CASE COMPREHENSIVE CANCER CENTER

STUDY NUMBER: **CASE 8314**

STUDY TITLE: *Phase I Dose Escalation Study of Stereotactic Body Radiotherapy for Carcinoma of the Head and Neck in High Risk Patients Who are Ineligible/Refuse Standard of Care Therapy*

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OTHER AGENT*(S):* **N/A**

SCHEMA

Informed Consent Provided	
	
REGISTRATION	
	
SBRT - DOSING SCHEMA	
Dose Level	**SBRT Dose**
Level 1	40 Gray in 5 fractions
Level 2	45 Gray in 5 fractions

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1.0 INTRODUCTION

1.1 HPV/p16 negative SCC-HN

There are well studied standard treatment approaches, both operative based, and non-operative based, for patients with squamous cell cancer of the head and neck (SCC-HN).[1-3] The great majority of patients who present with locally advanced SCC-HN are treated with definitive chemoradiotherapy (CRT).[4] Recent studies have emerged indicating that human papillomavirus (HPV) and/or p16 associated SCC of the oropharynx is increasing in incidence and has a biologically distinct pathogenesis and response to treatment than other head and neck cancers.[5,6] These patients have superior disease control rates and overall survival compared to the more traditional non-viral associated cancers. Patients with HPV/p16 negative disease, however, have inferior locoregional control rates when treated with standard chemoradiotherapy and clinical trials are currently investigating the addition of transoral robotic surgery or targeted systemic agents in an effort to intensify the current standard of care and improve outcomes.[7,8]

1.2 High risk patients ineligible for standard therapy

Among the HPV/p16 negative population, there is a subset of patients who are high risk for poor outcomes as they are ineligible for standard of care chemoradiotherapy, either due to advanced age, co-morbid illnesses, or because of patient refusal. These patients present a clinical challenge as their disease calls for very aggressive therapy, but patient factors precludes this possibility and often relegates them to substandard treatment options. In our practice, some of these high risk patients are treated with full course radiation, potentially with a targeted agent, some with a split course radiation approach and simply offered palliative treatment approaches. For those who undergo conventional 6-7 weeks of radiotherapy, treatment can be difficult to complete and be associated with significant morbidity. Loco-regional control outcomes are also inferior at 30-60%.[9-11]

As such, shorter, more tolerable, and potentially more effective treatments are needed in this high risk patient population with HPV/p16 negative SCC-HN.

1.3 Stereotactic Body Radiation Therapy (SBRT) in head and neck cancer

Stereotactic body radiotherapy (SBRT) is a technique that employs highly focused external beam radiation delivered in large doses over 1-5 treatments and has become a standard treatment approach for a variety of tumor types and clinical scenarios (e.g. medically inoperable lung cancer).[12] SBRT has become increasingly utilized in SCC-HN in patients who have recurrent previously irradiated disease. Doses most commonly employed range from 30-50 Gray (Gy) in 5 fractions (fx), with locoregional disease recurrence rates of 30-50%. Grade 3-5 toxicity can be significant including soft tissue or bone necrosis, fibrosis, dysphagia, carotid blowouts, and fistulization, and range from 3-18% among several series.[13] The University of Pittsburgh has the most extensive experience with this technique and has performed the only phase I dose escalation study testing the safety of SBRT in previously irradiated SCC-HN. They successfully escalated doses up to 44Gy in 5 fx without encountering grade 3-5 toxicity.[14] They have went on to treat >150 patients with ≥40Gy, without excessive morbidity.[15] We have treated 12 patients with SBRT in the reirradiation setting with varying doses of 35Gy in 5 fractions up to 45Gy in 5 fractions. Our preliminary experience suggests that it is feasible, planning according to traditional constraints is achievable and the short term toxicities are quite mild. We are awaiting maturity of our experience to assess long term severe late effects.

A summary of SBRT reirradiation studies in head and neck cancer are depicted in the following table:

Efficacy and Toxicity of Definitive Head and Neck SBRT Re-irradiation							
Study	**Number of Patients**	**SBRT Dose/ #fractions**	**Median f/u (months)**	**Median Survival/ 1y OS**	**Response Rate (CR+PR)**	**Local-Regional Progression**	**Toxicity**

Siddiqui, et al (2009)[16]	29	36-48Gy 5-8fx	36	7 mths 38%	69	4%	14% grade ≥3 (dysphagia, cataract, pain); 14% grade 4 (fistula/ulceration)†
Roh, et al. (2009)[17]	44 (35 evaluable)	18-40Gy 3-5fx	17	16 mths 52%	80%	11%	10% grade ≥4 (soft tissue/bone necrosis/death)
Unger, et al. (2010)[18]	38	21-35Gy 2-5fx	16	20 mths 40%	80%	32%	12% grade 4/5 (arterial bleed, death, fistula, soft tissue necrosis, dysphagia, trismus, cranial neuropathy)
Kodani, et al. (2011)[19]	21*	20-42Gy 3-8fx	28	16 mths 70%	62%	14%	28% late ≥ grade 3 (hemorrhage and death X 2 , mucositis, skin necrosis, chronic ulcer)
Cengiz, et al. (2011)[20]	46 (37 evaluable)	18-35Gy 1-5fx	7	12 mths 46%	57%	13.5%	13% carotid blowout (7/8 died)‡ 13% late ≥ grade 2(Soft tissue/bone necrosis, dysphagia)
Comet, et al. (2012)[21]	40	36Gy 6fx	26	14 mths 58%	79	23%	10% grade 3 (mucositis, dysphagia, fibrosis).
Vargo, et al. (2014)[22]	132	35-50Gy 5fx	6	7 mths 49%	75%**	44%	7% grade 3 (Dysphagia, Pain and Skin). No grade 4/5
OS = overall survival; † All fistulas occurred in the setting of tumor recurrence/progression rather than due to SBRT toxicity. ‡ All pts with carotid blowout had tumor completely surrounding carotid arteries, with no constraints applied to avoid the vessels. No patient with carotid artery dose <100% had CBO and only patients with >180 degrees of CA involved had CBO. * Includes only those patients with prior radiation. ** While not reported in this series, this rate was culled from several previous published reports from the UPitt experience.							

While SBRT in the re-irradiation setting has been shown to be safe with reasonable control rates, this technique has not been formally studied in the radiation naïve patient. As such, we propose a phase I dose escalation study in high risk patients who are ineligible/refuse standard of care therapy as a means of assessing the safety of such treatment in patients who may have prolonged survival compared to re-irradation

patients. We will also evaluate the efficacy of this far more tolerable and convenient regimen than our current commonly used approaches for these patients.

1.4 Proposal

We propose to conduct a phase I dose escalation trial of SBRT in high risk patients with locally advanced head and neck cancer who are ineligible/refuse standard chemoradiotherapy.

2.0 OBJECTIVES

2.1 Primary Objective: To explore the maximum tolerated dose of head and neck SBRT in a high risk patient population ineligible for standard chemoradiotherapy. Two dose levels will be used 40Gy, 45Gy all in 5 fractions.

2.2 Secondary Objectives:

2.2.1 Assess profiles of SBRT toxicity and examine patient (including co-morbidities), tumor and treatment related factors that are associated with SBRT related toxicity
2.2.2 identify any dose volume parameters that are associated with SBRT related toxicity
2.2.3 explore potential dose response relationships between higher SBRT dosing and radiographic response
2.2.4 assess impact of SBRT on patients quality of life

3.0 STUDY DESIGN

3.1 Dose Escalation

3.1.1 This is a phase I SBRT dose escalation study consisting of three dose levels: 40Gy and 45Gy all in 5 fractions.
3.1.2 Each dose level will have 6 patients allocated to them. We chose this number as twice the usual number of patients in a phase I chemotherapy related dose escalation protocol as a means of being conservative to ensure adequate capture of potential toxicities.
3.1.3 After all six planned patients are enrolled to the initial dose level, the study will be placed on temporary hold until all patients in that cohort are assessed at their 3 month post SBRT visit for DLTs. If $\leq$1 patient experiences a DLT, patients will be enrolled at the next dose level. If $\geq$3 patients experience a DLT, further accrual will be permanently halted and the study stopped. If 2 patients experience a DLT, then an additional 6 patients will be enrolled at the same dose level. In this setting, if $\leq$ 3/12 patients have a DLT, patients will be enrolled at the next dose level. If $\geq$ 4/12 patients have a DLT, further accrual

will be permanently halted and the study stopped and 35 Gy will not be recommended as safe.

3.1.4 The dosing strategy for the 2nd (45Gy) cohort will be identical to the first as outlined in 3.1.3. If ≤ 3/12 patients have a DLT in this 2nd cohort, then this will be the recommended phase II dose. If ≥ 4/12 patients have a DLT, then this dose level will be deemed unacceptably toxic and the 1st dose level will be considered the recommended phase II dose.

3.1.5 All patients will have ongoing assessments of DLTs, which can be delayed after SBRT and occur beyond 3 months. If a given dose is deemed safe and subsequent patients are entered into a higher dosing cohort and in continued follow up, additional DLTs are noted in the previously completed dosing cohort such that 2/6 patients experience DLTs, then accrual to the next higher dosing cohort will be halted and 6 additional patients will be accrued to the previously completed lower dosing level following the guidelines detailed above in section 3.1.3.

3.1.6 All toxicities will be scored per CTCAE v4.0 criteria. In our institutional experience of split course radiotherapy to 60-66Gy in a similar patient population, we encountered no grade 4/5 toxicities. However, given that this is SBRT and novel in this patient population, we are doing this study to assess the incidence of these grade 4/5 toxicities.

Dose limiting toxicities in this study will be defined as grade 4/5 toxicity:
- soft tissue or bone necrosis
- carotid blowout or other treatment related bleed
- aspiration
- infection
- fistula that is deemed as life threatening.

While grade 3 toxicities will be recorded as SAEs and reported as per IRB guidelines, they will not be considered DLTs or influence the dose escalation component of the study, given the high risk nature of the disease and the associated morbidities of uncontrolled disease.

3.1.7 All grade 3 toxicities will be recorded as serious adverse events but will not be scored as DLT, as these are somewhat expected and most often reversible complications associated with radiotherapy. Grade 1/2 events will be recorded, but will not be considered serious adverse events.

3.1.8 Symptoms and morbidity attributed to disease progression, as determined by the treating physician, and another co-investigator of the study, will not be considered a toxicity that will influence the dosing schema.

3.2 Patient Enrollment

We plan on enrolling a maximum of 18 patients to this study. This relies on the traditional 3+3 approach used in many chemotherapy phase I studies, but we have doubled the number in each arm to ensure we capture potential toxicities which can be delayed.

3.3 Expected Duration of Subject Participation

3.3.1 PreSBRT visits for dental evaluation (if indicated) and simulation. 5 visits for treatment over a 1.5 to 3 week time period.

3.3.2 Patients will be followed for one year after SBRT. All patients will be seen at least at 0.5, 3, 6, 9 and 12 months post SBRT. Additional visits will be made if clinically indicated based on patient symptomatology.

4.0 PATIENT SELECTION

Patients with cancer of the head and neck who are deemed unfit for continuous course standard cisplatin based chemoradiotherapy will be eligible. Patients with squamous cell cancer (mucosal or cutaneous; p16 positive or negative), adenocarcinoma, or salivary gland cancer are eligible.

A completed patient eligibility checklist is required following the approved standard operating procedure of the enrolling institution.

4.1 Inclusion Criteria

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

_____ 4.1.1 The patient must have squamous cell carcinoma, adenocarcinoma or malignant salivary gland cancer (e.g. acinic cell, adenoid cystic, mucoepidermoid, salivary duct carcinoma) proven by histologic diagnosis. Both mucosal and cutaneous cancers are eligible.

_____ 4.1.2 The patient must have clinical stage T1-4, N0-3, M0-1, stage II-IVC carcinoma as per the 7th edition of the AJCC staging manual. Patients with T1N0M0 will be ineligible. Patients with metastatic disease with a limited metastatic burden are eligible if obtaining local control is determined by their treating oncologist to be an important therapeutic goal.

_____4.1.3 The patient must have imaging documenting a primary tumor, or involved lymph node, ≥2.5cm in greatest dimension.

_____4.1.4 PET/CT is required for all patients, unless contraindicated. This may be acquired prior to study entry or after enrollment prior to SBRT planning.

_____ 4.1.5 The patient must have a history and physical documented within four weeks of registration and be deemed by a medical oncologist to be ineligible for standard continuous course chemoradiotherapy with Cisplatin, or refuse treatment with Cisplatin.

_____ 4.1.6 Performance status - Karnofsky PS ≥ 40

_____ 4.1.7 Age ≥18 years.

_____ 4.1.8 Female patients can not be of childbearing age, or if they are, must have a negative pregnancy test prior to enrollment and be willing to use contraceptives during treatment and continue for 6 additional months.

_____ 4.1.9 Patients 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 patient from study enrollment.

_____ 4.2.1 Patients with T1N0M0 stage I disease.

_____ 4.2.2 Patients who are receiving any other investigational agents.

_____ 4.2.3 Patients with non-malignant histology.

_____ 4.2.4 Patients with life expectancy <6 months.

_____ 4.2.5 Patients who cannot lie flat for 20 minutes.

_____ 4.2.6 Patients with prior history of head and neck radiotherapy (>40Gy) with significant areas of anticipated overlap

4.3 Inclusion of Women and Minorities

Both men and 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.

6.0 TREATMENT PLAN

6.1 Simulation/Planning CT and Co-registration

The patient will undergo a CT simulation for treatment planning with a recommended slice thickness of 1.5 mm, and a maximum allowed slice thickness of 3 mm. Patients will be immobilized using a 5pt aquaplast mask during the simulation. IV contrast should be used unless there is a contraindication (e.g. allergy or elevated creatinine). These images should be co-registered with the diagnostic PET/CT for planning purposes. If an MRI has been obtained, it should also be co-registered to aid in target delineation.

6.2 Radiation Planning

Radiation planning will utilize tissue heterogeneity corrections. The gross target volume (GTV) should be contoured and include all radiographically apparent areas of disease. There will be no clinical target volume (CTV) expansion on this volume. A planning target volume (PTV) will then be generated with a 2-3.5mm expansion of the GTV. A 2.5mm expansion is recommended but some variability is allowed for based on tumor location and motion and setup variability from patient to patient.

An optional elective CTV can be contoured and include areas thought to be at high risk of microscopic disease. This volume will be treated with 30Gy concurrently using a simultaneous integrated planning technique. While this will generally not be used for most patients, some patients with multifocal nodal disease may require more comprehensive lower dose coverage of their other nodal stations. The use of this target volume is at the discretion of the treating radiation oncologist.

The radiation dose will be prescribed to cover 95% of the PTV. Thus >95% of the PTV should receive the prescription dose (e.g. 35Gy in 5 fx). >99% of the GTV must also receive prescription dose. Rapid dose falloff outside the PTV is the priority and heterogeneity within the target is allowed. <0.03cc of tissue inside the PTV should receive >110% of the prescription dose.

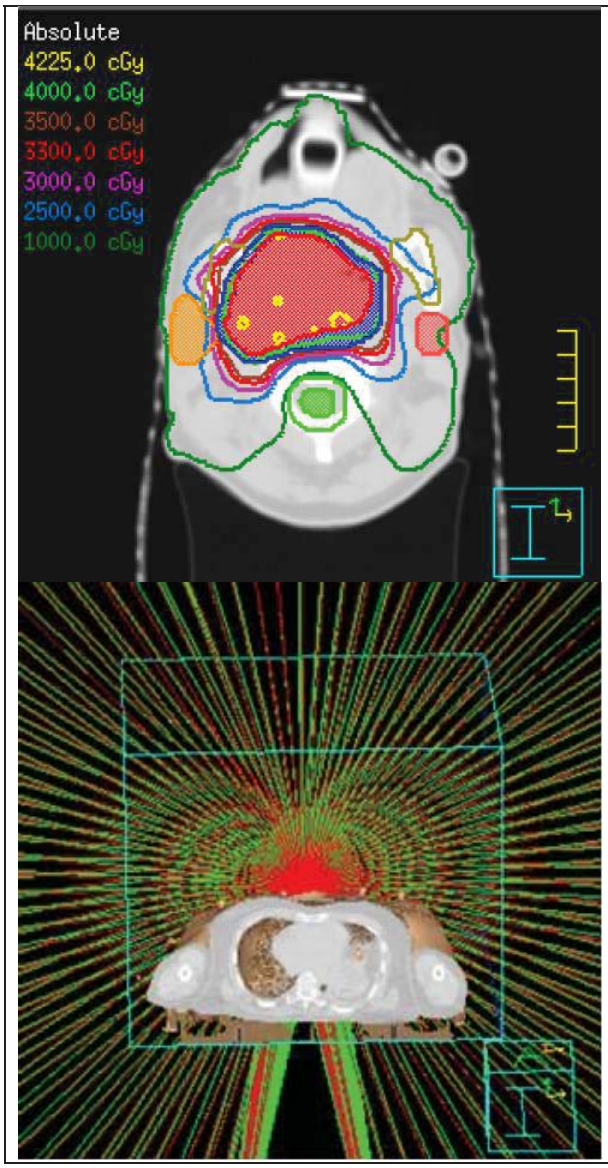
Normal structures to be contoured include the brainstem, brainstem planning risk volume (PRV=brainstem +3mm) brain, spinal cord, spinal cord PRV (spinal cord +5mm) eyes, optic nerves, optic chiasm, cochlea, parotids, submandibular glands, oral cavity, lips, larynx, supraglottis, constrictors, esophagus, trachea, carotid arteries, brachial plexus.

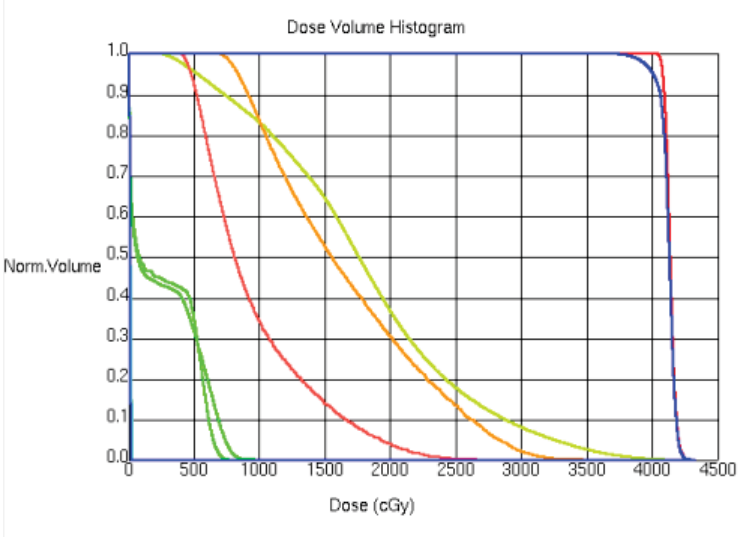
Effort should be made to minimize the dose to these structures as much as possible. Any normal structure involved with disease should be treated fully. However, the following constraints are considered hard constraints and cannot be violated, even if this compromises tumor coverage.

- Spinal cord – <0.03cc ≥ 25Gy
- Brainstem - <0.03cc ≥ 25Gy
- Optic nerves - <0.03cc ≥ 20Gy
- Optic chiasm - <0.03cc ≥ 20Gy
- Eyes - <0.03cc ≥ 25Gy
- Brachial Plexus - <0.03cc ≥ 30Gy

For patients that would require inclusion of >180 degrees of involvement of the carotid artery, PTV can be contracted to allow for more aggressive carotid sparing at the discretion of the treating radiation oncologist.

Representative SBRT treatment planning images and dose volume histogram plots





ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max
	ESOPHAGUS	new ct	5.9	36.0	18.0	8.0	0.00 %	0.00 %
	ORAL CAVITY	new ct	191.8	4087.6	1788.7	787.6	0.00 %	0.00 %
	PAROTID_L	new ct	389.0	2655.4	957.9	449.1	0.00 %	0.00 %
	PAROTID_R	new ct	679.0	3467.4	1663.7	635.7	0.00 %	0.00 %
	PTV	new ct	3412.2	4290.3	4123.7	66.2	0.00 %	0.00 %
	SPINAL CORD_PRV5	new ct	4.7	959.7	270.8	288.3	0.00 %	0.00 %
	SPINAL_CORD	new ct	5.3	766.5	265.1	266.7	0.00 %	0.00 %
	TRACHEA	new ct	--	25.5	12.5	4.7	0.00 %	0.00 %

6.3 **Treatment**

Patients will be treated on a linear accelerator equipped with cone beam CT image-guidance, or on a Cyberknife platform. Daily image guidance must be performed and confirmed by a physician or medical physicist before each treatment. If the shift exceeds 7mm, a second confirmatory image acquisition using the image guidance platform will need to be performed to confirm that residual error is <3mm. Residual error >3mm requires repositioning of the patient. Radiation fractions will be given with at least 40 hours between fractions and typically be delivered every other day (e.g. M, W, F, M, W). Twice weekly fractions are also acceptable (e.g. M, Th, M, Th, M). Total treatment time should be between 10-18 days.

6.4 **Duration of Follow Up**

Patients will be followed for toxicity for 1 year after treatment has been discontinued or until death, whichever occurs first. Following completion of this period of follow-up on-study patients will then be followed per standard of care as detailed below.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome.

Patients will be followed for one year after SBRT. All patients will be seen at 0.5, 3, 6, 9, 12 months after SBRT. At the three month visit, a post-SBRT PET/CT will be obtained to assess for disease response. CT of the neck and chest (preferably with contrast barring allergies or renal insufficiency) will be obtained at the 6 and 12 month visits. At each visit, patients will be assessed for Head and Neck toxicity using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. While no other toxicities are expected, any additional toxicity should also be scored by CTCAE version 4.0. In addition they will complete the FACT-H&N questionnaire (validated questionnaires to assess treatment related quality of life). When study follow-up is completed at 12 months, the patient will transition to standard follow-up off protocol with physician visits and head and neck exam every 3 months for year 2, every 4 months for year 3, every 6 months for year 4 and annually thereafter.

7.0 DOSING DELAYS / DOSE MODIFICATIONS

7.1 Modifications to the treatment schedule due to changes in patient condition are at the discretion of the treating physician. Such modifications are not expected as the expected acute toxicity of the treatment is minimal. If any patient requires dosing delay such that the total duration of the radiation course is greater than 18 days due to a clinical factor this will be reported.

7.2 There will be no dosing modifications made to the three predefined dosing cohorts. Accrual to the predefined dose cohorts will be performed according to Section 3.1.

8.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

The following is a list of AEs (Section 8.1) and the reporting requirements associated with observed AEs (Sections 8.3 and 8.4).

Adverse events will be followed until resolution or for a maximum of 30 days post study discontinuation. Serious adverse events that are still ongoing at the end of the study period will necessitate further follow-up to determine the final outcome.

8.1 Adverse Events and Potential Risks

8.1.1 SBRT

Treatment related head and neck toxicity will be monitored using the CTCAE version 4.0 instrument. Toxicity data will be continually assessed by the treating radiation oncologist each time a patient comes for a clinical visit, and the data will be entered into the database. Excessive toxicity that would lead to termination of the study includes the requisite number of grade 4 or 5 toxicities as detailed in 3.0 above.

8.2 Definitions

8.2.1 Adverse Events

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. In general, adverse events that are at least partially the result of (a) or (b) would be considered related to the research, whereas adverse events solely related to (c) or (d) would be considered unrelated to the research.

8.2.2 The significance of an adverse event is used to describe the patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning (i.e., moderate, severe or life threatening). Based on the National Cancer Institute Guidelines for the Cancer Therapy Evaluation Program, severity can be defined by the following grades of events:

Grades 1 are mild adverse events. (e.g., minor event requiring no specific medical intervention; asymptomatic laboratory findings only; marginal clinical relevance)

Grades 2 are moderate adverse events (e.g., minimal intervention; local intervention; non-invasive intervention or elective interventional radiological procedure; transfusion;).

Grades 3 are severe and undesirable adverse events (e.g., significant symptoms requiring hospitalization or invasive intervention; transfusion; therapeutic endoscopy or operation).

Grades 4 are life threatening or disabling adverse events (e.g., complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life–threatening physiologic consequences; need for intensive care or

emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation).

Grades 5 are fatal adverse event resulting in death.

8.2.3 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 12 hours OR
    - The admission is pre-planned (i.e., 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 patient or 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.

8.2.4 Expectedness

Adverse Events can be Expected or Unexpected.

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.

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.

8.2.5 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug/procedure.
- Probable – The AE is likely related to the study drug/procedure.
- Possible – The AE may be related to the study drug/procedure.
- Unlikely – The AE is doubtfully related to the study drug/procedure.
- Unrelated – The AE is clearly NOT related to the study drug/procedure.

8.3 Reporting Procedures for All Adverse Events

All participating investigators will assess the occurrence of any treatment related AEs throughout the subject's participation in the study. Subjects will be followed for toxicity one year after treatment has been discontinued or until death, whichever occurs first. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

The investigator is responsible for ensuring that all treatment related AEs observed by the investigator or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's case report form, subject's medical records, and/or any other institutional requirement. Source documentation must be available to support all adverse events.

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

The study team will provide the following for all adverse events:

- Description of the event
- Date of onset and resolution
- Grade of toxicity
- Attribution of relatedness to the investigational agent
- Action taken as a result of the event
- Outcome of event

In this study, descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 available at http://ctep.cancer.gov will be utilized for

AE reporting.

Adverse events will be reported to the IRB according to the IRB policies and procedures in reporting adverse events.

8.4 Serious Adverse Event Reporting Procedures

Serious adverse events that occur beginning with the signing of the informed consent form, during treatment, or within thirty days of the last dose of treatment must be reported to the Cleveland Clinic Principal Investigator.

8.5 Data Safety Toxicity Committee

It is the Case Comprehensive Cancer Center's Principal Investigator's responsibility to ensure that ALL serious adverse events are reported to the Case Comprehensive Cancer Center's Data Safety Toxicity Committee. This submission is simultaneous with their submission to the Sponsor or other Regulatory body.

9.0 STUDY PARAMETERS AND CALENDAR

9.1 Study Parameters

9.1.1 Screening Evaluation

Patients will complete the FACT H&N quality of life questionnaires at baseline.

9.2 **Calendar**

Assessment	Months Since Treatment					
	Baseline	0 Post Treatment (Last OTR Visit)	0.5 (1-3wks)	3	9	6, 12
Informed Consent	X					
Medical History	X					
Vitals[1]	X	X	X	X	X	X
Physical Exam[2]	X	X	X	X	X	X
PET/CT[3]	X			X		
CT neck and chest[4]						X
FACT-H&N survey	X		X	X	X	X
CTCAE Toxicity Assessment		X	X	X	X	X

[1] Height not required
[2] Focused head and neck exam at each visit with optional pharyngolaryngoscopy
[3] An additional PET/CT may be done after the 3 month time point to help clarify the etiology of abnormalities that are found clinically or radiographically to suggest potential recurrence/progression
[4] With contrast unless contraindicated

10.0 MEASUREMENT OF EFFECT

10.1 The primary endpoint of this dose finding study is safety and to assess the toxicity associated with escalating doses of SBRT. Secondary endpoints include disease response, as measured by clinical examination and the accompanying imaging studies obtained at 3, 6, and 12 months post SBRT. Response will be measured according to standard RECIST criteria as follows:

Response	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all targeted lesion(s), or significant shrinkage of disease and metabolic response with SUV <4. Residual tissue fullness, asymmetry or fibrosis that continues to improve on serial CT imaging after an initial decline (>50%) in SUV will be considered treatment effect.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of targeted lesion(s), taking as reference the baseline sum of diameters, and or a >50% decrease in tumor SUV.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of targeted lesions, taking as reference the *smallest sum*

	on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.0 DATA REPORTING/REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

11.1 **Data Reporting**

The OnCore Database will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore properly used is compliant with Title 21 CFR Part 11. Access to data through OnCore is restricted by user accounts and assigned roles. Once logged into the OnCore system with a user ID and password, OnCore defines roles for each user which limits access to appropriate data. User information and password can be obtained by contacting the OnCore Administrator at oncore-registration@case.edu.

OnCore 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 OnCore database. A calendar of events and required forms are available in OnCore.

11.2 **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.

11.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator or Co investigators 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 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.

11.2.2 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.

11.2.3 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 national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

11.2.4 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 Center 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.

11.2.5 Data Safety and Monitoring Plan

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

12.0 STATISTICAL CONSIDERATIONS

The main endpoint of this dose finding study is safety and to identify the maximum tolerated dose of SBRT in this patient population. Dose escalation studies typically involve a "3+3" design. However, as SBRT is a powerful treatment tool, and toxicities can be delayed, we erred on the conservative side and doubled our dose level population. As such, we have planned for accrual of 6 patients to each dose level. If sufficient DLTs are not seen in the third dose level (45Gy in 5 fraction), then an additional 6 patients will be accrued to this dose level to provide more robust safety information on this dose, which would become the recommended dose for future study. We also performed probability analysis using binomial distribution analysis to calculate the probability of escalating to each dose level, as demonstrated in the following table:

p of	Dose 1- p of <=1 DLT in	Dose 1- p of 2 DLT in 1st	Dose 1- p of <=1 DLT in	p for Next

DLT	1st 6 pts	6 pts	2nd 6 pts	Dose
0.15	0.78	0.18	0.78	0.91
0.2	0.66	0.25	0.66	0.82
0.25	0.53	0.30	0.53	0.69
0.3	0.42	0.32	0.42	0.56
0.4	0.23	0.31	0.23	0.31

For our secondary endpoints, we will also use Kaplan-Meier estimates to plot overall survival and local progression free survival. We will conduct trend tests to investigate the relationship between SBRT dose and response. Non-parametric methods, including but not limited to the Mann-Whitney test and Fisher's exact test, will be used to analyze patient, tumor and treatment related factors associated with SBRT related morbidity, including DLTs as well as grade 3 acute and late events. We will use repeated ANOVA measures to analyze the quality of life data.

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APPENDIX A: FACT-Head and Neck QOL Questionnaire

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy.....	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					

GS7	I am satisfied with my sex life.....	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

Appendix B Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	2	14	16
Ethnic Category: Total of All Subjects *	3	15	18
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	1	14	15
Racial Categories: Total of All Subjects *	2	16	18

Amendment Summary:

Study Title: *Phase I Dose Escalation Study of Stereotactic Body Radiotherapy for p16 Negative Squamous Cell Carcinoma of the Head and Neck in High Risk Patients Who are Ineligible/Refuse Standard of Care Therapy*

PI: Shlomo Koyfman,MD

Study ID: Case 8314

Protocol Changes (revised on 11-26-2014 from original submission on 10-08-2014. Footer date did not change)

- Removed HX4 and Threshold pharmaceuticals from Title page as Sponsor and Supplied Agent
- Removed HX4 component from Study Schema on pg 4
- Removed sections 1.4 and 1.5 from introduction describing background on HX4
- Removed section 5.0 discussing all details of HX4
- Removed HX4 component as second question of study in purpose section 1.6 (now 1.4)
- Removed HX4 uptake characteristics as secondary objective in section 2.2.1
- Removed HX4 imaging from PRE-SBRT visits in 3.3.1
- Removed HX4 scans and pre/post HX4 vitals from study calendar in section 9.2

Consent Form Changes

- Added Min Yao MD as CoPI from UH
- Removed discussion of HX4 as purpose #2 of the study from page 2
- Removed optional preSBRT HX4 imaging from study procedures (bottom pg 2)
- Removed reference to HX4 imaging in “before begin study” section top pg 3
- Removed HX4 reference in study schema under “study plan” section pg 4
- Removed HX4 imaging and pre/post HX4 vitals from study calendar on pg 5
- Removed reference to HX4 in “cost” section
- Removed “optional imaging component” and distinct signature area to agree to participate in HX4 component (pg 11)

Summary of Changes for CASE 8314: *Phase I Dose Escalation Study of Stereotactic Body Radiotherapy for p16 Negative Squamous Cell Carcinoma of the Head and Neck in High Risk Patients Who are Ineligible/Refuse Standard of Care Therapy v6-2-2015*

Rationale: The current protocol was designed as a phase I dose escalation protocol including 3 arms, 35Gy, 40Gy and 45Gy, all in 5 fractions. There is a substantial literature on SBRT in the reirradiation setting in which 40Gy in 5 fractions has been used and deemed safe by numerous institutions. I am the radiation oncology co-PI of a national RTOG foundation study that is investigating SBRT in the reirradiation setting, for which 40Gy is the dose being used. I initially erred on the side of being overcautious and started with 35Gy fearing that patients would be reluctant to enroll at higher doses. However, after screening numerous eligible patients, the #1 impediment to enrollment is patients fear that the dose is too low to be efficacious, especially once they are aware that we typically used 40Gy standardly in the re-irradiation setting. Several patients expressed willingness to enroll if we were already accruing to dose level 2, but were uncomfortable with dose level 1, especially as we are testing this approach in patients that are potentially curable.

Proposed Amendments:

1) As such, I am proposing an amendment to the protocol to drop the initially proposed dose level 1 and proceed with 40Gy in 5 fractions as our initial dose. The revised protocol would then only have 2 doses; 40gy and 45Gy in 5 fractions. This will also reduce the number of patients required (18 instead of 24) and hopefully a more expeditious completion of this trial. I have enclosed the tracked and clean versions of the revised protocol. All changes were made merely to reflect this change in dosing.
2) The only other change in the protocol is that we noticed a discrepancy in the eligibility criteria whereby stage II was deemed eligible, but T2N0M0 was stated to be ineligible. We have corrected the ineligibility checklist to state that T1N0M0 is ineligible, while Stage II or T2N0M0 disease will remain eligible. This clarification will remove confusion.

Thank you again for your time and review

Shlomo Koyfman, MD

SUMMARY OF CHANGES
Amendment 3, Version Date: September 30, 2016

CASE 8314, Phase I Dose Escalation Study of Stereotactic Body Radiotherapy for Carcinoma of the Head and Neck in High Risk Patients Who are Ineligible/Refuse Standard of Care Therapy

Study Chair: Shlomo Koyfman, MD; (216) 444-7552; koyfmas@ccf.org

1. Add Drs. Geiger, Joshi, Woody
2. Remove Dr. Nwizu
3. Change title
4. Revise eligibility criteria to include other histologies (adenocarcinoma, salivary gland cancer, p16 negative SCC, cutaneous SCC). This was necessary due to poor accrual. Because the HPV negative SCC population is waning, the study threatens to not meet accrual and be closed to due low numbers of eligible patients. As such, by expanding the eligibility criteria to other histologies, this will help the accrual goals. As this is primarily an SBRT safety study, the histologic variants should not have an impact on the safety of SBRT and therefore, the scientific rigor of assessing the safety of dose escalating SBRT in this context remains even with this broadening of eligibility criteria.