

NRG ONCOLOGY
Radiation Therapy Oncology Group

RTOG 0920

(ClinicalTrials.gov NCT #: 00956007)

**A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab
Locally-Advanced Resected Head and Neck Cancer**

Amendment 14: May 11, 2023

NRG ONCOLOGY

RTOG 0920

A PHASE III STUDY OF POSTOPERATIVE RADIATION THERAPY (IMRT) +/- CETUXIMAB FOR LOCALLY-ADVANCED RESECTED HEAD AND NECK 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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Title Page (Continued) (11-MAY-2023)

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<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU member's website (https://www.ctsuhelp.org).</p> <p>Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.</p>		
<p><u>For clinical questions (i.e. patient eligibility or treatment-related):</u> Contact the Study PI of the Lead Protocol Organization.</p>		
<p><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission):</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsuhelp@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p>The CTSU Website is located at https://www.ctsuhelp.org.</p>		

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SCHEMA (25-JAN-2016)

					Arm 1: Radiation Therapy Alone
R	For all	S	EGFR Expression	R	RT, 2 Gy/day, in 30 fractions
E	patients:	T	1. High ($\geq 80\%$ of cells	A	for a total of 60 Gy ^A
G	Mandatory	R	staining positive for EGFR)	N	
I	submission	A	2. Low ($< 80\%$ of cells	D	Arm 2: Radiation Therapy + Cetuximab
S	of tissue for	T	staining positive for EGFR)	O	At least 5 days prior to RT:
T	EGFR ^B	I	3. Not evaluable	M	cetuximab: Initial dose, 400 mg/m ²
E		F		I	
R	For	Y	Primary Site	Z	RT, 2 Gy/day in 30 fractions for a total of 60 Gy ^A
	oropharyngeal		1. Oral cavity	E	plus cetuximab: 250 mg/m ² /week x 6 weeks
	cancer		2. Larynx		
	patients:		3. Oropharynx p16+		plus
	Mandatory		4. Oropharynx p16-		cetuximab: 250 mg/m ² /week
	analysis for		5. Oropharynx p16 not		x 4 weeks post-RT
	HPV ^B		Evaluable		
					(cetuximab: 1 initial dose + 10 maintenance
			Use of IGRT		doses, a total of 11 doses)
			1. No		
			2. Yes		
			Clinical Stage		
			1. T1-3		
			2. T4a		

A. IMRT is mandatory. Dose is 60 Gy prescribed to at least 95% of the PTV. If IGRT is used, it should be daily to assure that error/variance is < 3.5 mm. Note: 66 Gy is permitted and optional.

B. Prior to stratification and randomization, **all patients** must consent to submission of tissue for required EGFR analysis; analysis results are expected in approximately 7-8 business days. At that time, patients with non-oropharyngeal carcinoma can be randomized. In addition, **patients with oropharyngeal carcinoma** must consent to use of the submitted tissue for required HPV analysis; analysis results are expected in approximately 7-10 business days. At that time, patients with oropharyngeal carcinoma can be randomized. See [Section 5.5](#) for details of registration/randomization.

(Note: The required analyses are not expected to cause delays in patients starting treatment, since this is an IMRT-mandatory study, and IMRT generally takes ≥ 7 days for institutional planning and QA procedures prior to start of RT).

Patient Population: (See [Section 3.0](#) for Eligibility) (17-JAN-2012)

Pathologically proven diagnosis of squamous cell carcinoma (including variants such as verrucous carcinoma, spindle cell carcinoma, carcinoma NOS, etc.) of the head/neck (oral cavity, oropharynx or larynx); clinical stage T2-T4a, N0-2, M0 or T1, N1-2, M0.

Required Sample Size: 700

ELIGIBILITY CHECKLIST – STEP 1 (14-JUN-2012)
(page 1 of 5)

Institution #
RTOG 0920
Case #

- _____(Y) 1. Does the patient have a histologically proven diagnosis of squamous cell carcinoma (including variants such as verrucous carcinoma, spindle cell carcinoma, carcinoma NOS, etc.) of the head/neck (oral cavity, oropharynx or larynx)?
- _____(N) 2. Is the primary of the hypopharynx?
- _____(Y) 3. Is the tumor clinical stage T1, N1-2 or T2-4a, N0-2, M0?
- _____(N) 4. Does the patient have distant metastases?
- _____(Y) 5. Was a general H&P by a Radiation Oncology and/or Medical Oncologist, an examination by an ENT/Head & Neck Surgeon, and chest x-ray (or chest CT scan or CT/PET of the chest) done within 8 weeks prior to registration?
- _____(Y) 6. Per the operative report, was a gross total resection of the primary tumor with curative intent completed within 7 weeks of registration?
- _____(Y) 7. Does the surgical pathology demonstrate one or more of the following “intermediate” risk factors?
- Perineural invasion;
 - Lymphovascular invasion;
 - Single lymph node > 3 cm or ≥2 lymph nodes (all < 6 cm) [no extracapsular extension];
 - Close margin(s) of resection (close margins defined as cancer extending to within 5 mm of a surgical margin);
 - T3 or T4a primary tumor;
 - T2 oral cavity cancer with > 5 mm depth of invasion.
- _____(Y) 8. Was the patient’s Zubrod Performance Status 0-1 within 2 weeks prior to registration?
- _____(Y) 9. Is the patient ≥ 18 years of age?
- _____(Y) 10. Does the patient have adequate bone marrow, hepatic, and renal function as specified in Sections 3.1.6-3.1.8?
- _____(Y) 11. Was the patient’s Na, K, Cl, glucose, Ca, Mg, and albumin levels assessed as required within 2 weeks prior to the start of registration?
- _____(Y) 12. 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) 13. If a woman of child bearing potential or a sexually active male, is the patient willing to use effective contraception while on treatment?
- _____(Y) 14. Did the patient provide study specific informed consent prior to study entry including consent for tissue submission for EGFR and HPV analyses?
- _____(N) 15. Did the patient have a prior invasive malignancy?

(Continued on next page)

ELIGIBILITY CHECKLIST – STEP 1 (23-JAN-2013)
(page 2 of 5)

Institution #
RTOG 0920
Case #

- _____(Y) If yes, is the prior malignancy within the parameters specified in Section 3.2.1?
- _____(N) 16. Per the operative and/or pathology report, were there positive margin(s) [tumor present at the cut or inked edge of the tumor], nodal extracapsular extension, and/or gross residual disease after surgery?
- _____(N) 17. Did the patient have previous systemic chemotherapy or anti-EGF therapy for the study cancer?
- _____(N) 18. Did the patient have previous irradiation to the head and neck that would result in overlap in radiation fields?
- _____(N) 19. Does the patient have severe, active co-morbidity, as defined in Section 3.2.5.1-3.2.5.7?
- _____(N) 20. Does the patient have grade 3-4 (CTCAE, v. 4) electrolyte abnormalities as specified in Section 3.2.5.8?
- _____(N) 21. Does the patient have a prior history of allergic reaction to cetuximab?

The following questions will be asked at Study Registration:

CREDENTIALING for IMRT (and IGRT, if used) IS REQUIRED BEFORE REGISTRATION.

- _____ 1. Institutional person randomizing 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's ID
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnicity
- _____ 11. Gender

(Continued on next page)

ELIGIBILITY CHECKLIST – STEP 1 (13-FEB-2013)
(page 3 of 5)

Institution #
RTOG 0920
Case #

- | | |
|------------|---|
| _____ | 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 |
| _____(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: causes of diabetes, Alzheimer's disease, and heart disease)? |
| _____(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. Tissue sent for HPV analysis? |
| _____ | 25. Disease Type (Oral cavity, Larynx, Oropharynx p16+, Oropharynx p16-, Oropharynx p16 not evaluable) |
| _____(Y/N) | 26. Use of IGRT? |
| _____(Y) | If yes, have pre-registration credentialing requirements in Section 5.2 been met? |
| _____ | 27. Clinical T-Stage (T1-3 vs. T4a) |

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 (25-JAN-2016)
(page 4 of 5)

Institution #
RTOG 0920
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 refusal;
 - 3) physician preference;
 - 4) failure to submit tissue assay;
 - 5) other
- _____ Specify the reason the patient cannot continue to Step 2.
- _____ 4. Patient Initials (First Middle Last)
- _____ 5. Verifying Physician
- _____ 6. Patient ID
- _____ 7. Calendar Base Date (for Step 2)
- _____ 8. Randomization date: (for Step 2)
- _____(Y/N) 9. Patient has consented to take part in the Quality of Life Study?
- _____ 10. If no, provide reason:
- 1) patient refused due to illness
 - 2) patient refused for other reason
 - 3) not approved by institutional IRB
 - 4) tool not available in patient's language
 - 5) other reason
- _____ If response is "2) Patient refused for other reason", specify the reason.
- _____ If response is "5) Other reason", specify the reason the patient will not participate in the quality of life component of the study.
- _____(Y/N) 11. If the patient agreed to participate in the quality of life component, did the patient agree to participate in VisionTree?
- _____(Y/N) 12. Will IGRT be used for patient positioning and margin reduction?

Continued on next page.

ELIGIBILITY CHECKLIST – STEP 2
(page 5 of 5)

Institution #

RTOG 0920

Case #

(assigned for Step 1)

_____ 13. Patient height

_____ 14. Patient weight

_____ 15. BSA

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Head and Neck Cancer — Postoperative Adjuvant Therapy

There are approximately 40,000 new cases of head and neck squamous cell carcinoma (SCCHN) diagnosed each year in the United States. Almost all of these patients have non-metastatic disease and are candidates for local-regional therapy in the form of surgery, radiotherapy (RT), or both. In the last decade, a major advance has occurred in the management of head and neck cancer by the addition of chemotherapy to local-regional therapy for selected patients (Bourhis 2004). This generally has been in the form of cisplatin-based chemotherapy given concurrently during RT. There are extremely strong data in support of concurrent chemoradiotherapy for locally advanced (stage III/IV) head and neck cancer being treated non-surgically (Bourhis 2004; Adelstein 2003; Calais 1999; Brizel 1998).

The adjuvant management of completely resected SCCHN is somewhat more controversial. In general, postoperative radiotherapy (PORT) is a standard of care for most stage III/IV and selected stage II resected cases (Forastiere 2001). In the last several years, several high-profile randomized trials have shown that the addition of concurrent chemotherapy to PORT improves outcomes for selected patients. The RTOG led a North American Intergroup trial comparing standard PORT with or without three cycles of high dose concurrent cisplatin (Cooper 2004). The patient population consisted of individuals who underwent complete resection but had positive resection margins at the primary tumor site, multiple pathologically positive lymph nodes in the neck, or one or more lymph nodes in the neck with extracapsular extension. This study showed the chemoradiotherapy had significantly improved local-regional control (LRC) and disease-free survival (DFS) but not overall survival, compared with PORT alone. The EORTC performed a very similar study of PORT +/- chemotherapy, showing that chemoradiotherapy improved overall survival in addition to LRC and DFS (Bernier 2004).

Bernier, et al. (2005) subsequently performed a meta-analysis of the RTOG and EORTC trials. In this exploratory analysis, the primary subgroups of patients who benefited significantly from the addition of chemotherapy were those with positive resection margins and/or nodal extracapsular extension. Other patients did not have a significant benefit from high dose concurrent cisplatin. Specifically in RTOG 95-01, this refers to patients with multiple positive nodes (pN2) without extracapsular spread (ECS). In the EORTC study, this refers to a potpourri of patients, including: pathologic T3-4, N0 cancers (except T3, N0 larynx cancer), perineural and/or vascular invasion irrespective of T-stage, or oral/oropharynx cancer with lymph node involvement at Level IV or V. The failure of cisplatin to significantly improve survival or other clinical outcomes does not, however, mean that these patients have a very good or excellent prognosis. As shown below in Table 1, multiple series of data report a rate of local-regional failure between 15 and 35% for these patients, despite adjuvant RT. Most patients who suffer local-regional failure cannot be salvaged with additional anti-cancer treatment and proceed to die from their cancer. The exact rate of local-regional failure probably depends upon multiple factors, including the number of clinical risk factors present (as described by the University of Florida), treatment related factors (such as the quality of surgery and/or RT, as well as the amount of time required to deliver treatment), and currently poorly understood biological/molecular features of patients' tumors. These complex factors make it very difficult to compare one study to another, particularly retrospective experiences harvested at different institutions over several decades. A relatively large prospective trial would thus provide valuable information to help physicians and patients more precisely identify the risk factors for local-regional recurrence (and other clinical outcomes) after surgery + RT.

Table 1: Outcomes in Patients with Resected Head and Neck Cancer with One or More Risk Factors for Recurrence (Other Than Positive Margin/ECS)

Study	Patient Population /Number of pts	Local-regional Control	Survival and/or Comments
Cooper (RTOG 95-01) [2004]	110 pts without ECS/+mgn but 2-4 + LN's	80% (crude)	2-yr. DFS 63%.
Cooper (RTOG 85-03) [1998]	108 pts with negative margins, N0-1 nodal stage (without ECS)	83% (5-yr.)	
EORTC	101 pts with negative margins and no nodal ECS	NS	2-yr. OS ~60%
Rosenthal (Penn) [2002]	90 pts with clear margins and N0-1 nodal stage (without ECS)	88% (3-yr.)	3-yr. OS 81%
Hinerman (Fla) [2004]	60 pts with oral cavity CA and only 1 risk factor for recurrence	83% (crude)	
Hinerman (Fla) [2006]	82 pts with resected laryngopharynx CA and "close" (<5mm) margins	85% (crude)	
Bastit (France) [2001]	76 pts with resected pharynx CA and lymphovascular and/or perineural invasion	75% (3-year)	
Fortin (Quebec) [2001]	287 pts with T1-3 and 0-2 nodes without ECS	85% (crude)	LRC was 77% for pts tx'd with Cobalt vs. 91% for 6MV
Pfreunder (2000)	66 pts with close but negative (<3mm) margins	71% (5-yr)	Sig. impact of RT dose (66 Gy cutoff) – 62% vs. 80%.
Lavaf (2007)	Approx. 5,800 pts with SEER Stage II (regionally advanced by direct extension but no regional lymph nodes involved)	Not available	Approx. 50% 5-year survival TNM and margin status data are not available. Tumor size highly predictive (p<0.002)
Langendijk (2005)	110 pts with close (1-5 mm) margins	65% (5-yr)	Subgroup analyses from a retrospective series of 801 pts treated with surgery + PORT.
Langendijk (2005)	128 pts with perineural invasion	69% (5-yr)	
Langendijk (2005)	155 pts with lymphovascular invasion	67% (5-yr)	

The reason for the failure of high dose cisplatin to improve outcomes in patients without positive margins/ECS is unclear. It is possible that a benefit does exist, but that the RTOG and EORTC studies were "underpowered" to detect it. If this were the case, the magnitude of benefit from cisplatin is probably small. It is important to note that concurrent chemoradiotherapy (particularly with high dose cisplatin) significantly increases toxicity compared with RT alone (Trotti 2003). In particular, acute mucositis and dysphagia are dramatically increased with chemotherapy. High dose cisplatin also causes significant constitutional and systemic toxicities that are well recognized and independent of the concomitant administration of RT. It is theoretically possible that these systemic toxicities might interfere with the ability of patients to tolerate and receive maximally effective dose intensity of RT. Although RTOG 95-01 did not show any obvious differences in major/unacceptable deviations in dose delivery of RT between the RT alone and RT/cisplatin arms, it is possible that more subtle differences in RT delivery and dose intensity could exist.

Given the toxicity of high dose cisplatin, two recent randomized studies were designed to attempt to demonstrate a benefit to low dose carboplatin as a radiosensitizer during postoperative RT. While both of these studies were relatively small and underpowered, they did not show any obvious benefit to carboplatin during RT (Argiris 2008; Racadot 2008). Another strategy has been to administer postoperative chemotherapy alone prior to RT; to date, this has not shown significant improvement (Laramore 1992).

1.2 Study Design

It is thus clear that alternatives to highly intense chemoradiotherapy (RT + high dose cisplatin) are needed in order to improve the therapeutic ratio for patients who are not candidates for concurrent chemoradiotherapy or for whom concurrent chemoradiotherapy is not necessarily indicated. Postoperative RT alone is the current standard of care for these patients, but it has a suboptimal outcome.

1.2.1 Epidermal Growth Factor Receptor (EGFR)

Since the design and conduct of RTOG 95-01 and the EORTC trial, much has been learned about the biology of squamous cell carcinoma of the head and neck. Two of the most important areas of advances have been in the study of epidermal growth factor receptor (EGFR) and in the study of human papillomaviruses (HPV).

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- α) 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; furthermore, EGFR blockade appears to result in radiosensitization. This hypothesis was proven in a randomized trial by Bonner, et al. (2006). In that study, patients with locally advanced, non-operative SCCHN were randomized to RT alone or RT with weekly cetuximab (an anti-EGFR monoclonal antibody). Local-regional control and survival were significantly improved with cetuximab. Specifically, the 3-year rate for freedom from local-regional progression and overall survival were 47% and 55% for RT/cetuximab, compared with 34% and 45% for RT alone. The relative reduction in the risk of local-regional progression and dying were 32% ($p=0.005$) and 26% ($p=0.03$) [Bonner 2006].

1.2.2 Cetuximab

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 \geq Grade 3 mucositis or dysphagia, no evidence of an increased rate of late effects, and no evidence of a worsening of 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.

The positive results of the Bonner randomized trial has led to the FDA approval for cetuximab as concurrent treatment with RT for locally advanced head and neck cancer. Although the FDA approval was quite broad, subgroup analysis of this study offers some potential insight regarding patient selection. The overall survival benefit from the addition of cetuximab was most significant in oropharynx cancer (hazard ratio 0.62), moderately significant in larynx cancer (hazard ratio 0.87), and not significant in hypopharynx cancer (hazard ratio 0.94). Oral cavity cancer was not included in the Bonner study, since most patients with oral cavity are treated with surgery prior to RT rather than definitive RT.

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).

Based upon the encouraging data described above, we propose testing cetuximab with postoperative RT for those patients who have a moderately high risk of recurrence and who do not clearly benefit from cisplatin concurrent chemotherapy. Specifically, the current study (RTOG 0920) will compare the current standard of care for these patients (RT alone) against RT with cetuximab. Our study is not identical to the Bonner design. In addition to the obvious difference that RTOG 0920 is a postoperative therapy study rather than a definitive RT study, there are major differences in study eligibility and stratification design. First, our study will include oral cavity cancer, since these patients are commonly treated with upfront surgery yet are at moderately high risk of local-regional recurrence. Our study will exclude patients with hypopharynx cancer, since they have a particularly poor prognosis irrespective of stage and treatment. (As noted above, the Bonner study did not show a benefit from the addition to cetuximab to RT for hypopharynx cancer). Fortunately, hypopharynx cancer is a relatively uncommon subtype of SCCHN in the U.S. and Canada.

1.2.3 Stratification by EGFR Expression

In the Bonner study, which began in 1998, stratification was performed based upon Karnofsky Performance Status (60-80 vs. 90-100); nodal involvement (N0 vs. N+); T-stage (T1-3 vs. T4); and RT technique (standard once daily vs. bid/intensified). Tissue for EGFR testing was obtained in many patients, but this was not used in the a priori study design. EGFR testing consisted of simply staining for the presence or absence of EGFR via immunohistochemical staining; not surprisingly nearly 100% of the samples were EGFR positive. In contrast, our study proposes to stratify patients based upon quantitative extent of EGFR expression (low vs. high). This is based upon a previous analysis of RTOG data performed by Ang, et al. (2002), in which the amount of EGFR present on tumor cells was quantified using an optical density technique and the percentage of tumor area staining positive for EGFR (staining index) was measured. The median amount of EGFR expression was used as the cutoff for statistical analysis. This study showed that patients with “low” EGFR expression had significantly better local-regional control and survival than patients with high EGFR expression. Patients in Ang’s analysis were treated with definitive RT alone. It is less clear if this observation is true for patients treated with both surgery and RT. It is also unclear if a potent anti-EGFR agent would be more effective, equally effective, or less effective in patients with lower or higher expression of EGFR. However, it is very plausible to suspect that differences exist; thus, we propose to stratify patients a priori based upon the amount of EGFR expression. We also will perform a secondary subgroup analysis of outcomes based upon these separate strata.

1.2.4 Post-RT Cetuximab

A final difference between the Bonner study and RTOG 0920 is that patients will continue to receive cetuximab for four weeks following the completion of RT. This is based upon preclinical data by Milas, et al. (2007) showing that radiocurability was improved by adding a few doses of cetuximab following RT plus concurrent cetuximab. More recent data indicate that this additional effect is mediated through reduction of the tumor cell clonogenicity and proliferation and also by enhancement of tumor necrosis most likely resulting from increased susceptibility of tumor vasculature and cells to cetuximab effect (see Attachment A) summarizing results presented at the 2008 AACR meeting). Since the goal of our clinical trial is the complete eradication of microscopic tumor cells and unequivocal cure of patients, these recent data must be taken very seriously. There is precedent for this design, including the EXTREME trial (Vermorken 2008) in which patients were randomized to chemotherapy alone or chemotherapy plus cetuximab. In that study (a positive study showing a benefit to cetuximab), chemotherapy was given for up to 6 cycles, but cetuximab was continued beyond chemotherapy. We believe that the addition of 4 weeks of cetuximab after RT will be well tolerated given the toxicity profile of RT/cetuximab.

1.3 **Clinical Studies of Cetuximab in Head and Neck Cancer**

The efficacy and safety of cetuximab in combination with radiation therapy was studied in a randomized controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) versus radiation therapy alone. In addition, cetuximab alone was studied in a single-arm, multi-center clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2-6 cycles of platinum-based chemotherapy. Since expression of EGFR has been detected in nearly all patients with head and neck cancer, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR expression prior to study entry.

1.3.1 Randomized, Controlled Trial in SCCHN

The efficacy and safety of cetuximab were studied in combination with radiation therapy 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 \geq N1 neck disease, a post-radiation therapy neck dissection was recommended. Starting 1 week before radiation, cetuximab was administered as a 400-mg/m² initial dose, followed by 250 mg/m² 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 \geq 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:

	Cetuximab + Radiation (n = 211)	Radiation Alone (n = 213)	Hazard Ratio (95% CL³)	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

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.

1.3.2 Single-Arm Trials of SCCHN

Cetuximab alone was studied in a single-arm, multi-center clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2-6 cycles of

a platinum-based chemotherapy. Patients received a 20-mg test dose of cetuximab on Day 1, followed by a 400-mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity. Upon progression, patients were given the option of receiving cetuximab plus the platinum regimen that they failed prior to enrollment. Tumor response and progression were assessed by an Independent Radiographic Review Committee (IRC). The median age was 57 years (range 23-77), 82% were male, 100% Caucasian, and 62% had a Karnofsky performance status of ≥ 80 . The objective response rate on the monotherapy phase was 13% (95% confidence interval (7%-21%). Median duration of response was 5.8 months (range 1.2-5.8 months).

1.4 Safety of Cetuximab in SCCHN Clinical Studies (25-JAN-2016)

Except where indicated, the data described below reflect exposure to cetuximab in 208 patients with locally or regionally advanced SCCHN who received cetuximab in combination with radiation and as monotherapy in 103 patients with recurrent or metastatic SCCHN. Of the 103 patients receiving cetuximab monotherapy, 53 continued to a second phase with the combination of cetuximab plus chemotherapy. Patients receiving cetuximab plus radiation therapy received a median of 8 doses (range 1-11 infusions). The population had a median age of 56; 81% were male and 84% Caucasian. Patients receiving cetuximab monotherapy, received a median of 11 doses (range 1-45 infusions). The population had a median age of 57; 82% were male and 100% Caucasian. The most serious adverse reactions associated with cetuximab in combination with radiation therapy in patients with head and neck cancer were:

- Infusion reaction (3%);
- Cardiopulmonary arrest (2%);
- Dermatologic toxicity (2.5%);
- Mucositis (6%);
- Radiation dermatitis (3%);
- Confusion (2%);
- Diarrhea (2%).

Fourteen (7%) patients receiving cetuximab plus radiation therapy and 5 (5%) patients receiving cetuximab monotherapy, discontinued treatment primarily because of adverse events.

The most common adverse events seen in 208 patients receiving cetuximab in combination with radiation therapy were acneiform rash (87%), mucositis (86%), radiation dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).

The most common adverse events seen in 103 patients receiving cetuximab monotherapy were acneiform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in the table below are based on the experience of 208 patients with locoregionally advanced SCCHN treated with cetuximab plus radiation therapy compared to 212 patients treated with radiation therapy alone (Cetuximab [Erbix™] package insert, 2006).

Incidence of Selected Adverse Events ($\geq 10\%$) in Patients with Locoregionally Advanced SCCHN				
Body System Preferred Term	Cetuximab plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1 – 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise	56	4	48	5
Fever ¹	29	1	13	<1
Headache	19	<1	8	<1
Infusion Reaction	15	3	2	0
Infection	13	1	9	1
Chills ¹	16	0	5	0
Digestive				
Mucositis/Stomatitis	93	56	94	52

Incidence of Selected Adverse Events (≥ 10%) in Patients with Locoregionally Advanced SCCHN				
Body System Preferred Term	Cetuximab plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
	Grades 1 – 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
	% of Patients			
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Respiratory				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
Skin/Appendages				
Acneiform Rash ³	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0
¹ Includes cases also reported as infusion reactions				
² Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction” or any event on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.				
³ Acneiform rash as defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin” or “exfoliative dermatitis”.				

1.4.1 Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in cetuximab in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the cetuximab plus radiation treatment groups.

1.5 **Summary of Results of Investigational Program**

1.5.1 Clinically Relevant Adverse Events Related to Cetuximab

Pooled adverse event (AE) data (preliminary or final) are available for 2,127 patients treated with cetuximab alone or in combination with chemotherapy and/or radiation therapy in 21 ImClone studies, 9 Merck KgaA, 2 BMS, and 1 ECOG study.

A total of 90.3% of the patients reported adverse events (AEs). Approximately two-thirds (64.8%) of patients reported at least one Grade 3 or 4 event. Cetuximab-related AEs were observed in 1,817 patients (85.4%). The most common composite groupings of adverse events deemed related to cetuximab as reported by investigators in all cetuximab trials (N = 1,817) include acneiform rash (76.2%), acne-like rash (72.4 %), fatigue/malaise/lethargy (30.1%), nausea/vomiting (24%), f mucositis/stomatitis (17.5 %), infusion-related symptoms (15.6%), diarrhea (15.4 %), and hypersensitivity reaction (5.3%).

The development of acute interstitial pneumonitis in patients treated with EGFR-targeted agents has recently been described (Investigator Brochure; see [Section 7.2.1](#) of the protocol to obtain a copy).

A detailed list of Serious Adverse Events (SAE) is presented in the Investigator Brochure. Noteworthy are SAEs leading to death: one from infusion reaction, and one from interstitial pneumonitis

Except where indicated, the data described below reflect exposure to cetuximab in 774 patients with advanced metastatic colorectal cancer. Cetuximab was studied in combination with irinotecan (n=354) or as monotherapy (n=420). Patients receiving cetuximab plus irinotecan received a median of 12 doses (with 88/354 [25%] treated for over 6 months), and patients receiving cetuximab monotherapy received a median of 7 doses (with 36/420 [9%] treated for over 6 months). The population had a median age of 59 and was 59% male and 91% Caucasian. The range of dosing for patients receiving cetuximab plus irinotecan was 1-84 infusions, and the range of dosing for patients receiving cetuximab monotherapy was 1-63 infusions.

The most **serious adverse reactions** associated with cetuximab were:

- Infusion reaction (3%);
- Dermatologic toxicity (1%);
- Interstitial lung disease (0.4%);
- Fever (5%);
- Sepsis (3%);
- Kidney failure (2%);
- Pulmonary embolus (1%);
- Dehydration (5%) in patients receiving cetuximab plus irinotecan, 2% in patients receiving cetuximab monotherapy;
- Diarrhea (6%) in patients receiving cetuximab plus irinotecan, 0% in patients receiving cetuximab monotherapy.

Thirty-seven (10%) patients receiving cetuximab plus irinotecan and 17 (4%) patients receiving cetuximab monotherapy discontinued treatment primarily because of adverse events. The most common adverse events seen in 354 patients receiving cetuximab plus irinotecan were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), nausea (55%), abdominal pain (45%), and vomiting (41%).

The most common adverse events seen in 420 patients receiving cetuximab monotherapy were acneiform rash (90%), asthenia/malaise (48%), nausea (29%), fever (27%), constipation (26%), abdominal pain (26%), headache (26%), and diarrhea (25%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Data in patients with advanced colorectal carcinoma in the tables below are based on the experience of 354 patients treated with cetuximab plus irinotecan and 420 patients treated with cetuximab monotherapy.

Incidence of Adverse Events (≥ 10%) in Patients with Advanced Colorectal Carcinoma				
Body System Preferred Term ^a	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise ^d	73	16	48	10
Abdominal Pain	45	8	26	9
Fever ^c	34	4	27	<1
Pain	23	6	17	5
Infusion Reaction	19	3	21	2

Incidence of Adverse Events (≥ 10%) in Patients with Advanced Colorectal Carcinoma				
Body System Preferred Term ^a	Cetuximab plus Irinotecan (n=354)		Cetuximab Monotherapy (n=420)	
	Grades 1 - 4	Grades 3 and 4	Grades 1 - 4	Grades 3 and 4
	% of Patients			
Infection	16	1	14	1
Back Pain	16	3	10	2
Headache	14	2	26	2
Digestive				
Diarrhea	72	22	25	2
Nausea	55	6	29	2
Vomiting	41	7	25	3
Anorexia	36	4	23	2
Constipation	30	2	26	2
Stomatitis	26	2	10	<1
Dyspepsia	14	0	6	0
Hematic/Lymphatic				
Leukopenia	25	17	<1	0
Anemia	16	5	9	3
Metabolic/Nutritional				
Weight Loss	21	0	7	1
Peripheral Edema	16	1	10	1
Dehydration	15	6	10	3
Nervous				
Insomnia	12	0	10	<1
Depression	10	0	7	0
Respiratory				
Dyspnea ^c	23	2	17	7
Cough Increased	20	0	11	1
Skin/Appendages				
Acneiform Rash ^e	88	14	90	8
Alopecia	21	0	4	0
Skin Disorder	15	1	4	0
Nail Disorder	12	<1	16	<1
Pruritus	10	1	11	<1
Conjunctivitis	14	1	7	<1

^a Adverse events that occurred (toxicity Grades 1 through 4) in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab plus irinotecan or in ≥10% of patients with refractory colorectal carcinoma treated with cetuximab monotherapy.

^b Asthenia/malaise is defined as any event described as “asthenia”, “malaise”, or “somnolence”.

^c Includes cases reported as infusion reaction.

^d Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.

^e Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

1.5.2 *Acne-Like Rash*

In clinical studies of cetuximab, dermatologic toxicities, including acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (e.g., blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneiform rash was reported in 89% (686/774) of all treated patients, and was severe (grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported. Non-suppurative acneiform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% grade 3) of patients receiving cetuximab plus irinotecan and in 90% (8% grade 3) of patients receiving cetuximab monotherapy. Acneiform

rash most commonly occurred on the face, upper chest, and back but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (e.g., blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneiform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

1.5.3 Nail Disorder

A related nail disorder, occurring in 14% of patients (0.4% Grade 3), is characterized as a paronychia inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

1.5.4 Infusion Reactions

In clinical trials, severe, potentially fatal infusion reactions were reported, one leading to death (see Section 1.3). These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving cetuximab plus irinotecan and 19% of patients receiving cetuximab monotherapy.

A 20-mg test dose was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

Severe infusion reactions occurred with the administration of cetuximab in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension.

1.5.5 Pulmonary Toxicity

Interstitial lung disease (ILD) was reported in 3 of 774 (< 0.5%) patients with advanced colorectal cancer receiving cetuximab. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with cetuximab and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

1.6 Use of High-Technology Radiotherapy (IMRT, IGRT)

In parallel with the advances in understanding the biology of head and neck cancer and integrating targeted systemic therapies, there have been technological improvements in RT. The most widely publicized technique for improving the therapeutic ratio of RT is intensity modulated radiation therapy (IMRT) [Press 2008]. IMRT employs fundamentally different means of planning and delivery of photon irradiation compared with conventional head and neck RT. Specifically, conventional RT combines 3 or 4 large fields in which the RT dose to most normal structures (e.g., parotid glands, pharyngeal walls) is the same as the dose to the target volumes of the tumor bed and cervical lymphatics. IMRT combines numerous small and irregularly shaped radiation beams of variable intensities to achieve a radiation dose distribution that conforms much better to these target volumes. In particular, the radiation doses received by the parotid glands are dramatically decreased with IMRT.

IMRT improves the dosimetry of RT – at least to the target volumes and the parotid glands – but its effects on clinical outcomes are less well documented. Small randomized trials of IMRT versus standard RT for nasopharynx cancer did not show a significant quality of life benefit (despite showing significantly increased parotid gland flow with IMRT) [Kam 2007; Pow 2006]. The RTOG now has performed two prospective (non-randomized) multi-center studies of IMRT. The first of these studies, RTOG 0022, was performed in early stage oropharynx cancer (treated with definitive RT rather than surgery). This study showed very good feasibility, toxicity profile, and excellent local control with IMRT (Eisbruch 2006). Long-term data, however, are still pending,

and cannot necessarily be extrapolated to more advanced head and neck cancer. A more intriguing analysis of IMRT within the RTOG experience has just been performed by Harari, et al. (2008). This was an analysis of RTOG 0234, a phase II randomized study of postoperative RT plus cetuximab, plus either cisplatin or docetaxel for high-risk resected SCCHN. Treating physicians were allowed to use IMRT or conventional 2D/3D radiotherapy. Both treatment arms were considered feasible without excessive toxicity. However, Harari's analysis strongly suggested that acute toxicity (mucositis and skin) was greater in those patients treated with IMRT compared with conventional RT. Long-term data from RTOG 0234 are not yet available.

Thus, despite some early evidence of advantages to IMRT, it does have limitations. Most notably, the emphasis has been on target volume coverage and parotid gland sparing. This may not be sufficient to improve the therapeutic ratio of head and neck irradiation. Other normal structures within the head and neck, such as the pharyngeal walls/constrictors may be important for post-RT eating function. With conventional IMRT, sparing structures other than the spinal cord/brain and parotids is complicated by their close proximity to the target volumes. Furthermore, the delivery of each day's IMRT treatment cannot be routinely guaranteed to replicate the pre-planned IMRT blueprint. This daily setup variation/error is the result of many factors, such as changes in patient weight or shape between daily treatments and imperfections in daily alignment of patients by radiation technologists. Excessive day to day variances could theoretically increase treatment toxicity or risk underdosing the target volume (Hong 2006; Manning 2001). In order to circumvent the underdosing concern, target volumes are typically artificially expanded by up to 1 cm in all directions prior to beginning the planning process for IMRT. A clinical target volume (CTV) that contains 64 cc of tissue may thus need to be expanded to a 125-cc planning target volume (PTV). In other words, in order to guarantee sufficient RT to a region of interest, the total volume heavily irradiated is approximately doubled. This has significant implications for toxicity.

Daily image-guided radiation therapy (IGRT) is a recently introduced technique to improve the accuracy of day-to-day radiotherapy, particularly IMRT. Each day, after the patient is positioned on the RT treatment table, multi-planar images of the target region are obtained before treatment. These images are correlated with the patient's original, pre-planned images, and variances are detected and corrected prior to actual treatment. A variety of techniques exist for achieving IGRT (Tome 2001; Thilman 2006). Techniques for IGRT in the head and neck may include daily orthogonal megavoltage flat plane images (portal films); orthogonal kilovoltage images; non-radiation-based optical guidance systems; and Linear Accelerator mounted cone-beam computed tomography (CT) scan devices. These machines are available with software components to determine the magnitude of variance/errors detected relative to the pre-planning data. This technology is increasingly available at both academic and community radiation oncology departments.

By using daily IGRT, it can be hypothesized that the magnitude of the CTV to PTV "safety margin" during pre-planning may be limited to 3 to 5 mm. Potentially even smaller margins might be feasible in selected cases. However, daily IGRT does not correct for all possible errors. For instance, intra-treatment motion of some structures within the head and neck (e.g., tongue or larynx) may occur and could significantly alter the geometry of target volumes and normal tissues during treatment. This trial will recommend a 5 mm CTV to PTV margin, although a specific margin will not be mandated (because this is subject to individual institutional processes).

It is hypothesized that by using rigorously planned and delivered IMRT/IGRT, highly effective sparing of critical normal tissues in the head and neck can be achieved. It is hoped that this will manifest itself as reduced late Grade 2 and Grade 3 adverse events (AEs) [especially dysphagia] compared with historical controls, as well as improvement in patient-reported outcomes (PROs) with respect to head and neck specific functions (swallowing function, speech, xerostomia).

1.7 Translational Science (04-JUN-2010)

This study has several embedded and integral translational science questions related to EGFR and HPV, respectively (this is in addition to harvesting and storing tissue samples for future exploratory analysis of other molecular factors in SCCHN). Presently, while much has been learned about the relationships among EGFR, HPV, and SCCHN, there is marked uncertainty regarding if and how this biological information should be used clinically. For example, the National Comprehensive Cancer Network (NCCN) guidelines do not currently recommend routine

testing for EGFR and/or HPV in SCCHN. If testing for one or both of these biologic factors were to be performed, there are no current recommendations at this time to alter therapy accordingly. In the future, however, it is likely that personalized intervention for SCCHN will be utilized in the clinic. For example, patients with HPV-related SCCHN might be irradiated to lower radiation doses than non-HPV related SCCHN (there are plans to test this hypothesis in other cooperative groups' studies). Data from this study with respect to the prognosis of HPV-related cancers will be useful adjunctive data toward this goal. RTOG 0920 also will test a priori whether patients with high or low expression of EGFR (high defined as $\geq 80\%$ of cells staining positive for EGFR; low defined as $< 80\%$ of cells staining positive) are more likely to benefit from an anti-EGFR agent (cetuximab). We predict that both subgroups will benefit but that patients with high expression of EGFR will nonetheless have a suboptimal outcome and thus, might benefit from additional intensification of treatment in future studies (e.g., combination RT/chemotherapy/anti-EGFR therapy). RTOG 0920 will be adequately powered to test this hypothesis.

1.7.1 *Translational Study of EGFR and Its Ligands and Stratification Based on EGFR*

This study will require mandatory submission of tissue for analysis of EGFR and, for patients with oropharyngeal carcinoma, HPV, i.e., patients who do not have available tissue and/or refuse to consent to tissue submission will not be eligible. The reason for mandatory EGFR submission is that this study uses a highly specific anti-EGFR therapy (cetuximab). Although cetuximab binds to the EGFR with high specificity and has proven benefit for SCCHN, it appears that only a modest proportion of patients truly benefit significantly from this agent (i.e., 11% response rate in platinum refractory disease; 13% absolute improvement in local-regional DFS compared with RT alone). Given that cetuximab is expensive and has toxicity, it is vital to identify the patient subpopulations that are most likely to benefit from this drug. At this time, it is unclear whether or not the levels of EGFR as assayed by immunohistochemistry correlate with activity (or lack of activity) of cetuximab. This differs from the situation for HER-2/breast cancer, in which amplification/overexpression is clearly associated with a positive response to the anti-HER-2 antibody trastuzumab.

It is hypothesized, however, that patients with SCCHN whose tumors harbor a mutation known as the vIII variant may be less responsive to cetuximab. The EGFRvIII mutation results in a truncated protein at the extracellular ligand binding domain, and results in constitutive activation of the tyrosine kinase independent of the ligand binding. Because cetuximab exerts antitumor effects by inhibiting the ligand binding, the activity of EGFRvIII with ligand independent activation would not be inhibited by cetuximab and small molecule EGFR tyrosine kinase inhibitors (e.g., erlotinib) that work directly at the tyrosine kinase domain might be more effective. It is estimated that up to 40% of SCCHN samples express the vIII variant in addition to wild-type EGFR (EGFRwt).

The question of the optimal methodology for analyzing and quantifying EGFR expression in SCCHN has been studied by investigators, including members of NRG Oncology. EGFR expression is ubiquitous in SCCHN and the levels of expression may be extremely high. Ang et al. studied the tissue samples from patients with non-operative locally advanced SCCHN treated in RTOG 90-03 (RT alone) [Ang 2002]. Tumor tissue samples were analyzed for EGFR expression using a technique to quantify the amount of immunohistochemical staining by an automated optical technique. The study showed a relatively broad range of EGFR mean optical density (MOD) or staining index (SI) among samples. There was a relatively high correlation between MOD and SI. The median MOD or SI for EGFR was used as a cutoff for binary analysis of outcomes. This resulted in an extremely strong correlation with overall survival, DFS, and local-regional control.

Furthermore, there is mounting evidence that EGFR ligand levels as well as the receptor are important in the pathway activation and as marks of prognosis and prediction of cetuximab response. A gene expression study by Chung, et al. (2004) found that a molecular subtype of SCCHN in 21/60 tumors (35%) had higher expression of EGFR ligands, TGF- α , and amphiregulin, and had worse disease-free survival compared to other subtypes. In addition, a study by Khambata-Ford, et al. (2007) has shown that higher expression levels of amphiregulin and epiregulin associated with cetuximab response and disease-free survival (HR 0.4558, 95% CI 0.2284-0.6177) in recurrent/metastatic colon cancer patients. We will examine three ligands, TGF- α , amphiregulin and epiregulin, which are dominant ligands in squamous epithelium. To avoid possible bias in randomization of patients to the study, the patient's physician or

institution cannot request the patient's EGFR level from NRG Oncology until the patient has completed study treatment.

1.7.2 Translational Study of HPV and Stratification Based on HPV

Another major change in the landscape of head and neck cancer research over the past decade has been the recognition of the increased incidence of HPV-related oropharynx cancer. HPV (mostly HPV 16) DNA can be detected in many human oropharyngeal SCC specimens, and strong evidence suggests that it is a causative agent. HPV infection is thought to cause cancer in the oropharynx by integration of the HPV early viral oncoproteins E6 and E7 into the genome of tonsillar mucosal epithelium; these oncoproteins induce tumorigenesis by deregulating the p53 and p16/Rb pathways (Gillison 2000).

An emerging body of literature suggests that HPV-related SCCHN (oropharynx cancer) has a number of important biologic and clinical differences compared with traditional SCCHN. Retrospective analysis revealed that HPV associated oropharynx SCCHN has a significantly better prognosis than non-HPV associated disease, possibly due to improved responsiveness to RT +/- chemotherapy (Gillison 2000; Mellin 2000; Schwartz 2001; Ringstrom 2002).

The above data strongly suggests that it is important to account for HPV in large scale clinical trials that include oropharynx cancer. Most notably, it is necessary to stratify for HPV-related cancer (yes vs. no) in order to assure that treatment arms are well balanced (An imbalance could very likely result in improved outcomes in the treatment arm that has more patients with HPV-related cancer). Thus, one of the stratifications in our study will be for HPV-related SCC of the oropharynx. Since HPV is not typically associated with non-oropharynx SCCHN, this will only specifically be done for oropharynx cancer. To avoid possible bias in randomization of patients to the study, the patient's physician or institution cannot request the patient's HPV status from NRG Oncology until the patient has completed study treatment.

There is still controversy regarding the best method to detect HPV in oropharyngeal tumors. The probable gold standard is to perform DNA analysis using PCR-based techniques; however, the technique is prone to false-positivity and is likely to be unwieldy for a large multicenter cooperative group trial at this time. Another method is to detect HPV 16 DNA in tissue sections using *in situ* hybridization (ISH). This method has high sensitivity and specificity but is technically challenging to perform requiring specialized equipment, resources, and facilities to provide a robust and reproducible assay. Moreover, its application and dissemination to peripheral testing centers may prove to be challenging moving forward. A widely used alternative for the detection of HPV is the use of immunohistochemical staining (IHC) for the p16 protein (which is generally overexpressed in HPV-positive oropharynx cancer). When the HPV was detected by ISH and compared to p16 staining, 100% of HPV positive tumors by ISH were positive by p16 expression using IHC (Fakhry 2008). This assay is currently widely used and does not require specialized facilities, resources, and equipment beyond that which is currently used in most pathology laboratories. Moreover, quantification is simplified by the dichotomous staining pattern in tumor cells (positive or negative). Therefore, this trial proposes to use p16 expression as a surrogate marker to assess HPV status in oropharyngeal specimens.

1.7.3 Translational Study of TP53 Mutation

Loss of function in p53, a tumor suppressor protein, by mutation or rapid degradation by oncoproteins E6 due to HPV infection has been associated with SCCHN. The location of mutations within the gene, TP53, can manifest as abnormally truncated protein (nonsense mutation), disruption of DNA binding capacities (missense mutation), or no functional consequences (silent mutation). We hypothesize that the patients with functionally disruptive TP53 mutations will have poor overall survival and time to disease progression. This hypothesis is based on the recent study by Poeta ML, et al. (Poeta 2007). They found that 53.3% of SCCHN patients had TP53 mutations; functionally non-disruptive 33%, disruptive 20%, and wild type 47%. The patients with any TP53 mutations associated with the worse overall survival compared to wild-type TP53 (HR to death, 1.4; 95% confidence interval 1.1-1.8, p=0.009) while the association was stronger with functionally disruptive TP53 mutation (HR 1.7; 1.3-2.4, p<0.001). Validation of the association will further the effort of clinical implementation of this assay and stratification of risks based on biology of the tumors.

1.7.4 Translational Study of CA Dinucleotide Repeats in EGFR Intron 1

There is evidence that the length of the repeats differ based on sex and race as well as the prognostic and predictive outcomes after standard of care and EGFR inhibitor treatments. We hypothesize that short CA dinucleotide repeats in EGFR intron 1 will associate with poor overall survival and time to disease progression. In a prognostic marker study of patients with metastatic colon cancer by Press, et al. (2008), women with both short repeats (< 20 CA(n) repeat alleles) had better overall survival while the opposite was true in men. Also, there are data that the numbers of repeats are predictive of EGFR inhibitor therapies. A study by Liu, et al. (2003), showed that Asians had a longer allele compared to Caucasians and African-Americans, suggesting that Asians would benefit more from EGFR inhibitors due to less expression of EGFR. In an Asian study of non-small cell lung cancer by Han, et al. (2007), a short CA repeat (sum of both alleles < or =37) was associated with better objective response to gefitinib (odds ratio 7.1, 95% confidence interval 1.2–40.8; p=0.029) and time-to progression (hazard ratio 0.54, 95% confidence interval 0.34–0.88; p=0.014), independent of EGFR mutation. However, the sex of the patients was not evaluated in the multivariate analyses. Based on these data and the diverse NRG Oncology patient population of mixed sex and race, the prognostic and predictive nature of this polymorphic variant can be further defined and validated. In addition, we will determine whole genome-wide single nucleotide polymorphism (SNP) using Affymetrix SNP chips to associate other polymorphic variants with response and toxicities as exploratory studies.

1.8 Quality of Life and Function Assessments (26-JAN-2018)

It is now well established that cancer of the head and neck often has profoundly debilitating effects on quality of life (QOL), function, and performance. In a recently reported phase III trial of cetuximab and radiation therapy (RT) for head and neck squamous cell carcinoma (HNSCC), cetuximab did not significantly increase RT-associated adverse effects (Bonner 2006). This study also found that addition of cetuximab to RT significantly improved locoregional control and increased overall survival without adversely affecting QOL (Curran 2007). However, with this limited experience, the acute and long-term impact of cetuximab on QOL remains largely unknown. Thus, assessments of QOL and key functions such as eating/swallowing (dysphagia) and xerostomia (dry mouth) are included as secondary end points in the current study.

QOL is a global, multidimensional construct that assesses the patient's overall sense of well-being and how it relates to disease and disease treatment (Murphy 2007). Thus, QOL must be assessed from the patient's perspective using validated patient-reported measures. As Murphy, et al. (2007) point out, an important issue in measuring QOL is the relationship of between function and the domains of QOL. It has been noted that evaluation of function separately from QOL yields distinct and important information that may not be captured in the context of QOL measures (Murphy 2007; Sarna 2008). Because function assessment may be undertaken using either subjective symptom measures or objective and clinician rated measures (Murphy 2007; Basch 2006; Jensen 2006), the relationship between patient reported function and QOL outcomes is not clear cut in the literature. Murphy, et al. (2007) recently concluded that the relationship between function and QOL in head and neck cancer varies and several studies have been conducted in an effort to further elucidate relationships. Recent studies using objective measures of dysphagia/swallowing and QOL measures found a correlation between aspiration measured by videofluoroscopy swallow studies and patient reported QOL measures (Nguyen 2005; Campbell 2004). Similarly, in other studies, speech and communication impairment was associated with changes in speech and communication domains of QOL measures (Meyer 2004), and change in taste, xerostomia, and other oral symptoms were found to have a significant impact on QOL (Duke 2005; Epstein 2001; Epstein 1999). While some studies have found significant associations, a notable number have reported no associations between function and QOL measures (List 1996; Hanna 2004; Finizia 1998; Deleyiannis 1999; Moore 1996; Friedlander 2002; Hertrampf 2004). In this study, while objective assessments of dysphagia such as videofluorography or videofluoroscopic swallowing studies could be employed (Logemann 2008), the cost and lack of appropriate technology and trained staff at most of the participating centers is prohibitive in a cooperative group setting.

Furthermore, the relationship between observer-based (clinician-rated) toxicity/function scoring and patient reported QOL has been recently documented (Sarna 2008; Basch 2006; Jensen 2006). In a cross-sectional study, Jensen (2006) showed poor to modest correlations between the DAHANCA toxicity scoring system and the various EORTC quality of life questionnaire domains. For example, clinician-rated dysphagia had the highest correlation with the EORTC

social eating component ($r=.58$, $p<.01$) [Jensen 2006]. Physician-rated dry mouth was more highly correlated with patient reported dry mouth ($r=.72$, $p<.01$). Sarna (2008) reported a disconnect between clinician-assessed dysphagia/esophagitis and patient-reported swallowing function and QOL in treated lung cancer patients (RTOG 9801). These findings demonstrate an important difference between patient- and physician-rated symptoms/function and highlight the importance of measuring patient reported function and QOL separately.

Thus recognizing that QOL and functional outcome assessment are two distinct components that should be measured and discussed separately, these outcomes will be measured using validated patient reported outcome (PRO) instruments that derive directly from the patient perspective and using "objective" clinician-rated measures as summarized separately below. While this may not be an optimal approach, it allows the assessment of the correlations of QOL and functional measures in this study.

1.8.1 Quality of Life (QOL) Assessments

Quality of life will be assessed using four validated, multidimensional patient-reported QOL measures including: the Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N); the Performance Status Scale for Head and Neck Cancer (PSS-HN); the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS); the Dermatology Life Quality Index (DLQI), and the EuroQol (EQ-5D).

The FACT-H&N is a multidimensional, patient self-report QOL instrument specifically designed and validated for use with head and neck cancer patients. The FACT-HN consists of a 27-item core scale (FACT-G) and is supplemented with a 12-item head and neck subscale targeting head and neck related symptoms and side effects (Cella 1993). The PSS-HN is a clinician/interviewer administered assessment that focuses on three functional areas: Normalcy of Diet, Eating in Public, and Understandability of Speech. The score on each of the three subscales ranges from 0-100, with higher scores indicating better performance (List 1996; List 1999; List 2000). The EQ-5D has been more frequently employed in cooperative group studies as a general QOL measure and for cost-utility analysis. The EQ-5D is a two-part questionnaire that the patient can complete in approximately 5 minutes. The first part of the EQ-5D consists of five items covering five areas: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these areas is graded on three levels: 1=no problems; 2=moderate problems; and 3=extreme problems. Health states are then derived from combinations of the leveled responses to the five dimensions. The second part of the EQ-5D is a visual analogue scale (VAS) valuing current health state, with 0 at bottom of the scale (worst imaginable health state) and 100 at the top (best imaginable health state) [Wu 2002]. The XeQOLS instrument is patient self-report measure that consists of 15 items on a 5-point Likert-type scale covering mouth/throat dryness and its impact on four major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues (Logemann 2008; Cella 1993; List 1996). The XeQOLS takes the patient approximately 5 minutes to complete.

The Dermatology Life Quality Index (DLQI) will be used to explore the impact of cetuximab-induced rash on quality of life. It is expected that rash (acneiform; maculo-papular), pruritis, and other visible consequences (CTCAE, v. 4) associated with cetuximab-induced rash will have a significant negative impact on quality of life (Boone 2007; Agero 2006; Shikiar 2005). Although the DLQI (Finley 1994) is designed to assess the impact of a wide range of skin disease on patient quality of life (Lennox 2004; Lewis 2004; Hongbo 2005; Shikiar 2005; Basra 2008), it has never been used in cancer-treatment related settings. Thus, use of DLQI will be exploratory in this study and represents the first time a dermatologic patient reported outcome measure is used for cetuximab-induced rash and in this population. The DLQI consists of 10 items and covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3 respectively; the response "not relevant" (and unanswered items) are scored as "0". A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. Higher scores indicate poorer HRQL (i.e., more impairment). The DLQI will be administered a baseline and at 3, 12, and 24 months after the start of radiation therapy. The relationship between the DLQI and 3 CTCAE, v. 4 dermatology

items (rash: acneiform; rash: maculo-papular; and pruritus) will be assessed as well as the relationship between the DLQI and the other QOL instruments.

The relationship between the EQ-5D and other QOL measures, such as the FACT-H&N, XEQOLS and the PSS-HN is not clearly understood. If the EQ-5D is highly correlated with either of these measures, it might provide an effective short form for collecting both QOL and utility data in HNSCC. The relationship of these 4 measures will be assessed in the current study.

1.8.2 Functional Assessments

Dysphagia will be assessed using the Normalcy of Diet component of the PSS-HN and the clinician-rated CTCAE, v. 4 dysphagia (difficulty in swallowing) item. The PSS-HN Normalcy of Diet subscale assesses the degree to which a patient is able to eat a normal diet. Ten categories are arranged from easy-to-eat at the low end to hard-to-eat at the high end. Scores range from 0-100, with those scores closer to 100 representing high level of function. The PSS-HN subscale allows for assessment and calculation of the percentage of patients on oral intake and the percentage of patients eating a normal diet. This study will assess the correlation between the CTCAE, v. 4 dysphagia (difficulty in swallowing) item and the PSS-HN Normalcy of Diet Scale at 3, 12, and 24 months from the end of radiation. Logemann (2008) found statistically significant decline at 3 months post-treatment (compared to pre-treatment baseline) in other measures of swallowing (percentage of patients eating < 50% orally; percentage of patients eating a normal diet), and the pattern of changes from these two measures was comparable to changes identified by videofluoroscopic swallow studies, suggesting that the former are suitable measures for evaluating swallowing function. The PSS-HN scale allows for assessment and calculation of similar outcome measures (i.e., percentage of patients on oral intake and percentage normal diet) in this trial.

To assess xerostomia and its impact on QOL in this study, the clinician-rated CTCAE, v. 4 dry mouth item and the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) will be used. The correlation between the CTCAE, v. 4 dry mouth item and the XeQOLS scale score will be assessed at 3, 12, and 24 months from the end of radiation.

1.8.3 Timeframe of Assessments

These patient-reported QOL and function measures and the clinician-assessed measures will be administered at baseline and at 3, 12, and 24 months from the end of radiation. The 3-month QOL assessment was chosen to coincide with usual practice of seeing a head and patient 2 weeks after completion of radiation therapy. This assessment will provide the immediate impact of radiation therapy +/- cetuximab on QOL. The 12-month QOL assessment was chosen to coincide with usual practice of seeing a head and patient 1 year after completion of radiation therapy. The Radiation Oncologists expect at this time that almost all acute toxicities related to radiation will be resolved, and they are interested in assessing the patient's QOL at that time. These 2 assessment time points for PRO outcomes are routinely used in NRG Oncology and other head and neck studies. PRO assessment has been added at 24 months from the start of radiation therapy to provide long-term data on cetuximab treated patients and on IGRT/IGRT treated patients. That time point was chosen because 80 to 90% of the patients who will progress do so by 2 years. For patients who are disease free then, the issue, it is felt, becomes the long-term sequelae of the treatments.

1.8.4 Optional Online Completion of QOL Assessments

Missing data are a significant problem, particularly for QOL assessments. Unlike data for traditional endpoints, such as survival, QOL data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform QOL statistical analyses and negatively impacts the clinical relevance of this effort. Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, NRG Oncology is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a new tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system (Gorgulho 2005; Gorgulho 2007; Pedroso 2006). The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It

is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be “pushed” to patients for completion at timed intervals (see <http://www.visiontree.com> for details). VisionTree has many clinical partners and clients, including ASTRO, University of California-San Francisco, Baylor College of Medicine, Duke University, Emory University, Harvard Medical School, Henry Ford Hospital, and University of Pennsylvania. ASTRO utilizes VisionTree outcomes online for maintenance of certification and for capturing quality measures. This technology would allow consenting patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes “missing data”.

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing QOL assessments at 6 months significantly improved using electronic technology. Based on this pilot data, NRG Oncology is offering VisionTree as an option in other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so.

For this trial, the baseline QOL forms must be completed in hardcopy at the time of enrollment. To complete subsequent QOL forms online, patients must have an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient’s e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

The patient’s e-mail address only will be used by NRG Oncology for this purpose. Patients will be sent e-mail reminders to complete QOL forms. A typical e-mail reminder would read: “Your Quality of Life forms for the study, RTOG 0920, are now due. Please go to <http://www.optimalcare.com>, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study.” The reminders will be created by NRG Oncology and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). The first reminder will be sent at the beginning of the “window” to complete a QOL form, with a second reminder halfway through the window period if the QOL forms are not yet completed at that time point. A maximum of 3 reminders will be sent for each of the 4 QOL time points (following the baseline QOL forms, which are completed in hardcopy). After a patient has completed all forms in the portal, a dialogue box will appear that says “Thank you for completing your Quality of Life forms,” and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC “At-A-Glance” form management system when QOL forms have been completed.

2.0 OBJECTIVES

2.1 Primary Objective

Test whether the addition of cetuximab to radiation therapy will improve overall survival (OS) in postoperative patients with intermediate risk following surgery

2.2 Secondary Objectives (04-JUN-2010)

2.2.1 Assess the impact of the addition of cetuximab to postoperative radiation therapy on the following:

- Disease-free survival (DFS);
- Acute dysphagia, dry mouth, skin toxicity, and other toxicities (CTCAE, v. 4) and their relationships to patient-reported outcomes at 3 months;

- Late dysphagia, dry mouth, skin toxicity, and other toxicities (CTCAE, v. 4) and their relationships to patient-reported outcomes at 12 and 24 months.
- 2.2.2** Tumor analysis of EGFR, specifically extent of EGFR overexpression by immunohistochemical (IHC) and FISH analysis, EGFRvIII expression, as well as association of these assay data with OS and DFS;
- 2.2.3** Tumor analysis of HPV infection (as defined by *in situ* hybridization), specifically, within the cohort of patients with oropharynx cancer, to perform an exploratory analysis of the impact of HPV on DFS and OS in this patient subset;
- 2.2.4** Tumor DNA analyses of *TP53* mutations for response prediction to cetuximab and prognosis;
- 2.2.5** Germline DNA analyses of polymorphic variants in EGFR intron repeats for response prediction to cetuximab.

2.3 Tertiary Objectives (Exploratory)

- 2.3.1** Assess the impact of the addition of cetuximab to postoperative radiation therapy on the following:
 - Local-regional control;
 - Patient-reported quality of life (QOL), swallowing, xerostomia, and skin toxicity based on head and neck specific instruments, including: the Performance Status Scale for Head and Neck Cancer (PSS-HN), the Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N), the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS), and the Dermatology Life Quality Index (DLQI);
 - Cost-utility analysis using the EuroQol (EQ-5D).
- 2.3.2** To evaluate the utility of IGRT as a means of enhancing the efficacy (i.e., local-regional control) of IMRT while reducing the acute and/or late toxicity (particularly xerostomia) and improving patient-reported outcomes (particularly scores with the XeQOLS);
- 2.3.3** To retrospectively compare the local regional control rate for patients treated with IMRT alone (no IGRT or cetuximab) with similar patients treated with external beam radiation alone in the postoperative trial, RTOG 95-01.

3.0 PATIENT SELECTION (07-APR-2014)

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 (17-JAN-2012)

- 3.1.1** Pathologically (histologically) proven diagnosis of squamous cell carcinoma (including variants such as verrucous carcinoma, spindle cell carcinoma, carcinoma NOS, etc.) of the head/neck (oral cavity, oropharynx or larynx); **Note:** Hypopharynx primaries are excluded because these patients have both a poor prognosis and high likelihood of post-radiation complications.
- 3.1.2** Clinical stage T1, N1-2 or T2-4a, N0-2, M0 including no distant metastases, based upon the following minimum diagnostic workup:
 - General history and physical examination by a Radiation Oncologist and/or Medical Oncologist within 8 weeks prior to registration;
 - Examination by an ENT or Head & Neck Surgeon, within 8 weeks prior to registration; a laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended but not required.
 - Chest x-ray (at a minimum) or chest CT scan (with or without contrast) or CT/PET of chest (with or without contrast) within 8 weeks prior to registration.
- 3.1.3** Gross total resection of the primary tumor with curative intent must be completed within 7 weeks of registration with surgical pathology demonstrating one or more of the following “intermediate” risk factors:
 - Perineural invasion;
 - Lymphovascular invasion;
 - Single lymph node > 3 cm or ≥ 2 lymph nodes (all < 6 cm) [no extracapsular extension];
 - Close margin(s) of resection, defined as cancer extending to within 5 mm of a surgical margin, and/or an initially focally positive margin that is subsequently superseded by intraoperative negative margins. Similarly, patients whose tumors had focally positive margins in the main specimen but negative margins from re-excised samples in the region of the positive margin are eligible. For questions or ambiguities about an individual case, contact Dr. Machtay and/or Dr. Holsinger prior to enrolling the patient.

- Pathologically confirmed T3 or T4a primary tumor; for questions or ambiguities about an individual case, contact Dr. Machtay and/or Dr. Holsinger prior to enrolling the patient.
- T2 oral cavity cancer with > 5 mm depth of invasion.
- 3.1.4** Zubrod Performance Status of 0-1 within 2 weeks prior to registration;
- 3.1.5** Age ≥ 18;
- 3.1.6** CBC/differential obtained within 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:
 - Absolute granulocyte count (AGC) ≥ 1,500 cells/mm³;
 - Platelets ≥ 100,000 cells/mm³;
 - Hemoglobin ≥ 8.0 g/dl (**Note:** The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable).
- 3.1.7** Adequate hepatic function, defined as follows:
 - Total bilirubin < 2 x institutional ULN within 2 weeks prior to registration;
 - AST or ALT < 3 x institutional ULN within 2 weeks prior to registration.
- 3.1.8** Adequate renal function, defined as follows:
 - Serum creatinine < 2 x institutional ULN 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:

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

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$
- 3.1.9** Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;
- 3.1.10** The following assessments are required within 2 weeks prior to the start of registration: Na, K, Cl, glucose, Ca, Mg, and albumin. 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.
- 3.1.11** Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control;
- 3.1.12** Patients must provide study specific informed consent prior to study entry, including consent for mandatory tissue submission for EGFR and for oropharyngeal patients, HPV analyses.
- 3.2 Conditions for Patient Ineligibility (23-JAN-2013)**
 - 3.2.1** Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; noninvasive cancers (For example, carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible) are permitted even if diagnosed and treated < 3 years ago. Patients with simultaneous primaries or bilateral tumors are excluded, with the exception of patients with bilateral tonsil cancers or patients with T1-2, N0, M0 resected differentiated thyroid carcinoma, who are eligible.
 - 3.2.2** Per the operative and/or pathology report, positive margin(s) [defined as tumor present at the cut or inked edge of the tumor], nodal extracapsular extension, and/or gross residual disease after surgery; **Note:** Patients whose tumors had focally positive margins in the main specimen but negative margins from re-excised samples in the region of the positive margin are eligible (see [Section 8.1](#)). For questions or ambiguities about an individual case, contact Dr. Machtay and/or Dr. Holsinger prior to enrolling the patient.
 - 3.2.3** Prior systemic chemotherapy or anti-EGF therapy for the study cancer; **note:** prior chemotherapy or anti-EGF therapy for a different cancer is allowable. See Section 3.2.1.
 - 3.2.4** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
 - 3.2.5** Severe, active co-morbidity, defined as follows:
 - Unstable angina and/or congestive heart failure requiring hospitalization within 6 months prior to registration;
 - Transmural myocardial infarction within 6 months prior to registration;
 - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;

- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
 - Idiopathic pulmonary fibrosis or other severe interstitial lung disease that requires oxygen therapy or is thought to require oxygen therapy within 1 year prior to registration;
 - Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
 - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; **note:** 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.
 - Grade 3-4 electrolyte abnormalities (CTCAE, v. 4):
 - Serum calcium (ionized or adjusted for albumin) < 7 mg/dl (1.75 mmol/L) or > 12.5 mg/dl (> 3.1 mmol/L) despite intervention to normalize levels;
 - Glucose < 40 mg/dl (< 2.2 mmol/L) or > 250 mg/dl (> 14mmol/L);
 - Magnesium < 0.9 mg/dl (< 0.4 mmol/L) or > 3 mg/dl (> 1.23 mmol/L) despite intervention to normalize levels;
 - Potassium < 3.0 mmol/L or > 6 mmol/L despite intervention to normalize levels;
 - Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.
- 3.2.6** 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.
- 3.2.7** Prior allergic reaction to cetuximab.

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 (25-JAN-2016)

- 4.1.1** Dental evaluation with management according to the guidelines in Appendix IV within 3 months prior to the start of treatment;
- 4.1.2** Assessment of swallowing function/dysphagia using CTCAE, v. 4 criteria within 2 weeks prior to the start of treatment.
- 4.1.3** Patients must be offered the opportunity to participate in the tissue/specimen collection for banking and translational research. If the patient consents to participate in this component, the site is required to submit the patient's specimens. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent form.
- 4.1.4** 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 treatment: the Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N); the Dermatology Life Quality Index (DLQI); the Performance Status Scale for Head and Neck Cancer (PSS-HN); the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS); and the EuroQol (EQ-5D).

Patients who consent to participate in the quality of life (QOL) component of this study have the option of completing QOL forms online from any location, including home, via VisionTree Optimal Care (VTOC). Patients without e-mail or Internet access are still able to participate in the QOL component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form.

If the patient wishes to complete QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g., Yahoo!, Hotmail, or AOL). **Note:** The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: <https://rtog.optimalcare.com> - medical team. RA login

information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.

See [Section 11.5.6](#) for further details.

4.2 Highly Recommended Evaluations/Management

- 4.2.1** Baseline postoperative re-staging/imaging of head, neck, and chest (e.g., CT with contrast, or CT/PET with or without contrast, and/or MRI of the head and neck) within 4 weeks prior to the start of treatment to rule out occult/rapid postoperative recurrence and/or second primary cancer; **Note:** Review of the RT treatment planning CT scan with the radiologist is acceptable.
- 4.2.2** Evaluation for prophylactic gastrostomy tube placement (especially if the patient is $\geq 10\%$ below ideal body weight) within 4 weeks prior to the start of treatment;
- 4.2.3** EKG within 8 weeks prior to the start of treatment.

5.0 REGISTRATION PROCEDURES (03-NOV-2014)

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: FOR THIS STUDY, IMRT IS MANDATORY; IGRT IS OPTIONAL and can be used without IGRT credentialing if not used for reducing margins. IGRT is mandatory when using reduced margins and for this, sites must be head and neck IGRT credentialed.

5.1 RT-Specific Pre-Registration Requirements (13-NOV-2017)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, the IROC Houston QA Center will notify your institution and NRG Headquarters when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

- Credentialing documentation received from IROC Houston for this trial-See section 5.1 Table for details.

Credentialing Requirements	Web Link for Procedures and Instructions: [www.irochouston.meanderson.org]	
	Treatment Modality	Key Information
	ns Photo	
Facility Questionnaire	✓	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	✓	To determine if your institution has completed the requirements above, please complete a “Credentialing Status Inquiry Form” found under Credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org).
Phantom Irradiation	✓	An IMRT Head and neck phantom irradiation provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that an institution, depending on its treatment delivery modalities, may be required to irradiate a phantom on different delivery machines such as TomoTherapy and CyberKnife
IGRT Verification Study	For reduced margins only	Institutions using reduced margins must be credentialed for bony tissue IGRT. Find details on CTSU's website (https://www.ctsuhouston.org) and the IROC Houston QA Center website (http://irochouston.mdanderson.org) Institutions that have previously been approved for IGRT may not need to repeat credentialing.
Credentialing Issued to:		
Institution		IROC Houston QA Center will notify the site that all desired credentialing requirements have been met. The site will need to upload a PDF of approval email from IROC Houston to the CTSU Regulatory Portal for RSS to be updated.

5.2 Preregistration Requirements for Head and Neck Image-Guided Radiotherapy (IGRT) Treatment Approach (For sites treating with reduced margins) (13-NOV-2017)

5.2.1 In order to utilize head and neck IGRT for reduced margins, the center must be credentialed for its use. See chart in section 5.1.

5.3 Pre-Registration Requirements for IMRT Treatment Approach (13-NOV-2017)

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. See chart in section 5.1.

5.4 Digital RT Data Submission to RTOG Using TRIAD (11-MAY-2023)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR; and
- TRIAD Site User role on an NCTN, ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at <https://triadinstall.acr.org/triadclient/>.

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

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

5.5 Regulatory Pre-registration Requirements (11-MAY-2023)

5.5.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at <https://ctepcore.nci.nih.gov/iam>. Investigators and clinical site staff who are significant contributors to research must register in the [Registration and Credential Repository](#) (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN must be rostered at the enrolling site with a participating organization.

Refer to the [NCI RCR](#) page on the [CTEP website](#) for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

5.5.2 CTSU Registration Procedures

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

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.cocccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (<https://www.ctsu.org>);
- Click on the *Protocols* tab in the upper left of the screen:
 - Enter the protocol number in the search field at the top of the protocol tree; or
 - Click on the By Lead Organization folder to expand, then select *NRG*, and protocol number *RTOG 0920*.
- Click on *Documents, Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Requirements for RTOG 0920 site registration:

- IRB approval (for sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- IROC Credentialing Status Inquiry (CSI) Form
- NOTE: For studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at <https://www.ctsuhouston.org/RSS/RTFProviderAssociation>, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. IRB/REB approved consent (English and native language versions*)
 - *Note: Institutions must also provide certification/verification of consent translation to NRG Oncology
- IRB/REB assurance number renewal information, as appropriate
- Credentialing documentation received from IROC Houston must be uploaded to the CTSU Regulatory Portal for RSS to be updated.

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.

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSUS (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
 - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

5.5.3 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

In addition to the requirements above, Canadian institutions must complete and submit the following documents to the CTSU Regulatory Office via the Regulatory Submission Portal:

- Health Canada's Therapeutic Products Directorates' Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form, and
- Research Ethics Board Attestation Form

5.5.4 Pre-Registration Requirements for Shipment of Cetuximab

US and Canadian Institutions:

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) available on the CTSU protocol website. U.S. and 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.

Non-Canadian International Institutions:

Please refer to your LOI Approval Notification.

5.6 **Registration (11-MAY-2023)**

5.6.1 Summary of Procedures

This study incorporates a two-step registration process.

All patients must consent to submission of tissue for EGFR analysis; see [Section 10.2](#) for details of submission. **Oropharyngeal carcinoma patients** also must consent to submit tissue for HPV analysis; see [Section 10.3](#) for details of submission. **All patients** can be registered after completing the Eligibility Checklist, STEP 1 via online registration; see [Section 5.6.2](#) for online registration instructions.

Institutions must submit the required tissue block for EGFR analysis to the NRG Oncology Biospecimen Bank (see [Section 10.5](#) for shipping information), using the case number obtained from STEP 1 registration. The Biospecimen Bank will determine the adequacy of the tissue and will send 2 unstained slides to Dr. Adel El-Naggar for EGFR analysis. The results of EGFR analysis are expected in approximately 7-8 business days, and NRG Oncology will inform sites by e-mail of the completion of the EGFR analysis. At this point, **non-oropharyngeal carcinoma patients** may be randomized; sites must complete the Eligibility Checklist, STEP 2 via online registration. **Note: EGFR analysis must be performed for all patients before proceeding to STEP 2.**

For patients with oropharyngeal carcinoma: the Biospecimen Bank will process 4 unstained slides from the tissue block submitted (for EGFR analysis) and will send the slides to Dr. Adel El-Naggar for HPV analysis. The results of the HPV analysis are expected in approximately 7-10 business days, and NRG Oncology will inform sites by e-mail of the completion of the HPV analysis. At this point, oropharyngeal carcinoma patients may be randomized; sites must complete the Eligibility Checklist, STEP 2 via online registration.

Physicians or institutions can request the patient's EGFR level and/or HPV status from NRG Oncology (215-717-0837 or 215-574-3170) after the patient has completed study treatment.

5.6.2 OPEN Registration Instructions

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

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

Access OPEN at <https://open.ctsu.org> or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at <https://www.ctsu.org> or <https://open.ctsu.org>. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

6.0 RADIATION THERAPY (18-MAY-2015)

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. IGRT IS OPTIONAL and can be used without IGRT credentialing if not used for reducing margins. IGRT is mandatory when using reduced margins, and for this, sites must be head and neck IGRT credentialed.

Protocol treatment must begin within 2 weeks after Step 2 registration (randomization).

6.1 Dose Specifications for both Arms

The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size (total of 30 fractions). Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV60 volume receives at least 60 Gy. As described in Section 6.4, PTV56 and PTV66 also may be defined. The spinal cord dose may not exceed 48 Gy to any volume larger than 0.03 cc.

6.2 Technical Factors (13-NOV-2017)

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 by the IROC Houston is acceptable.

6.2.2 Image Guidance for IGRT (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 conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy);
- Other mechanism, after discussion with the Study Chair and Medical Physics Co-chair.

The institution's procedure to register treatment day imaging dataset with the 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.

Management of Radiation Dose to the Patient from IGRT

Radiation doses from IGRT are small enough dose contributions that if there is only one imaging study done per treatment session, the dose does not need to be incorporated into treatment planning and is not expected to have any clinical relevance to the patient. However, the imaging dose to the patient may become significant if repeated studies are done 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 Target and Normal Tissue Volume Definitions (13-NOV-2017)

6.4.1 Definition of Target Volumes

CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus region(s) of grossly involved lymphadenopathy. This volume may approach the skin but should not approach < 2mm. It is recognized that after surgery, there can be considerable distortion of normal anatomy. If possible, map preoperative GTV(s) onto the postoperative radiation therapy planning CT scan, and add appropriate margins for microscopic spread (1.5-2 cm).

CTV60 also will include the ipsilateral pathologically positive hemineck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4 for all cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. For example, level 1 must be included for oral cavity cancer but is not mandatory for larynx cancer. Level 5a must be included for oropharynx cancer but is not mandatory for larynx cancer. For questions, contact the Principal Investigator, Dr. Machtay, or one of the Radiation Oncology Co-Chairs, Drs. Thorstad, Nguyen-Tan, and Quon.

CTV56: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this would apply to the contralateral hemineck being irradiated electively for base of tongue cancer. This volume should not approach the skin < 5 mm. This volume will receive approximately 1.85 Gy per day.

CTV66 Optional: This may be defined at the discretion of the treating radiation oncologist. This would include a region or regions felt to be at especially high risk for recurrence (e.g., an area of very close margin of resection). **Note:** This area will be receiving a daily fraction size of 2.2 Gy and thus, the volume of CTV66 should be kept **as small as possible**.

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 but is generally not recommended. It is also allowable to define two PTV's for a given CTV: 1) PTV Planning, which extends beyond the skin surface and is used for planning treatment segments; and 2) PTV Evaluation, which does not reach the skin surface within 2 mm and is used for evaluation of the dose volume histogram to determine if treatment goals have been met.

PTV Expansion Without Daily IGRT

For those institutions that are not using daily IGRT (see [Section 6.2.2](#)), 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 With Daily IGRT

For those institutions that are using daily IGRT (see [Section 6.2.2](#)), the minimum CTV-to-PTV expansion is 2.5 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)

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. For non-oral cavity cancers, the oral cavity will be defined as a composite structure consisting of the anterior $\frac{1}{2}$ to $\frac{2}{3}$ of the oral tongue/floor of mouth, buccal mucosa, and palate. For oral cavity cancers, the oral cavity will be defined as the subset of this composite structure that does not overlap with PTV.

Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan. Parotid gland volume will not include any portion of any of the CTVs, although they can overlap the PTVs.

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). This should not overlap the PTVs.

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): Obviously, for patients who have had a total laryngectomy, this structure is not applicable. 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. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

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.

6.5 Treatment Planning and Delivery

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

It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in 1 of 2 ways, either of which is permitted for this study.

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. In general, this technique is appropriate for irradiation of cancers of the oral cavity or oropharynx.
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. This technique in general is appropriate for irradiation of cancers of the larynx and/or oral/pharyngeal cancers that involve the hypopharynx.

6.5.2 Dose to Supraclavicular Nodal Region

Regardless of whether technique 1 (Match) or technique 2 (No Match) is used, the dose to the supraclavicular nodal region may be limited to 50 Gy if level 4 nodes were dissected and found to be negative or in the case of oral cavity cancer with level 3 nodes dissected and found to be negative.

6.5.3 IMRT Dose Prescription to PTVs

See [Section 6.4.1](#) for definitions of CTVs and PTVs. As described in Section 6.1, prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size. For inverse planning IMRT, the goal is for 95% of the PTV60 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV60 close to the skin may receive significantly less than 56 Gy. This is acceptable as long as cold spots within PTV60 do not exist at a depth deeper than 8 mm beneath the skin (see [Section 6.8](#), compliance criteria).

For prioritization, PTV60 will be the highest priority target structure. PTV66 and PTV56, if applicable, will be ranked in the IMRT planning as lower priority than PTV60 although higher priority than normal structures other than spinal cord and brain stem.

6.5.4 IMRT Dose Constraints to Normal Structures

Spinal Cord: The PRVcord (as defined in Section 6.4.2.) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRVbrainstem (as defined in Section 6.4.2.) 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. For non-oral cavity cancers, the maximum dose will be < 30 Gy. For oral cavity cancers, the maximum dose will be < 50 Gy.

Oral Cavity: Reduce the dose as much as possible. For non-oral cavity cancers, the mean dose should be < 30 Gy. For oral cavity cancers, the mean dose should be < 50 Gy. Efforts should be made to avoid hot spots (> 60 Gy) within the oral cavity, particularly for non-oral cavity cancers.

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. Additional planning goals may include: 1) At least 50% of one parotid will receive < 30 Gy; and/or 2) At least 20 cc of parotid tissue (from the combination of both glands) will receive < 20 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. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. Some recommended doses (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the esophagus exceeds 60 Gy.

Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. In patients with resected oral or oropharyngeal carcinoma, it is recommended that the dose to the larynx should be kept < 45 Gy whenever feasible.

Mandible: Reduce the dose as much as possible. It is recognized that particularly for oral cavity cancers, significant portions of the mandible will overlap the CTVs and/or PTVs; however, 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: For the typical case in which there is no CTV66, no more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 5% of the unspecified dose should exceed the level of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

6.5.5 Prioritization for IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV60
4. PTV56 (if applicable)
5. PTV66 (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 (25-JAN-2016)

Note: All structures marked “required” in the table below must be contoured and submitted for review. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name as listed.

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

Standard Name	Description
CTV_6000	Primary Tumor Bed plus involved nodes. Required
CTV_5600	At risk regions Required when applicable
CTV_6600	Optional higher dose region; should be kept small as possible. Required when applicable
PTV_6000	CTV-PTV 5 mm margin without IGRT; 2.5 mm with Daily IGRT. Required
PTV_6000-08	PTV_6000, not including portion of PTV_6000 near (<8 mm) skin Required
PTV_5600	CTV-PTV 5 mm margin without IGRT; 2.5 mm with Daily IGRT. Required when applicable
	PTV_5600, not including portion

PTV_5600-08	of PTV_5600 near (<8 mm) skin Required when applicable
PTV_6600	CTV-PTV 5 mm margin without IGRT; 2.5 mm with Daily IGRT. Required when applicable
PTV_6600-08	PTV_6600, not including portion of PTV_6600 near (<8 mm) skin Required when applicable
NonPTV6000	External minus PTV_6000 Required
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 Required
Lips	Lips Required
Mandible	Mandible Required
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles; should not include PTVs Required
Esophagus_Up	Cervical Esophagus Required
LarynxGSL	Glottic/Supraglottic larynx Required
External	External border of patient used to define Unspecified Tissue. Required

6.7 Documentation Requirements for IMRT Treatment Approach (13-NOV-2017)

- 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;

6.7.1 Additional Documentation Requirements for IGRT Treatment Approach

If an IGRT treatment approach is utilized, the following documentation is required:

- IGRT images obtained on the first day of treatment;
- One IGRT image data set per week of treatment; **Note: Sites should retain all daily images. Any or all of the institution's daily images may be subject to auditing.**
- Spreadsheet that includes data on daily pre-treatment variances based on analysis of daily IGRT. See CTSU website (<https://www.ctsu.org>) for the spreadsheet.

6.8 Compliance Criteria (03-NOV-2014)

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 five treatment days at a time and ten 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 two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

	Per Protocol	Minor Variation	Major Variation
Total RT dose to PTV_6000 (to 95%) of PTV_6000)	60-64 Gy	58-60 or 64-66 Gy	<58 or > 66 Gy
Minimum dose ("cold spot" within PTV_6000, not including portion of PTV_6000 near (<8 mm) skin)	56-60 Gy	54-56 Gy	< 54 Gy
Maximum dose ("hot spot" within PTV_6000*)	< 70 Gy	70-72 Gy	> 72 Gy
Maximum dose ("hot spot" outside of PTV_6000)	< 66 Gy	66-70 Gy	> 70 Gy
Total RT dose to PTV_5600 (to 95%) of PTV_5600)	56-60	54-56 or 60-62	<54 or >62
Minimum dose ("cold spot" within PTV_5600, not including portion of PTV near (<8 mm) skin)	52-56	50-52	<50
Total RT dose to PTV_6600 (to 95%) of PTV_6600)	66-70	64-66 or 70-72	<64 or >72
Minimum dose ("cold spot" within PTV_6600, not including portion of PTV near (<8 mm) skin)	62-66	60-62	<60
Definition of CTV_6000	Based on case review by study chair		
Definition of PTV_6000	Based on case review by study chair.		
Total RT dose to SpinalCord_05(0.03 cc)	< 48 Gy	48-50 Gy	> 50 Gy
Total RT dose to SpinalCord_05(0.01 cc)	< 50 Gy	50-52 Gy	> 52 Gy
Definition of SpinalCord_05	Based on case review by study chair		
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

*Not including the region of PTV60 that falls within PTV66 (if applicable)

6.9 R.T. Quality Assurance Reviews (07-APR-2014)

The Principal Investigator/Radiation Oncology Chair, Mitchell Machtay, MD, and the Radiation Oncology Co-Chairs, Wade Thorstad, MD, and Phuc Felix Nguyen-Tân, MD, will perform RT Quality Assurance Reviews. These reviews will be ongoing. RT Quality Assurance reviews will be facilitated by IROC Philadelphia.

6.10 Radiation Therapy Adverse Events (26-JAN-2018)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for AE reporting. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third to one half 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 on the appropriate case report form (see [Section 12.1](#)), 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 Adverse Event Reporting

See CTEP-AERS Expedited Reporting Requirements in Sections 7.5 and 7.6.

7.0 DRUG THERAPY (07-APR-2014)

Protocol treatment must begin within 2 weeks after Step 2 registration (randomization).

7.1 Arm 2 Treatment (03-NOV-2014)

7.1.1 Cetuximab Initial Dose (Prior to RT): Patients on Arm 2 will receive an initial dose of cetuximab, 400 mg/m², intravenously (*i.v.*) over 120 minutes. No chemotherapy or radiation will be given this day, and the 400 mg/m² initial dose of cetuximab will precede the first 250 mg/m² dose of cetuximab and the first radiation treatment by at least 5 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.

Cetuximab weeks 2-7 (concurrent with RT): Patients on Arm 2 will receive cetuximab, 250 mg/m², intravenously (*i.v.*) 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 before or after radiation therapy for a total of 6 doses.

Cetuximab weeks 8-11 (post-completion of RT): Patients on Arm 2 will receive cetuximab, 250 mg/m², intravenously (*i.v.*) over 60 minutes, on a weekly schedule after the completion of radiation therapy, for a total of 4 additional doses. The infusion rate of cetuximab must never exceed 5 mL/min. For these 4 additional doses, cetuximab should be given once a week for a total of 4 doses. There should be at least 5 days between two consecutive doses.

Note: Patients receive a total of 11 doses of cetuximab over 11 weeks, including the initial loading dose, 6 maintenance doses concurrent with radiation therapy, and 4 additional maintenance doses post-completion of radiation therapy.

In cases of delay in the completion of radiation therapy, then the concurrent doses of cetuximab may continue beyond week 7 without dose interruption until radiation therapy is completed, and then be followed by weekly infusion of the remaining doses of cetuximab post-radiation therapy. The total of number of cetuximab doses should remain as 11 and should not exceed 11. For example, if a patient receives the initial cetuximab loading dose, plus 7 maintenance doses concurrent with radiation therapy, then 3 additional maintenances doses post-completion of radiation therapy should be given.

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 *i.v.* 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 *i.v.* 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 Sections [1.4](#) and [1.5](#) for details and [Section 7.3.4](#) 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 7.3.4](#) 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 Cetuximab (IND Exempt) (08-MAR-2018)

Refer to package insert and investigator brochure for additional information. Note the black box warning for cardiopulmonary arrest in patients receiving radiation therapy in combination with cetuximab.

7.2.1 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.

7.2.2 Safety Precautions

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

7.2.3 Preparation and Administration

Cetuximab must not be administered as an *i.v.* 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.

Following the cetuximab infusion, a one-hour observation period is required.

7.2.4 Adverse Events

Cetuximab may be associated with significant toxicities, most commonly fatigue, skin rash/folliculitis and paronychia, and gastrointestinal effects, nausea and diarrhea. Hypomagnesemia is common. Of greatest concern is the potential for an allergic reaction, possibly anaphylaxis; see [Section 7.3](#) for details.

Other adverse events:

- Blood and lymphatic system: Anemia;
- Ear and labyrinth disorders: External ear inflammation, tinnitus;
- Eye disorders: Conjunctivitis, dry eye, uveitis, 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, infusion-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.

7.2.5 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.

7.2.6 Supply

Eli Lilly and Company (Eli Lilly) or its local affiliate will supply cetuximab free of charge to patients on study in the United States and Canada. The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42mg/mL sodium phosphate monobasic monohydrate, and Water for injection, USP.

7.2.7 Drug Ordering and Accountability

Eli Lilly and Company (Eli Lilly) or its local affiliate will supply cetuximab free of charge to patients on study in the United States and Canada. In the U.S., the drug will be distributed by a vendor, Biologics/McKesson., under contract to NRG Oncology. Please see shipping timelines in the section below. In Canada, the drug will be distributed by Eli Lilly Canada.

U.S. and Canadian Institutions

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) available on the [CTSU](#) website. U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office via the Regulatory Submission Portals as soon as the individual responsible for the study agent has been identified. This must be done prior to registration of the institution's first case.

Biologics/McKesson will ship a patient-specific supply of cetuximab with enough quantity to complete protocol treatment for a 200-pound individual (58 vials) once the site has randomized the patient. Since doses are dependent on the patient's BSA, sites can obtain additional per-patient supply for individuals over 200 pound by contacting Biologics/McKesson. It is possible that sites will have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for RTOG 0920 be utilized for this study. RTOG 0920 product must be segregated from other investigational or marketed product.

Cetuximab will be placed in a temperature controlled cooler with 3 pounds of gel packs. U.S. shipments will be sent via FedEx for Priority Overnight delivery for orders received 4 p.m. EST, Monday through Thursday. Orders received after 4 p.m. EST Monday through Thursday will be processed and shipped next business morning. **For Canadian sites, Eli Lilly Canada will ship the drug. Sites should allow 10 business days to receive drug.**

Drug deliveries are restricted during weekends and holidays. **Biologics/McKesson 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.**

Eli Lilly Canada observes the following holidays. Sites should plan ahead to accommodate patients being treated during restricted times.

Event	Date
New Year's Day	January 1, Friday
Family Day	February 15, Monday
Good Friday	March 25, Friday
Victoria Day	May 23, Monday
Canada Day	July 1, Friday
Eli Lilly Canada office closure	July 4, Monday
Civic Holiday	August 1, Monday
Labour Day	September 5, Monday
Thanksgiving	October 10, Monday
Christmas Day	December 25, Sunday
Boxing Day	December 26, Monday
Eli Lilly Canada office closure	December 30, Friday

Inside each shipping container will be a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping. This unit will be attached

to an information card. The LCD display will show OK (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alarm(s) have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing list. For questions regarding drug requisitioning, contact Biologics/McKesson.

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

Questions about supply and delivery should be directed to:

**McKesson Specialty Health
Clinical Research Services
845 Regent Boulevard, Suite 100B
Irving, TX 75093
Email: clinicalresearchservices@mckesson.com
Phone: Toll Free 800-693-4906
Fax: 919-256-0794**

Non-Canadian International Institutions

Please refer to your LOI Approval Notification.

7.2.8 Handling and Dispensing of Investigational Product

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

7.2.9 Drug Destruction

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, provided documented procedures for destruction are in place. At the completion of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed, including dates and quantities. If approved procedures for destruction are not in place and/or for questions regarding cetuximab destruction, please contact Biologics/McKesson at 800-693-4906.

7.3 Dose Modifications (23-JAN-2013)

7.3.1 Cetuximab Dose Levels

Study Agent	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 $\geq 10\%$ occurs, the cetuximab dose should be adjusted.

7.3.2 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.

7.3.3 Cetuximab Dose Modifications for Non-Hematologic Adverse Events

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 or reduce by 1 dose level
Other non-hematologic Adverse Events ^{b, c}	
Grade 4 (In the RT field, or possibly related to cetuximab, or likely to be exacerbated by continuation of cetuximab)	Hold drug until ≤ grade 3, then resume at 1 dose level reduction
Grades 2-4 (out of RT field that does not reverse to Grade 1 at time of treatment, or unrelated to cetuximab, or unlikely to be exacerbated by continuation of cetuximab)	Maintain dose levels For grade 4 out of RT field toxicity, drug should be held until < grade 3 and then resumed at the same level or reduced by 1 dose level

^aDose levels are relative to the previous dose. Dose reductions of cetuximab below the –2 dose level will not be allowed. 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.

^bWith the exception of infusion reaction or acne-like rash (rash/desquamation);

^cFor 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 sulphate 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 or reduce by 1 dose level
4	< 0.7	< 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level or reduce by 1 dose level

7.3.4 Cetuximab Infusion Reaction Management

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, but slow the infusion rate by 50%. 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 manifesting only as delayed drug fever, slow the infusion rate for cetuximab by 50% 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	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 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-Chairs should be contacted immediately to discuss and grade the reaction.

7.3.5 Cetuximab Special Instructions

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. Cetuximab doses held due to toxicity should not be made up. If a cetuximab dose is missed for reasons unrelated to drug toxicity, then the missed dose may be made up at the discretion of the investigator, at the next appropriate time point according to Section 7.1.1. If adverse events prevent the administration of cetuximab, the subject may continue to receive radiation therapy.

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.

Cetuximab should be immediately and permanently discontinued in patients who experience severe (grade 3 or 4) infusion reactions.

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 any of the terms below), cetuximab treatment adjustments should be made according to the Cetuximab Dose Modification table below. 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 ADL	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	Continue at 250 mg/m ²
		No Improvement; remains grade 3	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Reduce dose to 200 mg/m ²
		No Improvement; remains grade 3	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Reduce dose to 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.

7.4 Modality Review (07-APR-2014)

The Medical Oncology Co-Chair, Lillian L. Siu, MD, will perform a Systemic Therapy Assurance Review of all patients who receive or are to receive cetuximab 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, Not Per Protocol, 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 Medical Oncology Co-Chair, Dr. Siu, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at IROC Philadelphia. Dr. Siu 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.

7.5 **Adverse Events (26-JAN-2018)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be utilized until March 31, 2018, for AE reporting. CTCAE version 5.0 will be utilized for CTEP-AERS reporting beginning April 1, 2018; all study case report forms will continue to use CTCAE version 4.0. All appropriate treatment areas should have access to a copy of CTCAE versions 4.0 and 5.0, which can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Adverse events (AEs) that meet expedited reporting criteria defined in the table(s) below will be reported via the CTEP-AERS (CTEP Adverse Event Reporting System) application accessed via either 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.

7.5.1 **Adverse Events (AEs)**

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, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm].

7.5.2 **Serious Adverse Events (SAEs) —** Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.6 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.6. **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 drug experience, 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.

7.5.3 **Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)**

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system 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.

7.6 CTEP-AERS Expedited Reporting Requirements (25-JAN-2016)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP 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's 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 2 and 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 within 30 Days of the Last Administration of the Investigational 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 investigational 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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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.

¹Serious adverse events that occur more than 30 days after the last administration of investigational 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

²For 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.

NOTE: Deaths clearly due to progressive disease should **NOT** be reported via CTEP-AERS but rather should be reported via routine reporting methods (e.g., CDUS and/or CTMS).

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:

Not applicable to this study.

8.0 SURGERY (23-JAN-2013)

8.1 Intermediate Risk of Recurrence

Patients must have been found to have an “intermediate” risk of recurrence (see [Section 3.1.3](#)) after having undergone gross total surgical resection with curative intent of the primary tumor of the oral cavity, oropharynx, or larynx (excluding lip, nasopharynx, or sinuses) within 7 weeks of registration. Patients with a positive margin by intraoperative frozen section during any part of the primary tumor resection are eligible for this study, provided that a subsequent negative margin supercedes this initially positive margin. Only patients with positive margins on final pathology would be excluded from this study. Concurrent neck dissection should be performed with patients initially staged cN1 and above. However, for cN0 patients, selective neck dissection may or may not be required.

The following should be reported on the Operative Note (S2):

- Documentation of whether a transoral versus “open” transcervical approach was used in assessing the primary tumor;
- Documentation of how the neck was managed: excisional biopsy, superselective, standard selective neck, or modified radical;
- Documentation of whether robotics or laser microsurgery was used for visualization of the primary tumor during surgery.

8.2 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Dr. Holsinger, will perform a modified Quality Assurance Review after complete data for the first 50 cases enrolled has been received at NRG Oncology. This quality assurance review will specifically examine the issues related to eligibility and the presence of intermediate risk of recurrence (see [Section 3.1.3](#)). No S1 case report form is required for this study.

Dr. Holsinger will perform the next review after complete data for the next 50 cases enrolled has been received at NRG Oncology. 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 NRG Oncology, whichever occurs first.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

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, anti-emetics, topical mouth rinses, skin creams/ointments, etc. 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 Investigator, Dr. Machtay, or Medical Oncology Co-Chair, Dr. Siu.

10.0 TISSUE/SPECIMEN SUBMISSION (07-APR-2014)

10.1 Tissue/Specimen Submission (07-APR-2014)

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 Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology 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. **Note:** The NRG Oncology Biospecimen Bank will provide collection kits and instructions at no charge for the submission of specimens in this protocol.

In this study, it is required that tissue will be submitted to the NRG Oncology Biospecimen Bank for the purpose of EGFR analysis and HPV assay for oropharyngeal carcinomas. In addition, it is highly recommended (but optional) that fresh and archival tissues and blood be submitted for banking for future translational research. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for approved studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Tissue Collection for EGFR: Required (13-NOV-2017)

Patients must consent to participate in submission of tissue for EGFR expression levels.

Tissue from a biopsy or surgical specimen will be obtained, formalin fixed, and paraffin embedded in tissue blocks. Institutions must ship tissue blocks from patients to the NRG Biospecimen Bank by overnight courier. Prepaid Federal Express Labels can be requested from the Biospecimen Bank for this purpose (see [Section 10.5](#) for contact information). Upon determination that the specimen is adequate, 2 unstained sections will be sent to the Pathology Co-Chair, Dr. Adel El-Naggar, for quantitative analysis of EGFR by immunohistochemistry. EGFR analysis results are expected in approximately 7-8 business days. The specific hypothesis is that the relative improvement in disease-free survival (DFS) will be similar for patients with high (defined as $\geq 80\%$ of cells staining positive for EGFR) or low (defined as $< 80\%$ of cells staining positive) EGFR expression. However, the absolute values for DFS will be significantly greater for patients with low EGFR expression. Physicians or institutions can request the patient's EGFR level from NRG Oncology (215-574-3154 or 215-574-3170) after the patient has completed study treatment.

Institutions that are unable to submit a tissue block for the required EGFR analysis (and for patients with oropharyngeal carcinoma, the required HPV analysis) may instead take 6 unstained sections from the block then obtain three 3 mm core punches of the block and re-embed the core punches into a recipient paraffin for submission. Institutions can request an FFPE specimen plug kit (see **Appendix V**) from the NRG Oncology Biospecimen Bank free of charge for this purpose: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

If an institution is uncomfortable with obtaining the unstained sections and punches and wants to retain the tissue block, the site can send the entire block to the NRG Biospecimen Bank, and the Bank will obtain the unstained sections and the core punches from the block and return the remaining block to the site. Please indicate this request (to obtain the sections, perform the core punch procedure, and return the block) on the submission form. **Note:** For oropharyngeal carcinoma patients, there is a 10-day turnaround needed for HPV assays, so institutions should send the block by overnight courier to the Biospecimen Bank as soon as possible with their request.

The following material must be provided to the NRG Biospecimen Bank for EGFR expression:

- 10.2.1** Representative H & E stained slides (slides can be duplicate cut stained H&E; does not have to be diagnostic slide).
- 10.2.2** Corresponding Tissue Block (the block must match the H&E diagnostic slide)
 - A Pathology Report documenting that the submitted block contains 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.

- A copy of the gross description of the tumor must accompany the specimen in order to evaluate the closest margin and distance.
- A Specimen Transmittal (ST) Form stating that the tissue is being submitted for central review. Sites can access the form (no password required) at <http://www.rtog.org/members/forms/list.html> (under "Pathology"). The form must include the NRG Oncology protocol number and the patient's case number. If the patient is also enrolled on other NRG Oncology trials, this should be indicated on the form.
- EGFR analysis will be performed for every case by the Pathology Co-Chair, Adel El-Naggar.

10.3 Tissue Collection for HPV Analysis: Required (05-OCT-2011)

Patients with oropharyngeal carcinoma must consent to participate in use of submitted tissue for HPV analysis by p16 immunohistochemistry.

For patients with oropharyngeal carcinoma, the NRG Oncology Biospecimen Bank will process 4 unstained sections from the tissue block (submitted for EGFR analysis) and will send the sections to Dr. Adel El-Naggar who will determine HPV status by p16 immunohistochemistry within 7-10 business days. Specific hypotheses include: 1) HPV negative patients will have greater absolute benefit from the addition of cetuximab compared to HPV positive patients because HPV positive patients have an extremely good prognosis and the addition of cetuximab in the postoperative adjuvant setting may not add more benefit to RT alone; 2) HPV positivity will associate with low EGFR expression because the HPV positive tumors may not be driven by EGFR but by viral oncogene E6/E7 causing the loss of p53 and Rb; 3) EGFRvIII will associate with HPV negativity and treatment failure due to ligand-independent constitutive activation of the receptor, escaping the effects of cetuximab. Physicians or institutions can request the patient's HPV status from NRG Oncology (215-574-3154 or 215-574-3170) after the patient has completed study treatment.

10.4 Specimen Collection for Tissue Banking and Translational Research: Highly Recommended (But Optional) (13-NOV-2017)

Patients must be offered the opportunity to participate in the tissue/specimen collection for banking and translational research. If the patient consents to participate in this component, the site is required to submit the patient's specimens as specified below. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent form.

10.4.1 Peripheral Blood: Plasma, Serum, and Whole Blood

Note: Blood for research should be collected prior to the start of treatment (radiation therapy alone OR radiation + cetuximab) (see [Appendix I](#)).

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

A blood collection kit can be obtained free of charge from the Biospecimen Bank. **See Appendix VI for detailed collection instructions, including information pertaining to the blood collection kit. Note: The kit includes a shipping label.**

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 Form the storage conditions used and time stored.

10.4.2 Translational Research: TP53 Mutations and EGFR Intron 1

A recent study by Poeta, et al. (2007) has shown that patients with *TP53* mutations have poor overall survival and time to disease progression compared to patients with *TP53* wild type after surgical resection. We will determine the *TP53* mutation status in this study to validate the association and to further the effort of clinical implementation of this assay and stratification of risks based on biology of the tumors.

There is evidence that the length of the repeats in EGFR Intron 1 may be prognostic and predictive of outcomes after standard of care and EGFR inhibitor treatments (Press 2008; Liu 2003; Han 2007). We will examine the CA dinucleotide repeats in EGFR intron 1 and associations with poor overall survival and time to disease progression. By studying a diverse

NRG Oncology patient population of mixed sex and race, the prognostic and predictive nature of this polymorphic variant can be further defined and validated. In addition, we will determine whole genome-wide single nucleotide polymorphism (SNP) in these patients using Affymetrix SNP chips to associate other polymorphic variants with response and toxicities as exploratory studies.

10.4.3 *Summary of Specimens for Tissue Banking and Translational Research*

Specimens taken from patient:	Submitted as:	Shipped:
One H&E stained slide of the primary tumor	H&E stained slide: Must match block or unstained slides submitted	Slide shipped ambient to NRGBB-SF
Formalin-fixed paraffin embedded tumors	Tissue block. If a block is not available then 10 unstained slides (5 micron cut onto positively charged slides)	Blocks/slides sent ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Frozen serum samples containing minimum of 0.5 mL per aliquot in 1 mL cryovials (five)	Serum sent frozen on dry ice via overnight carrier to NRGBB-SF in batch shipments
PLASMA: 5-10 mL of anticoagulated whole blood collected in EDTA tube#1 (purple/lavender top) and centrifuge	Frozen plasma samples containing a 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Plasma sent frozen on dry ice via overnight carrier
Whole blood for DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Frozen whole blood samples containing 1-2 mL per aliquot in 12 mL cryovials (three)	Whole blood sent frozen on dry ice via overnight carrier to NRGBB-SF in batch shipments

Note: Blood for research should be collected prior to the start of treatment (radiation therapy alone OR radiation + cetuximab) (see [Appendix I](#)).

10.5 Submission of materials for Tissue Banking and Translational Research (13-NOV-2017)

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

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
NRG Oncology Biospecimen Bank—San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
Questions: 415-476-7864/FAX 415-476-5271; NRGBB@ucsf.edu

10.6 Reimbursement (03-NOV-2014)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new 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.

10.7 Confidentiality/Storage (05-OCT-2011)

(See the Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx> for further details.)

10.7.1 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.

- 10.7.2** 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 specimen is consumed/exhausted or 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 (06-DEC-2010):** See Appendix I for a summary of assessments and time frames.

11.1.1 Gross total resection/surgical pathology must be completed within 7 weeks prior to registration.

11.1.2 A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done within 8 weeks prior to registration.

11.1.3 An examination by an ENT or Head & Neck Surgeon must be done within 8 weeks prior to registration. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended but not required.

11.2 Evaluation During Radiotherapy (08-MAR-2018)

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

11.2.2 Arm 2 patients must have Na, K, Cl, glucose, Ca, Mg, and albumin testing every 3 weeks during radiation therapy, every 3 weeks after radiation therapy is completed, and during maintenance cetuximab infusion (weeks 8-11, and then every 3 weeks after the last dose of cetuximab, for a total of 9 weeks (weeks 12-20).

11.2.3 Biopsy of any lesion(s) suspicious for tumor recurrence is urged.

11.2.4 Arm 2 patients should have serum creatinine or creatinine clearance, AST or ALT, and bilirubin every 3 weeks after radiation therapy is completed, and during maintenance cetuximab infusion (weeks 8-11).

11.3 Evaluation in Follow Up (07-APR-2014)

11.3.1 A general history and physical by one of the following: a Radiation Oncologist, Medical Oncologist, an ENT, or a Head and Neck Surgeon must be done at 1 and 3 months post-XRT, then q3 months for 2 years, every 6 months for 3 years, then annually. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended at these time points but is not required.

11.3.2 Chest imaging (at minimum a chest x-ray or chest CT or CT/PET of chest) is required once per year for a total of 5 image sets.

11.3.3 Biopsy of any lesion(s) suspicious for tumor recurrence is urged.

11.4 Outcomes Criteria

11.4.1 No evidence of disease (NED): All patients must have not measurable tumor following surgery.

11.4.2 Local-Regional Relapse: Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; both imaging and biopsy confirmation are strongly recommended. LRR will be further subdivided into three subcategories:

In-Field Local-Regional Relapse

Review of the imaging of the local-regional relapse and the patient's previous IMRT treatment data reveals that the "epicenter" of the local-regional relapse is within CTV60 and received an estimated dose of at least 50 Gy.

Marginal Local-Regional Relapse

Review of the imaging of the local-regional relapse and the patient's previous IMRT treatment data reveals that the "epicenter" of the local-regional relapse was "near" CTV60. This is defined as an estimated dose to this region that is between 20 and 50 Gy.

Out-of-Field Local-Regional Relapse

Review of the imaging of the local-regional relapse and the patient's previous IMRT treatment data reveals that the "epicenter" of the local-regional relapse was not near CTV60 or CTV56 and received an estimated dose < 20 Gy. An example would be recurrence in the retropharyngeal nodal space for a patient with oral cavity cancer.

11.4.3 Distant Relapse: Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary lung mass/nodule should be considered a second primary upper aerodigestive neoplasm unless proven otherwise. If there is any question

whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Principal Investigator, Dr. Machtay.

11.4.4 Second Primary Neoplasm: All second primary neoplasms will be biopsy proven with documentation of specific histology. Modified rigorous criteria for a second primary (below) have been adapted from the definition by Warren and Gates (1932). Localized non-melanoma skin cancers are not considered new primary tumors.

- A distinct lesion separated from the primary tumor site by > 2 cm of normal epithelium;
- A new cancer with different histology;
- Any cancer, regardless of head and neck mucosal subsite, occurring 5 or more years after initial treatment;
- In the lung, new primary tumors, if squamous cell cancer, must have histologic findings of dysplasia or CIS.

11.4.5 Second Primary Upper Aerodigestive Neoplasm: The emergence of a new, invasive malignancy in the upper aerodigestive tract as a second primary should be documented. These neoplasms include lung cancer, esophageal cancer (including GE junction cancer), or 2nd primary head and neck cancer that is clearly remote from the index cancer (e.g., pyriform sinus cancer developing in a patient whose original diagnosis was tongue cancer). If there is any question whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Principal Investigator, Dr. Machtay.

11.5 Quality of Life and Functional Assessments (25-JAN-2016)

The assessments will be completed prior to the start of treatment (baseline) and at 3, 12, and 24 months from the end of RT.

11.5.1 The Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N) is a multidimensional, patient-self report quality of life (QOL) instrument specifically designed and validated for use with head and neck patients. The patient can complete the assessment in 5-10 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break.

11.5.2 The Performance Status Scale for Head and Neck Cancer (PSS-HN) consists of assessment of three functional areas (subscales): Normalcy of Diet, Eating in Public, and Understandability of Speech. The site research nurse or clinical research associate (CRA) will administer the PSS-HN. Interviewers are encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. The interviewer rates the patient on each scale based on the patient's responses to targeted questions. The PSS-HN takes approximately 5 minutes to complete.

11.5.3 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 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 **HP** case report form.

11.5.4 The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) consists of 15 items covering four major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues. The patient can respond to the 15 items in the scale in approximately 5 minutes. The Scale is only available in English.

11.5.5 The Dermatology Life Quality Index (DLQI) consists of 10 items and covers 6 domains including symptoms and feelings (e.g., felt itchy, sore, painful, embarrassed), daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3 respectively; the response "not relevant" (and unanswered items) are scored as "0". Items A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. Higher scores indicate poorer HRQL (i.e., more impairment). The patient can complete the DLQI in approximately 5 minutes.

11.5.6 Optional Online Completion of QOL Assessments

Patients who consent to participate in the quality of life (QOL) component of this study have the option of completing QOL forms online from any location, including home, via VisionTree Optimal Care (VTOC). The baseline QOL forms must be completed in hardcopy at the time of enrollment, but all subsequent QOL forms can be completed by the patient online. Patients without e-mail or Internet access can participate in the QOL component of the study by completing hardcopy (paper) forms. Indeed, at any time, any patient may choose to fill out their QOL form using the hardcopy form. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

If the patient wishes to complete QOL assessments online, the patient must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. The patient's e-mail address also will be used for password-protected access to VisionTree Optimal Care (VTOC). Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g., Yahoo!, Hotmail, or AOL). **Note:** The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: <https://rtog.optimalcare.com> - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.

VTOC will send patients e-mail reminders to complete QOL forms.. The first reminder will be sent at the beginning of the window for completion of the form, with a second reminder sent halfway through the window, if the form has not yet been completed. A maximum of 3 reminders will be sent for each of the 4 QOL assessment time points. After the patient has completed all forms, a dialogue box will appear thanking the patient for completing the QOL form(s), and the patient will no longer receive reminders for that time point.

Site Research Associates (RAs) will receive training in the use of VTOC via NRG Oncology webinars and educational sessions. The RA or study administrator will be informed via the VTOC "At a Glance" form management system when QOL forms have been completed or when the window for a particular form has closed. If the site RA receives a notice that forms have not been completed, she or he will contact the patient to remind the patient to fill out the QOL form or inquire why the forms have not been completed. The RA will complete the cover page for each form that was not completed (either via VTOC or in hardcopy) and will submit the cover page to NRG Oncology (see [Section 12.1](#)).

11.6 Criteria for Discontinuation of Protocol Treatment (23-JAN-2013)

- Unacceptable toxicity; see Sections [6.9](#) and [7.3](#) 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 Section 7.3.

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

12.0 DATA COLLECTION (11-MAY-2023)

Data should be submitted electronically via the NRG Oncology/RTOG web site, www.rtog.org.

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 (07-APR-2014)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)*	
Operative Note (S2)	
Surgical Pathology Report (S5)	
Pathology Report [biopsy report] (P1)	
Slides/Blocks (P2)	
Functional Assessment of Cancer Therapy-H &N [FACT] (FA)	Note: QOL forms completed online will be stored on the VisionTree, Inc. web site and transferred to NRG Oncology.
Performance Status Scale for H & N Cancer [PSS-HN] (QP)	
EuroQol [EQ-5D] (HP)	
University of Michigan Xerostomia-Related Quality of Life Scale [XeQOLS] (L4)	
Dermatology Life Quality Index [DLQI] (DL)	
Treatment Form (TF)*	Arm 2: At the completion or discontinuation of cetuximab
Initial Follow-up Form (F0)*	Within 1 week of end of RT
Follow-up Form (F1)*	From completion of RT, q3 months for 2 years, q6 months for 3 years, then annually; also at death
[FACT] (FA)	At 3, 12, and 24 months from the end of RT
[PSS-HN] (QP)	
[EQ-5D] (HP)	Note: QOL forms completed online will be stored on the VisionTree, Inc. web site and transferred to NRG Oncology.
[XeQOLS] (L4)	
[DLQI] (DL)	
QOL Forms Cover Sheets	Within 1 month of the QOL form being due (Note: Completed only if the patient did not complete a specific QOL form or if the patient completed a hardcopy of the form.

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see [Section 5.4](#) for account access and installation instructions.) (13-NOV-2017)

Item	Due
Preliminary Dosimetry Information (DD) Digital data submission includes the following: <ul style="list-style-type: none"> • DICOM CT Image • DICOM Structure • DICOM Dose • DICOM RT Plan • All required structures MUST be labeled per the table in Section 6.6. • Submit via TRIAD with the digital data listed above. Upon submission of the digital data via TRIAD, complete a Digital Data Submission Information form (DDSI) located at www.irocqa.org/Resources/TRIAD-for-RT-QA	Within 1 week of start of RT
IGRT Submission via TRIAD (see Section 6.7.1 for details) IGRT images obtained on first day of treatment (IG) One IGRT image data set per week of treatment (IG) IGRT Data Collection Spreadsheet on daily variances (SG)	Within 1 week of RT end
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	
Final Dosimetry Information Radiotherapy Form (T1) via web Daily Treatment Record (T5) [copy to HQ only]	Within 1 week of RT end

13.0 STATISTICAL CONSIDERATIONS (23-JAN-2013)

13.1 Primary Endpoint

Overall survival (OS)

13.2 Secondary Endpoints

- CTCAE, v. 4 adverse events: dysphagia, dry mouth, and skin and their relationships with patient-reported outcomes at 3 months;
- CTCAE, v. 4 adverse events: dysphagia, dry mouth, and skin and their relationships with patient-reported outcomes at 12 and 24 months;
- Other CTCAE, v. 4 acute (≤ 90 days from start of RT) adverse events;
- Other CTCAE, v. 4 late (> 90 days from start of RT) adverse events;
- Disease-free survival (DFS).

13.3 Tertiary Endpoints (Exploratory) (06-DEC-2010)

- Local-regional control;
- Quality of life as measured by Functional Assessment of Cancer Therapy-Head & Neck (FACT-HN) at baseline and 3, 12, and 24 months from end of RT;
- Xerostomia as measured by University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) at baseline and 3, 12, and 24 months from end of RT;
- Swallowing as measured by the normalcy of diet subscale in Performance Status Scale for Head and Neck Cancer (PSS-HN) at baseline and 3, 12, and 24 months from end of RT;
- Quality of life measured as measured by the EuroQol (EQ-5D) at baseline and 3, 12 and 24 months from end of RT;
- Skin toxicity as measured by the Dermatology Life Quality Index (DLQI) at baseline and 3, 12, and 24 months from end of RT.

13.4 Background and Sample Size Determination

13.4.1 Background and Sample Size Determination for Cetuximab Question

The target study population for this trial includes, but is not limited to, all patients that would have been eligible for either the RTOG 9501 or the EORTC 22931 trials, except for patients with positive margins and/or extracapsular extension (ECE). The subset of patients with positive margins and/or ECE did exceedingly poor in terms of efficacy outcomes and is excluded from this trial. The primary hypothesis is that the addition of cetuximab to postoperative radiation therapy (RT) will improve overall survival (OS) when compared to RT alone. A secondary endpoint includes a comparison of disease-free survival (DFS) and a tertiary (exploratory) endpoint includes a comparison of local-regional control (LRC). The survival experience for patients who did not have either positive margins or ECE and were treated with postoperative RT on the RTOG 9501 and EORTC 22931 trials will be used as an estimate for the control arm. In RTOG 9501, there were 94 such patients; 45 of those patients have died. Their estimated yearly hazard rate based on a 3-year Kaplan-Meier (1958) survival estimate was 0.1697 with a 95% confidence interval (CI) [0.1183, 0.2304]. In EORTC 22931, there were 56 such patients; 23 of those patients have died. Their estimated yearly hazard rate based on a 3-year Kaplan-Meier survival estimate was 0.1654 (0.1002, 0.2466). For planning purposes, the survival rate for the control arm will be assumed to follow an exponential distribution with a yearly hazard rate for OS of 0.1697. The results from the completed Bonner phase III trial show that there was a 26% reduction in the risk of death rate when cetuximab was given before and concurrently with RT without cisplatin (Bonner 2006). Therefore, this study will test for a similar effect for cetuximab when given in conjunction with postoperative RT in reducing the death rate.

The statistical software EaST for group sequential design was used for calculating the sample size with the Haybittle-Peto boundary for efficacy where the 3 interim significance levels were set at 0.005; then the significance level 0.0183 for the final analysis was derived in order to preserve a 0.025 significance level for the entire study. Futility will be tested using the lower boundary based on testing the alternative hypothesis at 0.005 level and because it was shown to have very little effect on the type I error, there will be no adjustment made to the sample size (Freidlin 2002).

Three hundred seven-two deaths will be required to detect a 26% reduction in the death rate with 80% statistical power using a 1-sided test at the 0.025 significance level with 3 interim tests. Six hundred thirty-four patients accrued over 6.6 years will be required. Adjusting by approximately 10% to allow for ineligibility and lack of data, **the total sample size required will be 700 patients**. The maximum study duration, including follow-up requirements, under the above constraints is 9.6 years, if the 3-year survival rate for the control arm is 60.1%.

In addition, a subset analysis using only HPV negative (HPV-) patients will compare the treatment arms. Patients with an oropharyngeal primary site who are either HPV positive (HPV+) or have unknown HPV status will be excluded in this analysis. Patients with a primary site other than oropharyngeal will be assumed to be HPV- because of the exceedingly low reported prevalence rate of HPV. It is estimated from RTOG 9501 and the EORTC trials that 35% of patients will be entered on RTOG 0920 with an oropharyngeal primary. In the completed ECOG trial, 23991, prospectively evaluating HPV status, 61% of the patients with an oropharyngeal primary were HPV+, and in the completed trial, RTOG 0129, the preliminary results from a retrospective review of HPV status in 122 oropharyngeal patients show a 63% incidence of HPV+ patients (Pajak 2008). The assumption will be made for analyses that all patients with non-oropharyngeal primaries are HPV negative (HPV-). In light of these data, it is projected that 20% of the RTOG 0920 study population will be HPV+. Restricted to the 508 (= 0.80×634) HPV- patients, there will be 80% statistical power to detect a 28% reduction in the OS failure rate using a 1-sided test at the 0.025 significance level, assuming that the trial is not reported earlier. This subset analysis will be done when there are 294 deaths among the HPV- patients. If the hazard rate for the control arm is approximately the same for HPV- patients as it is for all patients, 294 deaths are projected to occur for the subset analysis, approximately at the same time as the 372 deaths have occurred for the final treatment analysis of the entire

population. However, the hazard rate for HPV- patients is expected to be higher and thus, the subset analysis certainly can be performed at the same time as the “definitive” protocol treatment analysis.

13.4.2 Background and Statistical Power Determination for Evaluating the Addition of IGRT to IMRT

The yearly failure rate for the endpoint LRC in patients who did not have either positive margins or ECE and were treated with postoperative RT on the RTOG 9501 trial will be used as an estimate for the patients treated with IMRT but without IGRT (Table 1 below). For planning purposes, the following assumptions will be made to simplify the calculations:

1. The use of IMRT would not appreciably change the LRC rates observed in RTOG 9501 with RT;
2. The addition of cetuximab to postoperative RT will not appreciably change the LRC rates;
3. The yearly LRC failure rates in Table 1 will be used.

Table 1: Estimated Yearly Local-Regional Failure Rates

Year	Projected RTOG 0920 IMRT Alone	Observed RTOG 9501 RT Alone
1	13.5%	13.0%
2	13.5%	13.4%
3	4.0%	4.7%
4	4.0%	3.5%
5+	0.1%	0.0%

Currently, there are only a limited number of academic and community institutions using IGRT. During this study, the number of institutions using IGRT is expected to increase as the technology becomes more readily available on modern Linacs. Although it is projected now that 40% of patients will have received IMRT + IGRT, 3 other various percentages (30, 50, and 60%) also will be evaluated. Reductions of 25% and 30% in the LRC failure rate with the additional of IGRT will be evaluated. The significance level for a two-sided test was set at 0.05. The monthly accrual rate, its duration, and the follow-up interval from the sample size derivation for the cetuximab question were used. The statistical power for each scenario was derived by using the Lakatos method (1986).

Table 2: Statistical Power Associated with Evaluating the Addition of IGRT

Percentage of patients treated with IMRT and IGRT	25% reduction in local-regional failure rate with IMRT and IGRT	30% reduction in local-regional failure rate with IMRT and IGRT
30%	0.37	0.51
40%	0.43	0.58
50%	0.45	0.61
60%	0.44	0.60

As seen in Table 2, the statistical power is quite low for all scenarios. Given the results from the Bonner trial (2006), we do expect that cetuximab will reduce the local-regional failure rate; therefore, the statistical power will even be lower. Therefore, the impact of IGRT only will be estimated and reported with its 95% confidence interval. Furthermore, the estimate for IGRT effect will be derived from a Cox model with pathologic T-stage, performance score, and protocol treatment as covariates. These variables were selected to adjust for possible imbalance, since patients were not randomized between IMRT and IMRT+IGRT. This result will be viewed as hypothesis generating, not as definitively testing the addition of IGRT.

13.4.3 Background for Evaluating Local Regional Control in IMRT (without IGRT) Treated Patients

Since the intergroup postoperative randomized trial, RTOG 95-01, completed accrual in 2000, radiation planning and delivery has evolved. It is generally accepted that intensity modulated radiation therapy (IMRT) will minimize late toxicity (especially xerostomia) [Kam 2007; Pow 2006]. It has been assumed that IMRT will not “significantly” reduce the local-regional control (LRC) rates, but presently, there are no randomized studies available that definitively have tested this hypothesis. It should be noted that there are no published results from uncontrolled series to suggest that IMRT may compromise LRC rates. With the current widespread use of IMRT in the treatment of head and neck cancer, it would not be possible to launch a definitive randomized trial to test this question. For example, in the recently completed randomized trial for locally advanced head and neck cancer, RTOG 0522, 85% of patients are treated with IMRT.

The assumption that IMRT will not seriously compromise LRC rates will be assessed twice against the RTOG 95-01 LRC rates using the cohort of patients treated with IMRT alone in RTOG 0920. The first assessment will occur after these patients have been potentially followed for 1 year and the second time after potential follow up for 2 years. In RTOG 95-01, 86% [95% confidence interval 79-93] and 78% (70-87) LRC rates were observed at 1 and 2 years, respectively in the 93 patients treated with external beam irradiation only and that would have been eligible for RTOG 0920 (table below). Based upon these rates, it is projected that the 1- and the 2-year LRC rates would be 90% and 80% in RTOG 0920. An absolute decrease of 10% or more in either yearly estimated rate is considered unacceptable and would call into question the assumption about IMRT not adversely affecting LRC. If such a decrease is observed at either special analysis, the patient accrual to 0920 will be suspended. The NRG Oncology Data Monitoring Committee will review the results from the analysis and make a recommendation about the study's future disposition (e.g., discontinuation of further patient entries) to the NRG Oncology Group Co-Chair who, in turn, will act upon that recommendation. A particular concern is that the RTOG 0920 patients may be more elderly and possibly sicker than the RTOG 95-01 patients. The RTOG 95-01 trial had more stringent eligibility criteria because the patients could be randomized to receive concurrent chemotherapy with radiation therapy.

Assuming that the true LRC rate at 2 years is 80% with external beam irradiation, the 2-sided 95% confidence interval (assuming a binominal distribution) around it would have 70% as its lower limit with 64 evaluable patients. That sample size would result in 2-sided 99% confidence interval around an assumed true LRC rate at one year of 90% with 80% as its lower limit. The 2 interim analyses will be performed once the data are mature enough for the first 70 patients assigned to the radiation alone arm and for whom the participating institution does not elect to treat with IGRT added to IMRT. The additional 6 patients entered beyond the required 64 guards against loss to follow up and retrospective ineligibility. The timing of these analyses depends not only on the patient accrual rate but also on the percentage of patients treated without IGRT added to IMRT. With a projected patient accrual rate of 108 patients per year, 54 would be randomized to receive RT alone. If 80% of these patients initially entered are treated with IMRT but not with IGRT, the 2 special interim analyses are projected to occur at 3 and 4 years from the time the study opens to patient accrual. If that percentage is 70% instead of 80%, it will take an additional 6 months. These time intervals take into account the period of time to accrue the required 70 patients, the designated risk period for local-regional failure (one and two years), and an additional 6 months for data collection and analysis.

RTOG 95-01
Local-regional Control
Patients Potentially Eligible for RTOG 0920

RT only arm

Year	Estimate (%)	95% CI (%)	Cumulative Failures	At Risk
0	100.0	--	0	93
1	86.0	78.9, 93.1	13	71
2	78.4	69.9, 86.8	20	58
3	76.2	67.4, 84.9	22	49
Total			22	

13.4.4 Background and Statistical Power Determination for Evaluating Various Tumor Markers

EGFR Expression Levels

The specific hypothesis is that the relative improvement in OS will be similar for patients with high EGFR expression (defined as $\geq 80\%$ of cells staining positive for EGFR) or low EGFR expression (defined as $< 80\%$ of cells staining positive). However, the absolute values for OS will be significantly greater for patients with low EGFR expression.

Although baseline EGFR expression is a stratification variable for treatment assignment, all patients may not have it available for analysis. The protocol has strict time constraints to start postoperative RT. Since it is entirely possible that the initially submitted pathologic material maybe inadequate to determine HPV status and/or EGFR level within that time period, the patients will be classified as not evaluable for treatment randomization. However, every attempt will be made to appropriately classify these patients with respect to these 2 variables for tumor marker analysis. It is conservatively projected that the baseline EGFR expression will be available on 90% of the patients. The hypotheses will be tested with a Cox regression model with 3 covariates: 1) assigned treatment; 2) baseline EGFR expression; and 3) treatment by EGFR expression interaction. The covariate for baseline EGFR expression tests whether the patients with low EGFR have better OS while the covariate for interaction tests whether the treatment effect is similar within each EGFR subgroup. For planning purposes, it is assumed that patient accrual will not be discontinued in the trial or that trial is not reported early because of highly significant results. So at the time of final treatment analyses, there will be at least 335 deaths ($= 0.90 * 372$ events) observed in all patients and 247 deaths ($= 0.90 * 274$ events) in HPV- patients. It is projected that 40% to 60% of patients will be in the low EGFR group.

The equation described by Schoenfeld (1981) was used to calculate statistical power:

Number of failures = $(z_{1-\alpha/2} + z_{1-\beta})^2 / (\ln HR)^2 w (1 - w)$, where

$z_{1-\alpha/2}$ = normal deviate for the significance level

$z_{1-\beta}$ = normal deviate for the statistical power

HR = hazard ratio comparing favorable risk group (low EGFR values) to unfavorable risk group (high EGFR values)

w = prevalence rate of risk group

Table 3 below provides the statistical power to detect hazard ratios for OS of 1.50, 1.75, and 2.00 for prevalence rates of 40% or 50% or 60% in all patients and in HPV- patients. As seen in the table, there will be good power to detect a hazard ratio of 1.50 or greater. In fact, there is 80% statistical power to detect ratio of at least 1.4 in both patient groups. The

statistical power for DFS would be higher since its failure rate would be higher than death rate; thus resulting in more events.

Table 3: Statistical Power for All Patients and for HPV- with 2-Sided 5% Alpha

	All patients (335 deaths)			HPV- patients(247 deaths)		
	Hazard Ratio			Hazard Ratio		
Prevalence	1.50	1.75	2.00	1.50	1.75	2.00
40% (or 60%)	0.95	0.99	0.99	0.87	0.99	0.99
50%	0.95	0.99	0.99	0.88	0.99	0.99

In order to properly test the hypothesis that the treatment effect on OS is the same within each EGFR subgroup, a minimum relative 20% difference would have to be ruled out with 90% statistical power. Using the method of Peterson and George (1993), that would require over 3,000 cases under the following assumptions:

1. The patients are equally divided by EGFR subgroup and treatment assignment;
2. The high EGFR subgroup failed 1.5 times faster than low EGFR subgroup;
3. $86 (= 0.90 * 96)$ analyzable patients accrued per year for 6.6 years, and all patients were followed potentially for 3.0 years.

Modifying any of these assumptions will not substantially decrease the number of cases because of the small difference to detect. The estimate for interaction along with its 95% confidence will be reported. The closer this estimate is to 1, the more support is for the hypothesis that the treatment effect is the same within each EGFR subgroup.

HPV Positivity and Negativity

The following 3 hypotheses will be examined:

1. HPV negative patients will have greater absolute benefit from the addition of cetuximab compared to HPV positive patients;
2. HPV positivity will associate with low EGFR expression because the HPV positive tumors may not be driven by EGFR but by viral oncogene E6/E7, causing the loss of p53 and Rb;
3. EGFRvIII will associate with HPV negativity and treatment failure due to ligand-independent constitutive activation of the receptor, escaping the effects of cetuximab.

Hypothesis 1:

Although HPV status is a stratification variable for treatment assignment, all patients may not have it available for analysis. Since it is entirely possible that the initially submitted pathologic material may be inadequate to determine HPV status and/or EGFR level, patients will be classified as not evaluable for treatment randomization. However, every attempt will be made to appropriately classify these patients with respect to these 2 variables for tumor marker analysis. It is conservatively projected that the HPV expression will be available on 90% of the patients. The hypothesis will be tested with a Cox regression model with the following covariates: 1) treatment, 2) HPV status, and 3) treatment by HPV status interaction. The covariate for interaction tests whether the treatment effect is similar for the HPV+ and the HPV - patients. For planning purposes, it is assumed that the patient accrual will not be discontinued in the trial or that trial is not reported early because of highly significant results. At the time of final treatment analyses, there will be at least 335 deaths ($= 0.90 * 372$ events) observed in all patients. It is projected that 20% of patients will be HPV+. Using the method of Peterson and George (1993), an effect size of 50% or greater for this interaction can be detected with 80% statistical power under the following assumptions:

1. The patients are equally divided by treatment assignment within each HPV status;
2. The HPV- subgroup failed 1.5 times faster than the HPV+ subgroup;
3. The hazard ratio associated with smallest treatment effect ranges between 0.85 and 1.00;

4. $86 (=0.90 * 96)$ patients accrued per year for 6.6 years, and all patients were followed potentially for 3.0 years.

Modifying any of these assumptions will not substantially change the effect because only 20% of the patients are projected to be HPV+. The estimate for the treatment by HPV status interaction with its 95% confidence will be reported. A smaller effect for DFS would be detected, since its failure rate would be higher than the death rate; thus resulting in more events.

Hypothesis 2:

Although both baseline EGFR level and HPV status are stratification variables for treatment assignment, all patients may not have these data available for analysis. Since it is entirely possible that the initially submitted pathologic material may be inadequate to determine HPV status and/or EGFR level, patients will be classified as not evaluable for treatment randomization. However, every attempt will be made to appropriately classify these patients with respect to these 2 variables for tumor marker analysis. It is conservatively projected that the HPV expression will be available on 90% of the patients. It is projected that 20% of patients will be HPV+. There are no definitive data available to estimate the percentage of the HPV+ patients with low EGFR values; however, a published study showed 65% of p16 (surrogate of HPV status) positive tumors had low EGFR expression (Reimers 2007). With a projected sample size of 112 HPV+ patients and 457 HPV- patients and 80% statistical power, the detectable difference in the rate of patients with low EGFR values between these 2 subgroups would be approximately 0.15.

Hypothesis 3:

Although both baseline EGFR level and HPV status are stratification variables for treatment assignment, all patients may not have these data available for analysis. Since it is entirely possible that the initially submitted pathologic material may be inadequate to determine HPV status and/or EGFR level, the patients will be classified as not evaluable for treatment randomization. However, every attempt will be made to appropriately classify these patients with respect to these 2 variables for tumor marker analysis. It is conservatively projected that both the HPV status and EGFR expression will be available on 90% of the patients. However, EGFRvIII may not be determined in all patients because of limited tissue available. For planning purposes, it is projected that 90% of patients with both HPV status and baseline EGFR expression also will have a EGFRvIII value and that 20% of these patients will be HPV+. There are no data available to estimate the percentage of the HPV- patients with EGFRvIII present. With a projected sample size of 101 HPV+ patients and 411 HPV- patients and 80% statistical power, the detectable difference in the rate of patients with EGFRvIII present between these 2 subgroups will be approximately 0.16.

EGFR Ligand Expression Levels

The specific hypothesis is that patients with high values of EGFR ligand expressions (defined as the 4th quartile) will have better OS and DFS than patients with low values (defined as the 1-3rd quartile).

For planning purposes, it is assumed that EGFR ligand expression can be determined in 75% of the patients and that patient accrual will not be discontinued in the trial or that trial is not reported early because of highly significant results. At the time of final treatment analyses, there will be at least 279 ($= 0.75 * 372$) deaths (events) observed in all patients and 220 ($= 0.75 * 294$) deaths (events) in HPV- patients. It is projected that 25% of patients will be in the group with high EGFR ligand expression.

The equation described by Schoenfeld (1981) was used to calculate statistical power: Hazard ratio in this instance compares favorable risk group (high expressions) to unfavorable risk group (low expressions) and prevalence rate is for favorable risk group.

Table 4 below provides the statistical power to detect hazard ratios for OS of 1.50, 1.75, and 2.00 in all patients and in HPV- patients. As seen in the table, there will be good power to detect a hazard ratio of 1.50 or greater in both patient groups. If DFS was used instead of OS, there would be more failures at time of the analysis and thus, more statistical power. Hence, there is 99% statistical power to detect a ratio of ≥ 2.00 , reported by Khambata-Ford (2007) for DFS in recurrent/metastatic colon patients.

Table 4: Statistical Power for All Patients and for HPV- with 2-Sided 5% Alpha

All patients (279 events)			HPV- patients (220 events)		
Hazard Ratio			Hazard Ratio		
1.50	1.75	2.00	1.50	1.75	2.00
0.83	0.98	0.99	0.74	0.94	0.99

Evaluation of TP53 Mutations

The specific hypothesis is that the patients with *TP53* mutations will have poorer OS and DFS than patients with wild-type *TP53* mutations.

For planning purposes, the following assumptions will be made:

1. *TP53* mutation status can be determined in 75% of the patients;
2. 50% of patients will have *TP53* mutations;
3. Mutations will be distributed as follows: functionally non-disruptive=33% and functionally disruptive=20%. Thus, approximately 50% of all patients are projected to have no *TP53* mutations;
4. Patient accrual will not be discontinued in the trial or that trial is not reported early because of highly significant results;
5. Since the comparison will be made between patients with *TP53* mutations and patients with wild-type *TP53*, there will be at least 140 (= 372 * 0.75) deaths (events) observed in these 2 patient groups at the time of final treatment analyses;
6. After assessing the *TP53* mutational status, the mutations will be categorized into functionally non-disruptive and disruptive mutations for a subset analysis to further investigate the clinical effects of the mutations.

The equation described by Schoenfeld (1981) was used to calculate statistical power:

Hazard ratio in this instance compares unfavorable risk group (*TP53* mutation) to unfavorable risk group (wild-type *TP53*). The prevalence rate of favorable risk group was set at 0.50 but also prevalence rates of 0.40 and 0.60 will be evaluated. Table 5 below shows statistical power to detect hazard ratios for OS of 1.50, 1.75, and 2.00 for prevalence rates of 40% or 50% or 60% in all patients. As seen in the table, there will be excellent statistical power (> 90%) to detect a hazard ratio of ≥ 1.50 , and 80% statistical power to detect a ratio of at least 1.4 in all patients. The statistical power for DFS would be higher since its failure rate would be higher than the death rate; thus resulting in more events.

Table 5: Statistical Power for All Patients with 2-Sided 5% Alpha

	All patients (279 deaths)		
	Hazard Ratio		
Prevalence of pts with wild type <i>TP53</i>	1.50	1.75	2.00
40%	0.91	0.99	0.99
50%	0.92	0.99	0.99
60%	0.91	0.99	0.99

Evaluation of Polymorphic Variants in CA Dinucleotide Repeats in EGFR Intron 1

The specific hypothesis is that short CA dinucleotide repeats in EGFR intron 1 will be associated with poor OS and DFS.

For planning purposes, it is assumed that dinucleotide repeats in EGFR intron 1 can be determined in 75% of the patients and that patient accrual will not be discontinued in the trial or that trial is not reported early because of highly significant results. It is projected that 25%

of the study population will be female and < 5% will be Asian. At the time of final treatment analyses, there will be at least 279 ($= 0.75 * 372$) deaths (events) observed in all patients and 80 ($= 0.25 * 0.75 * 294$) deaths (events) in female patients.

The equation described by Schoenfeld (1981) was used to calculate statistical power:

Hazard ratio in this instance compares favorable risk group (short CA dinucleotide repeats in EGFR intron 1) to unfavorable risk group (long CA dinucleotide repeats in EGFR intron 1) and the prevalence rate is for the favorable risk group. Table 6 below shows statistical power to detect hazard ratios for OS of 1.50, 1.75, and 2.00 for prevalence rates of 40% or 50% or 60% in all patients and in only female patients. As seen in the table, there will be excellent statistical power (> 90%) to detect a hazard ratio of 1.50 or greater and 80% statistical power to detect ratio of at least 1.4 in all patients. However, there is only adequate statistical power (> 80%) to detect large ratio in the female patients. The statistical power for DFS would be higher since its failure rate will be higher than death rate; thus resulting in more events.

Table 6: Statistical Power for All Patients and Only Female Patients with 2-Sided 5% Alpha

	All Patients (279 deaths)			Female Patients (80 deaths)		
	Hazard Ratio			Hazard Ratio		
Prevalence	1.50	1.75	2.00	1.50	1.75	2.00
40% (or 60%)	0.91	0.99	0.99	0.42	0.68	0.85
50%	0.92	0.99	0.99	0.44	0.70	0.87

13.4.5 Background and Statistical Power Determination for Evaluating Factors Associated with Long-Term, Post-Radiotherapy Adverse Events and Patient-Reported Outcomes (PROs)

In this trial, long-term adverse events will be graded using CTCAE, v. 4, with particular attention to dysphagia, dry mouth, and skin toxicity (rash: acneiform; rash: maculo-papular; and pruritus). However, it is recognized that CTCAE (physician graded) does not always reflect the patient experience and quality of life (QOL). Therefore, patient-reported outcomes (PROs) will be studied with head and neck specific instruments, including: the Performance Status Scale for Head and Neck Cancer (PSS-HN), the Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N), the University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS), the Dermatology Life Quality Index (DLQI), and a cost-utility analysis will be done using the EuroQol (EQ-5D). Data will be collected at the baseline and at 3, 12, and 24 months from the start of treatment.

The following 5 hypotheses will be examined:

1. PROs will be similar in the 2 arms (i.e., the use of cetuximab does not result in decreased QOL);
2. Patients treated with IMRT + IGRT will have improved XeQOLS scores compared with patients treated with IMRT;
3. Clinician-rated functional assessment of dysphagia (CTCAE, v. 4 dysphagia) is at least moderately correlated ($r \geq 0.20$) with its PRO assessment (the Normalcy of Diet component of the PSS-HN);
4. Clinician-rated functional assessment of xerostomia (CTCAE, v. 4 dry mouth) is at least moderately correlated ($r \geq 0.20$) with its PRO assessment (the XeQOLS);
5. Clinician-rated skin toxicity (CTCAE, v. 4 rash: acneiform; rash: maculo-papular; and pruritus) is at least moderately correlated ($r \geq 0.20$) with its PRO assessment (the DLQI);
6. The EQ-5D is highly correlated ($r \geq 0.50$) with FACT-H&N, XeQOLS, the PSS-HN, and DLQI.

Hypothesis 1:

The primary question of interest is whether the addition of cetuximab to postoperative radiation therapy (RT) at 12-month assessment results in poorer PROs. In the Bonner study with

patients who received definitive RT, the addition of cetuximab did not adversely affect QOL. The effect of the addition of cetuximab at 3 months from start of RT also will be evaluated.

In this trial, the participation in the QOL component of the study is optional for patients. In the past, RTOG has not evaluated QOL in any postoperative RT trial; therefore, the projected percentage of patients with PRO/QOL data for the 12-month assessment will be based on the ongoing phase III trial, RTOG 0522, testing the addition of cetuximab to chemoradiation. RTOG 0522 uses the same PRO/QOL instruments, with the exception of the University of Michigan 15-item Xerostomia Related Quality of Life Scale (XeQOLS). In the first 78 patients entered into RTOG 0522 with potentially 12-month follow up, approximately 50% had both the baseline and the 12-month assessment; therefore, it is projected that half of the patients entered onto RTOG 0920 will have both assessments (158 patients per arm). Hypothesis 1 will be tested using the following 3 endpoints:

A. University of Michigan 15-item Xerostomia Related Quality of Life Scale (XeQOLS)

The endpoint for the XeQOLS will be differences between arms in the mean XeQOLS score for the baseline and the 12-month assessment. Only patients alive at 10 months with baseline (XeQOLS) scores will initially be included in this analysis. With 158 patients per arm and an effect size of 0.32 or higher, where the effect size is

$\delta = \frac{|\mu_1 - \mu_2|}{\sigma}$, where σ is the common standard deviation, under assumption of normal distribution, there is 80% statistical power to detect this effect.

B. Normalcy of Diet Subscale in the Performance Status Scale for Head and Neck Cancer (PSS-HN)

For the PSS-HN scale, the frequency of patients with scores of ≤ 50 (considered to be impaired swallowing or speech) on each of the 3 subscales (Normalcy of Diet; Eating in Public; and Understandability of Speech) will be estimated along with its 95% confidence interval for each treatment regimen at 12 months from start of treatment. These frequencies will be compared between the 2 treatments using the z-statistic for testing binomial proportions. Only patients alive at 10 months with baseline diet subscale scores will be included in this analysis. There are no data available to estimate the percentage of the patients on the postoperative RT arm with impaired swallowing or speech at 12 months in this study population. With projected sample size of 158 patients per arm and 80% statistical power, the detectable difference would be approximately 0.16 between the treatment arms.

C. Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N)

The primary patient-reported endpoint for the FACT-H&N will be differences between arms in the mean FACT-H&N score for the baseline and the 12-month assessment. Only patients alive at 10 months with baseline FACT-H&N scores will be included in this analysis. With 158 patients per arm and an effect size of 0.32 or higher, where the effect

size is $\delta = \frac{|\mu_1 - \mu_2|}{\sigma}$, where σ is the common standard deviation, there is 80% statistical power to detect this effect.

Hypothesis 2:

The ideal way to determine whether patients treated with IMRT + IGRT will have improved Xerostomia Related Quality of Life Scale (XeQOLS) scores would be in a study in which patients are randomly assigned to IMRT +/- IGRT. This randomization would not be possible because many NRG Oncology institutions do not have IGRT capabilities or because some radiation devices with IGRT capabilities cannot be utilized without IGRT.

As the proposed study is written, the treating institution decides on a patient-by-patient basis whether or not IGRT will be utilized. An exploratory analysis will be performed looking at this question. The analysis will be done with multivariate regression models to correct for potential prognostic factors, including protocol cetuximab treatment, tumor site, stage, patient age, pretreatment performance status, and type and extent of surgery performed prior to IMRT. The number of patients available for analysis will be for the same as for the protocol treatment evaluation described above. It is expected that the number of institutions with IGRT capabilities will steadily increase over the time in which the study is active and by the time the study is complete, most institutions will have IGRT capabilities.

The same 12-month PRO/QOL endpoints will be analyzed in a similar fashion for the treatment comparison. The statistical power associated with the evaluation of the 12-month PRO/QOL endpoints was generated under the assumption that 40% (i.e., 126) of 316 patients will have received IMRT + IGRT, and 60% (i.e., 190) will receive IMRT without IGRT. The primary patient-reported endpoint for the XEQOLS and FACT-H&N respectively will be differences between arms in their respective mean score for the baseline and the 12-month assessment. Only surviving patients at 10 months with their baseline scores will initially be included in this analysis. With 126 patients treated with IMRT + IGRT, 190 patients treated with IMRT without IGRT and an effect size of 0.33 or higher, where the effect size is

$\delta = \frac{|\mu_1 - \mu_2|}{\sigma}$, where σ is the common standard deviation, under assumption of normal distribution, there is 80% statistical power to detect this effect.

For the PSS-HN diet subscale, the frequency of patients with scores of ≤ 50 (considered to be impaired swallowing) will be compared between IMRT +/- IGRT using the z-statistic for testing binomial proportions. Only surviving patients at 10 months with baseline diet subscale scores will be included in this analysis. There are no data available to estimate the percentage of the patients on postoperative RT arm with impaired swallowing at 12 months in this study population. With projected sample size of 126 IMRT+ IGRT patients and 190 IMRT without IGRT patients and 80% statistical power, the detectable difference would be approximately 0.17.

Hypotheses 3-5:

Patients with a PRO data collection form received within 2 months of the 12-month assessment will be included in the analyses of these hypotheses, as long as they had a clinical assessment of dry mouth, dysphagia, and skin toxicity (rash/acneiform; rash/maculo-papular; and pruritus) during that study timeframe. It is projected that there will be approximately 300 such patients.

Hypothesis 6:

Patients with an EQ-5D data form received within 2 months of the 12-month assessment will be included in the analyses of this hypothesis, as long as they had at least one of the other PRO data forms (FACT-H&N, XEQOLS, the PSS-HN, and DLQI) completed during that study timeframe. It is projected that there will be approximately 300 such patients.

13.5 Patient Accrual

The study design is based on a 79-month accrual period with an average of approximately 9.0 patient entries per month. However, during the first 6 months following activation, little accrual is anticipated while the trial is approved by institutional IRBs. It is projected that 11 patients in total will be entered during study months 1-6 (none in months 1-3; 3 patients in the 4th month; and 4 patients in months 5-6), and then the average monthly accrual rate after study month 6 will be 9.5 patients. If the total accrual during months 13 through 18 of the study is $\leq 20\%$ of the targeted accrual (≤ 11 cases in total), then the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual is between 21-49%, then the protocol will continue to accrue subject to approval of the NRG Oncology Data Monitoring Committee (DMC) and NCI-CTEP. If continued, the study has to accrue at least 50% of targeted accrual (≥ 15 cases in total) during months 22 through 24 in order to remain open beyond 2 years.

13.6 Randomization (23-FEB-2012)

Patients will be stratified by 4 variables: Pretreatment EGFR level (high [$\geq 80\%$ of cells staining positive for EGFR] vs. low [$< 80\%$ of cells staining positive for EGFR] vs. EGFR not evaluable); Primary Site (Oral cavity, Larynx, Oropharynx HPV positive, Oropharynx HPV negative, Oropharynx HPV not evaluable); use of IGRT (no vs. yes), and clinical stage (T1-3 vs. T4a). To avoid possible bias in randomization of patients to the study, the patient's HPV status will not be provided to the patient's physician or institution until the patient has completed study treatment. The treatment allocation scheme described by Zelen (1974) will be used because it balances patient factors other than institution. The protocol has strict time constraints to start postoperative RT.

13.7 Analysis Plan (11-MAY-2023)

13.7.1 Statistical Methods

This study will be analyzed using all eligible patients with follow up based on the treatment arm to which they were randomized, regardless if they started the assigned treatment. In addition, a

second efficacy comparison will be performed as a sensitivity analysis for the primary endpoint of survival using all patients entered on RTOG 0920 by their randomized treatment assignment.

The Spearman method will be used to calculate the correlation coefficients with their associated 95% confidence levels.

DFS and OS rates will be estimated using the Kaplan-Meier method (1958). The distributions of the OS and DFS will be compared between treatment arms with a one-sided, stratified log rank test (Mantel 1966). The patients will be stratified by EGFR level (high vs. low vs. not evaluable) and primary site/HPV status (oropharyngeal HPV positive vs. oropharyngeal HPV negative/oral cavity/larynx vs. oropharyngeal HPV not evaluable). Since the use of IGRT is not projected to significantly affect overall survival, it was not included as a stratification variable for the cetuximab efficacy analysis. This minimizes the number of cells for the log rank test. Since protocol treatment has to start within 2 weeks of protocol registration, it is expected that some of patients will not have an EGFR level and/or HPV status available at the time of randomization because the tissue submission was inadequate; these patients will be randomized as not evaluable. Most of these patients subsequently will have the unknown value for the stratification variable determined. However, values of the stratification variables at the time of randomization will be used for both OS and DFS endpoints in primary/secondary efficacy analysis. It is very possible that some stratification cells defined by oropharyngeal HPV positive patients or oropharyngeal HPV undetermined patients may have less than 20 patients. In those situations, the oropharyngeal HPV undetermined patients will be considered HPV positive and the cells combined accordingly. Sensitivity analysis also will be performed, restricting it to patients with known values for both stratification variables that are either before or after randomization.

Local-regional progressions in head and neck cancer trial mostly occur during the first two years and so death or distant metastasis without LRP can greatly influence the treatment effect, the associated p-value, and hence the interpretation of the trial. Therefore, local-regional control will be analyzed the following two ways:

1. Cumulative incidence curves comparing the treatment arms where LRP is considered as a failure and death or distant metastasis without LRP as a competing risk (Kalbfleisch 1980). The distributions of this failure pattern will be compared between treatment arms with the failure-specific log rank test (Prentice 1978).
2. Cumulative incidence curves comparing the treatment arms where death or distant metastasis with LRP is considered as a failure and LRP as a competing risk (Kalbfleisch 1980). The distributions of this failure pattern will be compared between treatment arms with the failure-specific log rank test (Prentice 1978).

The results from two approaches in this exploratory analysis for objectives (Sections 2.3.1 and 2.3.2) will be reported. Approach 1 will provide an estimate the efficacy for new treatment (cetuximab) and new radiation technique (IGRT) respectively and will be interpreted supporting their use if the associated p-value is less than $p < 0.10$ and if approach 2 does not show for patients treated with cetuximab or IGRT an increase in death rate without LRP progression especially during the first two years.

All failure times will be measured from the date of treatment randomization to the date of failure, competing risk, or last follow up. Table 7 shows how each first event will be counted for LRC and DFS. 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 OS, death from any cause will be considered a failure.

Table 7: Definition of Failure for LRC and DFS

First Event	Local-Regional Control (1)	Local-Regional Control (2)	Disease-free Survival
None	Censored	Censored	Censored
Local-regional progression or recurrence	Failure	Competing risk	Failure
Distant metastasis	Competing risk	Failure	Failure
Death due to study cancer or from unknown causes	Failure	Competing risk	Failure
Death due to any other reason	Competing risk	Failure	Failure

For the endpoints in Sections 13.1.2.1, 13.1.2.2, and 13.1.2.3, only adverse events (AEs) assessed to be definitely, probably, or possibly related (if relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of \geq grade 3 acute and late AEs (specifically, dry mouth, dysphagia, skin, and all) 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 groups.

A 2-sided van Elteren's test with $\alpha = 0.05$ will be used to test whether the distribution of the Functional Assessment of Cancer Therapy-Head & Neck [FACT-H&N] and University of Michigan Xerostomia-Related Quality of Life Scale [XeQOLS] at 3, 12, and 24 months from start of RT scores is the same in the treatment arms. Van Elteren's test is an extension of the stratified Wilcoxon rank-sum test. It will be obtained from the generalized Cochran-Mantel-Haenszel (CMH) test for mean difference using the standardized midranks (also known the modified ridit scores) [Stokes 1995].

13.7.2 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. 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. After this study has been opened 1.5 years, the study design assumptions made about percentage of HPV+ oropharyngeal patients entered on 0920 will be checked semiannually. If the observed frequency of HPV+ patients is greater by at least 10% than the projected frequency of 20%, the implication of this increased frequency will be assessed in terms of when the projected final (definitive) treatment analysis will be performed. If timing of that analysis is lengthened by more than a year, a recommendation of increasing the sample size will be explored.

13.7.3 Significance Testing for Early Termination and Reporting

Three interim treatment comparisons will be performed when the following are observed: 25% (93 deaths), 50% (186 deaths), and 75% (279 deaths) of the 372 required number of deaths. Only the primary endpoint of survival will be tested in the interim analysis. The efficacy will be tested using Haybittle-Peto boundaries of 0.005 for interim tests and 0.0183 for final analysis to preserve an overall alpha level of 0.025 for the study. The futility will be tested using the lower boundary based on testing the alternative hypothesis at 0.005 level. The results will be reported to the NRG Oncology DMC with the treatment blinded.

Table 8: Nominal Significance Levels

Interim Test	Number of Events	p-value for Efficacy	p-value for Futility
1	93	≤ 0.005	< 0.005
2	186	≤ 0.005	< 0.005
3	279	≤ 0.005	< 0.005
Final Analysis	372	≤ 0.0183	N/A

At each planned interim analysis, the results from the test for assessing treatment efficacy and futility will be reported to the NRG Oncology DMC. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the treatment effect, with respect to OS, is highly significant or if it is not likely to be; that is, if the p-value is less than the nominal value specified in a sequential design for either efficacy or futility. Before making such a recommendation, the accrual rate, treatment compliance, safety of the treatments, and the importance of the study also are taken into consideration with the p-value. The DMC will then make a recommendation about the trial to the NRG Oncology Group Chair.

13.7.4 *First Special Interim Analysis of Local Regional Control (LRC) in IMRT Treated Patients*

The interim analysis will be performed on the first 70 patients assigned to the radiation alone arm and for whom the participating institution does not elect to treat with IMRT and IGRT. It will occur after these 70 patients have been potentially followed for 1 year. The 1-year rate for LRC will be computed, and if it is less than 80%, the patient accrual to 0920 will be suspended. The NRG Oncology Data Monitoring Committee will review the results from the analysis as soon as possible and make a recommendation about the study's future disposition (e.g., discontinuation of further patient entries) to the NRG Oncology Group Chair who, in turn, will act upon that recommendation. The analysis will include pretreatment characteristics of this patient cohort.

13.7.5 *Second Interim Analysis of Local Regional Control (LRC) in IMRT Treated Patients*

The interim analysis will be performed on the first 70 patients assigned to the radiation alone arm and for whom the participating institution does not elect to treat with IMRT and IGRT. It will occur after these 70 patients have been potentially followed for 2 years. The 2-year rate for LRC will be computed, and if it is less than 70%, the patient accrual to 0920 will be suspended. The NRG Oncology Data Monitoring Committee will review the results from the analysis as soon as possible and make a recommendation about the study's future disposition (e.g., discontinuation of further patient entries) to the NRG Oncology Group Chair who, in turn, will act upon that recommendation. The analysis will include pretreatment characteristics of this patient cohort.

13.7.6 *Analysis for Reporting the Initial Cetuximab Treatment Results First*

The analysis reporting these treatment results will be carried out as described in Section 13.7.7. Only eligible patients with both on-study and follow-up information will be included in the primary treatment analysis. 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 13.1.

The difference in OS between the control arm and the experimental arm will be tested using the stratified one-side log-rank test at the significance level of 0.0183 given that the 3 interim analyses are carried out and show no statistical significance. The stratification will be done by EGFR level (high vs. low vs. not evaluable) and primary site/HPV status (oropharyngeal HPV positive vs. oropharyngeal HPV negative/oral cavity/larynx vs. not evaluable) [See [Section](#)

[13.5.1](#)]. The differences in DFS times between the treatment arms will be tested with the one-sided, stratified log rank test as described above at the 0.025 significance level given no interim analysis. Differences in LRC will be tested as described in Section 13.5.1.

A subset analysis using only HPV- patients will compare the protocol treatment arms with respect to the primary and all the secondary endpoints (Section 13.2.1). In addition, subset analyses using patients treated with each radiation technique (IMRT alone vs. IMRT+ IGRT) will compare the protocol treatment arms with respect to the secondary endpoints of adverse events (Sections 13.1.2.1-13.1.2.3).

13.7.7 Time-Driven Definitive Analysis:

The statistical analysis plan changes were done in accordance with the NCI Policy for Major Design Amendments for Ongoing Randomized Clinical Trials. The specifics for the changes were performed by a statistician independent from the trial.

Due to a lower than expected event rate for the primary endpoint, overall survival (OS), throughout the trial (the trial will not reach the third interim analysis for possibly three more years), the primary endpoint analysis will be performed with the number of OS events reported through June 1, 2023 (or completion of this amendment, whichever is later). The proposed date allows for a minimum of 5 years of potential follow-up on all randomized patients. The primary endpoint analysis will use a one-sided alpha of 0.0183 as specified in the initial design (see first paragraph in Section 13.7.2). The original study design called for randomization of 634 patients (increased to 700 to allow for ineligibility and dropouts), which was projected to yield 372 events, providing 80% power to detect a hazard ratio (HR) of 0.74, based on a one-sided, three interim analyses, and stratified logrank test at the overall 0.025 alpha level.

Analysis of OS in the control arm using data as of 3/15/2023 yields estimated 5- and 10-year survival rates of 69% and 57%, respectively, with a total of 95 observed events (deaths) among 287 patients. The number of observed events in years 5, 6, 7, 8, and 9 post-randomization was 10, 1, 1, 3, 3, and 3, respectively. With an additional 3 months of follow-up received to June 1, we therefore expect to see only about 1-2 additional deaths in the control arm, and thus assume there will be 97 control deaths and $97 \times 0.74 = 72$ experimental arm deaths, or 169, by this time.

The table below gives the power to detect an HR of 0.74 based on 169 events, as well as the HR that can be detected with 169 events at powers of 55%, 66%, and 79%.

Projected # of OS events in both arms by 6/1/2023	HR	Power (1-sided alpha of 0.0183)
169	0.74	45%
169	0.71	55%
169	0.68	66%
169	0.64	79%

Thus, there will be 45% power to detect the original assumed HR of 0.74. With 79% power, a true HR of 0.64 can be detected. Note that this revised analysis plan was developed independent of any information from accruing data other than the current control group event rate.

13.7.8 Analysis for Reporting the Results with Addition of IGRT to IMRT

The analysis of RT delivery technique (IMRT vs. IMRT with IGRT) will be done at same time as the initial cetuximab treatment analysis. Its results probably will be considered exploratory since the patients were randomized to the RT delivery technique. They will be reported separately from the cetuximab results. Only eligible patients who started IMRT and with follow-up information will be included in this analysis. The components of this analysis are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion by RT techniques;
- Distribution of important baseline prognostic variables and protocol treatment assignment by RT techniques;
- Frequency and severity of adverse events by RT techniques.

The estimate for IGRT effect on LRC will be derived from a Cox model with other factors added to correct for possible serious imbalance in their distributions between the techniques. The estimate for IGRT effect on the XeQOLS and the FACT respectively will be derived from multivariate regression models with other factors added to correct for possible serious imbalance in their distributions between the two treatment technique patient groups. These imbalances are possible since patients are not randomized between IMRT and IMRT+ IGRT. The other factors include cetuximab treatment, tumor site, stage, patient age, pretreatment performance status, and type and extent of surgery performed prior to IMRT. These results will be viewed as hypothesis generating, not as definitively testing the addition of IGRT.

13.7.9 *Analysis for Reporting PRO Data*

The analysis for hypotheses 1 and 3-6 in Section 13.2.4 will be done following the analyses of cetuximab treatment and the RT delivery techniques. The analysis of hypothesis 2 will be done as part of RT delivery technique analysis (Section 13.5.5) The results from these analyses will be considered exploratory, since the patient's participation was strictly voluntary for each PRO assessment. The results probably will be reported separately from the cetuximab treatment results. Only eligible patients with follow-up information will be included in these analyses.

13.7.10 *Analysis for Reporting Tumor Markers*

The analysis for the hypotheses for various tumor markers in Section 13.2.3 will be done following the analyses of cetuximab treatment and the RT delivery techniques. The results will be reported separately. Only eligible patients with both on-study and follow-up information will be included in these analyses.

13.8 Gender and Minorities

Men and women of all races and ethnic groups are eligible for this study.

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered the possible interactions (treatment by race and treatment by gender). The study was designed under the assumption of the same results between the gender and among the races. Based on accrual to RTOG's previous protocol, RTOG 0234, we project that 78% of patients enrolled on this study will be male, 90% white, and 4% Hispanic. The following table provides the projected number of patients in each race, ethnicity, and gender group.

Projected Distribution of Gender and Minorities

Ethnic Category	Gender		
	Females	Males	Total
Hispanic or Latino	4	15	19
Not Hispanic or Latino	172	509	681
Ethnic Category: Total of all subjects	176	524	700
Racial Category			
American Indian or Alaskan Native	0	3	3
Asian	3	7	10
Black or African American	3	30	33
Native Hawaiian or other Pacific Islander	0	0	0
White	170	484	654
Racial Category: Total of all subjects	176	524	700

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APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS (23-JAN-2013)

*See [Sections 11.1-11.3](#) for exceptions and details

Assessments	Within 8 wks prior to registration	Within 4 wks prior to registration	Within 2 wks prior to registration
General H&P by Rad Onc and/or Med Onc	X*		
ENT/Surgeon's exam	X*		
CT with contrast, or CT/PET, and/or MRI of H & N	Recommended within 4 weeks prior to treatment		
Chest x-ray (or chest CT or CT/PET)	X		
Pathology Assessment (Gross total resection within 7 wks prior to registration)	X*		
Performance status			X
CBC w/ diff & AGC		X	
Bilirubin, AST or ALT			X
Serum creatinine or creatinine clearance			X
Na, K, Cl, glucose, Ca, Mg, albumin			X
Serum pregnancy test (if applicable)			X
Dental eval	Within 3 months prior to start of treatment		
Assessment of swallowing function	Within 2 weeks prior to treatment		
Eval for G-tube placement	Recommended within 4 weeks prior to treatment		
EKG	Recommended within 8 weeks prior to treatment		
QOL/Functional Assessments: FACT-H&N; PSS-HN; EQ-5D; XeqOLS; DLQI	Prior to treatment (Baseline)		

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING RT (23-JAN-2013)

*See [Sections 11.1-11.3](#) for exceptions and details

Assessments	Weekly	Every 3 wks	As clinically indicated
General H&P by Rad Onc and/or Med Onc	X*		
CT with contrast, or CT/PET, and/or MRI of H & N			X
Chest x-ray (or chest CT or CT/PET)			X
Biopsy			If suspicion of tumor recurrence
Performance status	X		
CBC w/ diff & AGC	Prior to start of treatment		
Bilirubin, AST or ALT		X	
Serum creatinine or creatinine clearance		X	
Na, K, Cl, glucose, Ca, Mg, albumin		X*	
Adverse event eval	X		
Blood for research-if patient consents	Prior to start of treatment		

APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP (08-MAR-2018)

*See [Sections 11.1-11.3](#) for exceptions and details

	Both Arms: At 1 mo. post-XRT	Both Arms: q3 mos. post-XRT, then q3 mos. x 2 yrs, q6 mos. x 3 yrs, then annually	Both Arms: As clinically indicated
General H&P by Rad Onc and/or Med Onc	See Section 11.3 for details of assessments		
ENT/Surgeon's exam			
CT with contrast, or CT/PET, and/or MRI of H & N		As clinically indicated	After 5 years, as clinically indicated
Chest x-ray (or chest CT or CT/PET)		X*	
Biopsy			If suspicion of tumor recurrence
Performance status	X	X	
CBC w/ diff & AGC	X		X
Bilirubin, AST or ALT	X*		
Serum creatinine or creatinine clearance	See Section 11.2 for details of assessments		
Na, K, Cl, glucose, Ca, Mg, albumin	See Section 11.2 for details of assessments		
Assessment of swallowing function	X	X	
Adverse event eval	X	X	
QOL/Functional Assessments: FACT-H&N; PSS-HN; EQ-5D; XeqOLS; DLQI	At 3, 12, and 24 months from the end of radiation 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 or
5	Death

APPENDIX III: AJCC STAGING SYSTEM, 6TH EDITION

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
T4 (lip)	Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
T4a (oral cavity)	Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face
T4b	Tumor invades masticator space, pterygoid plates or skull base and/or encases internal carotid artery

PHARYNX

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
T4a	Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

APPENDIX III (Continued)

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 minor thyroid cartilage erosion (e.g., inner cortex).
- T4a** 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** 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, or with impaired vocal cord mobility
- T3** Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
- T4a** Tumor invades through 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** 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** 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** Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

APPENDIX III (Continued)

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

DISTANT METASTASIS (M)

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

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, N0-2, M0
	Any T, N2, M0
Stage IVB	T4b, Any N, M0
	Any T, N3, 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

APPENDIX IV (Continued)

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: NRG ONCOLOGY FFPE SPECIMEN PLUG KIT INSTRUCTIONS (13-NOV-2017)

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
DON'T remove specimen from the

Use a separate punch tool for you have any questions or need Site that have the capacity to should submit a fresh H&E from



proper specimen ID and Block ID.
punch.

every specimen. Call or e-mail us if additional specimen plug kits. embed the blocks may do so. They the punch block.



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- San Francisco and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the ST form the request to perform the plug procedure and return of the block. Include a return request form with a return airbill

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: NRGBB@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

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

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

APPENDIX VI: NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS (13-NOV-2017)

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood (as specified by the protocol):

Kit contents: (Note: Sites are responsible for providing blood draw tubes):

- Thirty (30) 1 ml cryovials for plasma and serum – all time points
- Three (3) 2 ml cryovials for whole blood
- Biohazard bags (7) and Absorbent shipping material (7)
- One Styrofoam container (inner) and Cardboard shipping (outer) box per case
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

(A) Serum (if requested): Red Top Tube

- ❑ Label five 1ml cryovials for the serum collected. Label them with the study and case number, collection date, 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 a minimum of 0.5 ml serum into each of the five as many cryovials as are necessary for the serum collected labeled with study and case numbers, collection date, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze tubes upright 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 the ST Form.

(B) Plasma (If requested): Purple Top EDTA tube #1

- ❑ Label five 1ml cryovials for the plasma collected. Label them with the study and case number, collection date, and time point, and clearly mark cryovials “plasma”.

Process:

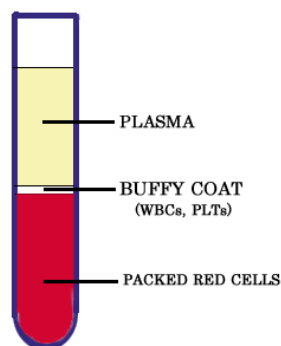
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature 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 a minimum of 0.5 ml plasma into each of the five cryovials as necessary for the plasma collected labeled with study and case numbers, collection date, 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 tubes upright at -70 to -90°C.
6. Store frozen plasma 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 the ST Form.

(continued on next page)

APPENDIX VI

BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2 (one 5 ml or 10 ml tube)

- ☐ Label three 1ml cryovials as necessary for the whole blood collected. Label them with the study and case number, collection date, and time point, and clearly mark cryovials "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 1.0-2.0ml blood into three 2ml cryovials as necessary for the blood collected labeled with study and case numbers, collection date, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze tubes upright immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to batch 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.

Freezing and Storage:

- ☐ Freeze Blood samples in a -80°C 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: Monday-Tuesday only).
 - 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: Monday-Tuesday only).
 - OR:**
 - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ☐ 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.
- ☐ Include all NRG Oncology paperwork in a sealed plastic bag 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 from breaking the tubes.
- ☐ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.

(continued on next page)

APPENDIX VI

NRG ONCOLOGY BLOOD COLLECTION KIT INSTRUCTIONS (continued)

- ❑ *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. **Add padding to avoid the dry ice from breaking the tubes.***
- ❑ **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail NRGBB@ucsf.edu or call (415)476-7864.**

Shipping Address:

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