UTSouthwestern
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Comprehensive Cancer Center

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SCCC-01318: STU 122017-043
A Phase II Trial of Glottic Larynx Stereotactic Ablative Radiotherapy (LT-SABR) for Early-Stage Glottic Larynx Cancer

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Signature Page

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

Amendment/Version #: _____7_____

STU 122017-043
A Phase II Trial of Glottic Larynx Stereotactic Ablative Radiotherapy (LT-SABR) for Early-Stage Glottic Larynx Cancer

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

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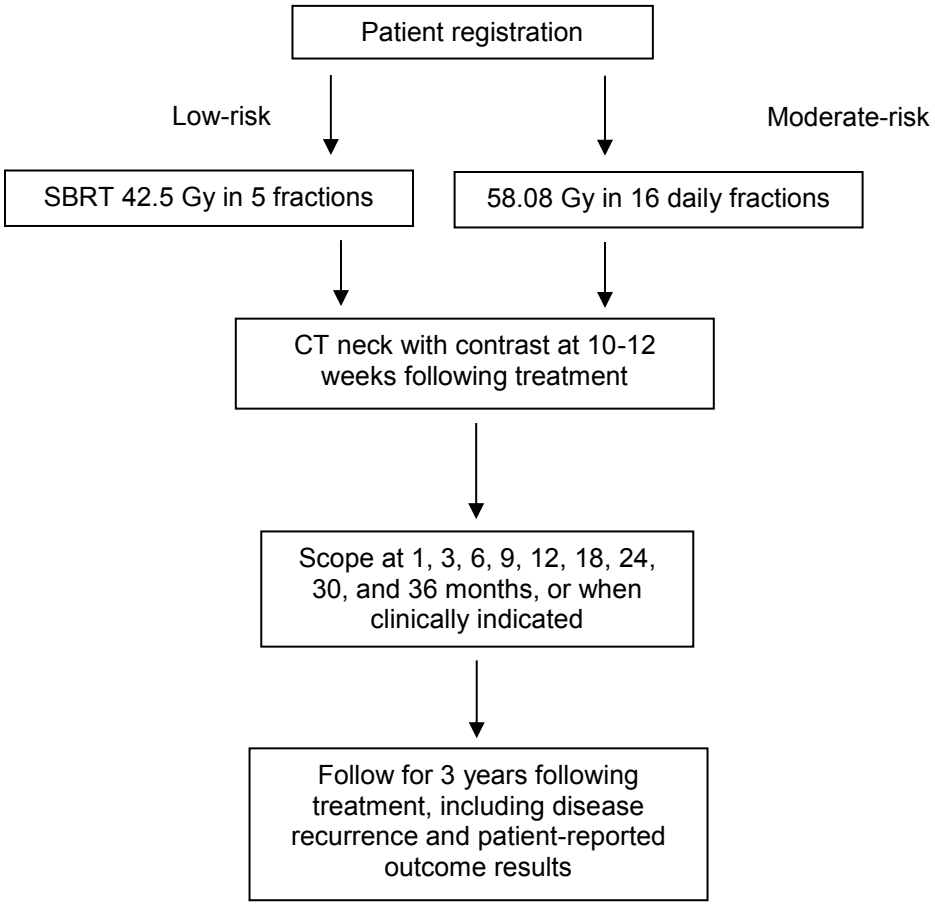
LIST OF ABBREVIATIONS (EXAMPLES)

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DM	Distant Metastasis
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
DSS	Disease Specific Survival
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GRBAS	Grade-Roughness-Breathiness-Aesthenicity-Strain
H&P	History & Physical Exam
HPV	Human Papillomavirus
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IMRT	Intensity Modulated Radiation Therapy
IND	Investigational New Drug
IV (or iv)	Intravenously
LC	Local Control
LR	Local Recurrence
LRC	Locoregional Control
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OFLR	Out of Field Local Recurrence
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response

PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
p.o.	peros/by mouth/orally
PR	Partial Response
RC	Regional Control
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Regional Recurrence
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SEER	Surveillance Epidemiology and End Results
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
VHI	Voice Handicap Index
VMAT	Volumetric Modulated Arc Therapy
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	**Phase II Trial of Stereotactic Body Radiotherapy (SBRT) for Early-stage Glottic Larynx Cancer**
Short Title	A Prospective Phase II Trial of SBRT for Early Glottic Larynx Cancer
Protocol Number	122017-043
Phase	Phase 2
Methodology	Prospective Study
Study Duration	3 years to accrue plus additional 3 years of follow-up
Study Center(s)	Single center
Objectives	To determine the local control and quality-of-life outcomes of using SBRT for early-stage glottic larynx cancer
Number of Subjects	25
Diagnosis and Main Inclusion Criteria	Stage I-II glottic larynx cancer
Study Product(s), Dose, Route, Regimen	Highly focal SBRT, delivered either every other day (low-risk) or daily (moderate-risk)
Duration of administration	3 weeks
Reference therapy	N/A
Statistical Methodology	The study has 85.6% power to detect a local control probability difference of 15% (95% vs. 80%) using a two-sided, one-sample log-rank test at a 0.10 significance level.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Laryngeal cancer is the most common non-cutaneous head and neck malignancy affecting an estimated 13,430 patients in 2016 in the United States.[1] Over 75% of laryngeal cancers involve the true vocal cords or the glottic larynx, with over 90% of these cancers detected at early-stages (defined as carcinoma *in situ* and cT1-T2 tumors) when they are potentially curable using a single-modality. Local therapies are highly effective at curing early-stage glottic larynx cancer, as rates of nodal involvement and metastatic disease are less than 5%.[2-4] Treatment outcomes with radiation or surgical approaches for early-stage glottic cancer yield local control rates for Tis and T1 tumors typically greater than 90%, and for T2 tumors 70-80%, with ultimate local control rates exceeding 90% after surgical salvage.[2, 5]

Treatment Options

There are multiple voice-preserving local treatment options for early-stage glottic laryngeal cancer in the current NCCN guidelines.[6] These include conventional or minimally hypofractionated radiation therapy, transoral oral laser microsurgery (TLM) or open CO2 laser surgery, and hemilaryngectomy. Radiation therapy delivered in a small dose per fraction to the glottic larynx remains a common treatment for Stage Tis, T1, and T2 glottic tumors. Among 2338 patients treated with T1 glottic cancers in the Linked SEER-Medicare data files from 1991-2009, 47% were treated with radiation alone, 39% with local surgery and radiation, and 14% with local surgery alone.[7] Treatment with radiation therapy is typically delivered in 2 to 2.25 Gy daily fractions over 5.5-7 weeks.[8, 9] Endoscopic surgery via CO2 laser excision involves the removal of the gross tumor with a 2-3 mm margin thereby preserving the involved vocal cord while achieving reasonable voice outcomes.[10] Hemilaryngectomy is another surgical voice preservation option particularly for selected Stage T2 lesions where the involved vocal cord and paraglottic space are removed, with additional resection of the ipsilateral arytenoid and/or anterior commissure if involved.[10, 11]

Radiation Therapy Technique

Classically, early glottic larynx cancers were treated with an opposed lateral technique, were 2 opposing radiation beams were designed using a 5 x 5 cm or 6 x 6 cm field to cover the entire glottic larynx. This technique was effective and necessary before radiation treatments were able to be designed using CT planning, with the added ability of being able to measure dose to specific anatomic regions. With the advent of CT-based planning both 3D conformal radiation therapy (varying radiation fields to offer a more conformal dose distribution) and intensity modulated radiation therapy (IMRT; inverse radiation planning designed to limit the dose to specific organs while maximizing dose to a target), radiation treatment for early glottic larynx cancers has become more complex.

Carotid Sparing Radiation Therapy

Treatment using opposed lateral technique often includes both carotid arteries in the field, delivering a high dose to a ~5-6 cm of both carotid arteries. The data addressing the risk of stroke following radiation to the carotid arteries is controversial, although population-based studies have suggested an increase in late risk of ischemic events following radiation therapy of head and neck cancers.[12, 13] Because of the concern of unnecessary and potentially avoidable radiation therapy to the carotid arteries, dosimetric studies of early glottic larynx cancer began to emerge which demonstrating a significantly reduced radiation dose to the carotids with 3D conformal radiation planning and further dose reduction to the carotid arteries with IMRT.[14-17] Following these studies, many groups have begun to report outcomes with IMRT for treatment of early larynx cancers and all groups, thus far, have reported local control rates of >80%.[18-20]

Hypofractionated radiation therapy

Hypofractionated laryngeal irradiation initially began during World War II due to a shortage of hospital beds and despite the use of rather primitive radiation techniques, the cure rates were similar between 5 week and 3 week treatment courses.[21] In a more contemporary radiation setting, a randomized phase III clinical trial from Japan showed promising outcomes with a mildly hypofractionated radiation approach of 56.25-63 Gy in 2.25 Gy daily fractions for early stage glottic larynx cancer. The trial demonstrated an improved local control, of 92% vs. 77% at 5 years in favor of hypofractionation compared with conventional 60-66 Gy in 2 Gy daily fractions; the toxicity outcomes were similar with both approaches.[9] As a result of this trial, 63 (T1)-65.25 (T2) Gy in 28-29 fractions is one of the two recommended radiation regimens for early glottis cancer in the U.S.[22] These trials support the feasibility of moderate hypofractionation in the current clinical landscape. Extreme hypofractionation remains a possibility to improve both patient convenience and treatment cost.

In fact, we have completed a phase I dose-escalation trial of larynx stereotactic body radiotherapy (SBRT), and the results will be detailed throughout this discussion.

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

Radiotherapy is well established and a recommended treatment for treatment of early glottic larynx cancer by the NCCN. Additionally, a few separate groups have reported outcomes with hypofractionated radiation regimens with minimal late grade 3 or greater toxicities.

Study	Site	Design	N	Stage	Fractionation	Dose / Fraction	Target	Late toxicities
Al-Mamgani et al, 2015[23]	Rotterdam, Netherlands	Prospective collected	30	T1a	58.08 in 16 fractions	3.63 Gy	Single cord	1/30 temp laryngeal edema
Ermis et al. 2015[24]	Yorkshire, UK	Retrospective		Tis-T2	55 Gy in 20 fractions	2.75 Gy	Larynx	1/132 (<1%) non-fx larynx
Laskar et al, 2012[25]	Mumbai, India	Retrospective	652	T1	50 Gy in 15 fractions, 55 Gy in 16 fractions, 60 Gy in 24 fractions, 62.5 Gy in 25 fractions	3.3 Gy, 3.43 Gy, 2.5 Gy, 2.5 Gy	Larynx	23.4% Persistent Laryngeal edema
Short et al, 2006[26]	Aukland, NZ	Retrospective	145	T1-T2	52.5-55 Gy in 20 fractions	2.63 Gy, 2.75 Gy	Larynx	One grade 3 toxicity
Gowda et al, 2003[27]	Manchester, UK	Retrospective	200	T1	50-52.5 Gy in 16 fractions	3.12 Gy, 3.28 Gy	Larynx	1/200 (0.5%) severe late toxicity

Table 1. Published hypofractionated radiation therapy studies addressing early stage larynx cancer with associated local control and late toxicities.

1.3 Other Agents

All patients on the study will be treated with radiotherapy alone.

1.4 Rationale

This study is premised on two related but different concepts. The first is that treatment volume reduction should lead to significantly improved acute and late laryngeal function, including voice and swallowing outcomes. The second is that for many patients, the treatment volume is small enough to compact the treatment schedule into just 5 fractions, which should lead to vastly

improved convenience. In fact, a shorter radiation therapy treatment course over 2.5-3 weeks, compared with the typical 5.5-6 weeks offers both a logistical advantage by improving not only the convenience, but also a potential cost advantage be requiring less treatment time on the machine.

A few considerations are necessary when considering treatment with highly focal radiotherapy, with or without extreme hypofractionation:

- Does focal treatment of the glottic larynx reduce dose to surrounding organs while offering similar rates of local control rates compared with treatment of the entire larynx?
- Can hypofractionated radiation therapy be delivered with acceptable acute and late toxicities?
- What treatment dose and fractionation is appropriate for the phase II portion of this trial?
- What radiation modality is the best option for delivery of dose-escalated, focal glottic larynx cancer?

Local control and organ sparing with a highly focal treatment

Based on data supporting focal IMRT technique for limiting radiation dose to the carotid arteries, a few academic groups have investigated a more focal radiation field by targeting the involved cord or site of disease, rather than unnecessarily radiating the entire larynx in every case. This highly-focused radiation therapy offers potential advantages, in both the ability to limit radiation dose to the uninvolved vocal cord, arytenoids, laryngeal cartilages, pharynx, spinal cord and carotid arteries, while allowing for dose-escalated radiation therapy to the disease itself.

A group from the Erasmus medical center recently published a report where they treated 31 patients with T1a glottic larynx cancers with single vocal cord irradiation to the entire cord using IMRT and daily cone beam CT scans for setup.[23] The clinical target volume (CTV) included the entire cord from a 1mm axial-sliced planning scan, as well as the maximal intensity projection from a 4D respiratory-gated CT scan. For tumors involving the anterior commissure (AC), the entire AC was included in the CTV. From the CTV, the group expanded 3mm circumferentially and 5mm superior-inferior for all but the initial 4 patients. With the reduced treatment volumes, they employed a higher dose per fraction at 3.63 Gy x 16 fractions and reported 100% local control at 2 years with no grade 3 or greater late toxicities. There was only 1 case of laryngeal edema in an actively smoking patient, and it fully resolved with steroids. Importantly, 78% of patients on this study were characterized as smoking. In addition, the median planning target volume (PTV) size was 10.6 cc, with a range of 8.1-13.7 cc. This is highly promising and supports the early results from our phase I trial, which will be described next.

For the phase I portion of our trial, we similarly focused our treatment volumes on the tumor alone and used a 4D CT gated breathing scan to develop the CTV with an added 2 mm, and then we circumferentially added a 3 mm PTV to create the final treated volume. A total of 30 patients were enrolled. With this highly focal treatment volume, we have achieved high local control rates of the first 2 dose levels (Figure 1) while substantially limiting the radiation dose delivered to nearby organs (Table 1). The 13 patients enrolled on the highest dose arm (42.5 Gy in 5 fractions) have not experienced any local failures thus far.

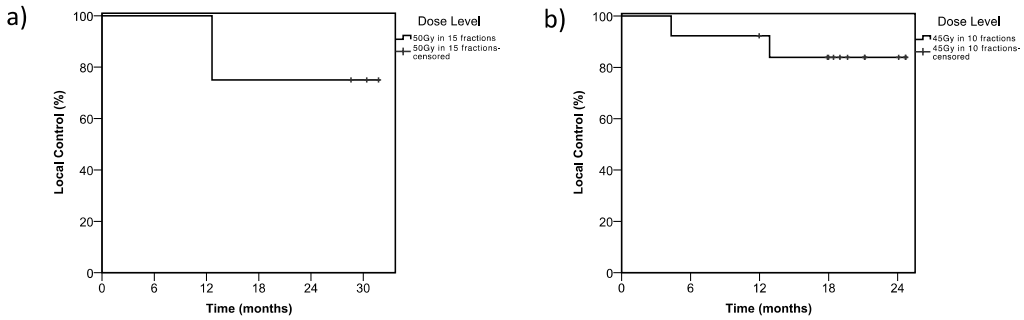


Figure 1. Kaplan Meier plots of local control of the first 2 dose levels including a) 4 patients treated with 50 Gy in 5 fractions with a 2-year actuarial local control of 75% (median follow-up 29 months [range 28-32]) and b) 12 patients treated with 45 Gy in 10 fractions with a 2-year actuarial local control of 84.4% (median follow-up 20 months [range 12-25]).

Safety of Dose-Escalated Radiation Therapy

Table 2 demonstrates the late toxicities that have been reported with hypofractionated radiation therapy using different doses. The only series reporting toxicities with single vocal cord irradiation was Al Mamgani et al.[23] who reported no grade 3 or greater late toxicities at a median follow-up of 30 months. The group did report grade 2 acute dermatitis among 7 (23%) or dysphagia among 10 (33%) patients and only a single patient with grade 2 laryngeal edema that resolved with steroids.

Study	Site	Design	N	Stage	Fractionation	Dose / Fraction	Target	Local control	Late toxicities
Al-Mamgani et al, 2015[23]	Rotterdam, Netherlands	Prospective collected	30	T1a	58.08 in 16 fractions	3.63 Gy	Single cord	100% at 2 years	1/30 temp laryngeal edema
Ermis et al. 2015[24]	Yorkshire, UK	Retrospective	132	Tis-T2	55 Gy in 20 fractions	2.75 Gy	Larynx	85.6% at 5 years	1/132 (<1%) non-fx larynx
Laskar et al, 2012[25]	Mumbai, India	Retrospective	652	T1	50 Gy in 15 fractions, 55 Gy in 16 fractions, 60 Gy in 24 fractions, 62.5 Gy in 25 fractions	3.3 Gy, 3.43 Gy, 2.5 Gy, 2.5 Gy	Larynx	84% at 10 years	23.4% Persistent Laryngeal edema
Short et al, 2006[26]	Aukland, NZ	Retrospective	145	T1-T2	52.5-55 Gy in 20 fractions	2.63 Gy, 2.75 Gy	Larynx	95% (LRC) at 5 years	One grade 3 toxicity
Gowda et al, 2003[27]	Manchester, UK	Retrospective	200	T1	50-52.5 Gy in 16 fractions	3.12 Gy, 3.28 Gy	Larynx	93% at 5 years	1/200 (0.5%) severe late toxicity

Table 2. Published hypofractionated radiation therapy studies addressing early stage larynx cancer with associated local control and late toxicities.

From the phase I portion of our study, there have been only 3 cases of grade 2 or greater soft tissue necrosis. Because of these small numbers, statistical comparisons are not informative. The three cases are briefly summarized below:

- Active smoking male with a large volume irradiated (17 cc) on dose level 2 (45 Gy in 10 fractions), required a tracheostomy and gastrostomy due to necrosis 5 months after treatment. He subsequently experienced a local failure.

- Active smoking male with a large volume irradiated (21.3 cc) on dose level 3 (42.5 Gy in 5 fractions). He required a feeding tube and had profound dysphonia 6 months after treatment, but he has since recovered with conservative measures, such that he can now eat most foods and communicate over the phone.

- Non-smoking male with a relatively small volume irradiated (4.9 cc) on dose level 3 (42.5 Gy in 5 fractions). He spent 24-48 hours in a casino and then developed odynophagia and dysphonia from necrosis 17 months after treatment. These complications have completely recovered with conservative measures.

In summary, 2 of 7 patients with large volume PTVs (10 cc or higher) developed symptomatic necrosis, and 2 of 6 active smokers developed symptomatic necrosis. Of note, 5 additional patients quit within 1 month of starting radiotherapy, and none developed a complication.

From a voice quality perspective, the Voice Handicap Index results were excellent, such that only two patients (out of 30) experienced a worsening of their VHI score. In both cases, the ipsilateral arytenoid dose was 31% higher than the prescription dose in the first cohort. Although these numbers are very small, we are extrapolating this result to minimize the arytenoid dose in the future and keep it within 102% of the prescription dose.

Radiation Dose and Fractionation for the current study

The goal of treatment with radiation therapy is to deliver as high of a dose as possible to the target (tumor), while minimizing the dose to the normal tissues where late-side effects can drastically affect patient quality of life. Radiation dose delivered in the tissues can be accurately calculated using a universal survival curve (USC), which includes both the linear quadratic model and the multitarget model. To estimate the tumoricidal dose and late-toxicity dose delivered by different radiation fractionation schemes, a biologically effective dose (BED) is typically reported [28].

$BED_{\alpha/\beta} = nd\ (1 + d/(\alpha/\beta))$, where n= number of fractions delivered, and d= dose / fraction.

Assuming an α/β of 10 for a rapidly growing tumor and an α/β of 3 for late toxicities of normal tissues, the BED of prior hypofractionated radiation regimens are shown in Table 3.

Study	Fractionation	Dose / Fraction	BED_{10}	BED_3
Proposed Phase II Doses	**Moderate risk: 58.08 Gy in 16 fx Low-risk: 42.5 Gy in 5 fx**	**3.63 Gy 8.5 Gy**	**79.2 Gy 78.6 Gy**	**128.4 Gy 162.9 Gy**
UTSW Phase I	50 Gy in 15 fractions 45 Gy in 10 fractions 42.5 Gy in 5 fractions	3.33 Gy 4.5 Gy 8.5 Gy	66.7 Gy 65.3 Gy 78.6 Gy	105.6 Gy 112.5 Gy 162.9 Gy
Al-Mamgani et al, 2015[23]	58.08 in 16 fractions	3.63 Gy	79.2 Gy	128.4 Gy
Ermis et al. 2015[24]	55 Gy in 20 fractions	2.75 Gy	70.1 Gy	105.4 Gy
Short et al, 2006[26]	52.5-55 Gy in 20 fractions	2.63 Gy, 2.75 Gy	66.3 Gy 70.1 Gy	98.5 Gy 105.4 Gy
Yamazaki et al, 2006[9]	63 Gy in 28 fractions	2.25 Gy	77.2 Gy	110.3 Gy

Conventional	66 Gy in 33 fractions 70 Gy in 35 fractions	2 Gy	79.2 Gy 84 Gy	110 Gy 116.7 Gy

Table 3. Biologically effective doses (BED) of prior hypofractionated radiation regimens used for early stage glottic larynx cancer, assuming an α/β of 10 for a rapidly growing tumor, an α/β of 6 for a slow-moderate growing tumor and an α/β of 3 for late toxicities of normal tissues.

Given that patients with a larger PTV and active smoking history were at greater risk for toxicity (albeit encompassing only 3 patients in total) **in our study**, we have therefore decided to treat this population with the Dutch regimen. In particular, patients with:

- PTV greater than or equal to 10 cc
- Smoking within 1 month of registration

will be treated with daily SBRT at a dose of 58.08 Gy in 16 fractions. Because patients with small tumors from the phase I portion of the trial had minimal toxicity with treatment, we propose to continue the dose of 42.5 Gy in 5 fractions for tumors less than 10 cc.

Radiation Therapy Delivery

There are a number of different techniques used to deliver highly-focal, inverse planned radiation therapy. The Erasmus group used a static-field IMRT approach.[23] Static-field IMRT is a commonly used approach where the beam angles are pre-chosen and then the radiation delivery is inversely planned by the planning system. The downside of static-field IMRT is that 7-9 beam treatment requires up to 30 minutes to complete.

Another approach for treating a highly focal target that we employed in the phase I portion of the study, is to treat with a Cyberknife treatment planning system. The advantage of the Cyberknife system is that the radiation beams can be delivered from hundreds of different non-coplanar beam angles without manual adjustment of the treatment table. This technique proved to be effective given the high local control rates in the phase I portion of the trial, and it will be a treatment option for the phase II portion of the trial. However, the Cyberknife treatment planning system does have 2 specific drawbacks. First, unlike treatment planning systems that align patients prior to treatment using a cone-beam CT (CBCT) scan, the Cyberknife uses orthogonal x-rays to verify target position. Because the larynx isn't clearly visible using orthogonal x-rays, it must be tracked using fiducial markers. Fiducial markers placed either on the skin or subcutaneously outside of the larynx might not accurately represent where the larynx is located, especially if the patient has substantial external neck motion (i.e. substantial neck motion when breathing). The second limitation of using Cyberknife technology is the prolonged treatment time compared with other techniques. In the phase I portion of our study, the median treatment time on the Cyberknife was 38 minutes and ranged from 20-54 minutes. This is a long time to be positioned in an aquaplast treatment mask, provided there are suitable alternatives available, and it allows for more time where a mobile structure like the larynx can move out of the tracked treatment field (i.e. with swallowing).

A third option for treating a focal larynx cancer is with the use of volumetric modulated arc therapy (VMAT), which is essentially an IMRT treatment delivered from nearly 360 degrees around the patient. This allows for many more beam angles than static field IMRT and it also allows for a much quicker treatment. One group recently compared 2-arc VMAT with a typical 8-field IMRT plan for early stage larynx cancer and reported that both target volume coverage and homogeneity were comparable between VMAT and IMRT, while VMAT was superior for carotid-artery sparing. Additionally, VMAT delivery time was significantly faster than with IMRT (3-5 minutes vs. 5-10 minutes).[29] Another study supports the substantially reduced treatment time with arc therapy vs. IMRT.[30] Because of the promising results with VMAT treatment delivery, either modality (i.e. CyberKnife or VMAT) is acceptable for treatment on this protocol.

Summary points

1. Local control rates using a highly focal radiation target appear to be as good as conventional radiation therapy (≥80%)

2. Highly focal radiation therapy targeting only the involved site of disease plus a small margin delivers an extremely low dose of radiation dose nearby structures based on both the Dutch Erasmus and the UT Southwestern Phase I studies.

3. A reduced dose to nearby structures might improve toxicities, such as esophagitis and stroke from carotid atherosclerosis and could reduce the decline in voice function from contralateral cord dose. However, long-term follow-up of voice quality of life following focal larynx radiation therapy is not yet available from the phase I portion of this trial.

4. Hypofractionated radiation therapy appears to be safe, although there were three cases of soft tissue necrosis in the phase I trial. Current smoking status and larger PTV volume (> 10cc) all had qualitatively higher rates of necrosis.

5. Based on the phase I study, we propose using a dose of 42.5 Gy in 5 fractions for low-risk tumors: tumors with a PTV < 10cc, no recent smoking, and disease limited to the vocal process. This provides both an adequate tumoricidal dose, and a limited dose to normal tissues. Remaining patients will be irradiated using the Dutch 16 fraction regimen.

6. Treatment with either Cyberknife or VMAT will be acceptable.

With these observations, this study aims to maintain a high rate of local control while maintaining acceptable acute side-effects and improving late side-effects. We anticipate that this approach will improve late toxicities, patient convenience, and treatment cost. Moreover, because the delivered biologically equivalent dose is the same as conventional radiotherapy but delivered over a substantially shorter time period, it is also possible that local control will be superior with this technique as well.

1.5 Correlative Studies

1.5.1. For patients treated with VMAT, we will perform an analysis of CBCT imaging during treatment, to determine the optimal patient-specific PTV margin.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the risk of local failure following SBRT treatment of early glottic larynx cancers.

2.2 Secondary Objectives

2.2.1 To determine patient-reported outcomes (PRO) following treatment with SBRT.

2.2.2 To describe the rates of grade 3-5 acute and late toxicities following treatment with SBRT.

2.2.3 To characterize patient utilities using EQ5D following treatment with SABR.

2.2.4 To determine the patterns-of-failure following SBRT. Specifically, 2-year cumulative risk of in-field, marginal, and out-of-field local failure, regional and distant failure, laryngectomy-free survival, disease-specific survival and overall survival following treatment with SBRT.

2.3 Exploratory Objectives

2.3.1. Identify a method to optimize PTV margins for patients treated with VMAT.

2.3.2. Identify tissue and circulating predictors of locoregional failure.

2.4 Endpoints

2.4.1 Primary endpoint: 2-year risk of local failure (i.e. anywhere in the larynx) following SBRT treatment of early glottic larynx cancer

2.4.2 Secondary endpoints:

2.4.2.1 Patient-reported outcomes: Difference in PRO voice quality measures between baseline and 1, 3, 6, 12, 18 and 24 months following treatment:

2.4.2.1.1 VHI voice-quality score
2.4.2.1.2 MDADI

2.4.2.2 Rate of grade 3-5 acute (start of treatment through 90 days from the completion of treatment) and late (after 90 days from the completion of treatment) adverse events, according to NCI's CTCAE v4.0 toxicity criteria.

2.4.2.3 Average patient utilities (derived from EQ-5D) at baseline, 6, 12 and 24 months from the end of treatment

2.4.2.5 Cumulative risk of marginal and out-of field local failure at 2 years from the start of treatment with death and prior in-field local failure as a competing risk

2.4.2.6 Cumulative incidence of regional failure and distant metastasis at 2 years, with death and prior locoregional failure as competing risks

2.4.2.7 Laryngectomy-free survival probability at 2 years

2.4.2.8 Overall survival at 2 years

3.0 SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria

3.1.1 Pathologically-proven diagnosis of squamous cell carcinoma *in situ*, squamous cell carcinoma or squamous cell variants (sarcomatoid, verrucous, basaloid, and papillary subtypes) involving the glottic larynx.

3.1.2 Clinical stage I-II (AJCC, 7th edition) with direct laryngoscopy showing no evidence of greater than stage II true glottic larynx cancer and PET/CT or CT neck showing no evidence of regional disease.

3.1.3 Age ≥ 18 years.

3.1.4 ECOG Performance Status 0-2

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

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

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

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

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

3.1.8 Patients with cognitive impairment or other limited decision making capacity with the ability to understand and willingly sign written informed consent or have the consent signed by a designated legally authorized representative (LAR).

3.2 Exclusion Criteria

3.2.1 AJCC stage III or stage IV larynx cancer

3.2.2 Involvement of the arytenoid cartilage beyond the vocal process.

3.2.3 Prior chemotherapy for treatment of the targeted larynx lesion.

3.2.4 Synchronous primaries in the head and neck

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

3.2.6 Subjects smoking in excess of 1 pack of cigarettes per day.

3.2.7 Subjects may not be receiving any other investigational agents.

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

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

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Radiation will be delivered twice per week for 5 fractions (42.5 Gy cohort, low-risk) or daily for 16 fractions (58.08 Gy cohort, moderate-risk).

Low-risk is defined by:

- PTV less than 10 cc, AND
- No reported smoking within 1 month from registration

Moderate-risk is defined by:

- PTV greater than or equal to 10 cc, OR
- Smoking within 1 month from registration (no more than 1 pack per day)

4.1.1 Radiation Therapy

4.1.1.1 CT simulation

Patients will be simulated in a thermoplastic mask extending from the scalp through upper chest (e.g. “5 point mask”), using 1 mm thick slices. For SBRT planning, a CT simulation with IV contrast and a 4-D respiratory CT-scan focusing on the larynx are recommended but not required.

For Cyberknife patients treated with skin tracking, four gold fiducials will be placed on the skin, two on each side of the neck and at different vertical alignments in the vicinity of the larynx. Small tattoos will be placed at the site of each skin fiducial in order to replicate the fiducial placement for treatment.

For VMAT patients, the isocenter will be placed on the mask.

4.1.1.2 Primary tumor delineation and targeting

GTV: The gross tumor volume (GTV) will be contoured based on laryngoscopic findings by the investigator. Additional anatomic tumor location information obtained from biopsy procedure can be used to help guide GTV volumes. GTV volumes should be confirmed in both the sagittal and coronal views to verify that the involved areas of the vocal cord are covered.

ITV: From the 4DCT at the time of simulation, the MIP, average, maximum inhalation and maximum exhalation scans from the 4D CT scan will be imported. The ITV should include the GTV plus any motion seen on the 4DCT scans.

CTV: this trial will not include a CTV volume.

PTV: The planning target volume (PTV) will include the ITV plus a 3 mm left-right and anterior-posterior expansion and a 5 mm cranio-caudal expansion.

4.1.1.3 Dose prescription

Patients treated on the 5 fraction regimen will be irradiated two times per week, with at least 2 days between fractions (i.e. Monday-Wednesday). Attempts should be made to start treatment on a Wedneday and end treatment on a Monday, to minimize the total treatment time.

Patients treated on the 16 fraction regimen will be irradiated once per day, every day.

4.1.1.4 Treatment planning

Patients will be treated using either CyberKnife or VMAT. Voxel doses will be calculated using the smallest voxel resolution available (i.e. 1.5 for VMAT plans in Eclipse and 1.25 for Cyberknife).

4.1.1.5 Coverage constraints

All plans must be normalized such that 95% of the volume of each PTV is covered by the prescription dose.

At a volume of 0.03 cc within each PTV volume, the dose should not exceed 115% of the prescription anywhere in the plan.

The arytenoid should not receive more than 102% or 105% of the prescription for the 5 and 16 fraction regimens, respectively.

4.1.1.6 OAR constraints: 5 fraction

MANDATORY (see below):
Spinal cord: Dmax (0.035cc) < 20 Gy
Spinal cord + 5 mm: Dmax (0.035cc) < 25 Gy
Ipsilateral arytenoid: Dmax (0.035cc) < 43.35 Gy (102% of prescription)

RECOMMENDED:
Uninvolved vocal cord(s): Dmax (0.035cc) <41.4 Gy, Dmean <36.8 Gy
Contralateral arytenoid: Dmax (0.035cc) < 23 Gy
Ipsilateral carotid: Dmax (0.035cc) <23 Gy, Dmean <11.2 Gy
Contralateral carotid: Dmax (0.035cc) <23 Gy, Dmean <11.2 Gy
Laryngeal cartilage: Dmax (0.035cc) <46 Gy
Cricoid cartilage: Dmax (0.035cc) <41.4 Gy
Inferior constrictor and cricopharyngeus: Dmax (0.035cc) <23 Gy
Thyroid gland: Dmean <15.3 Gy

4.1.1.7 OAR constraints: 16 fraction

MANDATORY (see below):
Spinal cord: Dmax (0.035cc) < 35 Gy
Spinal cord + 5 mm: Dmax (0.035cc) < 40 Gy
Ipsilateral arytenoid: Dmax (0.035cc) < 61 Gy (105% of prescription)

RECOMMENDED:
Uninvolved vocal cord(s): Dmax (0.035cc) < 56.3 Gy, Dmean <50.05 Gy
Contralateral arytenoid: Dmax (0.035cc) < 31.3 Gy
Ipsilateral carotid: Dmax (0.035cc) < 31.3 Gy, Dmean <15.2 Gy
Contralateral carotid: Dmax (0.035cc) < 31.3 Gy, Dmean <15.2 Gy
Laryngeal cartilage: Dmax (0.035cc) < 62.6 Gy
Cricoid cartilage: Dmax (0.035cc) < 56.3 Gy
Inferior constrictor and cricopharyngeus: Dmax (0.035cc) < 31.3 Gy
Thyroid gland: Dmean <20.8 Gy

The standard names for these structures and compliance criteria are below.

Name	**Per protocol**	**Variation acceptable**	**Variation unacceptable**
PTV	≥95% of PTV covered by the prescription dose Max hot spot ≤115%	<95%, ≥90% of PTV covered by prescription dose >115%, ≤120%	< 90% > 120%
IL_arytenoid and CL_arytenoid	Max hot spot ≤ 102% (5 fraction) Max hot spot ≤ 105% (16 fraction)	Max hot spot ≤ 105% (5 fraction) Max hot spot ≤ 108% (16 fraction)	Max hot spot > 105% (5 fraction) Max hot spot < 108% (16 fraction)
Cord	≤ 20 Gy (5 fraction) ≤ 35 Gy (16 fraction)	>20 Gy, ≤ 25 Gy (5 fx) >35 Gy, ≤ 37.5 Gy (16 fx)	> 25 Gy > 37.5 Gy
Cord_exp	≤ 25 Gy (5 fraction) ≤ 40 Gy (16 fraction)	>25 Gy, ≤ 30 Gy (5 fx) >40 Gy, ≤ 42.5 Gy (16 fx)	> 30 Gy > 42.5 Gy
OARS	Description	See Section 4.1.9.2 for constraints	
VC_uninv	Uninvolved vocal cord and arytenoid, either 1 or both uninvolved vocal cords contoured with a 2 mm separation from PTV		
Carotid_IL	Ipsilateral carotid contoured from the inferior aspect of the hyoid to 1 cm below the cricoid		
Carotid_CL	Contralateral carotid contoured from the inferior aspect of the hyoid to 1 cm below the cricoid		
Arytenoid_IL	Ipsilateral arytenoid contoured on the bone window with a 2 mm separation from PTV		
Arytenoid_CL	Contralateral arytenoid contoured on the bone window with a 2 mm separation from PTV		
Laryngeal_cartilage	Laryngeal cartilage contoured with a 3-5 mm brush with a 2 mm separation from PTV		
Cricoid_cartilage	Cricoid cartilage contoured with a 3-5 mm brush with a 2 mm separation from PTV		

Thyroid	Enhancing thyroid gland
IC_CP	Inferior constrictor & cricopharyngeaus contoured from the inferior aspect of the hyoid to 1 cm below the inferior aspect of the cricoid

4.1.1.8 Treatment fractionation

5 fraction: Patients will receive one fraction per day, twice per week, with at least two days between fractions.

16 fraction: Patients will receive one fraction per day, 5 days per week

4.1.1.9 Treatment delivery

The CyberKnife machine provides multiple systems that can be used for setting up and imaging patients. The majority of patients in the phase I study were treated with spine tracking, and there were no marginal failures (i.e. no data to suggest the tumors were “missed.”); moreover, the spine and larynx are intimately related to each other anatomically.

We also used skin markers for tracking in 2 patients, and it was successful in 1 patient and non-usable in the second patient.

Thus the daily imaging technology will be up to physician discretion. Either spine tracking or skin fiducials may be used.

For treatment with VMAT, daily pre-treatment CBCT must be used for verification of patient set-up and successful treatment delivery with VMAT. At least one intra-arc CBCT is mandatory, as is a post-treatment CBCT.

4.1.1.10 Documentation and quality assurance

Every CT simulation scan with target and normal structures will be reviewed by the PI and co-PI.

4.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table in Section 5.4. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0.

4.2.1. Radiation Therapy

The dose constraints for radiation therapy are described in 4.1.1.6 and 4.1.1.7. No alterations in treatment doses are allowable per protocol.

4.3 Concomitant Medications/Treatments

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

- Anti-emetics
- Non-opiate and opiate pain medications
- Anti-diarrheals

- Nutritional supplementation
- Anti-depressants

The use of anti-oxidant vitamins in excess of a daily vitamin is not allowed.

4.4 Other Modalities or Procedures

For patients receiving 5 fractions, we recommend administering a dexamethasone 4 mg oral tablet one hour prior to each radiation treatment session at the discretion of the treating physician.

4.5 Duration of Therapy

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

- Local, in-field disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.6 Duration of Follow Up

Subjects will be followed for a minimum of **3 years** after completion of treatment or until death, whichever occurs first. Specifically, subjects will be followed at 1, 3, 6, 9, 12, 18, 24, 30, and 36 months following treatment. Subjects removed from therapy for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

Patients who are not able to complete the treatment or required follow-up procedures due to cognitive impairment will be removed from the study and treated and/or followed using standard-of-care procedures.

4.8 Subject Replacement

Subjects may be replaced in the study if they do not complete radiotherapy. Inadequate receipt of treatment may lead to a higher than expected recurrence rate, and therefore these patients may be replaced. Patient replacement must be verified through review of the case by the P.I.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

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

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

5.1.1 *Informed Consent*

5.1.1.1. Patients with cognitive impairment will be approached for trial if all other eligibility criteria are met and determined if s/he can sign willingly or require a LAR at enrollment.

5.1.2 *Medical history*

Complete medical and surgical history, history of infections

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria*

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight, office laryngoscopy and assessment of performance status (see Appendix A)

5.1.7 *PET-CT or CT scan of neck*

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting. All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A copy of the CTCAE v4.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

5.1.9 *Pregnancy test (for females of child bearing potential)*

See section 3.1.5.1 for definition.

5.1.10 *QoL Questionnaires and Symptom Questionnaires*

EORTC QLQ-C30, H&N 35, VHI, and EQ-5D. These forms will be referred to collectively as QoL Questionnaires.

5.2 Procedures During Treatment

5.2.1 Day 1

- First fraction of radiotherapy per standard, departmental stereotactic protocol

5.2.2 Weekly during treatment

- Clinical assessment including ECOG PS
- Toxicity assessment

5.2.3 Four weeks after treatment end

- Interim history
- Physical exam, vital signs, ECOG PS (vital signs are not required when patient has a Telehealth visit)
- Flexible laryngoscopy to assess tumor response and toxicity
- Quality of life and voice quality assessment

5.3 Follow-up Procedures

Patients will be seen by a radiation oncologist at 1 month (+/- 1 week) and 3 months (+/- 1 week) from the completion of treatment. More frequent visits are encouraged if the patient requires additional help with recovery and rehabilitation

Patients will then be seen every 3 months (+/- 2 weeks) for the first year, and then at least every 6 months (+/-2 weeks) until the end of the 3rd year. Subsequent and intervening follow-up visits will be made per physician preference. These protocol mandated procedures will occur at each follow-up:

- Interim history
- Physical exam, vital signs, ECOG PS (vital signs are not required when patient has a Telehealth visit)
- Laryngoscopy to assess tumor response and toxicity
- Quality of life and voice quality assessment (months 1, 3, 6, 12, 18, 24 and 36)

5.4 Time and Events Table

	Pre-study	Weekly during RT	4 weeks after completion	Follow-up*
Assessment		X	X	
Informed Consent	X			
History and Physical Exam	X		X	X
Performance Status	X	X	X	X
Toxicity Evaluations		X	X	X
PET/CT or CT-scan of Neck	X[&]			X (3 months)
Laryngoscopy	X		X	X
Serum or urine β-HCG (females)	X			
HR-QoL/Utility Forms 1) EQ-5D 2) EORTC-QLQ C30 + HN 35 3) VHI	X		X	X (months 1, 3, 6, 12, 18, 24 and 36)

[&] PET/CT can also be performed in place of baseline CT Neck and Chest

* These protocol mandated procedures will occur at each follow-up:

- Interim history
- Physical exam, vital signs, ECOG PS (vital signs are not required when patient has a Telehealth visit)
- Laryngoscopy to assess tumor response and toxicity
- Quality of life and voice quality will be assessed at visits 1, 3, 6, 12, 18, 24 and 36 months from the end of treatment.

Neck CT or PET-CT is required 3 months (+/- 1 week) after the completion of radiotherapy, but subsequent scans only for a clinical indication.

5.5 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety,

behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

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

5.5.2 Subject withdraws consent (termination of treatment and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator);

5.5.5 Subject experiences toxicity that makes continuation in the protocol unsafe;

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

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

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

5.5.9 If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented.

6.0 MEASUREMENT OF EFFECT

Early-stage larynx cancers are almost never visible on neck CT. The imaging is not used for response assessment but rather assessment of occult nodal disease (at diagnosis) or subsequent nodal recurrence (at 3 months). Clinical examination is sufficient at other time points.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

This treatment is hypofractionated radiotherapy as described above.

7.2 Adverse Event Monitoring

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

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

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

7.2.1 Definition

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

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

Acute Adverse Events

Adverse events occurring in the time period from the start of treatment, through 90 days post treatment will be considered acute adverse events.

Late Adverse Events

Adverse effects occurring in the time period from the end of acute monitoring, to 36 months post treatment, will be defined as late adverse events. These events will include all adverse events reported directly to a member of the study team and will be captured, assessed, graded and reported as appropriate.

In addition, the study team will review encounters in the following select specialty categories relevant to study endpoints: radiation oncology, medical oncology, and otolaryngology. The queried encounters will be limited in scope based on categorization of events; namely, encounters that related to any head and neck or gastrointestinal event or problem.

Severity

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

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

Serious Adverse Events

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

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or

- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

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

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

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

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

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

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

AND

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

AND

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

Follow-up

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

7.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

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

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

Note: This includes all events that occur within the acute adverse events reporting period as defined in section 7.2.1. Any event that occurs during the late adverse event period as defined in section 7.2.1 and is attributed (possibly, probably, or definitely) to the treatment must also be reported accordingly.

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

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

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

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

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site, or other designee. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if

further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized).*

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

Telephone reports to: Dr. David Sher, M.D. Phone: 214-645-8525
Written reports to: David J. Sher, M.D. The University of Texas Southwestern Medical Center ATTN: Sarah Neufeld, Project Manager 2201 Inwood Road Dallas, TX. 75390-9303 Fax: 214-648-5923 UTSW SCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

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

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

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

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

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

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

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

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

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance/

7.4 Unblinding Procedures

N/A

7.5 Stopping Rules

N/A

8.0 DRUG/TREATMENT INFORMATION

Not applicable for this trial.

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Specimen Banking

No specimen banking will be explicitly performed for this study.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

10.1.1 Primary endpoint: 2-year risk of local failure (i.e. anywhere in the larynx) following SBRT treatment of early glottic larynx cancer

10.1.2 Secondary endpoints:

10.1.2.1 Patient-reported outcomes: Difference in PRO measures between baseline and 1, 3, 6, 12, 18, 24 and 36 months following treatment:

10.1.2.1.1 VHI voice-quality score
10.1.2.1.2 EORTC QLQ30 and HN35 scores

10.1.2.2 Rate of grade 3-5 acute (start of treatment through 90 days from the completion of treatment) and late (after 90 days from the completion of treatment) adverse events, according to NCI's CTCAE v4.0 toxicity criteria.

10.1.2.3 Average patient utilities (derived from EQ-5D) at baseline and 1, 3, 6, 12, 18, 24 and 36 months from the end of treatment

10.1.2.4 Cumulative risk of marginal and out-of field local failure at 2 years from the start of treatment with death and prior in-field local failure as a competing risk

10.1.2.5 Cumulative incidence of regional failure and distant metastasis at 2 years, with death and prior locoregional failure as competing risks

10.1.2.6 Laryngectomy-free survival probability at 2 years

10.1.2.7 Overall survival at 2 years

10.2 Sample Size and Accrual

The general perception in the radiotherapy community is that radiotherapy for early stage glottic larynx cancer leads to a local control probability of approximately 95%. Given there are some T2 patients on the study (bigger tumors), we use the 2-year local control rate of 90% rather than 95% with the non-inferiority margin of 15%. The hazard rates for 2-year local control probabilities of 90% and 75% are 0.0527 and 0.1438, respectively. With a sample size of 25 patients, this study has more than 80% power to detect a non-inferiority against an upper hazard ratio bound of 2.73 (=0.1438/0.0527) using a log-rank test at a significance level of 0.1 when the actual hazard ratio is 1.0 and the reference group hazard rate is 0.0527. Patients will be accrued for a period of 3 years with 2-year follow-up. This assumes that a local control outcome inferior to 75% would obviate the potential benefit of highly focal radiation treatment.

Our prior phase I study included a nearly identical patient population and took just over 3 years to complete; however, this protocol has 2 periods of a 90 day halt on new accrual because it was a phase I study. Therefore we expect the present proposal to be completed in 2.5 to 3 years.

10.3 Data Analyses Plans

10.3.1 Primary endpoint: 2-year cumulative risk of local failure (i.e. anywhere in the larynx) following SBRT treatment of early glottic larynx cancer

This endpoint will be calculated using cumulative incidence statistics, with death as a competing risk.

10.3.2 Secondary endpoints:

Patient-reported outcomes: Difference in PRO voice quality measures between baseline and 1, 3, 6, 12, 18, 24, and 36 months following treatment:

10.3.2.1 VHI voice-quality score

10.3.2.2 EORTC QLQ-C30

- Global health status
- Physical functioning scale
- Role functioning scale
- Emotional functioning scale
- Cognitive functioning scale
- Social functioning scale

10.3.2.3 EORTC HN35

- Speech
- Social eating
- Social contact

These patient reported outcomes are single numeric scores that are collected at baseline, 1, 3, 6, 12, 18, 24 and 36 months from treatment. Patients with disease recurrence will be excluded. The changes in these outcomes from baseline to these timepoints will be analyzed using generalized estimated equations (GEE).

10.3.2.4 Rate of grade 3-5 acute (start of treatment through 90 days from the completion of treatment) and late (after 90 days from the completion of treatment) adverse events, according to NCI's CTCAE v4.0 toxicity criteria.

Only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. The rates of all Grade 3-5 adverse events, and death during or within 30 days of discontinuation of protocol treatment will be characterized. Predictors of high-grade acute and late toxicity will be determined using multivariable logistic regression.

10.3.2.5 Average patient utilities (derived from EQ-5D) at baseline, 3, 6, 12, 18, 24 and 36 months from the end of treatment

The average patient utilities (derived from EQ-5D) at baseline, 3, 6, 12, 18, 24 and 36 months from the end of treatment will be described. Changes in patient utility will be analyzed using generalized estimated equations (GEE). These models will be used to estimate the beta coefficient for dysphonia and grade 2-3 dysphagia, to produce an estimate of the utility decrement from this toxicity.

10.3.2.6 Cumulative risk of marginal and out-of-field local failure at 2 years from the start of treatment with death and prior in-field local failure as a competing risk

These outcomes will be calculated using classic cumulative incidence statistics, and the Fine-Gray method will be used to calculate univariable predictors of recurrence.

10.3.2.7 Cumulative incidence of regional failure and distant metastasis at 2 years, with death and prior locoregional failure as competing risks

These outcomes will be calculated using classic cumulative incidence statistics, and Gray's test will be used to calculate univariable predictors of recurrence.

10.3.2.8 Laryngectomy-free survival probability at 2 years

Kaplan-Meier statistics will be used, with death or laryngectomy serving as events.

10.3.2.9 Overall survival at 2 years

Kaplan-Meier statistics will be used.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

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

11.2 Institutional Review Board (IRB) Approval and Consent

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

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

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

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

For patients with cognitive impairment or other limited decision making capacity, the subject and/or their LAR will be given a full explanation of the study and will be given the opportunity to review the consent form. Consent form may be signed by the patient and/or legal guardian if investigator determines that subject is willingly able to sign and complete protocol specific procedures for the duration of the study. Safeguards and/or precautions that will be taken to minimize risks/harms during the conduct of the study for individuals with cognitive impairment or other limited decision making capacity include, but is not limited to:

- Extra time to review to the ICF (e.g. phone call over the phone with the patient or LAR, then present ICF and give days to weeks for full consideration of all benefits and risks)

- Peer to peer conversation, if requested by the patient and/or LAR, between the treating research physician and the patient's primary caregiver, to discuss the protocol treatment and discuss the trial's impact to the patient's ongoing care. This will require a signed medical release waiver
- Discuss the option of having a social worker involved as needed not only for the patient and LAR to receive resources as needed, but also to advise the research team of any potential risks/harms to the patient due to the patient's impairment and its progression

11.3 Required Documentation (for multi-site studies)

Not applicable.

11.4 Registration/Randomization Procedures

Research staff will have online access to UTSW REDCap, and all patients will be registered electronically through REDCap. All subjects consenting to participate in any aspect of the trial must be registered on REDCap before initiating protocol activities. The eligibility checklist and confirming documentation will be entered electronically through the system.

All research data will be recorded and entered into Case Report Forms using REDCap.

Following registration, research staff from CRO will review all relevant data to ensure eligibility criteria have been met.

The first number of the subject's ID will refer to the treatment site. The ordering is:

01: UTSW

We will use this system in the future event of collaboration with other departments.

New subjects will receive a secondary number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc. Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a tertiary number in the order of enrollment.

For example, the first patient consented and enrolled at UTSW will have the number 01-001-001.

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

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

11.5 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for this and all SCCC Investigator Initiated Trials. REDCap will be used for

electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements, as appropriate for the project.

Trial monitoring will be conducted no less than annually and refers to the review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeliness and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

Toxicity reviews will be performed at the end of study. These reviews will be documented by the study team and/or the UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC).

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

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

11.6 Adherence to the Protocol

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

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

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

➢ **Reporting requirement**: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

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

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others

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

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

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

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

11.6.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in 1 or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventative action within a reasonable time frame.

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

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

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

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

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

11.7 Amendments to the Protocol

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

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

11.8 Record Retention

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

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

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

11.9 Obligations of Investigators

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

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

12.0 REFERENCES

1. Miller KD, Siegel RL, Lin CC*, et al.* Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66(4):271-89.

2. Mendenhall WM, Parsons JT, Stringer SP*, et al.* The role of radiation therapy in laryngeal cancer. CA Cancer J Clin 1990;40(3):150-65.

3. Parsons JT, Mendenhall WM, Stringer SP*, et al.* Radiotherapy Alone for Moderately Advanced Laryngeal Cancer (T2-T3). Semin Radiat Oncol 1992;2(3):158-162.

4. Rubinstein M, Armstrong WB. Transoral laser microsurgery for laryngeal cancer: a primer and review of laser dosimetry. Lasers Med Sci 2011;26(1):113-24.

5. Ganzer U. [Prognosis of laryngeal cancer since 1960. Results of a literature review and a survey]. Laryngorhinootologie 1990;69(1):1-5.

6. Pfister DG, Spencer S, Brizel DM*, et al.* Head and Neck Cancers, Version 1.2015. J Natl Compr Canc Netw 2015;13(7):847-55; quiz 856.

7. Misono S, Marmor S, Yueh B*, et al.* T1 glottic carcinoma: do comorbidities, facility characteristics, and sociodemographics explain survival differences across treatment? Otolaryngol Head Neck Surg 2015;152(5):856-62.

8. Mendenhall WM, Amdur RJ, Morris CG*, et al.* T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy. J Clin Oncol 2001;19(20):4029-36.

9. Yamazaki H, Nishiyama K, Tanaka E*, et al.* Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. Int J Radiat Oncol Biol Phys 2006;64(1):77-82.

10. Wetmore SJ, Key JM, Suen JY. Laser therapy for T1 glottic carcinoma of the larynx. Arch Otolaryngol Head Neck Surg 1986;112(8):853-5.

11. Ogura JH. Management of early cancer of the vocal cord--laryngofissure, hemilaryngectomy, irradiation. Trans Pac Coast Otoophthalmol Soc Annu Meet 1963;44:245-7.

12. Smith GL, Smith BD, Buchholz TA*, et al.* Cerebrovascular disease risk in older head and neck cancer patients after radiotherapy. J Clin Oncol 2008;26(31):5119-25.

13. Dorresteijn LD, Kappelle AC, Boogerd W*, et al.* Increased risk of ischemic stroke after radiotherapy on the neck in patients younger than 60 years. J Clin Oncol 2002;20(1):282-8.

14. Rosenthal DI, Fuller CD, Barker JL, Jr.*, et al.* Simple carotid-sparing intensity-modulated radiotherapy technique and preliminary experience for T1-2 glottic cancer. Int J Radiat Oncol Biol Phys 2010;77(2):455-61.

15. Gomez D, Cahlon O, Mechalakos J*, et al.* An investigation of intensity-modulated radiation therapy versus conventional two-dimensional and 3D-conformal radiation therapy for early stage larynx cancer. Radiat Oncol 2010;5:74.

16. Chera BS, Amdur RJ, Morris CG*, et al.* Carotid-sparing intensity-modulated radiotherapy for early-stage squamous cell carcinoma of the true vocal cord. Int J Radiat Oncol Biol Phys 2010;77(5):1380-5.

17. Matthiesen C, Herman Tde L, Singh H*, et al.* Dosimetric and radiobiologic comparison of 3D conformal, IMRT, VMAT and proton therapy for the treatment of early-stage glottic cancer. J Med Imaging Radiat Oncol 2015;59(2):221-8.

18. Zumsteg ZS, Riaz N, Jaffery S*, et al.* Carotid sparing intensity-modulated radiation therapy achieves comparable locoregional control to conventional radiotherapy in T1-2N0 laryngeal carcinoma. Oral Oncol 2015;51(7):716-23.

19. Choi HS, Jeong BK, Jeong H*, et al.* Carotid sparing intensity modulated radiotherapy on early glottic cancer: preliminary study. Radiat Oncol J 2016;34(1):26-33.

20. Berwouts D, Swimberghe M, Duprez F*, et al.* Intensity-modulated radiotherapy for early-stage glottic cancer. Head Neck 2016;38 Suppl 1:E179-84.

21. Paterson R. Studies in optimum dosage. Br J Radiol 1952;25(298):505-16.

22. Pfister DG, Ang K, Brockstein B*, et al.* NCCN Practice Guidelines for Head and Neck Cancers. Oncology (Williston Park) 2000;14(11A):163-94.

23. Al-Mamgani A, Kwa SL, Tans L*, et al.* Single Vocal Cord Irradiation: Image Guided Intensity Modulated Hypofractionated Radiation Therapy for T1a Glottic Cancer: Early Clinical Results. Int J Radiat Oncol Biol Phys 2015;93(2):337-43.

24. Ermis E, Teo M, Dyker KE*, et al.* Definitive hypofractionated radiotherapy for early glottic carcinoma: experience of 55Gy in 20 fractions. Radiat Oncol 2015;10:203.

25. Laskar SG, Baijal G, Murthy V*, et al.* Hypofractionated radiotherapy for T1N0M0 glottic cancer: retrospective analysis of two different cohorts of dose-fractionation schedules from a single institution. Clin Oncol (R Coll Radiol) 2012;24(10):e180-6.

26. Short S, Krawitz H, Macann A*, et al.* TN/TN glottic carcinoma: a comparison of two fractionation schedules. Australas Radiol 2006;50(2):152-7.

27. Gowda RV, Henk JM, Mais KL*, et al.* Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital Experience. Radiother Oncol 2003;68(2):105-11.

28. Fowler JF. 21 years of biologically effective dose. Br J Radiol 2010;83(991):554-68.

29. Kim YS, Lee J, Park JI*, et al.* Volumetric modulated arc therapy for carotid sparing in the management of early glottic cancer. Radiat Oncol J 2016;34(1):18-25.

30. Atalar B, Gungor G, Caglar H*, et al.* Use of volumetric modulated arc radiotherapy in patients with early stage glottic cancer. Tumori 2012;98(3):331-6.

13.0 APPENDICES

Appendix A: ECOG Performance Status

ECOG PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).

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

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

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

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

5 Death (Karnofsky 0).

Appendix B: EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ⌊_⌊_⌊_⌊_⌋

Your birthdate (Day, Month, Year): ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

Today's date (Day, Month, Year): 31 ⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌊_⌋

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

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

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix C: EORTC QLQ-H&N35

EORTC QLQ - H&N35

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

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

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Appendix D: Voice Handicap Index (VHI)

VOICE HANDICAP INDEX (VHI)

Jacobson, Johnson, Grywalski, Silbergleit, Jaconsen, Berringer
Recreated by D.E. Cross 2-09

Name: _____ Date: _____ D.O.B. _____ Age: _____

Male ___ Female ___ Physician: _____ Dx: _____

Instructions: These are statements that many people have used to describe their voices and the effects of their voices on their lives. Check the response that indicates how frequently you have the same experience.

		Never	Almost Never	Sometimes	Almost Always	Always
F1.	My voice makes it difficult for people to hear me	O	O	O	O	O
P2.	I run out of air when I talk.	O	O	O	O	O
F3.	People have difficulty understanding me in a noisy room.	O	O	O	O	O
P4.	The sound of my voice varies throughout the day	O	O	O	O	O
F5.	My family has difficulty hearing me when I call them throughout the house.	O	O	O	O	O
F6.	I use the phone less often than I would like.	O	O	O	O	O
E7.	I'm tense when talking with others because of my voice	O	O	O	O	O
F8.	I tend to avoid groups of people because of my voice	O	O	O	O	O
E9.	People seem irritated with my voice.	O	O	O	O	O
P10.	People ask "What's wrong with your voice?"	O	O	O	O	O
F11.	I speak with friends, neighbors, or relatives less often because of my voice.	O	O	O	O	O
F12.	People ask me to repeat myself when speaking face-to-face.	O	O	O	O	O
P13.	My voice sounds creaky and dry.	O	O	O	O	O
P14.	I feel as though I have to strain to produce voice.	O	O	O	O	O
E15.	I find other people don't understand my voice problem.	O	O	O	O	O
F16.	My voice difficulties restrict my personal and social life.	O	O	O	O	O
P17.	The clarify of my voice is unpredictable	O	O	O	O	O
P18.	I try to change my voice to sound different.	O	O	O	O	O
F19.	I feel left out of conversations because of my voice.	O	O	O	O	O
P20.	I use a great deal of effort to speak.	O	O	O	O	O
P21.	My voice is worse in the evening.	O	O	O	O	O
F22.	My voice problem causes me to lose income.	O	O	O	O	O
E23.	My voice problem upsets me.	O	O	O	O	O

		Never	Almost Never	Sometimes	Almost Always	Always
E24.	I am less out-going because of my voice problem.	O	O	O	O	O
P25.	My voice problem makes me handicapped.	O	O	O	O	O
P26.	My vice "gives out" on me in the middle of speaking.	O	O	O	O	O
E27.	I feel annoyed when people ask me to repeat.	O	O	O	O	O
E28.	I feel embarrassed when people as me to repeat.	O	O	O	O	O
E29.	My voice makes me feel incompetent.	O	O	O	O	O
E30.	I'm ashamed of my voice problem.	O	O	O	O	O

Please circle the word that matches how you feel your voice is today.

Normal Mild Moderate Severe

Appendix E: EQ 5D

EQ 5D

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

ANXIETY / DEPRESSION

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

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

YOUR HEALTH TODAY = ☐

Patient's initials: _____

Today's date: _____