Subplan	Fractional dose deprioritized OAR (d_H), *a* (cGy)	Fractional dose deprioritized OAR (d_H), *b* (cGy)	Fractional dose deprioritized OAR (d_H), *c* (cGy)	Fractional dose deprioritized OAR (d_H), *d* (cGy)	Fractional dose deprioritized OAR (d_H), *e* (cGy)	PTV_7000 coverage (%)	PTV_5600 coverage (%)
A							
B							
C							
D							
E							

Treatment Subplan	Diff in dose between TFRT subplan and conventional IMRT plan for deprioritized OAR, *a* (cGy)	Diff in dose between TFRT subplan and conventional IMRT plan for deprioritized OAR, *b* (cGy)	Diff in dose between TFRT subplan and conventional IMRT plan for deprioritized OAR, *c* (cGy)	Diff in dose between TFRT subplan and conventional IMRT plan for deprioritized OAR, *d* (cGy)	Diff in dose between TFRT subplan and conventional IMRT plan for deprioritized OAR, *e* (cGy)
A					
B					
C					
D					
E					

APPENDIX IV

ENGLISH

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31.	Have you had pain in your mouth?	1	2	3	4
32.	Have you had pain in your jaw?	1	2	3	4
33.	Have you had soreness in your mouth?	1	2	3	4
34.	Have you had a painful throat?	1	2	3	4
35.	Have you had problems swallowing liquids?	1	2	3	4
36.	Have you had problems swallowing pureed food?	1	2	3	4
37.	Have you had problems swallowing solid food?	1	2	3	4
38.	Have you choked when swallowing?	1	2	3	4
39.	Have you had problems with your teeth?	1	2	3	4
40.	Have you had problems opening your mouth wide?	1	2	3	4
41.	Have you had a dry mouth?	1	2	3	4
42.	Have you had sticky saliva?	1	2	3	4
43.	Have you had problems with your sense of smell?	1	2	3	4
44.	Have you had problems with your sense of taste?	1	2	3	4
45.	Have you coughed?	1	2	3	4
46.	Have you been hoarse?	1	2	3	4
47.	Have you felt ill?	1	2	3	4
48.	Has your appearance bothered you?	1	2	3	4

Please go on to the next page

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

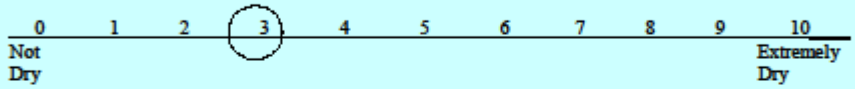
Please go on to the next page

APPENDIX A: Xerostomia Questionnaire

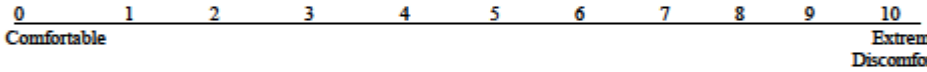
Xerostomia Questionnaire (XQ)

Below are several questions that will help describe the dryness in your mouth and how that dryness affects your daily life. Please encircle the number that corresponds to your condition during the last week, in each of the following areas:

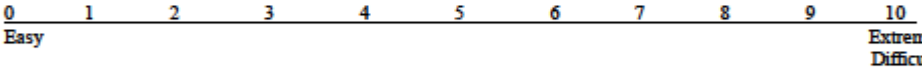
Example:
If your mouth is dry part of the time (such as only at night) you might circle "5."
If your mouth is dry only at certain times such as during exercise, you might circle "3" (see below).



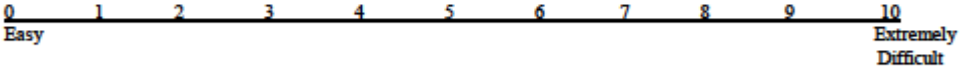
1. Rate the discomfort of your dentures due to dryness (if you do not wear dentures, please check ___)



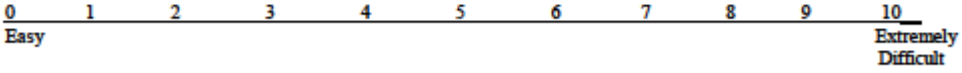
2. Rate the difficulty you experience in speaking due to dryness of your mouth and tongue:



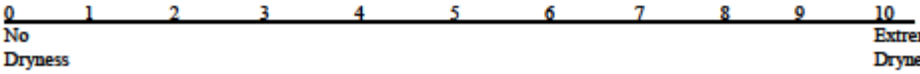
3. Rate the difficulty you experience in chewing food due to dryness:



4. Rate the difficulty you experience in swallowing food due to dryness



5. Rate the dryness your mouth feels when eating a meal:



APPENDIX V

Radiation Oncology SAE Report Form

Study Number (PRMC):

ID Number: Patient Initials: _____

Event Date: _____ Event End Date: _____ Initial Report Date: _____

Follow Up Report Date: _____

Death Date: _____

Event: _____ **Grade: _____**

Start of treatment date: _/__/__ **End of treatment date: __/__/__**

Date of most recent treatment: __/__/__

Radiation Intervention

Type of Radiation:

Total Dose (to date):

Date of last treatment:

Schedule:
Number of fractions:
Number of elapsed days:

Action taken with Radiation

Event Narrative:

_____
_____
_____
_____

Treating Physician Comments:

_____
_____

_____
_____

PI Comments:

_____
_____
_____
_____
_____
_____

Protocol Attribution:

☐ Not related
☐ Not likely related
☐ Possibly related
☐ Probably related
☐ Definitely related

Relationship to Radiation:

☐ Not related
☐ Not likely related
☐ Possibly related
☐ Probably related
☐ Definitely related

If event is unrelated or unlikely related, please state what event is likely related to (disease, etc):

_____

Expected: ☐ Yes ☐ No

Outcome:

☐ Resolved completely
☐ Resolved with sequelae
☐ Not yet recovered
☐ Fatal
☐ Unknown

Investigator Signature: _____ Date: _____

Nurse Signature: _____ Date: _____