NRG ONCOLOGY

RTOG 1016

PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Research Foundation, Inc.; and SWOG.

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PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER

Protocol Agents (10/17/13)

Agent	Supply	NSC #	IND #
Cisplatin	Commercial	N/A	Exempt
Cetuximab	Commercial	N/A	Exempt

Participating Sites (10/17/13)

☐ US Only
☐ Canada Only
☒ US and Canada
☒ Approved International Member Sites

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PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER

CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (2/23/16)		
To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to Section 5.0 of the protocol for instructions on using the OPEN system. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19103 Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' web site is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility or treatment-related questions Contact the Study PI of the Lead Protocol Organization.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' web site https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU web site is located at https://www.ctsu.org		

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NRG ONCOLOGY

RTOG 1016

Phase III Trial of Radiotherapy Plus Cetuximab versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer

SCHEMA (6/25/13)

			T Stage		
			1. T1-2		
R		**S**	2. T3-4	**R**	**Arm 1 (Control)**:
E		**T**	**N Stage**	**A**	Accelerated IMRT, 70 Gy for 6 weeks
G	**Mandatory p16**	**R**	1. N0-2a	**N**	+ high dose DDP (100 mg/m^2) Days 1 and 22
I	**analysis**	**A**	2. N2b-3	**D**	(Total: 200 mg/m^2)
S		**T**	**Zubrod**	**O**	
T		**I**	**Performance**	**M**	**Arm 2**: Accelerated IMRT, 70 Gy for 6 weeks
E		**F**	**Status**	**I**	+ cetuximab (400 mg/m^2)
R		**Y**	1. 0	**Z**	loading dose pre-IMRT, then
			2. 1	**E**	250 mg/m^2 weekly during IMRT,
			Smoking History		and for 1 week after IMRT for a total
			1. ≤ 10 pack-years		of 8 doses of cetuximab
			2. > 10 pack-years		

Patients must be positive for p16, determined by the Innovation Center CLIA lab at The Ohio State University (OSU) prior to Step 2 registration (randomization); see 10.2 for details of tissue submission. Patients must consent to submission of tissue for this analysis. Patients also must consent to provide their smoking history by completing that portion of the computer-assisted self interview (CASI) head and neck risk factor survey tool.

For this study, IMRT is mandatory. IGRT credentialing is mandatory when using PTV margins < 5 mm. See Section 5.0 for required pre-registration credentialing for IMRT (and for IGRT, if used for margin reduction).

Patient Population: (See Section 3.0 for Eligibility)
Squamous cell carcinoma of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls); stage T1-2, N2a-3, or T3-4 any N; patient tumor must be p16 positive

(10/17/13) Required Sample Size: **834**

ELIGIBILITY CHECKLIST – STEP 1
(page 1 of 5)

NRG Oncology Institution #
RTOG 1016
Case #

_____ (Y) 1. Is there pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma (including the histological variants papillary squamous cell carcinoma and basaloid squamous cell carcinoma) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls)? **Note**: Cytologic diagnosis from a cervical lymph node (from a paraffin block, not from smears) is sufficient in the presence of clinical evidence of a primary tumor in the oropharynx. Clinical evidence should be documented, may consist of palpation, imaging, or endoscopic evaluation, and should be sufficient to estimate the size of the primary (for T stage).

_____(Y) 2. Does the patient have clinically or radiographically evident measurable disease at the primary site or at nodal stations? (Tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site. Limited neck dissections retrieving ≤ 4 nodes are permitted and considered as non-therapeutic nodal excisions. Fine needle aspirations of the neck are insufficient due to limited tissue for central review. Biopsy specimens from the primary or nodes measuring at least 3mm-5mm are required).

_____(Y) 3. Does the patient have clinical stage T1-2, N2a-N3 or T3-4, any N including no distant metastasis?

_____(Y) 4. Was a general history and physical examination performed by a radiation oncologist and medical oncologist within 8 weeks prior to registration?

_____(Y) 5. Was the patient examined by an ENT or head and neck surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 8 weeks prior to registration?

_____(Y) 6. Was the imaging specified in Section 3.1.4.3 performed within 8 weeks prior to registration?

_____(Y) 7. Was the patient's Zubrod Performance Status 0-1 within 2 weeks prior to registration?

_____(Y) 8. Is the patient ≥ 18 years of age?

_____(Y) 9. Does the patient have adequate bone marrow, hepatic, and renal function as specified in Section 3.1?

_____(Y) 10. Has the patient agreed to provide their smoking history via the computer-assisted self interview (CASI) head and neck risk factor survey?

_____(Y) 11. For women of childbearing potential, was a serum pregnancy test completed within 2 weeks of registration?

_____(Y) If yes, was the serum pregnancy test negative?

___(Y/NA) 12. If a woman of child bearing potential or sexually active male, is the patient willing to use effective contraception throughout their participation in the treatment phase of the study and at least 60 days following the last study treatment?

Continued on next page

NRG Oncology Institution #
RTOG 1016
Case #

_____(Y) 13. If the patient is HIV positive, does the patient have no prior AIDS-defining illness and have CD4 cells of at least 350/mm^3?

_____(Y) 14. Did the patient provide study specific informed consent prior to study entry, including consent for mandatory submission of tissue for required, central p16 review and consent to participate in the computer-assisted self interview (CASI) survey questions regarding smoking history?

_____(N) 15. Does the patient have cancer considered to be from an oral cavity site (oral tongue, floor mouth, alveolar ridge, buccal or lip) nasopharynx, hypopharynx, or larynx?

_____(N) 16. Does the patient have a carcinoma of the neck of unknown primary origin?

_____(N) 17. Does the patient have Stage T1-2, N0-1 cancer?

_____(N) 18. Does the patient have distant metastasis or adenopathy below the clavicles?

_____(N) 19. Was a gross total excision of both primary and nodal disease performed? (This includes tonsillectomy, local excision of primary site and nodal excision that remove all clinically and radiographically evident disease).

_____(N) 20. Does the patient have simultaneous primaries or bilateral tumors?

_____(N) 21. Does the patient have prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years?

_____(N) 22. Did the patient have prior systemic chemotherapy for the study cancer? (prior chemotherapy for a different cancer is allowable).

_____(N) 23. Did the patient have prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

_____(N) 24. Does the patient have any of the severe, active co-morbidities specified in Section 3.2?

_____(N) 25. Does the patient have a prior allergic reaction to cisplatin or cetuximab?

_____(N) 26. Has the patient received prior cetuximab or other anti-EGFR therapy?

<u>The following questions will be asked at Study Registration</u>:
CREDENTIALING for IMRT (and IGRT, if used) IS REQUIRED BEFORE REGISTRATION.

_____ 1. Institutional person randomizing case.

Continued on next page

NRG Oncology Institution #
RTOG 1016
Case #

_____(Y)	2.	Has the Eligibility Checklist been completed?
_____(Y)	3.	In the opinion of the investigator, is the patient eligible?
_____	4.	Date informed consent signed
_____	5.	Patient Initials (First Middle Last)
_____	6.	Verifying Physician
_____	7.	Patient ID
_____	8.	Date of Birth
_____	9.	Race
_____	10.	Ethnicity
_____	11.	Gender
_____	12.	Country of Residence
_____	13.	Zip Code (U.S. Residents)
_____	14.	Method of Payment
_____	15.	Any care at a VA or Military Hospital?
_____	16.	Calendar Base Date
_____	17.	Randomization date
_____	18.	Medical Oncologist's name
_____(Y/N)	19.	Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?
_____(Y/N)	20.	Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?
_____(Y/N)	21.	Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?
_____(Y/N)	22.	Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Continued on next page

NRG Oncology Institution #
RTOG 1016
Case #

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____(Y/N) 24. Did the patient agree to complete the entire computer-assisted self interview (CASI) survey (not just the required smoking history portion) at baseline?

_____(Y/N) 25. Did the patient agree to complete the demographic work status questionnaire at baseline?

_____ 26 Specify T stage (T1-2 vs. T3-4)

_____ 27. Specify N stage (N0-2a vs. N2b-3)

_____ 28. Zubrod performance status (0 vs. 1)

The patient's smoking history for stratification will be provided to NRG Oncology by the required completion of the computer-assisted self interview (CASI) head and neck risk factor survey by the patient (see Section 3.1.10).

_____(Y/N) 29. Will IGRT be used for patient positioning?

_____(Y/N) 30. Will IGRT be used for patient positioning and margin reduction?

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

ELIGIBILITY CHECKLIST –STEP 2 (10/17/13)
(page 5 of 5)

NRG Oncology Institution #
RTOG 1016
Case #
(assigned for Step 1)

_____ 1. Institutional person randomizing case

_____(Y/N) 2. Is the patient able to continue protocol treatment?

_____ 3. If no, specify the reason the patient cannot continue to Step 2:
1) progression of disease;
2) patient is not p16 positive;
3) patient refusal;
4) physician preference;
5) failure to submit tissue assay;
6) other

_____ Specify the reason the patient cannot continue to Step 2.

_____ 4. Patient's Initials

_____ 5. Verifying Physician

_____ 6. Patient's ID number

_____ 7. Calendar Base Date (for Step 2)

_____ 8. Randomization date: (for Step 2)

_____ (Y/N) 9. Is the patient positive for p16 (determined by the OSU Innovative Center CLIA lab)?

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Background

1.1.1 Oropharynx Cancer: Current State of Practice and Purpose of This Trial

Non-operative management of oropharynx cancer has become the preferred approach over the last decade (NCCN). Advances in combining systemic therapy and radiation technology have been associated with improved survival and declining use of surgery, although at the cost of increased acute and late toxicity burden (GORTEC; TAME; RTOG 0129). The extent to which improved outcomes are attributable to advances in therapy or shifts in the biology and etiology of oropharynx carcinoma is now under intense scrutiny (Gillison 2010). The recent recognition and rapid rise in the incidence of human papilloma virus-associated carcinoma of the oropharynx has prompted a re-evaluation of past trial outcomes and a call for HPV-specific studies to rigorously evaluate new prognostic factors and new treatment approaches with less morbidity.

The overall goal of this trial is to identify a less toxic approach in HPV-associated cancer of the oropharynx with the high survival currently associated with aggressive chemoradiation approaches. We aim to show that targeted bioradiation will substantially reduce the burden of acute toxicity, result in faster recovery and return to function, carry lower rates of late effects, with similar rates of long-term survivorship, compared to conventional chemoradiation.

Acknowledgments: Clinical aspects of the present study design were informed by numerous investigators in the head and neck research community who participated in discussions conducted by the NCI Previously Untreated Locally-Advanced Task Force (PULA) (a subcommittee of the NCI H&N Steering Committee) led by Drs. David Adelstein and Drew Ridge, as well as contributions form the Quality of Life (QOL)/Toxicity Working Group led by Jolie Ringash under the direction of PULA. The translational objectives and biospecimen selections were informed by numerous investigators who participated in discussions conducted by the NCI Head and Neck Tumor Biology and Imaging Task Force lead by Drs. John Waldron and Thomas Carey.

1.1.2 Lessons from Past Phase III Trials

Altered fractionation in radiation therapy (RT) alone has been shown to improve local-regional control (LRC) with small impact on survival. Concurrent chemoradiation became standard of care with larger gain in survival (meta-analysis). RTOG 0129 compared once a day RT with accelerated RT plus chemotherapy. There was not a difference in tumor control or survival outcomes. While the role of fractionation in the chemotherapy setting has not been fully settled, this trial suggests that accelerated RT can be traded for 1 dose of cisplatin to effectively offset tumor repopulation. When considering all head and neck cancer sites, randomized clinical trials investigating primary radiotherapy alone have demonstrated that hyperfractionation with either accelerated or concomitant boost primary radiation therapy improved local-regional control in comparison to standard fractionation radiotherapy (Fu 2000). Meta-analyses indicate that these altered fractionation schedules may translate into survival gains (Bourhis 2006). Six-fractions per week (weeks 2-6) is supported by the DAHANCA randomized trial (Overgaard 2003) and has become a common U.S. standard (NCCN H&N Guidelines 2010; http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). This schedule facilitates the application of IMRT using integrated boost planning (dose painting) and has become the most common technique among NRG Oncology centers. This will also be the standard used in RTOG 1016.

With regards to chemoradiation, only a few randomized controlled trials have restricted enrollment to patients with a diagnosis of oropharyngeal cancer, and the majority have compared primary radiotherapy to chemoradiotherapy. A GORTEC trial (94-01) demonstrated improved 5-year overall survival, disease-free survival, and local-regional control with chemoradiotherapy with carboplatin/5-FU compared to standard fractionation radiotherapy (Denis 2004). An Italian 3-arm phase III trial restricted to oropharyngeal cancer patients demonstrated a similar, although non-significant, doubling of overall, relapse-free, and local-regional control with standard fractionation radiotherapy and concomitant carboplatin/5-FU therapy when compared to radiotherapy alone (either standard or hyperfractionated radiotherapy) [Fallai 2006]. Meta-analyses also indicate superior survival for patients when treated with concurrent chemoradiotherapy when compared to standard fractionation

radiotherapy alone, and subgroup analyses indicate patients with oropharyngeal cancer benefit (Pignon 2009). There is an estimated 6.5% absolute benefit in survival at 5-years with concomitant chemotherapy, and the benefit appears superior for platinum monotherapy when compared to other chemotherapy regimens.

1.1.3 Epidermal Signaling, Head and Neck Cancer. and Radiation Response

EGFR is expressed at very high levels in the majority of human head and neck squamous cell carcinoma (SCC). Furthermore, pre-clinical data indicate that it is not merely a 'bystander' but is intimately associated with the malignant phenotype of SCCHN. EGFR activation in response to a ligand (e.g., EGF or TGF-alpha) results in phosphorylation of its intracytoplasmic tyrosine kinase domain, leading to a cascade of signal transduction within the cell. This ultimately leads to DNA synthesis, cell proliferation, anti-apoptosis, and transcription of growth factors such as pro-angiogenic molecules. Blockade of this pathway is an effective anti-neoplastic strategy. Inhibition of EGFR signaling by means of either antibody blockage of EGF binding or small molecule inhibition of the cytoplasmic tyrosine kinase domain has been shown to increase radiation responsiveness in vitro. Extensive clinical data indicate that EGFR over expression is associated with poor overall survival and decreased local-regional control after radiotherapy. A recently completed correlative study in RTOG 90-03 confirmed that EGFR expression, as measured by immunohistochemistry, was higher than the median and was associated with a greater risk of death and local-regional recurrence when compared to tumors with expression at or lower than the median (Chung 2010).

1.1.4 Clinical Trials of Cetuximab and Radiation Therapy

Cetuximab is a humanized monoclonal mouse antibody that binds to the extracellular ligand binding domain of the EGFR, thereby preventing activation and dimerization of the receptor. Cetuximab blockade disrupts EGFR signal transduction and results in inhibition of tumor growth and metastasis in animal models. Cetuximab is FDA approved for therapy of metastatic colon cancer and in combination with radiation therapy for the primary treatment of head and neck cancer.

The efficacy and safety of cetuximab were studied in combination with radiation therapy (RT) in a randomized, controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck versus radiation alone. In a multi-center controlled clinical trial, 424 patients with Stage III-IV SCC of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized 1:1 to receive cetuximab plus radiation therapy (211 patients) or radiation therapy alone (213 patients). Stratification factors were Karnofsky Performance Status (60-80 versus 90-100); nodal stage (N0 versus N+); tumor stage (T1-3 versus T4 using AJCC 1998 staging criteria); and radiation therapy fractionation (concomitant boost versus once-daily versus twice daily). Radiation therapy was administered from 6-7 weeks as once daily, twice daily, or concomitant boost. The planned radiation therapy regimen was chosen by the investigator prior to enrollment. For patients with ≥ N1 neck disease, a post-radiation therapy neck dissection was recommended. Starting 1 week before radiation, cetuximab was administered as a 400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly for the duration of radiation therapy (6-7 weeks). All cetuximab-treated patients received a 20-mg test dose on Day 1. Cetuximab was administered 1 hour prior to radiation therapy, beginning week 2.

Of the 424 randomized patients, 80% were male and 83% were Caucasian. The median age was 57 years (range 34-83). There were 258 patients enrolled in U.S. sites (61%) and 166 patients (39%) in non-U.S. sites. Ninety percent of patients had baseline Karnofsky Performance Status ≥ 80; 60% had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient characteristics were similar across the study arms. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented below:

Table 1; Summary of Endpoints from the Phase III Trial of Radiation +/- Cetuximab

	Cetuximab + Radiation (n = 211)	Radiation Alone (n = 213)	Hazard Ratio (95% CI[3])	Stratified Log-rank p-value
Locoregional control				
Median Duration	24.4 mo	14.0 mo	0.68 (0.52-0.89)	0.005
Overall Survival				
Median duration	49.0 mo	29.3 mo	0.74 (0.57-0.97)	0.03

a CI = confidence interval

These data lead to FDA approval of the combination of cetuximab and radiation therapy for initial therapy of patients with local-regionally advanced head and neck cancer (Bonner 2004).

Cetuximab appears to have less toxicity than high dose cisplatin. In the phase III study of cetuximab and radiotherapy for locally advanced non-operative SCCHN, 93% of patients received the prescribed cetuximab dose, which compares very favorably to the compliance rate of high dose cisplatin in RTOG 95-01 (61%) [Bonner 2006]. Furthermore, the Bonner study showed no evidence that cetuximab increased the rate of ≥ Grade 3 mucositis or dysphagia, no evidence of an increased rate of late effects, and no evidence of a worsening of quality of life (QOL) relative to RT alone. This is in contrast to the literature with concurrent platinum-based chemoradiotherapy, which suggests that certain long-term side effects such as feeding tube dependence are greatly increased relative to RT alone.

Updated results with 5-year survival were recently reported and demonstrated 5-year survival of 45.6% in the cetuximab plus radiotherapy group versus 36.4% in the radiotherapy alone group (Bonner 2010). An analysis of associations between patient and tumor factors and overall survival was performed and offers some potential insight regarding patient selection. Patients with oropharyngeal primary tumors, early T stage, advanced N stage, high Karnofsky performance status, male gender, and young age demonstrated benefit from the addition of cetuximab to radiation. Concomitant boost radiotherapy also was associated with improved survival, whereas response appeared independent of EGFR expression. It has been noted that many of these patient and clinical factors also are associated with a diagnosis of an HPV-associated head and neck cancer, supporting a hypothesis that cetuximab may be preferentially beneficial to this group of patients. However, tumor specimens are not available for HPV determination in this trial, so a direct testing of this hypothesis is not possible. Furthermore, data indicate a paradoxical inverse association between HPV presence and EGFR expression and that EGFR expression may be associated with poor local-regional control only in the HPV-negative patient population (Hong 2010)

RTOG 0522, comparing accelerated RT and cisplatin with or without cetuximab, completed accrual in early 2009. Results expected in 2011 should clarify the role of cetuximab in the chemoradiation setting. Approximately 70% of the patients in this trial had cancers of oropharynx origin. Approximately 70% of those are anticipated to be HPV-associated (approximately 440 patients). RTOG 0522 did not include prospective HPV testing and is not expected to lead to a clear answer regarding best management in the HPV subset.

The Bonner study is not the only data in support of cetuximab as a valuable treatment against head and neck cancer. In platinum-refractory recurrent/metastatic SCCHN, cetuximab has a response rate of approximately 11% (Vermorken 2007), providing further clinical evidence that it is working via a pathway (or pathways) distinct from DNA damaging agents such as platins or RT. In first-line therapy for recurrent/metastatic SCCHN, the addition of cetuximab to 5-FU/platinum significantly improved overall survival (Vermorken 2008).

The EXTREME study (Vermorken 2008) was the first randomized study to demonstrate a benefit in overall survival (10.1 vs. 7.4 months, HR=0.797, p=0.036) with a molecular-targeted therapy added to the classical platinum plus fluorouracil combination in the first-line treatment of recurrent and/or metastatic SCCHN. Two hundred twenty-two patients in the control arm received 6 cycles of cisplatin or carboplatin plus fluorouracil, while 220 patients in the experimental arm received platinum and fluorouracil at the same doses in combination with weekly cetuximab. In this latter arm, patients could receive maintenance cetuximab alone for 6 months after completion of the 6 treatment cycles with chemotherapy. Grade 3 or 4 adverse events were encountered in 76% of patients in the control arm versus 82% of patients of patients in the experimental arm (p=0.19). Bone marrow toxicity was more common in the control arm, whereas the addition of cetuximab to platinum and fluorouracil resulted in slightly more frequent hypomagnesemia, sepsis, vomiting, diarrhea, and acne-like rash. Ten deaths (3 in the cetuximab group and 7 in the chemotherapy-alone group) were considered by the investigators to be treatment related.

1.1.5 Human Papillomavirus and Head and Neck Cancer

In 2007, a panel of experts convened by the International Agency for Research on Cancer reviewed data on the relationship between HPV and head and neck cancer and concluded that HPV is a cause of oropharynx and possibly oral cavity cancer (IARC Monographs 2007). HPV-associated cancers have been shown to be distinct from HPV-negative cancers with regard to risk factor profiles (Gillison 2008), clinical and molecular characteristics (Gillison 2000), treatment response and prognosis (reviewed in Lassen 2010). HPV-associated cancers arise from the lingual and palatine tonsils within the oropharynx, are poorly differentiated and present with early T stage and advanced N stage. When compared to patients with HPV-negative tumors, patients with HPV-positive tumors are more frequently male, young, and with good performance status (Ang 2010). First reported by Gillison and colleagues to be associated with survival (Gillison 2000), a meta-analysis of retrospective studies reported that patients with HPV-positive status oropharynx cancers had an estimated 50% reduction in risk of death when compared to patients with HPV-negative tumors (Ragin 2007).

1.1.6 Secondary Analysis of HPV in Clinical Trials

More recently, secondary analyses of several prospective multicenter clinical trials have confirmed tumor HPV status to be an important predictor of prognosis for patients with head and neck squamous cell carcinoma (Table 2).

In the only trial to date to prospectively evaluate the effect of tumor HPV status on survival outcomes, ECOG investigators reported that response rates to an induction regimen of paclitaxel and carboplatin were higher for HPV-positive than HPV-negative patients (Fahkry 2008). Chemoradiation with weekly paclitaxel and standard fractionation radiotherapy to 70 Gy was administered after induction. After a median follow up of approximately 40 months, both progression-free (PFS) and overall survival (OS) were superior for the HPV-positive patients. In the analysis restricted to the oropharynx patients, patients with HPV-positive tumors had less than half the risk of death when compared to HPV-negative patients; however, adjustment was made only for performance status due to small sample size. University of Michigan investigators so reported higher response rates to a single cycle of cisplatin and 5-FU among HPV-positive patients when compared to HPV-negative patients. After concurrent chemoradiation with high-dose cisplatin and standard fractionation radiotherapy to 70 Gy, patients with HPV-positive tumors had improved OS and disease-specific survival, but the sample size was insufficient for adjustment for other prognostic factors (Worden 2008). In a DAHANCA 5 trial in which patients with stage I-IV pharyngeal cancer were treated with standard fractionation radiation therapy to 66-68 GY, p16 positive tumors (as surrogate for tumor HPV status) had improved local-regional control (LRC) and disease-free survival after adjustment for tumor and nodal stage (Lassen 2009). A phase III trial in which patients were randomized to chemoradiation with cisplatin plus or minus tirapazamine observed improved 2-year overall and failure-free survival in oropharynx patients with p16 positive tumors. There was a trend toward improved local-regional control with the addition of tirapazamine for p16-negative patients (Rischin2010). A previously reported DAHANCA analysis similarly suggested a differential response to the hypoxic radiosensitizer nimorazole in favor of the p16 negative patient, but the sample size for the p16 positive subset was small and many p16 positive tumors were non-oropharyngeal primary tumors in this analysis (Lassen 2010). From these analyses it can be concluded that HPV-positive tumors have higher response rates to platinum-

based induction chemotherapy, radiation alone, or chemoradiation and that the survival difference between HPV-positive and negative patients observed in prospective analyses is similar to that observed in retrospective case series. Additionally, the improved survival among HPV-positive patients appears to be independent of the specific treatment approach, as long as the approach is within the standard of care. However, all of these trials were of insufficient size to demonstrate that the improved survival for the HPV-positive patient is independent of other important prognostic factors, including smoking.

Table 2: Tumor HPV Status and Survival Outcomes in Reported Prospective Clinical Trials

Author and Co-operative Grp	N	XRT	Induction	Concurrent	Median F/U	HPV+	Time	HPV+	HPV-	P-value	Hazard Ratio HPV+ vs -
Fakhry ECOG	96	70 Gy	2 cycles paclitaxel 175mg/m2 carbo AUC6	weekly paclitaxel 30mg/m2 x 7	39 mo	40%	2-year	95%	62%	0.005	0.36
Rischin TROG	195	70 Gy	none	cisplatin +/- tirapazamine	27 mo	28%	2-year	94%	77%	0.007	0.29
Gillison RTOG 0129	323	70-72 Gy	none	cisplatin 100mg/m2 x2 or 3	4.8 yrs	64%	3-year	79%	46%	0.002	0.44
Settle TAX324	119	70-74 Gy	3 cycles taxotere 75mg/m2 cisplatin 100mg/m2 5-FU 1000mg/m2/day x 4	weekly carboplatin AUC 1.5 x 7	67 mo	50%	5-year	93%	35%	<0.001	0.2
Lassen DHA NCA5	156	62-68 Gy	none	nimorazale 1200mg/m2/day x 30	>60 mo	22%	5-year	62%	26%	0.003	0.44

NRG Oncology investigators recently reported an analysis of the effect of tumor HPV status on survival outcomes in RTOG 0129 (Ang 2010) in which patients with advanced stage III-IV head and neck cancers (excluding T1, T2-N1 and M1) were randomized to receive accelerated radiation with 2 doses of high-dose cisplatin (100 mg/m2), or standard fractionation and 3 cycles of high dose cisplatin. In an analysis restricted to oropharynx patients, 64% were found to have HPV-positive tumors. Patients with HPV-positive tumors had significantly superior OS and PFS after a median follow up of 4.5 years (Figure 1). Patients with HPV- positive tumors had a 58% reduction in the risk of death and a 51% reduction in risk of progression or death after adjustment for other factors, including age, race, t stage, n stage, smoking, and treatment assignment. HPV-positive patients had significantly improved LRC and a reduced rate of second cancers, and although a slight reduction in risk of distant metastases (DM) was observed at 3 years (8.7 vs. 14.6, p= 0.23), it was not statistically significant (Table 3). In this trial, there was very high agreement between tumor HPV status and p16 expression by immunohistochemistry, and stratification of results by p16 status in lieu of HPV status yielded similar findings. Lower rates of local-regional failure and deaths due to other causes among HPV-positive patients were subsequently reported in an analysis of oropharynx patients enrolled in a phase III trial in which patients with stage III-IV disease were randomized to

receive concurrent high dose cisplatin with or without tirapazamine and standard fractionation (Rischin, 2010).

Figure 1: RTOG 0129 Survival by HPV and p16 Status

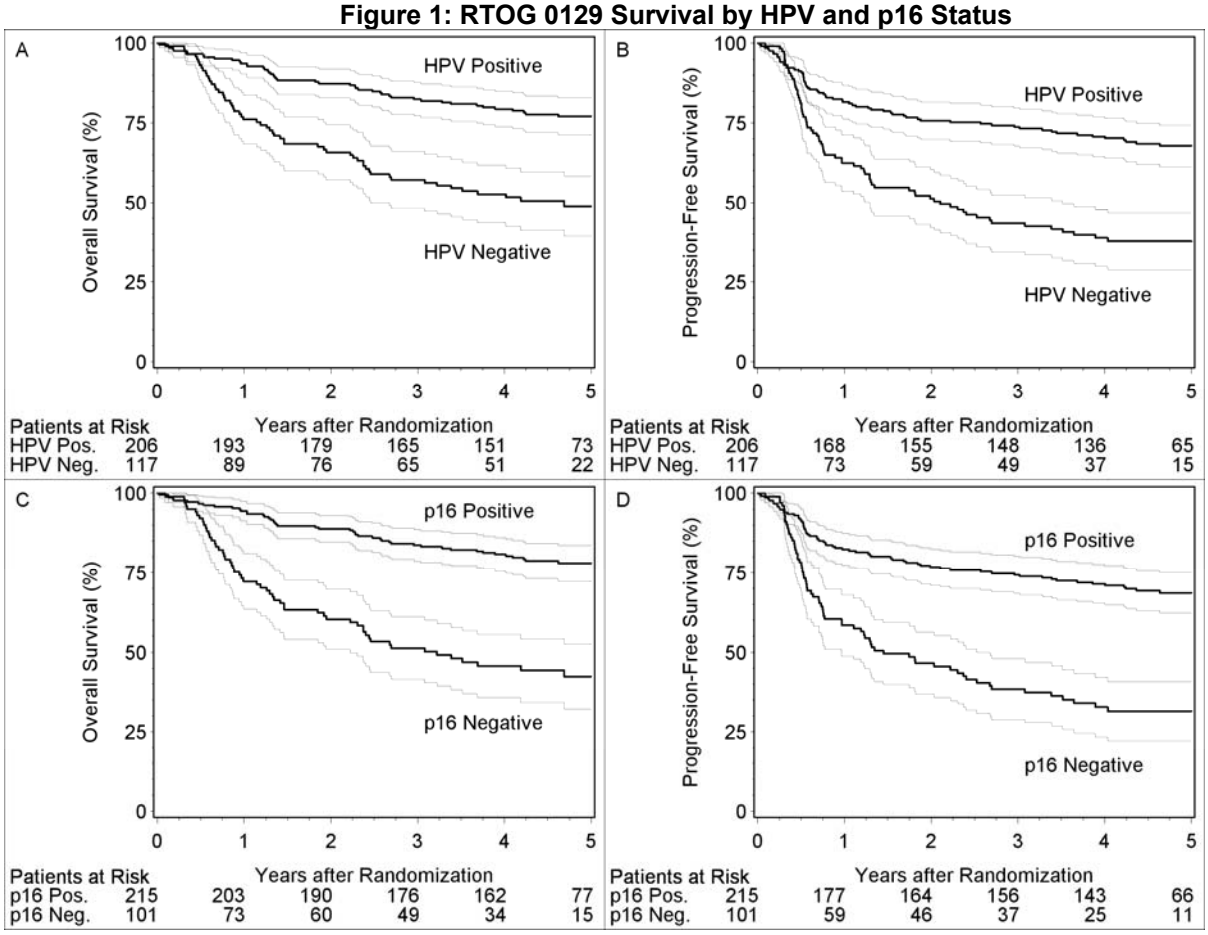

Table 3: RTOG 0129 Pattern of Failure by HPV and p16 Status

	HPV Positive	HPV Negative	p16 Positive	p16 Negative
First failure, all patients	(n=206)	(n=117)	(n=215)	(n=101)
Local-regional progression	25 (12.1%)	31 (26.5%)	27 (12.6%)	29 (28.7%)
Local-regional progression & distant metastases	1 (0.5%)	2 (1.7%)	1 (0.5%)	2 (2.0%)
Distant metastases	21 (10.2%)	17 (14.5%)	21 (9.8%)	15 (14.9%)
Dead-study cancer NOS	2 (1.0%)	7 (6.0%)	2 (0.9%)	7 (6.9%)
Dead-no progression	17 (8.3%)	15 (12.8%)	16 (7.4%)	15 (14.9%)
Alive-no progression	140 (68.0%)	45 (38.5%)	148 (68.8%)	33 (32.7%)
First failure, failures only	(n=66)	(n=72)	(n=67)	(n=68)
Local-regional progression	25 (37.9%)	31 (43.1%)	27 (40.3%)	29 (42.6%)
Local-regional progression & distant metastases	1 (1.5%)	2 (2.8%)	1 (1.5%)	2 (2.9%)
Distant metastases	21 (31.8%)	17 (23.6%)	21 (31.3%)	15 (22.1%)
Dead-study cancer NOS	2 (3.0%)	7 (9.7%)	2 (3.0%)	7 (10.3%)
Dead-no progression	17 (25.8%)	15 (20.8%)	16 (23.9%)	15 (22.1%)

1.2 RTOG 1016 Trial Design and Rationale

This is a randomized phase III, 2 arm trial. The control arm is accelerated radiotherapy (RT), 70 Gy in 6 weeks (AFX-C) plus concurrent high dose CDDP for 2 cycles. This will be compared to accelerated RT (70 Gy in 6 weeks) plus weekly cetuximab, as used in the Bonner and RTOG 0522 trials, which included 8 doses of cetuximab.

This is a head-to-head comparison of concurrent chemoradiation (RT + CDDP) versus RT plus a molecular targeting agent (cetuximab) that has been approved by the FDA for frontline therapy in loco-regionally advanced head and neck cancer. The prevailing global practice (per NCCN and H&N investigators) is that radiation plus cetuximab is used as a less toxic alternative to chemoradiation for those patients not medically fit for cisplatin-based concurrent chemoradiation. This stems from the large body of clinical trial data supporting the use of concurrent chemoradiation versus only a single mature trial testing radiation plus cetuximab. It is possible, however, that the more favorable toxicity profile associated with cetuximab relative to CDDP could be utilized in the care of patients with a relatively good prognosis. Subsite and secondary analyses strongly suggest that the best outcomes with RT plus cetuximab were achieved in younger oropharynx patients treated with altered fractionation (Bonner 2010), without any detriment of quality of life (QOL), as compared to RT alone (Bonner 2006). The optimal indication for cetuximab has been a major question in head and neck cancer since approval by the FDA. This is a unique opportunity to formally compare outcomes for these 2 approaches in prognostically favorable oropharynx cancer patients medically fit for cisplatin-based chemoradiation using biomarker-directed (HPV) patient selection.

This trial is designed as a classical non-inferiority study, and a 9-percentage point lower boundary at 5 years was selected for the inferiority margin for the cetuximab arm. Given the relative survival benefit associated with the addition of platinum-based chemotherapy (HR 0.81, 95%CI 0.78-0.86; Pignon 2009) or cetuximab (HR 0.74, 95%CI 0.57-0.97; Bonner 2004) to radiotherapy, it is reasonable to consider it unlikely that accelerated radiation therapy with cetuximab will reach this level of non-inferiority. The primary outcome measure is the hazard ratio between the 2 trial arms. The selection of a threshold for inferiority is a safeguard against the unexpected possibility that there is a direct interaction between HPV status and the effect of cetuximab or CDDP in combination with radiation. Acute and late toxicity are important secondary domains that will be carefully recorded and may help in defining appropriate care for HPV-related head and neck squamous cell carcinoma (HNSCC) in the future. There also will be sufficient power to test the possibility that RT plus cetuximab may be superior to chemoradiation. The existing level I evidence endorsed by the FDA, strong preliminary data in the oropharynx population, and independent prognostic value of HPV status all support equipoise in this phase III comparison. While recent studies also have suggested smoking history as an independent determinant of outcome, the proposed trial provides an excellent opportunity to test this hypothesis.

In addition, other large phase III trials are in progress (NCIC-CTG) or in planning stages (TROG), which will compare radiation plus molecular targeting agents versus chemoradiation in oropharynx cancer (NCIC-CTG and TROG, personal communications, 2010). The NCIC-CTG and TROG trials will use a fully humanized antibody (panitumumab) thought to be similar in activity to cetuximab but with lesser dermatologic and allergic toxicity profiles. In the proposed trial, cetuximab was chosen, as currently there is level I evidence for the efficacy of this agent. The study chairs feel that changing the molecular targeted agent may introduce an unknown confounder in the interpretation of the trial if non-inferiority is rejected on the basis of trial outcome. The NCIC-CTG trial, opened approximately 18 months ago, stratifies by anatomic subsite, includes HPV testing, and compares accelerated RT, 70 Gy in 6 weeks, plus panitumumab to standard fractionation RT, 70 Gy in 7 weeks, with high dose cisplatin. TROG is developing a study for HPV-positive cancers comparing RT, 70 Gy, plus panitumumab to RT, 70 Gy, with weekly cisplatin. Thus, a large volume of data is anticipated testing the targeted bioradiation approach against chemoradiation in the HPV-associated population to be available in the future. A future inter-group meta-analysis, after completion of the individual studies, would have considerable statistical power to narrow the margin of non-inferiority assuming that these interventions are equally effective.

NRG Oncology has a large experience with cetuximab in head and neck cancer (RTOG 0234 and 0522) in which safety and compliance has been demonstrated. The conduct of multiple EGFR-inhibitor confirmatory trials is desirable as it can potentially alleviate concern by NCCN head and neck panel members of having a single supporting trial. The application of cetuximab in HPV-associated cancers provides a rare opportunity to validate the activity of this agent, in a biomarker selected population when it

is generally not possible to repeat a trial after an agent is approved by the FDA based on a single phase III trial.

1.3 Rationale for Eligibility

Eligibility will include all Stage III-IV HPV-positive patients (as determined by the surrogate, p16 expression), excluding T1-2, N0-1 or M1. The decision to include patients with more than a 10 pack-year smoking history was a difficult one. However, this trial design incorporates a comparison of 2 standard-of-care treatment options for patients with oropharynx cancer, independent of tumor HPV status or smoking status. Furthermore, while the recursive partitioning analysis of 0129 strongly suggests smoking is an independent prognostic factor, this is based on an unplanned analysis of trial data. This trial will provide the opportunity for prospective evaluation of these findings.

1.4 Rationale for Study Arms

- Retrospective comparison for outcomes of HPV-positive versus HPV-negative cancers using different treatment strategies (RT alone, surgery/post-op RT, induction chemoradiation followed by chemoradiation) have consistently reported improved outcomes and prognosis for the former group (Table 2).
- A recent update of the Bonner cetuximab trial has confirmed improved long term (5-year) survival and local regional control (Bonner 2010). Subgroup analyses (forest plots) have indicated improved hazard ratios for oropharynx (versus other sites), twice a day (versus once a day), N0 (vs. N1-3) , and T1-3 (vs. T4). A recent additional analysis comparing once a day versus twice a day fractionation demonstrated a strong advantage with altered fractionation (AF: either hyperfractionation or accelerated concomitant boost) over conventional fractionation (CF) [Bonner, personal communication. May 2010; manuscript in process). This argues for using AF in the cetuximab arm of RTOG 1016.
- Recent analysis of the DAHANCA trials 6 and 7 suggest accelerated RT is beneficial in both HPV-positive and HPV-negative cancers (Overgaard 2010).
- Analysis of RTOG 0129 revealed that patients randomized to receive either accelerated fractionation radiotherapy with concomitant boost with 2 cycles of high-dose cisplatin or standard fractionation radiotherapy with 3 cycles of high-dose cisplatin had similar overall and progression-free survival. The hazard ratios associated with treatment assignment were similar among HPV-positive and HPV-negative patients. Although there were no differences in high-grade acute or late toxic events, several toxicities known to be associated with cisplatin were significantly lower in the 2 versus 3 cycles, including hematologic and metabolic toxicities. However, late grade 3-4 mucous membrane toxicities were higher in the accelerated arm (4% vs. 1%, p=0.04). In addition, in RTOG 0129, only 69% of patients treated with SFX received all 3 planned cycles of cisplatin, while 88% of patients treated with AFX-C received both planned cycles. Thus, the accelerated arm had higher treatment compliance and fewer cisplatin-related hematologic and metabolic events. In a non-inferiority design, per-protocol analysis is usually considered as a sensitivity measure in addition to intent-to-treat analysis, so it is essential to have good compliance.
- Based on these aggregate data suggesting the benefit of acceleration in RT alone and acceleration in RT + cetuximab, the transmutability of time, and chemotherapy (acceleration~1 cycle of chemotherapy), and the need to control for time as a treatment variable impacting tumor repopulation, accelerated fractionation (with 2 cycles of cisplatin in arm 1) has been selected for both arms of this trial.

1.5 Toxicity, Patient-Reported Outcomes (PROs) and Quality of Life (QOL) (2/23/16)

Note: The Quality of Life (QOL) component closed to accrual on 2/28/13 (with the exception of the optional baseline Work Status Questionnaire and baseline BRASS; see Sections 11.7.5 and 11.7.6). For patients already enrolled on the QOL component, sites must submit follow-up QOL as specified in Section 12.1 and in Appendix I, Assessments in Follow Up.

The overall goal of this trial is to identify a high-survival, less-toxic approach in HPV-associated cancer of the oropharynx. The aim is to show that targeted bioradiation will substantially reduce the burden of acute toxicity, improve swallowing function and recovery, and improve overall QOL, as compared to conventional chemoradiation. As such, this is the first U.S. phase III trial to formally address the tandem priorities of cure and recovery from HPV-associated H&N cancer.

Survival (the primary study endpoint) is expected to be high (> 80%) in both study arms. Understanding the magnitude of differences in toxicity and the patients' perspective in health-related outcomes is vitally important to future decision-making and treatment selection for this patient population.

Protocol-specific Toxicity Assessments are defined as evaluations (critical to the primary trial analysis) performed by the clinical team (doctor, nurse and research associate) and will include clinician-reporting and grading of CTCAE (v. 4) symptoms, findings on physical examination, and laboratories.

Patient-Reported Outcome (PRO) assessments are reported directly by the patient, without assistance from health care providers or staff. PRO tools for this study include all quality of life (QOL) surveys, the behavior and risk factor survey (BRASS), work status survey (as affected by cancer diagnosis and treatment) and a new tool, the PRO-CTCAE, that permits direct patient-reporting of side effects and health status from the patient perspective.

Six time points have been chosen for protocol-specific Toxicity and PRO assessments (see Sections 1.5.1 and 1.5.2). The tools and time points selected are designed to capture most of the short and longer term effects of modern combined modality therapies using IMRT. Short term assessments include baseline status, end of treatment (week 5 or 6 of radiation) where the maximum changes from acute toxicity will likely be seen, and 2 acute recovery assessments at 3 and 6 months, when swallowing function generally returns and some patients are able to begin to return to work. Most late phase changes will be evident between 6 months and 2 years when swallowing function may continue to improve and certain late effects will appear (e.g. dry mouth, pain syndromes, soft tissue necrosis, bone necrosis).

Protocol-specific Toxicity and PRO assessments will evaluate and compare (and hypothesize and project differences between) concurrent cisplatin-radiation versus cetuximab-radiation in the following areas:

Clinician Reported Toxicity Endpoints

- Reduction in 10 key acute toxicity rates by > 50%;
- *Reduction in overall number of acute high-grade events (T-score) by > 50%;
- Reduction in acute high-grade (3-4) dysphagia by > 50%;
- Reduction in feeding tube usage by > 50%;
- Reduction in 4 key late effects by > 50%;
- Comparison of rates of in- and out-of-field skin effects;
- Comparison of hearing by standardized audiometric testing for ototoxicity.

Quality of Life and Patient Reported Outcomes (PROs)

- Improved acute phase global QOL (baseline to 6 months);
- Improved acute phase swallowing QOL domain;
- Same or better late phase (2-year) swallowing QOL domain;
- Improved return to work status;
- Comparison of clinician and patient reporting of toxicity (CTCAE and PRO-CTCAE);
- Comparison of patient-reported hearing changes (HHIA-S)
- Explore cost utility analysis via the EuroQol (EQ-5D) and medicare cost sampling and modeling.

*This study will focus on 2 hypothesis-defined Toxicity and PRO outcomes that are critical for decision making in future treatment selection decisions: Overall acute toxicity burden (T-score) and long-term swallowing function (QOL swallowing domain).

We hypothesize that:

1) overall acute toxicity burden (T-score) in the cetuximab arm will be significantly lower than the cisplatin arm, and
2) long-term (2-year) swallowing function (QOL swallowing domain) in the cetuximab arm will be better than or similar to the concurrent cisplatin arm.

Interpretation of combined primary (survival) and secondary (Toxicity-PRO) endpoints:

Assuming the primary endpoint (non-inferior survival) is met and both of these toxicity outcome goals are met, then concurrent cetuximab and radiotherapy would be considered an effective and less toxic alternative to concurrent cisplatin, in locally advanced HPV-associated carcinoma of the oropharynx.

The principle endpoint that will power the QOL analysis is a significant difference in the QOL swallowing domain. While QOL reporting has been optional in previous NRG Oncology H&N trials, more than 90% of patients have chosen to participate. Toxicity-PRO data collection will be monitored twice a year to ensure adequate participation. Once sufficient Toxicity-PRO data are collected (~400 patients), protocol-specific PRO assessments will be discontinued (for approximately the last 300 patients enrolled), in order to minimize resource and patient data collection burdens.

1.5.1 Schedule of Toxicity-PRO Assessments

Protocol-specific Toxicity-PRO assessments will occur on a limited schedule over the first 2 years (see the sections below). After 2 years, these protocol-specific Toxicity and PRO assessments will be discontinued. Routine follow up and cancer status evaluations will occur as per the NRG Oncology traditional follow-up schedule during and after completion of the 2-year Toxicity and PRO outcomes evaluation phase. Beyond 2 years, hard coding of CTCAE late effects will revert to the NRG Oncology standard collection method similar to RTOG 0522 (9 hard-coded items).

Although pre-determined analytic Toxicity and PRO assessments will be collected at only 6 time-points, all follow-up evaluations performed over the first 2 years (baseline, end treatment, 1, 3, 6, 9 12, 15, 18, 21, and 24 months) will include case report forms (CRFs) instructing sites regarding collection of hard coded CTCAE terms. This is to avoid the need for 2 separate forms at different assessment points over the first 2 years.

Note: Previous NRG Oncology head and neck trials have collected data on a follow-up calendar based on time from the beginning of radiation therapy. For RTOG 1016, all assessments (including cancer status evaluations and Toxicity-PRO assessments) will be administered from the end of the 6-week course of radiation. In Arm 2, cetuximab will be given 1 week prior and 1 week after completion of radiation (this is not expected to substantially change the reported toxicity rates that identify the worst grade of events over the preceding interval).

Protocol-Specific Toxicity Assessments will take place at 11 assessment time points per routine NRG Oncology follow-up schedule: baseline, end of treatment, and at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months from the end of treatment.

Protocol-Specific PRO Assessments will occur at 6 of the 11 routine assessment time points: baseline, end of treatment, and at 3, 6, and 12 months from the end of treatment.

Importance and Feasibility of Toxicity and PRO Data Collection

Rigorous collection of Toxicity and PRO outcomes are equally as important as the collection of survival data for the comparative evaluation of the risks and benefits in this trial. The data collection plan for RTOG 1016 is overall very similar to data collection tools and work burdens of recent NRG Oncology H&N trials. NRG Oncology H&N trials (RTOG 0129 and 0522) have had good compliance to QOL data capture in the first 2 years of follow-up (63% at 1 year 0522; 59% at 2 years 0129), indicating that the current study will have sufficient power to discern differences in 2 year QOL domains. Compliance with collecting functional outcomes on RTOG 0522 using the PSS-H&N also has been strong at the critical time points chosen for this trial: 81% at end of treatment, 65% at 1 year, 53% at 2 years (RTOG 0522).

The addition of a Work Status survey, the H&N PRO-CTCAE tool, and the Hearing Handicap Inventory for Adults (HHIA-S) are the new PRO tools included in this study, adding less than 10-15 min to each evaluation. Compared to the traditional alcohol/tobacco-related head and neck population, the HPV population has a higher education level, stronger social support, and is likely to be comfortable with web and tablet-based methods of information sharing. Patients choosing to enroll in this study, which focuses on the goals of cure and recovery, should be capable and motivated to report their outcomes directly using computer-assisted

self interview (CASI). Electronic survey methods, now widely used in health outcomes research, have been shown to reduce burden for patients, improve data quality and staff work efficiency, and to enhance data privacy.

1.5.2 Clinician-reported Toxicity Assessment Tools

Toxicity-related tools will be collected and reported by clinical staff at 11 assessments on the standard NRG Oncology schedule: baseline, end of treatment, and at 1, 3, 6, 12, 15, 18, 21, and 24 months from the end of treatment.

Traditional clinician-reported endpoints will be captured by "hard-coding" data capture on case report forms. Collectively, completion of these forms requires < 30 minutes for the patient-clinician-research associate interaction.

- Hard-coded CTCAE events (10-15 minutes);
- Nutrition/feeding tube (5 minutes);
- Dental status (< 5 minutes).

As discussed below in Section 1.5.3, these clinician-reported data should be obtained after the patient has completed the QOL PRO tools. This order of patient reporting first, followed by clinician reporting is important to follow as much as possible, both for research purposes and to help the patients get their needs and any toxicity clarifications addressed.

1.5.3 PRO and QOL Assessment Tools

Six PRO tools will be completed by the patient at 6 assessment time points: baseline, end of treatment, and at 3, 6, and 12 months from the end of treatment.

- EORTC QLQ-C30 (7 minutes);
- EORTC QLQ H&N35 (7 minutes);
- EuroQol (EQ-5D) [1 minute];
- PRO-CTCAE (< 5 minutes);
- Work Status Questionnaire (< 2 minutes);
- The Hearing Handicap Inventory for Adults (HHIA-S) [< 2 minutes].

See Section 11.7 for a description and source for each tool. As demonstrated in other recent NRG Oncology head and neck trials, we anticipate over 90% participation (by separate consent) in the QOL component of this trial (defined as the package of PRO tools listed above). Some of the questions in this QOL package will seem redundant, including repetition of the same areas by the clinical team. This repetition is a key aim of the study (patients to report some information directly and reduce a portion of the clinical interview in future trials). It is anticipated that this will facilitate efficiency of the clinical encounter in this trial (shorter interviews), since the patient will have recently thought about these side effects and their quality of life issues. In addition to the tablet-based application, as a back up, the surveys will be available through an web-based internet application.

As discussed above in Section 1.5.2, patients will complete electronic surveys in clinic (on tablet PCs or online) prior to the clinical encounter. Every attempt to collect the QOL PROs prior to clinician visit should be made, but if not possible, very soon thereafter.

1.5.4 CTCAE Clinical versus Patient-Reported CTCAE (PRO-CTCAE) Assessments

Approximately 25 protocol-specific adverse event (AE) items will be assessed and reported by the clinical team (using CTCAE, v. 4) and separately reported by the patient (see the sections below) at each of the 6 protocol-specific Toxicity and PRO assessment time points. PRO-CTCAE endpoints were selected for comparison that can be primarily (and some preferentially) reported by the patient.

1.5.5 Quality of Life

In comparing the use of concurrent cisplatin and radiation versus concurrent cetuximab and radiation, the main differences in toxicity and QOL are expected to be short term (up to 6 months). Currently, there are only limited data documenting the short-term effects of concurrent treatment on QOL in head and neck cancer. NRG Oncology has significant experience with using the FACT-H&N tool to measure long-term QOL (RTOG 90-03 and 0522); however, these studies have collected data at only baseline, 1 year, and beyond. Thus, the paired EORTC QOL tools, the QLQ-C30 and QLQ-H&N35, will be used in this trial, as these assessments have been documented to be more comprehensive and sensitive to short-term changes in several head and neck studies, as described below.

Curran reported QOL in the randomized phase III trial comparing radiation alone to radiation plus cetuximab using the EORTC tools at 4 weeks and 4, 8, and 12 months post- treatment (Curran 2007). Data compliance was high in both arms (80-89% at 4 months and 65-73% at 1 year). There were no significant differences between the arms over time, arguing that the addition of cetuximab to radiation had no impact on QOL measures. In particular, skin effects did not appear to impact social or role functioning.

Most relevant to the current trial, the Curran (2007) study detected large post-baseline decreases (at 4 weeks post-RT) for worst post-baseline scores for all QLQ-C30 and QLQ-H&N35 multi-item symptom scales particularly for swallowing (34.2), sensory problems (41.2) and social eating scales (34.4). This is in contrast to only 6% change in short-term (at 2-month follow up) global and domain-specific values using the FACT-H&N tool in the Trans-Tasmanian Radiation Oncology Group (TROG) QOL study reported by Ringash, in which 3 cycles of cisplatin was used, with or without tirapazamine (Ringash 2009). In the Curran cetuximab study, significant declines also were noted for all multi-item sub-scales of the QLQ-H&N35, particularly for the swallowing, sensory, and social eating sub-scales. All QLQ-H&N35 single item scales showed a worsening of symptoms from baseline, including: teeth, trismus, dry mouth, cough, feeling ill, pain medications, supplements, and feeding tube use. All QOL measures improved during a several month recovery period and returned to baseline by 1 year, as noted in several H&N QOL studies (Curran 1998; Abdel-Wahab 2005; Ringash 2009).

Similar sizable short-term decreases in QOL measures have been noted using the EORTC tools in a large nasopharynx IMRT cohort (Fang 2008) and the Tax 324 trial (van Herpen 2010), supporting the choice of the EORTC tools as particularly sensitive to short-term change. In addition, the EORTC tools represent one of the most comprehensive measures of global and head and neck-specific QOL. The QLQ-H&N35 includes several areas (trismus, sticky saliva, cough, and teeth) not covered by the FACT-H&N. The FACT-H&N single item question about swallowing and eating functions is vague, whereas the EORTC tools contain more relevant phrasing and multi-item scales for both swallowing and senses. The items in the EORTC tools will complement the limited item set selected for the PRO-CTCAE evaluation (see PRO-CTCAE section below).

Based on our comparative analysis of QOL data from trials evaluating chemoradiation or cetuximab and radiation, the EORTC paired tools are the most likely to detect differences in short-term QOL as a consequence of differences in the toxicity profiles associated with each agent. Due to the higher acute toxicity burden associated with cisplatin, larger declines in short-term QOL are anticipated in the cisplatin arm.

1.5.6 Swallowing Function **(6/25/13)**

Diminished swallowing function has been shown to be the key injury with the greatest impact on QOL (Langendijk 2008). A requirement for feeding tube support may interfere with role and social functioning and is associated with significant stigma, psychological distress, and cost. Measuring the outcomes of swallowing function can performed in a number of ways, including diet assessment, videofluoroscopy, and patient perspectives. Objective assessments using barium swallow tests, etc., are not feasible in a large phase III study, in part due to a lack of technical standards. There is no gold standard for swallowing assessment (Langendijk 2008). As a critical trial endpoint, a number of measurement methods for swallowing will be used:

- Clinician-reported swallowing assessment tools;
- Hard-coded CTCAE events (Dysphagia);
- Feeding tube use;
- Weight loss;
- *EORTC QLQ H&N35 Swallowing Domain;
- PRO-CTCAE (dysphagia).

We have compared and contrasted data on swallowing function between the Bonner trial and the RTOG 0522 oropharynx cohort: CTCAE Dysphagia (60% vs. 30%), peak feeding tube (69% vs. 39%), and feeding tube rates at 1 year (28% vs. 18%). Comparative data on the PSS-H&N-Diet subscale are not available; however, based on differences in the other measures

listed, a similar 40-50% difference is projected at 3-6 months. We anticipate feeding tube rates in the cetuximab arm will be the same or better than in the cisplatin arm of RTOG 1016.

Feeding tube placement will be at the discretion of local investigators. Increased application of IMRT organ sparing techniques (as described in Sections 6.5.3 and 6.5.4), smaller average primary tumor volumes in HPV cancers, increasing sophistication of supportive care, and increased awareness of swallowing therapy during treatment, make swallowing outcomes projections uncertain.

1.5.7 Skin Toxicity

The absence of cisplatin-related effects in the cetuximab arm will be somewhat offset by higher rates of out-of-field rash and possibly higher in-field, high-grade skin reactions associated with cetuximab. The potential impact of rash on social and role functioning will be explored by comparing these domains in the QLQ-H&N35. As noted in the cetuximab QOL study (Curran 2007), these skin reactions recover within 4-6 weeks and did not affect the overall QOL measure or the H&N specific QOL domains of social functioning or role functioning as measured by the EORTC-QLQ tools in their study; however, these tools do not inquire specifically about skin effects. Skin (both in and out of the H&N-irradiated area) will be evaluated using specific hard-coded clinician-reported CTCAE items. We have significant experience with collecting hard-coded cetuximab-related skin events on more than 450 patients on RTOG 0522. Since cetuximab and cisplatin are given concurrent with accelerated radiation (which is responsible for most of the local effects), determining the contribution of each agent on in-field skin toxicity or detecting differences in overall or domain-specific areas of QOL is not anticipated. The focus will be on clinician-reported CTCAE skin toxicity, and patient-reported perspectives on skin and other selected toxicities using the PRO-CTCAE items.

1.5.8 Acute and Late Toxicity Profiles

General Toxicity Profiles

It is generally accepted that cisplatin and cetuximab involve very different toxicity profiles and that the overall burden of acute toxicity is lower with cetuximab. Cisplatin enhances radiation-related epithelial reactions, causes life-threatening neutropenia, and carries high gastrointestinal effects. Chemoradiation has been shown to impact QOL and head and neck-specific domains for up to 1 year (data below). Functional outcomes from chemoradiation (dry mouth, dental effects, swallowing disorders, neurosensory, and mood disorders) can persist for the remainder of survivorship, which is expected to be > 70% at 5 years in the HPV-associated head and neck population. Cetuximab combined with radiation causes an acneiform rash in > 85% patients and may enhance in-field skin reactions, but otherwise has a low agent-specific toxicity profile. Because there is no dose reduction of radiation, it is anticipated that only a few late effect or long-term toxicities (cisplatin-related) will be lower in the cetuximab arm: auditory, pain, and neurosensory. However, consequential effects on mucosa, soft tissue, and neural tissues may increase the risk of fibrosis, dysphagia, cranial neuropathies, or other late effects. These events will be collected using specific Toxicity-PRO tools for up to 2 years; standard late effects methods will be used thereafter. NRG Oncology follows all patients for life to collect long-term survivorship issues.

Estimated Differences in Acute Toxicity Profiles

To estimate the expected rates of toxicity in RTOG 1016, acute toxicity data was extracted from RTOG 0522 (using identical chemoradiation to RTOG 1016), specifically for a cohort of oropharynx cancers treated with IMRT (N=278 for acute, and N= 270 for late toxicity). The median follow-up on this cohort is 1.9 years (range: 0.3- 4.0).

The acute toxicity data from Bonner study was examined as well as data from the cohort of oropharynx patients treated with IMRT from the RTOG 0522 trial. Late toxicity was not reported in the Bonner study. RTOG 0522 used CTCAE v. 3.0 and select CTC terms were “hard-coded” to ensure assessments at standard time-points: 5 acute effect terms were collected and 10 late effect terms through this method. While there are several pitfalls in comparing toxicity data between 2 different trials, the large difference in acute toxicity profiles between cisplatin and cetuximab suggest this approach is reasonable for projecting rates between the 2 arms of the current study. Approximately 60% of the patients in the Bonner trial received altered fractionation, whereas all patients on RTOG 0522 received accelerated radiation. No patients in the Bonner trial received IMRT (all 2D), whereas all

patients in the 0522 cohort received IMRT. All patients enrolled on RTOG 1016 will receive IMRT.

Based on comparative review of these data, detectable reductions are anticipated in 10 specific acute effects items in which cetuximab is expected to carry significantly lower (> 50% reduction) acute toxicity: (auditory < 10 versus 28%); bone marrow-leukopenia/anemia (5% versus 71%), grade 3+ dysphagia (26% versus 61%), grade 3+ nausea (2% versus 12%), vomiting (3% versus 8%), peripheral sensory (0% versus 6%), pain (28% versus 71%), renal (0% versus 7%), and fatigue (4% versus 10%).

Estimated Difference in Overall Acute Toxicity Burden (T-score)
Routine reporting of adverse events will be performed using the CTCAE v. 4.0 terminology and grading system. Data will be summarized by the traditional listing of all event terms by body system and by grade. The "worst grade summary method" (WGSM) of reporting toxicity profiles, as long practiced by the cooperative groups will be reported, including a summary of lower toxicity (grade 1-2) versus higher toxicity (grade 3-4) events. This traditional representation of toxicity profiles permits a broad overview and sense of toxicity burden for each treatment approach.

NRG Oncology investigators have noted that the WGSM is prone to systematic under-reporting in combined modality treatment programs (Trotti 2007). This is due to a number of factors, including loss of data when patients experience more than 1 event in each grade category. This reporting issue was evaluated and an alternative summary method was developed for acute toxicity burden (T-score; relative toxicity burden value) that includes all high grade events experienced by a treatment group. An analysis of > 2300 patients treated between 1990 and 2000 in 5 trials involving 13 treatment groups of increasing treatment intensity showed a relative 5-fold difference across treatment approaches, whereas the traditional WGSM showed only a 2-fold difference. The figure below demonstrates that under-reporting was systematic and occurred to a greater degree in the more intensive programs: once a day (T~100) versus twice a day radiation (T~150-200), single or multi-agent chemotherapy (T~300-400), once a day radiation with multi-agent chemotherapy, or accelerated radiation with single or multi-agent chemotherapy (T~400-600). Of note, RTOG 99-14 used accelerated radiation (concomitant boost schedule) with 2 doses of concurrent cisplatin, mirroring the control arm of RTOG 1016. The relative T-value for this approach is at the upper end of the acute toxicity burden range tested by RTOG in the 1990s (a 2D RT era).

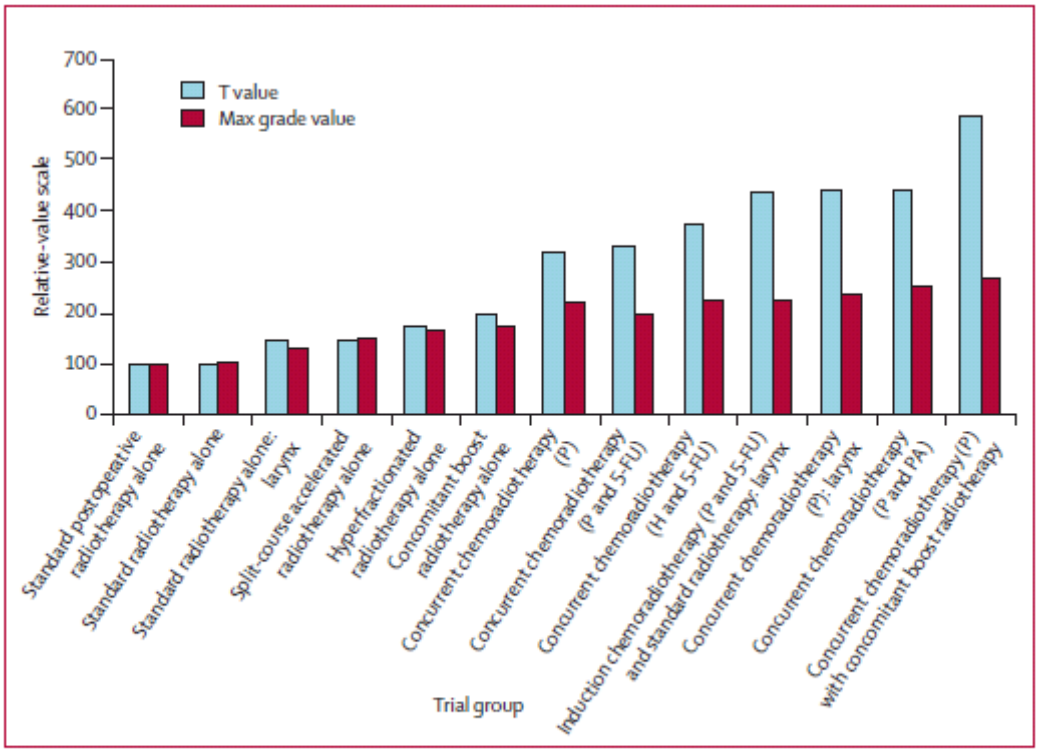

Figure 1: **Acute toxicity relative risk values (T_{RR}) and relative max-grade values for 13 head and neck treatment groups ranked by increasing relative risk**
P=platinum. H=hydroxyurea. 5-FU=fluorouracil. PA=paclitaxel.

Figure from Trotti 2007

RTOG 1016 will utilize accelerated radiation in both arms (70 Gy in 6 weeks, 6 fractions/week, weeks 2-6), and will compare cetuximab versus cisplatin. Since cetuximab has an overall lower toxicity profile, and events are generally concentrated in one organ (skin), we estimate relative T-scores to be in the range of 200 for the cetuximab arm and approximately 400 for the cisplatin arm. This would indicate an approximate 2-fold difference in toxicity burden. Acute toxicity burden is the major focus for testing this alternative method of treatment and is the main endpoint for the toxicity hypothesis. There is no widely accepted or common summary metric for this global measure. Relative T-values should be useful in quantitatively assessing differences in overall acute adverse event profiles and toxicity burden.

Estimated Differences in Late Toxicity
Late toxicity rates of interest from the RTOG 0522 oropharynx cohort (N=270; median follow up of 1.9 years) were examined. Late toxicity was not reported by the Bonner study. Detectable reductions of > 50% are anticipated in 4 specific late effects items: auditory, hemoglobin, pain, and peripheral sensory neuropathy. Each of these late effects are likely related to cisplatin toxicities. Potential differences in swallowing function, fibrosis, and other late effects are discussed in the sections above.

Early Deaths
Deaths due to toxicity or within 30 days of completing radiation were not reported in the Bonner study (it is assumed in the current study that there will be no toxic deaths from cetuximab). There is, however, some risk of severe allergic reaction to cetuximab. In RTOG 0522, grade 3-4 hypersensitivity occurred in 2.2% of oropharynx patients treated with IMRT on the cetuximab arm. In the RTOG 0522 oropharynx cohort (N=278), 6 patients (2.2%) died from toxicity or within 30 days of completing treatment (2 patients died of treatment-related causes and 4 additional patients died within 30 days of treatment from other causes). This is consistent with the experience for a similar patient population treated with the same regimen

(accelerated fractionation with concurrent cisplatin, but non-IMRT) on RTOG 0129 (2.8%). Early death is an important consideration in global assessment of risk and will be reported using standard definitions and methods.

Dental Health

A direct observer-rated assessment of dental complications is desired to document short- and long-term dental health in HPV oral cancer survivors. CTCAE, v. 4.0 includes 1 term for tooth loss but does not quantify the degree of tooth loss and does not give a global assessment of dental and oral health. A literature review did not identify a well-validated general oral instrument.

A simple 5-point global health dental scale was created for this trial (see Appendix VII). The language reflects assessment of oral hygiene and teeth at baseline by dentists in order to determine the need for extractions, cleaning, and future interventions; thus, it has high face and content validity. The 5-point ordinal scale, mimicking CTCAE structure, rates dental health as edentulous, excellent, good, fair, or poor.

In addition to overall assessment of dental health changes over time, a dental "count" will be performed at each of the designated outcome assessments (Appendix I). This will involve simply counting the number of native teeth at each visit, not including bridges or partial or full dentures. A diagram of 32 teeth will be provided to assist in dental count. The percent change from baseline in number of teeth over time will be reported. Loss of teeth (up to 10 years follow up) should give a quantitative measure of changes in dental health in the HPV-associated population treated with IMRT.

PRO-CTCAE

It is recognized that clinician-reported adverse events (AEs) may substantially under-report the incidence and severity of symptoms occurring as a consequence of treatment (Basch 2010). In response to this awareness, the NCI has developed a set of patient-reported items (called PRO-CTCAE) that complement the CTCAE and capture the patient's perspective on the subjective aspects of adverse events (Hay 2010). The potential for under-reporting of adverse events is particularly likely with symptoms such as fatigue, pain, and depression, which can only be gauged accurately by the person experiencing the symptom, and with long-term head and neck symptoms, such as mouth dryness, voice hoarseness, and difficulty swallowing, which are often subtle and may be difficult for clinicians to grade using standard CTCAE grading methods. Several CTCAE scales (e.g., taste changes, hair loss) only include 2-3 severity ratings, whereas the PRO-CTCAE offers a 5-point response scale. PRO-CTCAE H&N information will complement the clinician CTCAE reporting, as well as the other PRO measures.

A collection of 25 H&N specific items, entitled "PRO-CTCAE H&N", (see separate attachments) will be used for the current study. The recall period or response frame for PRO-CTCAE items is 'within the past seven days'. This differs from the NRG Oncology traditional clinical evaluation which is ""since your last visit". This is an inherent and recognized difference in the 2 reporting systems.

The goal of including PRO-CTCAE in this trial is 2-fold: 1) to gather further information for the NCI about the feasibility of implementing this measure in clinical trials and to examine its validity and sensitivity as a measure of the patient experience of adverse symptoms during treatment and across the early post-treatment period and through long-term follow-up; and 2) to characterize the patient experience of AEs immediately following treatment with targeted biotherapy (radiation + cetuximab) versus conventional chemoradiation (radiation + cisplatin) and during long-term follow up. As such, the aims will be:

1. Assess the feasibility of administering the PRO-CTCAE via paper (and/or electronic) at selected time points, as measured by the proportion of patients who complete the form at each time point;
2. Compare patient versus clinician reporting of analogous adverse symptoms as measured by the PRO-CTCAE and CTCAE, respectively;

3. Examine the validity of individual PRO-CTCAE items in relation to other PRO measures being administered;
4. Compare the proportion of patients in each arm with each adverse symptom at each time point.

Work Status

The ability of a patient who is gainfully employed prior to a cancer diagnosis to continue to work through treatment or return to work after treatment is an important factor in the societal and personal costs of cancer. Verdonck-deLeeuw, et al. (2010) recently reported employment and return to work status in 85 head and neck cancer survivors after surgery, radiation, or chemoradiation. The population was mixed in terms of head and neck anatomic subsites. Of the 53 patients who were employed at the time of diagnosis, 44 patients returned to work, (83%): 28 to the same work, 7 to adapted work, and 9 to other work. The median time to return to work was 6 months (range 0–24 months), and 71% of the patients returned to work within 6 months after treatment. Barriers to return to work included loss of appetite, decreased social functioning, anxiety, and oral dysfunction, such as xerostomia, trismus, sticky saliva, and problems with teeth, all of which are associated with head and neck cancer treatment.

Information regarding employment and return to work status will be collected using brief a study-specific work status questionnaire, completed by patients without assistance from clinical or research staff, in less than 5 minutes. Computer assisted methods using skip patterning may shorten this time. This information will be collected on the same schedule as other Toxicity-PRO assessments (baseline, end of treatment, 3, 6, 12, and 24 months from end of treatment). Elements from the NRG Oncology standard demographics form will be used to determine the patient's age, education level, marital status, number of children, and number of comorbidities.

We hypothesize that due to lower overall acute toxicity burden and faster recovery time, a significantly higher proportion of the patients treated with cetuximab will be able to continue working at least part-time during treatment, that patients treated with cetuximab will miss fewer days of work during and immediately after treatment, and that the time to return to full work will be shorter in the cetuximab arm compared to the cisplatin arm. The analysis will control for demographic, socioeconomic, health, and work-related variables, and include job type, income, insurance status, and employer accommodation.

Hearing Handicap Inventory for Adults (HHIA-S)

Hearing loss significantly impacts QOL by causing communication breakdowns that elicit feelings of shame, guilt, and incompetency that negatively affect self-esteem and social identity (Hetu 1996). Individuals with handicapping hearing loss are less likely to engage in social interactions and tend to experience greater difficulty in the workplace than those with normal hearing (Tye-Murray 2009). Anti-neoplastic drugs, particularly cisplatin, cause permanent damage to the auditory system and can be exacerbated by concurrent radiotherapy. At particular risk are patients with good pre-treatment hearing levels, as this is a significant independent predictive factor for post-treatment hearing loss (Zuur 2007). As patients with HPV-associated oropharyngeal cancer often are younger with good performance status (Ang 2010), they typically have very good hearing and therefore, are at high risk for post-treatment hearing loss. Given the risk for auditory damage from chemoradiation and the potential social and vocational hardships this treatment may impose, hearing loss is a critical QOL outcome for this subject population.

Hearing QOL outcomes will be measured using the Hearing Handicap Inventory for Adults screening version (HHIA-S) at each interval: baseline, end of treatment, and at 3, 6, 12, and 24 months from the end of treatment. The HHIA-S is a validated, 10-item self-assessment questionnaire designed to assess emotional and social/situational perceived hearing handicap (Newman 1990; Newman 1991). Patients will complete the questionnaire without the assistance of clinical or research staff in approximately 2 minutes. We hypothesize that the toxic effects of cetuximab on the auditory system will be significantly less than for cisplatin.

1.6 Outcomes and Cost Effectiveness

Incorporation of advanced technology and biologics into cancer treatment results in an increase in the incremental cost of care. As the cost of cancer care and health care overall rises, becoming a higher percentage of the U.S. Gross Domestic Product (GDP), an increasing emphasis is being placed on the value of higher cost interventions. An economic analysis has been incorporated into this study because cetuximab has a higher incremental cost as compared to cisplatin. NRG Oncology has used decision models informed with actual clinical trial data to perform economic analysis of clinical trials in the past (Konski 2005; Konski 2006). The decision models have used costs which have been modelled; NRG Oncology has found the cost estimated by modelling is close to the actual cost as measured by relative value units multiplied by a Medicare conversion factor (Owen 2001; Konski 2009). The decision models also have used utilities that were obtained from the literature to inform the model instead of utilities actually collected from the trial participants themselves. This study will use the EuroQol (EQ-5D) to calculate the health-related quality of life (HRQOL) for patients. The HRQOL or quality adjusted survival is calculated by multiplying the utilities or preference for the patient's current health state by the time period, which can by expressed as a quality adjusted life year (QALY). The resultant economic analysis would be a cost-utility analysis, as it incorporates the HRQOL into the analysis. The EQ-5D will be used to calculate utilities and QALY on RTOG 0522.

1.7 Epidemiological and Translational Research

In the approximately 10-year period of enrollment and observation prior to analysis of this trial, we anticipate significant knowledge to be gained with regard to epidemiological and molecular differences between HPV-positive and HPV-negative patients and predictors of response to radiotherapy, cisplatin and cetuximab chemotherapy. Thus, the principal objective for the translational research for this study is to bank high quality biospecimens (serum, whole blood, paraffin tumor) on a very high proportion of patients who enroll in the trial. The specimens will be stored for future hypothesis generated research.

1.7.1 Objectives

- To determine the effect of tobacco exposure on overall and progression-free survival for patients with HPV-positive oropharynx cancer

  We hypothesize that tobacco exposure will be the strongest predictor of overall and progression-free survival in patients with HPV-positive cancer. The hazard of death will increase per unit increase in tobacco exposure (measured in pack-years or years of smoking) and will be independent of treatment assignment.
- To determine whether established risk factors for development of head and neck cancer (in addition to tobacco exposure) also are associated with overall and progression free survival.

  We hypothesize that genetic alterations associated with response to therapy and patient prognosis are largely determined by the risk factors which contributed to cancer development; therefore these factors will be stronger predictors of outcome than commonly used clinical parameters such as tumor stage.
- To determine whether specific molecular profiles (inclusive of genomic, proteomic, and mRNA or miRNA expression) in tumor, genomic DNA or serum (as appropriate) are associated with overall or progression-free survival; this will include analysis of interaction effects by treatment arm (e.g. determinants of cisplatin or cetuximab sensitivity or resistance).

  We hypothesize that distinct molecular biomarkers will be predictive of progression after treatment with cisplatin or cetuximab therapy.
- To investigate associations between changes in serum biomarkers or HPV-specific cellular immune responses measured at baseline and three months with overall or progression-free survival

  We hypothesize that HPV-specific T cell responses induced by chemoradiation or bioradiation (immune responses might be more prominent as some to the effect of cetuximab might be mediated through ADCC) will be associated with improved survival.

1.7.2 Rationale

Objective 1

Tobacco smoking is a major risk factor for head and cancer. In addition to its etiologic role, there is evidence that smoking alters treatment response, risk of recurrence, rates of second primary cancers, and overall survival for patients with head and neck cancer (Duffy 2009). Cigarette smoking during radiation therapy for early stage head and neck cancer increased risk of recurrence and death from cancer as well as death from any cause: smoking during therapy had a more pronounced effect on treatment outcomes than smoking during the year prior to or after completion of therapy (Meyer 2008). A history of smoking has been associated with reduced response to platinum-based induction chemotherapy (Fountzilas 1997) and also with lower rates of complete response to radiation therapy (Browman 1993).

Epidemiological data indicate that tobacco smoking is not a strong co-factor for HPV-positive head and neck cancer (Gillison 2008; Applebaum 2007). With regard to survival outcomes, the independent effects of tobacco exposure and tumor HPV status on patient survival have been unclear, given the strong inverse correlation between the two. However, there is growing evidence that the biological behavior and treatment response of HPV-positive head and neck cancer may be modified by tobacco exposure. In a single-institution case-series of patients with tonsillar cancer, patients who were current smokers at diagnosis were found to have an estimated 4-fold increase in risk of cancer death when compared to former/never smokers after consideration of tumor stage and p21 and cyclin D expression (surrogates for HPV-positive disease) [Hafkamp 2008]. In bivariate analysis, the University of Michigan has reported that current smoking was associated with worse survival among patients with HPV-positive oropharyngeal cancer (Kumar 2008). In a more recent analysis from University of Michigan, patients with HPV-positive oropharynx cancer who were former or never smokers were less likely to develop distant metastases and disease-recurrence (in univariate analysis) when compared to HPV-positive current smokers (Maxwell 2010).

In our analysis of RTOG 0129, both tumor HPV status and tobacco smoke exposure (measured in pack-years or duration of smoking) were strong and independent predictors of progression-free and overall survival for oropharynx cancer. In proportional hazards modeling, risk of death significantly increased by 1% per pack-year of tobacco exposure, after adjustment for tumor HPV status, age, race, T stage, N stage, and performance status. Recursive partitioning analysis was used to evaluate which factors of significance in a multivariate proportional hazard model had greatest influence on patient survival. In this analysis, the tumor HPV status of OPSCC was found to be the major determinant of OS in recursive partitioning analysis, followed by tobacco-smoking (≤ 10 vs. >10 pack-years), then nodal stage (N0-2a vs. N2b-3) for HPV-positive and tumor stage (T2-3 vs. T4) for HPV-negative OPSCC patients. This analysis classified OPSCC patients into three risk groups: low (reference; 93% 3-year OS), intermediate (HR 3.54, 95% CI 1.91-6.57; 70.8% 3-year OS), and high-risk (HR 7.16, 95% CI 3.97-12.93; 46.2% 3-year OS) of death. HPV-positive patients were low-risk except smoking plus high (N2b-3) nodal stage assigned them to intermediate-risk, and HPV-negative patients were high-risk unless they were nonsmokers with T2-3 tumors and thus intermediate-risk.

Smoking has been linked with specific genetic alterations such as p53 mutations and with specific and global methylation patterns in head and neck cancer (Marsit 2009), and these patterns may differ in HPV-positive vs negative cancers in smokers and non-smokers (Marsit 2006). However, the specific genetic or epigenetic changes induced by tobacco smoking that negatively effect the survival of both HPV positive and negative oropharynx cancer patients have not been clearly defined to date. The likelihood of such genetic “hits” appears to increase along a biological continuum of increasing tobacco pack-years. However, the 10 pack-year cut-point that best predicted survival in RTOG 0129 in recursive partitioning analysis is perhaps more useful for risk-based clinical trial design. This is the basis for the choice of the 10 pack-year cut-point used for stratification for RTOG 1016.

It has previously been recommended that all cooperative groups assess tobacco exposure via a standardized and centralized questionnaire (Gritz 2005). For cancers in addition to

head and neck cancer, tobacco exposure has been associated with clinical trial outcome by means of increased toxicity due to comorbidity, increased risk of second primary tumors, and perhaps by direct modification of the tumor response to treatment (Gritz 2005). Nicotine has been shown to interact with both the mitogen activated protein (MAP) kinase and akt pathways and may inhibit apoptosis in response to therapy (Heusch 1998); West 2003). Nicotine has been reported to reduce the cytotoxic effects of cisplatin and radiation of head and neck cancer cell lines in vitro (Onada 2001).

Our data from RTOG 0129 further underscores the importance of measurement of tobacco exposure, given that HPV and tobacco were the strongest predictors of clinical outcome for oropharynx cancer patients.

We will utilize a questionnaire to ascertain lifetime tobacco exposure at baseline. This questionnaire is based upon validated epidemiological surveys of tobacco exposure with high agreement with repeat testing (kappa>0.80) and strong associations with head and neck cancer risk (D'souza 2007; Gillison 2008). The survey obtains all data acquired in RTOG 9003, 0129, and 0522 as well as all the critical elements recommended for routine tobacco exposure measurement in clinical trials. The survey will collect data necessary for calculation of tobacco pack-years from cigarette use only for stratification because this is what was done in our analysis of RTOG 0129 (other sources of tobacco exposure were not previously measured by RTOG). Although < 5% of US tobacco smokers use forms other than cigarettes, to accomplish our research objectives (not for stratification) the survey collects data on lifetime use of pipe, cigar and smokeless tobacco. Standard conversion factors for cigar use and pipe use are used to account for non-cigarette smoking exposure. Ages at initiation and start of regular use (defined as daily for one month or more) and cessation of cigarette use will be obtained due to strong associations between years of use and PFS and OS in RTOG 9003 and 0129. Successful quit attempts of one year or longer, quantitative measures of intensity of use (e.g. cigarettes per day) will be obtained. After survey completion, a standard formula for calculation of lifetime, cumulative total-pack years of exposure that is programmed into the questionnaire will immediately provide a summary of patient exposure for stratification. Data will be automatically sent by e-mail to NRG Oncology staff.

Objective 2

Cancer arises by the accumulation of genetic and epigenetic changes in genes involved in cell cycle control, signal transduction, apoptosis, tissue homeostasis and angiogenesis. Given the majority of head and neck squamous cell carcinomas are attributable to environmental exposures and lifestyle choices, the genetic events that promote carcinogenesis in the upper airway are largely environmentally induced. Indeed, it has been estimated that the majority of human cancers are attributable to environmental exposures. Tobacco use, alcohol drinking, oral human papillomavirus infection, Epstein-Barr infection, diets low in fruit and vegetables and high in processed meets, and poor oral hygiene (and possibly marijuana use) are established risk factors for head and neck cancers. These exposures (and perhaps as yet undetermined factors) are therefore likely responsible for the genetic profile of head and neck cancers.

Alteration of the tumor suppressor gene p53 is a common early genetic event in head and neck cancers (Boyle 1993). Tobacco exposure is associated with the frequency and type of p53 mutations found in tumors (Brennan 1995). In an analysis by Brennan and colleagues, p53 mutations were present in 47% of smokers but only 14% of non-smokers. Patients without a history of smoking and drinking had p53 mutations which occur at CpG sites, indicating they occurred as a result of methylation, whereas the majority of mutations that occurred in smokers were consistent with tobacco-carcinogen induced mutations. p53 mutations identified in human lung cancers among patients with exposure to four human carcinogens (including benzo[a]pyrene) are identical to those induced by these carcinogens in exposed mice (Kucab 2010). Importantly, the type of p53 mutation is also associated with prognosis in patients with surgically resected head and neck cancer (Poeta 2007), after consideration of clinical factors such as tumor site, stage, and treatment.

In HPV-positive oropharynx cancers, the p53 pathway is inactivated by protein-protein interaction with the HPV oncoprotein E6, which targets p53 for inactivation by the proteosome. Self-reported oral sexual behaviors have been associated with oral HPV infection and risk of HPV-associated cancers. In our analysis of RTOG 0129, tumor HPV status was the single strongest predictor of patient prognosis, followed by measures of tobacco exposure and tumor stage. Therefore, it has been shown that the most important risk factors for development of head and neck cancer are also the greatest predictors of response to therapy and patient survival. This is likely because these factors determine the molecular profile of the cancers. We therefore propose to measure risk behaviors through epidemiologically sound methods, in order to further investigate associations between risk behaviors and patient prognosis. The survey covers the following domains: demographics, tobacco use, alcohol use, marijuana use, family history of cancer, diet, oral hygiene, and sexual behavior.

Of particular interest in this analysis will be marijuana use. Whether marijuana use is a risk factor for head and neck cancer remains controversial. In case-control studies in which cases were not stratified by HPV status, marijuana use has (Zhang 1999) and has not (Berthiller 2009) been associated with HNSCC, and in one study, was reported to reduce odds of HNSCC (Liang 2009). However, in a case-control study in which cases were stratified by HPV status, lifetime and cumulative measures of marijuana use were associated with HPV-positive but not HPV-negative HNSCC (Gillison 2008). Additionally, marijuana contains many of the same carcinogens as are found in tobacco smoke (Moir 2008). Therefore, marijuana use (together with or without tobacco use) may have the biological capability to modify the therapeutic response of a patient with an HPV-positive tumor analogous to tobacco smoking.

Objective 3

As a greater understanding of molecular mechanisms underlying cancer pathogenesis is achieved, molecularly targeted therapy becomes a reality and predictors of response are identified. For example, only women with Her-2 positive breast cancer benefit from trastuzumab and patients with metastatic colon cancer with mutated KRAS do not benefit from cetuximab. As of 2010, there are no biomarkers predictive of response to cisplatin or cetuximab for patients with oropharynx cancer, regardless of tumor HPV status. What is clear is that: (1) tumor HPV status is the strongest, independent "molecular" prognostic factor identified to date for patients with head and neck cancer; (2) patients with HPV-positive tumors have half the risk of death when compared to HPV-negative patients, regardless of therapy as long as it is within the standard of care; and (3) the absolute difference in survival for the HPV-positive and HPV-negative patients at five years when treated with primary radiotherapy with or without concurrent chemotherapy is approximately 30%. Although tumor HPV status is predictive of improved survival, in 2010 it is not an indication for selection of any particular therapeutic agent or modality. During the eight-year period of enrollment and observation for this clinical trial, we anticipate considerable knowledge to be gained regarding molecular differences between HPV-positive and HPV-negative patients and predictors of response to therapy. Below, we discuss the state of the art in 2010, to provide examples of the type of analyses we expect to be able to perform with prospective collection of biospecimens from patients enrolled in this trial. We do expect, however, that the specific questions to be addressed, biomarkers to be evaluated and the methods used will change significantly over the next eight years. Our objective is to collect a range of samples at particular time points to facilitate future investigation.

Predictors of disease progression or death among HPV-positive oropharynx patients: It is clear that progression-free survival is superior for HPV-positive oropharynx cancer patients when compared to HPV-negative patients. Disease progression or death nevertheless occurs in approximately 30% of HPV-positive patients at three years after treatment with accelerated fractionation radiotherapy and high dose cisplatin per RTOG 0129. While tobacco exposure (see above) appears to be important, as of 2010, expression of several proteins involved in signal transduction, cell-cycle control or apoptosis have been proposed as biomarkers of poor outcome in HPV-positive patients. These include EGFR expression (Hong 2010), cyclin D1 expression (Hafkamp 2009; Hong 2010), p53 expression (Wallace

2010), and Bcl-2 expression (Nichols 2010). However, all have yet to be prospectively investigated in a study of sufficient size to evaluate the independent effects of these markers among HPV-positive patients. Additionally, 16q loss has been associated with favorable survival for the HPV-positive patient by comparative genomic hybridization (Klussman 2009). All of these biomarkers, with the exception of 16q loss (evaluable by FISH), can be evaluated by immunohistochemistry on paraffin-embedded tissues. The table below shows the prevalence of these factors among patients with HPV-positive oropharynx cancer and associations with particular disease outcome measures.

Factor	% HPV-positive with factor	Outcome measure	Hazard Ratio univariate	95% CI
EGFR	78	Local-regional failure	6.6	2.1-40.0
Cyclin D1	27	Local-regional failure	3.5	1.9-7.2
P21	63	Disease-specific survival	0.4	NR
Bcl-2	40	Overall survival	4.0	1.2-13.6
P53	40	Disease-specific survival	1.7	NR
16q loss	29	Overall survival	NR	NR

Of particular interest for the HPV-positive patient is the role of cell mediated immunity against the viral tumor-specific antigens, E6 and E7, and patient prognosis. It has been hypothesized that primary therapy with chemo-radiation and resulting tumor-cell death may induce a cellular immune response specific to HPV-infected cells, contributing to improved patient prognosis. Indeed, HPV transformed mouse tonsillar epithelial cell tumors are cleared after exposure to cisplatin or radiation only in immune competent mice (Spanos 2009). Preliminary studies in human subjects are ongoing to investigate changes in HPV-specific CD8+ and CD4+ T cells before and after therapy.

Much of the improved survival for the HPV-positive patient is attributable to improved local-regional control. The risk of distant metastasis for the HPV-positive patient is non-significantly reduced. Several clinical trials have demonstrated that cisplatin administration can reduce the development of distant metastases for patients with head and neck cancer, but whether or not cetuximab has this potential is unclear. Individuals at risk for distant metastases and their response to therapy may, in theory, be measurable through detection of circulating tumor cells (CTC) or circulating nucleic acids at baseline, and changes before and after therapy might be predictive of distant failure. The number of CTC (cutpoint of ≥5 CTC per 7.5 mls blood) has been shown to be associated with poor prognosis in patients with early stage breast (Saloustro 2010), and metastatic prostate and lung cancer. In cervical cancer patients, a combination of EpCAM selection of CTC and RT-PCR for HPV oncogene transcripts was successful in detecting CTC in cervical cancer patients (Weismann 2009). However, the technology for selection of CTC from lymphocytes in peripheral blood is evolving (from size exclusion, density centrifugation, positive or negative antibody-based magnetic automatic cell sorter with microfluidics to fiber-optic array scanning technology) to approaches resulting in higher yields and detection in a higher proportion of patients (Pantel 2010; Lin 2010). However, in 2010, samples stored at room temperature require processing within 72 hours. Measurement of circulating nucleic acids derived from tumor cells may be more feasible in archived specimens. In the case of HPV-positive cancers, real-time PCR quantitation of the viral genome or transcripts in serum or plasma or whole blood would be tumor specific (Capone 2000).

Although several biomarkers have been associated with prognosis for patients with head and neck cancer, (e.g. p53 mutations, EGFR expression, EGFR gene amplification), as of 2010, there are no biomarkers predictive of response to a specified therapy. The design of RTOG 1016 provides a unique opportunity for the prospective collection of biospecimens from a large cohort of patients with HPV-positive oropharynx cancer randomized to receive radiation sensitization with either cisplatin or cetuximab, two standard of care options for therapy for this patient population which have not been compared to date. This study design provides a unique opportunity to identify specific predictors of disease control and survival which may be: (1) observed in both treatment arms and therefore indicative of response to radiation therapy; (2) observed only in the cisplatin arm and therefore indicative of response

to a DNA damaging agent; (3) observed only in the cetuximab arm and therefore indicative of response to EGFR pathway inhibition. It must be emphasized that we describe factors below which would be investigated in 2010. However, we anticipate the state of the science to change significantly over the next eight years. Our objective is to collect and bank specimens which will be available to address important hypotheses which will advance the field when data are mature.

Predictors of response or resistance to cetuximab therapy: Activation of the EGFR signaling pathway is frequently observed in head and neck squamous cell carcinoma, and elevated expression of EGFR is associated with poor survival, radiation resistance, and local-regional failure. Although inhibition of EGFR signaling with cetuximab has improved overall survival in combination with primary radiotherapy (Bonner 2006; Bonner 2010) or in combination with chemotherapy in the metastatic setting (Vermorken 2008), there are no biomarkers predictive of therapeutic benefit from cetuximab. For example, EGFR expression is not predictive (Bonner 2010) and EGFR activating mutations are infrequent in head and neck cancer (Sharafinski 2010). Potential biomarkers of interest as predictors of response to cetuximab therapy at this time would include: (1) EGFRvIII, a truncated form of the EGFR possibly present in as many as 42% of HNSCC (Wheeler 2010). EGFRvIII would be expected to reduce response to cetuximab because the ligand binding and cetuximab binding sites are deleted (Sok 2006). (2) Loss of the tumor suppressor gene, Phosphatase protein homolog to tensin (PTEN,) an inhibitor of the PI3/akt signaling pathway activated by EGFR. PTEN loss would be expected to be associated with resistance to cetuximab; (3) EGFR ligand (EGF, TGF-alpha, amphiregulin, epiregulin, betacellulin and heparin-binding EGF-like growth factor) expression in tumors. Epiregulin and amphiregulin expression have been associated with improved response rate, progression-free survival, and overall survival in patients with KRAS wildtype colon cancer in response to cetuximab therapy (Jacobs 2009): (4) Nuclear EGFR expression. Translocation of EGFR to the nucleus has been associated with activation of cyclin D1, DNA-dependent protein kinase and resistance to cetuximab (Li 2009); (5) Tumor expression of IL-6 and NFK-beta or serum levels. These have been associated with resistance to cetuximab (Chen 2010). (6) Downstream indicators of EGFR signal transduction, e.g. p-EGFR, p-STAT signaling, pAKT; (7) Polymorphisms in the EGFR associated with skin rash (e.g. EGFR-R521K or CA-SSR) (Klinghammer 2010; Huang 2009). Development of a significant rash is the only strong and consistent predictor of clinical benefit from cetuximab therapy, but there are no identified predictors of skin rash development. (8) Serum proteomic profile classified as “poor” vs “good” for response to EGFR-target agents as measured by MALDI MS (VerisStrat, Biodesix, Inc Steamboat Springs CO). Analysis of three small clinical trials in head and neck cancer patients treated with gefitinib, erlotinib or cetuximab has revealed an association between a “good” profile and improved overall survival in univariate analysis, but no association with treatment with a taxane (Chung 2010).

Cetuximab, being a monoclonal antibody (mAb), may exert antitumor effects through antibody-dependent cell-mediated cytotoxicity (ADCC) via binding of the Fc portion of the mAb to Fcγ receptors expressed on macrophages and natural killer cells. Specific genetic polymorphisms in the FcγRIIa (CD 32, expressed primarily on macrophages) and FcγRIIIa (CD16, expressed on macrophages and NK cells) receptors can affect antibody affinity and target cell lysis (Bowles JA 2005). In support of this hypothesis, in vitro studies have shown effector cells expressing a homozygous FcγRIIIa-158V/V (valine) were more effective after cetuximab treatment at lysis of head and neck cancer cells expressing the EGFR and induced larger amounts of inflammatory cytokines and chemokines (Lopez-Albaitero 2009). Based on these studies, patients homozygous for FcγRIIa-131H/H (histidine) and FcγRIIIa-158V/V (valine) would be expected to have higher binding affinity and greater ADCC in response to mAb therapy than carriers that are either heterozygous or homozygous for the FcγRIIa131R (arginine) or FcγRIIIa-158F(phenylalanine). Indeed, homozygous individuals for FcγRIIa-131H/H (histidine) and FcγRIIIa-158V/V (valine) were shown to have improvements in progression-free survival after treatment with cetuximab for colon cancer (Bibeau 2009) and after treatment with trastuzumab for metastatic Her-2 positive breast cancer, (Musolino 2008) and were also shown to have higher response rates after treatment of follicular lymphoma with rituximab (Paiva 2008).

Predictors of response or resistance to cisplatin therapy: Meta-analyses have determined that the addition of platinum chemotherapy given concurrently to radiation therapy yields the greatest absolute improvement in survival for patients with head and neck cancer. Cisplatin remains first line therapy in both the primary and recurrent/metastatic settings for head and neck cancer patients, and yet, in HPV-positive patients 30% will progress or die within three years. Several mechanisms of cisplatin resistance have been identified, (Basu 2010) but of particular interest is the role of DNA repair pathways that mediate cisplatin cytotoxicity. Paradoxically, polymorphisms in DNA damage repair pathways that might increase risk for HNSCC for an individual might also increase survival in response to DNA damaging agents such as radiation and cisplatin. Because of inherent genomic instability, somatic mutations in DNA repair pathways in cancers might induce greater radiation or chemosensitivity than that in normal tissue. Cisplatin cytotoxicity is primarily attributable to intra-strand crosslinks repaired by the nucleotide excision repair (NER) pathway. Activity of the NER pathway is associated with cisplatin sensitivity/resistance, in particular alterations in the level of ERCC1 mRNA or protein. Single nucleotide polymorphisms in NER pathway proteins ERCC1, XPD and XRCC1 are associated with overall survival in patients with stage IV head and neck cancer treated with cisplatin (Quintela-Fandino 2006). In a recently published metaanalysis, low expression of one of the NER pathway proteins, ERCC1, was associated with increased response and survival after cisplatin therapy in patients with advanced NSCLC (Chen 2010). Studies to date in head and neck cancer patients are inconsistent, but suggest ERCC1 expression may be associated with response to cisplatin and radiation therapy (Jun 2008; Handra-Luca 2007; Fountzilas 2009; Koh 2009). Co-expression of Snail and ERCC1 may identify tumors with cisplatin resistance (Hsu 2010). Additional DNA repair pathways, such as the mismatch repair pathways (MMR) implicated in familial colon cancer, may also be important in mediating cisplatin-induced apoptosis.

In addition to the examples of specific pathways and mechanisms noted above, it must be acknowledged that technical improvements in genomic, transcriptional and miRNA profiling on paraffin embedded materials are being made rapidly. Such broad molecular profiling may identify as yet identified pathways important in overall survival in the entire study population or specific to one of the treatment arms.

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine whether substitution of cisplatin with cetuximab will result in comparable 5-year overall survival

2.2 Secondary Objectives (6/28/12)

2.2.1 To monitor and compare progression-free survival for “safety”;
2.2.2 To compare patterns of failure (locoregional vs. distant);
2.2.3 To compare acute toxicity profiles (and overall toxicity burden);
2.2.4 To compare overall quality of life (QOL) short-term (< 6 months) and long-term (1 year)
2.2.5 To compare quality of life Swallowing Domains short-term and long-term;
2.2.6 To compare clinician-reported versus patient-reported CTCAE toxicity events;
2.2.7 To explore differences in the cost effectiveness of cetuximab as compared to cisplatin;
2.2.8 To explore differences in work status and time to return to work;
2.2.9 To compare patient-reported changes in hearing as measured by the HHIA-S;
2.2.10 To compare CTCAE, v. 4 late toxicity at 1, 2, and 5 years
2.2.11 To evaluate the effect of tobacco exposure (and other exposures) as measured by standardized computer-assisted self interview (CASI) on overall survival and progression-free survival;
2.2.12 To pilot computer-assisted self interview (CASI) collection of patient reported outcomes in a cooperative group setting;
2.2.13 To determine whether specific molecular profiles are associated with overall or progression-free survival;

2.2.14 To investigate associations between changes in serum biomarkers or HPV-specific cellular immune responses measured at baseline and three months with overall or progression-free survival.

3.0 PATIENT SELECTION (6/3/14)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.1 Conditions for Patient Eligibility (6/25/13)

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma (including the histological variants papillary squamous cell carcinoma and basaloid squamous cell carcinoma) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls); **Note**: Paraffin-embedded cytology specimens are acceptable for p16 evaluation, but cytology smears are not.

Cytologic diagnosis from a cervical lymph node) is sufficient in the presence of clinical evidence of a primary tumor in the oropharynx. Clinical evidence should be documented, may consist of palpation, imaging, or endoscopic evaluation, and should be sufficient to estimate the size of the primary (for T stage).

3.1.2 **Patients must be positive for p16, determined by the OSU Innovation Center CLIA lab prior to Step 2 registration (randomization)**; see 10.2 for details of tissue submission;

3.1.3 Patients must have clinically or radiographically evident measurable disease at the primary site or at nodal stations. Tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site. Limited neck dissections retrieving $\leq$ 4 nodes are permitted and considered as non-therapeutic nodal excisions. Fine needle aspirations of the neck are insufficient due to limited tissue for retrospective central review. Biopsy specimens from the primary or nodes measuring at least 3-5 mm are required.

3.1.4 Clinical stage T1-2, N2a-N3 or T3-4, any N (AJCC, 7th ed.; see Appendix III), including no distant metastases, based upon the following minimum diagnostic workup:

- General history and physical examination by a radiation oncologist and medical oncologist within 8 weeks prior to registration;
- Examination by an ENT or head and neck surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 8 weeks prior to registration;
- One of the following combinations of imaging is required within 8 weeks prior to registration:
  a) A CT scan of the neck (with contrast) and a chest CT scan (with or without contrast);
  b) **or** an MRI of the neck (with contrast) and a chest CT scan (with or without contrast);
  c) **or** a CT scan of neck (with contrast) and a PET/CT of neck and chest (with or without contrast);
  d) **or** an MRI of the neck (with contrast) and a PET/CT of neck and chest (with or without contrast).

Note: A CT scan of neck and/or a PET/CT performed for radiation planning and read by a radiologist may serve as both staging and planning tools.

3.1.5 Zubrod Performance Status 0-1 within 2 weeks prior to registration

3.1.6 Age ≥ 18;

3.1.7 CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function, defined as follows:

- Absolute neutrophil count (ANC) $\geq$ 1,500 cells/mm^3;
- Platelets $\geq$ 100,000 cells/mm^3;
- Hemoglobin $\geq$ 8.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb $\geq$ 8.0 g/dl is acceptable.

3.1.8 Adequate hepatic function, defined as follows:

- Bilirubin $\leq$ 2 mg/dl within 2 weeks prior to registration;
- AST or ALT $\leq$ 3 x the upper limit of normal within 2 weeks prior to registration;

3.1.9 Adequate renal function, defined as follows:

- Serum creatinine ≤ 1.5 mg/dl within 2 weeks prior to registration or creatinine clearance (CC) ≥ 50 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$\text{CCr male} = \frac{(140 - \text{age}) \times (\text{wt in kg})}{(\text{Serum Cr mg/dl}) \times (72)}$$

CCr female = 0.85 x (CrCl male)

3.1.10 **Patients must provide their smoking history (for stratification) via the computer-assisted self interview (CASI) head and neck risk factor survey tool.**

3.1.11 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;

3.1.12 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study and until at least 60 days following the last study treatment.

3.1.13 Patients who are HIV positive but have no prior AIDS-defining illness and have CD4 cells of at least 350/mm^3 are eligible. Patient HIV status must be known prior to registration. Patients must not be sero-positive for Hepatitis B (Hepatitis B surface antigen positive or anti-hepatitis B core antigen positive) or sero-positive for Hepatitis C (anti-Hepatitis C antibody positive). However, patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B). HIV-positive patients must not have multi-drug resistant HIV infection or other concurrent AIDS-defining conditions.

3.1.14 Patient must provide study specific informed consent prior to study entry, including consent for mandatory submission of tissue for required, central p16 review and consent to participate in the computer-assisted self interview (CASI) survey questions regarding smoking history.

3.2 Conditions for Patient Ineligibility

3.2.1 Cancers considered to be from an oral cavity site (oral tongue, floor mouth, alveolar ridge, buccal or lip), nasopharynx, hypopharynx, or larynx, even if p16 positive, are excluded. Carcinoma of the neck of unknown primary site origin (even if p16 positive) are excluded from participation.

3.2.2 Stage T1-2, N0-1;

3.2.3 Distant metastasis or adenopathy below the clavicles;

3.2.4 Gross total excision of both primary and nodal disease; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease.

3.2.5 Simultaneous primaries or bilateral tumors;

3.2.6 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.7 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

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

3.2.9 Severe, active co-morbidity, defined as follows:

3.2.9.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;

3.2.9.2 Transmural myocardial infarction within the last 6 months;

3.2.9.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;

3.2.9.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration;

3.2.9.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.2.9.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition with immune compromise greater than that noted in Section 3.1.13; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be

significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.10 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.11 Prior allergic reaction to cisplatin or cetuximab;

3.2.12 Prior cetuximab or other anti-EGFR therapy.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management (6/3/14)

4.1.1 Na, K, Cl, glucose, Ca, Mg, and albumin within 2 weeks prior to the start of treatment as part of standard of care pre-treatment management; Note: Patients with an initial magnesium < 0.5 mmol/L (1.2 mg/dl) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) at the investigator's discretion.

4.1.2 Protocol-specific dental assessment (see Appendices VI and VII) by a physician or designee (such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist) to assess number of teeth and overall dental health within 8 weeks prior to the start of treatment with management according to the guidelines in Appendix IV;

4.1.3 Audiogram within 12 weeks prior to start of treatment;

4.1.4 Protocol-specific assessment of swallowing by clinical staff via CTCAE, v. 4 (dysphagia) within 4 weeks prior to the start of treatment;

4.1.5 If the patient consents to complete the entire head and neck risk factor survey at baseline (optional) via the computer-assisted self-interview (CASI), sites are required to provide it following Step 1 registration.

4.1.6 If the patient consents to complete the optional demographic Work Status Questionnaire (baseline) via the iPAD, sites are required to provide it after Step 1 Registration.

The Quality of Life (QOL) component closed to accrual on 2/28/13. Note: For patients already enrolled on the QOL component, sites must submit follow-up QOL as specified in Section 12.1.

If the patient consents to participate in the quality of life (QOL) component of the study, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment: QLQ-C30, QLQH&N35, EQ-5D, PRO-CTCAE-H&N, HHIA-S, and Work Status Questionnaire (baseline);

4.2 Highly Recommended Evaluations/Management

4.2.1 EKG within 8 weeks prior to start of treatment;

4.2.2 **"**Whole body" PET scan within 8 weeks prior to start of treatment; "whole body" PET/CT may be limited to neck and chest. Note: CT scan of neck and/or PET/CT performed for radiation planning may serve as both staging and planning tools.

4.2.3 Evaluation by a nutritionist and/or swallowing therapist within 2 weeks prior to the start of treatment, to include evaluation for placement of prophylactic gastrostomy or other type of feeding tube; note: The decision to place a feeding tube should be individualized and may consider a number of factors including: prior weight loss, current nutritional status, size and location of the primary tumor (impacting high dose target volume), availability of feeding tube placement services, availability of speech and swallowing specialists, and social support. Feeding tubes may be placed after start of treatment at the discretion of the clinical team. If a tube is placed, the site will document on the appropriate case report form (see Section 12.1) if the tube was placed prophylactically (as a preventative measure) or therapeutically (because of nutritional compromise or other clinical indications).

5.0 REGISTRATION PROCEDURES (10/17/13)

Access requirements for OPEN and TRIAD:

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Note: **This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See below for information on installing TRIAD for submission of digital RT data prior to enrolling patients.**

Note: FOR THIS STUDY, IMRT IS MANDATORY. Use of IGRT and IGRT credentialing is MANDATORY when using PTV margins < 5 mm.

5.1 Image-Guided Radiotherapy (IGRT) (6/3/14)

If an institution uses IGRT for margin reduction, that institution must be credentialed **both for IMRT and for head and neck image-guided radiotherapy (IGRT)** in order to be eligible to enroll patients onto this trial. Sites that have been approved by NRG Oncology for head and neck IGRT credentialing will not have to re-credential for IGRT on this study. Institutions can use IGRT as a patient setup aid without credentialing, but standard margins must be used until they complete the credentialing process.

The institution or investigator must update an existing or complete a new Facility Questionnaire specifically for this study. This information is available on the Imaging and Radiation Oncology Core (IROC) Houston (former Radiological Physics Center [RPC]) web site at http://irochouston.mdanderson.org.

5.2 Pre-Registration Requirements for Image-Guided Radiotherapy (IGRT) Treatment Approach (for sites that utilize this approach for margin reduction) (6/3/14)

5.2.1 In order to utilize IGRT for margin reduction, the center must be credentialed for its use. This means the institution must have met technology requirements and have provided the baseline physics information. This information is available on the NRG Oncology/RTOG web site: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1016 .

In order to become credentialed for head and neck IGRT, the institution must have already become credentialed for head and neck IMRT. Institutions that have not been credentialed by NRG Oncology to perform head and neck IMRT MUST apply for IMRT credentialing as described below in Section 5.3.

5.2.2 IGRT Credentialing Process

Each institution interested in using reduced margins will be required to undergo credentialing for head and neck IGRT (review of at least one case from each institution). The first step is for the institution or investigator to update an existing or complete a new Facility Questionnaire and a Credentialing Status Inquiry Form. This information is available on the IROC Houston web site, http://irochouston.mdanderson.org. **Note**: Sites that have been approved for Head and Neck IGRT credentialing will not have to repeat IGRT credentialing for this trial.

Next, the institution must submit a series of daily treatment images along with a spreadsheet of IGRT data from an anonymized head and neck cancer patient. See the NRG Oncology/RTOG web site, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1016, for the spreadsheet. This series must include a minimum of 5 daily pre-treatment images. These images must be selected to fall on 5 sequential treatment days. Pre-treatment images may include three-dimensional (3D) volumetric images (either fan- or cone-beam CT with Megavoltage (MV) or kilovoltage (KV) x-ray or Orthogonal (MV or KV) 2D images. These images and the spreadsheet will be reviewed by the Medical Physics Co-chairs, Søren Bentzen, PhD, and/or James Galvin, PhD, prior to credentialing. IGRT data and the completed spreadsheet are submitted to TRIAD. Select Benchmark submission (see Section 5.4). IROC Houston will notify the institution that the institution is credentialed.

5.3 Pre-Registration Requirements for IMRT Treatment Approach (6/3/14)

5.3.1 In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston

web site. Visit http://irochouston.mdanderson.org and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with IROC Houston must be successfully completed (if the institution has not previously met this IMRT credentialing requirement on another NRG Oncology IMRT Head and Neck study). Instructions for requesting and irradiating the phantom are available on the IROC Houston web site, http://irochouston.mdanderson.org; select “Credentialing” and “NRG Oncology”. Upon review and successful completion of the phantom irradiation, IROC Houston will notify both the registering institution and NRG Oncology that the institution has completed this requirement. Subsequently, IROC Houston will notify the institution that the IMRT credentialing requirement has been met.

5.4 Digital RT Data Submission Using TRIAD

TRIAD is the American College of Radiology’s (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. Users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the NRG Oncology/RTOG web site Core lab tab.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.5 Regulatory Pre-Registration Requirements (6/3/14)

5.5.1 This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member web site http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov.

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in

the conduct of NCI-sponsored clinical trials).Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov .

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Site registration forms may be downloaded from the RTOG 1016 protocol page located on the CTSU members' web site. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG 1016
- Click on the Site Registration Documents link

Requirements for RTOG 1016 site registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB);
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB);
- CTSU RT Facilities Inventory Form (if applicable);
- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)
  *Note: Institutions must provide certification of consent translation to NRG Oncology
- IRB/REB assurance number renewal information, as appropriate

Non-English Speaking Canadian and Non-North American Institutions:
*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

Submit completed forms along with a copy of your IRB Approval and Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Check the status of your site's registration packets by querying the RSS site registration status

page of the members' section of the CTSU web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.5.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

All pre-registration requirements must be met before registering the first case. In addition to the requirements above, Canadian institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the NRG Oncology/RTOG web site, www.rtog.org, under protocol-specific materials/Canadian resources. Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified

Prior to clinical trial commencement, Canadian institutions must complete and fax (215-569-0206) or e-mail (CTSURegulatory@ctsu.coccg.org) the following forms to the CTSU Regulatory Office Health Canada's Therapeutic Products Directorates:

- Clinical Trial Site Information Form
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form

5.5.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

For institutions that do not have an approved LOI for this protocol:
International sites must receive written approval of submitted LOI forms from NRG Oncology prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

For institutions that have an approved LOI for this protocol:
All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.6 Registration for Use of the CASI System and iPAD (6/25/13)

5.6.1 Registration into the CASI System

Prior to registration of the institution's first case, participating institutions must register into the CASI system for access to computer software and hardware (iPAD) for administration of the following:

1) the mandatory smoking survey for all participants;
the optional QOL Patient-Reported Outcomes assessments (QOL component closed 2/28/13);
2) the optional head and neck cancer risk factor survey;
3) and the optional baseline demographic Work Status Questionnaire.

Note: Institutions must have site IRB approval and have completed all pre-registration requirements before registering into the CASI system.

Guidelines for registering into the CASI system and getting a clinical research associate (CRA) user account are available on the NRG Oncology/RTOG web site, www.rtog.org, on the 1016 protocol page, under "Miscellaneous".

When the CRA user account is established, an "iPAD and CASI Survey User Manual", which provides detailed instructions, will be automatically be e-mailed to the institution.

Institutions should e-mail questions or requests for further information to RTOG1016@osumc.edu

5.6.2 Access to Institution's Local WiFi Network

Prior to registration of the institution's first case, participating institutions should gain access or confirm access to their local WiFi network. Sites will need the name of their local network, user

name and password for the local network, and an IT contact at the institution who will assist with setting up network access on the iPAD.

5.7 Registration

5.7.1 Two Step Registration **(6/3/14)**

- All patients must consent to submission of tissue to the NRG Oncology Biospecimen Bank for p16 analysis.
- Institutions must complete the Eligibility Checklist at Step 1 registration.
- The patient must complete the smoking history survey on the iPAD following Step 1 registration.
- The patient has the option of completing the entire head and neck risk factor survey via the computer-assisted self-interview (CASI) following Step 1 registration.
- The patient has the option of completing the baseline demographic Work Status Questionnaire on the iPAD following Step 1 registration.
- Institutions will submit the patient's tissue to the Biospecimen Resource using the case number obtained from Step 1 registration (see Section 10.2 for details of submission).
- The results of the p16 analysis are expected in approximately 5 business days, and NRG Oncology will inform sites by e-mail of the completion of the HPV analysis. At this point, institutions must complete Step 2 registration, and the patient can be randomized.

5.7.2 OPEN Registration Instructions **(6/3/14)**

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site, https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN:

- See Section 5.0 for obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of NRG Oncology, you must have an equivalent 'Registrar' role on the NRG Oncology roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the

site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (10/17/13)

Note: This trial is not utilizing the services of the ITC for dosimetry digital treatment data submission. See Section 5.4 for information on installing TRIAD for submission of digital RT data prior to enrolling patients.

NOTE: FOR THIS STUDY, IMRT IS MANDATORY. Use of IGRT and IGRT credentialing is MANDATORY when using PTV margins < 5 mm.

Protocol treatment must begin within 2 weeks after Step 2 registration.

6.1 Dose Specifications (6/25/13)

It is recognized that the total doses to subclinical sites have crept higher over the last decade as dose-painting simultaneous integrated boost (SIB) techniques have evolved. In this trial, dose will be slightly reduced to low risk subclinical sites (50-52.5 Gy IMRT or 44 Gy low neck anterior field) in an effort to effect a potentially modest impact in late toxicity to soft tissue and bone.

IMRT will be delivered in 35 fractions over 6 weeks, 6 fractions weekly (typically, with 2 fractions one day per week at least 6 hours apart) in one plan (SIB). Concomitant boost using separate IMRT plans is not allowed.

Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

6.1.1 The primary tumor and involved nodes (CTV1) will typically consist of a 0.5-1.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion and will be prescribed 2 Gy/fraction, total 70 Gy (see Section 6.1.3 for details of prescription for PTV1).

High-risk sub-clinical disease sites, which include possible local subclinical infiltration at the primary site (primary site CTV2) and first echelon nodes, which are not clinically or radiographically involved (nodal CTV2), should be expanded by 3-5 mm to create PTV2. PTV2 should receive 1.6 Gy/fraction to a total dose of 56 Gy. (This dose assumes an alpha/beta ratio of 10 Gy for tumor and 0.7 Gy loss for each day of extending treatment time beyond the time required to deliver the dose at 2 Gy/fraction; 56/1.6 over 6 weeks would result in BED2 of approximately 52 Gy).

Lower-risk targets (PTV3) (such as neck nodal levels which are not first echelon nodes and are not adjacent to levels containing grossly involved nodes) will be prescribed 50-52.5 Gy (at 1.43-1.5 Gy/fraction, BED2 = approximately 40-45 Gy).

6.1.2 Treatment of the low neck: see details in Section 6.5.1. If the low neck is treated, the preferred technique is to treat with isocentric matching AP or AP-PA fields with larynx block, matched to the IMRT portals just above the arytenoids. The dose will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 44 Gy in 22 daily fractions. Whole-neck IMRT is allowed. Involved low neck nodes will receive total 60 Gy in 30 fractions. This can be achieved by either boosting the low neck field with an additional 16 Gy in 8 fractions, by an AP or AP-PA fields, or by planning the whole neck using IMRT. In cases of gross involvement of the vallecula or low neck, whole-neck IMRT should be considered. Whole-neck IMRT may also be considered if level VI is considered to be at risk due to gross involvement of level IV nodes.

6.1.3 All plans must be normalized such that 95% of the volume of the PTV1 is covered with prescription dose of 70 Gy. Additionally:

- At 1 cc PTV1 volume on the DVH curve, the dose should not be > 110% of the prescribed dose.

- At a volume of 0.03 cc within the PTV1 volume on the DVH curve, the dose should not be < 95% of the prescribed dose.
- For any volume of tissue outside the PTVs that has a size of 1 cc, the dose should not be > 74 Gy.

6.2 Technical Factors

6.2.1 Treatment Planning/Delivery: Megavoltage energy photon beam irradiation is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT for previous NRG Oncology trials is acceptable.

6.2.2 Image Guidance for IGRT When Using Reduced Margins (see Section 5.2.2)

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV helical conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);
- Other mechanism, after discussion with the Co-Principal Investigator, Andy Trotti, MD, and the Medical Physics Co-chair, Søren Bentzen, PhD.

The institution's procedure for registering daily treatment imaging datasets with a reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level;
- If the fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room x-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) and automatic (e.g., based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g., optic nerves and/or optic chiasm).

Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are less than 2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5-5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided (see next section).

Management of Radiation Dose to the Patient from IGRT

Estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems. The doses from helical MV CT scan on a tomotherapy unit were estimated to be in the range of 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on the Elekta Synergy machine. The doses for MV cone beam CT are in the range of 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These dose estimates apply to a single imaging procedure, and the 2 cGy dose is used as a typical fraction size for comparison purposes within the treated region. It is important to point out that the imaging dose typically covers parts of the patient's anatomy that are outside the high-dose region that is treated therapeutically, and that it is sometimes necessary to repeat the procedure a number of times during, before, or after a single fraction delivery. The imaging dose to nearby critical structures may become significant when repeated IGRT procedures are performed for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patients must have an immobilization device (e.g. Aquaplast mask) made prior to treatment planning CT scan.

6.3.2 The treatment planning CT scan should be performed with IV contrast so that the major vessels of the neck are easily visualized. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm.

6.4 Treatment Planning/Target Volumes (6/25/13)

6.4.1 Definition of Target Volumes: See Section 6.1.1.

Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered if it is judged clinically that the skin is at risk but is generally not recommended.

- PTV expansion w**ithout** credentialing for daily IGRT: For those institutions that are not using daily IGRT (see Section 6.2.2) specifically for margin reduction, the minimum CTV-to-PTV expansion should be 5 mm (a larger expansion may be necessary for a target volume subject to significant inter-fraction variability such as the tongue). In general, the CTV-to-PTV expansion (without IGRT) should not exceed 10 mm.
- PTV expansion w**ith** credentialing for daily IGRT: For those institutions that are using daily IGRT (see Section 6.2.2) for margin reduction, the minimum CTV-to-PTV expansion is 3.0 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability, such as the non-immobilized oral tongue).In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

6.4.2 Definition of Normal Tissues/Organs at Risk (OARs): **NOTE**: **Only the parts of the normal tissues/organs at risk outside the PTVs will be considered for dose optimization purposes.**

Spinal Cord: The cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self explanatory. The oral cavity will be defined as a composite structure consisting of the anterior ½ to $^{2}/_{3}$ of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan.

OARpharynx: This will be defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (GSL): This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis.

Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

6.4.3 In cases of weight loss > 10% or significant shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask will be adjusted or re-made in order to preserve adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan. The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

6.5 Treatment Planning and Delivery

6.5.1 Management of the Low Neck/Supraclavicular Region (Match versus No Match)

It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in several ways, any of which is permitted for this study. Patient-specific QA measurements are required for all IMRT treatments. When a field "match" technique is used for treating the lower neck, patient-specific measurements should include a verification of the dose coverage in the gap region for each patient

1. Match: The upper cervical lymphatics and primary tumor bed are treated with IMRT. The lower cervical lymphatics and supraclavicular region are treated with a single AP (or occasionally APPA for larger patients with posterior neck at high risk) non-IMRT technique. The latter non-IMRT field(s) is matched to the upper neck IMRT fields. This technique requires comprehensive mid-line spinal cord blocking in the lower neck fields. This technique also allows for a simultaneous blocking of portions of the larynx, hypopharynx, and cervical esophagus in the lower neck fields. Matching 2 IMRT plans is allowed.
2. No Match: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), e.g., the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms.

6.5.2 IMRT Dose Prescription to PTVs

See Sections 6.1 and 6.4 for definitions of CTVs and PTVs and their prescribed doses. The goal is for 95% of the PTV70 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 66.5 Gy. It is recognized that portions of the PTV70 close to the skin may receive significantly less than 66.5 Gy. This is acceptable as long as cold spots within PTV1 do not exist at a depth deeper than 8 mm beneath the skin (see Section 6.8, compliance criteria).

For planning prioritization and priorities in dose coverage, in the final plan, PTV1 will be the highest priority target structure. PTV2 and PTV3, if applicable, will be ranked in the IMRT planning as lower priority than PTV1m although usually at a higher priority than normal structures other than spinal cord and brain stem.

6.5.3 Doses to Normal Structures **(6/28/12)**

Spinal Cord: The PRVcord (as defined in Section 6.4) should not exceed ≤ 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRVbrainstem (as defined in Section 6.4) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.

Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy.

Oral Cavity: Reduce the dose as much as possible. The mean dose should be < 30 Gy for the non-involved oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the non-involved oral cavity.

Parotid Glands: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy. Taking into account new data suggesting monotonous improvement in saliva as dose is reduced, without a threshold (Dijkema 2010), the objective will be to reduce the mean doses to both parotid glands as much as possible.

Contralateral submandibular gland: If contralateral level I is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.

OARpharynx: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.

Cervical Esophagus: Reduce the dose as much as possible. Some recommended (but treatment goals include: Mean dose < 30 Gy.

Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. The glottic larynx mean dose is recommended to be ≤20 Gy. If whole-neck IMRT is used, , under-dosage of PTV2/PTV3 adjacent to the glottic larynx will be limited to <10% receiving < 95% prescribed dose (this under-dosage is similar to that caused by the laryngeal block inserted in the split-field IMRT; Webster 2009).

Mandible: Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy.

Unspecified Tissue Outside the Targets: No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more.

6.5.4 Prioritization for IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV1
4. PTV2(if applicable)
5. PTV3 (if applicable)
6. a. OARpharynx
   b. Parotid gland contralateral to primary tumor site
7. a. GSL
   b. Esophagus
8. a. Lips
   b. Oral Cavity
9. a. Parotid gland ipsilateral to primary tumor site
   b. Mandible
10. Unspecified tissue outside the targets

6.6 Critical Structures (7/16/14)

Note: All required structures must be labeled as listed in the table below for digital RT data submission. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD.

Standard Name	Description
GTV	Primary tumor and involved nodes **Required**
CTV_7000	Primary tumor and involved nodes **Required**
PTV_7000	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT

	Required
CTV_5600	First Echelon nodal regions **Required when applicable**
PTV_5600	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT **Required when applicable**
CTV_5000	Lower risk nodal regions **Required when applicable**
PTV_5000	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT **Required when applicable**
CTV_5250	Lower risk nodal regions **Required when applicable**
PTV_5250	CTV to PTV expansion should be 5 mm minimal margin without IGRT; 3 mm minimal margin with Daily IGRT **Required when applicable**
SpinalCord	Spinal Cord **Required**
SpinalCord_05	Planning risk Volume of 5 mm **Required**
BrainStem	Brain Stem **Required**
BrainStem_03	Planning Risk Volume of 3 mm **Required**
Parotid_L	Left Parotid **Required**
Parotid_R	Right Parotid **Required**
OralCavity	Oral Cavity **Optional**
Lips	Lips **Optional**
Mandible	Mandible **Optional**
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles; should not include PTVs **Optional**
Esophagus	Cervical Esophagus **Optional**
Larynx	Glottic/Supraglottic Larynx **Optional**
External	External border of patient used to define Unspecified Tissue **Required**
PTV_7000_8mm	Minimum dose(cold spot within PTV1 not including portion of PTV near (<8mm) skin) defined for a point that is 0.03cc in size **Required**
NonPTV_7000	Maximum dose (hot spot > 1cc outside the PTVs) **Required**

6.7 Documentation Requirements for IMRT Approach (10/17/13)

- Pre-treatment Radiation therapy planning CT scan;
- If IGRT is not used, then orthogonal images that localize the isocenter placement of IMRT are required. This information should be archived by the submitting institution, so it can be made available for possible future review;

6.8 Compliance Criteria (6/28/12)

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed 5 treatment days at a time and 10 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

All treatment plans are to be normalized to provide exactly 95% volume coverage of the PTV1 with 70 Gy.

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
Total RT dose to PTV1 (to 95% of the PTV)	70 Gy	None	None
Minimum dose ("cold spot" within PTV1, not including portion of PTV near (<8 mm) skin) defined for a point that is 0.03 cc in size	66.5 Gy (equals 95% of prescribed dose)	< 66.5 but > 63 Gy	≤ 63 Gy
Maximum dose ("hot spot" > 1cc) within PTV1	≤ 77 Gy	> 77 but ≤ 82 Gy	> 82 Gy
Maximum dose ("hot spot" > 1cc outside the PTVs)	< 74 Gy	74-77 Gy	> 77 Gy
Total dose to PTV2 (to 95% of the PTV)	56 Gy	≥ 45 but < 56 Gy	< 45 Gy
Total dose to PTV3 (to 95% of the PTV)	50-52.5 Gy	≥ 40 but < 50 Gy	< 40 Gy
Total RT dose to spinal cord PRV (0.03 cc)	≤ 50 Gy	≥ 50 but ≤ 52 Gy	> 52 Gy
Definition of Spinal cord PRV	Based on case review by Co-Principal Investigator, Dr. Trotti or other designated reviewer		
Overall RT treatment time	< 45 days	46-50 days (without a medically appropriate indication for delay)	> 50 days (without a medically appropriate indication for delay).
Non-Medically Indicated Treatment Interruptions	0-2	2-4	> 4

6.9 R.T. Quality Assurance Reviews (6/3/14)

The Co-Principal Investigator, Andy Trotti, MD, the Radiation Oncology Co-Chairs, Avraham Eisbruch, MD, and Paul Harari, MD, and the designated Radiation Oncology reviewers, Min Yao, MD, and James Caudell, MD, will perform RT Quality Assurance Reviews. These reviews will be ongoing. RT Quality Assurance reviews will be facilitated by IROC Philadelphia.

Use of H&N IMRT (and associated QA) was begun in 2005 in RTOG 0522, as an optional technique. At the close of the accrual phase, approximately 90% of cases enrolled on 0522 (> 800 patients) were treated with IMRT. Oropharynx cases comprised 70% of the study population. IMRT has been a standard of care in the U.S. beginning in 2005 and is now widely used in practice. Analysis of the contouring scores and dose plans from RTOG 0522 will be performed in 2011, after completion of final reviews and reporting of the primary trial analysis. RTOG 1016-specific educational materials regarding contouring and treatment planning of tonsil and base of tongue cases will be offered at NRG Oncology semi-annual meetings and online.

6.10 Radiation Therapy Adverse Events

Grade 3-4 (CTCAE, v. 4) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a

feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g. greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in Appendix IV), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

6.11 Radiation Therapy Adverse Event Reporting (3/26/14)

See CTEP-AERS Expedited Reporting Requirements in Section 7.8.

7.0 DRUG THERAPY (6/3/14)

Protocol treatment must begin within 2 weeks after Step 2 registration.

7.1 Treatment

7.1.1 Arm 1: Cisplatin with Concurrent Radiation Therapy (RT) (12/4/12)

Patients will receive cisplatin, 100 mg/m^2, administered intravenously on days 1 and 22 of the treatment course (Note: cisplatin given within 24 hours of days 1 and 22 due to holidays, for example, is acceptable). Weekends count as days.

Use the actual body weight for all patients. There should be no dose modifications because of obesity.

Cisplatin can be given either before or after the radiation therapy fraction that is given on the same day. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation resumes.

High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens should be followed. In the absence of such guidelines:

- For acute nausea and vomiting, premedication should include a 5-HT3 antagonist, such as granisetron 1 mg iv; ondansetron, up to 16 mg iv; or palonosetron, 0.25 mg iv; plus a corticosteroid, such as dexamethasone, up to 20 mg iv. Palonosetron has a longer half life (40h) than the first generation 5HT3 antagonists.
- Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone. Potential delayed nausea regimens include:

    1. The NK-1 antagonist, aprepitant (125 mg p.o.), may be added for prevention of delayed emesis on the day of cisplatin administration and for two consecutive days thereafter (80, 80), with a corticosteroid, such as dexamethasone on days 1-4. Fosaprepitant 115 mg iv may be substituted for the aprepitant 125 mg on day 1. Dexamethasone should be reduced on day 1 to 12 mg and delivered at up to 8 mg total daily for the 3 days following cisplatin administration. A 5HT3 antagonist (e.g. granisetron, ondansetron) may be also given for the 3 days following cisplatin administration, only if palonosetron was not given prior to chemotherapy.
    2. Delayed emesis also may be managed by the addition of dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4mg bid x 2 days, beginning on the day after chemotherapy; and oral metoclopramide 0.5 mg/kg (usually 20-40 mg) qid x 2-4 days. A 5HT3 antagonist (e.g. granisetron, ondansetron) may also be given for up to 3 days after cisplatin administration, only if palonosetron was not given prior to chemotherapy.

Patients must receive vigorous hydration and diuresis. A suggested regimen is prehydration with a 1 liter of D5N S over 2-4 hours and mannitol, 12.5g iv bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m^2, in 500-1000 ml NS is administered over 1-2 hours followed by an additional 1 to 1.5 liters of fluid. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management.

Overnight hospitalization for hydration after cisplatin should be considered if it is allowed by the patient's insurance company. Additional iv hydration and BUN/creatinine check also should be considered, if necessary, later in the week after cisplatin administration, in order to address any dehydration or severe fluid/electrolyte imbalance.

7.1.2 Arm 2: Cetuximab with Concurrent Radiation Therapy (RT) **(12/4/12)**

Cetuximab Initial Dose (prior to RT): Patients on Arm 2 will receive an initial dose of cetuximab, 400 mg/m^2, intravenously (iv) over 120 minutes. No radiation will be given this day, and the 400 mg/m^2 initial dose of cetuximab will precede the first 250 mg/m^2 dose of cetuximab and the first radiation treatment by at least 5, but no more than 7, days (the day of the loading dose is not included in these 5 days). The infusion rate of cetuximab must never exceed 5 mL/min.

Use the actual body weight, even if the BSA is > 2.0. The cetuximab dose always will be calculated using the actual body weight.

Cetuximab Weeks 2-8 (concurrent with RT and for 1 week after RT): Patients on Arm 2 will receive cetuximab, 250 mg/m^2, intravenously (iv) over 60 minutes on a weekly schedule. The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week on Monday or Tuesday for a total of 6 doses concurrent with radiation therapy and for one additional dose after RT completed.

Note: Patients receive a total of 8 doses of cetuximab over 8 weeks, including the initial loading dose, 6 doses concurrent with radiation therapy, and 1 additional dose post-completion of radiation therapy. If a dose of cetuximab is omitted, it will not be made up or added to the end of treatment. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

CAUTION: Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses (a severe reaction occurred in one patient following the 8th dose). The infusion reaction may occur during the infusion or be delayed until any time after the infusion. All patients will be premedicated with diphenhydramine hydrochloride, 50 mg, (or an equivalent antihistamine) by iv 30-60 minutes prior to the first dose of cetuximab in an effort to prevent an infusion reaction. At the discretion of the treating physician, dexamethasone, 20 mg, and an H2 blocker also may be administered iv. Premedications are recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine or dexamethasone may be reduced.

The medical staff must closely observe patients for treatment-related adverse events, especially infusion reactions (see Section 7.5.4 for management) during the cetuximab infusion and during a post-infusion observation hour. For the initial cetuximab infusion, vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be monitored prior to the administration of cetuximab, a half hour into the infusion, at the completion of the infusion, and 60 minutes post the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. In the event that a patient experiences an infusion reaction, see Section 7.5.4 for proper management.

For subsequent infusions, vital signs should be taken pre- and post-infusion; however, it is recommended that the patient be observed for 1 hour post-infusion. For the duration that

patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits. **Patients should be instructed to report any delayed reactions to the investigator immediately**

7.2 Cisplatin (for Arm 1 patients) (10/17/13)

Refer to the package insert for detailed pharmacologic and safety information

7.2.1 Formulation: 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.

7.2.2 Mechanism 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.

7.2.3 Administration: Cisplatin will be given as a bolus, infused over 1-2 hours along with appropriate hydration and anti-emetics.

7.2.4 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.

7.2.5 Adverse Events: 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 excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.

7.2.6 Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meet the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.3 Cetuximab (for Arm 2 patients) (10/17/13)

Refer to package insert for detailed pharmacologic and safety information. Note the black box warning for cardiopulmonary arrest in patients receiving radiation therapy in combination with cetuximab.

7.3.1 Formulation

Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant.

7.3.2 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

7.3.3 Preparation and Administration

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.

Infusion Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administration must be through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
2. Place the syringe into the syringe driver of a syringe pump and set the rate.
3. Administration must be through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
4. Connect up the infusion line and start the infusion after priming the line with cetuximab.
5. Repeat procedure until the calculated volume has been infused.
6. Use a new needle and filter for each vial.
7. Maximum infusion rate should not exceed 5 mL/min.
8. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

(6/25/13) Following the cetuximab infusion, a one-hour observation period is required.

7.3.4 Adverse Events **(6/25/13)**

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; see Section 7.5 for details.

Other adverse events:

- Blood and lymphatic system: Anemia;
- Ear and labyrinth disorders: External ear inflammation, tinnitus;
- Eye disorders: Conjunctivitis, dry eye, uvelitis, watering eyes;
- Gastrointestinal disorders: Diarrhea, nausea, abdominal pain, cheilitis, constipation, dry mouth, dyspepsia, oral mucositis, vomiting;
- General disorders and administration site conditions: Fatigue, fever, chills, edema limbs, flu-like symptoms, infustion-related reaction, non-cardiac chest pain;
- Metabolism and nutritional disorders: Anorexia, dehydration, hypocalcemia, hypomagnesemia;
- Musculoskeletal and connective tissue disorders: arthralgia, back pain, myalgia;
- Nervous system disorders: Headache, syncope;
- Respiratory, thoracic, and mediastinal disorders: Allergic rhinitis, bronchospasm, cough, dyspnea, hoarseness, and rarely, pneumonitis and non-cardiogenic pulmonary edema;
- Skin and subcutaneous tissue disorders: dry skin, rash acneiform, rash maculo-papular, alopecia, nail loss, photosensitivity, pruritus, purpura, skin ulceration, urticaria, and rarely, Palmar-plantar erythrodysesthesia syndrome;
- Vascular disorders: hypotension, thromboembolic event.

Note: Cetuximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3.5 Storage Requirements/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

7.3.6 **(2/23/16)** Supply

Commercially available in the U.S. and provided free of charge to Canadian sites by Eli Lilly and Company or its local affiliate.

Canadian Institutions

Cetuximab will be distributed by a vendor, Biologics, Inc., under contract to NRG Oncology. Biologics will place the cetuximab in a Biologics logo box for easy identification at the site. Biologics will ship a patient-specific supply of cetuximab with enough quantity to complete protocol treatment for a 200-pound individual (43 vials) once the site has registered the patient. Since doses are dependent on the patient's BSA, sites can obtain additional per-patient supply for individuals over 200 pounds by contacting Biologics.

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF), which is available on the NRG Oncology/RTOG web site (www.rtog.org, under protocol-specific materials/Canadian resources) Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

Biologics will ship the order "same day" for all orders received before 4 p.m. EST, Monday through Thursday via FedEx International Priority. Orders received after 4 p.m. EST, Monday through Thursday and any time on Friday will be processed and shipped the next business morning.

Drug deliveries are restricted during weekends and holidays. Biologics observes the following holidays: New Year's Day, Memorial Day, July 4th, Labor Day, Thanksgiving Day and the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Upon notification of a new patient enrollment, Biologics will place an outbound call to the site contact to confirm that the site's shipment is being processed. Biologics' distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx OneCall Solution (live support). Real-time monitoring enables Biologics to mitigate potential delivery delays.

At the completion of the trial, unused supplies of cetuximab will be destroyed at the site according to the institution's policy for drug destruction. Sites should complete the drug destruction form located on the NRG Oncology/RTOG website www.rtog.org (under protocol-specific materials/Canadian resources) and send the form to Biologics (see contact information below).

Questions about supply and delivery should be directed to:
Elliott Lee, Clinical Research Program Manager
Clinical Research Services
Biologics, Inc.
120 Weston Oaks Court
Cary, NC 27513-2256
(800) 693-4906/(919) 459-4990

Non-Canadian International Institutions
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.4 Dose Modifications for Cisplatin (7/16/14)

7.4.1 Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200/mm^3, hold the second chemotherapy treatment but not the radiation until ANC ≥ 1200/mm^3, then treat at 100% dose.

Neutropenic fever (i.e. ANC <1000/mm^3 with a single temperature of > 38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than 1 hour) will require a 25% dose reduction of the second cisplatin dose.

7.4.2 Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000/mm^3, hold the second chemotherapy treatment but not the radiation until platelets are ≥ 75,000/mm^3, then treat at 100% dose.

Thrombocytopenia that results in bleeding will require a 25% dose reduction of the second cisplatin dose.

7.4.3 Neurotoxicity: If grade 2 neurotoxicity developed, hold cisplatin (but continue RT) until toxicity improves to < grade 1, then reduce the second cisplatin dose to 80 mg/m^2.

If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin, but continue RT.

7.4.4 Renal Adverse Events: Cisplatin dose should be based on the serum creatinine or creatinine clearance immediately prior to the second cisplatin dose using the following guidelines:

Note: If creatinine is > 1.5 mg/dl, creatinine clearance must be calculated (Cockcroft-Gault) in order to make dose adjustment. If the calculated clearance is 50 mL/min or above, a 24-hour urine collection is not needed, but if the calculation is less than 50 mL/min, a 24-hour urine collection is mandated, and the cisplatin dose will be determined as follows:

Serum Creatinine		Creatinine Clearance	Cisplatin Dose
≤ 1.5 mg/dl	or	> 50 ml/min	100 mg/m^2
> 1.5 mg/dl	and	40-50 ml/min	50 mg/m^2
> 1.5 mg/dl	and	< 40 ml/min	Hold drug*

*Cisplatin should be held (but the RT continued) and the creatinine measured weekly, until it is < 1.5 mg/dl or the creatinine clearance is > 50 ml/min, and then the second dose of cisplatin should be given at the reduced dose of 50 mg/m^2.

7.4.5 Nausea and Vomiting: Maximum supportive therapy will be given, and cisplatin will be continued at full dose for ≤ grade 2 nausea and vomiting. For grade 3 nausea and vomiting refractory to supportive therapy, cisplatin will be held until recovery to < grade 2. No dose reductions will be made.

7.4.6 Mucositis: Significant mucositis (grade 3-4, CTCAE, v. 4) is expected from radiation and cisplatin and should not be a reason for a treatment break, unless it significantly interferes with fluid intake or nutrition. Aggressive supportive care is encouraged.

7.4.7 Ototoxicity: For clinical hearing loss not requiring a hearing aid, reduce cisplatin to 50 mg/m^2. For hearing loss requiring a hearing aid, discontinue cisplatin. For grade 2-3 tinnitus (CTCAE, v. 4) at the time of retreatment, hold cisplatin until improvement to grade 1 or less and then reduce the 2nd dose of cisplatin to 50 mg/m^2. If tinnitus does not improve to grade 1 or less by the last day of radiation therapy, discontinue cisplatin.

An audiogram is strongly recommended when there is any report of significant change in hearing and/or an increase in tinnitus.

7.4.8 For any other grade 3-4 non-hematologic adverse events possibly related to cisplatin, hold cisplatin until toxicities have recovered to grade 1 or less.

7.4.9. If the second dose of cisplatin is delayed more than 21 days because of hematologic, neurologic, renal, or other adverse events, that dose will be omitted. If a weight change of ≥ 10% occurs, the second cisplatin dose should be adjusted.

7.5 Dose Modifications for Cetuximab

7.5.1 Cetuximab Dose Levels

	Starting Dose	**Dose Level –1**	**Dose Level –2**
Cetuximab	400 mg/m^2 (week 1 only)		
Cetuximab	250 mg/m^2 (weekly)	200 mg/m^2 (weekly)	150 mg/m^2 (weekly)

Note: If a weight change of ≥ 10% occurs, the cetuximab dose should be adjusted.

7.5.2 Cetuximab Dose Modifications for Hematologic Adverse Events

Cetuximab will not be dose reduced or held for hematologic adverse events, such as neutropenia, neutropenic fever, or thrombocytopenia.

7.5.3 Cetuximab Dose Modifications for Non-Hematologic Adverse Events **(12/4/12)**

Toxicity Grade (**CTCAE, v. 4)**	**Cetuximab Dose** [a]
Renal-Calculated Creatinine Clearance	
≥ 50 mL/min	Maintain dose levels
< 50 mL/min	Maintain dose levels
Fatigue (Asthenia) ≥ Grade 3	Maintain dose levels
Nausea/Vomiting ≤ Grade 2 with maximal medical management ≥ Grade 3 with maximal medical management	Maintain dose levels Hold drug until ≤ grade 2, then resume at same dose level
Other Non-hematologic Adverse Events [b, c]	
Grade 3- 4, if possibly related to cetuximab, or likely to be exacerbated by continuation of cetuximab, e.g. diarrhea, except for weight loss or mucositis	Hold drug until < grade 3, then resume at 1 dose level reduction
Any grade 1-2	Maintain dose levels

[a]Dose levels are relative to the previous dose. Dose reductions of cetuximab below the –2 dose level will not be allowed. If a dose reduction below the -2 dose is mandated by the toxicity grade, cetuximab will be permanently discontinued. In any case of cetuximab treatment delay, there will be no re-loading infusion, and all subsequent treatment will be at the assigned dose level.

[b]With the exception of infusion reaction ;

[c]For depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician. (see table below for management of hypomagnesemia).

Hypomagnesemia

Electrolyte repletion, principally magnesium, was necessary in some patients treated with cetuximab and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence monitoring during and after cetuximab treatment is recommended:

CTCAE, v. 4 Grade	Serum Magnesium		Guidelines for management	Action
	mg/dL	mmol/L		
1	< LLN – 1.2	< LLN – 0.5	Consider replacement with IV magnesium sulfate 2-5 g in normal saline or D5W. Infusion schedule based on institutional guidelines.	Maintain dose and schedule
2	< 1.2 – 0.9	< 0.5 – 0.4	As above for grade 1 and consider prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) if grade 2 of higher hypomagnesemia persists.	Maintain dose and schedule
3	< 0.9 – 0.7	< 0.4 – 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level
4	< 0.7	< 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then reduce by 1 dose level

7.5.4 Cetuximab Infusion Reaction Management **(6/28/12)**

CTCAE, v. 4 Adverse Event Grade	Treatment Guidelines[a]
Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	For mild infusion reactions manifesting only as delayed drug fever, consider administering prophylactic antihistamine medications for subsequent doses. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.
Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	For moderate infusion reactions, slow the infusion rate for cetuximab by 50% when the drug is restarted and consider administering antihistamine medications and/or steroidal medications. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	**NO FURTHER STUDY DRUG THERAPY.** Severe infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.
Grade 4: Life-threatening consequences; urgent intervention indicated	**NO FURTHER STUDY DRUG THERAPY.** Life threatening infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

[a]**Study Therapy Retreatment Following Infusion Reactions: Once a cetuximab infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second infusion reaction > grade 2 with the slower infusion rate, the infusion should be stopped, and the subject should receive no further cetuximab treatment. If a subject experiences a Grade 3 or 4 infusion reaction at any time, the subject should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an infusion reaction of Grades 1-4, the Study Chair or Medical Oncology Co-Chair should be contacted immediately to discuss and grade the reaction.**

7.5.5 Cetuximab Special Instructions **(6/25/13)**

Weekly cetuximab will continue if radiation therapy is being held. If cetuximab is omitted for more than four consecutive infusions for adverse events due to cetuximab, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the subject should be discontinued from further cetuximab therapy. If adverse events prevent the administration of cetuximab, the subject may continue to receive radiation therapy.

If a dose of cetuximab is omitted, it will not be made up or added to the end of treatment. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

Management of Cetuximab Infusion Reactions

Severe or life threatening (grade 3 or 4) infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see below.

Treatment of Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

Cetuximab-related Rash

- Manifestations
  Rash associated with EGFR-inhibitors is a relatively new dermatologic condition. It appears to be "acneiform" but it is NOT considered a form of acne; rather, it is a form of folliculitis. Skin changes may be manifested in a number of ways: erythema; follicle based papules, which may ulcerate; pain; itching; cosmetic disturbance; and/or nail disorders. The rash may become infected and transform into cellulitis.
- Grading of Cetuximab-induced Rash
  According to physician judgment, if a patient experiences ≥ grade 3 rash (according to either the "outside of the radiation field" or the "inside of the radiation field" definitions below), cetuximab treatment adjustments should be made according to the Cetuximab Dose Modification table that follows. In patients with mild and moderate skin adverse events, cetuximab should continue without adjustment.

  NOTE: Rash intensity (i.e., the size and number of papules or the level of discomfort and extent of erythema) may be an important consideration. However, the absolute number of lesions, **without associated physical discomfort**, does not necessarily constitute a basis for a dose reduction or delay. Rash considered "intolerable" (because of pain, itching, or appearance) or that has failed to respond to symptomatic management may be considered grade 3 and thus prompt dose reduction or delay of cetuximab. **The clinical judgment of the treating physician is critical to grading and will ultimately dictate dose modification.**
- Acute Skin Changes
  - Rash Occurring **Outside** of the Radiation Field: Should be graded using the following CTCAE, v. 4 terms. A rash complicated by secondary infection or cellulitis should be graded per additional CTCAE terms.

	1	2	3	4
Pruritus*	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/acneiform*	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADLI	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences
Paronychia*	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-

*Onset of grade 3 will require modification. See the table below, "Cetuximab Dose Modification Guidelines for Dermatologic Changes".

- Rash Occurring **Inside** the Radiation Field: Acute radiation dermatitis may be exacerbated by cetuximab or chemotherapy. The severity of such rash should be graded using CTCAE, v. 4 criteria for radiation dermatitis (table below).

	1	2	3	4
Radiation recall reaction (dermatologic); Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

- *Late Skin Changes* A potential late change of interest is consequential scarring/pock marking **in or out of the radiation field**. This may be reported by using the MedDRA code, "Skin and subcutaneous tissue disorders - Other, specify", with the following protocol-specific grading scale as guidance:
  - Grade 1: Mild (seen only on close inspection)
  - Grade 2: Moderate (scarring, intervention or cosmetic coverage/intervention indicated)
  - Grade 3: Severe (significant disfigurement, deep scarring, or ulceration)
  - Grade 4: Deep cratering/scarring, skin necrosis, or disabling

Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)			
	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at 250 mg/m^2
		No Improvement; remains grade 3	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at Dose Level -1 (200 mg/m^2)
		No Improvement; remains grade 3	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at Dose Level -2 (150 mg/m^2)
		No Improvement; remains grade 3	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Drug Related Rash Management

Patients developing dermatologic adverse events while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Below are suggestions for managing cetuximab-induced rash*:

- **Antibiotics**: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear. Some clinicians have used oral minocycline (Minocin), mupirocin (Bactroban), or topical clindamycin (Cleocin). Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.
- **Antihistamines**: Benadryl or Atarax may be helpful to control itching.
- **Topical Steroids**: The benefit of topical steroids is unclear.
- **Retinoids**: No data to support use. Use is not advised.
- **Benzoyl peroxide**: Should NOT be used--may aggravate rash.
- **Makeup**: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena, Dove, or Ivory Skin Cleansing Liqui-Gel.
- **Moisturizers**: Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream or Vaseline Intensive Care Advanced Healing Lotion.
- **Sunlight**: It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.
- **Over-the-counter medications**: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

*Adapted from Perez-Soler R, Delord J, Halpern A, et al. HER1/EGFR inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR Inhibitor Rash Management Forum. *The Oncologist*. 10:345–356, 2005.

7.6 Modality Review (6/3/14)

The Co-Principal Investigator, Maura Gillison, MD, PhD and the Medical Oncology Co-Chair, David Adelstein, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1.

The scoring mechanism is: **Per Protocol, Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Co-Principal Investigator, Dr. Gillison and the Medical Oncology Co-Chair, Dr. Adelstein will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at IROC Philadelphia. Drs. Gillison and Adelstein will perform the next review after complete data for the next 20 cases enrolled has been received at IROC Philadelphia. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at IROC Philadelphia, whichever occurs first.

7.7 Adverse Events (3/26/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613)

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

7.7.1 Adverse Events (AEs) (3/26/14)

Definition of an AE: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.7.2 Serious Adverse Events (SAEs)

— Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.8 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.8. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.7.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (6/25/13)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS **within 30 days of AML/MDS diagnosis.**

Secondary Malignancy:
A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:
A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.8 CTEP-AERS Expedited Reporting Requirements (2/23/16)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613.

Submitting a report via CTEP-AERS serves as notification to NRG Oncology and satisfies NRG Oncology requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Oncology Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies a CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

CTEP defines expedited AE reporting requirements for phase 3 trials as described in the table below. **Important:** All AEs reported via CTEP-AERS also must be reported on the AE section of the appropriate case report form (see Section 12.1). As of 2/1/16, NRG Oncology will submit all SAEs to Eli Lilly Global Patient Safety, FAX 866-644-1697 or 317-453-3402.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies within 30 Days of the Last Administration of the Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of the agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

(7/16/14) <u>Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:</u>
The following are protocol specific exceptions to expedited reporting via CTEP-AERS. Report the following AEs in an expedited manner only if they exceed the grade in parentheses next to the AE: lymphocyte count decrease (grade 4), nausea (grade 3), vomiting (grade 3), diarrhea (grade 3), dehydration (grade 3), and mucositis (grade 3). Routine adverse event reporting on the case report form fulfills safety reporting requirements for these events at the aforementioned grades.

8.0 SURGERY

Surgery is expected to play only a limited role in favorable risk HPV-associated cancers. Locoregional progression is expected in <10% of patients. The role of neck dissection has been declining in recent years, in part due to higher response rates with use of concurrent chemotherapy and a high rate of negative specimens when planned neck dissections are performed in cancers of the oropharynx. In fact, this may be a reflection of the growing proportion of HPV-associated cancers (29% of oropharynx cases in RTOG 90-03; 60% in RTOG 0129).

8.1 Post-Treatment Imaging/Timing

The initial post-radiation imaging evaluation will be performed at 12 weeks after the completion of radiotherapy with contrast-enhanced CT, MRI, and/or PET/CT based on the preference of treating clinicians. PET/CT is preferred to facilitate pre-and post-treatment evaluation of metabolic response and the need for post-treatment neck dissection. If physical examination and imaging suggest residual disease at the primary site, a biopsy will be performed to confirm residual disease; otherwise, patients will undergo serial follow up.

8.2 Post-Treatment Surgical Salvage of Residual Disease

Treatment of residual disease at the primary site will be determined by the treating clinicians and the clinical situation, and surgical resection, re-irradiation, chemotherapy, or palliative care will be done. If the primary site is cleared of residual disease yet residual disease at the cervical nodal basin is suggested by imaging/clinical evaluation, then selective neck dissection will be performed unless a cytologic sampling of the node is negative. Post-treatment “planned” neck dissection will be defined as being performed for residual disease and within 20 weeks (140 days) of completion of radiotherapy. Positive neck specimens removed within 140 days will be considered part of the initial treatment plan and not considered as failures of initial management; positive specimens upon neck dissection beyond 140 days will be considered regional failures. Note that this is relaxed from the traditional definition of 105 days (15 weeks) in order to permit resolution of HPV-associated adenopathy, which is commonly cystic and has a somewhat slower regression rate. Such post-treatment consolidation neck dissections will encompass only the areas (typically only levels 2 and 3) initially involved in the side of the neck in question. The extent of neck dissections performed for nodal recurrence, nodal progression, or salvage of disease at the primary will be determined by the treating surgeon. In the case of negative PET in patients who did not achieve clinical or CT/MRI-based radiological nodal CR, follow-up PET scans are recommended every 3-4 months for 24 months, then every 6 months for years 3-5, as well as careful recording of the clinical dimensions of the residual abnormality.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

9.1.1 All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site’s source documents as concomitant medication. These may include analgesics, antiemetics, topical mouth rinses, skin creams/ointments, etc.

9.1.2 In general, HIV-positive patients who are on a stable HAART regimen should continue HAART while receiving chemotherapy. However, for patients who are newly diagnosed with HIV, it is preferable to defer initiation of HAART until after chemotherapy is completed. HAART regimens containing zidovudine and stavudine should be avoided during chemotherapy due to concerns for overlapping toxicity with chemotherapy. In addition, the protease inhibitor atazanavir (RayatazTM) can cause a physiologically unimportant hyper-hyperbilirubinemia; however, in the setting of chemotherapy, some experts suggest switching that drug for another equally effective one. If HAART is withheld during chemotherapy, it should be resumed promptly after conclusion of the last cycle of chemotherapy.

9.2 Non-permitted Supportive Therapy

9.2.1 The use of amifostine as a radioprotector is not allowed. The use of granulocyte colony-stimulating factor or erythropoietin is not allowed. Any exceptions must be approved by the Principal Investigators, Dr. Trotti or Dr. Gillison, or the Medical Oncology Co-Chair, Dr. Adelstein. Transfusion is to be performed at the discretion of the treating physician.

10.0 TISSUE/SPECIMEN SUBMISSION (6/3/14)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission. If the patient consents to participate in the specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note**: Sites are <u>not</u> permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncoloyg encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncoloyg Biospecimen Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions. The NRG Oncology Biospecimen Bank also collects tissue for central review of pathology. Central review of tissue can be for eligibility and/or analysis.

In this study, tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of p16 testing (mandatory) at the Innovation Center at The Ohio State University (OSU) and for banking and translational research (highly recommended).

10.2 Specimen Collection For Central p16 Analysis — Mandatory

The H & E slide and the formalin-fixed, paraffin-embedded tissue block, punch biopsy, or section taken from a biopsy must be submitted to the NRG Oncology Biospecimen Bank in San Francisco to facilitate central p16 analysis within 1 week of study entry. Cytopathology smears are inadequate for p16 determination and thus, are not acceptable for central review. Paraffin-embedded cytopathology (cell block) may be evaluable depending on the cellularity of the specimen, but tissue is preferred.

The NRG Oncology Biospecimen Bank will ship the unstained sections to the Innovation Center CLIA lab at The Ohio State University (OSU) for p16 determination within 2 business days of receipt of the specimens at the Biospecimen Resource (based upon ongoing experience with RTOG 0920). The Innovation Center at OSU will report the tumor p16 status to NRG Oncoloyg within 2 business days of receipt. The total time from receipt of samples to reporting of p16 results is therefore anticipated to be approximately 5 business days. NRG Oncology will inform sites by e-mail of the results of the HPV determination.

Note: Regardless of smoking history, all oropharynx cancers of eligible stage should be considered for study enrollment and evaluated for tumor p16 status. Fifty percent of HPV-positive patients enrolled in a prior RTOG study had a history of tobacco smoking. Investigators are therefore encouraged to evaluate all oropharynx cancer patients for trial eligibility. The use of mandatory central p16 testing is not intended to discourage institutional p16 testing. However, current data suggest that p16 testing has not been standardized at a national level, resulting in up to 30% discordance between local and central testing. Therefore, central confirmation of p16 is required for randomization.

The following material must be provided to the NRG Oncology Biospecimen Bank for central testing (Mandatory):

10.2.1 Representative **H & E stained slides** from the area with the highest grade within the tumor (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide);

10.2.2 **A corresponding paraffin block of tumor** (the block must match the H&E being submitted); **Note:** The block is preferred, but if sites are unable to provide the block, then the site can submit **either** of the following:

- One H & E and two 5 micron unstained slides cut onto positively charged slides **AND** two 2 mm cores of the block taken with a punch tool is acceptable. The unstained slides should be cut before punching the cores from the block. A specimen plug kit can be requested from the NRG Oncology Biospecimen Bank (see Appendix V for instructions).

  OR
- If the site will not release the block or allow punches to be taken, then the H & E **AND** a minimum of 10 five micron unstained slides cut onto positive charged (adherent) slides is an acceptable substitute.

10.2.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.2.3 A Specimen Transmittal (ST) Form stating that the tissue is being submitted for Central Review. The Form must include the NRG Oncology protocol number and the patient's case number.

10.2.4 Central Review will be performed for every case at the NRG Oncology Biospecimen Bank for adequacy of tumor tissue.

10.2.5 Tumor p16 expression will be evaluated in a CLIA certified laboratory at the Innovation Center of The Ohio State University by means of immunohistochemical analysis with a mouse monoclonal antibody (MTM Laboratories, Westborough, MA) visualized with use of an autostainer (Discovery XT, Ventana, Tucson, AZ) and a secondary detection kit (iVIEW DAB Detection Kit, Ventana) by standard protocol. Positive p16 expression will be defined as a strong and diffuse nuclear and cytoplasmic staining in 70% or more of the tumor cells.

10.3 Specimen Collection for Tissue Banking and Translational Research—Highly Recommended (10/17/13)

For patients who have consented to participate in the tissue/blood component of the study (See Appendix I).]

The overall objective of collecting specimens for translational research is to prospectively establish a repository of both risk factor profiles and biospecimens from patients enrolled in RTOG 1016 to facilitate future hypothesis generated research.

See Appendix V for detailed collection instructions, including information pertaining to collection kits. Note: Kits can be requested from the NRG Oncology Biospecimen Bank, RTOG@ucsf.edu, and include a pre-paid shipping label for shipment of frozen biospecimens.

10.3.1 Tumor Tissue

Tissue for banking will be taken from the tumor tissue block for central review (see Section 10.2.2).

10.3.2 Serum, Plasma, and Whole Blood Collection

Serum, plasma, and whole blood will be collected pre-treatment. In addition, plasma and serum will be collected at the 3- and 6-month follow-up visits. If a site misses the pre-treatment collection time point, they may collect the whole blood specimen at any time during treatment or at follow up.

The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection, time point of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, and method and time point of storage (for example, stored at -80° C for 3 days) must be included.

10.3.3 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

10.3.4 Specimen Collection Summary **(6/28/12)**

Specimens for Central Review (Mandatory) and Tissue Banking/ Translational Research (Highly Recommended)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Mandatory representative H&E stained slides of the primary tumor for central review (and banking if the patient consents)	Pre-treatment	Mandatory H&E stained slide	Slide shipped ambient
Mandatory: A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment OR two 5 micron slides AND two 2 mm diameter core of tissue, punched from the tissue block with a punch tool for central review (and banking if the patient consents)	Pre-treatment	Mandatory paraffin-embedded tissue block or punch biopsy **Note**: 10 unstained slides are permitted ONLY if site is not able to submit a block or provide a punch.	Block or punch (or unstained slides) shipped ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge for banking if the patient consents	Pre-treatment and at 3- and 6-month follow-up visits	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (5 to 10)	Serum sent frozen on dry ice via overnight carrier (Mon-Wed)
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) and centrifuge for banking if the patient consents	Pre-treatment and at 3- and 6-month follow-up visits	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (5 to 10)	Plasma sent frozen on dry ice via overnight carrier (Mon-Wed)
DNA: 5-10 mL of anticoagulated whole blood in purple/lavender EDTA tube #2 (purple/lavender top) and mix for banking if the patient consents	Pre-treatment; **Note**: if site missed this collection, the site may collect whole blood at any other time during treatment or follow up.	Frozen whole blood samples containing 1 ml per aliquot in 1 mL cryovials (3 to 5)	Whole blood sent frozen on dry ice via overnight carrier (Mon-Wed)

10.3.5 Submit materials for Tissue Banking, Central Review, Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-urgent/Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Urgent FFPE and Frozen Specimens
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Reimbursement (6/3/14)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the National Clinical Trials Network (NCTN) Program. This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system.

10.5 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/biospecimen/tissuefaq.html for further details.)

10.5.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for central review will be retained until the study is terminated. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters: See Appendix I for a summary of assessments and time frames.

11.2 Pre-Treatment Evaluations (6/25/13)

11.2.1 One of the following combinations of imaging is required within 8 weeks prior to registration:

a) A CT scan of the neck (with contrast) and a chest CT scan (with or without contrast);
b) or an MRI of the neck (with contrast) and a chest CT scan (with or without contrast);
c) or a CT scan of neck (with contrast) and a PET/CT of neck and chest (with or without contrast);
d) Or an MRI of the neck (with contrast) and a PET/CT of neck and chest (with or without contrast);

Note: A CT scan of neck and/or PET/CT performed for radiation planning and read by a radiologist may serve as both staging and planning tools.

11.2.2 Evaluation by a nutritionist and/or swallowing therapist is highly recommended within 2 weeks prior to the start of treatment and should include evaluation for placement of prophylactic gastrostomy or other type of feeding tube. The decision to place a feeding tube should be individualized and may consider a number of factors including: prior weight loss, current nutritional status, size and location of the primary tumor (impacting high dose target volume), availability of feeding tube placement services, availability of speech and swallowing specialists, and social support. Feeding tubes may be placed after start of treatment at the discretion of the clinical team. If a tube is placed, the site will document on the appropriate case report form (see Section 12.1) if the tube was placed prophylactically (as a preventative measure) or therapeutically (because of nutritional compromise or other clinical indications).

11.2.3 Patients who are HIV positive but have no prior AIDS-defining illness and have CD4 cells of at least 350/mm^3 are eligible. Institutions must perform a CD4 count for patients with known HIV infection prior to Step 1 registration to determine eligibility.

11.3 Evaluation During Radiotherapy

11.3.1 A brief history & physical by a Radiation Oncologist and/or Medical Oncologist must be done weekly.

11.3.2 Biopsy of any lesion(s) suspicious for tumor recurrence is recommended.

11.4 Evaluation in Follow Up (6/25/13)

11.4.1 A brief history & a physical examination by a Radiation or Medical Oncologist or an ENT or Head & Neck Surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), must be done at 1 and 3 months from the end of radiation treatment, then every 3 months through year 2, every 6 months for 3 years, then annually.

Radiographic imaging (CT, MRI, or PET as appropriate) at these time points is highly recommended if disease progression is suspected by the treating physician. If performed, radiographic imaging to evaluate the patient for both local-regional recurrence and distant metastases is highly recommended (see Section 11.5.1).

11.4.2 Chest imaging: A chest CT or a PET/CT of chest **is required once per year** for a total of 5 image sets.

11.4.3 Biopsy of any lesion(s) suspicious for tumor recurrence is recommended as clinically indicated.

11.4.4 The initial post-radiation imaging evaluation at 3 months after the completion of radiotherapy **is highly recommended to assess response but is not required.** The imaging can be contrast-enhanced CT, MRI, or PET/CT of the head and neck or "whole body" PET/CT (minimum neck and chest) based on the preference of the treating clinician.

11.5 Measurement of Response/Progression

11.5.1 Response versus "Tumor Clearance" versus Cancer Progression

Response and confirmation of local (primary site) or regional (neck) "tumor clearance" are not endpoints in this study. Clinical or radiographic evidence of progressive local-regional disease beyond 20 weeks should be documented in the clinical record and ideally confirmed by local or regional biopsy, neck dissection, or salvage surgery. CT or MRI (of head and neck region, with CXR or Chest CT), or PET/CT (including chest anatomy) may be used as radiographic evaluation of overall cancer status. The primary, neck and chest portions of the scans should be evaluated and reported separately. The CT portion of a PET/CT may serve as sufficient radiographic evaluation of the chest. If CT or MRI is used for evaluation of the head and neck region, CXR or CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals as outlined above in Section 11.4.

11.5.2 Local or Regional Progression

Local (primary site) or regional (neck) progression is defined as clinical or radiographic evidence of progressive disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) to document the precise pattern of failure if possible. Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians.

11.5.3 Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

11.5.4 Second Primary Neoplasm

Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

11.6 Criteria for Discontinuation of Protocol Treatment (6/25/13)

- Unacceptable toxicity; see Sections 7.4 and 7.5 for further information.
- Progression of disease;
- Development of a 2nd primary upper aerodigestive tract malignancy (e.g., lung cancer, esophagus cancer, 2nd primary head and neck cancer);
- A delay in protocol treatment, as specified in Sections 7.4 and/or 7.5.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

11.7 Quality of Life and Functional Assessments (6/25/13)

The QOL component was closed to accrual on 2/28/13 (with the exception of the optional baseline Work Status Questionnaire and baseline BRASS; see Sections 11.7.5 and 11.7.6 below). Note: For patients already enrolled on the QOL component, sites must submit follow-up QOL as specified in Section 12.1.

To minimize selection bias, all patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment. If the patient consents to participate in the

quality of life (QOL) component of the study, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment.

After 400 consecutive patients have been enrolled into the optional QOL component, this component will close. However, all patients should continue to be offered participation in the baseline head and neck risk factor survey.

The assessments below (with the exception of the Head and Neck Risk Factor Survey [Section 11.7.6]) will be completed at the following time points: pre-treatment (baseline), end of treatment, and at 3, 6, and 12 months from the end of treatment. Target windows for data collection will be: 1) for end of treatment should be collected within 2 weeks of the last day of radiation therapy; 2) at 3 and 6 months should be collected within +/- 2 weeks of these time-points; and 3) at 12 months within +/- 4 weeks of this time-point. However, if not possible, data should still be collected outside of these windows and analysis will account for the timing of data collection. The Head and Neck Risk Factor Survey will be administered once, at baseline.

All QOL/functional assessments, the PRO-CTCAE H&N, and the head and neck cancer risk factor surveys listed below will be collected from patients at clinic visits via iPAD computers or an online CASI system (Guidelines for registering into the CASI system are available on the RTOG web site, www.rtog.org, on the 1016 protocol page, under "Miscellaneous"). To complete electronic questionnaires, site research personnel who have been trained to use the CASI iPAD and/or online systems should remain available to patients to assist them if necessary. Versions of the surveys are available on the RTOG web site for submission to site's IRBs.

11.7.1 The EORTC QLQ-C30

The EORTC QLQ-C30, v. 3.0 is a 30-item self-reporting questionnaire grouped into 5 functional subscales (role, physical, cognitive, emotional, and social functioning). In addition, there are 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting), questions concerning common symptoms in cancer patients, and 2 questions assessing overall quality of life. It has been translated and validated in 81 languages. The patient can complete the QLQ-C30 in approximately 7 minutes. Sites can check the web site for the specific languages available: http://groups.eortc.be/qol/translations.htm

11.7.2 The EORTC QLQ-H&N35

The Head and Neck module of the EORT QLQ-C30 is a 35-item self-reporting questionnaire that the patient can complete in approximately 7 minutes. The patient answers questions about head and neck pain, swallowing, saliva, eating, and social interactions. The QLQ-H&N35 has been translated and validated in over 20 languages. Sites can check the web site for the specific languages available: http://groups.eortc.be/qol/translations.htm

11.7.3 The EuroQol (EQ-5D) has been frequently used in cooperative group studies as a general QOL measure and for cost-utility analysis It is a two-part questionnaire that the patient can complete in approximately 5 minutes. The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at http://www.euroqol.org/. The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the QOL cover page.

11.7.4 PRO-CTCAE H&N

PRO-CTCAE is a new outcome measure recently developed by the NCI designed to capture the patient's self-report of adverse events (Hay 2010). A subset of items drawn the PRO-CTCAE system have been aggregated into a head and neck specific tool for use in this trial (PRO-CTAE H&N). The PRO-CTCAE H& N measure tailored for use in this study consists of 25 items that evaluate the presence and/or severity of a range of symptoms, as well as the degree to which the symptom/toxicity interferes with usual function. Individuals respond to the questionnaire items using a 5-point Likert scale, and the PRO-CTCAE H&N requires approximately 10 minutes to complete. In most circumstances, the patient will complete the QOL and PRO-CTCAE-H&N tools prior to the clinical encounter, thus most likely facilitating responses to the clinical team on the same information. At this time, PRO-CTCAE is available only in English. PRO-CTCAE is designed to be completed by the patient without assistance from research staff similar to other quality of life measures.

11.7.5 Work Status Questionnaire H&N

The Work Status Questionnaire H&N is a study-specific survey designed to be completed by the patient without assistance from clinical or research staff, if the patient chooses to complete it on the iPAD at baseline. . This is a new survey tool, adapted from previous studies, and was customized specifically for RTOG 1016. It is available only in English at this time and can be completed in less than 5 minutes.

11.7.6 The Behavioral Risk Assessment Survey System (BRASS)

The Behavioral Risk Assessment Survey System (BRASS) is a computer-assisted self-interview (CASI) head and neck risk factor survey. The domains covered by the survey include demographic profiles, alcohol use, tobacco use, marijuana use, sexual behavior, family history of cancer, oral hygiene, and diet. The entire survey is anticipated to take the patient approximately 20 minutes or less to complete using CASI methods. Institutions also can download a copy of the BRASS for site IRB review on the NRG Oncology/RTOG web site, next to the protocol. Because of the sensitive nature of the data, data are completely de-identified, will not be assessable to clinical staff, and will be protected by a Certificate of Confidentiality from the National Institutes of Health.

Patients enrolled to this trial already will have completed a short version of the tobacco-related section of the BRASS survey regarding smoking history, required for stratification (see Section 3.1.10). Depending on the patient's smoking history, these questions can be completed in 1-5 minutes. Additional questions regarding the other domains will be collected via BRASS if the patient chooses to complete these on the iPAD at baseline..

11.7.7 Hearing Handicap Inventory for Adults (HHIA-S)

The Hearing Handicap Inventory for Adults screening version (HHIA-S) is a 10-item self-reporting questionnaire designed to measure patients' reactions to their hearing loss. There are social/situational and emotional subscales (5 items each) that assess self-perceived hearing handicap in various daily listening situations. The patient can complete the questionnaire in approximately 2 minutes.

12.0 DATA COLLECTION

Data should be submitted to:

NRG Oncology*
1818 Market Street, Suite 1600
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (2/23/16)

Item	Due
BRASS Tobacco: Smoking history **(PQ)**	Within 1 week of step 1 registration
Demographic Work Status Questionnaire **(FQ)**	
Demographic Form **(A5)**	Within 2 weeks of study entry
Initial Evaluation Form **(I1)**	
HIV Status **(I3)**	
Pathology Report **(P1)**	
Slides/Blocks **(P2)**	
Baseline QOL **(SA)** (includes QLQ-C30; QLQ-H&N35; PRO-CTCAE; HHIA-S)	
EQ-5D **(HP)**	
QOL Cover Page **(CP)**	
BRASS: Optional survey **(PF)**	

Note: The baseline PQ, FQ, SA, CP, and PF will be completed on the iPAD.	
Follow-up QOL **(SB)** (includes QLQ-C30; QLQ-H&N35; PRO-CTCAE; Work Status Questionnaire; HHIA-S)* EQ-5D **(HP)***	At end of treatment, and at 3, 6, and 12 mos. from end of treatment
QOL Cover Page **(CP)***	
Note: If the institution is not provided with an iPAD for the follow-up survey, a hardcopy of the SB and CP will be completed.	
Treatment Form **(TF)**	At end of treatment
Surgery Form **(S1)** Operative Note **(S2)** Surgical Pathology Reports **(S5)**	For patients who have surgery for the cancer under study: Within 2 weeks of surgery
Short-term Follow-up Form **(F0)**	At 1 and 3 mos. from end of treatment, then q3 mos. through year 2
Long-term Follow-up Form **(F1)**	q6 mos. for 3 yrs; then annually

***Note** The QOL documents listed above should be submitted per the schedule provided in Appendix I for all patients who consented to participate in the QOL component prior to its closure on 2/28/13. Baseline forms (shaded) are no longer necessary.

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD) (6/3/14)

Item	**Due**
Preliminary Dosimetry Information	
Digital Data Submission Digital data submission includes the following: • CT data, critical normal structures, all GTV, CTV, and PTV contours • Digital beam geometry for beam sets • Doses for sets of concurrently treated beams • Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.6. • All Digital RT Data must be in DICOM format. • RTOG 1016 Datasheet, located on the NRG Oncology/RTOG web site at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1016 is to be submitted via TRIAD with RT Digital Data listed above	Within 1 week of start of RT

Upon submission of the digital data via TRIAD, complete an online DigitalData Submission Information (DDSI) located in the Forms section on the NRG Oncology/RTOG web site at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1016 Note: All simulation and portal films and/or digital film images will be kept by the institution and only submitted if requested.	Due within 1 week of start of RT
Final Dosimetry Information Radiotherapy Form **(T1) via web** Daily Treatment Record **(T5) [copy to HQ only]**	Due within 1 week of RT end

12.2.1 TRIAD (10/17/13)
See Section 5.4 for account access and installation instructions.

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

13.1.1 Overall survival

13.2 Secondary Endpoints (6/28/12)

13.2.1 Progression-free survival;
13.2.2 Local-regional failure;
13.2.3 Distant metastasis;
13.2.4 Second primary cancers;
13.2.5 Pattern of failure;
13.3.6 Early deaths;
13.2.7 Acute toxicities (CTCAE, v. 4) and overall toxicity burden at end of treatment and at 1, 3, and 6 months from end of treatment;
13.2.8 Late toxicities (CTCAE, v. 4) at 1, 2, and 5+ years;
13.2.9 Feeding tube rate at 1 year;
13.2.10 Quality of life: EORTC QLQ-C30 and EORTC QLQ-H&N35, including swallowing domains, at baseline, end of treatment, 3, 6, and 12, months;
13.2.11 PRO-CTCAE-H&N at baseline, end of treatment, and at 3, 6, and 12 months from end of treatment;
13.2.12 Health utility: EQ-5D at baseline, end of treatment, and 3, 6, and 12 months from end of treatment;
13.2.13 Work Status Questionnaire at baseline, end of treatment, and 3, 6, and 12 months from end of treatment;
13.2.14 Dental Status at baseline and 12, 24, 60, and 120 months from end of treatment;
13.2.15 Hearing quality of life outcomes as measured by the HHIA-S at baseline, end of treatment, and at 3, 6, and 12 months from the end of treatment;
13.2.16 Behavioral Risk Assessment Survey System (BRASS) at baseline only;
13.2.17 Translational research analysis.

13.3 Randomization and Stratification

Patients will be randomized to 1 of 2 treatment arms. Additionally, patients will be stratified according to T stage (T1-2 vs. T3-4); N stage (N0-2a vs. N2b-3); Zubrod performance (0 vs. 1); and Smoking history (≤ 10 pack-years vs. > 10 pack-years).

13.4 Sample Size

The primary objective is to compare the overall survival between the control arm and the experimental arm. The null hypothesis is a hazard ratio greater than 1.4; the alternative hypothesis is a hazard ratio of 1. For the RTOG 0129 p16 + patients, the overall death rate for the first 4 years were 5.6%, 5.9%, 5.8%, and 3.5%, respectively. With 43% of living patients censored during 5th year, the estimated yearly death

rate was 10.0%. For the RTOG 90-03 p16 + patients, the 4-year survival rate was 53.2%, and the 10-year survival rate was 31.5%. Assuming an exponential failure rate between those time points, the resulting yearly death rate post-4 years would be 8.4%. For planning purposes, a different exponential death rate is assumed for the first 4 years and after 4 years for the control arm. The yearly death rate of 5.3% for the first 4 years will be assumed and 10% yearly death after 4 years will be evaluated. A group sequential design with 3 interim analyses based on Haybittle's boundary will be used. The significance level for a one-sided test, the statistical power, and the noninferiority hazard ratio were set at 0.05, 0.80, and 1.4, respectively. A total of 600 analyzable patients are targeted. Adjusting by approximately 15% to allow for ineligibility, lack of data (e.g. no follow up post-study entry), **the total sample size required is 706 patients**. The total number of events required is 219 deaths. So, to reject the null hypothesis of inferiority, we would need to observe a hazard ratio of approximately 1.12 or better by assuming log rank test divided by total information (proportional to the total number of expected deaths) of the study approximate the observed hazard ratio.

From the latest data from RTOG 0522 (2/22/13), overall death rates for p16+ patients (N=235) are 8.2%, 3.33%, 3%, 3% and 3% for the first 5 years for the 2 arms combined. We used data from both arms because the survival curves are similar and failure rate estimates are more reliable. This also is confirmed by the 5-year survival on the control arm of 0522 after multiple imputations of p16 and pack years (Ang 2013). At this time, the combined (blinded) failure rate from 1016 is not reliable due to the short median follow up of 0.467 years. Since the observed death rates in RTOG 0522 and in the current trial are lower than those in RTOG 0129, which was used for the initial design, the resulting trial time to completion will be at least 5 years longer than originally projected. Additionally, we have observed a higher than 10% ineligibility rate due to reasons described below. Thus, we propose to increase the sample size in order to finish the study within the timeframe outlined in the original design and to guarantee statistical power for the primary comparison. A group sequential design with 3 interim analyses based on Haybittle's boundary will be used. The significance level for a one-sided test, the statistical power, and the noninferiority hazard ratio were set at 0.05, 0.80, and 1.45, respectively. A total of 800 analyzable patients are needed. Allowing for 4% of patients to be retrospectively declared ineligible after randomization, **the targeted accrual is 834 patients**. Adjusting by approximately 20% to allow for ineligibility (In RTOG 1016, patients were not randomized for the following reasons: 5.3% not p16-positive; 5.2% patient refusal; 1.2% physician preference; 0.4% disease progression; 0.4% failure to submit tissue assay; and 2.5% for other reasons. In addition, 3.5% of patients were determined ineligible after randomization and 0.5% were randomized but did not receive any protocol therapy), it is estimated that we will need a total sample size of 1000 patients to obtain 800 analyzable patients, but if the rate of ineligibility is lower, the total number of patients required would be less than 1000. The total number of events required is 180 deaths. So, to reject the null hypothesis of inferiority, we would need to observe a hazard ratio of approximately 1.13 or smaller by assuming log rank test divided by total information (proportional to the total number of expected deaths) of the study approximate the observed hazard ratio. According to this design, the OS difference between the 2 arms at 5 years is 7.6% as compared to 9% in the original design (73.4% vs. 81%), and the total study duration will be 8.15 years.

Note: Participation of HIV-positive individuals who meet the eligibility criteria is encouraged. However, the required sample size of 706 is based on the total number of HIV uninfected individuals enrolled into the study. The experience of the HIV-positive individuals will be analyzed and reported separately. The cohort of HIV+ patients will be assessed in a preliminary observational manner to gain insight into the feasibility of enrolling and treating this population on randomized phase III trials in the NCI-sponsored Cooperative Group Program. This effort is aimed at expanding access to cancer clinical trials for HIV infected persons who are healthy form the point of view of their HIV disease but who have cancer and are otherwise eligible for investigational cancer investigational therapeutics.

The treatment analysis will be intent to treat and restricted only to eligible patients and may possibly exceed 600 patients. A yearly accrual rate of 180 patients is projected after the study is opened 6 months. With that accrual rate, the final definitive treatment for this component would occur 8.5 years after study is initially opened. If the alternative hypothesis of noninferiority is accepted based on the proposed analyses, a test of superiority also will be conducted if the cetuximab arm is shown to be more effective than the control arm. With the 600 analyzable patients and a one-sided type I error of 0.05, there will be 80% power to detect a 30% reduction of hazard rate based on intention to treat analysis.

(10/17/13) The treatment analysis will be intent to treat and restricted only to eligible patients and may possibly exceed 800 patients. With the current accrual rate, if the alternative hypothesis of noninferiority is accepted based on the proposed analyses, a test of superiority also will be conducted if the cetuximab arm is shown to be more effective than the control arm. With the 800 analyzable patients and a one-sided type I error of 0.05, there will be 80% power to detect a 30% reduction of hazard rate based on intention to treat analysis; this requires 2 more years of follow up and 195 deaths.

Death due to toxicity or within 30 days of completing radiation was not reported in the Bonner study (it is assumed in the current study that there will be no toxic deaths from cetuximab). In the RTOG 0522, the oropharynx cohort (N=278), 6 patients (2.2%), died from toxicity or within 30 days of completing treatment (2 patients died of treatment-related causes and 4 additional patients died within 30 days of treatment from other causes). There is 55% and 99% power to detect a difference of 2% or 5% (0 vs. 2% or 5%) between the arms with a two sided type I error rate of 5%.

(10/17/13) Death due to toxicity or within 30 days of completing radiation was not reported in the Bonner study (it is assumed in the current study that there will be no toxic deaths from cetuximab). In the RTOG 0522, in the oropharynx cohort (N=278), 6 patients (2.2%), died from toxicity or within 30 days of completing treatment (2 patients died of treatment-related causes and 4 additional patients died within 30 days of treatment from other causes). There is 81% and 99% power to detect a difference of 2% or 5% (0 vs. 2% or 5%) between the arms with a two sided type I error rate of 5%.

Based on comparative review of adverse events data, detectable reductions are anticipated in 9 specific acute effects items in which cetuximab is expected to carry significantly lower (> 50% relative reduction) acute toxicity with a one-sided alpha of 0.05: (auditory < 10 versus 28%, power=0.99); bone marrow-leukopenia/anemia (5% versus 71%, power=0.99), grade 3+ dysphagia (26% versus 61%, power=0.99), grade 3+ nausea (2% versus 12%, power=0.99), vomiting (3% versus 8%, power=0.81), peripheral sensory (0% versus 6%, power=0.09), pain (28% versus 71%, power=0.99), renal (0% versus 7%, power=0.99), and fatigue (4% versus 10%, power=0.87).

(10/17/13) Based on comparative review of adverse events data, detectable reductions are anticipated in 9 specific acute effects items in which cetuximab is expected to carry significantly lower (> 50% relative reduction) acute toxicity with a one-sided alpha of 0.05 and 800 patients: (auditory < 10 versus 28%, power>0.99); bone marrow-leukopenia/anemia (5% versus 71%, power>0.99), grade 3+ dysphagia (26% versus 61%, power>0.99), grade 3+ nausea (2% versus 12%, power>0.99), vomiting (3% versus 8%, power=0.91), peripheral sensory (0% versus 6%, power>0.99), pain (28% versus 71%, power>0.99), renal (0% versus 7%, power>0.99), and fatigue (4% versus 10%, power=0.94).

As described in Section 1.5.7, we expect to detect a between arm T score difference of 200 for overall acute toxicity burden. The following table shows statistical power with a two-sided type I error rate of 0.05 and different standard deviations for two sample independent t test.

SD	1000	800	600	400
Power	68%	86%	98%	99%

(10/17/13) As described in Section 1.5.7, we expect to detect a between arm T score difference of 200 for overall acute toxicity burden. The following table shows statistical power with 800 patients, a two-sided type I error rate of 0.05 and different standard deviations for two sample independent t test.

SD	1000	800	600	400
Power	80%	94%	>99%	>99%

Late toxicity was not reported by the Bonner study. Detectable relative reductions of ≥ 50% are anticipated in 4 specific late effects items with a one-sided alpha of 0.05 and 270 patients from each arm: auditory (27% versus 13.5%, power=0.98), hemoglobin (15% versus 7.5%, power=0.80), pain (35% versus 17.5%, power=0.99), and peripheral sensory neuropathy (11% versus 5.5%, power=0.70).

(10/17/13) Late toxicity was not reported by the Bonner study. Detectable relative reductions of ≥ 50% are anticipated in 4 specific late effects items with a one-sided alpha of 0.05 and 360 patients from each

arm: auditory (27% versus 13.5%, power>0.99), hemoglobin (15% versus 7.5%, power=0.92), pain (35% versus 17.5%, power>0.99), and peripheral sensory neuropathy (11% versus 5.5%, power=0.82).

(10/17/13) We anticipate feeding tube rates in the cetuximab arm will be the same or better than in the cisplatin arm of RTOG 1016. Assuming 28% vs. 18% at 1 year and a one-sided alpha of 0.05, we have 92% power to detect this difference with 360 patients on each arm available for this analysis at 1 year.

13.4.1 Feasibility

The exact enrollment mix of T-N stages, smoking history, and accrual rates cannot be precisely projected. A sensitivity analysis seen below explores 3 scenarios in which patient accrual and the number of events (deaths) may be 10%, 33%, or 50% lower than projected from historical estimates. This indicates that even under worse-case conditions, the accrual time changes somewhat (4.35, 5.88, and 7.79 years), but time to analysis will not be more than 8.7, 8.8, and 8.97 years. This analysis strongly supports the feasibility and likelihood of completing enrollment and analysis within a relatively narrow timeframe. In the following table, yearly accrual and hazard rates are reduced by 10%, 33%, and 50% with the same analyzable number of patients. The accrual is then adjusted by 15% (to approximately 700) to account for ineligibility, lack of data (e.g. no follow up post-study entry), and non-compliance. Study durations are derived to achieve same survival difference at 5 year.

	Yearly Accrual	Accrual Duration	Study Duration	Total Analyses	Sample Size Analyzable
10%	162	4.35	8.7	4	600
33%	120	5.88	8.8	4	600
50%	90	7.79	8.97	4	600

13.4.2 Definitions of Failure

The following table shows how each first event will be counted for progression-free survival, local-regional failure, and distant metastasis. Anything not explicitly in the table (e.g., second primary tumor) is not considered an event, and the patient will continue to be followed for failure. For overall survival, death from any cause will be considered a failure. All failure times will be measured from randomization to the date of failure, competing risk, or last follow-up.

First event	**Progression-Free Survival**	**Local-Regional Failure**	**Distant Metastasis**
None	Censored	Censored	Censored
Local-regional progression or recurrence	Failure	Failure	Competing risk
Distant metastasis	Failure	Competing risk	Failure
Death due to study cancer or from unknown causes	Failure	Failure	Competing risk
Death to due any other reason	Failure	Competing risk	Competing risk
Salvage surgery of primary with tumor present/unknown	Failure	Failure	Competing risk
Salvage neck dissection with tumor present/unknown, > 20 weeks from end of RT	Failure	Failure	Competing risk

13.5 Analysis Plan

13.5.1 Routine Interim Analysis to Monitor Study Progress

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events.

13.5.2 Interim Analysis to Monitor Progression-Free Survival (PFS)

We plan to monitor futility of the difference between the control arm and the experimental arm with respect to PFS on a yearly basis during first 4 years of the trial starting from year 2. Additional analyses can be added if necessary. The purpose is to detect a significantly worse

PFS for the experimental arm as compared to the control arm and if found, the patient accrual to the trial would be discontinued. The statistical monitoring boundary will be based on testing the alternative hypothesis of hazard ratio of 1.0 at a one-sided alpha level of 0.001, as recommended by Freidlin and Korn (2002). The NRG Oncology Data Monitoring Committee (DMC) will review the results of these analyses.

(10/17/13) We plan to monitor futility for the difference between the control arm and the experimental arm with respect to PFS on a yearly basis during the accrual phase of the trial starting from year 2. Additional analyses can be added if necessary. After the trial is reopened for sample size increase, the futility analysis will be based on the primary endpoint, overall survival, when about 20% of the total required deaths are observed. The purpose is to detect a significantly worse PFS and/or OS for the experimental arm as compared to the control arm and if found, then patient accrual to the trial would be discontinued. The statistical monitoring boundary will be based on testing the alternative hypothesis of hazard ratio of 1.0 at a one-sided alpha level of 0.001, as recommended by Freidlin and Korn (2002). The NRG Oncology Data Monitoring Committee (DMC) will review the results of these analyses.

13.5.3 Analysis for Reporting the Treatment Results **(2/23/16)**

The analysis reporting the treatment results will be carried out after 180 failures have been observed, unless the criteria for early stopping are met. The usual components of this analysis are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the endpoints described in Section 6.1.

The difference in overall survival (OS) distributions between the control arm and the experimental arm will be tested using the one-sided log-rank test at the significance level of 0.0494 for noninferiority, given that the 3 interim analyses are carried out and show no statistical significance. If the number of interim analysis is other than 3, then the significance level will be adjusted accordingly.

13.5.4 Interim Analysis for Data Monitoring Committee

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis. The significance testing of efficacy will be performed at a designated time as outlined below and the results reported to the NRG Oncology DMC with a recommendation for possible early reporting. As further long-term survival information from RTOG 0129 and RTOG 0522 regarding P16 positive patients becomes available (HPV analysis of 0522 expected in 2012), the study design assumptions will be re-evaluated. If the death rate is much lower than the projected rate or if the observed difference of survival is less than projected, the implication of this decreased rate, survival difference and accrual will be assessed in terms of when the projected final (definitive) treatment analysis will be performed. If the timing of that analysis is lengthened by more than a year, increasing the sample size will be explored.

(10/17/13) Overall survival monitoring for both efficacy and futility will be performed when there are 45 OS events (25% information), 90 OS events (50% information, around 1 year from completion of accrual), 135 OS events (75% information, around 2.4 years from completion of accrual) and 180 OS events as required for the final analysis are reported. A Haybittle-Peto boundary will be utilized for efficacy monitoring. For futility, the statistical monitoring boundary will be based on testing the alternative hypothesis at a one-sided alpha of 0.005, as recommended by Freidlin and Korn (2002). If judged to be necessary, futility analysis also can be performed in between the above planned interim analyses using the same rule. For efficacy, the statistical monitoring boundary will be based on testing the null hypothesis at one-sided alpha level of 0.001.

13.5.5 Interim Analysis for Special Reporting **(2/23/16)**

The reporting paradigm developed at CTEP specifically for noninferiority trials (if all 9 conditions and other requirements are met as in Korn 2005) may be used in order to keep the oncology community apprised of trial outcomes. There may be a release of limited and specific survival

and the toxicity data for presentation at a major cancer meeting such as ASCO, and the first outcome publication will utilize at least 2-year minimum follow up after all the patients have been enrolled (ideally >50% of the total required deaths). The survival and the toxicity results will be reported without any statistical significance values, and a detailed reporting plan will be developed and needs to be approved by the DMC prior to the first report of results.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.5.6 Final Analysis **(2/23/16)**

The PFS and OS rates will be estimated for both treatment arms using the Kaplan-Meier method (1958). Their distributions will be compared between treatment arms with a one-sided log rank test (Mantel 1966). The confidence interval approach will be used for the final analysis; if the upper 95% bound is below 1.45 with 180 deaths, then the radiation plus cetuximab arm is noninferior to concurrent chemoradiation arm. If the upper 95% bound is above 1.45, then radiation plus cetuximab is inferior. The cumulative incidence method will be used to estimate local-regional failure rates, distant metastasis, and second primary tumor rates, and the failure rates for the experimental treatment will be compared against the control using a failure-specific log-rank test. Multivariate analysis will be performed using the Cox proportional hazards model.

An overall toxicity analysis will be done 2 ways: 1) The first method will be based upon only adverse events (AEs) attributed by investigator to be definitely, probably, or possibly related (if relationship is missing, it will be considered related) to protocol treatment; 2) The second method will be based upon all reported AEs regardless of attribution. Rates of specific acute toxicity profiles and late toxicity profiles will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test between the 2 treatment arms. Overall acute toxicity burden scores will be compared using two sample t test.

13.6 Statistical Considerations for Translational Research (10/17/13)

13.6.1 Sample Size and Power

We consider below the sample size and power for objectives 2 and 3 (see Section 1.7.1) noted above. In this analysis, variables of interest from objective 2 would be considered as self-reported behaviors, e.g. smoking status. For objective 3, variables of interest would include presence or absence of a biomarker in the tumor. Given that submission of tumor samples will be required for patient eligibility, it is projected that 100% of randomized patients will be analyzable for tumor marker evaluation (for high priority analyses), giving a total of 800 analyzable patients or 400 per arm.

For dichotomized variables, the statistical power can be calculated by the method of Schoenfeld (1981). The table below shows statistical power to detect hazard ratios of 1.25, 1.50, 1.75, 2.00, 2.25, and 2.50 for prevalence rates of 10%, or 20%, or 30%, etc., for overall survival (arms combined) and overall survival (single arm). Progression-free survival (not shown) has more events and thus more statistical power than overall survival. Statistical power will be the same if prevalence rate is 1-prevalence. The significance level was set at 0.05. As seen in the table, there will be > 80% power (given prevalence of >20% of the factor of interest in the study population) to detect a hazard ratio of 1.75 or greater for two arms combined or a hazard ratio of 2.5 or greater for one arm only. Given the large hazard ratios reported for EGFR, Cyclin D1, etc., noted in the literature as potential modifiers of outcomes in HPV-positive patients (see table below), we will have sufficient statistical power to detect the expected hazard ratios. For example, for Bcl-2, with hazard ratio 4.0 and 40% of patients over-expressed, the statistical power is >99%.

Potential Biomarkers of Disease Outcome Among HPV-Positive Patients Reported in the Literature

Factor	% HPV-positive with factor	Outcome measure	Hazard Ratio univariate	95% CI
EGFR	78	Local-regional failure	6.6	2.1-40.0
Cyclin D1	27	Local-regional failure	3.5	1.9-7.2
P21	63	Disease-specific survival	0.4	NR
Bcl-2	40	Overall survival	4.0	1.2-13.6
P53	40	Disease-specific survival	1.7	NR
16q loss	29	Overall survival	NR	NR

Statistical Power to Detect Various Hazard Ratios (OS, Arms Combined, 180 events)

	Hazard Ratio					
Prevalence	1.25	1.5	1.75	2	2.25	2.5
0.1	0.14	0.37	0.61	0.79	0.90	0.95
0.2	0.22	0.58	0.85	0.96	0.99	0.99
0.3	0.27	0.70	0.93	0.98	0.99	0.99
0.4	0.31	0.75	0.95	0.99	0.99	0.99
0.5	0.32	0.77	0.96	0.99	0.99	0.99

Statistical Power to Detect Various Hazard Ratios (OS, One Arm, 90 Events)

Prevalence	Hazard Ratio					
	1.25	1.5	1.75	2	2.25	2.5
0.1	0.09	0.21	0.35	0.50	0.63	0.74
0.2	0.13	0.33	0.56	0.74	0.86	0.93
0.3	0.16	0.42	0.68	0.85	0.94	0.97
0.4	0.17	0.46	0.73	0.89	0.96	0.98
0.5	0.18	0.48	0.75	0.90	0.97	0.99

13.6.2 Analysis Plan

Recursive partitioning analysis (RPA) is a mathematical technique that tests the association of variables with a specific outcome (e.g., overall survival). It is used to segregate groups of patients who have similar outcomes. Relying solely on Kaplan-Meier estimates and the log-rank test, RPA requires absolutely no knowledge of the biological behavior of a disease. Instead, mathematical cut points divide the database into multiple samples. The cut points (also known as splits) can be then combined based on clinical decisions, sample size, or statistical significance. The terminal branches then represent homogeneous groupings. All patients belong to one, and only one, group.

The patients will be initially divided into two subgroups based upon previously defined (or hypothesized) cut points one or more tumor markers, and these two groups will be referred to as favorable and unfavorable risk groups. In univariate analysis, the log-rank test will be used to test for PFS and OS differences between the favorable and unfavorable risk groups; a failure-specific log-rank test will be used for LRF.

Univariable and multivariable analysis will be performed using the Cox proportional hazards model for OS and PFS. Potential covariates evaluated for the multivariate models would be assigned treatment, age, Zubrod performance status, T-stage, N-stage, primary site, smoking history, other risk behaviors, as well as tumor markers. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here. Then the tumor

marker or combination of markers (or combination of behavioral risk factors) will be added to the model to test for significance.

In addition, exploratory analysis will be performed to determine if there is any outcome difference between the marker risk group and treatment arm. A Cox regression model will be used with the following covariates: 1) assigned treatment; 2) marker status; and 3) assigned treatment by marker status interaction. The covariate for interaction will provide an estimate as to whether the treatment effect is similar for the marker + and the marker - patients.

The analysis of one individual marker will include only patients with that marker. However, the analysis of two or more markers will include all patients with at least one determination of the multiple tumor makers. The assumption is made that the other tumor maker values are missing completely at random. The missing tumor values will be imputed 10 times, and the average value along with the pooled standard error associated with the parameter estimates for each tumor marker in the Cox model analysis will be reported. The tumor marker study population will be compared with the patients without a value for that tumor marker to determine if there are any differences with respect to distribution of baseline variables or outcome.

13.7 Statistical Considerations for Quality of Life (6/25/13)

The focus of the quality of life (QOL) analysis is the change of QOL score as measured by the EORTC QLQ at 6 months from baseline and patterns of scores over time points and the change of score of the EORTC swallowing domain at 2 years from baseline with data from first 400 patients. Overall, the mean summary score of the EORTC QLQ-C30 and QLQH&N35 and the subscales including the swallowing domain will be determined. The mean change from baseline at each time point will be summarized using mean and standard deviations for each arm. Mean change from baseline will be compared between the arms using a two sample t test. If data normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis. Mean change from baseline will be tested using an omnibus F test followed by individual comparisons of change scores at different time points within each treatment group. The same analysis will be conducted for between group comparisons at each time point. The primary QOL outcome for the study will be a comparison between arms of the EORTC QLQ change score from baseline to 6 months and the change score of the swallowing domain from baseline to 2 years. In addition to comparing the change scores at end of treatment, 3, 6, and 12 months from end of treatment to baseline, overall trends in the EORTC QLQ and subscale scores will be modeled using the general linear mixed-effect model. This model will be used to compare the differences of scores over time between the 2 arms and to compute least squares mean and SEs, including clinical variables and treatment by visit interaction terms. The model also allows for adjustments using stratification variables and other covariates of interest. The use of general linear mixed modeling allows flexibility in analyzing data with missing responses.

For quality of life endpoints, based on results from 175 patients enrolled on RTOG 0522 and Ringash (2004), the mean change score is approximately half of the standard deviation. Also, from the results of Osoba (1998) and Curran (2007), we expect a meaningful between group change from baseline of 10 points on the EORTC QLQ (approximately half of the standard deviation as observed in Curran 2007) for a one-sided test with alpha of 0.05 and 90% power, we will need 140 analyzable patients for the 2 arms. Based on prior trials in head and neck cancers, the attrition rate is 35% at 6 months, we expect 216 patients will need to be recruited for the evaluation at 6 months. Even if the change from baseline were as small as 0.375 of the standard deviation, it would be detectable in the planned trial; we would need 246 analyzable and 398 total patients at 6 months with 90% statistical power and one sided alpha of 0.05. With these sample sizes for the above two design effect sizes, if the compliance rate is 55% at two years, we will have 85% and 85% power with one side alpha of 0.05 for both overall QOL and the swallowing domain.

To handle poor compliance and missing data, efforts will be made to minimize attrition due to avoidable factors. To assess missing data mechanism, we will compare possible differences between patients who dropped out of the study against those who remained in the study with respect to imbalance factors such as treatment, baseline scores, clinical and demographic data. We will undertake sensitivity analyses to investigate reasons for missingness (e.g., by drop-out), considering various factors as mentioned earlier. A logistic regression model will be used to summarize number of missing data and to test if the dropout process is missing completely at random (MCAR). Analysis of complete cases and cases with multiple

imputations for missing observations (before death or progression) will be done to check robustness of the main results. A pattern mixed model or selection model may be used to assess treatment effect to see if it is dropout dependent. The EORTC QLQ non-worsened vs. worsened for the arms will be compared using Fisher's exact test for each time point and modeled using a longitudinal model for binary outcomes based on the general estimating equation (GEE) approach.

13.8 Gender and Minorities (10/17/13)

Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	20	20
Not Hispanic or Latino	120	694	814
Ethnic Category: Total of all subjects	120	714	**834**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	12	12
Asian	3	3	6
Black or African American	0	54	54
Native Hawaiian or other Pacific Islander	0	0	0
White	117	645	762
Racial Category: Total of all subjects	120	714	**834**

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APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (6/3/14)
*See Sections 11.2-11.4 for exceptions and details

Assessments	Within 8 weeks prior to registration	Within 2 weeks prior to registration
Eligibility-related tissue collection	Prior to Step 2 registration	
Smoking history survey (CASI)	Prior to Step 2 registration	
History	X	
Rad Onc exam	X	
Med Onc exam	X	
ENT or H&N Surgeon exam	X	
Chest imaging	*X (see Section 11.2.1)	
Performance Status		X
CDC w/diff & ANC		X
Total bilirubin; AST or ALT		X
Creatinine or Creatinine Clearance		X
Serum pregnancy test (if applicable)		X
Na, K, Cl, glucose, Ca, Mg, albumin	Within 2 weeks prior to treatment	
*CD4 count for pts. with known HIV	Prior to Step 1 registration	
Dental assessment	Within 8 weeks prior to treatment	
Swallowing eval (Section 4.1.4)	Within 4 weeks prior to treatment	
Audiogram	Required: Within 12 weeks prior to treatment	
Whole body PET/CT	Recommended: Within 8 weeks prior to treatment	
Nutrition/feeding tube eval	*Recommended: Within 2 weeks prior to treatment See Section 11.2.2	
CT or MRI or PET/CT of neck, with contrast	X	
Adverse event eval	Evaluation of condition prior to treatment	
The QOL component was closed to accrual on 2/28/13 QOL/Functional Assessments –if the patient consents: QLQ-C30; QLQ-H&N35; EQ-5D; PRO-CTCAE-H&N; Work Status, HHIA-S: Prior to start of treatment		
Risk Factor Survey (CASI) –if the patient consents: Prior to start of treatment		
Specimen collection for banking- if the patient consents: Prior to start of tx		

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT (6/25/13)

*See Sections 11.2-11.4 for exceptions and details

Assessments	Weekly during radiation	As clinically indicated
History	*brief history	*brief history
Rad Onc exam		
Med Onc exam	X	
Performance Status	X	
CDC w/diff & ANC	X	
Creatinine or Creatinine Clearance	X	
Na, K, Cl, glucose, Ca, Mg, albumin	X	
Whole body PET/CT		X
CT or MRI or PET/CT of neck, with contrast		X
Biopsy		If suspicion of tumor recurrence
Adverse Event eval	X	X

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (10/17/13)

*See Sections 11.2-11.4 for exceptions and details

Assessments	**At 1 month post-XRT**	**q3 mos. from end of RT for 2 yrs; q6 mos. for 3 yrs; then annually**	**As clinically indicated**
History	brief history	brief history	
Exam by Rad Onc or Med Onc or ENT or H&N Surgeon	X	*X	
Chest imaging		*X	
Performance Status	X	X	
CDC w/diff & ANC	X		
Total bilirubin; AST or ALT	X		
Na, K, Cl, glucose, Ca, Mg, albumin	X		
Dental assessment		At 12, 24, 60, and 120 months from end of treatment	
Whole body PET/CT		*X	X
Nutrition/feeding tube eval		X	
CT or MRI or PET/CT of neck, with contrast		*X	After 5 years, as clinically indicated
Biopsy			If suspicion of tumor recurrence
Adverse event eval	X	X	X
QOL/Functional Assessments –if the patient consented and is one of the 400 accrued to QOL component (closed to accrual 2/28/13): QLQ-C30; QLQ-H&N35; EQ-5D; PRO-CTCAE-H&N; Work Status, HHIA-S	End of treatment	At 3, 6, and 12 months from end of treatment	
Specimen collection for banking- if the patient consents		At 3 and 6 months from end of treatment	

APPENDIX II: ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
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**
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**
3	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

APPENDIX III: STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

HEAD & NECK

STAGING-PRIMARY TUMOR (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ

LIP and ORAL CAVITY

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
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
T4a	Moderately advanced local disease*
	(lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
	(oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced disease
	Tumor invades masticator space, pterygoid plates or skull base and/or encases internal carotid artery

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

NASAL CAVITY and PARANASAL SINUSES

Maxillary Sinus

T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease
	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx or clivus

Nasal Cavity and Ethmoid Sinus

T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate,

	or cribriform plate
T4a	Moderately advanced local disease
	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

PHARYNX

Nasopharynx

T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity with out parapharyngeal extension*
T2	Tumor with parapharyngeal extension*
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

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.

Hypopharynx

T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a	Moderately advanced local disease
	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.*
T4b	Very advanced local disease
	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

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.

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

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

REGIONAL LYMPH NODES (N) Nasopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph 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	Metastasis in a lymph node, more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis
MX	Distant metastasis cannot be assessed

STAGE GROUPING, Excluding Nasopharynx

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 IVB	T4b, Any N, MO
	Any T, N3, M0
Stage IVC	Any T, Any N, M1

STAGE GROUPING Nasopharynx

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1-T3, N1, M0
	T3, N0, M0
Stage IVA	T4a, N0-2, M0
	T1-3, N2, MO
Stage IVB	Any T, N3, M0
	T4b, Any N, M0
Stage IVC	Any T, Any N, M1

APPENDIX IV: MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures

The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX V: INSTRUCTIONS FOR RTOG 1016 BIOSPECIMEN COLLECTION
(6/3/14)

Shipping Instructions:

US Postal Service Mailing Address: <u>For Non-urgent or Non-frozen Specimens Only</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For Urgent FFPE and Frozen Specimens</u>
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the ST Form has the consent boxes checked off.
- ❑ Check that all samples are labeled with NRG Oncology study and case number, and include date of collection as well as collection time point.

- ❑ **<u>FFPE Specimens:</u>**
  - ○ Slides should be shipped in a plastic slide holder/ slide box. Place a small wad of padding in top of container If you can hear the slides shaking they are likely to be break during shipping.
  - ○ FFPE Blocks can be wrapped with paper towel, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap. Place padding in top of container so that if you shake the container the blocks are not shaking. If you hear them shaking they are likely to be breaking during shipping.
  - ○ Slides, Blocks or Plugs can be shipped ambient or with a cold pack either by USPS to the USPS address (94143) or by Courier to the Street Address (94115). Do NOT ship on Dry Ice.

- ❑ **<u>Frozen Specimens</u>**:
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - ○ Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80C until ready to ship.

- ❑ **For questions regarding collection/shipping, please contact the NRG Oncology Biospecimen Bank by e-mail at: RTOG@ucsf.edu; or (415)-476-7864; or fax (415)-476-5271**

Continued on next page

NRG Oncology FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

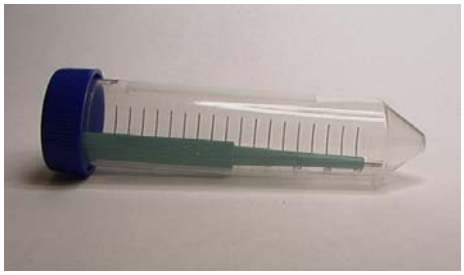
Step 1

If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2

Label the punch tool with the proper specimen ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3

Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.

Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-urgent and Non-frozen Specimens Only
NRG Oncology Biospecimen Bank
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Urgent FFPE and Frozen Specimens shipments
NRG Oncology Biospecimen Bank
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

NRG Oncology BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood.

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty five (25) 1 ml cryovials
- Absorbent shipping material (3)
- Biohazard bags (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- Specimen Transmittal (ST) Form
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers

Preparation and Processing of Serum, Plasma and Whole Blood:

A) Serum: Red Top Tube

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 10) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, 3 or 6 month follow up post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

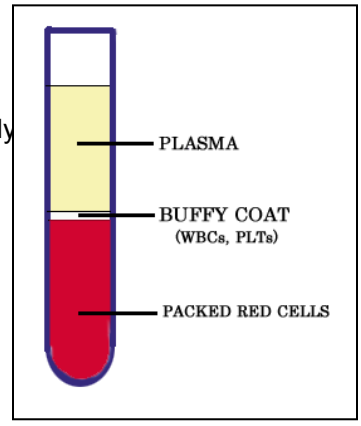
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on ST Form.

B) Plasma: Purple Top EDTA tube #1

- ❑ Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5to 10) labeled with NRG Oncology study case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma at -70 to -90° C until ready to ship on dry ice.
7. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on ST Form.

C) **Whole Blood For DNA: Purple Top EDTA tube #2**

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovial(s) "blood".

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen -70 to -90° C until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on ST Form.

Storage and Shipping:

Freezing and Storage:

- ☐ Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).

  OR:
  - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).

  OR:
  - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- ❑ Include all NRG Oncology paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.*
- ❑ For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415) 476-7864 or fax (415) 476-5271

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115
For questions, call: 415-476- (7864) or e-mail: RTOG@ucsf.edu

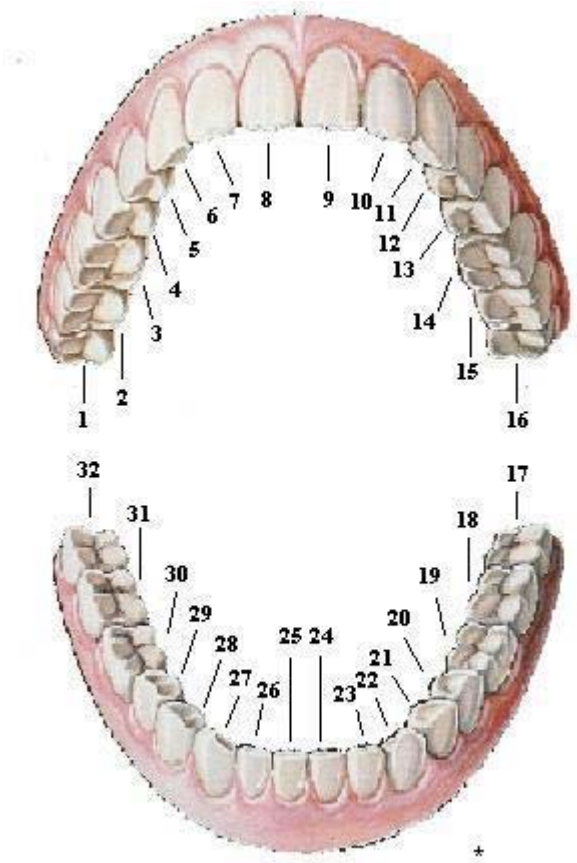
APPENDIX VI: DENTAL TOOTH COUNT DIAGRAM
(12/10/13)

Use the diagram below as a guide to count the number of native teeth in place, not including full or partial dentures or bridges.

The exact location of teeth does not need to be recorded, only the total number of native teeth in place (attached to bone in mandible or maxilla) on the day of evaluation.

This exam should be completed by a physician or designee, such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist.

Date of evaluation: Total number of native teeth in place (0-32):



APPENDIX VII: RTOG 1016 DENTAL EFFECTS HEALTH SCALE (12/10/13)

0 Normal: Edentulous, with no gingival disease; native teeth in place with gingiva in excellent condition.
1 Mild changes/good dental health: mild periodontal inflammation-routine cleaning indicated; < 5 restorations indicated; no extractions indicated.
2 Moderate/fair dental health: moderate periodontal inflammation; deep periodontal cleaning indicated; 6 or more restorations indicated; less than full mouth extractions indicated.
3 Severe changes in dental health: widespread periodontal disease with extensive procedure/surgery indicated; full mouth extractions indicated.
4 Life-threatening dental condition: extensive abscess, extensive soft issue or bone infection, sepsis; urgent intervention indicated.