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STU 052016-044

INFIELD: A Prospective Phase II Study of Involved Field Elective Volume De-Intensification for Oropharyngeal and Laryngeal Squamous Cell Carcinoma treated with Intensity Modulated Radiation Therapy

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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_____

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Principal Investigator (PI) Name: **__David J. Sher MD, MPH_____**

PI Signature: _____

Date: _____

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TABLE OF CONTENTS

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
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
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
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase

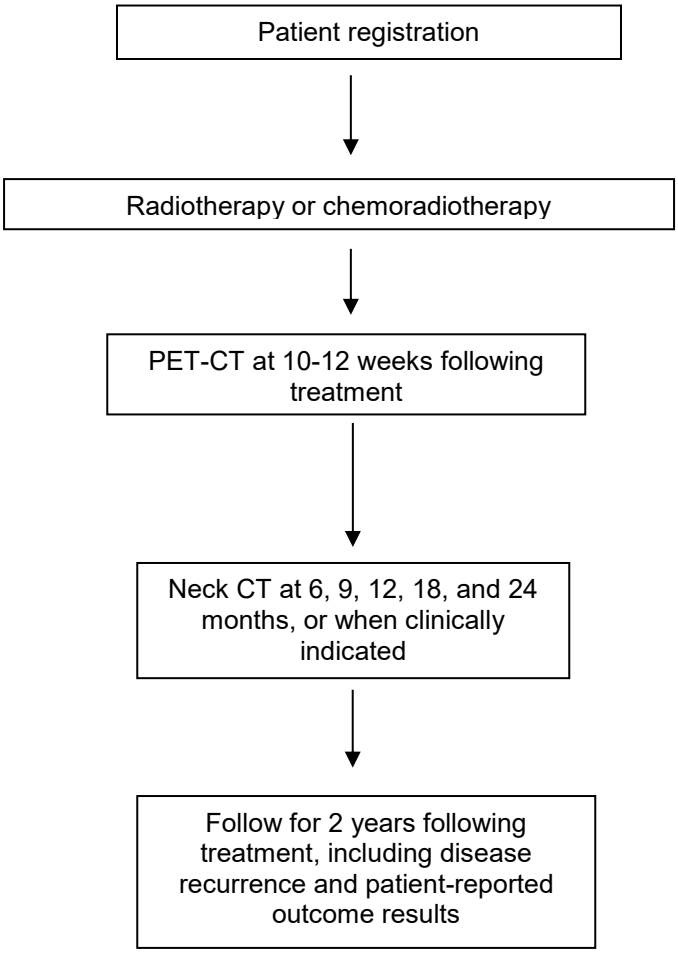
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA

STUDY SUMMARY

Title	Full title of protocol
Short Title	Shortened title(match this to title used it ClinicalTrials.gov)
Protocol Number	The standard protocol number used to identify this study
Phase	Clinical study phase (e.g., Phase 1, 2, 3 or 4)
Methodology	Design attributes such as single blind, double blind or open label; randomized, placebo or active placebo control; cross-over design, etc.
Study Duration	Estimated duration for the main protocol (e.g., from start of screening to last subject processed and finishing the study)
Study Center(s)	Single-center or multi-center; if multi-center, note number of projected centers to be involved
Objectives	Brief statement of primary study objectives
Number of Subjects	Number of subjects projected for the entire study (e.g., not for simply one site, rather for all sites combined)
Diagnosis and Main Inclusion Criteria	Note the main clinical disease state under study and the key inclusion criteria (i.e. not the entire list that will appear later in the protocol, rather only the key inclusion criteria)
Study Product(s), Dose, Route, Regimen	Study drug name(s) (generic name, though can also state marketed name if name-brand used in the study) and/or description of non-drug therapy (i.e., radiation, surgery, etc.);include dose, route and regimen
Duration of administration	Total duration of drug product administration (including any open-label lead-in, if applicable)
Reference therapy	Note if there is a standard reference therapy against which the study product is being compared, or if the reference is a placebo
Statistical Methodology	A very brief description of the main elements of the statistical methodology to be used in the study (as few lines as possible)

STUDY SCHEMA



STUDY SUMMARY

Title	**INFIELD: A Prospective Phase II Study of Involved Field Elective Volume De-Intensification for Oropharyngeal and Laryngeal Squamous Cell Carcinoma treated with Intensity Modulated Radiation Therapy**
Short Title	INFIELD: A Prospective Phase II Study of Involved Field Elective Volume De-escalation
Protocol Number	STU 052016-044
Phase	Phase 2
Methodology	Prospective study
Study Duration	2 years to accrue plus additional 2 years of follow-up
Study Center(s)	Multi-center
Objectives	To determine the risks and quality-of-life-benefits of using a tailored strategy of elective volume de-intensification.
Number of Subjects	67
Diagnosis and Main Inclusion Criteria	Stage I-IVB oropharyngeal squamous cell carcinoma, treated with definitive radiotherapy or chemoradiotherapy. Stage I-IVB laryngeal squamous cell carcinoma, excluding glottis T1-2 carcinoma
Study Product(s), Dose, Route, Regimen	Intensity modulated radiation therapy (IMRT) with or without chemotherapy (if given, either cisplatin, cetuximab, or carboplatin-paclitaxel)
Duration of administration	7 weeks of radiotherapy or chemoradiotherapy
Reference therapy	N/A
Statistical Methodology	. A sample size of 60 achieves a 90% power to detect a non-inferiority difference of 0.1 using a one-sided exact test with a significance level (alpha) of 0.05. These results assume a baseline risk of 0.03 and that the actual difference is 0.0

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Oropharyngeal (OPC) and laryngeal cancer (LXC) are the most common sites of head and neck cancer disease treated with primary radiotherapy (RT) or chemoradiotherapy (CRT). For example, in the two most recent large RTOG randomized trials involving primary CRT, these two disease sites comprised 86% and 93% of the entire cohort of RTOG 0129 and 0522, respectively (1, 2).

Outcomes following radiotherapy depend strongly on disease site. Patients with OPC are now dichotomized into human papillomavirus (HPV)-related disease (HPV-positive), and HPV-negative disease. The outcomes are dramatically improved in patients with virally-mediated cancer, with 8-year overall survival (OS), progression-free survival (PFS), locoregional recurrence (LRR) and distant metastasis (DM) risks of 70.9%, 64%, 19.5% and 10.3% versus 30.2%, 23.3%, 52.4% and 16.1% for HPV-positive versus HPV-negative, respectively.

The survival outcomes for patients with laryngeal cancer have remained roughly stable over the years. In RTOG 9111, definitive CRT using conventional radiotherapy led to 5-year OS, LRR and DM of 55.1%, 32.3%, and13.6%, respectively (3). In a more recent study (also using conventional radiotherapy), induction chemotherapy plus CRT for LXC led to a crude risk of locoregional and distant failure of 20% and 8.3% at a median follow-up of only 36 months, suggesting similar rates of disease success over time (4).

Radiotherapy has evolved dramatically over the past 20 years, such that now intensity modulated radiation therapy (IMRT) is the standard-of-care. IMRT allows the physician to contour (i.e. target) regions for specific doses of radiotherapy, while also specifying normal structures (termed organs-at-risk, OAR) that should be avoided. The use of IMRT has been shown to reduce xerostomia in randomized trials (5). However, IMRT still targets the same lymph node regions as conventional 2D radiotherapy, despite our ability to tailor the radiotherapy volume and dose to specific areas.

It is notable that the majority of disease sites treated with radiotherapy no longer receive elective/prophylactic radiotherapy to clinically-negative areas, including lung, pancreas, and lymphoma. Fields that eliminate or minimize elective irradiation are termed “involved-field.” In this study, we aim to improve acute and long-term toxicity of IMRT for OPC and LXC by delivering a conservative form of involved-field radiotherapy, using a lower dose while also sparing tissue with an established, very low risk of occult microscopic disease.

1.2 Study Agent(s) Background and Associated Known Toxicities

Radiotherapy and chemoradiotherapy are established treatments for oropharyngeal squamous cell carcinoma. This study is evaluating a radiation dose paradigm that should be equally or more tolerable – in both the short- and long-term – than the established outcomes. The dose to known gross disease is the same as in these studies, but the dose to the areas with potential microscopic disease, termed elective volumes, will be lowered or eliminated.

The allowed chemotherapy regimens are standard agents that have been used in prospective phase II and III studies and are considered feasible treatments according to the NCCN guidelines.

To provide a rough estimate of acute and late toxicities, in the control arm of RTOG 0129 (conventional radiotherapy plus bolus cisplatin), 73.7% of patients experienced a non-hematologic acute grade 3-5 toxicity, and 39.1% of patients developed acute grade 3-5 mucositis/stomatitis (6) . A total of 9.4% of patients developed febrile neutropenia. However, only 3.7% of patients were diagnosed with late (i.e. after 90 days from the start of RT)

mucositis/stomatitis. **Thirty-six** percent of patients experienced any late grade 3-5 toxicity, the majority of which were esophageal (8%), “other” (8%), or salivary gland (4%).

1.3 Other Agents

Patients with stage I and II disease will be treated with radiotherapy alone. Patients with stage III (T1-2 N1) may be treated with radiotherapy alone or concurrent chemoradiotherapy. Patients with stage III (T3N0-1) and IVA-B cancers will be treated with concurrent chemoradiotherapy.

The specific systemic therapy agent will be left to the physician. The four allowed chemotherapy regimens are bolus cisplatin,weekly cisplatin, cetuximab (weekly, including 1 week before treatment), and carboplatin-paclitaxel (weekly, over the course of treatment).

1.4 Rationale

Before proceeding with the rationale section, it is critical to note that radiotherapy targets two basic types of treatment volumes: gross disease and microscopic disease. Gross disease, termed gross tumor volume (GTV) receives the highest dose level, and microscopic disease, termed clinical target volume (CTV) receives a lower dose level. Frequently (but not always) there are several CTV dose levels, depending on the risk of microscopic disease. The critical organs-at-risk (salivary glands, oral cavity, pharyngeal constrictors, larynx and esophagus) almost always abut areas that may harbor microscopic disease but are relatively distant (1 cm or more) from GTV. In practical terms, this means that the dose to structures crucial to long-term quality-of-life are determined by the elective, CTV, dose rather than the radiation to the known gross disease.

When we think about reducing the intensity of treatment to the CTV, we aim to minimize the subsequent risk of solitary elective recurrence (i.e. first and only failure). That is, the risk of recurrence in an elective region before any other treatment failure, either local or distant. A patient who has an elective recurrence synchronous with (or after) an in-field or distant recurrence was not harmed by the less intense elective treatment, because the disease would have recurred anyway.

There are thus three key questions in considering how to manage elective volume irradiation. First and second, how frequent are solitary elective recurrences and at what elective dose are these outcomes achieved? Thirdly, what is the risk of any microscopic disease in the first place?

Frequency of solitary elective recurrences, and required dose

With respect to the patterns-of-recurrence and required elective dose, although RTOG 0129 did not describe the patterns-of-failure relative to the irradiation field, many other studies have shown that the vast majority of recurrences occur within the high-dose zone. In a retrospective study from Dana-Farber Cancer Institute, the risk of recurrence within the elective volume (56-63 Gy) was 1%, and results were very similar from Dandekar et al, which showed only a 2% elective failure risk in regions treated to 54-56 Gy(7, 8). In a very large study from MD Anderson (776 oropharyngeal cancer patients), only 7 patients (< 1% of total) failed outside of the high-dose zone, with the low-dose irradiated to 50 Gy (9). There were no elective volume failures in a 71-patient retrospective study of oropharyngeal cancer from UCSF (54 Gy in 33 fractions) (10). In a carefully-performed patterns-of-failure study from Ghent University Hospital, there were no solitary elective nodal failures (out of 140, with the majority oropharynx [35%] or larynx [28%]) in the primarily irradiated neck, in which the elective neck received 56 Gy in 35 fractions (11).

Bedi et al described 69 patients treated with 50 Gy in 35 fractions to the low-risk elective neck, with no recurrences at a median 2.5 years of follow-up (12).

In a very large study (376 patients, 70% OPC and 16% LXC) from Belgium, although 11.1% (41 patients) developed a regional recurrence, only 11 patients (3% of total) developed a solitary regional recurrence. Moreover, only 2 patients (<1% of total) developed a solitary elective regional recurrence in an area that received between 46-50 Gy (13).Studer et al. described the patterns-of-failure in 202 head and neck cancer patients (70% OPC and LXC) treated with IMRT (14) . In this series, 99 patients underwent prophylactic neck dissection after RT, and 29 nodes were still positive; 28 out of these 29 (96.5%) were only positive in gross disease. Out of the 103 patients who did not receive a prophylactic neck dissection, 27 (26%) patients developed an isolated nodal relapse. However, out of these 27 patients, only 1 (4%) occurred in the elective PTV. Importantly, salvage surgery was performed in 24 of these individuals (89%) and was successful in 21/24 (88% of attempted surgeries, 78% of all recurrences), despite nearly all of these recurrences reflecting in-field failures.

Similarly, there were only 6 solitary elective recurrences out of 264 (50% OPC, 37% LC) patients treated to 50 Gy in 34 fractions in van den Bosch et al (15). Importantly, this latter paper evaluated almost 1200 lymph nodes, and found that elective nodal recurrence **always occurred in a previously visualized (presumed benign) lymph node**. Thus, the nodes at-risk appear to be visible at diagnosis. Moreover, the risk of recurrence in these radiologically-negative nodes was only 0.4% (at 2 years) if the summed diameter of the lymph node was less than 17 mm. In summary, it seems clear that solitary elective recurrences are very rare, if a radiologically-clear region has microscopic disease, 50 Gy is nearly always sufficient to sterilize it.

In fact, the drive to lower the elective dose even further led to a Belgian randomized controlled trial comparing 50 Gy with 40 Gy to the elective neck, with 100 patients in either arm. A preliminary study showed significantly improved dosimetry in the dose to the swallowing structures, with significantly less grade 3 dysphagia at 3 months (2% vs 11%, p=0.03)(16). With longer follow-up, the authors found no difference in local control but significant improvements in grade 3 dysphagia at 6 months and borderline improvement at 2 years (p=0.065) (ESTRO, 2014, OC-0058).

Risk of disease in level IB (submandibular nodes)

The second issue is the probability of any microscopic disease in a given lymph node level, because if that risk is sufficiently low, no irradiation is required at all. Although the original IMRT experience treated all lymph node stations in the neck to parallel older irradiation techniques, there is now a substantial volume of pathologic and radiotherapeutic data supporting a very low risk of occult disease in radiologically-negative regions. Several surgical series have shown a low risk of disease in ipsilateral level IB in oropharyngeal cancer. For example, Sanguineti et al showed that out of 91 patients with resected, HPV-positive oropharyngeal cancer with a lymph node 10 mm or smaller in level IB, the risk of level IB pathologic involvement was 2.5% (17). In a surgical series of 104 oropharyngeal patients who underwent neck dissections, there were no occult metastases to level IB (18)

Parallel surgical studies in larynx cancer confirm similar patterns of disease. dos Santos et al performed 100 consecutive dissections for patients with T3-4 or N1-N2c disease, and only 2 (2%) patients had level I involvement (19). Mercante et al dissected 150 patients with larynx and hypopharynx cancer, finding no patients with level IB disease (20).

Primary radiation-based series also show a very low risk of microscopic disease in level IB. Tam et al reported on 125 node-positive OPSCC patients from Memorial Sloan-Kettering Cancer Center treated with bilateral submandibular sparing radiotherapy, including 26% T3-4 disease and 76% N2b or N2c, finding no submandibular recurrences (21) . In a very large patterns-of-failure study, Kjems study excluded level IB in the IMRT for all oropharyngeal and laryngeal cancers (unless it was clearly involved or the oral cavity was involved), and there was only 1 oropharyngeal patient (out of 469) and no larynx patients (out of 253) with a level IB recurrence when it wasn't initially included in the field (22). Thus excluding level IB from the treatment field is extremely reasonable in the absence of overt involvement or oral cavity extension.

Risk of disease in level V (posterior neck nodes)

The risk of level V disease is similarly low, and in fact, it is often not dissected in oropharyngeal cancer. The absolute risk of level V disease in Sanguineti et al was only 2.6% (17). Naiboglu et al. reported on the nodal pathology of 107 patients (43 oropharynx, 16 larynx) who underwent level V neck dissection (23). Although level V was involved in 13 patients (12.1%), it was only positive when nodes in levels II-IV were positive. Similarly, Spriano et al dissected 346 clinically N0 necks in patients with larynx cancer, and only 10 out of 604 (1.6%) level V nodes were involved (24). In a node dissection study including 72 OPC and LXC patients, only 1 patient had a positive level V (1.4%) node without other nodes also being involved ((25).

Mohindra et al reported on a series of 35 patients with oropharyngeal cancer treated with radiotherapy in which level V was spared ipsilaterally, and there were no recurrences in this echelon (26). In the Kjems study, in which level V in OPC or LXC was only included if obviously involved, there were no level V recurrences (22).

The preponderance of extant data thus supports sparing level V as well if that side has a low burden of nodal disease. Thus we would only treat level V if the patient has 2 or more involved nodes on a given side.

Risk of disease in level IV (low neck nodes)

Level IV lymph nodes start at the cricoid and extend inferiorly into the supraclavicular fossa. Although they are nearly always included in the typical irradiation field, the surgical data actually suggests the risk is very low if the (superior) level III is uninvolved. For example, Sanguineti et al showed that the risk of occult level IV disease was just over 2.5% when level III lymph nodes were 8 mm or less(17). This estimate was supported by an oropharyngeal cancer surgical series from Lim et al, in which there were only 3 occult level IV metastases out of 104 necks, and all three occurred in combination with level III metastases (18). In a similar report from Lodder et al from Erasmus Medical Center, there was only 1 skip metastasis to level IV alone out of 92 oropharyngeal neck dissections (27). Chone et al performed a prospective study of results from laryngeal cancer neck dissections, finding that while 25% of 54 necks had level IV disease, they only were positive if level II or III was positive (28). Similarly, Lim et al reported on 72 clinically N0 neck dissections, finding that only 3.5% of all necks contained level IV disease, all of which were ipsilateral, and there were skip metastases to level IV in only 2 necks (1.4% of all necks) (29) . As perhaps the best evidence that sparing level IV is oncologically sound, Kjem et al routinely spared level IV if level III was not clinically involved in OPC and LXC, and there were no solitary level IV recurrences (22).

University of Chicago experience

As one final supporting example to motivate this study, investigators at the University of Chicago performed a prospective phase II study titled RAVD (response-adapted volume de-escalation), in which all patients received 2 cycles of induction chemotherapy, and good responders (50% or greater) received treatment just to the gross disease, without elective irradiation.(30) It's notable that the investigators used a large margin on gross disease (1.5 cm), presumably encompassing neighboring microscopic disease, but this group received no intentional elective irradiation. Patients without a good response received 45 Gy to the first uninvolved nodal echelon and then a boost to 75 Gy to gross disease plus 1.5 cm. No other elective nodal stations were irradiated. Of the 93 patients, 71 had OPC, and 7 had LXC. Much of the neck was still spared, even in poor responders. Since the majority (72%) of patients had ipsilateral disease, most patients did not receive contralateral levels III and IV irradiation, and several presumably did not receive any contralateral RT at all. Despite this somewhat radical change in treatment fields, there were **no solitary nodal failures**. There were 13 locoregional recurrences and only one out-of-field failure, which occurred simultaneous to an in-field recurrence.

Summary points

1. Many organs-at-risk border elective treatment volumes rather than gross disease.

2. Solitary elective volume failures are extremely rare (0-5%).

3. 50 Gy to the elective regions is sufficient to sterilize microscopic disease and may even be too high, as randomized data suggest 40 Gy may be adequate.

4. Failures in elective nodal regions occur in *previously identified*, radiologically-negative, lymph nodes, as opposed to tissue without any prior evidence of a "benign" node.

5. Occult disease in level IB is extremely rare.

6. Occult disease in level V is extremely rare if levels II-IV contain minimal disease.

7. Occult disease in level IV is extremely rare if level III is uninvolved, and in general, as shown by the University of Chicago study, skip metastases (i.e. level III is involved without prior level II involvement) are very unusual.

Given these observations, this study aims to significantly improve the acute and late morbidity of patients with oropharyngeal and laryngeal squamous cell carcinoma both by tailoring the elective irradiation only to regions with a legitimate risk of recurrence (> 5%) and by lowering the elective dose to 40 Gy. Level IB will not be electively treated unless it is involved with pathologic or suspicious lymphadenopathy. Level V will not be treated unless two or more ipsilateral nodal levels are involved (or level V itself has pathologic or suspicious adenopathy). Levels III and IV will only be irradiated if the immediately proximal level contains pathologic lymphadenopathy (i.e. level III irradiated if level II is positive; level IV irradiated if level III is positive). We anticipate that this approach should dramatically improve the acute and late complication profile.

1.5 Correlative Studies

NA

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine the risk of solitary elective volume recurrence following elective volume and dose de-escalation.

2.1.1.1 Definition: solitary means that the recurrence occurred without a preceding or synchronous in-field or distant recurrence

2.2 Secondary Objectives

2.2.1 To determine patient-reported outcomes (PRO) following treatment with elective volume and dose de-escalation.

2.2.2 To describe the rates of grade 3 and 4 acute and late toxicities following elective volume and dose de-escalation.

2.2.3 To estimate the rates gastrostomy dependence at 3, 6, 12 and 24 months following treatment.

2.2.4 To characterize patient utilities following treatment with elective volume and dose de-escalation.

2.2.5 To determine 2-year overall and progression-free survival following elective volume and dose de-escalation.

2.2.6 To describe the patterns-of-failure following elective volume and dose de-escalation.

2.3 Exploratory Objectives

NA

2.4 Endpoints

2.4.1 Primary endpoint: 2-year crude risk of solitary elective volume recurrence (SEVR).

2.4.2 Secondary endpoints:

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

2.4.2.1.1 EORTC QLQ-C30 Summary score
2.4.2.1.2 EORTC QLQ-C30 Physical and role functioning subscales
2.4.2.1.3 EORTC HN35 Dry mouth and sticky saliva subscales
2.4.2.1.4 MDADI global, emotional, functional and physical subscales
2.4.2.1.5 EQ-5D global score (0-100)

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 Prevalence of gastrostomy-dependence at 3, 6, 12 and 24 months from the end of treatment.

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

2.4.2.5 Overall survival probability at 2 years from the start of treatment

2.4.2.6 Progression-free survival probability at 2 years from the start of treatment

2.4.2.7 Cumulative incidence of locoregional recurrence at 2 years, with death as a competing risk

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

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 of the oropharynx or larynx. Squamous cell carcinoma of unknown primary is not allowed.

3.1.2 Patients must have clinically or radiographically evident measureable disease at the primary site and/or nodal stations. Patients may undergo a diagnostic tonsillectomy, and diagnostic lymph node excision (≤ 2 nodes) is also allowable.

3.1.3 Clinical stage I-IVB (AJCC, 7th edition); stages I-II glottic cancer are excluded

3.1.4 Age ≥ 18 years.

3.1.5 ECOG Performance Status 0-2

3.1.6 Adequate organ and marrow function as defined below:

- leukocytes	≥ 3,000/mcL
- absolute neutrophil count	≥ 1,500/mcL
- platelets	≥ 100,000/mcl
- total bilirubin	within normal institutional limits
- AST(SGOT)/ALT(SPGT)	≤ 2.5 X institutional upper limit of normal

3.1.7 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.

3.1.6.1 A female of child-bearing potential is any woman (regardless of sexual orientation, 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).

3.1.8 Negative serum pregnancy test within 2 weeks before registration for women of childbearing potential.

3.1.9 Neck CT and/or neck MRI, and whole body PET-CT.

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

3.2 Exclusion Criteria

3.2.1 Distant metastasis or adenopathy below the clavicles.

3.2.2 Inability to undergo PET-CT.

3.2.3 Stage I and II glottic carcinoma.

3.2.4 Gross total excision of both the primary and nodal disease.

3.2.5 Synchronous non-skin cancer primaries outside of the oropharynx and larynx, except for synchronous well-differentiated thyroid cancer; in the latter case, surgery may occur before or after INFIELD treatment, provided all other eligibility criteria are met.

3.2.6 Prior invasive malignancy with an expected disease-free interval of less than 3 years.

3.2.7 Prior systemic chemotherapy for the study cancer; prior chemotherapy for a remote cancer is allowable

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

3.2.9 Subjects may not be receiving any other investigational agents.

3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to the chemotherapy agents in this study (if necessary).

3.2.11 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 would limit compliance with study requirements.

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

3.2.13 History of immunosuppression, including HIV, and organ or stem cell transplant, or an autoimmune condition previously treated with immunosuppressive therapy.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

The overall treatment approach (RT with or without systemic therapy) is defined by the AJCC stage and described as follows:

- AJCC stage IVA, IVB or T3N0-1 stage III: radiotherapy with concurrent systemic therapy
- AJCC stage III (T1-2 N1): radiotherapy with concurrent systemic therapy OR accelerated radiotherapy alone (6 fractions per week)
- AJCC stage II: radiotherapy alone OR accelerated radiotherapy alone (6 fractions per week)
- AJCC stage I: radiotherapy alone (5 fractions per week)

There is controversy on how to manage T1-2 N1 head and neck cancer and either chemoradiotherapy or accelerated radiotherapy are viable approaches. It will be up to physician discretion as to which paradigm is applied to a given patient. The difference in the effective elective dose is expected to be trivial between these approaches.

The radiotherapy plan wil be delivered in 2 sequential courses. The first course involves 20 fractions of 2 Gy per fraction to the entire volume (gross disease and elective). The second

course involves 15 fractions (thus, total of 35 fractions), at either 2 Gy (gross disease) or 1.6 Gy (microscopic disease and suspicious node) per fraction.

4.1.1 Radiation Therapy

4.1.1.2 CT simulation

Patients will be simulated in a thermoplastic mask extending from the scalp through upper chest (e.g. “5-point mask”).

IV contrast is recommended but not mandatory.

4.1.1.3 Primary tumor delineation and targeting

The primary gross tumor volume (pGTV) will be contoured on the planning CT, using radiographic and clinical information to define its extent.

The pGTV will be expanded by 5 mm to create the pPTV70.

For patients with T1N0 OPSCC, pGTV plus 5 mm will create the pPTV66.

4.1.1.4 Primary elective volume delineation and targeting.

The creation of the primary clinical target volume (pCTV1), which is the primary elective volume, is a multi-step process. First, the pGTV will be expanded by 5-8 mm. Then any contours in structures that are a natural barrier to spread (e.g. bone) will be deleted. The pCTV1 is then expanded by 5-8 mm to create pPTV64; note this volume receives 40 Gy in the first 20 fractions, and then 1.6 Gy per fraction.

A lower dose primary clinical target volume (pCTV2) will be designed by expanding the pGTV by typically 5-10 mm and deleting contours in structures that are a natural barrier to spread. The specific width here is reliant on physician discretion. The pCTV2 is then expanded by 5-8 mm to create pPTV40.

4.1.1.5 Nodal tumor delineation and targeting.

Visible lymph nodes will be categorized as benign, suspicious, or involved. By definition, a node is “involved” if it meets any of the following criteria:

- Max SUV is greater than 3.0 (31)
- The short-axis diameter is $\geq$ 1.5 cm (level II), $\geq$ 0.8 cm (retropharyngeal nodes), or $\geq$ 1.0 cm for other nodal stations
- The node shows central necrosis or heterogeneous enhancement
- Lymph nodes whose max SUV is greater than mean liver SUV may be considered “involved” at the discretion of the treating physician. (32)

A node is “suspicious” if it doesn’t meet the above criteria, but:

- The combined diameter of the lymph node is 17 mm or more (15), OR
- Max SUV is greater than mean liver SUV(32)
- Lymph nodes whose max SUV is greater than mean blood pool may be considered “suspicious” at the discretion of the treating physician. (32)

The nodal gross tumor volume (niGTV or nsGTV for involved or suspicious nodes) will be contoured on the planning CT, using radiographic and clinical information to define its extent. The nodes will be expanded by 5 mm to create the PTVs.

Lymph node stations will be contoured according to RTOG consensus guidelines (description and atlas included at https://www.rtog.org/CoreLab/ContouringAtlases/HNAtlases.aspx)

Contouring and dosing schemes are as followed:

4.1.1.5.1 Any involved node receives 70 Gy (nPTV70). The elective CTV must include this node plus 5 mm expansion to account for microscopic extranodal extension.

4.1.1.5.2 Any suspicious node receives 64 Gy (nPTV64). In the first course, the node is treated to 40 Gy in 2 Gy fractions, then 1.6 Gy per fraction for 15 fractions. The station containing that node is treated in the elective CTV. The elective CTV must include this node plus 5 mm expansion to account for microscopic extranodal extension.

4.1.1.5.3 For oropharynx primaries, level II is treated bilaterally (except in early-stage tonsil cancer, see Section 4.1.1.6.3). For either side of the neck, if level II does not contain an involved node then levels III-IV are not treated. If level III does not contain an involved node, then level IV is not treated. Level V is only treated if 2 levels of the neck are involved. When level IV and level V are treated, the entire level is included.

4.1.1.5.4 For larynx primaries, levels II-III are treated bilaterally. For either side of the neck, if level III does not contain an involved node, then level IV is not treated. Level V is only treated if 2 levels of the neck are involved. When level IV and level V are treated, the entire level is included.

4.1.1.5.5 A suspicious node does **not** lead to treatment of the next elective station.

4.1.1.5.6 Level IB is never treated unless it includes an involved or suspicious node, or there is oral cavity extension of the oropharynx primary tumor.

4.1.1.5.7 If level II has an involved node, then upper level II (above the subdiagstric node) is treated to 40 Gy (nCTV40) because of poor salvage rates. If level II does not have an involved node, then its cranial border is the subdigastric node.

4.1.1.5.8 Larynx cancer with subglottic extension should have level IV and level VI included in the nCTV40.

4.1.1.5.9 For oropharynx cancer, ipsilateral retropharyngeal nodes are included (i.e. in the CTV40) if level II includes an involved lymph node, or there is an involved or suspicious lymph node in the retropharyngeal station. For larynx cancer, ipsilateral retropharyngeal lymph nodes are never included unless there are involved or suspicious lymph nodes in the retropharyngeal station. For both oropharyngeal and laryngeal cancer, if there is an involved retropharyngeal node, then elective retropharyngeal nodes on both side of the neck are treated to 40 Gy (i.e. included in the nCTV40).

4.1.1.5.10 The PTV64 and PTV40 may be reduced to 1 mm if it is abutting an organ-at-risk.

4.1.1.5.11 A node that is biopsied and positive should be treated as an involved node. A node that is biopsied and negative may be treated as a negative node, regardless of imaging findings.

4.1.1.5.12 The ipsilateral and contralateral retropharyngeal nodes may be included in nCTV40 if there is soft palate invasion.

All elective nodal CTV's are expanded by 5 mm, except 3 mm medially.

All PTV's are trimmed by 3 mm inside skin to arrive at the final structure, unless there is skin involvement, in which case bolus placement may be used to ensure adequate skin dose.

4.1.1.6 Contours under special conditions

4.1.1.6.1 If the patient underwent a diagnostic tonsillectomy with a pathologically positive result, the tonsillar fossa should be contoured as psCTV. The psCTV is then expanded by 5 mm to create the psPTV40 (margins 2 mm or more) or psPTV64 (margins less than 2 mm). The PTV is trimmed by 3 mm inside skin to arrive at the final structure.

4.1.1.6.2 If the patient underwent a diagnostic lymph node excision, the resection "bed" (where the previous lymph node(s) was) should be contoured as nsCTV. The nsCTV is then expanded by 5 mm to create nsPTV40 (no ECE) or nsPTV64 (ECE). The PTV is trimmed by 3 mm inside skin to arrive at the final structure.

4.1.1.6.3 Patients with T1-2 N0-1 tonsillar cancer without soft palate extension and base of tongue extension should receive ipsilateral radiotherapy if there is no radiographic evidence of extracapsular extension and no involved nodes on the contralateral side.

4.1.1.6.4 Patients with T1-2 N2a-b tonsillar cancer without soft palate extension and base of tongue extension, without radiographic evidence of ECE, and without contralateral involved

nodes, may receive ipsilateral radiotherapy only after discussion with Principal Investigator Dr. Sher.

4.1.1.6.5 Patients requiring an emergent tracheostomy will have levels IV and VI covered, and the tracheostomy site should be included in the 40 Gy (pCTV40). The tracheostomy site may be included in the 64 Gy volume (pCTV1) at the discretion of the treating physician.

4.1.1.6.6 If a suspicious node is seen in a level below an untreated level, the intervening level is included in the 40 Gy volume. For example, if level 4 includes a suspicious node but level 3 was not otherwise being treated, level 3 should be included in the 40 Gy volume.

4.1.1.7 Dose prescription

Structure	Description	1st course dose (20 fractions)	2nd course dose (15 fractions)	Total dose (35 fractions)
Primary tumor	Gross primary disease	40 Gy	30 Gy	70 Gy
Elective primary volume	Microscopic disease around primary tumor	40 Gy	24 Gy	64 Gy
Involved lymph nodes	Gross nodal disease	40 Gy	30 Gy	70 Gy
Suspicious lymph nodes	Lymph nodes of possible malignant potential	40 Gy	24 Gy	64 Gy
Elective lymph nodes	Regions of microscopic nodal disease	40 Gy	0 Gy	40 Gy
Prescribed volumes under special conditions				
Tonsil resection bed, high-risk	Resected tonsillar fossa with close or positive margins	40 Gy	24 Gy	64 Gy
Tonsil resection bed, low-risk	Resected tonsillar fossa with negative margins	40 Gy	0 Gy	40 Gy
Lymph node excision bed, high-risk	Resected lymph node bed with ECE	40 Gy	24 Gy	64 Gy
Lymph node excision bed, low-risk	Resected lymph node bed without ECE	40 Gy	0 Gy	40 Gy

The radiation treatment will be delivered in two courses.

Course 1: All PTV's receive 40 Gy in 2 Gy fractions.

Course 2: All PTV70 structures (primary and nodes) will then receive 30 Gy in 15 fractions. All PTV64 structures (primary CTV and suspicious nodes) will then receive 24 Gy in 15 fractions.

Summary of prescription doses (expansions for setup error are described in 4.1.1.4 and 4.1.1.5)

Summary of elective nodal volumes (descriptions are described in 4.1.1.4 and 4.1.1.5) [Note: RP = retropharyngeal]

Any lymph node station containing an involved or suspicious node will be included in the 40 Gy volume. The table below describes the treatment levels if that lymph node station is radiologically benign (i.e. no involved or suspicious lymph nodes)

Station	Oropharynx	Larynx	Note
I	Only if oral cavity extension of primary tumor	NEVER	
II	ALWAYS	ALWAYS	Cranial border is subdiagstric node if neck does not have an involved node; otherwise, cranial border is jugular foramen Lateralized tonsil cancers may undergo ipsilateral RT per 4.1.1.6.3 and 4.1.1.6.4
III	Only if level II includes an involved node	ALWAYS	
IV	Only if level III includes an involved node	Only if level III includes an involved node, there is subglottic extension, or emergency tracheostomy	
V	Only if 2 levels of the neck include involved nodes	Only if 2 levels of the neck include involved nodes	Both Va and Vb are included in the volume
VI	NEVER	Subglottic extension, or emergency tracheostomy	
RP	Only if level II includes an involved node	NEVER	If there is an involved RP node, bilateral RP stations are treated

4.1.1.8 Treatment planning

Radiotherapy must be delivered using intensity modulated radiation therapy (IMRT). The IMRT may be implemented using any delivery platform, including volumetric modulated arc therapy (VMAT), step and shoot IMRT, or helical tomotherapy (HT).

4.1.8.1 Coverage constraints

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

At least 99% of the volume of each PTV should receive 95% of the dose (i.e. V95 $\geq$ 99%).

The dose should not exceed 77 Gy anywhere in the plan.

4.1.8.2 OAR constraints

MANDATORY:
Spinal cord: maximum point dose 45 Gy
Spinal cord + 5 mm: maximum point dose < 54 Gy
Brainstem: maximum point dose 54 Gy
Brainstem + 5 mm: maximum point dose 60 Gy

RECOMMENDED:
Contralateral parotid: mean < 15 Gy
Contralateral submandibular gland: mean < 30 Gy
Cochlea: maximum < 40 Gy, mean < 20 Gy
Oral cavity (must be 5 mm from PTV: mean < 20 Gy
Constrictors (should exclude PTV from structure): mean < 20 Gy
Post-arytenoid and cricoid space: mean < 10 Gy
Cervical esophagus: mean < 10 Gy
Ipsilateral superficial parotid: mean < 18 Gy
Larynx (glottic larynx up to hyoid): mean < 20 Gy
Ipsilateral masseter: mean < 20 Gy
Contralateral masseter: mean < 15 Gy
Brachial plexus: max 60 Gy unless in PTV70, where max 66 Gy
Mandible: maximum point dose < 71 Gy, preferably < 66 Gy.
Cerebellum: maximum dose < 45 Gy, mean < 15 Gy
Temporal lobe: maximum dose < 40 Gy. mean < 5 Gy

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

Name	Per protocol	Variation acceptable	Variation unacceptable
pGTV	Not applicable		
pCTV64	Not applicable		
pCTV40	Not applicable		
niGTV70	Not applicable		
nsGTV64	Not applicable		
nCTV40	Not applicable		
PTV70	95% of PTV70 covered by 70 Gy	None	< 95%

	99% of PTV70 covered by 66.5 Gy Max hot spot ≤ 75 Gy	97% of PTV70 covered by 66.5 Gy Max hot spot ≤ 77 Gy	< 97% > 77 Gy
PTV64	95% of PTV64 covered by 64 Gy 99% of PTV64 covered by 60.8 Gy	93% of PTV64 covered by 64 Gy 97% of PTV64 covered by 60.8 Gy	< 93% < 97%
PTV40	95% of PTV40 covered by 40 Gy 99% of PTV40 covered by 38 Gy	93% of PTV40 covered by 40Gy 97% of PTV40 covered by 38 Gy	< 93% < 97%
Cord	≤ 45 Gy	≤ 50 Gy	> 50 Gy
Exp_Cord (Cord+5 mm)	≤ 54 Gy	≤ 56 Gy	≥ 56 Gy
Brainstem	≤ 54 Gy	≤ 57 Gy	> 57
Exp_Brainstem	≤ 60 Gy	None	None
OARS	Description	See Section 4.1.9.2 for constraints	
CL_parotid	Contralateral parotid (defined by site of tumor)		
IL_parotid	Ipsilateral parotid		
IL_sup_parotid	Ipsilateral superficial parotid		
CL_SMG	Contralateral submandibular gland		
IL_SMG	Ipsilateral submandibular gland		
OC	Oral cavity		
Constrictors	Pharyngeal constrictors		
PACS	Post-arytenoid and cricoid space		
Cerv_esoph	Cervical esophagus		
Larynx	Larynx		
Ipsi_mass	Ipsilateral masseter		
CL_mass	Contralateral masseter		
Mandible	Mandible		
R_plexus	Right brachial plexus		
L_plexus	Left brachial plexus		
R_cerebellum	Right cerebellum		
L_cerebellum	Left cerebellum		

4.1.1.9 Treatment fractionation

Patients receiving chemotherapy will receive one fraction per day, 5 days per week, for 35 fractions. Patients receiving cetuximab may be treated with 6 fractions per week, since the original randomized study showing cetuximab leads to a survival benefit allowed this fractionation. Patients who miss more than 1 planned treatment should make up the missed day(s) with a second daily fraction more than 6 hours apart.

Patients receiving conventional radiotherapy alone will receive one fraction per day, 5 days per week, for 35 fractions (33 fractions if T1). Patients who miss

more than 1 planned treatment should make up the missed day(s) with a second daily fraction more than 6 hours apart.

Patients treated with accelerated radiotherapy with receive 6 fractions per week, for 35 fractions. The second daily fraction should be 6 hours or more after the first fraction. Patients who miss more than 1 planned treatment should make up the missed day(s) with a second daily fraction more than 6 hours apart.

Patient with a total treatment time 1-5 days beyond prescribed is an acceptable variation, and more than 5 days break is an unacceptable variation. The reasons for treatment break must be documented.

4.1.1.10 Treatment delivery

Daily CBCT (cone-beam CT) or megavoltage CT must be used for patient set-up.

4.1.1.11 Re-planning

If a patient loses a significant amount of weight on treatment, or the tumor contour changes substantially, repeat CT simulation and planning is allowed. However, the gross tumor volume may not be reduced due to tumor shrinkage. The original extent of disease must be included in the replanned GTV.

4.1.1.12 Documentation and quality assurance

Every CT simulation scan with target and normal structures, as well as the radiation treatment plan, will be reviewed by Principal Investigator Dr. David Sher within 3 fractions of the initiation of treatment.

4.1.2 Drug therapy

Concurrent systemic therapy will be implemented per Section 4.1. The specific agent is at physician discretion, choosing between cisplatin (bolus or weekly), cetuximab, and carboplatin-paclitaxel. All of these regimens are NCCN-endorsed, and so there is no reason to expect that the effective elective dose would be meaningfully different among them; because the side effect profiles are so different, it is important to allow investigator discretion for each individual patient.

4.1.2.1 Systemic therapy regimens

4.1.2.1.1 Bolus cisplatin (every 3 weeks)

4.1.2.1.2 Weekly cisplatin

4.1.2.1.3 Weekly cetuximab

4.1.2.1.4 Weekly carboplatin and paclitaxel

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. Dose adjustments should be made according to the system showing the greatest degree of toxicity

4.2.1 Radiation therapy

The dose constraints for radiation therapy are described in 4.1.1.9. No alterations in treatment doses are allowable per protocol.

4.2.2 Systemic therapy

The dose modifications for each systemic agent should be performed per the standard-of-care at each local treating facility. Each regimen is considered a national standard-of-care per NCCN guidelines.

4.2 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
- Antidiarrheals
- Nutritional supplementation
- Anti-depressants

The use of anti-oxidant vitamins is prohibited

4.3 Other Modalities or Procedures

Gastrostomy tubes are optional for patients on this study.

Physicians should attempt to avoid gastrostomy if patients are receiving radiotherapy alone OR ipsilateral radiotherapy (with or without concurrent systemic therapy).

However, gastrostomy tubes are <u>strongly recommended</u> in the following scenarios:

- More than 10% body weight loss prior to diagnosis (prophylactic)
- Treatment with chemoradiotherapy and BMI < 25 (prophylactic)
- More than 10% body weight loss on treatment (reactive)

The gastrostomy tube should be removed after patients maintain a stable or increasing weight for 2 weeks without enteral supplementation.

4.4 Duration of Therapy

Protocol therapy will end under the following conditions:

- 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".

4.5 Duration of Follow Up

Patients will be followed for 2 years from the completion of treatment.

4.6 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 treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.7 Subject Replacement

Subjects may be replaced in the study if they do not complete radiotherapy. Because this treatment is less intensive than conventional radiotherapy, we do not feel that treatment non-compliance is a risk of the protocol therapy. However, inadequate receipt of treatment may lead to a spuriously high recurrence rate, and therefore these patients may be replaced. Patient replacement must be verified through review of the case by Principal Investigator Dr. Sher

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

5.1.2 Medical history

Complete medical and surgical history

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

5.1.7 Performance status

Performance status evaluated prior to study entry according to Appendix B.

5.1.8 Adverse event assessment

Baseline adverse events will be assessed. See section 6 for Adverse Event monitoring and reporting.

5.1.9 Hematology

5.1.10 Blood and urine draw for correlative studies

See Section 9.0 for details.

5.1.11 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.12 Pregnancy test (for females of child bearing potential)

See section 3.1.6.1 for definition.

5.1.13 Dental evaluation (if patient not edentulous)

5.1.14 Tumor assessment

Patients must have dedicated neck imaging (neck CT with intravenous contrast if not contraindicated; otherwise neck MRI with or without contrast if not contraindicated; otherwise neck CT with contrast), and whole body PET-CT.

5.1.15 Completion of PRO instruments (before treatment)

- EORTC QLQ-30
- EORTC HN35
- MDADI
- EQ-5D

5.2 Procedures During Treatment

5.2.1 During each week of radiotherapy

- Physical exam, vital signs by radiation oncologist
- Assessment of performance status
- Adverse event assessment

5.2.2 During each week of chemotherapy

- Standard procedures per local treating facility

5.3 Time and Events Table

5.3.1 Pre-treatment assessments

Assessments	Time Points
	≤30 days prior to registration
Histological or Cytological Confirmation of Tissue Diagnosis	At any point prior to registration
History and physical with weight and Vital Signs	X
Performance Status	X
Dental evaluation	X
CBC with differential, platelets	X
Serum chemistries	X
Dedicated neck imaging	X (within 60 days of registration)
Whole body PET-CT	X (within 30 days of registration)
Serum pregnancy test (if applicable)	X
Adverse event assessment	X
Patient reported outcome assessment • EORTC QLQ-C30 • EORTC HN35 • MDADI • EQ-5D	X (before treatment)

5.3.2 Assessments during treatment

Assessments	Time points
	Weekly during treatment
History and physical with weight and vital signs	X
Performance Status	X
CBC with differential and platelets	X (if receiving systemic therapy)
Creatinine, ALT and AST, total bilirubin, alkaline phosphatase	X (if receiving systemic therapy)
Adverse event assessment	X

5.3.3 Assessments following treatment

Assessments	Time Points (after treatment)
History and physical with weight and vital signs	X (1, 3, 6, 9, 12, 18, 24 months)
Performance Status	X (1, 3, 6, 9, 12, 18, 24 months)
Adverse event assessment	X (1, 3, 6, 9, 12, 18, 24 months)
PET-CT	X (3 months)
Dedicated neck imaging (CT or MRI)	X (6, 12, 18, 24 months)
Patient reported outcomes • EORTC QLQ-C30 • EORTC HN35 • MDADI • EQ-5D	X (1, 3, 6, 12, 24 months)

5.4 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:

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

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

5.4.3 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);

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

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

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

5.4.8 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;

5.4.9 Lost to follow-up. 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

6.1 Antitumor Effect

Because this protocol is treating known regions of cancer with standard-of-care radiotherapy doses, treatment response is not an endpoint of this study.

Rather, the secondary endpoints involve assessments of locoregional and distant recurrence, which will be defined in this section.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with radiotherapy.

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with radiotherapy.

Local recurrence (LR). Biopsy-proven cancer originating from the primary tumor (i.e. base of tongue, tonsil, soft palate, pharyngeal wall, or larynx).

In-field local recurrence (IFLR). Local recurrence in which the > 50% of the recurrent disease is within the 95% isodose line of the PTV 64.

Elective volume local recurrence (EVLR). Local recurrence that is not an IFLR AND > 50% of the recurrent disease is within the 95% isodose line of the PTV 40.

Out-of-field local recurrence (OFLR). Local recurrence that is not an IFLR or EVLR

Regional recurrence (RR). Biopsy-proven cancer in a lymph node basin above the clavicles.

In-field regional recurrence (IFRR). Regional recurrence in which > 50% of the recurrence disease is within the 95% isodose line of the PTV 70 (or PTV 64 for a suspicious lymph node).

Elective volume regional recurrence (EVRR). Regional recurrence that is not an IFRR and > 50% of the recurrent disease is within the 95% isodose line of the PTV 40.

Out-of-field regional recurrence (OFRR). Regional recurrence that is not a IFRR or EVRR.

Distant metastasis (DM). Recurrent cancer below the clavicles. Biopsy is strongly recommended but not mandated. If biopsy is not obtained, the initiation of anti-cancer therapy is assumed to indicate metastasis, with the date of scan prompting therapy serving as the date of metastasis.

6.1.2 Definition of progression

Local and regional progression require biopsy confirmation, which will be used as the date of progression.

Biopsy confirmation of metastatic disease is strongly preferred, but otherwise consensus clinical opinion based on radiologic and clinical findings is acceptable.

6.1.3 Solitary elective volume regional recurrence (SEVR)

Solitary elective volume regional recurrence (SEVR) is the development of an EVLR, EVRR, or OFRR in the absence of prior or synchronous LR, IFRR, IFRR or DM.

6.1.4 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression (LR, RR, or DM) or death.

6.1.5 Overall survival

Overall survival (PFS) is defined as the duration of time from start of treatment to time of progression (LR, RR, or DM) or death.

6.2 Safety/tolerability

Analyses will be performed for all subjects having received at least one dose of study radiotherapy. The study will use the CTCAE version 4.0 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html).

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update (in drug studies), please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

7.1.1 Contraindications

There are no special contraindications for this study beyond typical contraindications to radiation therapy or chemotherapy (when indicated).

7.1.2 Special Warnings and Precautions for Use

None

7.1.3 Interaction with other medications

None

7.1.4 Adverse Reactions

Head and neck radiotherapy and chemoradiotherapy are associated with many acute and late side effects. Since this study is a de-intensified version of RT and CRT, by definition Adverse Event Monitoring

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. All adverse events after radiation treatment will be captured at the time of radiation oncology follow-up. 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 drug, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

[Inserted from Adverse Event Definitions and Reporting Section – Appendix II of the SCC DSMC Plan]

7.2.1 Definitions

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, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporarily 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.

Adverse Events will be reported as indicated by the appropriate following table (see below).

Acute Adverse Events
Adverse events occurring in the time period from the signing of the informed consent, through 90 days post treatment will be known as acute adverse events. All acute adverse events will be assessed and reported as per below.

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) Version 4.0. 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

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and 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 prolong 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 and/or HRPP

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 treatmen

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) 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 treatment. 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)

All SAE/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/UPIRSOs occurring during the protocol-specified monitoring period 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.

The UTSW study team is responsible for submitting SAEs/UPIRSOs to the SCCC DSMC Coordinator. 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/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 when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the DOT Manager or lead coordinator 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/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: Sandra Morones, Clinical Research Manager 214-645-1477
Written reports to: Department of Radiation Oncology Clinical Research Office The University of Texas Southwestern Medical Center Attention: Sarmistha Sen, Project Manager 2201 Inwood Road Dallas, Texas 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/IRB

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/IRB 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 IRB within 5 working days of PI 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 PI 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/research-administration/irb/assets/policies-combined.pdf.

7.4 Unblinding Procedures

NA

7.5 Stopping Rules

Conditional power (CP) is the probability that the final study result will be statistically significant, given the data observed thus far and a specific assumption about the pattern of the data to be observed in the remainder of the study, such as assuming the original design effect, or the effect estimated from the current data, or under the null hypothesis. Conditional power will be computed when the first 30 patients were followed for 2 years. If the conditional power is less than 50%, the trial will be discontinued.

8.0 DRUG/TREATMENT INFORMATION

8.1 Cisplatin

- Other names for the drug(s): Platinol
- Classification - type of agent: cytotoxic chemotherapy
- Mode of action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.
- Storage and stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.
- Protocol dose: Bolus or weekly
- Preparation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.
- Route of administration for this study: Intravenous
- Incompatibilities: Cisplatin may interact with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided. There is a total loss of cisplatin in 30 minutes at room temperature when mixed with metoclopramide and sodium metabisulphite in concentrations equivalent to those that would be found on mixing with a commercial formulation of metoclopramide. Cisplatin and sodium bisulphite have been known to react chemically. Such antioxidants might inactivate cisplatin before administration if they are present in intravenous fluids.
- Availability: Commercially available
- Side effects: Human toxicity includes nausea, vomiting, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretorytracts. Myelosuppression, often with delayed erythrosuppression, is expected. Please see the package insert for a comprehensive list of adverse events.
- Nursing implications: N/A

8.1.1 Return and Retention of Study Drug

N/A

8.2 Cetuximab

- Other names for the drug(s): Erbitux
- Classification - type of agent: biologic
- Mode of action: Unknown. Binds to the EGFR receptor (epidermal growth factor receptor)
- Storage and stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.
- Protocol dose: Loading and then weekly
- Preparation: Cetuximab must not be administered as an iv push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter. Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE. Cetuximab can be administered via infusion pump or syringe pump.
- Route of administration for this study: Intravenous
- Incompatibilities: It should not be mixed with any other compounds.
- Availability: Commercially available
- Side effects: Cetuximab may be associated with significant toxicities, most commonly fatigue, skin rash/folliculitis and paronychia, and gastrointestinal effects, nausea and diarrhea. Hypomagnesia is common. Of greatest concern is the potential for an allergic reaction, possibly anaphylaxis. Please see the package insert for a comprehensive list of adverse events.
- Nursing implications: N/A

8.2.1 Return and Retention of Study Drug

N/A

8.3 Paclitaxel

- Other names for the drug(s): Taxol
- Classification - type of agent: cytotoxic chemotherapy
- Mode of action: Microtubule inhibitor

- Storage and stability: All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours. Paclitaxel vials should be stored between 2°-25°C (36°-77°F).

- Protocol dose: Weekly

- Preparation: Paclitaxel is a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial); 100 mg/16.7ml vial; or 300 mg/50 ml vial, in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D5W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. **Note**: Formation of a small number of fibers in solution (acceptable limits established by the USP Particular Matter Test for LVP's) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the *i.v.* fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

- Route of administration for this study: Intravenous

- Incompatibilities: Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Prior administration of cisplatin may increase myelosuppression because of reduced clearance of paclitaxel. Ketoconazole, verapamil, diltiazem, quinidine, dexamethasone, teniposide, etoposide, vincristine, and cyclosporine may inhibit paclitaxel metabolism, based on in vitro data.

- Availability: Commercially available

- Side effects:
    - Hematologic: neutropenia, leukopenia, thrombocytopenia, anemia
    - Gastrointestinal: nausea/vomiting, diarrhea, mucositis
    - Hepatic: elevated liver function tests
    - Cardiac: heart block, bradycardia
    - Neurologic: peripheral neuropathy, arthralgia/myalgia
    - Dermatologic: alopecia, onycholysis
    - Reproductive: Infertility; may be teratogen
    - Miscellaneous: moderate–severe hypersensitivity reactions, flushing, rash, dyspnea, fatigue

- Nursing implications: N/A

8.3.1 Return and Retention of Study Drug

N/A

8.4 Carboplatin

- Other names for the drug(s): Paraplatin
- Classification - type of agent: cytotoxic chemotherapy
- Mode of action: Second generation tetravalent organic platinum compound. Like cisplatin, carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Cell-cycle nonspecific.
- Storage and stability: Store the unopened vials at controlled room temperature 15° - 30°C (59°-86°F). Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.
- Protocol dose: Weekly
- Preparation: Add 5, 15, or 45 ml sterile water, normal saline, or 5% dextrose to the 50, 150, or 450 mg vial, respectively. The resulting solution contains 10 mg/ml. The desired dose is further diluted, usually in 5% dextrose.
- Route of administration for this study: Intravenous
- Incompatibilities: General: Needles or intravenous administration sets containing aluminum parts that may come in contact with paraplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.
- Availability: Commercially available
- Side effects:
    - *Hematologic*: Thrombocytopenia, neutropenia, leukopenia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.
    - *Gastrointestinal*: Nausea and vomiting (less severe than with cisplatin), treatable with moderate doses of antiemetics.
    - *Dermatologic*: Rash, urticaria.
    - *Hepatic*: Abnormal liver function tests, usually reversible with standard doses.
    - *Neurologic*: Rarely peripheral neuropathy.
    - *Renal:* Elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).
    - *Other*: Pain, asthenia.
        - Miscellaneous: moderate–severe hypersensitivity reactions, flushing, rash, dyspnea, fatigue
- Nursing implications: N/A

8.4.1 Return and Retention of Study Drug

N/A

9.0 CORRELATIVES/SPECIAL STUDIES

9.1 Specimen Banking

Subject samples collected for this study (blood, urine and biopsy tissue) will be retained at UT Southwestern according to approved UTSW protocol 11210: Tissue Procurement and Outcome Collection for Radiotherapy Treated Patients.

Collaborating institutions will be encouraged to collect the same specimens per local institutional protocols, but that will not be paid for by UTSW or this study.

If funding ultimately becomes available, we will perform genomic studies on these specimens to assess their ability to predict survival, local, and distant recurrence.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

10.1.1 Primary endpoint: 2-year crude risk of solitary elective volume recurrence (SEVR).

10.1.2 Secondary endpoints:

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

10.1.2.1.1 EORTC QLQ-C30 Summary score
10.1.2.1.2 EORTC QLQ-C30 Physical and role functioning subscales
10.1.2.1.3 EORTC HN35 Dry mouth and sticky saliva subscales
10.1.2.1.4 MDADI global, emotional, functional and physical subscales
10.1.2.1.5 EQ-5D global score (0-100)

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 Prevalence of gastrostomy-dependence at 3, 6, 12 and 24 months from the end of treatment.

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

10.1.2.5 Overall survival probability at 2 years from the start of treatment

10.1.2.6 Progression-free survival probability at 2 years from the start of treatment

10.1.2.7 Cumulative incidence of locoregional recurrence at 2 years, with death as a competing risk

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

10.2 Stopping rule

Conditional power (CP) is the probability that the final study result will be statistically significant, given the data observed thus far and a specific assumption about the pattern of the data to be observed in the remainder of the study, such as assuming the original design effect, or the effect estimated from the current data, or under the null hypothesis. Conditional power will be computed when the first 30 patients were followed for 2 years. If the conditional power is less than 50%, the trial will be discontinued.

10.3 Sample Size and Accrual

The primary hypothesis is that the risk of elective or out-of-field failure (i.e. in largely unirradiated tissue) is less than 10% more than the baseline risk. As a general rule, the 10% threshold is used as a reason to irradiate a given region, which is why we chose this number. A sample size of 60 achieves a 90% power to detect a non-inferiority difference of 0.1 using a one-sided exact test with a significance level (alpha) of 0.5. These results assume a baseline risk of 0.03 and that the actual difference is 0.0

Note that patients who develop recurrent disease that is not SEVR are not censored, since those patients would not have benefitted from dose to the elective regions (since they failed elsewhere, regardless). The same logic holds for patients who die. Thus, the only patients who need to be replaced are those who are lost to follow-up so there is no 2-year endpoint. With the conservative assumption of 10% loss to follow-up, the final sample size will be 67 patients.

10.4 Data Analyses

10.3.1 Primary endpoint (SEVR)

The crude risk of 2-year solitary elective volume recurrence will be calculated among all patients who are followed for at least 2 years. Patients who die before 2 years without an SEVR will be included in the denominator. A binomial 95% confidence interval will be calculated.

10.3.1.1 Comparison of SEVR risks by p16 status and anatomic site

Given the recognized difference in locoregional recurrence risk and survival between patients with p16-positive oropharyngeal cancer with p16-negative oropharyngeal cancer, we will perform several analyses on the risk of SEVR as a function of p16 status, as well as by anatomic site of origin. These comparisons will be important to confirm that the risk of solitary elective recurrence does not vary by histology or disease site. In addition to using SEVR as the endpoint, we will also include any elective volume recurrence as the outcome. These comparisons will include:

- p16-positive versus p16-negative OPC
- p16-positive, minimal smokers ($\leq$ 10 pack-year) versus p16-positive smokers and p16-negative OPC

- OPC versus larynx site

10.3.2 Secondary endpoints

10.3.2.1 Patient reported outcomes

Each of the patient reported outcomes are single numeric scores that are collected at baseline, 1, 3, 6, 12, and 24 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).

10.3.2.2 Toxicity

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.

10.3.2.3 Gastrostomy dependence

The prevalence of gastrostomy use at 3, 6, 12 and 24 months will be described. Predictors of gastrostomy-dependence will be determined using multivariable logistic regression.

10.3.2.4 Patient utilities

The average patient utilities (derived from EQ-5D) at baseline, 3, 6, 12 and 24 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 grade2-3 xerostomia and grade 2-3 dysphagia, to produce an estimate of the utility decrement from this toxicity.

10.3.2.5 Overall survival

Overall survival outcomes will be estimated using the Kaplan-Meier approach. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for key covariates of interest, including age, T and N stage, and smoking status. Overall survival will be calculated from the initiation of treatment.

10.3.6 Progression-free survival

Progression-free survival outcomes will be estimated using the Kaplan-Meier approach. The Cox proportional hazard regression model will be used to determine hazard ratios and 95% confidence intervals for key covariates of interest, including age, T and N stage, and smoking status. Progression-free survival will be calculated from the initiation of treatment.

10.3.7 Locoregional recurrence and distant metastasis

The cumulative incidence of locoregional and distant failure will be estimated using cumulative incidence statistics, with death serving as the competing risk. A comparison of these endpoints will be performed using Gray's test.

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.

11.3 Required Documentation (for multi-site studies)

Before the study can be initiated at any site, the following documentation must be provided to the research office.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federal-wide Assurance letter
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if {institution} holds the IND. Otherwise, the affiliate Investigator's signature on the protocol is sufficient to ensure compliance)
- A copy of the IRB-approved consent form
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.4 Registration/Randomization Procedures

All subjects must be registered with through RedCap before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Study Coordinator. To register a subject, call (214) 648-1821 Monday through Friday, 9:00AM-5:00PM.

Research staff from all participating sites 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
02: Rush

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. The third patient consented and second enrolled at Rush will have the number 02-003-002.

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 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 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

Other institutions participating in this trial as sub-sites will be expected to enter data into REDCap and upload de-identified source materials when instructed by the Simmons Cancer Center study team to facilitate remote source to case report form verification.

In order to facilitate remote source to case report form verification, the Simmons Comprehensive Cancer Center study team will require other institutions participating in this trial as sub-sites to enter data into the selected EDC system and upload selected de-identified source materials when instructed

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT and/or the CRO Multi-Center IIT Monitor. This review includes but is not limited to accuracy of case report forms, protocol compliance, timeless 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.

For further information, refer to the UTSW SCCC IIT Management Manual.

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 local 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 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.

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 Major Deviations (also called **violations**): include any departure **from IRB-approved** research that:

- Harmed or placed subject(s) or others at risk of harm (i.e., did or has the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of

the study)

➢ **Reporting requirement**: Major deviations must be promptly reported to the IRB within 5 working days of PI awareness.

11.6.4 Minor Deviations: include any departure from IRB-approved research that:

- Did not harm or place subject(s) or others at risk of harm (i.e., did not or did not have the potential to negatively affect the safety, rights, or welfare of subjects or others), or
- Did not affect data quality (e.g., the completeness, accuracy, reliability, or validity of the data) or the science of the research (e.g., the primary outcome/endpoint of the study)

  ➢ **Reporting requirement**: Minor deviations should be tracked and summarized in the progress report at the next IRB continuing review.

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.

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13.0 APPENDICES

Appendix A: AJCC Staging

PRIMARY

Oropharynx
T1 Tumor 2 cm or less in greatest dimension

T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension

T3 Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis

T4a Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*

T4b Very advanced local disease
Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or\ skull base or encases carotid artery *Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

Larynx

Supraglottis
T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following:\ postcricoid area, pre-epiglottic tissues, paraglottic space, and/or inner cortex of thyroid cartilage

T4a Moderately advanced local disease Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis
T1 Tumor limited to the vocal cord(s) [may involve anterior or posterior commissure] with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation, and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a Moderately advanced local disease
Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis
T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation

T4a Moderately advanced local disease
Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx\ (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease
Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

NODE

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension
N2 Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N2a Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastases in a lymph node, more than 6 cm in greatest dimension

STAGE GROUPING

Stage 0
Tis, N0, M0

Stage I
T1, N0, M0

Stage II
T2, N0, M0

Stage III
T3, N0, M0
T1-3, N1, M0

Stage IVA
T4a, N0-1, M0
Any T, N2, M0

Stage IVA
T4a, N0-2, M0
T1-3, N2, MO

Stage IVB
T4b, Any N, MO
Any T, N3, M0

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 C (EORTC QLQ-30)

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

Specimen

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

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Specimen

Appendix D (EORTC HN-35)

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

Specimen

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

specimen

Appendix E: MDADI

The M. D. Anderson Dysphagia Inventory

This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing.

The following statements have been made by people who have problems with their swallowing. Some of the statements may apply to you.

Please read each statement and circle the response which best reflects your experience in the past week.

My swallowing ability limits my day-to-day activities.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

E2. I am embarrassed by my eating habits.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

F1. People have difficulty cooking for me.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P2. Swallowing is more difficult at the end of the day.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

E7. I do not feel self-conscious when I eat.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

E4. I am upset by my swallowing problem.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P6. Swallowing takes great effort.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

E5. I do not go out because of my swallowing problem.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

F5. My swallowing difficulty has caused me to lose income.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P7. It takes me longer to eat because of my swallowing problem.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P3. People ask me, "Why can't you eat that?"

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

E3. Other people are irritated by my eating problem.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P8. I cough when I try to drink liquids.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

F3. My swallowing problems limit my social and personal life.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

F2. I feel free to go out to eat with my friends, neighbors, and relatives.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P5. I limit my food intake because of my swallowing difficulty.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P1. I cannot maintain my weight because of my swallowing problem.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

E6. I have low self-esteem because of my swallowing problem.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

P4. I feel that I am swallowing a huge amount of food.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

F4. I feel excluded because of my eating habits.

Strongly Agree | Agree | No Opinion | Disagree | Strongly Disagree

Thank you for completing this questionnaire!

Appendix F: 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 ❑

Patient ID: _____
Date: ___/___/____

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

YOUR HEALTH TODAY = ☐