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RT-083 A phase II investigation of contralateral arytenoid sparing IMRT for T1a and T2a larynx cancer with detailed analysis of post-treatment laryngeal function

Supported by: Department of Radiation Oncology

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1.0 Introduction

Parallel opposed portal external beam radiation is the standard nonsurgical treatment for T1-2N0 glottic cancer.[1] This technique involves treatment of the entire larynx for tumors that are small and limited. Although technological advances now allow radiation oncologists selectively to target and avoid adjacent sub-portions of any organ, these tools have not been applied T1-2N0 glottic cancer due to the perceived low toxicity of standard therapy. However, radiotherapy for early glottic cancer is not without functional side effects [2] and it is not known whether post-treatment function after whole larynx radiation is superior to a more targeted surgical approach[3]

This is a phase II study to treat unilateral glottic cancer (Stage T1a and T2aN0) with intensity modulated radiation therapy (IMRT). In view of the anticipated small volume of disease at presentation and need to limit the potential for a "marginal miss", treatment will include the entire involved vocal fold, anterior commissure, and the anterior 1/3 of the contralateral vocal fold thus sparing the contralateral arytenoid cartilage and musculature ("contralateral arytenoid sparing IMRT"). In addition, we propose to perform sophisticated objective and patient reported measures regarding speech outcomes for two years after the completion of therapy at specified intervals, to better gain an understanding of the effects of therapy. Our findings will have the potential to dramatically advance the field of early larynx cancer therapy by demonstrating the efficacy of limiting the volume of uninvolved larynx that receives radiation and comprehensively assessing the functional outcomes of said therapy.

1.1 Study Rationale

T1-2N0 glottic squamous cell carcinoma (SCC) is traditionally treated with simple, parallel opposed radiation fields [4] with a gratifying control rate [1,5-7]. Although the technological sophistication of the administration of external beam radiation has increased dramatically in the past 50 years, treatment of early stage larynx cancer has changed little since 1964 [5]. The reason for this is twofold: the efficacy of radiation therapy prescribed in this manner and the perceived low toxicity of treatment.

The favorable toxicity profile of parallel opposed radiation for early glottic tumors is largely a result of the low incidence of nodal metastases [8], permitting omission of elective nodal irradiation from treatment plans. Thus, most radiosensitive normal tissues[9] are clear of the radiation field. Large single-institution retrospective experiences of both primary radiation [5,10] and transoral surgery [8] report long term serious complications on the order of 1%. Randomized trials of primary radiation [6,7,11] report higher rates of long term toxicity, approaching 10%, perhaps due to more careful prospective reporting. The combination of low long term toxicity and excellent efficacy is appealing, however early larynx tumors are typically quite small [8] and parallel opposed radiotherapy results in treatment of the entire larynx, complicating salvage operations when necessary . Typical head and neck radiation assessments of toxicity [12] may not be applicable.

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The excellent treatment outcomes of early larynx cancer and its incidence [13] (which may be rising) suggest that survivorship concerns merit greater consideration than previously afforded in the reported experiences. One facet of head and neck cancer survivorship that can uniquely be addressed in early larynx cancer is radiation dose to the carotid arteries, because elective lymphatic radiation is not required. External beam radiotherapy is an independent risk factor for accelerating carotid atherogenesis [14]; head and neck cancer patients treated with radiation have been demonstrated in some data sets to have an increased risk of ischemic stroke [15,16]. In parallel opposed radiation, the carotid arteries generally receive a dose of radiation similar to that of the tumor (Figure 2). By contrast, they can be significantly avoided without compromising target coverage through IMRT, and pilot studies have demonstrated encouraging results with this technique [17].

However, it is difficult to assess the benefit of 'carotid artery avoidance IMRT'. It is impossible to spare the artery completely [18] and it is unknown whether the development of a cerebrovascular event is dose-dependent. In addition, the median time to an occurrence is roughly 10 years [15] after the completion of radiation, making any current determination of the efficacy of the change impossible. By contrast, determining the benefit of "contralateral arytenoid sparing IMRT" does not suffer from such limitations. Dose-volume relationships in the development of head and neck radiation toxicity are well described for advanced head and neck tumors [19] and it is reasonable to expect that similar dose volume parameters can be defined for early larynx cancer. The assessment of toxicity for early glottic cancer must focus on vocal quality and deglutition.

Any new application of highly conformal intensity modulated radiotherapy must account for organ motion during treatment (intrafraction uncertainty) and setup error (interfraction uncertainty). For the larynx, organ motion will be expected to be secondary to respiration. Although it is intuitive that the larynx moves with respiration, the movement relative to the contralateral cord is relatively minimal in early larynx cancer patients. A 4DCT analysis demonstrated that internal vocal cord motion is approximately 1 mm in all measured planes, suggesting that single vocal cord irradiation would not be hampered by respiratory motion[20]. To correct for daily setup uncertainty, daily CBCT registration and correction reduces random positioning errors to less than 1 mm[21]. Despite these small displacements, the uncertainty of single vocal cord IMRT combined with the success of conventional treatment demands caution. Using proposed contouring expansions (section 5.2.3) the following normal tissue goals were obtained on the 5 most recent TIS/T1a/T2a patients treated at FCCC:

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	Contralateral Aretynoid	Ipsilateral Carotid Artery	Contralateral Carotid Artery	Inferior Pharyngeal Constrictor	Esophageal Verge	Spinal Cord
1	21.36	53.3	4.7	43.2	54	16.8
2	16.9	32.3	7.5	38	34	20
3	33.3	39	4	35	28	14
4	12	46.5	6	50	33.7	22
5	20.5	29	12.4	43.1	20.5	9
MEAN	**20.81**	**40.02**	**6.92**	**41.86**	**34.04**	**16.36**

[1]All doses listed in Gy

[2]All dose listed are mean dose to organ except spinal cord (maximum dose to a point)

In this planning exercise, reducing dose to the spinal cord well below the standard dose of 45 Gy was prioritized because 1.) standard parallel opposed radiation delivers negligible dose to the spinal cord and 2.) second tumors in this population are not uncommon[22] and diagnosis of such may require an additional course of head and neck radiation which would be complicated by unnecessary dose to the spinal cord.

Many recent studies have attempted to document the voice outcomes following treatment of early glottic carcinomas[2,3,20-26]. Using many different instruments, these analyses suggest that regardless of treatment modality and radiation fractionation, some voice dysfunction is common after treatment. In view of the high cure rates associated with this disease, the functional outcomes of each modality become especially important. Clinician awareness and patient education regarding potential side effects and declines in voice and/or swallow function can help guide the decision-making process. Thus, the functional outcomes of early glottic cancer patients undergoing treatment with IMRT are of substantial importance as well.

The above referenced studies document voice changes based both upon perception of clinicians and patients. The present study will incorporate the most commonly used tools employed in these studies. Objective clinician analysis most commonly includes use of a validated, perceptual scale, such as the GRBAS scale (APPENDIX) [27]. In this scale, each of the named vocal characteristics is assigned a score of 0 to 3, where 0 represents normal and 3 represents severe. This is done by experienced listeners (in this study, two speech and language pathologists and a laryngologist). Typical objective measures include measurements of fundamental phonation frequency (F0, measured in Hz), maximal phonation times (MPT, measured in seconds), jitter (percent frequency perturbation), shimmer (percent amplitude perturbation), and noise-to-harmonic ratio (NHR). These measurements are performed using electro-acoustic analysis of a recorded voice sample. Further objective analysis will be performed using laryngovideostroboscopy. This is performed using a transnasal or transoral endoscope, which records vocal fold movement

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and vibration using a strobe light source. These recordings will then be evaluated for amplitude, symmetry, and periodicity of the vocal fold mucosal wave; presence or absence of glottic closure; and degree of mobility by measuring the angle of abduction of each vocal fold from the midline. The most widely used subjective patient perception tool is the VHI, which is a validated, self-administered 30 item questionnaire covering three domains: functional, physical, and emotional (APPENDIX) [28]. This questionnaire will be administered at each visit and takes less than 10 minutes to complete.

Deglutition changes following treatment of early glottic carcinomas with radiation are not well-studied. Peretti et al. reviewed swallow outcomes following transoral laser surgery for T2-T3 cancers, and found that up to 4% of patients develop aspiration with high patient-perceived difficulty with swallowing[23]. Another study reviewed quality of life concerns in patients who had undergone endoscopic laser resection of T1-T2 cancers, and found that two issues of highest concern to recovering patients were salivary production/control and swallowing[29]. Similar data are unavailable for patients undergoing radiation therapy.

The proposed study will therefore include objective and subjective measures of swallow function. Objective evaluation will be employed using the Penetration-Aspiration Scale as well as the Functional Outcome of Swallowing Scale [30,31]. Subjective evaluation will be performed using the validated EAT-10, which is a 10 item self-administered questionnaire that takes 1-2 minutes to complete [32]

2.0 Objectives

To define a new treatment technique for T1a larynx cancer that maintains excellent local control with less extensive radiation fields

Hypothesis: Contralateral arytenoid sparing IMRT for T1a larynx cancer maintains the excellent local control associated with whole larynx radiation and results in functional outcomes at 24 months after therapy that are suggestive of improved function when compared to historical controls

2.1 Primary Objectives and Endpoints

Voice quality outcomes at 24 months after contralateral arytenoid sparing IMRT for T1a/T2a larynx cancer

Two year local control with contralateral arytenoid sparing IMRT for T1a/T2a larynx cancer

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2.2 Endpoints

2.1.1 Primary endpoint

Demonstrate a 50% improvement in the VHI (voice handicap index) score at 24 months after the completion of therapy

2.2.2 Secondary Endpoints

Demonstrate a similar 2-yr local control of (>85%) with IMRT therapy for T1a and T2aN0 larynx cancer

Evaluate clinician-reported voice quality at defined intervals up to 24 months after the completion of radiation using the Grade, Roughness, Breathiness, Asthenia, and Strain (GRBAS) scale

Use the Eating Assessment Tool (EAT-10) to evaluate patient-reported satisfaction with swallowing at up to 24 months after the completion of radiation

Evaluate clinician-reported measures of swallowing 24 months after the completion of radiation as measured by fiberoptic endoscopic evaluation of swallowing (FEES) using the penetration, aspiration scale (PAS) scores for 3 commonly evaluated textures (cookie, puree, thin).

2.3 Purpose/Specific Aim of this Research Study: To define a new treatment technique for T1a larynx cancer that maintains excellent local control with less extensive radiation fields

2.4 Hypothesis: Contralateral arytenoid sparing IMRT for T1a larynx cancer maintains the excellent local control associated with whole larynx radiation and results in functional outcomes at 24 months after therapy that are suggestive of improved function when compared to historical controls

3.0 Study Plan

3.1 Description of Study Design, Population and Duration of Study Therapy

This is a single arm phase II study. All subjects will be treated with the standard fractionation for T1a glottic cancer at FCCC: 63 Gy in 28 fractions[6] for T1a and 65.25 Gy in 29 fractions[33] for T2a.

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Subjects will be patients referred to FCCC or Temple for treatment of T1 glottic cancer. Patients will be approached for trial accrual during the pretreatment process. Patients will be provided with the informed consent document to educate themselves regarding the rationale of the study. Patients with T1a larynx cancer that agree to the functional assessment of the study will be identified as potential candidates. The duration of protocol assessment is 24 months.

Subjects will be seen in follow-up at least every 3 months for the first year and every 4 months for the second year after therapy for tumor surveillance, consistent with the standard of care.

Subjects will also be seen by speech therapy on a separate schedule, consistent with current institutional practice of voice rehabilitation after this therapy. At the 1,3,6,12, and 24 months follow-up patient reported questionnaires and functional assessments will be captured and recorded

Number of subjects per year projected at FCCC/Temple	Total number of subjects at FCCC/Temple	Number of subjects nationally or internationally (if applicable	Number of subjects at collaborating institutions (if applicable)
Up to: 4	Up to: 30	0	0

4.0 Patient Selection Inclusion & Exclusion

4.1 Inclusion Criteria

4.1.1 Patients with histologically proven invasive squamous cell carcinoma arising from the true vocal cord.

4.1.2 T1a and T2a squamous cell carcinoma of the glottic larynx (tumor limited to one vocal cord with normal cord mobility).

4.1.3 Squamous cell carcinoma in-situ of a single vocal cord (Tis) is eligible.

4.1.4 Minimum age of entry is 18 years.

4.1.5 Patients must be able to read and write English to comply with the questionnaire portions of the protocol.

4.1.6 ECOG performance status of 0 or 1.

4.2 Exclusion Criteria

4.2.1 Patients with verrucous or adenocarcinoma

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4.2.2 Patients with T1 tumors on both cords (T1b)

4.2.3 Patients with T2b-T4 true larynx tumors

4.2.4 Patients with primary supraglottic tumors that involve the true larynx

4.2.5 Patients with a prior or concurrent malignancy (other than non-melanoma skin cancer or carcinoma in-situ of the cervix) are ineligible unless the previous cancer was treated 5 years or more prior to the current tumor and the patient has remained continually disease free

4.2.6 Prior radiation to the head and neck

4.2.7 Pregnant or breastfeeding. A negative blood-pregnancy test is required for women of childbearing potential (WOCBP) within 14 days prior to her CT stimulation for treatment planning. Refer to section 4.4 for further detail.

4.3 Inclusion of Women and Minorities

Men and women, regardless of race, ethnic group or sexual orientation are eligible for this study.

4.4 Pregnancy

The effects of radiation therapy on the developing human fetus at the recommended therapeutic dose are known to be teratogenic. For this reason women of child-bearing potential (WOCBP) and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of treatment. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

Prior to study enrollment, WOBCP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In additional, men enrolled on this study should understand the risks to any sexual partner of childbearing potential.

All WOCBP must have a negative pregnancy test within *14 days* prior to CT stimulationfor treatment planning. If the pregnancy test is positive, the patient must not receive the CT nor protocol treatment and must not be enrolled in the study.

WOCBP is defined as follows: Any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or a bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea $\geq$ 12 consecutive months, or women on hormone

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replacement therapy (HRT) with documented plasma follicle-stimulating hormone (FSH) level > 35 mIU/ml). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be WOCBP.

4.5 Patient Registration

Participants may be registered from 8:00 am to 5:00 pm EST excluding holidays by emailing the Investigator-Sponsored Research Unit (ISRU) at: **FCCC.MONITOR@fccc.edu.** Eligible participants will be entered on study centrally once the following items have been received by email:

- Completed registration form
- Consent and HIPAA signature pages
- Eligibility checklist

Following registration, participants must begin protocol treatment within 14 calendar days of registration. Issues that would cause treatment delays must be discussed with the Sponsor-Investigator. If a registered participant does not receive protocol therapy following registration, the participant will be recorded as withdrawn from study. The Study Monitor must be notified as soon as possible if a participant does not begin protocol treatment as scheduled. For additional registration questions, please email **FCCC.MONITOR@fccc.edu** or call **(215) 728-5544.**

The FCCC ISRU will notify the site by email once registration is confirmed and the sequence number has been assigned. Participants must be registered and have received a sequence number prior to the initiation of treatment.

Exceptions to the current registration policies will not be permitted.

5.0 Treatment Plan

This is a single arm phase II study. All subjects will be treated with the standard fractionation for T1a glottic cancer at FCCC/Temple: 63 Gy in 28 fractions[6] for T1a and 65.25 Gy in 29 fractions[33] for T2a as detailed below.

5.1 Targets

5.1.1 The immobilization device must include neck and shoulder immobilization. An aquaplast face mask is required. The shoulders can either be immobilized by a shoulder depression device or an extended aquaplast configuration

5.1.2 Treatment planning CT scan in the immobilized position will be required to define the tumor, clinical and planning target volume.

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5.1.3 CT thickness must be ≤3mm for the CT simulation. The CT must include the entire larynx

5.1.4 The GTV, CTV, and PTV and normal tissues must be outlined on the CT slices in which they exist

5.2 Volume and ICRU Reference Point Definitions

5.2.1 The Gross Tumor Volume (GTV) is defined as all gross disease determined from CT, clinical information and endoscopic findings. T1a tumors are small by definition. There are tumors for which a GTV will not be readily available on the CT scan due to small size of the tumor or gross tumor extirpation by a biopsy procedure. For patients where a clear GTV is not evident, no GTV volume will be defined

5.2.2 The Clinical Target Volume is defined as the area thought to contain gross disease and areas potentially at risk for microscopic disease. Regardless of whether a GTV is evident on imaging, the CTV will be very simular for every patient

5.2.2.1 Superior border: Superior extent of the arytenoid cartilage

5.2.2.2 Inferior border: Inferior extent of the true vocal fold

5.2.2.3 Lateral border: Outer aspect of the ipsilateral thyroid cartilage

5.2.2.4 Medial border: Air within the larynx at the midline of the body

5.2.2.5 Anterior: Volume will completely treat the anterior commissure and up to the anterior 1/3 of the contralateral vocal fold, in order to minimize the risk of marginal miss

5.2.2.6 Posterior border: Posterior aspect of the arytenoid cartilage. Inferiorly, the arytenoid cartilage will not be visible on slices that extend to the inferior extent of the true vocal fold. The posterior border in this region should include the ipsilateral portion of the cricoid cartilage immediately inferior to the arytenoid and the adjacent ipsilateral cricoarytenoid musculature

5.2.3 The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variabilities of treatment setup and internal organ motion. An asymmetric PTV will be employed due to concerns of deglutition preferentially displacing the larynx in the superior/inferio and anterior/posterior orientations. Mid-neck anatomy does not allow for a 10 mm anterior/posterior margin. Thus 5 mm was chosen

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5.2.3.1 Superior/inferior PTV expansion: 10 mm

5.2.3.2 Anterior/Posterior 5 mm

5.2.3.3 Meidal/Lateral: 3 mm

5.2.4 After completion of contouring as detailed in 5.2.2 and 5.2.3 the superior/inferior extent of the PTV will be measured. If it measures less than 4.0 cm, it will be extended to such a length (the typical treated length for standard therapy) by copying and extending the most superior and most inferior contour superiorly and inferiorly (respectfully) until a 4 cm field is achieved.

5.3 Targets and Critical Normal Tissue Definitions

5.3.1 Targets

5.3.1.1 There will be a single target for this protocol – a single PTV. There will be no elective nodal irradiation

5.3.2 Dose

5.3.2.1 Tis and T1a: 63 Gy in 28 fractions T2a: 65.25 Gy in 29 fractions

5.3.3 Critical Normal Tissue Structures

5.3.4. GSL

5.3.4.1 A secondary volume of GSL – PTV will be createdThis will be defined as the glottic and supraglottic larynx, including the tip of the epiglottis, the aryepiglottic folds, arytenoids, false cords, and true cords, bounded by the thyroid cartilage laterally, anteriorly the anterior edge of the pre-epiglottic fat, and posteriorly bounded by the anterior edge of the pharyngeal wall or the posterior edge of the arytenoid and/or cricoid cartilage.

5.3.5 Contralateral arytenoid

5.3.5.1 The arytenoids are small, 3-sided pyramidal structures that sit superior to the cricoid cartilage in the posterior larynx. They are small (mean volume estimated at 0.312 cc). An attached supplement demonstrates 2 contouring examples. No attempt will be made to differentiate the artetynoid and corniculate cartilage

5.3.6 Ipsilateral carotid artery

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5.3.6.1 Both carotid arteries will be contoured on all slices that include a PTV plus 1-2 slices above and below.

5.3.7 Contralateral carotid artery

5.3.8 Spinal Cord

5.3.8.1 The cord will be contoured on all slices that include a PTV plus 1-2 slices above and below

5.3.9 Inferior pharyngeal constrictor

5.3.9.1 Defined as the pharyngeal musculature beginning at the level of the inferior hyoid superiorly and extending to the esophageal verge inferiorly.

5.3.10 Esophageal verge

5.3.10.1Extending superiorly from the inferior phyarngeal constrictor extending inferiorly to the most inferior level with a PTV contour

5.4 Planning

5.4.1 The treatment for each patient will be inverse planned. Either step-and-shoot intensity modulated radiation therapy (IMRT) or volumetric arc therapy (VMAT) will be employed. if ste-and-shoot IMRT is employed, beams that enter through the contralateral arytenoid should be avoided to help with dosimetric goals.

5.4.2 Dose specification

5.4.2.1 95% of the PTV will receive the prescription dose

5.4.2.2 ≥99.5% of the PTV will receive 95% of the prescription dose

5.4.2.3 < 1% of the PTV will receive > 110% of the prescription

5.4.2.4 Prescription will be 63 Gy in 28 fractions (T1a an dTis) or 65.25 Gy in 29 fractions

5.4.3 Critical Normal Tissue Structures Guidelines

Spinal cord: < 25 Gy; deviation acceptable <30 Gy

5.4.3.1 Contralateral Arytenoid: Mean Dose ≤ 21 Gy

5.4.3.2 Ipsilateral carotid artery: < 45 Gy

5.4.3.3 Contralateral carotid artery < 10 Gy

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5.4.3.4 Spinal cord: 0.1 cc < 20 Gy

5.4.3.5 Inferior pharyngeal constrictor: Mean Dose < 31.5 Gy

5.4.3.6 Esophageal Verge: < 20 Gy

5.4.4 Doses are prescribed as above. IMRT prescribing requires prioritization. Prioritization for this investigation is as below:

5.4.4.1 PTV 63

5.4.4.2 Contralateral arytenoids

5.4.4.3 Inferior pharyngeal constrictor

5.4.4.4 Esophageal verge

5.4.4.5 Spinal cord

5.4.4.6 Contralateral carotid artery

5.4.4.7 Ipsilateral carotid artery

5.5 External beam equipment and beam delivery methods

5.5.1 4 or 6 MV beams are required

5.6 Daily Treatment Localization/IGRT

5.6.1 Daily image guidance (IGRT) is required. This may be achieved with the following technique:

5.6.1.1 Linear accelerator mouth kV and MV conebeam CT images

5.6.1.2 CT on rails images

5.6.2 Treatment day procedure to register the imaging dataset are as follows:

5.6.2.1 Region of interest (ROI) for fusion is the larynx

5.6.2.2 Both manual and automatic types of registration can be used.

5.6.2.3 The result of the fusion must be visually checked for the alignment of the cartilages of the larynx (thyroid and cricoid cartilage) and the adjacent bony anatomy (cervical spine).

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5.6.2.4 In the instance of a disagreement between cartilage and spine alignment, cartilage alignment will be prioritized

5.6.2.5 Following the registration, the translational corrections will be applied to the treatment couch. If one or more corrections are larger than 5 mm, imaging must be repeated.

5.6.2.6 Special consideration of first fraction of radiation: If one of more corrections are larger than 10 mm, it will be assumed that the patient was swallowing during acquisition and the image will be repeated. If the repeat image similarly requires a larger than 10 mm, the start of radiation will be cancelled for that day. The same treatment localization will then be performed on the next clinic day. Should a shift larger than 10 mm be required again, it will be assumed that the patient was swallowing during the CT simulation acquisition, introducing a systematic error. In this situation, a new CT simulation and a new treatment plan will be required.

5.7 Concomitant Medications, Supportive Care, Excluded Therapies and Restrictions

Patients should receive full supportive care therapies concomitantly during the study when appropriate. Any disease progression requiring other forms of specific anti-tumor therapy will be cause for early discontinuation of study treatment.

Use of concurrent investigational agents is not permitted.

5.8 Duration of Therapy

In the absence of treatment delays due to adverse events, patients will receive 6 weeks of treatment unless one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Patient becomes pregnant
- Patient decides to withdraw from the study or
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator.

5.9 Duration of Follow up

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Patients will be followed for 24 months after completion of radiation. Patients removed from study for unacceptable adverse events that are related to the study treatment will be followed until resolution or stabilization of the adverse event.

5.10 Criteria for Discontinuation

Patients will be removed from study when any of the criteria listed in Section 5.8 applies. The reason for study removal and the date the patient was removed must be documented in the medical record and case report form.

6.0 Risks to Participants

Limited field radiation may not be as successful as whole larynx RT and there may be an increased risk of treatment failure

It is unknown if unilateral radiation introduces asymmetric function in the larynx. However, single vocal cord targeted therapy (surgery) causes no noticeable asymmetric symptoms[3] (reduced comfort and exacerbated throat clearing), so the risk is anticipated to be small

7.0 Potential Benefits to Participants

Patients will have more dedicated follow-up with laryngology – this potentially will lead to better post-treatment function.

Patients will receive therapy to a smaller volume, and potentially have improved functional outcomes as a consequence.

8.0 Cost to Participants

There are no unanticipated costs to participants in this trial. IMRT is a covered service by insurance/Medicare in the treatment of larynx cancer. Stroboscopy is a covered service for the follow-up of patients with larynx cancer.

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9.0 Study Calendar

	Screening	Pre-TX	WK 1 RT	WK 2 RT	WK 3 RT	WK 4 RT	WK 5 RT	WK 6 RT	TREATMENT COMPLETE	1 Month	3 Month	6 Month	9 Month	12 Month	16 Month	20 Month	24 Month
Medical History[C]	X																
Physical Exam[C]	X																
Vital Signs[B,C]	X									X	X	X	X	X	X	X	X
Performance Status[C]	X									X	X	X	X	X	X	X	X
Pregnancy Test[A]		X[A]															
CT Neck[C]		X															
CT Simulation		X															
Informed Consent[C]	X																
Video Stroboscopy and Functional Assessment[D]		X						X		X	X	X		X			X
Patient Questionnaire – EAT-10		X						X		X	X	X		X			X
Adverse Event Evaluation								X		X	X	X	X	X	X	X	X
IMRT			X	X	X	X	X	X									

A) A Serum pregnancy test must be performed on WOCBP within 14 days prior to exposure to radiation. The first study-related exposure is at the time of the CT scan of the neck.
B) Vital signs include temperature, blood pressure, pulse, respiration rate
C) All screening procedures must be obtained within 30 days of registration.
D) During the assessment the following forms will be completed:
-Voice Handicap Index (VHI)
-Grade, roughness, breathiness, asthenia, and strain (GRBAS) scale
-Penetration aspiration scale (PAS)

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10.0 Adverse Events

10.1 Definitions

10.1.1 Adverse Events (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, treatment or procedure regardless of whether it is considered related to the medical treatment or procedure *(NCI CTEP Guidelines March 28, 2011)*

10.1.2 Serious Adverse Event (SAE) is an AE that is fatal or life threatening, requires inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly/ birth defect, or results in any important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent any of the above outcomes. A "life-threatening" adverse event places the patient at immediate risk of death in the judgment of the investigator or sponsor.

10.1.3 Severity Rating

The investigator will evaluate the severity of each adverse event. NCI Common Terminology Criteria for Adverse Events (CTCAE v.4.0) or study specific toxicity tables provided in the protocol define severity. If not included in CTCAE v.4.0, severity is expressed in numerical grade using the following definitions:

1. Grade 1: Mild-asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. Grade 2: Moderate-minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL.
3. Grade 3: Severe-severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.
4. Grade 4: Life-threatening consequences; urgent intervention indicated.
5. Grade 5: Death related to AE

10.1.4 Attribution/Relationship to study drug

1. Definite – clearly related
2. Probable – likely related
3. Possible – may be related
4. Unlikely – doubtfully related
5. Unrelated – clearly not related

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10.1.5 Expectedness

An Expected Adverse Event is one where the specificity or severity is consistent with the current information available from the resources.

An Unexpected Adverse Event is one where the nature, severity, or frequency of the event is related to participation in the research is not consistent with either:

1. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts: or
2. The expected natural progression of any underlying disease, disorder, or condition of the subject (s) experiencing the adverse event and the subjects(s) predisposing risk factor profile for the adverse event. (OHRP Guidance on reviewing unanticipated problems 2007)

10.2 Recording and Reporting Responsibilities

10.2.1 Investigative site recording responsibilities:

1. Upon identification of an AE or SAE, the site investigator will utilize the above definitions to properly classify the event. Each category listed above must be recorded for each event.

2. All AEs and SAEs will be recorded in the "AE case report forms" (CRF) and in progress reports with details about the grade and attribution of each episode, action taken with respect to the study drug, and the patient's outcome will be recorded in the CRF. All events will be recorded on case report forms for the duration of the study until they resolve.

3. All SAEs will be recorded on the FDA MedWatch form 3500a. After submitting the initial report it may be necessary to submit follow up reports to the ISRU, Sponsor and the FDA should the event require further investigation.

10.2.2 Investigative site reporting responsibilities:

1. The investigator/ site is responsible to report all SAEs to the ISRU within 24 hours of becoming aware of the event. A written report must follow within 48 hours.

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2. Each investigator is responsible to report all AEs/SAEs to their local IRB following guidelines set by that IRB. The FCCC OCR reserves the right to request an event be reported to the IRB at their discretion. Copies of events reviewed by the IRB must be emailed to SAE.FCCC@fccc.edu.

3. If the investigator or IRB feels the event warrants a revision to the informed consent that was not already initiated by the ISRU, draft revisions will be made in track changes and submitted to the ISRU for consideration. Any consent revisions must receive ISRU approval **prior** to submission to the IRB.

4. Any investigator who is in doubt of whether a particular AE needs to be reported is directed to call the FCCC ISRU for confirmation with the Principal Investigator

5. If the results of an investigator or OCR investigation show an adverse event not initially determined to be reportable is so reportable, the investigator will report the event following the above guidelines based on the date the determination is made.

6. Copies of all related correspondence and reporting documents must be submitted to the ISRU and will be maintained in a regulatory file.

The participating site should report events to:

Investigator-Sponsored Research Unit
Office of Clinical Research
Fox Chase Cancer Center
SAE.FCCC@fccc.edu

10.2.3 OCR Reporting Responsibilities:

1. Adverse events which meet all of the following criteria must be reported to all participating institutions for IRB submission within 2 weeks of notification of the event.
   i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
   ii. Possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

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iii. Serious (refer to above definition) or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

2. If the adverse event requires modification of the study protocol and informed consent, these changes will be provided to all participating institutions in the form of an amendment from the OCR for each site's IRB of record along with the report of the adverse event.
3. Copies of all related correspondence and reporting documents will be maintained in a centralized regulatory file for this study at ISRU.

10.3 Pregnancy

All WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

In the event of a confirmed pregnancy in a patient participating in the study, the Investigator must immediately notify the Fox Chase Cancer Center Investigator-Sponsored Research Unit.

11.0 Statistical Analysis

This is a single arm phase II trial. Prior head and neck investigations of IMRT to minimize 3D conformal toxicity have anticipated (and demonstrated) a 30% decrease in symptoms when IMRT is utilized[38]. Non-randomized analyses have suggested that the benefit of IMRT approaches a 50% decrease in symptoms[39]. Thus, to be conservative, the null hypothesis of this analysis is that two year VHI scores will be 33% lower than baseline. This represents a decline from an average VHI global score of 44 to about 29, a decline of 15 points. Our alternative of interest is a 50% decline in VHI global score, a decline of 22 points. L. Di Nicola et al (ref) tabulated such scores and we have taken their estimate of the standard deviation at baseline of VHI global score, std = 8.5. We used this same value for the 2 year score, which is not given by Di Nicola, but is close to the 3 year score when VHI scores have further declined. This, in turn, gives the std of baseline less 2 year scores of 8.5 times 1.414. VHI average scores are estimated to be normally distributed.

We will obtain baseline and 2 year VHI scores for an initial cohort of 15 patients. We will terminate the study after the first 15 patients have been evaluated at 2 years if their average decline is less than 15. Otherwise we will recruit an additional 15 patients. If the overall average of all 30 patients is at least 19.2 we will reject the null hypothesis. The design has 50% chance of early stopping under the null and a 2.58% chance of early stopping in error. The overall type I error is 5% and the study power is 85%.

We will test the null hypothesis that at most 85% of patients will achieve local control versus the alternative that at most 95% of them will. If less than 13 of the initial cohort

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of 15 experience local control, we will interrupt the study for futility. If at least 28 of 30 acquire local control we will reject the null and declare the local control rate to be 95%. The chance of early stopping for lack of local control is 40% when the true local control rate is 85%. The chance of early stopping in error is 3.6%. The overall power is 81% and overall type I error is 15.1%.

12.0 Data and Safety Monitoring Plan

This is a deintensification study – patients will be receiving a smaller field of radiation to the same dose as standard therapy.

Therefore, this study is felt to represent a minimal risk to patient safety outside of the primary endpoint.

Even though the investigational treatment is the same dose as prescribed in the standard of care but to a smaller volume, unknown factors relating to toxicity will not be discounted. We accept the possibility of at most 5% SAEs among our patients and will consider the treatment too toxic if a 20% SAE rate is encountered.

If 3 patients have a SAE within the first cohort of 15 treatments, the trial will be terminated.

If 5 patients among the 30 experience a DLT the treatment will be considered too toxic and will not be pursued further. The chance of early termination if the SAE rate is 5% is 3.62% and the rate of early termination when the true SAE rate is 20% is 60.2%.

The overall chance of declaring the treatment too toxic in error is 4.34% and this chance when the true toxic rate is 20% is 79.3%.

Per standard institutional protocol, patients will have acute toxicity monitored at least weekly using CTCAE v4.0.

12.1 Monitoring Plan

FCCC ISRU will monitor the medical and study records of each participant accrued throughout the course of the study. In addition, the ISRU will collect and report data to the study Principal Investigator who will review these data on a regular basis at a rate dependent on subject accrual. All serious adverse events (SAEs) will be reviewed on a real time basis first by the study site PI and subsequently by the ISRU and study PI as applicable.

12.2 Data Safety Monitoring Board

Interim analysis of toxicity, outcome and ongoing scientific investigations may be performed at least every 6 months by the Fox Chase Cancer Center

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Data Safety Monitoring Board (FCCC DSMB). In this capacity the FCCC DSMB will serve as an advisory committee to the OCR. The FCCC DSMB will review those aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Plan (DSMP). If the committee decides that changes should be made to this trial, it will make recommendations in writing to the Study Principal Investigator, the Associate Director of Clinical Research, and the Protocol Management Executive Committee, which, in turn, have the authority to approve or disapprove these recommendations. These changes will be discussed with the Study Principal Investigator before they are implemented. These changes may include early termination of accrual. Other changes might include altering the accrual goals or changing the eligibility criteria for the trial.

13.0 Administrative

This study will be conducted in accordance will local, state and Federal regulations and according to accepted good clinical practice guidelines.

13.1 Data Reporting

The FCCC Study Monitor will request case report forms to be completed within 2 weeks of the protocol visit. Participating sites are responsible to respond to queries prior to the next scheduled monitoring visit.

The ISRU is responsible for compiling and submitting data to the study PI and statistician on an ongoing basis for monitoring as described in the data safety monitoring plan and reporting to the Extramural Data and Safety Monitoring Board.

All patient information will be stored in an EDC system accessible only to the study team members for the purpose of entering, reviewing and analyzing data. Any paper records, such as case report files, produced will be stored in in a secure location.

The ISRU is responsible for distributing and tracking review of all Safety Reports and study specific Serious Adverse Events

13.2 Retention of Records

The FCCC ISRU must be notified of any plans to move records to an offsite location prior to doing so.

13.3 Informed Consent

The IRB approved informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her

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participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in each patient's study file or medical record with a copy in the study file.

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Appendix I

FCCC Health Voice, Airway, and Swallowing Center

Eating Assessment Tool – 10 (EAT-10)

Circle the appropriate response:

To what extent are the following scenarios problematic for you?	0 = No problem 4 = Severe problem				
1. My swallowing problem has caused me to lose weight.	0	1	2	3	4
2. My swallowing problem interferes with my ability to go out for meals.	0	1	2	3	4
3. Swallowing liquids takes extra effort.	0	1	2	3	4
4. Swallowing solids takes extra effort.	0	1	2	3	4
5. Swallowing pills takes extra effort.	0	1	2	3	4
6. Swallowing is painful.	0	1	2	3	4
7. The pleasure of eating is affected by my swallowing.	0	1	2	3	4
8. When I swallow food sticks in my throat.	0	1	2	3	4
9. I cough when I eat.	0	1	2	3	4
10. Swallowing is stressful.	0	1	2	3	4
	TOTAL				

Participant Signature:_____

Date:_____

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