

NRG ONCOLOGY

RTOG 0522

A RANDOMIZED PHASE III TRIAL OF CONCURRENT ACCELERATED RADIATION AND CISPLATIN VERSUS CONCURRENT ACCELERATED RADIATION, CISPLATIN, AND CETUXIMAB (C225) [FOLLOWED BY SURGERY FOR SELECTED PATIENTS] FOR STAGE III AND IV HEAD AND NECK CARCINOMAS

Study Team (1/14/14)

Medical Oncology Co-Chair

Rita Axelrod, MD
Thomas Jefferson University Hospital
834 Chestnut St./314 Ben Franklin Bldg
Philadelphia, PA 19107
215-955-4670/FAX 215-923-9131
rita.axelrod@Jefferson.edu

Principal Investigator/Radiation Oncology U.S.

David Rosenthal, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Suite 97
Houston, TX 77030
713-563-2300/FAX 713794-5573
dirosenthal@mdanderson.org

Medical Oncology Co-Chair

Eric Sherman, MD
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021
212-639-8229/FAX 212-717-3487
shermane@mskcc.org

Former Principal Investigator/Radiation Oncology

Kian Ang, MD (Deceased)
MD Anderson Cancer Center

Surgical Oncology Co-Chair

Randal Weber, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 441
Houston, TX 77030
713-792-6920/FAX 713-794-4662
rsweber@mdanderson.org

Radiation Oncology Co-Chair, Canada

Phuc Felix Nguyen-Tân, MD
CHUM Hospital Notre Dame
1560 Sherbrooke Street East
Montreal, Quebec, CA H2L 4M1
514-890-8254/FAX 514-412-7537
felix.nguyen.chum@ssss.gouv.qc.ca

Physics Co-Chair

James Galvin, PhD
Jefferson Medical College
111 S. 11th Street
Philadelphia, PA 19107
215-955-8855/FAX 215-955-0412
james.galvin@mail.tju.edu

PET Co-Chair

David Schwartz, MD
UT Southwestern
5801 Forest Park Rd.
Dallas, TX 75390
214-645-7667/FAX 214-645-7622
david.schwartz@utsw.edu

(Study Team continued on next page)

NRG ONCOLOGY

RTOG 0522

Study Team (Continued) (1/26/16)

Quality of Life Co-Chair

Marcie List, PhD
Univ. of Chicago Cancer Research Center
5841 S. Maryland, MC 1140
Chicago, IL 60637
773-702-6180/FAX 773-702-9311
mlist@medicine.bsd.uchicago.edu

Translational Research Co-Chair

Adel El-Naggar, M.D., Ph.D.
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 085
Houston, TX 77030
713-792-3109/ FAX 713-792-5532
anaggar@mdanderson.org

Outcomes Co-Chair

André Konski, MD
University of Pennsylvania
701 E. Marshall Street
West Chester, PA 19380
610-431-5530/Fax 610-431-5144
andre.konski@uphs.upenn.edu

Senior Statistician

Qiang Zhang, PhD
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-574-3197/FAX 215-928-0153
ezhang@acr.org

Document History (10/17/13)

	Version/Update Date	Broadcast Date
Amendment 10	January 26, 2016	TBD
Amendment 9	January 14, 2014	February 11, 2014
Amendment 8	October 17, 2013	November 13, 2013
Amendment 7	August 17, 2011	September 9, 2011
Amendment 6	February 23, 2011	March 2, 2011
Amendment 5	December 9, 2010	December 23, 2010
Update	September 1, 2009	September 1, 2009
Closure	March 3, 2009	March 3, 2009
Amendment 4	August 25, 2008	October 23, 2008
Amendment 3	February 14, 2007	March 27, 2007
Amendment 2	January 8, 2007	February 8, 2007
Amendment 1	June 2, 2006	June 20, 2006
Update	February 2, 2006	February 2, 2006
Update	November 23, 2005	November 23, 2005
Update	November 22, 2005	November 22, 2005
Activation	November 22, 2005	November 22, 2005

NRG Oncology
1-800-227-5463, ext. 4189

This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.

This study is supported by the NCI Cancer Trials Support Unit (CTSUS) [1/26/16]

Institutions not aligned with the NRG Oncology will participate through the CTSUS mechanism as outlined below and detailed in the CTSUS logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSUS Member Web site located at <http://members.ctsu.org>
- Send completed **site registration documents** to the CTSUS Regulatory Office. Refer to the CTSUS logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSUS. Refer to the CTSUS logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by NRG Oncology. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to NRG Oncology unless otherwise directed by the protocol. Do not send study data or case report forms to CTSUS Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by NRG Oncology. Please send query responses and delinquent data to NRG Oncology and do not copy the CTSUS Data Operations. Each site should have a designated CTSUS Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and NRG Oncology.

INDEX (1/26/16)

Schema

Eligibility Checklist

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Additional Pretreatment Evaluations/Management
- 5.0 Registration Procedures
- 6.0 Radiation Therapy/Functional Imaging
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Tissue/Specimen Submission
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Form
- Appendix II - Performance Status Scoring
- Appendix III - Staging System
- Appendix IV - Surgical Management of the Neck
- Appendix V - Neck Dissection Specimen: Documentation/Processing
- Appendix VI - Dental Management
- Appendix VII - Specimen/Blood Kit Procedure
- Appendix VIII - CTSU Logistics

NRG ONCOLOGY

RTOG 0522

A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas

SCHEMA

	Primary Site				
	1. Larynx			8-9 Weeks Post-Treatment	Selected Patients
	2. Non-Larynx				
			^b Arm 1		^b Required Neck
	Nodal Status		Accelerated Fractionation	Reassessment	Dissection:
S	1. N0	^a R	by Concomitant Boost	Required CT scan	Persistent nodal
T	2. N1, N2a, N2b	A	(AFX-CB) or IMRT	or MRI for N2-N3 ^c	disease, but
R	3. N2c, N3	N	plus cisplatin	and N1-N2c patients ^c	Complete response
A		D			of primary
T	Zubrod Status	O		These patients also	
I	1. 0	M		can receive post-	For details of
F	2. 1	I	^b Arm 2	treatment PET/CT	surgery for primary,
Y		Z	Accelerated Fractionation	scan	see Section 8.0
	Use of IMRT	E	by Concomitant Boost		
	1. No		(AFX-CB) or IMRT	If suspicion of relapse:	
	2. Yes		plus cisplatin	Directed biopsy	
			plus cetuximab		
	Pre-Treatment				
	PET/CT				
	1. No				
	2. Yes				

- a. **(6/1/06)** See Section 5.1-5.4 for pre-registration requirements. **NOTE:** It is mandatory that the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.
- b. See Sections 6.0, 7.0, and 8.0 for details of radiation therapy, drug therapy, and surgery.
- c. All patients with N2a, N2b, and N3 disease and patients with ≤ 3 cm nodes on one side (N1) or both sides (a subset of N2c) with questionable neck findings

Patient Population: (See Section 3.0 for Eligibility)

Squamous cell carcinoma of the oropharynx, hypopharynx, or larynx; selected stage III-IV disease (T2N2-3M0, T3-4 any N M0)

Required Sample Size: 945 (8/25/08)

RTOG Institution # _____

RTOG 0522

ELIGIBILITY CHECKLIST (8/25/08)

Case # _____

(page 1 of 4)

- _____(Y) 1. Does the patient have pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx?
- _____(Y) 2. Does the patient have selected stage III or IV disease (T2N2-3M0, T3-4 any N M0)? [Note: Patients with T1, any N, or T2N1 tumors are not eligible]
- _____(Y) 3. Was a history/physical examination completed within 4 weeks prior to registration, including assessment of weight and weight loss in past 6 months and an examination by a Medical Oncologist?
- _____(Y) 4. Was a Chest x-ray, Chest CT scan, or PET/CT scan completed within 6 weeks prior to registration?
- _____(Y) 5. Was a CT scan or MRI of the head and neck (of the primary tumor and neck nodes) or PET/CT scan completed within 6 weeks prior to registration?
- _____(Y) If a PET/CT was used (instead of a CT scan or MRI) was the CT a high quality scan with contrast?
- _____(Y) 6. Was the left ejection fraction determined by ECHO and/or MUGA technique within 12 weeks of registration?
- _____(Y) 7. Is the Zubrod 0-1?
- _____(Y) 8. Is the patient at least 18 years of age?
- _____(Y) 9. Were the following lab parameters confirmed within 2 weeks prior to study entry?
- Absolute neutrophil count (ANC) \geq 1,800 cells/mm³
 - Platelets \geq 100,000 cells/mm³
 - Hemoglobin \geq 8.0 g/dl
 - Bilirubin \leq 1.5 mg/dl
 - AST or ALT \leq 2x the upper limit of normal
 - Serum creatinine \leq 1.5 mg/dl
 - Creatinine clearance (CC) \geq 50 ml/min
- _____(Y/NA) 10. For women of childbearing potential, was a pregnancy test completed within 2 weeks of registration?
- _____(Y/NA) 11. If a male participant or a woman of child bearing potential, is the patient agreeable to practice effective birth control throughout the treatment phase of the study (until at least 60 days following the last study treatment)?
- _____(Y/N) 12. Is there a history of prior invasive malignancy (other than non-melanomatous skin cancer)?
- _____(Y) If yes, has the patient been disease free for greater than three years?
- _____(N) 13. Does the patient have simultaneous primaries or bilateral tumors?

(Continued on the next page)

RTOG Institution # _____

RTOG 0522

ELIGIBILITY CHECKLIST (8/25/08)

Case # _____

(page 2 of 4)

- _____ (N) 14. Has the patient had a gross total excision (e.g., by tonsillectomy) of the primary tumor?
- _____ (N) 15. Has the patient had prior systemic chemotherapy for the study cancer?
- _____ (N) 16. Has the patient had prior radiotherapy to the region of study cancer that would result in overlap of radiation therapy fields?
- _____ (N) 17. Is the primary tumor site oral cavity, nasopharynx, sinuses, or salivary gland?
- _____ (N) 18. Has the patient had initial surgical treatment other than the diagnostic biopsy of the primary site or nodal sampling of neck disease?
- _____ (N) 19. Does the patient have any of the severe comorbid conditions listed in Section 3.2.8 that would exclude him/her from participation, including the following CTCAE, v. 3.0 electrolyte abnormalities?
 - Calcium < 7 mg/dl or > 12.5 mg/dl;
 - Glucose < 40 mg/dl or > 250 mg/dl;
 - Magnesium < 0.9 mg/dl or > 3 mg/dl
 - Potassium < 3 mmol/L or > 6 mmol/L;
 - Sodium < 130 mmol/L or > 155 mmol/L
- _____ (N) 20. Has the patient had a prior allergic reaction to the study drugs involved in this protocol?
- _____ (N) 21. Has the patient had prior therapy that specifically and directly targets the EGFR pathway?
- _____ (N) 22. Has the patient had a prior severe infusion reaction to a monoclonal antibody?
- _____ (Y) 23. Has the patient signed a study-specific consent form?

The following questions will be asked at Study Registration:
IMRT CREDENTIALING IS REQUIRED BEFORE REGISTRATION

_____ (N/Y) Specify use of IMRT

If participating in the PET component, **PET CREDENTIAL IS REQUIRED BEFORE REGISTRATION.**

_____ (NA/Y) Confirm PET credentialing through PET Core Laboratory

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (above) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- _____ 5. Patient's Initials (First Middle Last) [May 2003; If no middle initial, use hyphen]

(Continued on the next page)

RTOG Institution # _____

RTOG 0522

ELIGIBILITY CHECKLIST (6/1/06)

Case # _____

(page 3 of 4)

- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Randomization date: This date will be populated automatically.
- _____ 17. Medical Oncologist's Name
- _____ (Y/N) 18. Tissue/Blood kept for cancer research?
- _____ (Y/N) 19. Tissue/Blood kept for medical research?
- _____ (Y/N) 20. Allow contact for future research?
- _____ 21. Specify primary site (Larynx vs. Non-Larynx)
- _____ 22. Specify nodal status (N0 vs. N1, N2a, N2b vs. N2c, N3)
- _____ 23. Specify Zubrod status (0 vs. 1)
- _____ 24. Specify pre-treatment PET/CT (No vs. Yes)
- _____ (N/Y) 25. Will PET/CT scans be submitted to the ACRIN PET Core Laboratory? (Scans only will be accepted if the institution is PET credentialed and N stage= N2a, N2b, N2c [with right or left side equal to N2a or N2b], or N3)
- _____ If yes, confirm N stage (N2a, N2b, N2c [with right or left side equal to N2a or N2b], or N3)

(Continued on next page)

RTOG Institution # _____

RTOG 0522

ELIGIBILITY CHECKLIST (6/1/06)

Case # _____

(page 4 of 4)

_____(N/Y)

26. Did the patient agree to participate in the Quality of Life component of the study?

If no, please specify the reason from the following:

1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify _____

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/RTOG audit.

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Treatment of Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)

The treatment of locally advanced (stage III-IV) HNSCC has been the subject of intensive investigation during the last two decades. Up to ten years ago, surgical resection, often followed by adjuvant radiotherapy, was the preferred therapy in most cases despite the resulting cosmetic and functional impairment affecting quality of life (QOL).

Attempting to improve therapy outcome, several radiobiologically sound, altered-fractionation regimens were designed and subjected to phase III testing. Collectively, clinical trials revealed that hyperfractionation and various accelerated fractionation regimens improved local-regional control (LRC) and in some trials, also survival.¹ RTOG 90-03 was a large randomized trial comparing standard fractionation (SFX) against hyperfractionation (HFX), accelerated fractionation with split-course (AFX-S), and accelerated fractionation by concomitant boost (AFX-CB) in the management of patients with stage III-IV HNSCC. Between September 1991 and August 1997, 1113 patients were enrolled. Analysis undertaken in September of 1999 revealed that AFX-CB ($p=0.050$) and HFX ($p=0.045$), but not AFX-S ($p=0.67$), yielded a significantly higher LRC rate than SFX.² There was no difference in the incidence of persistent grade 3 or grade 4 late toxicity among the arms at one year or longer follow up. Since hyperfractionation is much more costly and labor-intensive, the RTOG investigators have recommended AFX-CB as the new standard radiotherapy for intermediate-stage (e.g., T2 and favorable T3, N0-1) HNSCC and for further clinical testing for more advanced HNSCC. RTOG's ongoing phase III trial, 0129, compares the efficacy of the combination of AFX-CB with cisplatin to that of SFX with cisplatin.

Results of many recently published phase III trials³⁻⁹ show that chemotherapy given concurrently with radiation yields better LRC and survival rates than radiation alone in patients with locally advanced HNSCC. Two trials also have shown the benefit of concurrent radiation-chemotherapy given in the postoperative adjuvant setting.¹⁰⁻¹¹ In earlier trials, cisplatin was given in a dose of 100 mg/m², administered during weeks 1, 4, and 7 of radiotherapy (approximately a third of patients were not able to tolerate the last dose). The systemic and mucosal toxicities of such a high-dose, intermittent cisplatin regimen can be severe. There are now four trials showing LRC and/or survival benefit of alternative cisplatin regimens, i.e., 5 doses of 20 mg/m² over 5 consecutive days or 4 doses of 25 mg/m² over 4 sequential days during weeks 1, 4, and 7¹²⁻¹³ weekly doses of 50 mg during the 7-9 weeks course of postoperative radiotherapy¹⁴, or 6 mg/m²/day, 5 days a week during the 7 weeks course of radiotherapy.⁹ Taken together, the available data suggest that a cumulative cisplatin dose of 200 mg/m² given either every 3 weeks, weekly, or daily during the course of radiotherapy yields therapeutic benefit.

Currently, the combined radiation-chemotherapy regimen most extensively tested for the management of locally advanced HNSCC is the combination of conventionally fractionated radiotherapy (70 Gy in 35 fractions over 7 weeks) with cisplatin, 100 mg/m², every 3 weeks. Consequently, the majority of head and neck oncologists consider this concurrent radiation and cisplatin as the current standard-of-care for patients with locally advanced HNSCC seeking non-surgical therapy.

1.2 Proposed Trial: Rationale and Design

1.2.1 Role of Epidermal Growth Factor Receptor (EGFR) in Predicting and Modulating HNSCC Radiation Response

Progress in the understanding of tumor biology has opened an exciting new era for research. For example, as summarized in several recent publications,^{15,16-18} preclinical and correlative biomarker studies from various laboratories have detected EGFR as a predictor of radiation response of HNSCC and have identified EGFR and its down-stream signaling molecules as appealing targets for therapeutic intervention.

A correlative study performed by RTOG investigators using tumor samples of patients with stage III-IV HNSCC enrolled on a previous phase III RTOG trial, 90-03, for example, revealed that EGFR overexpression was a strong, independent predictor of LRC after standard radiotherapy regimen. Patients with higher expression of EGFR had significantly lower overall survival (HR=1.72, $p=0.0073$) and LRC (HR=2.02, $p=0.0013$).¹⁵ These results were confirmed in an analysis of a second arm from RTOG 90-03 (unpublished).

Inspired by the results of preclinical and correlative studies, a phase III trial was designed in 1998 to test the efficacy of the combination of radiation with cetuximab, an anti-EGFR antibody,

versus radiotherapy alone in the treatment of locally advanced HNSCC. The results of this international trial, presented at the 2004 annual meeting of the American Society of Clinical Oncology,¹⁹ showed that the combination of cetuximab and radiation yielded LRC (two-year estimated rate: 56% vs. 48%; median progression-free interval: 36 months vs. 19 months; $p=0.02$) and survival advantage (three-year estimated rate: 57% vs. 44%; median survival time: 54 months vs. 28 months; $p=0.02$) without added hematologic and mucosal toxicities over radiotherapy alone in comparable subsets of patients. Thus, the international trial provided the proof-of-principle for selective tumor targeting in the treatment of locally advanced HNSCC and other neoplasms expressing a high level of EGFR.

Since local-regional recurrence remains the main pattern of relapse, the proposed phase III trial is designed to assess whether adding cetuximab to a radiation-cisplatin regimen will further improve both disease-free survival (DFS) and LRC (in all patients) but also survival in patients with stage III-IV disease. Survival in patients with laryngeal cancer may not be affected, since the intergroup larynx trial showed that the surgical salvage rate is generally high.²⁰

1.2.2 Study Hypotheses

This phase III trial addresses two hypotheses. The primary hypothesis is that since EGFR affects cellular response to radiation and to cytotoxic agents, the addition of a neutralizing antibody, cetuximab, to a concurrent radiation-cisplatin regimen will enhance HNSCC response resulting in improved disease-free survival (DFS). The secondary hypothesis is that the addition of cetuximab to a concurrent radiation-cisplatin regimen will improve overall survival in patients with HNSCC without added toxicity and will improve LRC.

1.2.3 Study Design

The use of intensity-modulated radiotherapy (IMRT) will be permitted (and recorded in stratification) since increasing numbers of participating centers have been credentialed and have implemented such precision radiation technology to spare normal tissue.

Selection of the control arm

The control therapy was tested in a phase II RTOG trial, 99-14.²¹ Briefly, a total of 84 patients with stage III-IV HNC meeting the eligibility criteria were enrolled, of whom 76 patients were analyzable. The estimated two-year local-regional relapse and distant metastasis rates were 34.7% and 16.1%, respectively. The estimated two-year overall survival and disease-free survival rates were 71.6% and 53.5%, respectively. Three patients (4%) died of protocol treatment. Nineteen patients (25%) had acute grade 4 toxicity and 49 (63%) had acute grade 3 toxicity. The two-year cumulative incidence of late grade 3-5 toxicities was 51.3%. Because of this encouraging outcome (among the lowest local-regional relapse rate observed in a multi-institutional trial), RTOG investigators decided to move forward with evaluating the combination of AFX-CB with cisplatin in a phase III trial (0129), which is projected to complete accrual of 720 patients by August 2005.

Selection of the experimental arm

The experimental regimen has not been tested in multi-institutional setting. A single institutional trial tested a similar regimen enrolled 22 patients.²² With a median follow up of 41 months, the estimated 3-year survival rate was 76%, in spite of the occurrence of 2 fatal events (1 pneumonia and 1 unknown cause). Grade 3-4 toxicities were typical of concurrent cisplatin and radiation. In addition, grade 3-4 acne-like rash (19%) and hypersensitivity (5%) were observed. The observation that cetuximab does not increase mucosal reactions or induce systemic toxicity other than skin rash and rare allergic reaction¹⁹ encouraged us to move forward with testing the addition of cetuximab to accelerated fractionation and cisplatin.

RTOG has extensively tested accelerated fractionation delivered by 3-D conformal technique (AFX-CB). In a large randomized trial conducted in Denmark (DAHANCA, $N > 1400$), accelerated fractionation delivering 6 fractions a week has been shown to yield a better local control rate than standard fractionation given 5 fractions per week.²³ Accelerated fractionation by IMRT will be delivered in 6 fractions per week during five of the six treatment weeks, similar to the fractionation used in DAHANCA. Since the volume of tissues receiving high dose radiation is generally smaller with IMRT than with 3-D CRT, the tolerance to the IMRT regimen would not be worse than AFX-CB.

1.3 Cetuximab (8/25/08)

Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells and competitively inhibits the binding of epidermal growth factor

(EGF) and other ligands, such as transforming growth factor- α . (Erbix[®] package insert, 2007). Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production. The EGFR is a transmembrane glycoprotein that is a member of a subfamily of type I receptor tyrosine kinases including EGFR (HER1), HER2, HER3, and HER4. The EGFR is constitutively expressed in many normal epithelial tissues, including the skin and hair follicle. Over-expression of EGFR is also detected in many human cancers including those of the colon and rectum.

In vitro assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that over-express the EGFR. No anti-tumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. The addition of cetuximab to irinotecan or irinotecan plus 5-fluorouracil in animal studies resulted in an increase in anti-tumor effects compared to chemotherapy alone.

1.3.1 Human Pharmacokinetics

Cetuximab administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy exhibits nonlinear pharmacokinetics. The pharmacokinetics of cetuximab were similar in patients with squamous cell carcinoma of the head and neck (SCCHN) and those with colorectal cancer (Erbix[®] package insert, 2007). The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m². Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses >200 mg/m², it appeared to plateau. The volume of distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m².

Following a 2-hour infusion of 400 mg/m² of cetuximab, the maximum mean serum concentration (C_{max}) was 199 μ g/mL (range: 70-380 μ g/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m² produced a mean C_{max} of 168 μ g/mL (range 120-170 μ g/mL). Following the recommended dose regimen (400 mg/m² initial dose/250 mg/m² weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 μ g/mL, respectively. The mean half-life was 112 hours (range 75-188 hours).

1.3.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbent assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving cetuximab has not been adequately determined. The incidence of antibodies to cetuximab was measured by collecting and analyzing serum pre-study, prior to selected infusions and during treatment follow-up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients (Erbix[®] package insert, 2007). In patients positive for anti-cetuximab antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The observed incidence of anti-cetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-cetuximab antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

1.4 Clinical Studies of Cetuximab in Squamous Cell Carcinoma of the Head and Neck Cancer and Colorectal Cancer Efficacy (8/25/08)

1.4.1 Squamous Cell Carcinoma of the Head and Neck

The efficacy and safety of cetuximab in combination with radiation therapy was studied in a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) of the oropharynx, hypopharynx or larynx 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.

1.4.2 Colorectal Cancer

The efficacy and safety of cetuximab plus best supportive care (BSC) were evaluated in a multicenter, open-label, randomized, clinical trial of 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer versus BSC alone. The efficacy and safety of cetuximab alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). Cetuximab was further evaluated as a single agent in a third clinical trial (57 patients). All trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

1.4.3 Squamous Cell Carcinoma of the Head and Neck: Randomized, Controlled Trial

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. 424 patients with Stage III/IV SCCHN 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 American Joint Committee on Cancer 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. Starting 1 week prior to radiation, cetuximab was administered as a 400-mg/m² initial dose, followed by 250 mg/m² 2 weekly for the duration of radiation therapy (6-7 weeks). 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 US sites (61%) and 166 patients (39%) in non-U.S. sites. Ninety percent of patients had baseline Karnofsky Performance Status > 80; 60% had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient characteristics were similar across the study arms. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

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

Clinical Efficacy in Locoregionally Advanced SCCHN

	Cetuximab + Radiation (n = 211)	Radiation Alone (n = 213)	Hazard Ratio (95% CI^a)	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.

1.4.3.1 Single-arm Trial

Cetuximab alone was studied in a single-arm, multicenter clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days of a platinum-based chemotherapy regimen. 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. 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 was 13% (95% confidence interval (7%-21%)). Median duration of response was 5.8 months (range 1.2-5.8 months).

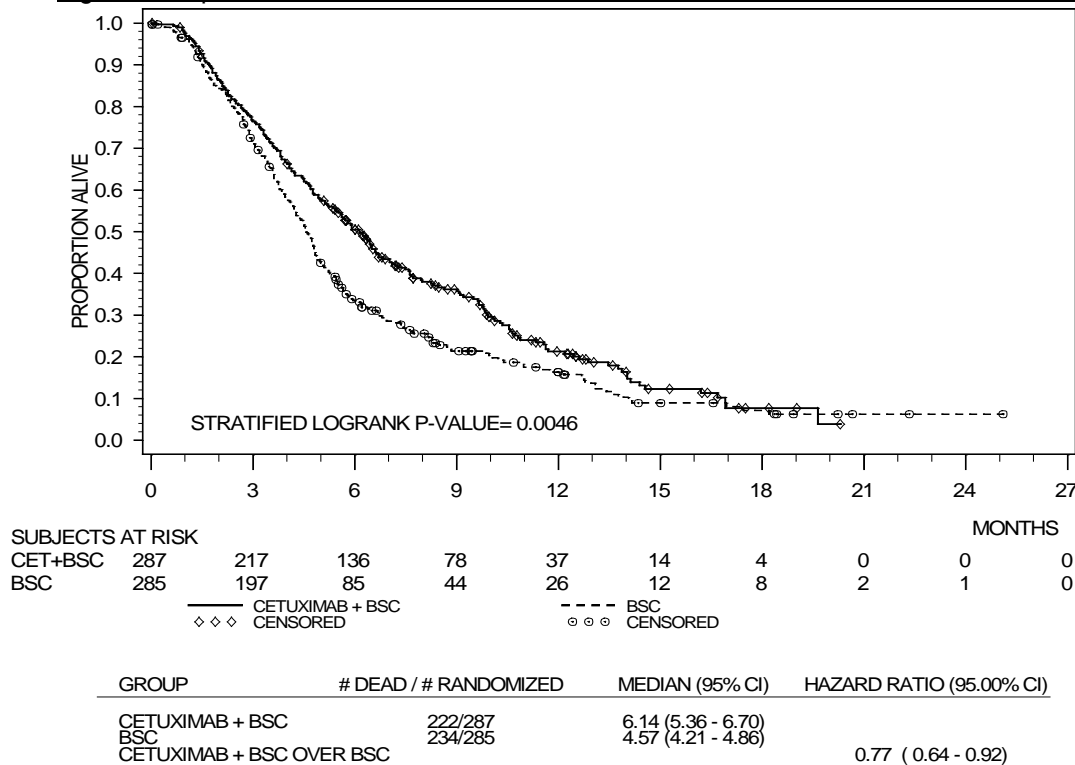
1.4.4 Colorectal Cancer: Randomized, Controlled Trials

A multicenter, open-label, randomized, clinical trial was conducted in 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer. Patients were randomized (1:1) to receive either Erbitux® plus best supportive care (BSC) or BSC alone. Erbitux® was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity.

Of the 572 randomized patients, the median age was 63 years, 64% were male, 89% were Caucasian, and 77% had baseline ECOG Performance Status of 0–1. All patients were to have received and progressed on prior therapy including an irinotecan-containing regimen and an oxaliplatin-containing regimen.

The main outcome measure of the study was overall survival. The results are presented in Figure 1.

Figure 1: Kaplan Meier Curve for Overall Survival in Patients with Metastatic Colorectal Cancer



In another multicenter, clinical trial conducted in 329 patients with EGFR-expressing recurrent metastatic colorectal cancer, patients were randomized (2:1) to receive either Erbitux® plus irinotecan (218 patients) or Erbitux® monotherapy (111 patients). Erbitux® was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. In the Erbitux® plus irinotecan arm, irinotecan was added to Erbitux® using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the median age was

59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status \geq 80. Approximately two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux® plus irinotecan or Erbitux® monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux® plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux® monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

Another randomized, multicenter, clinical trial was conducted in 329 patients with EGFR-expressing recurrent metastatic colorectal cancer. Patients were randomized (2:1) to receive either Erbitux® plus irinotecan (218 patients) or Erbitux® monotherapy (111 patients). Erbitux® was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly until disease progression or unacceptable toxicity. In the Erbitux® plus irinotecan arm, irinotecan was added to Erbitux® using the same dose and schedule for irinotecan as the patient had previously failed. Acceptable irinotecan schedules were 350 mg/m² every 3 weeks, 180 mg/m² every 2 weeks, or 125 mg/m² weekly times four doses every 6 weeks. Of the 329 patients, the median age was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status \geq 80. Approximately two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux® plus irinotecan or Erbitux® monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux® plus irinotecan, the objective response rate was 23% (95% confidence interval 18%–29%), median duration of response was 5.7 months, and median time to progression was 4.1 months. In patients receiving Erbitux® monotherapy, the objective response rate was 11% (95% confidence interval 6%–18%), median duration of response was 4.2 months, and median time to progression was 1.5 months. Similar response rates were observed in the pre-defined subsets in both the combination arm and monotherapy arm of the study.

1.4.5 EGFR Expression and Response

Since expression of EGFR has been detected in nearly all SCCHN tumor specimens, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR expression prior to study entry.

Patients enrolled in the colorectal clinical studies were required to have immunohistochemical evidence of positive EGFR expression. Primary tumor or tumor from a metastatic site was tested with the DakoCytomation EGFR pharmDx™ test kit (Erbitux® package insert, 2007). Specimens were scored based on the percentage of cells expressing EGFR and intensity (barely/faint, weak to moderate, and strong). Response rate did not correlate with either the percentage of positive cells or the intensity of EGFR expression.

If assessment for EGFR expression is required, it should be performed by laboratories with demonstrated proficiency in the specific technology being utilized. In the registrational trials for cetuximab, EGFR expression was tested with the DakoCytomation EGFR pharmDx™ test kit. Regardless of the test utilized, improper assay performance, including use of sub-optimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

1.5 Safety of Cetuximab in Clinical Studies (1/26/16)

1.5.1 Anticipated Adverse Events

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 data below reflect exposure to Erbitux® in 1373 patients with colorectal cancer or SCCHN in randomized phase 3 (Studies 1 and 3) or phase 2 (Studies 2 and 4) trials treated at the recommended dose and schedule for a median of 7 to 14 weeks.

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal: Renal failure occurred in 1% of patients with colorectal cancer.

1.5.2 Squamous Cell Cancer of the Head and Neck

The data in the table below contains selected adverse events in 420 patients receiving radiation therapy either alone or with Erbitux® for locally or regionally advanced SCCHN in Study 1. Erbitux® was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 8 infusions (range 1–11).

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			
Body as a Whole				
Asthenia	56	4	49	5
Fever ¹	29	1	13	1
Headache	19	<1	8	<1
Infusion Reaction ²	15	3	2	0
Infection	13	1	9	1
Chills ¹	16	0	5	0
Digestive				
Nausea	49	2	37	2
Emesis	29	2	23	4
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
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 reaction.

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 occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.

³ Acneiform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

1.5.2.1 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.

1.5.3 Colorectal Cancer

The following table contains selected adverse events in 562 patients receiving best supportive care (BSC) alone or with Erbitux® monotherapy for metastatic colorectal cancer.¹ Erbitux® was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly).

Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma¹ Treated with Erbitux® Monotherapy				
Body System Preferred Term	Erbitux® plus BSC (n=288)		BSC alone (n=274)	
	Any Grades²	Grades 3 and 4	Any Grades	Grades 3 and 4
	% of Patients			
Dermatology				
Rash/Desquamation	89	12	16	<1
Dry Skin	49	0	11	0
Pruritus	40	2	8	0
Other-Dermatology	27	1	6	1
Nail Changes	21	0	4	0
Body as a Whole				
Fatigue	89	33	76	26
Fever	30	1	18	<1
Infusion Reactions ³	20	5		
Rigors, Chills	13	<1	4	0
Pain				
Abdominal Pain	59	14	52	16
Pain-Other	51	16	34	7
Headache	33	4	11	0
Bone Pain	15	3	7	2
Pulmonary				
Dyspnea	48	16	43	12
Cough	29	2	19	1
Gastrointestinal				
Constipation	46	4	38	5
Diarrhea	39	2	20	2
Vomiting	37	6	29	6
Stomatitis	25	1	10	<1
Other-Gastrointestinal	23	10	18	8
Mouth Dryness	11	0	4	0
Infection				
Infection without neutropenia	35	13	17	6

Incidence of Selected Adverse Events Occurring in $\geq 10\%$ of Patients with Advanced Colorectal Carcinoma ¹ Treated with Erbitux [®] Monotherapy				
Body System Preferred Term	Erbitux [®] plus BSC (n=288)		BSC alone (n=274)	
	Any Grades ²	Grades 3 and 4	Any Grades	Grades 3 and 4
	% of Patients			
Neurology				
Insomnia	30	1	15	1
Confusion	15	6	9	2
Anxiety	14	2	8	1
Depression	13	1	6	<1

¹ Adverse reactions occurring more frequently in Erbitux[®] treated patients compared with controls.

² Adverse events were graded using the NCI CTC, V 2.0.

³ Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

The most frequently reported adverse events in 354 patients treated with Erbitux[®] plus irinotecan in clinical trials were acneiform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grade 3/4 adverse events included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneiform rash (14%).

Additional safety information in patients with colorectal cancer is available in the Cetuximab Investigator Brochure, 2006.

1.5.4 Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of cetuximab included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, and/or cardiac arrest (Erbitux[®] package insert, 2007). Severe (NCI CTC Grade 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient.

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue cetuximab in patients with serious infusion reactions.

1.5.5 Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in clinical trials.¹ Interrupt cetuximab for acute onset or worsening of pulmonary symptoms. Permanently discontinue cetuximab for confirmed ILD.

1.5.6 Dermatologic Toxicity

Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychia inflammation, and infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, cheilitis) occurred in patients receiving cetuximab therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving cetuximab in clinical trials.¹ Severe acneiform rash occurred in 1–17% of patients.

Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving cetuximab for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during cetuximab.

1.5.7 Cetuximab Use in Combination with Radiation and Cisplatin

The safety of cetuximab in combination with radiation therapy and cisplatin has not been established. Death and serious cardiotoxicity were observed in a single-arm trial with cetuximab, radiation therapy, and cisplatin (100 mg/m²) in patients with locally advanced SCCHN (Erbix[®] package insert, 2007). Two of 21 patients died, one as a result of pneumonia and one of an unknown cause. Four patients discontinued treatment due to adverse events. Two of these discontinuations were due to cardiac events.

1.5.8 Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving cetuximab and was severe (NCI-CTC Grade 3 and 4) in 6–17%.¹ The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of cetuximab. Replete electrolytes as necessary.

1.5.9 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. Carefully consider use of cetuximab in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab.

1.6 **Biomarker Studies**

1.6.1 Results of the Radiation Therapy Oncology Group (RTOG) Head and Neck Translational Research Program

A correlative study was carried out using tumor specimens of patients with locally advanced HNSCC enrolled on a phase III trial of the RTOG, 90-03,² and randomized to receive the standard radiotherapy regimen (SFX).¹⁵ This work revealed no correlation between EGFR expression and T-stage, N-stage, AJCC stage grouping, and RPA classes²⁴ (r: -0.07-0.17). However, patients with higher than median EGFR expression were found to have significantly lower overall and disease-free survival rates (p=0.0006 and p=0.0016, respectively) secondary to significantly higher (p=0.0031) local-regional relapse rate. Multivariate analysis showed that EGFR expression was an independent, strong predictor of survival and of local-regional relapse after radiotherapy.

Given the potential for clinical application, a follow up study was undertaken using specimens of patients enrolled on RTOG 90-03 and randomized to receive concomitant boost regimen (AFX-CB) to address the reproducibility of the quantitative immunohistochemical assay, validate the predictive value of EGFR, and test whether EGFR was a mitogenic marker. This study revealed a high reproducibility of the assay and confirmed the absence of correlation between EGFR expression and tumor stage and other clinical prognostic variables (r: -0.20-0.18). The results validated the previous finding that higher tumor EGFR expression predicted for worse survival, disease-free survival, and local-regional relapse with hazard ratios (HR) of 1.97, 2.15, and 3.12, respectively. Combined analysis revealed that the EGFR expression had even a higher impact on the tumor control in the AFX-C regimen, which improved outcome by offsetting tumor proliferation. This finding suggests that EGFR expression is a major indicator for tumor radiosensitivity rather than for tumor clonogen proliferation.

1.6.2 Biomarker Studies: Design and Hypotheses

Given the established track record of the RTOG Head and Neck Translational Program, it is prudent to follow through with similar correlative biomarker studies to test whether EGFR expression level predicts for response to a radiation-cisplatin regimen with or without cetuximab. In addition, the predictive value of the expression of one or more of the down-stream molecules,

i.e., mitogen-activated protein kinase (MAPK), protein kinase AKT, signal transducer and activator (STAT)-3, and protein kinase C (PKC), will be assessed

The primary hypothesis is that EGFR expression level measured by image analysis based quantitative immunohistochemical assay predicts for LRC and survival, i.e., higher EGFR expression predicts for lower local-regional control and poorer survival. The secondary hypothesis is that the effect of EGFR overexpression is mediated predominantly by one of its four down-stream signaling pathways, i.e., PI-3K/AKT.

1.7 Positron Emission Tomography (PET) and CT Imaging

1.7.1 Background and Rationale

Unlike anatomical imaging techniques such as CT and MRI, positron emission tomography (PET) is a “physiological” imaging technique. The most commonly used PET radiotracer for cancer has been [F-18] fluorodeoxyglucose (FDG-PET). Neoplastic cells exploit anaerobic glycolysis more than surrounding normal tissues, due to intracellular signaling abnormalities, high metabolic rate, and poor vascular supply. FDG is converted within these cells to 2-deoxyglucose-6-phosphate, which cannot be utilized by the glycolytic pathway and becomes trapped within the cells.

Pre-treatment PET scans have been incorporated in the staging work up of head and neck cancer patients in an increasing number of centers. A number of groups (reviewed by Vermeersch, et al²⁵) have shown FDG-PET to have higher staging sensitivity and specificity for *de novo* or recurrent head and neck cancer than clinical examination, CT, or MRI. Combined PET/CT imaging has an advantage over PET imaging alone by providing greater sensitivity and more precise anatomic localization of FDG uptake with corresponding CT information.²⁶ Combined scanners are quickly becoming the standard of care in North America, comprising at least 90% of current medical center scanner purchases.

Several clinical studies suggest that highly elevated baseline FDG uptake by primary HNSCC, quantified as the standardized uptake value (SUV), predicts for worse prognosis.²⁷ Schwartz, et al at the University of Washington showed in a cohort of 54 patients that greater than median primary tumor FDG-PET SUV was associated with inferior local control and disease free survival. In thirty-seven patients, Minn, et al²⁸ showed that >median primary FDG SUV predicted for advanced clinical stage and poor overall disease survival. Brun, et al²⁹ obtained FDG-PET images in 47 patients treated with definitive radiotherapy. They found that >median baseline primary tumor FDG SUV predicted for inferior response to radiotherapy, local disease control, and overall survival. Systematic study of FDG-PET in this phase III setting will permit large-scale, multi-institutional validation of these findings.

In previous cooperative group trials, systematic use of planned neck dissection surgery following radiotherapy was generally recommended for patients having N2-3 disease at diagnosis. However, due to lack of controlled studies, no consensus could be reached as to whether patients presenting with N2-3 disease that regresses completely at 6-10 weeks after completion of radio-chemotherapy would benefit from planned neck dissection. Proponents of planned neck dissection argue that nodal relapse is difficult to salvage and uncontrolled neck disease causes morbidity. Opponents of planned neck dissection contend that the neck dissection specimens of complete responders rarely harbor microscopic residual tumor and that isolated nodal relapse rate is low without surgery. Since the cost of neck dissection is not negligible and the procedure is associated with moderate morbidity, it is prudent to assess its need in a prospective trial.

An objective of this trial is to assess the role of FDG-PET/CT scans in determining the overall clinical outcomes and the need for nodal dissection. Few data exist to document the ability of FDG-PET/CT to accurately assess disease status immediately following radiation treatment. One small series examined the accuracy of post-radiotherapy FDG-PET (without CT) for neck assessment prior to planned neck dissection. Yao, et al³⁰ showed a 100% negative predictive value (NPV) in the neck for a series of 12 patients undergoing dissection. The current effort will address the neck staging accuracy of FDG-PET/CT post-radiotherapy by comparing imaging results with corroborative pathology in patients undergoing dissection. It should be noted that the ideal timing of post-treatment FDG-PET/CT imaging following radiotherapy has not been firmly established, but the results of several series indicate that the optimal interval is between six weeks and four months post-treatment.³¹ In the proposed study, an eight to nine week

interval was chosen, since dissection is technically easiest when performed within ten weeks of radiotherapy. Demonstration of accurate assessment of neck disease radioresponse FDG-PET/CT within this specific time interval would therefore ensure optimal clinical relevance.

1.7.2 PET/CT Imaging: Design and Hypotheses

All patients eligible for entry onto this trial will be eligible for PET/CT imaging analysis. A pre-treatment FDG-PET/CT scan is highly recommended for all patients. A post-treatment FDG-PET/CT scan is recommended 8-9 weeks after completion of treatment (in addition to the required CT scan or MRI) before any nodal dissection is performed for the following patients: The following patients will be assessed 8-9 weeks post-treatment with CT scan or MRI: All patients with N2a, N2b, and N3 disease and patients with ≤ 3 cm nodes on one side (N1) or both sides (a subset of N2c) with questionable neck findings. The pre- and post-treatment PET/CT scan findings will be correlated with the histologic findings of neck dissection specimens (pathologic negative versus positive) and tumor outcome endpoints.

We hypothesize that pre-treatment $SUV_{max} > \text{median}$ predicts for poor clinical outcome, that negative post-treatment PET in patients with N2-3 disease predicts for high pathologic complete response rate ($> 85\%$) in the neck, and that negative post-treatment PET in patients with N2-3 disease predicts for a low overall nodal relapse rate ($\leq 10\%$).

1.8 Quality of Life Evaluation and Health Utilities

1.8.1 It is now well recognized that comprehensive treatment evaluation must include assessment of the patient's function and quality of life. In HNSCC, both the disease and its treatment have the potential to significantly impact key functions, such as eating, speaking, and socializing. Most recently, investigators have documented the effects of intensive chemoradiotherapy regimens. While these treatments minimize surgery and consequently disfigurement, they have other significant immediate, delayed and potentially long-term side effects that may profoundly influence quality of life (QOL).

Radiosensitizing chemotherapy given in combination with radiation increases the severity of severe mucositis, sticky saliva, pain, dry mouth, hoarseness, skin irritation and difficulties in swallowing and tasting, with many of these symptoms persisting years after treatment completion.³²⁻³⁸ For example, in studies of patients on regimens similar to those used in the current protocol, List and colleagues observed that on treatment, up to three-quarters of patients reported moderate to severe problems with dry mouth, swallowing, tasting, sticky saliva and hoarse voice. While there was some improvement in most symptoms over 12 months, there was little change in dry mouth, and over a third of patients continued to report difficulties with sticky saliva and swallowing. In addition, patients' diets remained extremely restricted with a half to three-quarters on a soft food diet at 12 months.^{36,37,40,41} Longer follow-up (2-4 years post-treatment) of these patients suggested some continued recovery in ability to eat a full range of foods and comfort in eating with others, although a third still had significant restrictions in diet and there was little change in other QOL or symptom domains after twelve months.⁴⁰ Recent longer term follow up of a second cohort of patients treated with intensive chemoradiotherapy has shown virtually no change in any QOL dimension, report of symptoms, or performance status from 12 months to 2-4 years post-treatment completion.⁴²

There are to date, very few, if any data on the impact of adding novel biologic agents, such as cetuximab, to these already intensive chemoradiotherapy regimens. While such agents might be expected to add little toxicity, empirical documentation of the effects is critical. As more and more trials are beginning to use, and often times, *add* these new biologic agents, it is important to demonstrate that these agents do not significantly worsen either QOL or performance/function. Second, there is also very limited data on the longer-term outcomes of patients on these regimens. As described above, while some small single arm cohort studies have suggested relatively long term continued impairment (and even worsening) in some areas, examination of the late effects in a large study is warranted. This study will be one of the first to prospectively and systematically assess QOL and performance up to 5 years post-treatment.

The EuroQol (EQ-5D) is more and more frequently being employed in cooperative group studies for cost utility analysis. It also is of interest to understand the relationship between the EQ-5D and other QOL measures, such as the Functional Assessment of Cancer Therapy (FACT). If the EQ-5D is highly correlated with the FACT, depending on the specific questions of interest, it might prove to be an effective short form for collecting both QOL and utility data.

Thus, the current study will employ the FACT-H&N, the EQ-5D, and the Performance Status Scale for Head and Neck Cancer (PSS-HN).

1.8.2 The Performance Status Scale for Head and Neck Cancer (PSS-HN)

The PSS-HN is a clinician rated instrument consisting of assessment of three functions (subscales): Normalcy of Diet, Eating in Public, and Understandability of Speech. The interviewer rates the patient on each scale based on the patient's responses to targeted questions. Scores on each subscale range from 0-100, with higher scores indicating better performance. It has been demonstrated to be reliable and valid in head and neck cancer patients.^{39,43} The site research nurse or clinical research associate (CRA) will determine the score on each of the subscales by performing a clinical evaluation and unstructured interview format. The PSS-HN takes approximately 5 minutes to complete. Note: The PSS-HN has been translated into 12 languages and will be made available to institutions by Dr. List at no charge.

- The Normalcy of Diet subscale assesses the degree to which a patient is able to eat a normal diet. Ten food 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 a higher level of function. Scores are computed by assessing the highest-ranking food the patient is able to eat.
- The Eating in Public subscale was designed to assess comfort in socializing, specifically the degree to which the patient eats in the presence of others. There are five categories describing the patients' eating patterns. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. Scores are computed based upon patient's report of with whom he/she eats and in what type of setting.
- The Understandability of Speech subscale is a five-item scale, which assesses how well the patient can be understood by others, regardless of voice quality or nature of speech. Scores range from 0-100 with those scores closer to 100 representing a higher level of function. The scores are computed by assessing the degree to which the observer is able to understand the patient's speech.

In addition, sites will document feeding tube status, dentition, and presence or absence of a tracheostomy on case report forms.

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

The FACT-H&N is a multidimensional, self-report QOL instrument specifically designed and validated for use with head and neck cancer patients. The core scale (FACT-G) consists of 27 core items assessing patient well-being in four areas: Physical, Social/Family, Emotional, and Functional. Items are rated on a five-point scale: 0-"not at all", 1- "a little bit", 2-"somewhat", 3-"quite a bit" and 4-"very much". This core questionnaire is supplemented with a twelve-item head and neck subscale targeting head and neck related symptoms and side effects.⁴⁴⁻⁴⁵ Overall QOL is the sum of the core items of the FACT-G. The head and neck subscale is not included in overall summary score but will be looked at separately. Note: The FACT-H&N has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at <http://www.facit.org/translation/licensure.aspx>.

1.8.4 The EuroQol (EQ-5D)

Although developed in Europe, the Multi-Attribute Health Utility Measurement using the EuroQol (EQ-5D) is an instrument that will be used in this study as a global QOL score and for cost-utility analysis comparing the two treatment arms in the future. It has been used in the United States and Canada.⁴⁶⁻⁴⁹ However, there are no published reports of use of the EQ-5D in the evaluation of patients with locally head and neck cancer; however, Trippoli, et al. compared the EQ-5D to the 36-item Short Form Health Survey (SF-36) in assessing QOL in patients with non-small cell lung cancer.⁵⁰ They found strong correlation in the measurements produced by the two forms. Conner-Spady, et al. found the EQ-5D to be responsive to clinically large changes associated in forty women with breast cancer undergoing high dose chemotherapy and bone marrow transplantation.

The EQ-5D is a two-part questionnaire that the patient can complete in approximately 5 minutes.⁵¹ The EQ-5D has been translated into 33 languages with the available translations listed on the EQ-5D web site, <http://www.euroqol.org>. The first part of the EQ-5D consists of five items covering five dimensions: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on three levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the leveled responses to the five dimensions, generating 243 (3 to the 5th) health states to

which unconsciousness and death are added.⁵² The second part is a visual analogue scale (VAS) valuing current health state, measured on a ten-point interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. Both the five-item index score and the VAS score are transformed into a utility score between 0 "Worst health state" and 1 "Best health state". The index score or the VAS will be utilized and entered into the cost-utility equation, depending on the health state(s) of interest.⁵³

The EQ-5D data collection form and the FACT-H&N will be completed by the patient, while the PSS-HN will be completed by site research nurse or CRA. The PSS-HN and the EQ-5D will be administered pretreatment, during one of the last 2 weeks of treatment, at 3 and 12 months from start of treatment, then annually for years 2-5. The FACT-HN will be administered pretreatment, and annually in years 1 and 5.

2.0 OBJECTIVES

2.1 Primary Objective (8/25/08)

Evaluate whether the addition of cetuximab to a concurrent radiation-cisplatin regimen will improve progression-free survival in patients with locally advanced squamous cell carcinoma (SCC) of the oropharynx, hypopharynx, or larynx;

2.2 Secondary Objectives (8/25/08)

- 2.2.1** Assess the impact of the addition of cetuximab to a concurrent radiation-cisplatin regimen on the following:
- Overall survival of patients with locally advanced squamous cell carcinoma (SCC) of the oropharynx, hypopharynx, or larynx;
 - Local-regional control of patients with locally advanced squamous cell carcinoma (SCC) of the oropharynx, hypopharynx, or larynx;
 - Acute and late adverse events;
 - Quality of life and health utilities;
- 2.2.2** Correlate the expression of EGFR and its down-stream molecules and pre-treatment PET scan findings with outcome in patients participating in this component of the trial;
- 2.2.3** Correlate pre-treatment PET scan findings with progression-free survival, overall survival, and local-regional control in patients participating in this component of the trial;
- 2.2.4** Correlate post-treatment PET scan findings with nodal response and nodal relapse in patients participating in this component of the trial.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (8/17/11)

- 3.1.1** Pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx;
- 3.1.2** Selected stage III or IV disease (T2N2-3M0, T3-4 any N M0); Note: Patients with T1, any N, or T2N1 tumors are not eligible.
- 3.1.3** Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:
- 3.1.3.1** History/physical examination within 4 weeks prior to registration, including assessment of weight and weight loss in past 6 months and an examination by a Medical Oncologist;
 - 3.1.3.2** Chest x-ray (or Chest CT scan or PET/CT scan) within 6 weeks prior to registration; see Section 6.11 for details of PET scans.
 - 3.1.3.3** CT scan or MRI of the head and neck (of the primary tumor and neck nodes) or PET/CT scan within 6 weeks prior to registration; see Section 6.11 for details of PET scans. **Note:** A PET/CT can only be used instead of a CT scan or MRI if the CT is a high quality scan with contrast.
 - 3.1.3.4** Left ejection fraction determined by ECHO and/or MUGA technique within 12 weeks of registration;
- 3.1.4** Zubrod Performance Status 0-1;
- 3.1.5** Age \geq 18;
- 3.1.6** Adequate bone marrow function, defined as follows:
- 3.1.6.1** Absolute neutrophil count (ANC) \geq 1,800 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study;

- 3.1.6.2 Platelets $\geq 100,000$ cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study;
- 3.1.6.3 Hemoglobin ≥ 8.0 g/dl based upon CBC/differential obtained within 2 weeks prior to registration on study (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:
- 3.1.7.1 Bilirubin ≤ 1.5 mg/dl within 2 weeks prior to registration on study; For patients with Gilbert's disease as the sole cause of elevated bilirubin, please contact the PI, Dr. Ang.
- 3.1.7.2 AST or ALT $\leq 2x$ the upper limit of normal within 2 weeks prior to registration on study;
- 3.1.8 Adequate renal function, defined as follows:
- 3.1.8.1 Serum creatinine ≤ 1.5 mg/dl within 2 weeks prior to registration
- 3.1.8.2 Creatinine clearance (CC) ≥ 50 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

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

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$

- 3.1.9 Pregnancy test within 2 weeks prior to registration for women of childbearing potential;
- 3.1.10 Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 60 days following the last study treatment);
- 3.1.11 Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (8/25/08)

- 3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years;
- 3.2.2 Patients with simultaneous primaries or bilateral tumors are excluded.
- 3.2.3 Gross total excision (e.g., by tonsillectomy) of the primary tumor; however, partial removal of the tumor to alleviate an impending airway obstruction does not make the patient ineligible.
- 3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
- 3.2.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- 3.2.6 Primary site of tumor of oral cavity, nasopharynx, sinuses, or salivary glands;
- 3.2.7 Initial surgical treatment, excluding diagnostic biopsy of the primary site or nodal sampling of neck disease; radical or modified neck dissection is not permitted.
- 3.2.8 Severe, active co-morbidity, defined as follows:
- 3.2.8.1 Current uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, recent myocardial infarction (within prior 6 months), uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction;
- 3.2.8.2 Left Ventricular Ejection Fraction $< 45\%$;
- 3.2.8.3 Transmural myocardial infarction within the last 6 months;
- 3.2.8.4 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- 3.2.8.5 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- 3.2.8.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- 3.2.8.7 Any uncontrolled condition, which in the opinion of the investigator, would interfere in the safe and timely completion of study procedures;
- 3.2.8.8 CTCAE, v. 3.0 grade 3-4 electrolyte abnormalities:
 - Calcium < 7 mg/dl or > 12.5 mg/dl;
 - Glucose < 40 mg/dl or > 250 mg/dl;
 - Magnesium < 0.9 mg/dl or > 3 mg/dl;
 - Potassium < 3 mmol/L or > 6 mmol/L;
 - Sodium < 130 mmol/L or > 155 mmol/L

- 3.2.9 Pregnant or lactating women 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.
- 3.2.10 Prior allergic reaction to the study drug(s) involved in this protocol;
- 3.2.11 Prior therapy that specifically and directly targets the EGFR pathway;
- 3.2.12 Prior severe infusion reaction to a monoclonal antibody.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Additional Mandatory Pre-treatment Evaluations/Interventions

Not applicable for this study.

4.2 Additional Highly Recommended Pre-treatment Evaluations/Interventions (8/25/08)

The following pre-treatment evaluations/interventions are not required but are highly recommended:

- 4.2.1 PET/CT scan within 6 weeks prior to registration; (see Section 6.11 for details of PET/CT scans);
- 4.2.2 Dental evaluation and, if applicable, prophylaxis within 12 weeks prior to treatment (see Appendix VI);
- 4.2.3 Serum albumin within 2 weeks prior to treatment;
- 4.2.4 Baseline audiogram within 12 weeks prior to registration;
- 4.2.5 Nutritional evaluation for a prophylactic gastrostomy (PEG) tube placement anytime prior to treatment; Note: In RTOG 99-14, a completed phase II trial assessing the feasibility of combining accelerated fractionation by concomitant boost with cisplatin, 79% of patients who did not have prophylactic PEG placement prior to treatment required placement of PEG during treatment.

5.0 REGISTRATION PROCEDURES (1/26/16)

NOTE: It is mandatory the treating physician determine the radiation therapy technique (3D-CRT vs. IMRT) to be used prior to the site registering the patient.

5.1 Pre-Registration Requirements for 3D-CRT Treatment Approach

Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3D-CRT Quality Assurance Guidelines may enter patients to this study.

- 5.1.1 The 3D Questionnaire must be sent to the Washington University Image-Guided Center (ITC) for review prior to entering any cases. This questionnaire (one per institution) can be accessed on the ITC web site, <http://itc.wustl.edu>. Upon review and successful completion of “Dry-Run” or “Benchmark” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3D CRT Head and Neck trials may enroll patients on this study without further credentialing by the ITC.

5.2 Pre-Registration Requirements for IMRT Treatment Approach

In order to utilize IMRT, the institution must have met technology requirements and have provided the baseline physics information described on the Advanced Technology Consortium (ATC) web site, <http://atc.wustl.edu>. As it pertains to this study, the ATC includes the Image-Guided Therapy Center (ITC) at Washington University; the Radiological Physics Center (RPC) at MD Anderson Cancer Center; and, St. Louis and RTOG RT Quality Assurance.

Credentialing by ATC for participation in RTOG IMRT studies is mandatory for treatment of patients with IMRT. Therefore, institutions that have NOT been credentialed to participate in RTOG 0022 or RTOG 0225 MUST apply for IMRT credentialing as described in Section 5.2.1.

5.2.1 IMRT Certification Process (For institutions not previously certified for RTOG head and neck – specific IMRT studies)

- 5.2.1.1 First, the institution or investigator anticipating the use of IMRT on this study must complete a new IMRT Facility Questionnaire (see <http://atc.wustl.edu>). The IMRT Facility Questionnaire requests information regarding the training and experience of the IMRT team; IMRT treatment planning and treatment equipment; and in-house QA procedures.
- 5.2.1.2 Next, the institution must successfully complete an IMRT “dry-run” or benchmark case with the ITC. This will require that the institution set up an FTP account for digital data submission by contacting the ITC (itc@castor.wustl.edu).

5.2.1.3 Finally, an IMRT phantom study with the Radiological Physics Center (RPC) at MD Anderson Cancer Center must be successfully completed (if the institution has not previously met this credentialing requirement on another RTOG IMRT study). Instructions for requesting and irradiating the phantom are available at the RPC web site, <http://rpc.mdanderson.org/rpc/> by selecting “Credentialing” and “RTOG”.

5.3 PET Credentialing (For institutions participating in the PET component of the study) [8/25/08]

5.3.1 The PET Core Laboratory will collect PET scans for the following patient population: Patients with N2a, N2b, N2c (with right or left side equal to N2a or N2b), and N3. The PET Core Laboratory will collect at least one test case from each site prior to enrollment of the site’s first patient. The PET Core Laboratory will evaluate and resolve issues associated with image transfer capabilities and image set compatibility.

5.3.2 All sites must access the application and instructions for submitting a single test case on the ACRIN web site at <http://www.acrin.org/petcorelab.html>. Sites should check the “not applicable” box for the uniform phantom information and test case #2. Sites will submit the application via email or fax, 215-923-1737.

5.3.3 **Note:** When a site has completed the application and is ready to submit a test case, the site will e-mail the PET Core Laboratory at petcorelab@phila.acr.org to confirm image file compatibility and method of submission best suited to the site’s particular PET/CT equipment (e.g., electronics, media, etc.). The institution should expect an e-mail response from the PET Core Laboratory within 3 business days.

5.3.4 **Canadian sites** participating in FDG-PET in studies must enroll patients in the Health Canada Safety Awareness Protocol or another Health Canada approved clinical study for FDG-PET and provide a copy of the institution’s “No Objection Letter” for that study to RTOG with study regulatory documents.

5.4 Regulatory Pre-Registration Requirements (8/25/08)

5.4.1 **U.S. sites and Canadian sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English Version)
- IRB/REB assurance number

5.4.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

5.4.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.4.2.2 Note: International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form_1-2007.pdf.

Approved international sites fax copies of the documentation below, along with the completed International REC Certification Form, http://www.rtog.org/pdf_forms.html?members/forms_Certification.doc to RTOG Headquarters (215-574-0300) prior to registration of the institution’s first case:

- REC approval letter;
- Informed Consent (English Version);
- Federalwide Assurance (FWA) number.

5.5 Registration

5.5.1 Online Registration (8/17/11)

Patients can be registered only after eligibility criteria are met.

Institutions must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The Investigator must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- The institution must complete the Password Authorization Form (<http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219>), and fax it

to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (<http://www.rtog.org>), going to "Data Center Login" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY/FUNCTIONAL IMAGING (8/25/08)

Note: Radiotherapy can be given with 3D conformal (3D-CRT) or with Intensity Modulated RT (IMRT) techniques; however, the chosen modality must be used for the entire course of treatment. See pre-registration requirements for IMRT in Section 5.1. Patients will be stratified by the radiation technique used. It also should be noted that IMRT generally has little advantage for patients with laryngeal carcinoma with no demonstrable or limited nodal disease, as it is not necessary to irradiate whole parotid glands in these patients.

Missed treatments due to holidays or logistic reasons can be compensated for by delivering additional BID treatments with a minimum interfraction interval of 6 hours or by treating on a Saturday or Sunday.

It is highly recommended that dosimetry information be submitted digitally; see Section 12.2. Sites unable to submit digitally will contact RTOG Headquarters, RTQA Department, 215-574-3219.

6.1 Dose Specifications (See Section 6.4 for definition of target volumes.) [6/1/06]

6.1.1 3D Radiotherapy

6.1.1.1 The initial target volume encompassing the gross and subclinical disease sites will receive 1.8 Gy per fraction, five fractions a week to 54 Gy in 30 fractions over 6 weeks. The boost volume covering gross tumor and clinically/radiologically involved nodes will receive boost irradiation of 1.5 Gy/Fx delivered as a second daily fraction (with at least a six-hour interval) for a total of 12 treatment days (18 Gy total). The boost irradiation should commence during week 4 of the large field irradiation at the latest at 32.4 Gy/18 Fx of the initial target volume (i.e., latter part of week 4). All treatment times must be documented on the treatment record. The primary tumor and clinically/radiologically-involved nodes (PTV_{HD}) will thus receive 72 Gy in 42 fractions over 6 weeks, and uninvolved upper neck nodes (PTV_{ED}) will receive an elective dose of 54 Gy in 6 weeks.

6.1.1.2 When desired, PTV_{INT} can receive a total dose of 63 Gy, i.e., by delivering 9 fractions of 1.5 Gy to PTV_{INT} before making a second cone down to PTV_{HD}.

6.1.1.3 Clinically/radiologically negative posterior neck should receive a minimum dose of 50.4 Gy at 3 cm.

6.1.1.4 The uninvolved lower neck nodes will receive 1.8 Gy per fraction at 3-cm depth to a total dose of 50.4 Gy in 28 fractions in 5.6 weeks through a matching AP or AP/PA lower neck field. Involved lower neck nodes can receive a total dose of up to 69-72 Gy when it is possible to limit the dose to the brachial plexus to ≤ 60 Gy. If this is not possible, the total dose can be limited to 60 Gy, in which case, neck dissection is mandatory regardless of the response.

6.1.2 IMRT

6.1.2.1 IMRT will be given in 35 fractions over 6 weeks, which requires delivery of 6 fractions per week during 5 of the 6 treatment weeks. The sixth fraction can be delivered either on Saturday or as a second daily fraction, with at least a six-hour interfraction interval, on one of the weekdays (see Section 1.2.3). The primary tumor and involved nodes (PTV_{HD}) will receive 2 Gy per fractions and subclinical disease sites (PTV_{ED}) will receive 1.6 Gy per fraction. The total doses will thus be 70 Gy and 56 Gy, respectively.

6.1.2.2 When desired, CTV_{INT} can receive 1.7 - 1.8 Gy per fractions to a total dose of 59.5 - 63 Gy.

6.1.2.3 It is recommended that in patients with oropharyngeal cancer, the low neck or supraclavicular regions be treated with isocentric matching AP or AP/PA fields, with larynx block, matched to IMRT portals just above the arytenoids. This technique yields the most efficient sparing of the lower laryngeal structures and the esophageal inlet. The dose will be 2.0 Gy per fraction at 3-cm depth to a total dose of 50 Gy in 25 fractions in 5 weeks. Involved lower neck nodes can receive a total dose of up to 66-70 Gy when it is possible to limit the dose to the brachial plexus to ≤ 60 Gy. If this is not possible, the total dose can be limited to 60 Gy, in which case, neck dissection is mandatory regardless of the response. If the use of an isocentric match technique results in an insufficient coverage margin for the primary tumor (e.g., involvement of the vallecula), then the primary tumor and all nodal volumes should be treated using IMRT.

6.1.2.4 All plans must be normalized such that 95% of the volume of the PTV_{HD} is covered with the prescription dose of 70Gy. Additionally:

- No more than 20% of the PTV_{HD} should receive $\geq 110\%$ of the prescribed dose;
- No more than 1% of any PTV_{HD} or PTV_{ED} should receive $\leq 93\%$ of the prescribed dose;
- No more than 1% or 1 cc of the tissue outside the PTVs should receive $\geq 110\%$ of the prescribed dose to the PTV_{HD}.

6.2 Technical Factors

6.2.1 Photon beams of ≥ 4 MV and/or electron beams from 6-25 MeV are required.

6.2.2 Treatment distance must be $\geq \square 80$ cm SAD for isocentric techniques.

6.2.3 IMRT: Megavoltage equipment capable of delivering intensity modulated beams using a step-and-shoot technique with a multileaf collimator or using dynamically moving leaves. Additionally, a binary multileaf collimator or tomotherapy can be used to modulate the beam. Other techniques, e.g. physical compensators, are acceptable as long as dose specifications and constraints are satisfied.

6.3 Immobilization, Simulation, and Localization

6.3.1 Immobilization

Although a thermoplastic head mask may suffice for conformal radiotherapy, the use of a head and shoulder mask is recommended for better reproducibility. The use of a thermoplastic head and shoulder mask is mandatory for IMRT. The margins used for expansion of the CTVs to PTVs are discussed in Section 6.4.4.

6.3.2 Planning CT scan

A treatment planning CT scan is mandatory for defining target volumes (see Section 6.4). CT scan thickness should be at most 0.5 cm for conformal radiotherapy or 0.3 cm for IMRT. The treatment planning CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be include in the CT scan.

6.4 Treatment Planning/Target Volumes

6.4.1 CT based treatment planning is mandatory for every patient. For 3-D radiotherapy, isodose distributions (composite of all fields) in representative transverse planes through the center of the primary and involved nodal volumes are required. For IMRT, the treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV (CTV with a 5 mm margin) and critical normal structures. An "inverse" planning with computerized optimization should be used.

6.4.2 Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when

applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

6.4.3 Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV₁ represents GTV plus a margin of generally 1 cm and CTV₂ represents GTV with a margin of about 2 cm and nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g., 59-63 Gy) to a volume (CTV_{INT}) that is slightly larger than CTV₁. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues.

(The guidelines for CT based delineation of lymph node levels can be found at the RTOG web site: <http://www.rtog.org/hnatlas/main.html>).

6.4.4 **(6/1/06) Planning Target Volume (PTV_{HD} and PTV_{ED})** represents an additional margin around CTV₁ and CTV₂ to compensate for the variability of treatment set up and internal organ motion. A minimum margin of 0.5 cm around the CTV is required in all directions to define each respective PTV, except for situations in which the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously. A minimum margin of 3 mm can be used in all directions as long as an institution implements a study to define the appropriate magnitude of the uncertain components of the PTV. NOTE: The results of this study must be forwarded to the Image-Guided Therapy Center (ITC) [see Section 12.2.1] for approval before reduced margins can be used. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

6.4.5 The density corrected dose distributions shall be calculated and the dose prescription is to be based on a dose distribution corrected for heterogeneities.

6.5 Critical Structures (6/1/06)

6.5.1 Spinal cord: A margin of 0.5-1cm around the spinal cord may be added to create a Planning Organ at Risk Volume (PRV). The dose to any point within the spinal cord should not exceed 48 Gy to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube).

6.5.2 Parotid glands: When using IMRT, the objective is to limit the mean dose to at least one gland to ≤ 26 Gy; alternatively at least 20 cc of the combined volume of both parotid glands to < 20 Gy or at least 50% of one gland to <30 Gy.

6.5.3 Glottic larynx: In patients with oropharyngeal carcinoma without extension to the larynx, placing the isocenter just above the arytenoids and irradiating the lower neck with an anterior matching field with larynx block can minimize the dose to the glottic larynx. Alternatively, the dose to the larynx should be kept <45 Gy whenever feasible.

6.5.4 Brachial plexus: The dose to the brachial plexus must be limited to ≤ 60 Gy in patients with level IV node(s).

6.5.5 Unspecified tissue outside the target volumes: ≤ 100% of the dose prescribed to CTV₁. No more than 5% of the non-target tissue can receive greater than the dose to CTV₁.

6.6 Documentation Requirements

6.6.1 Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy.

6.6.2 Weekly verification or orthogonal images are required.

6.6.3 Isodose plans for 3-D radiotherapy and IMRT and DVHs of GTV, CTVs, and critical normal structures for IMRT.

6.7 Compliance Criteria (8/25/08)

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). **Missed treatments due to holidays or logistic reasons can be compensated for by delivering additional BID treatments with a minimum interfraction interval of 6 hours or by treating on a Saturday or Sunday.**

Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and ideally, should not exceed 5 treatment days at a time and 10 treatment days in total. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Plan normalization should provide coverage of 95% of the volume of the PTV of the GTV (PTV_{HD}) with the prescribed dose of 69.96 Gy. No more than 1% of the volume of the PTV_{HD} should receive less than 64 Gy. Additionally, no more than 20% of the PTV of the GTV should receive more than 76 Gy, and no more than 5% of this volume should receive more than 79 Gy. These numbers describe the DVH shown in the figure below with the diamond shaped symbols.

Obviously, better DVHs (i.e., with smaller amounts of either underdose or overdose) are preferable.

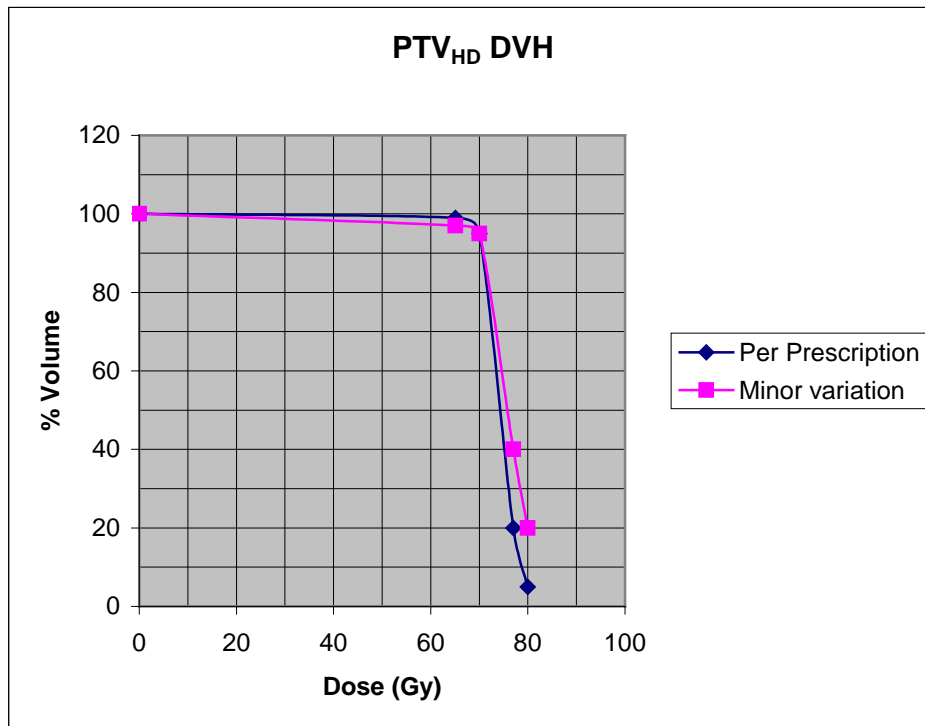
A region of “minor deviation” is also defined in the figure as the DVH represented by the square symbols. Deviations of this magnitude are not desirable, but will be deemed acceptable. That is, a DVH with at least 97% of the volume receiving 64 Gy is acceptable as a minor deviation. Additionally, as a minor deviation for the overdose region, as much as 40% of the PTV_{HD} volume can receive 76 Gy and up to 20% of this volume can receive 79 Gy. DVHs for the PTV_{HD} falling outside the limits for a minor deviation (i.e., increased under or overdose) will be scored as unacceptable “major deviations.”

The DVHs for the other target regions should deliver the prescribed dose, as much as possible, to at least 95% of the volume of that PTV.

Overall Evaluation	Radiotherapy Prolongation*	Total Dose Variation 3-D RT	Total Dose Variation IMRT**
Per Protocol	≤ 5 days	≤ 4% deviation from prescribed dose	See parameters in the figure and table below
Minor Variation (Acceptable)	6-10 days	> 4% to ≤ 9%	See parameters in the figure and table below
Major Deviation (Unacceptable)	> 10 days	> 9%	Deviations greater than presented in the figure/table below

*These criteria are to be reassessed based on the results of the recently completed RTOG trial, 0129.

****Note:** For IMRT, prescription dose is the isodose surface that encompasses at least 95% of the planning target volume (PTV) with no more than 20% of any PTV_{HD} receiving ≥ 110% of the prescribed dose and no more than 1% of any PTV_{HD} and PTV_{ED} receiving ≤ 93% of the prescribed dose.



Dose (Gy)	Per Prescription	Minor variation
65	99%	97%
70	95%	95%
77	20%	40%
80	5%	20%

6.8 R.T. Quality Assurance Reviews (2/2/06)

The Principal Investigator, Kian Ang, M.D. and the Radiation Oncology Co-Chairs, David Rosenthal, M.D. and Phuc Felix Nguyen-Tân, M.D., will remotely perform RT Quality Assurance Review after complete data for the first 25 cases enrolled have been received by the ITC (see section 12.0). Drs. Ang, Rosenthal, and Nguyen-Tân will perform remote reviews on subsequent blocks of 25 cases after complete data for these cases have been received by the ITC. 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 have been received, whichever occurs first.

6.9 Radiation Adverse Events (12/9/10)

As of January 1, 2011, this study will utilize the Common Terminology Criteria for Adverse Events (CTCAE), version 4 for grading of all adverse events reported via AdEERS; all RTOG case report forms will continue to use CTCAE, v. 3.0. A copy of the CTCAE, v. 4 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>) or the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>). All appropriate treatment areas should have access to a copy of the CTCAE, v. 4.

Grade 3-4 therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

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

6.10 Radiation Adverse Event Reporting

See AdEERS Expedited Reporting Requirements in Section 7.7.

6.11 Functional Imaging: FDG-PET/CT Imaging (1/8/07)

A pre-treatment PET/CT scan is highly recommended for all patients on study. A post-treatment FDG-PET/CT scan is recommended 8-9 weeks after completion of treatment before any nodal dissection is performed for the following patients: All patients with N2a, N2b, and N3 disease and patients with ≤ 3 cm nodes on one side (N1) or both sides (a subset of N2c) with questionable neck findings. **Note:** If the CT portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest.

Note: For institutions participating in the PET component of the study, **PET CREDENTIALING IS REQUIRED BEFORE REGISTERING A PATIENT.** See Section 5.3 for details of PET credentialing.

Canadian sites participating in FDG-PET in studies must enroll patients in the Health Canada Safety Awareness Protocol or another Health Canada approved clinical study for FDG-PET and provide a copy of the institution's "No Objection Letter" for that study to RTOG with study regulatory documents.

6.11.1 *PET Image and Scanner Compatibility Requirements*

All imaging must be conducted on a combined PET/CT scanner with full ring PET and four slice or greater multi-detector CT. The scanner should be operating in high-sensitivity 2D mode, if

available. 3D mode is permissible for patients imaged on combined PET/CT scanners without a 2D mode.

Note: Scanners with less than four slice capability may be acceptable, but these scanners must be reviewed by the PET Co-Chair, David Schwartz, MD, on a case-by-case basis. Sites should contact Dr. Schwartz at 713-563-2381.

6.11.2 Pre-FDG Injection: Patient Preparation

Height and weight will be recorded before each PET scan. Patients will observe a four to six-hour fasting period prior to FDG injection. Patients with a history of medically controlled diabetes will be counseled to check serial blood sugars prior to each scan to ensure that values average below 200 mg/dL. For these patients, a blood sugar measurement will be performed after a six-hour fast to gauge fasting tolerance. Serum glucose concentration will be measured for all patients prior to scanning and must be less than 200 mg/dL to proceed to imaging.

6.11.3 FDG Injection

A dose of 10-20 mCi of ¹⁸F-FDG will be infused intravenously. As per best clinical practice, administration of 0.5 mg of alprazolam 5-15 minutes prior to FDG injection to relax the patient and to reduce neck ¹⁸F-FDG muscle uptake should be considered. The patient will lie quietly for at least 30 minutes, and scanning will begin 50-70 minutes following the FDG injection.

6.11.4 PET Imaging

Imaging must encompass the vertex of the head down through the entire pelvis. The recommended imaging protocol incorporates two discrete phases, and is as follows: During the first phase, head and neck scanning will be performed with full neck extension. The patient will initially be imaged with a 120 KeV/300 mA, 0.5-second detector rotation time ("high mA") CT scan with intravenous contrast (100 cc contrast bolus administered at 1.5 cc/second, with a 50 second scan delay and with the scan started inferiorly, moving cranially), followed by a 120 KeV/80 mA, 0.8-second detector rotation time ("low mA") CT scan for PET attenuation correction, followed lastly by PET scanning. Alternatively, an initial low mA CT scan may be performed for attenuation correction, followed by a high mA CT scan with intravenous contrast. Standard manufacturer recommendations for specific low and high mA CT scanning parameters can be substituted for those listed above. Two fields of view (approximately 15 cm) will be used for head and neck PET imaging. Patients then will be allowed to rest their necks for 1-2 minutes. For the second phase of imaging, the neck will be shifted into neutral position, and the remainder of the body will be surveyed per routine local institutional protocol with arms raised above the head to allow for optimal thoracic and upper abdominal imaging. At least four to five PET fields of view will be used for this phase. Images will be reconstructed via the filtering algorithm provided by the scanner manufacturer.

6.11.5 Assessment at 8-9 Weeks Post-Treatment (1/8/07)

A post-treatment FDG-PET/CT scan is recommended 8-9 weeks after completion of treatment before any nodal dissection is performed for the following patients: All patients with N2a, N2b, and N3 disease and patients with ≤ 3 cm nodes on one side (N1) or both sides (a subset of N2c) with questionable neck findings. The post-treatment PET/CT scan should be done on the same scanner, as specified above. It is anticipated that most patients with stage N2-3 disease at presentation and all with residual adenopathy will undergo neck dissection. Surgery should take place within 2 weeks of post-treatment FDG-PET/CT imaging (9-10 weeks post-radiotherapy). Bilateral neck dissection, if necessary, can take place in two stages. See Section 8.1 for details of surgery. **Note:** If the CT portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest.

6.11.6 Maximum Standardized Uptake Value (SUVmax)

SUV normalized by specific injected dose and patient weight will be calculated using vendor-provided software. Maximum standardized uptake value (SUVmax) will be defined as (tissue activity) ($\mu\text{Ci/ml}$)/(injected dose (mCi)/(patient weight [kg]) within the voxel having the highest activity within a given region of interest (ROI). This will be determined for ROIs within the primary tumor and within the involved cervical node with highest FDG uptake. It is strongly recommended that an experienced head and neck radiologist assist with delineation of tumor volumes.

Detection of primary and nodal disease by FDG-PET/CT will not be classified according to an FDG SUV threshold. Instead, malignancy will be qualitatively determined by FDG uptake greater than surrounding normal soft tissue within a CT-delineated anatomic (primary disease or nodal) abnormality. FDG-PET ROIs delineation will be generated on the PET/CT scanner

workstation. Each ROI must encompass the entire FDG-avid lesion of interest, with boundaries guided by CT delineation. Maximum standardized uptake values (SUVmax) for primary tumor and nodal disease will be recorded for these manually generated ROIs.

6.11.7 Image Submission to PET Core Laboratory (8/25/08)

All images to be collected from PET/CT are to be sent to the PET Core Laboratory of the American College of Radiology Imaging Network (ACRIN) [see Section 12.3]. Images must be sent in DICOM digital format. Hardcopy films will not be accepted for this study.

The PET Core Laboratory can provide software that allows for electronic transmission and de-identification of images (images that have been scrubbed of all participant identifiers). To obtain the images submission software, sites will e-mail Triad-Support@phila.acr.org or call 215-940-8840.

In the event electronic transmission can not be attained, images can be sent on media. For submission on media, the media type must be limited to MOD, CD, DVD-RW or DVD-RAM. Media will be returned to the institution as soon as possible.

The header recorded on DICOM formatted image data often contains information identifying the participant by name. These identifiers must be scrubbed and the images labeled with RTOG protocol number and the patient's case number before the images are transferred to ACRIN. If using ACRIN software, header scrubbing is accomplished automatically.

For further information concerning submission of PET/CT images, sites will e-mail the PET Core Laboratory at petcorelab@phila.acr.org. Institutions should expect an e-mail response to questions from the Pet Core Laboratory within 3 business days.

6.11.8 Functional Imaging Adverse Events

There is a negligible risk of exposure to radiation from PET imaging. Less likely adverse events include potential bruising or bleeding and/or infection at the site of the injection of the tracer. Serious allergic reactions to the tracer are rare.

6.11.9 Function Imaging Adverse Event Reporting

See AdEERS Expedited Reporting Requirements in Section 7.7.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

7.1 Treatment

7.1.1 Arms 1 and 2: Cisplatin (With Concurrent RT)

7.1.1.1 (8/25/08) Patients will receive cisplatin, 100 mg/m², administered intravenously on days 1 and 22 of the treatment course (Note: cisplatin given within 24 hours of days 1 and 22 due to holidays, for example, is acceptable) . **Note:** Patients on Arm 2 will begin cisplatin and RT the week after the initial dose of cetuximab (see Section 7.1.3). Weekends count as days. Use the actual body weight as long as the BSA is ≤ 2.0. **If the BSA is > 2.0, recalculate using the ideal weight, and use the recalculated BSA to determine the dose with no cap or use a cap with a BSA of 2.0, whichever is higher.** Use the formulas below:

Males (kg): 51.65 + (1.85 x (height [inches] – 60))

Females (kg): 48.67 + (1.85 x (height [inches] – 60))

7.1.1.2 (6/1/06) High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly emetogenic regimens should be followed. In the absence of such guidelines:

- For acute nausea and vomiting, premedication should include a 5-HT₃ antagonist, such as granisetron 1 mg *i.v.*; ondansetron, up to 32 mg *i.v.*; or palonosetron, 0.25 mg *i.v.*; plus a corticosteroid, such as dexamethasone, up to 20 mg *i.v.*. Palonosetron has a longer half life (40h) than the first generation 5HT₃ antagonists.
- Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone. Potential delayed nausea regimens include:

- 1) The NK-1 antagonist, aprepitant (125 mg *p.o.*), may be added for prevention of delayed emesis on the day of cisplatin administration and for two consecutive days thereafter (80, 80), with a corticosteroid, such as

dexamethasone on days 1, 2, and 3. Dexamethasone should be reduced on day 1 to 12 mg and delivered at up to 8 mg total daily for up to 4 days total. 5HT3 antagonist (e.g., granisetron, ondansetron) may be given for 3 days, only if palonosetron was not given prior to chemotherapy.

- 2) Delayed emesis also may be managed by the addition of dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4mg bid x 2 days, beginning day after chemotherapy; oral metoclopramide 0.5 mg/kg (usually 20-40 mg) in addition qid x 2-4 days; 5HT3 antagonist (e.g., granisetron, ondansetron) may be given for 3 days, only if palonosetron was not given prior to chemotherapy. Adjust dexamethasone downward if aprepitant was given in the preceding four days.

7.1.1.3 Patients must receive vigorous hydration and diuresis. A suggested regimen is pre-hydration with a 1 liter of D5N S over 2-4 hours and mannitol, 12.5 g *i.v.* bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m², in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management.

Overnight hospitalization for hydration after cisplatin is strongly encouraged if it is allowed by the patient's insurance company. Additional *i.v.* hydration and BUN/creatinine check should be strongly considered later in the week after cisplatin administration, in order to prevent dehydration and severe fluid/electrolyte imbalance.

7.1.2 Dose Modifications for Cisplatin, Day 22

7.1.2.1 (8/25/08) Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Per CTCAE, v. 3.0, febrile neutropenia is fever of unknown origin without clinically or microbiologically documented infection; ANC < 1.0 x 10⁹/L, fever > 38.5°C.

7.1.2.2 Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are ≥ 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction.

7.1.2.3 Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Continue RT (Arm 1). Continue RT/cetuximab (Arm 2).

7.1.2.4 (6/1/06) Renal Adverse Events: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

Note: If creatinine is > 1.2 mg/dl, clearance must be done in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

Creatinine Clearance	Cisplatin Dose
> 50 ml/min.	100 mg/m ²
40-50 ml/min.	50 mg/m ²
< 40 ml/min.	Discontinue and notify Drs. Axelrod or Sherman

7.1.2.5 Other Adverse Events:

- Mucositis: Grade 4 will require a 25% dose reduction (see Section 6.9)
- Ototoxicity: For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue RT (Arm 1). Continue RT/cetuximab (Arm 2).
- If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

7.1.2.6 If the second dose of cisplatin is delayed more than 21 days because of hematologic or renal adverse events, that dose will be omitted.

7.1.2.7 (8/25/08) If a weight change of ≥ 10% occurs, the cisplatin dose should be adjusted.

7.1.3 Arm 2: Cetuximab (With Concurrent RT and Cisplatin) (8/25/08)

7.1.3.1 Initial Dose: Patients on Arm 2 will receive an initial dose of cetuximab (C225), 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** (radiation treatment should begin no later than 7 days after the initial dose of cetuximab). The infusion rate of cetuximab must never exceed 5 mL/min. **Use the actual body weight, even if the BSA is ≥ 2.0. Cisplatin dose will be calculated in ideal body weight (or with a BSA cap of 2.0) for patients with a BSA over 2.0. Cetuximab always will be calculated using actual body weight.**

Weeks 1-7 (concurrent with RT and cisplatin): After the initial dose of C225, systemic therapy with C225 and chemotherapy is to commence within 24 hours from the start of radiotherapy. Patients on Arm 2 will receive cetuximab, 250 mg/m², intravenously (*i.v.*) over 60 minutes prior to radiation therapy and cisplatin. The cisplatin and radiation therapy can be given in any order; however, radiation therapy and cisplatin should be given within 24 hours of starting the cetuximab infusion. The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week on Monday or Tuesday for a total of 7 doses (patients receive cetuximab for a total of 8 weeks, including the initial dose; therefore, the last dose of cetuximab may be given the week after completion of RT).

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.

(6/1/06) The medical staff must closely observe patients for treatment-related adverse events, especially infusion reactions (see Section 1.3.3 for details and Section 7.4.4 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 7.4.4 for proper management.

For subsequent infusions, vital signs should be taken pre- and post-infusion; however, it is recommended that the patient be observed for 1 hour post infusion. For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits. **Patients should be instructed to report any delayed reactions to the investigator immediately.**

7.2 Cisplatin (Cis-Diamminedichloroplatinum, DDP) [6/1/06]

Refer to package insert for additional information.

7.2.1 Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

7.2.2 Mechanism of Action: The mechanism of action of DDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand

cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

7.2.3 Preparation: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours.

7.2.4 Administration: Intravenous.

7.2.5 Adverse Events

The following adverse events are anticipated:

- Hematologic: Myelosuppression, often with delayed erythrosuppression; rarely, acute leukemia
- Gastrointestinal: Nausea, vomiting, anorexia, loss of taste;
- Dermatologic: Alopecia;
- Renal: Elevation of BUN, creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient); hyperuricemia; much more severe and prolonged adverse events have been observed in patients with abnormal or obstructed urinary excretory tracts;
- Hepatic: Hypomagnesemia, hypokalemia, hypocalcemia,
- Neurologic: Restlessness; involuntary movements; loss of coordination; seizures; peripheral neuropathy;
- Allergic: Flushing, bronchoconstriction, tachycardia, hypotension;
- Other: Ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus); muscle cramps; weakness

7.2.6 Storage: Intact vials of the dry powder and the aqueous injection should be stored at room temperature (15-25°C) and protected from light; the vials and injection should not be refrigerated.

7.2.7 Supply: Commercially available.

7.3 Cetuximab (C225) [IND exempt] (1/26/16)

7.3.1 Formulation

Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant. For more information on this agent, refer to the FDA approved Package Insert. The investigator's brochure is available on the RTOG web site, www.rtog.org/investbrochure.html.

7.3.2 Safety Precautions

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

7.3.3 Preparation and Administration

Cetuximab must not be administered as an IV push or bolus.

Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

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

Syringe Pump:

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

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

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

7.3.4 Adverse Events

- Infusion reaction: Characterized by airway obstruction (e.g., bronchospasms, stridor, hoarseness), urticaria, hypotension; infusion reactions occur in about 3% of patients, rarely with fatal outcome (< 1 in 1,000)
- Pulmonary: Interstitial lung disease (less than 0.5% of cases, usually reported in patients with pre-existing fibrotic lung disease), pulmonary emboli, dyspnea, increased cough
- Hematologic: Leukopenia, anemia
- Gastrointestinal: Nausea, vomiting, diarrhea, constipation, dyspepsia, abdominal pain, anorexia, stomatitis, kidney failure,
- Dermatologic: Rash, acne, dry skin, pruritus, ulceration, alopecia, nail disorder
- Circulatory: Deep vein thrombosis
- Neurological: Headache, depression
- Allergy: Allergic reaction, anaphylactoid reaction
- Ocular: Conjunctivitis
- Other: Hypomagnesemia, asthenia, weight loss, dehydration, fatigue/malaise, insomnia, fever, chills, myalgia, arthralgia, sepsis, infection, peripheral edema

7.3.5 Storage Requirements/Stability

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

7.3.6 Supply

Eli Lilly and Company or its local affiliate will supply cetuximab free of charge to patients on study. 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.

7.3.7 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.

7.3.8 Drug Destruction and Return

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, according to the institution's policy for drug destruction. 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. For questions regarding cetuximab destruction, contact Eli Lilly at iits_usmail-oncology@lilly.com.

7.4 Cetuximab Dose Modifications

7.4.1 Cetuximab Dose Levels

	Starting Dose	Dose Level –1	Dose Level –2
Cetuximab (C225)	400 mg/m ² (week 1 only) 250 mg/m ² (weekly)	200 mg/m ² (weekly)	150 mg/m ² (weekly)

(8/25/08) If a weight change of $\geq 10\%$ occurs, the cetuximab dose should be adjusted.

7.4.1 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.

7.4.3 Cetuximab Dose Modifications for Non-Hematologic Adverse Events (8/25/08)

NCI CTCAE Toxicity Grade (CTCAE v. 3.0)	Cetuximab Dose ^a
Renal-Calculated Creatinine Clearance	
≥ 50 mL/min	Maintain dose levels
< 50 mL/min	Maintain dose levels
Fatigue (Asthenia)	
\geq Grade 3	Maintain dose levels
Nausea/Vomiting	
\leq Grade 2 with maximal medical management	Maintain dose levels
\geq Grade 3 with maximal medical management	Maintain dose levels
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 \leq grade 3
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

^aDose levels are relative to the previous dose. Dose reductions of C225 below the –2 dose level will not be allowed. In any case of C225 treatment delay, there will be no re-loading infusion. “Held” C225 doses will be made up at the assigned dose level, although no cetuximab doses should be given more than 4 weeks after the completion of radiation therapy.

^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.

7.4.4 Cetuximab Infusion Reaction Management (6/1/06)

CTCAE v. 3.0 Adverse Event Grade	Treatment Guidelines ^a
Grade 1: Transient flushing or rash; drug fever < 38° C (< 100° F)	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: Rash; flushing; urticaria; dyspnea; drug fever ≥ 38 C (≥ 100° F)	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: Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy- related edema/angioedema; hypotension	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: Anaphylaxis	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 C225 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 C225 treatment. If a subject experiences a Grade 3 or 4 infusion reaction at any time, the subject should receive no further C225 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.

7.4.5 Cetuximab Special Instructions

If C225 is omitted for more than four consecutive infusions for adverse events due to C225, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the subject should be discontinued from further C225 therapy. If adverse events prevent the administration of C225, the subject may continue to receive radiation therapy.

7.4.5.1 Management of Cetuximab Infusion Reactions (6/1/06)

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.

7.4.5.2 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.

7.4.5.3 Cetuximab-related Rash (6/1/06)

➤ 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. 3.0 terms. A rash complicated by secondary infection or cellulitis should be graded per additional CTCAE terms.

	1	2	3	4
Pruritus/itching*	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/desquamation*	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering \geq 50% BSA	Generalized, exfoliative, ulcerative, or bullous dermatitis
Rash/acne/acneiform*	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration, or desquamation	-
Nail changes*	Discoloration; ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nail bed(s)	Interfering with 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 the CTCAE v. 3.0 criteria for radiation dermatitis (table below).

	1	2	3	4
Rash: dermatitis associated with radiation – Select: – Chemo-radiation – 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	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site

- **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, "Dermatologic injury, 'other'", 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 (\geq Grade 3)

	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement to \leq 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 \leq 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 \leq Grade 2	Reduce dose to 150 mg/m ²

Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)

	Cetuximab	Outcome	Cetuximab Dose Modification
		No Improvement; remains grade 3	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

7.4.5.3.1 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.

7.5 Modality Review

The Medical Oncology Co-Chairs, Rita Axelrod, MD and Eric Sherman, MD, will perform a Drug Therapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **per protocol; variation acceptable (Minor); variation acceptable (NOS); deviation unacceptable; not evaluable for chemotherapy review; or incomplete chemotherapy**. 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-Chairs, Rita Axelrod, MD and Eric Sherman, MD, will jointly perform a Quality Assurance Review after complete data for the first 25 cases enrolled have been received at RTOG Headquarters. Drs. Axelrod and Sherman will alternate performing reviews on subsequent blocks of 25 patients after the complete data for these cases becomes available at RTOG Headquarters. This schedule may be modified during the trial in light of preliminary results. 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 RTOG Headquarters, whichever occurs first.

7.6 Adverse Events (1/26/16)

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

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

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

7.6.1 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. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.6.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in section 7.7 will be reported via CTEP-AERS. . SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in section 7.7.

Definition of an SAE: Any adverse drug 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. 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.

7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) (10/17/13)

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.

7.7 CTEP-AERS Expedited Reporting Requirements (1/26/16)

7.7.1 Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days¹ of the Last Dose of the Investigational Agents in this Study, cisplatin (Arm 1) or cisplatin and cetuximab (Arm 2).

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP-AERS (Adverse Event Expedited 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 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 an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS AdEERS 24-hour notification must be followed by an 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 an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the 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 System as “expedited reporting NOT required” must still be reported to fulfill safety reporting obligations. Sites must bypass the “NOT Required” assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

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:

- o “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.
- o “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

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

Effective Date: May 5, 2011

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

8.1 Neck Dissection (1/8/07)

The following patients will be assessed 8-9 weeks post-treatment with CT scan or MRI: All patients with N2a, N2b, and N3 disease and patients with ≤ 3 cm nodes on one side (N1) or both sides (a subset of N2c) with questionable neck findings. A post-treatment PET/CT scan is optional (see Section 4.1.6). **Note:** If the CT portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest.

PET/CT is investigational in this study; therefore, PET/CT findings should not affect the decision of neck dissection.

A neck dissection is **required** for patients with persistent nodal disease, any stage, if a palpable abnormality or worrisome radiographic abnormality persists in the neck 8-9 weeks after completion of therapy. A neck dissection is **optional** for patients with multiple positive lymph nodes or with lymph nodes exceeding 3 cm in diameter at pre-treatment (N2a, N2b, N3) who achieve a complete clinical and radiographic response in the neck. Surgery will be performed within 2 weeks once the decision for neck dissection is made. The status of the primary tumor should be assessed thoroughly at the beginning of the surgical procedure before undertaking nodal dissection. Presence of persistent disease at the primary site, confirmed by frozen section, will be considered a failure of protocol treatment. Further treatment of such a patient will depend on the clinical situation and are at the discretion of the treating physicians.

For Patients Undergoing a Neck Dissection

Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed *en bloc*. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon, and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as "nodal clusters." These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix V.

8.1.1 Institutions must submit a Surgery Form (**S1**) for all patients. In addition, institutions must submit a Surgical Operative Report (**S2**) and a Surgical Pathology Report (**S5**) for patients who have surgery to the primary site and/or to regional nodes post-treatment (see Section 12.1).

8.2 Surgical Removal (Salvage) of the Primary Tumor

Directed biopsies at the site of the index lesions will not be performed in the absence of suspicion for relapse. Criteria for biopsy after chemoradiation include a persistent mucosal abnormality or imaging studies that are suspicious for persistent or recurrent disease at 8-9 weeks after completion of therapy. Options for salvage therapy will depend upon the clinical situation and are at the discretion of the treating physicians. Surgical removal (salvage resection) of the primary tumor will be performed, if possible, when biopsy-proven cancer remains more than three months after completion of therapy. The nature of the surgical resection will be dictated by the extent of tumor at the initial evaluation. The operation will be conducted using accepted criteria for primary surgical treatment of the cancer.

Tissues for pathologic evaluation of margins should be taken from the patient (rather than the surgical specimen itself). However, the specimen itself should be marked at sites corresponding to the evaluated margins in order to assess sampling error in obtaining clear margins. If gross tumor remains or when no effort to remove tumor has been made, the patient will be considered

to have "gross residual disease." In the absence of residual disease, if the cancer extends to within 5 mm of a surgical margin, the patient would be considered to have "close" margins.

8.3 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Randal Weber, MD, will perform a Quality Assurance Review of patients undergoing neck dissection or salvage surgery after complete data for the first 25 cases enrolled has been received at RTOG Headquarters. Dr. Weber will perform the next review after complete data for the next 50 cases enrolled has been received at RTOG Headquarters. 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 RTOG Headquarters, 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. The use of amifostine and pilocarpine is discouraged in light of the overlapping adverse event profile with cetuximab and possible impact on the endpoints. If amifostine or pilocarpine is administered, it should be documented on the Treatment Form (TF) and the Follow-up Form (F1).

9.2 Non-permitted Supportive Therapy

9.2.1 Hematopoietic Growth Factors

The routine use of erythropoietic growth factors (e.g., darbepoetin, erythropoietin) is strongly discouraged. Granulocytic growth factors (e.g., filgrastim) should not be used concurrently during radiation therapy unless radiation therapy has been stopped to allow for recovery of neutropenia and fever. Radiation therapy, cetuximab, and/or chemotherapy should not be resumed within 48 hours of the last dose of filgrastim.

10.0 TISSUE/SPECIMEN SUBMISSION (8/17/11)

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

Sites participating in RTOG 0522 should follow the instructions below.

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for planned and future translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue and blood will be submitted to the RTOG Biospecimen Resource for the purpose of conducting biomarker studies as described below and for banking for future translational research. Submission of tissue and blood is highly recommended.

10.1 Biomarker Studies

10.1.1 As discussed in Section 1.4, the RTOG Head and Neck Translational Program has had an excellent track record for conducting correlative biomarker studies. Relevant to this protocol is the finding that higher than median EGFR expression was associated with a significantly lower overall and disease-free survival rates ($p=0.0006$ and $p=0.0016$, respectively) secondary to significantly higher ($p=0.0031$) LR relapse rate. Multivariate analysis showed that EGFR expression was an independent, strong predictor of survival and of LR relapse after radiotherapy {Ang, 2002 #42}.

Given the potential for clinical application, a follow up study was undertaken, which showed a high reproducibility of the assay and validated the previous finding that higher tumor EGFR expression predicted for worse survival, disease-free survival, and local-regional relapse with hazard ratios of 1.97, 2.15, and 3.12, respectively. Combined analysis revealed that the EGFR expression had even a higher impact on the tumor control in the AFX-C regimen, which improved outcome by offsetting tumor proliferation.

In this trial, an extension of the prior study is planned, testing whether EGFR expression level predicts for response to a radiation-cisplatin regimen with or without cetuximab. In addition, assessment of the predictive value of the expression of one or more of the down-stream molecules, i.e., mitogen-activated protein kinase (MAPK), protein kinase AKT, signal transducer and activator (STAT)-3, and protein kinase C (PKC), also is planned.

10.1.2 Hypotheses (2/23/11)

The primary hypothesis is that EGFR expression level measured by image analysis based quantitative immunohistochemical assay predicts for local-regional control and survival (i.e., higher EGFR expression predicts for lower local-regional control and poorer survival), in patients receiving radiation-cisplatin regimen. The secondary hypothesis is that the effect of EGFR overexpression is mediated predominantly by one of its four down-stream signaling pathways, i.e., PI-3K/AKT. Previously published assay and correlative analysis methods will be used to test these hypotheses. The assays will be performed at the University of Texas M.D. Anderson Cancer Center (Drs. El-Naggar and Ang).

10.2 Specimen Collection for Translational Research and Tissue Banking (8/17/11)

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 One H&E stained slide of the primary tumor, collected before initiation of treatment;

10.2.2 A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Biospecimen Resource (see Appendix VII). Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block or core (or slides) contain tumor. The report must include the RTOG 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.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.2.5 Peripheral blood will be collected before initiation of treatment by venipuncture and shipped using RTOG collection kits. Sites will collect 5-10 mL of whole blood in a red-top tube and 5-10 mL of whole blood in 2 EDTA tubes. Red top tube is spun down for serum. One EDTA tube is mixed and aliquotted for DNA. The second EDTA tube is spun for plasma and lymphocytes/buffy coat cells. (See Appendix VII for detailed collection and shipping instructions). Collection kits are available by contacting the RTOG Biospecimen Resource (see contact information below).

Specimens should be sent with a Specimen Transmittal Form documenting the date of collection of the serum, plasma, or whole blood; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -20° C, must be included. Questions regarding blood collection or shipment should be directed to the RTOG Biospecimen Resource (see contact information below). Ship by express overnight service, Monday through Wednesday (Monday-Tuesday from Canadian sites); avoid a weekend or holiday arrival date, and DO NOT ship on Thursday or Friday.

10.2.6 Recurrent Tumors

Because a cohort of patients treated on RTOG 0522 will manifest tumor recurrence at some point following protocol treatment, specimens from the recurrent tumors are desired for study as these specimens represent valuable biologic materials following treatment with radiation and study drugs. Specimens from recurrent tumors should be sent to the RTOG Biospecimen Resource according to the specifications in Section 10.2.1-10.2.5. Such tumor recurrences may derive from the locoregional head and neck area, or from a distant metastatic site if the clinical impression and pathology review are most consistent with recurrence of the squamous cell carcinoma of the head and neck that originally caused the patient to be enrolled on RTOG 0522.

10.2.7 HPV Analysis of Oropharyngeal Carcinoma Specimens (2/23/11)

For patients with oropharyngeal carcinoma, the RTOG Biospecimen Resource at UCSF will process 2 unstained sections from the tissue submitted and will send those sections for formal determination of HPV status by *in situ* hybridization.

The results of a biomarker study conducted using samples of RTOG 0129 showed that a p16 immunohistochemical (IHC) assay had a stronger correlation with survival and progression-free survival than HPV *in situ* hybridization.⁶⁸ Based on this finding, it was decided to move forward with p16 IHC assay. As an investigator moved from Johns Hopkins to the Ohio State University, the p16 IHC assay will be performed at the Ohio State University. To assess inter-laboratory and inter-observer reproducibility of the p16 IHC, a similar assay also will be performed at the University of Texas M.D. Anderson Cancer Center (by Dr. El-Naggar).

10.2.8 Storage Conditions (8/17/11)

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.

10.2.9 Summary of Specimens for Translational Research/Tissue Banking (8/17/11)

Specimens taken from patient:	Collected When:	Submitted as:	Shipped:
One H&E stained slide of the primary tumor	Pre-treatment	H&E stained slide	Slide sent ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a skin punch or 15 unstained slides	Pre-treatment	Paraffin-embedded tissue block or a 2 mm punch biopsy or 15 unstained slides	Block or punch sent ambient
SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge	Pre-treatment	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube#1 (purple/lavender top) and centrifuge	Pre-treatment	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
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) and mix	Pre-treatment If site missed this collection time point they may collect this specimen at any other time point instead but must note this on the STF.	Frozen whole blood samples containing 1 mL per aliquot in 1 mL cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier
Recurrent tumor specimens taken from the patient:	Pre-treatment If site missed this collection time point they may collect this specimen at any other time point instead but must note this on the STF.		
One H & E stained slide of the recurrent tumor	At time of recurrence	H & E stained slide	Slide sent ambient
A paraffin-embedded tissue block of	At time of	Paraffin-embedded	Block or punch

the recurrent tumor or a 2 mm diameter core of tissue, punched from the tissue block with a skin punch	recurrence	tissue block or punch biopsy	sent ambient
--	------------	------------------------------	--------------

10.2.10 Submit materials for Translational Research and Tissue Banking as follows:

Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, DHL, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

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

10.3 Reimbursement (8/17/11)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (<http://www.rtog.org/LinkClick.aspx?fileticket=Csxzt1v1hEk%3d&tabid=323>). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage (8/17/11)

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

10.4.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resource 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.

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

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (10/17/13)

	Pre-Study Entry	Weekly During Treatment	From End of Treatment		From Start of Treatment			Follow Up ⁿ
			4 Weeks	8-9 Weeks	6 Mos	9 Mos	12 Mos	
Assessments								
Evaluations								
Complete history/physical	X ^a			X	X	X	X	X
Zubrod, weight	X ^a	X	X	X	X	X	X	X
ECHO or MUGA	X ^b							
Medical Oncology Exam	X ^a	X ⁱ		X				
Protocol-specific AE Eval, including mucosal assessment (see Section 11.2)	X	X	X	X	X	X	X	X
Dental evaluation	X ^c							
Nutritional evaluation	X ^c							
Audiogram	X ^c							
Imaging								
CXR or thoracic CT	X ^d				X ^k		X ^k	X ^k
CT/MRI of tumor/primary site	X ^d			X ^l	X ^l		X ^l	X ^l
PET/CT scan	X ^{c,d}			X ^{c,l}				
Labs								
CBC, Diff, Platelets	X ^e	X ^j						X
Mg ⁺⁺	X ^e	X ^j	X		X	X	X	X
Calcium, glucose, potassium, sodium	X ^e	X ⁱ						
Bilirubin, AST or ALT, Serum creatinine	X ^e	X ^j			X ^m	X ^m	X ^m	X ^m
Creatinine clearance	X ^e							
Serum albumin	X ^c							
Pregnancy Test	X ^f							
Tissue/blood for TRP	X ^g							
Quality of Life Assessments								
PSS-HN	X ^h	X ^h	X ^h				X ^h	X ^h
EQ-5D	X ^h	X ^h	X ^h				X ^h	X ^h
FACT-H&N	X ^h						X ^h	X ^h

- Within 4 weeks prior to registration;
- Within 12 weeks prior to registration;
- Not required but highly recommended (see Section 4.2 and Appendix VI)
- Within 6 weeks prior to registration;
- Within 2 weeks prior to registration;
- For women of childbearing potential, within 2 weeks prior to registration;
- Primary tumor tissue and peripheral blood, taken before the initiation of treatment (see Section 10.2);
- If the patient consents to participate in the quality of life component of the study, the PSSHN and EQ-5D will be administered pretreatment, during one of the last 2 weeks of treatment, at 3 and 12 months from start of treatment, then annually for years 2-5; FACT-HN will be administered pretreatment, and annually in years 1 and 5;
- Every 3 weeks, no later than 72 hours prior to chemotherapy (cisplatin) cycle and within 48 hours of cetuximab;
- Weekly and within 24 hours prior to chemotherapy and within 48 hours of cetuximab;
- In follow up, CXR or thoracic CT scan or PET scan will be done at 6 months (+/- 1 month) in year 1, then annually

- L) In follow up, CT scan/MRI of the head and neck (plus optional PET/CT) will be done 8-9 weeks after completion of radiation for all N2a-b and N3 patients and for selected N1-N2c patients (see Section 8.1 for details). For all patients, CT scan/MRI of the head and neck should be done at 6 months from the start of treatment in year 1, then annually for 5 years. If special circumstances (e.g., patient unable to lie supine) prevent routine imaging, evaluation of the primary site may be done by visual inspection (e.g., visual endoscopy) [Note: For N0 disease, the scan at 8-9 weeks is not necessary, but all other scans must be done as specified];
- m) Creatinine only;
- n) Follow up will be at 8-9 weeks post-treatment and at 6, 9, and 12 months from start of treatment for year 1, every 3 months for year 2, every 6 months for years 3-5, and then annually.

11.2 Evaluation During and Post-Treatment

11.2.1 Protocol-Specific Adverse Event Evaluation (6/1/06)

In an effort to improve the capture and consistency of adverse event (AE) reporting, essential adverse events commonly associated with head and neck treatment are to be assessed at baseline, during treatment, and at follow up using **CTCAE version 3.0**. A **CTCAE Grading Tool**, containing a subset of CTCAE terms, is available on the RTOG web site next to the protocol, to facilitate grading. In addition, the spiral bound CTCAE booklet distributed by the NCI can be used, as can the ‘**electronic search tool**’ on the RTOG web site under the RA Corner (adverse events) [Select the appropriate category (i.e., gastrointestinal, neurology, etc.), and then find the AE term in alphabetical order]. Additional AE terms and grading criteria can be accessed online at <http://ctep.cancer.gov/reporting/ctc.html>

Essential protocol-specific adverse events to be collected are as follows:

At baseline on I1 form:		
<u>Category</u>	<u>AE term</u>	<u>Ref page in CTCAE</u>
Gastrointestinal:	Dysphagia (difficulty swallowing)	21
During treatment on TF form:		
<u>Category</u>	<u>AE term</u>	<u>Ref page in CTCAE</u>
Pulmonary/ Upper Respiratory	Edema, larynx (includes need for tracheostomy)	57
Gastrointestinal	Dysphagia (difficulty swallowing)	21
	Mucositis/stomatitis (clinical exam) [specify oral cavity, pharynx, or larynx primary site]	24
Dermatology/Skin	Pruritus/Itching	15
	Rash/desquamation [face (out of field), trunk, extremities]	15
	Rash: Acne/acneiform	15
	Nail changes	15
	Rash: dermatitis associated with radiation- Select: Radiation (radiation dermatitis may be exacerbated by C225, but in-field skin changes are graded using the radiation scale)	15
	Rash: dermatitis associated with radiation- Select: Chemoradiation	15

During follow-up on F1 form:		
Category	AE term	Ref page in CTCAE
Neurology	Neuropathy: sensory	50
Pain	Pain-select: Neuralgia/peripheral nerve	
Auditory	Hearing: patients without baseline audiogram and not in monitoring program	2
Pulmonary/Upper Respiratory	Edema, larynx (includes need for tracheostomy)	57
Gastrointestinal	Dysphagia (difficulty swallowing)	21
	Mucositis/stomatitis (clinical exam)- [specify oral cavity, pharynx, or larynx primary site]	24
Dermatology/Skin	Rash/desquamation [for late effects/scarring out of RT field – face, trunk, or extremities]	15
	Induration/fibrosis (skin and subcutaneous tissue)	44
	Osteonecrosis (includes necrosis of mandible, maxilla, skull)	45
Musculoskeletal/ Soft Tissue	Soft tissue necrosis (MUCOSAL ulceration requiring wound care, hyperbaric, or surgical intervention)	46
	Soft tissue necrosis (DERMIS/SOFT TISSUE ulceration requiring wound care, hyperbaric, or surgical intervention)	46

*Local reaction of the skin and mucous membranes should be evaluated and scored at least weekly during treatment.

- 11.2.2** In addition to protocol-specific AEs (AE terms provided on protocol-specific forms), additional AEs experienced during treatment and in follow up must be documented on Adverse Event (AE) form. **When reporting additional AEs, please refrain from using the ‘Other, Specify’ mechanism. This should be the exception, not the rule in the rare event that a suitable CTCAE term cannot be found. If this is absolutely necessary, the investigator must make a note to this affect in the source documentation.** See section 12.1 for submission schedule.
- 11.2.3** For patients without a feeding tube, a nutritional evaluation based on acute reactions and Zubrod status should be done weekly during treatment. Status of feeding tube and placement/removal of a tracheostomy should be documented on the Follow-up Form (F1).
- 11.2.4** Whenever possible, patients will be evaluated at two-week intervals after completion of treatment until their acute reactions have resolved.
- 11.2.5** Assessment for possible neck dissection should take place 8-9 weeks after completion of treatment, and dissection should take place within 2 weeks once the decision for neck dissection is made.
- 11.2.6** Treatment for recurrence depends on the site of relapse and is at the discretion of the treating physician.

11.3 Measurement of Response

11.3.1 Tumor Clearance (8/25/08)

A patient will be considered to have complete response if there is no measurable or palpable tumor either on clinical or radiographic (CT scan or MRI) examination.

The *PET* portion of a PET/CT scan is investigational and therefore should not be used in determining a patient's response to treatment for purposes of evaluating efficacy endpoints, such as progression-free survival. If the *CT* portion of a PET/CT is done with contrast and a radiologist formally reviews and reports the findings on head and neck and thoracic regions, then there is no need to order additional diagnostic CT/MRI of the head and neck or chest x-rays or CT scan of the chest. The primary tumor and regional nodes will be evaluated and reported separately.

11.3.2 Local or Regional Relapse

Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.

11.3.3 Local or Regional Progression

Progression is defined as an estimated increase in the size of the tumor (product of the perpendicular diameters of the two largest dimensions) of greater than 25%, taking as reference the smallest value of all previous measurements or appearance of new areas of malignant disease.

11.3.4 Distant Metastasis

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

11.3.5 Second Primary Neoplasm

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

11.3.6 Discontinuation of Protocol Treatment (1/8/07)

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease;
- Unacceptable adverse events [at the discretion of the treating physician(s)];
- Patient refusal.

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

11.3.7 Discontinuation of Follow-Up Assessments (8/17/11)

Follow-up assessments may be discontinued for either of the following reasons:

- Patient refusal;
- Patient's withdrawal of consent; the treating institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual. Data for patients that withdraw consent will not be used for any analysis.

11.4 Quality of Life Assessments

11.4.1 The Performance Status Scale for Head and Neck Cancer (PSS-HN) consists of assessment of three functions (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. Note: The PSS-HN has been translated into 12 languages and is available to institutions at no charge. Contact Dr. List, the QOL Co-Chair, for these translations.

11.4.2 Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N) is a multidimensional, QOL instrument specifically designed and validated for use with HNC patients that the patient can complete 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. Note: The FACT-H&N has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at <http://www.facit.org/translation/licensure.aspx>.

11.4.3 The EuroQol (EQ-5D) is a two-part questionnaire that the patient can complete in approximately 5 minutes. Note: The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at <http://www.euroqol.org/>. The site research nurse or CRA should encourage the patient not to skip questions on the EQ-5D or take breaks during the completion of this questionnaire, as this will invalidate the assessment. If this occurs, sites will document it on the Health Utility Measurement (HP) form.

12.0 DATA COLLECTION (1/26/16)

12.1 Summary of Data Submission to RTOG (8/17/11)

Data should be submitted to:

**NRG Oncology
1818 Market Street, Suite 1720
Philadelphia, PA 19103**

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.

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Slides/Blocks (P2)	
Performance Status Scale for H &N Cancer (PSS-HN) [QP]	
Functional Assessment of Cancer Treatment (FACT-H&N) [FA]	
Health Utility Measurement (EQ-5D) [HP]	
Nodal Diagram (I7)	
*PET Assessment Form (IM)	
*If participating in PET component of study	
<u>Preliminary Dosimetry Information for 3D-CRT Approach</u>	Within 1 week of start of RT
It is highly recommended that dosimetry information be submitted digitally. Sites unable to submit digitally will contact RTOG Headquarters, RTQA Department, 215-574-3219. For digital submission, See Section 12.2.	
<u>Final Dosimetry Information for 3D-CRT Approach</u>	Within 1 week of RT end
For digital submission, See Section 12.2	
Treatment Form (TF)	At completion or discontinuation of systemic treatment
Surgical Form (S1)	At 9 months from start of treatment (or earlier, if surgery occurs prior to 9 months from start of treatment)
Surgical Operative Report (S2)	
Surgical Pathology Report (S5)	
Performance Status Scale for H &N Cancer (PSS-HN) [QP]	During 1 of the last 2 weeks of treatment, at 3 and 12 months from the start of systemic treatment, then annually for years 2-5
Health Utility Measurement (EQ-5D) [HP]	
Functional Assessment of Cancer Treatment (FACT-H&N) [FA]	Annually in years 1 and 5
*PET Assessment Form (IM)	At 8 weeks post-systemic therapy
*If participating in PET component of study	
Follow-up Form (F1)	At 8-9 weeks post-treatment and at 6, 9, and 12 months from the start of treatment ; every 3

months for year 2; every 6 months for years 3-5; then annually and at death.

12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1) [8/25/08]

<u>Item</u>	<u>Due</u>
Preliminary Dosimetry Information †Digital Data Submission Form (DDSI) CT data, critical normal structures, all GTV, CTV, and PTV contours (C1, C3) Simulation films and/or digital film images for all initial treatment fields and orthogonal set up pair First day port films (or digital images) of all initial treatment fields and orthogonal set up pair Digital beam geometry for initial and boost beam sets Doses for initial and boost sets of concurrent treated beams Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV) Hard copy isodose distributions for total dose plan as described in QA guidelines† (T6)	Within 1 week of start of RT
Final Dosimetry Information Radiotherapy Form (T1) [copy to HQ and ITC] Daily Treatment Record (T5) [copy to HQ and ITC] Simulation films and/or digital film images (or digital images) of all boost treatment fields and orthogonal set up pair (T8) First day port films of all boost treatment fields and orthogonal set up pair (T8) Modified digital patient data as required through consultation with Image Guided Therapy QA Center	Within 1 week of RT end

†Available on the ATC web site, <http://atc.wustl.edu/>

12.2.1 Digital Data Submission to ITC (1/8/07)

Digital data submission may be accomplished using magnetic tape or the Internet.
For network submission: The FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:
itc@castor.wustl.edu

For tape submission: Please contact the ITC about acceptable tape types and formats.
Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423

12.3 Summary of Data Submission to ACRIN (8/25/08)

Note: Data submission is for sites participating in the PET component of this study. Sites must contact the PET Core Laboratory at petcorelab@phila.acr.org **prior** to submitting data for their **first** case (see Section 5.3 for details). Institutions should expect an e-mail response from the Pet Core Laboratory within 3 business days.

Data should be submitted by mail or fax to:

ACRIN Headquarters
 PET Core Lab
 1818 Market Street, Suite 1600
 Philadelphia, PA 19103
 FAX 215-923-1737

<u>Item</u>	<u>Due</u>
PET Image Submission	
Images and Technical Assessment Form (TA) Pre-Treatment PET Scan (C4)	Within 14 days of registration
Images and Technical Assessment Form (TA) Post-Treatment PET Scan (C5)	Within 14 days of week 9

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint (8/25/08)

Progression-free survival

13.1.2 Secondary Endpoints (8/25/08)

13.1.2.1 Overall survival;

13.1.2.2 Local-regional control;

13.1.2.3 Mucositis toxicity (Rates of \geq grade 3, clinical exam; see Section 11.2.1);

13.1.2.4 Other toxicity (Rates of \geq grade 3);

13.1.2.5 Protocol treatment delivery;

13.1.2.6 Death during or within 30 days of discontinuation of protocol treatment;

13.1.2.7 Quality of life (PSS-HN and EQ-5D);

13.1.2.8 Quality of life (FACT-G);

13.1.2.9 Correlation of expression of EGFR or its down-stream molecules (e.g., MAPK, AKT, Stat-3, PKC) with progression-free survival, overall survival, and local-regional control;

13.1.2.10 Correlation of pre-treatment PET/CT scan findings with progression-free survival; overall survival, and local-regional control;

13.1.2.11 Correlation of post-treatment PET/CT scan findings with pathologic nodal complete response and nodal relapse rate at two years (Failure: relapse/progression in the regional nodes) in clinical N2-3 patients.

13.2 Treatment Comparison: Background and Sample Size Determination

The control regimen, accelerated fractionation by concomitant boost (AFX-CB) plus cisplatin, has been evaluated in a single arm phase II trial (RTOG 99-14) and is being tested in a phase III protocol (RTOG 0129) against standard fractionation (SFX) plus cisplatin. As of October 14, 2004, there were only 36 deaths reported in RTOG 0129; hence, it is far too early to perform the first planned interim survival comparison between the two arms. Given the encouraging results from the phase II trial (Tables 1 and 2 below), there is a good chance that AFX-CB plus cisplatin will prove to be better than SFX plus cisplatin, and it is very unlikely that it will be significantly worse. Therefore, the proposed trial will adopt AFX-CB plus cisplatin as its control arm (Arm 1).

Table 1: Estimated Yearly Conditional Failure Rates for Disease-Free Survival*

Year	Projected RTOG 0522 AFX-CB + cisplatin	RTOG 99-14 AFX-CB + cisplatin	RTOG 90-03 AFX-CB	RTOG 91-11 SFX + cisplatin	RTOG 91-11 SFX
(% Larynx)	(20%)	(12%)	(15%)	(100%)	(100%)
1	40.0%	39.4%	52.2%	27.9%	44.3%
2	12.0%	11.5%	15.1%	15.7%	21.4%
3	12.0%	NA	15.2%	16.9%	12.6%
4	7.5%	NA	10.5%	20.7%	16.7%
5	7.5%	NA	6.1%	9.1%	16.3%

Table 2: Estimated Yearly Conditional Failure Rates for Overall Survival*

Year	Projected RTOG 0522 AFX-CB + cisplatin	RTOG 99-14 AFX-CB + cisplatin	RTOG 90-03 AFX-CB	RTOG 91-11 SFX + cisplatin	RTOG 91-11 SFX
(% Larynx)	(20%)	(12%)	(15%)	(100%)	(100%)
1	20.0%	19.5%	32.0%	14.5%	12.3%
2	12.0%	12.2%	26.9%	13.3%	14.5%
3	12.0%	NA	16.3%	8.3%	14.2%
4	12.0%	NA	11.5%	11.3%	10.1%
5	12.0%	NA	8.8%	10.3%	4.4%

*RTOG 90-03 tested three altered fractionation radiation schedules without chemotherapy in locally advanced head and neck cancer (including laryngeal primary sites) against standard once-daily radiation (SFX). One of the altered fractionation schedules (AFX with concomitant boost during the last 12 days) is used on both arms in this study. RTOG 91-11 tested two regimens for laryngeal preservation: standard once-a-day radiation (SFX) and SFX + concurrent cisplatin. RTOG 99-14 was a phase II trial evaluating AFX-CB + concurrent cisplatin.

Currently, no firm data are available for estimating the effect of cetuximab given in conjunction with radiation and cisplatin in reducing the failure rate. The results from a completed international phase III trial show that there was a 30% reduction in the risk of local-regional failure (LRF) and death when cetuximab was given before and concurrently with radiotherapy without cisplatin.^{22, 47} It should be noted that approximately 55% of patients on this study received AFX-CB. Based on this result, we hypothesize a 25% reduction in the yearly failure rate for the primary endpoint, disease-free survival (DFS). Table 1 shows the yearly conditional failure rates for DFS with various RTOG protocol regimens and their respective percentage of patients with laryngeal primary. The estimated percentage (20%) of such patients for the 0522 control arm is based upon the January 2005 statistical summary report for the active study, RTOG 0129, in which 22.5% of patients currently on study have a laryngeal primary. Notable is that the DFS failure rates are not exponentially distributed (e.g., a constant rate over time). For planning purposes, DFS yearly conditional failure rates for the 0522 control arm were projected based on past RTOG studies. It should be noted that the yearly failure rates decrease over time with the highest rate associated with the first year. Under this assumption, the two- and five-year DFS rates for the control arm would be 52.8% and 39.8% respectively. With a 25% hypothesized reduction, these rates would become 62.0% and 50.0%.

The Lakatos method⁵⁴ was used for calculating the sample size with three planned interim analyses that will include futility testing. The nominal significance level for each interim test was set at 0.001 (see Section 13.7.4 for further details). A total of 392 DFS failures (total from both arms combined) are required to detect a 25% reduction in the DFS risk of failing with 80% statistical power using a one-sided test at the 0.025 significance level. A total of 681 analyzable patients are required. Adjusting by approximately 5% to allow for ineligibility and lack of data (no baseline information or no follow up post-study entry), the total sample size required is 720 patients. The treatment analysis will be restricted only to eligible patients with follow-up data and may possibly exceed 681 patients.

13.2.1 *Rational for Changing the Primary Endpoint and Increasing the Sample Size (8/25/08)*

There has been no interim analysis performed, protocol-specified or otherwise, of the efficacy data. The primary endpoint for the study has been amended from disease-free survival (DFS) to progression-free survival (PFS) [See section 13.1.1]. The principal reason for this change is that PFS is defined similarly to the endpoint event-free survival (EFS) that the French Head and Neck Meta-Analysis Group has reported to be a suitable surrogate endpoint for overall survival.⁵⁵ The RTOG Head and Neck Steering Committee members fully support this endpoint.

The amended primary endpoint will allow the results from this study to be compared with results reported by the French Meta-Analysis Group. With the PFS/EFS endpoint, the development of a second primary tumor (SPT) is not considered a failure, in contrast to DFS in which it is considered a failure. In addition, the data from the previous trial (RTOG 90-03) showed that some patients coded as not having a complete response did not develop local-regional tumor progression at subsequent follow-up examinations and were considered as a local regional failure for analysis in this study. A major reason for this discrepancy is that the primary tumor or nodal region may not appear completely normal after eradication of cancer (e.g., edema, structural deformation caused by tumor, fibrotic remnant). Radiation Oncologists generally do

not consider the lack of complete response (“persistent disease”) as a local-regional failure unless the tumor actually recurs at subsequent follow up.

The control regimen in RTOG 0522, accelerated fractionation by concomitant boost (AFX-CB) plus cisplatin, has been evaluated in a single arm phase II trial (RTOG 99-14) and was then tested in a phase III protocol (RTOG 0129) against standard fractionation (SFX) plus cisplatin. As of April 2008, using data available from both studies, the yearly PFS failure rates were computed in oropharynx/hypopharynx/larynx patients from RTOG 99-14 and 0129 (Arm 2) and are presented in the table below. Patients with an oral cavity primary were excluded because they were not eligible for RTOG 0522.

Estimates Based Upon RTOG 99-14 and 0129 Trials						Study Design Assumption for the 0522 Control Arm	
Year	Estimated Conditional Yearly PFS Failure Rate (%)	95% Confidence Interval	Estimated PFS Rate (%)	Cumulative Failures / Censored	Patients at Risk	Yearly DFS Failure Rate (%)	DFS Rate (%) / PFS rate (%)
0.0	0.0	-	100.0	0	408	0.0	100.0
1.0	29.7	25.3, 34.2	70.3	121 / 2	285	40.0 / 30.0	60.0 / 70.0
2.0	14.1	10.0, 18.2	60.5	160 / 18	230	12.0	52.8 / 61.6
3.0	10.6	6.3, 14.9	54.5	181 / 81	146	12.0	46.5 / 54.2
4.0	1.8	0.0, 4.2	53.3	183 / 146	79	7.5	43.0 / 50.1
5.0	10.7	2.6, 18.8	46.6	189 / 192	27	7.5	39.8 / 46.6
6.0	8.3	0.0, 19.4	43.0	191 / 198	19	5.0	37.7 / 44.1
Total failures				193			

To evaluate the adequacy of the original target sample size, the yearly failure rates for DFS in the current protocol will be used for PFS, with the exception of the first year where 0.30 will be used because the original calculations included patients with oral cavity primaries. The resulting projected PFS rates with these estimates are similar to those observed in RTOG 99-14 and RTOG 0129 patients as seen in the table above at 1 year (70.3% observed vs. 70.0% projected), 2 years (60.5% vs. 61.5%), and 5 years (46.6% vs. 46.6%).

The protocol currently calls for a total of 681 analyzable patients to detect a 25% reduction in the DFS risk of failing with 80% statistical power using a one-sided test at the 0.025 significance level with 3 interim analyses, where the patient accrual was projected to take 4.5 years and patients are then followed for another 4 years. Using monthly patient accrual information observed as of April 2008, the accrual is projected to take only 3.5 years, since the monthly accrual rate is higher than projected, with median monthly accrual of 19 cases. Using the projected PFS yearly failure rates and 3.5 year accrual period, the statistical power would be reduced to 74.5% to detect a 25% reduction in the PFS risk of failing. If the post-accrual period was extended from 4.0 to 5.0 years keeping the study duration the same as originally planned, the statistical power would be slightly improved to 76.4%. Rather than further lengthening the study duration to achieve the desired statistical power of 80%, the sample size could be increased so there would be numerically more patients experiencing failures during the first 3 years when the yearly failure rates are higher.

One alternative would be to accrue patients for an additional 6 months (new sample size = 800 analyzable patients) and follow them for 4 years post-treatment. The resulting statistical power would be 81.5%. A second alternative would be to accrue patients for an additional 12 months (new sample size = 900 analyzable patients) but follow them for 3 years post-treatment. The

resulting statistical power would be 84.3%. The latter alternative was chosen because the time to projected final analysis will be slightly shortened from 8.5 years (4.5 years of accrual and 4.0 years follow-up post-accrual) to 7.5 years (0.5 protocol startup, 4 years of accrual, and 3.0 years follow-up post-accrual) with increased statistical power to perform subset analyses based upon HPV status (see Section 13.2.2).

In summary, a total of 900 analyzable patients are required to test for 25% reduction in the PFS risk of failing with 84% statistical power using a one-sided test at the 0.025 significance level with three interim tests. Adjusting by approximately 5% to allow for ineligibility and lack of data (no baseline information or no follow up post-study entry), **the total sample size required is 945 patients**. The treatment analysis will be restricted to eligible patients with follow-up data and may possibly exceed 900 patients. The final analysis reporting the treatment results will be carried out after 434 PFS failures (or 239 on the control arm) have been observed, unless the criteria for early stopping are met.

13.2.2 HPV Determination and Analysis (8/25/08)

Based on the published literature,⁵⁶⁻⁵⁷ it is generally accepted that the prognosis for HPV positive (HPV+) patients is much more favorable than that for HPV negative (HPV-) patients; it is also generally accepted that HPV positivity is almost exclusively found in patients with an oropharyngeal primary. In the completed ECOG trial 2399 prospectively evaluating HPV status, 61% of the patients with an oropharyngeal primary were found to be HPV+, and the HPV+ patients had a reduction in the risk of death and disease progression of 73% and 64%, respectively, in comparison to HPV- patients. The preliminary results from ongoing evaluation of HPV status in 122 RTOG 0129 patients with an oropharyngeal primary are similar: 63% incidence of HPV+ and 69% reduction in the risk of dying.⁵⁸ The assumption will be made for analyses that all patients with non-oropharyngeal primaries are HPV-.

As of April 2008, 69% of patients entered on RTOG 0522 had an oropharyngeal primary. In light of the ECOG trial 2399 and the RTOG 0129 results, it is projected that 42% of the entire RTOG 0522 study population will be HPV+ oropharyngeal patients and 28% will be HPV- oropharyngeal patients. The determination of the HPV status of patients enrolled on 0522 will be done retrospectively, and it is projected that 80% of oropharyngeal patients will have their HPV status determined. With these stipulations, the study population will be distributed as follows: 34% oropharyngeal HPV+; 22% oropharyngeal HPV-; 14% oropharyngeal with undetermined HPV status; 30% non-oropharyngeal HPV- . With the revised sample size of 900 patients, there is projected to be 468 HPV- patients and 306 HPV+ patients available for analysis with 126 oropharyngeal patients with undetermined HPV status.

Subset analyses comparing the treatments within the HPV+ and the HPV- patients will be performed at the same time as the protocol-designated final analysis is performed comparing the treatment arms. For planning purposes, it is assumed that patient accrual will not be discontinued, that the trial is not reported early because of highly significant results, and that the patients were equally distributed between the 2 treatment arms within each HPV subgroup. With 468 HPV- patients projected, there will be 75% statistical power to detect the 25% reduction and 80.0% statistical power to detect 32% reduction. With oropharyngeal HPV+ patients, the PFS failure rate will be much lower. Two hypothesized reductions of 50% and 67% in PFS failures were evaluated. To detect a protocol-targeted treatment effect of 25% in 306 oropharyngeal HPV+ patients, there will be 25% and 19% statistical power associated with these 2 scenarios. Therefore, the treatment effect in the HPV+ patients will be estimated by hazard ratio with a 95% confidence interval with the purpose of hypothesis generation for future studies. In addition, exploratory analysis will be performed to determine if whether the benefit from the addition of cetuximab differs by HPV status. A Cox regression model will be used with the following covariates: 1) assigned treatment; 2) HPV status; and 3) assigned treatment by HPV status interaction. The covariate for interaction will provide an estimate as to whether the treatment effect is similar for the HPV+ and the HPV- patients.

The 3 analyses described above initially will be performed using all patients with non-oropharyngeal primaries and with patients with oropharyngeal primaries for which the HPV status has been determined. Given that missing determinations is a common problem with tumor marker studies, a sensitivity analyses will be done to investigate reasons for the lack of HPV determination in oropharyngeal patients (e.g., due to patient drop out, various clinical factors, and/or participating institutions). A logistic regression will be used to analyze the

oropharyngeal patients with and without HPV determination. If HPV status is missing, it will be imputed using patient characteristics reported in the oropharyngeal patients from the ECOG study 2399 and RTOG 0129, and analysis will be performed to check robustness of the results using the oropharyngeal patients with HPV determination.

13.3 Tumor Markers: Background and Statistical Power Considerations

Tumor marker evaluation will be first completed in RTOG 0129 patients treated with chemoradiation because 0129 immediately preceded 0522. The prognostic tumor markers found in RTOG 90-03 patients with various radiation schedules and their cut points will be tested to confirm their prognostic value in 0129. The other markers also will be tested for their possible prognostic value in the 0129 patients. The data from RTOG 90-03 patients will be combined with the data from 0129 patients to explore the prognostic value of various combinations of the downstream molecules. The findings from the 0129 tumor marker evaluation will be used to further define hypotheses to be tested in this study. The tumor marker component for this protocol will then be accordingly revised.

(8/25/08) For planning purposes, it is assumed that the patient accrual will not be discontinued in the trial before reaching its target. Based on RTOG 0129, it is projected that 60% of randomized patients will be analyzable for tumor marker evaluation, giving a total of 410 analyzable patients or 205 per arm. With the revised sample size (see Section 13.2.1), there will be a total of 540 analyzable patients or 270 per arm.

If one of the hypothesis to be tested is the prognostic value of EGFR for overall survival (OS) in patients treated with chemoradiation and cetuximab, patients will be divided into two groups: one with high EFGR values (unfavorable) and other with low EFGR values (favorable). It would then be expected that 40% to 60% of patients would be in the low EFGR group based upon previous data.

The equation described by Schoenfeld⁵⁹ 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 shows statistical power to detect hazard ratios for survival of 1.50, 1.75, and 2.00 for prevalence rates of 40%, or 50%, or 60%. The proposed analysis will be done when there are at least 105 deaths on the cetuximab arm with tumor marker determination. The significance level was set at 0.05. As seen in the table, there will be good power to detect a hazard ratio of 1.75, which was seen in RTOG 90-03 for OS.

Table 3: Statistical Power with 105 Events (Deaths) and 5% Alpha

Prevalence	Hazard Ratio		
	1.50	1.75	2.00
40% (or 60%)	0.53	0.80	0.93
50%	0.54	0.81	0.94

13.4 PET/CT Evaluation: Background and Statistical Power Considerations

Pre-treatment PET/CT scans have been incorporated in the staging work up of head and neck cancer patients in an increasing number of centers. Controversy persists as to whether patients presenting with N2-3 disease that regresses completely at 8-9 weeks after completion of radio-chemotherapy would benefit from neck dissection. This study component is designed to assess the possible prognostic value of pre-treatment PET/CT scan for local-regional failure (LRF) and OS and also the value of PET/CT done after completion of treatment to determine the need for

neck dissection in patients initially presenting with N2-3 disease (with the exception of bilateral nodes, N2c, all measuring < 3 cm) by estimating the predicted true negative value. The specific hypotheses to be tested are:

- Pre-treatment FDG SUV_{max} > median value associated with the primary disease predicts for poor clinical outcome;
- Pre-treatment FDG SUV_{max} > median value for the largest of the FDG SUV_{max} values associated with the nodal disease predicts for poor clinical outcome;
- Pre-treatment FDG SUV_{max} > median value associated with the primary and nodal disease both greater than their respective median values predicts for poor clinical outcome;
- Negative post-treatment PET/CT in patients initially presenting with N2-3 disease who achieve a clinical complete nodal response predicts a high pathologic complete response rate (> 85%) in the neck;
- Negative post-treatment PET/CT in patients initially presenting with N2-3 disease who achieve a clinical complete nodal response predicts for a low nodal relapse rate (< 10%) at two years.

13.4.1 Statistical Power for Pre-Treatment PET/CT Scan Analysis (8/25/08)

Because of budgetary restraints and a competing National Oncology PET Registry (NOPR) study, pre-treatment PET/CT scans were collected only on patients with clinical N2-3 disease. As of June 2008, 65% of the patients enrolled on this protocol have clinical N2-3 disease (which is consistent with the original projection), and 30% of these patients had a pre-treatment PET/CT scan. With the increased accrual of 900 patients to this trial, it is now projected that 600 patients will have clinical N2-3 disease, and 180 of these patients would be available for correlating PET/CT scan findings with nodal disease status post-treatment, which is far less than the previous projection of 50%.

The PET/CT analysis will be done after the analysis for reporting the treatment efficacy results that will be performed with the protocol required 434 progression-free survival (PFS) failures. Approximately 100 PFS failures, 67 deaths, and 50 local-regional failures are anticipated. The equation described by Schoenfeld⁵⁹ was used to calculate the statistical powers reported in Tables 4-6 with a significance level of 0.05. Two of the three variables evaluated as possible prognostic variables are based on the median value for the FDG SUV_{max} values associated with the primary and nodal disease respectively. The third variable is based upon patients having both their FDG SUV_{max} values (primary and nodal disease) above their respective median. Thus, the percentage of patients satisfying this requirement theoretically can vary from 50% to 0%. Tables 4-6 were amended to reflect the lower number of projected events.

Table 4 below shows statistical power to detect hazard ratios for PFS of 1.50, 1.75, 2.00, and 2.25 for various divisions of patient population, i.e., one group with 10%, 20%, 30%, 40%, or 50%.

Table 4: PFS — Statistical Power With 100 Events and 5% Alpha

% in one group	Hazard Ratio			
	1.50	1.75	2.00	2.25
0.10 (or 0.90)	0.22	0.38	0.54	0.68
0.20 (or 0.80)	0.36	0.6	0.79	0.9
0.30 (or 0.70)	0.45	0.72	0.88	0.96
0.40 (or 0.60)	0.51	0.78	0.92	0.97
0.50	0.52	0.79	0.93	0.98

Table 5 below shows statistical power to detect hazard ratios for OS of 1.50, 1.75, 2.00, and 2.25 for various divisions of patient population, i.e., one group with 10%, 20%, 30%, 40%, or 50%. Table 5: OS — Statistical Power with 67 Events and 5% Alpha

% in one group	Hazard Ratio			
	1.50	1.75	2.00	2.25
0.10 (or 0.90)	0.16	0.27	0.39	0.51
0.20 (or 0.80)	0.26	0.44	0.62	0.75
0.30 (or 0.70)	0.33	0.55	0.73	0.86
0.40 (or 0.60)	0.36	0.61	0.79	0.9
0.50	0.38	0.62	0.8	0.91

Table 6 below shows statistical power to detect hazard ratios for LRC of 1.50, 1.75, 2.00, and 2.25 for various divisions of patient population, i.e., one group with 10%, 20%, 30%, 40%, or 50%.

Table 6: Local-Regional Control (LRC) — Statistical Power with 50 Events and 5% Alpha

% in one group	Hazard Ratio			
	1.50	1.75	2.00	2.25
0.10 (or 0.90)	0.13	0.21	0.31	0.4
0.20 (or 0.80)	0.2	0.35	0.5	0.63
0.30 (or 0.70)	0.25	0.44	0.61	0.74
0.40 (or 0.60)	0.28	0.49	0.67	0.8
0.50	0.29	0.5	0.68	0.81

(8/25/08) In summary, the statistical power is sufficiently high enough to detect a higher hazard ratio of at least 2.00 for PFS and at least 1.75 for OS and LRC.

13.4.2 Precision of Estimates for Post-Treatment PET/CT Scan Analysis in Patients With Clinical N2-3 Disease

It should be noted that patients and institutions could decline to have the second PET/CT scan performed. Based upon the current 0129 trial, it is estimated that 460 (67%) patients enrolled on this protocol will have clinical N2-3 disease. It is projected that 50% of N2-3 patients will have a post-treatment PET/CT because of lack of insurance coverage and further, because of the protocol requirement of a combined PET/CT scanner (see Section 6.11). Thus, potentially there would be 230 patients available for correlating PET/CT findings with nodal disease status post-treatment. The protocol calls for N2-3 patients with less than complete clinical nodal response to undergo neck dissection while it is optional for patients with complete clinical nodal response. The rate of neck dissection in patients with less than complete clinical nodal response is projected to be 90% while the rate in patients with complete clinical nodal response is 50%. Because of a possible selection bias in the clinical complete responders going to neck dissection, the correlation of PET/CT findings with pathologic response will be done not only in all patients but also within these two clinical nodal response subsets. Based upon previous RTOG studies, the projected clinical complete nodal response rate is 50%. Using the projected estimates, there will be approximately 58 patients with a clinical nodal complete response available to correlate PET/CT findings with pathologic response and 104 patients with less than clinical nodal complete response. In addition, since not all patients who had a post-treatment PET/CT evaluation will undergo neck dissection, the two-year nodal relapse rates will be estimated and compared by post-treatment PET/CT finding (negative and positive) within the nodal response subset. The only results available for post-treatment PET/CT scan come from relatively small institutional series and may not provide a reliable estimate of the percentage of patients with negative PET/CT scan. Our best estimate would be 40% negative post-treatment

PET/CT scan rate. Of particular interest will be clinical nodal complete responders who have a negative PET/CT. Based upon the assumptions, there will be 23 such patients available to correlate with pathologic nodal response and 46 available to estimate the two-year nodal relapse rate.

(8/25/08) As June 2008, 65% of the patients enrolled on this protocol have clinical N2-3 disease, which is consistent with original projection. However, approximately 25% of these patients will have a post-treatment PET/CT scan, which is far less than the original projection of 50%. With the increased accrual of 900 patients to this trial, it is now projected that 600 patients will have clinical N2-3 disease, and 150 of them would be available for correlating PET/CT scan findings with nodal disease status post-treatment. Using the projected estimates above, there will be approximately 38 patients with a clinical nodal complete response available to correlate PET/CT scan findings with pathologic response, and 68 patients with less than a clinical nodal complete response. In addition, since not all patients who had a post-treatment PET/CT evaluation will undergo neck dissection, the 2-year nodal relapse rates will be estimated and compared by post-treatment PET/CT finding (negative and positive) within the nodal response subset. The only results available for post-treatment PET/CT scan come from relatively small institutional series and may not provide a reliable estimate of the percentage of patients with negative PET/CT scans. The best estimate would be a 40% negative post-treatment PET/CT scan rate. Of particular interest will be clinical nodal complete responders who have a negative PET/CT. Based upon the assumptions, there will be 15 such patients available to correlate with pathologic nodal response, and 30 patients available to estimate the 2-year nodal relapse rate.

13.5 Patient Accrual

The average monthly patient accrual rate to the past two randomized trials (97-03 and 0129) for a similar patient population were 12.7 and 23.8 cases, respectively, excluding the first 6 months during which IRB approvals were obtained in individual institutions. In light of these rates, the projected annual accrual rate will be 15 cases per month (180 per year). At this rate, it will take approximately 54 months to reach the target accrual, assuming that there will be very little accrual during first 6 months while institutions are obtaining IRB approval. From past studies in this patient population, accrual has generally exceeded the projection. However, the study statistician will recommend to the Data Monitoring Committee (DMC) that the trial be discontinued if accrual is less than 10 per month for a six-month period between months 12 and to 18.

(8/25/08) As April 6, 2008, a total of 507 patients were enrolled on the study. The average monthly accrual for the previous 6 months (September 2007 through March 2008) was 33.2 patients and for the accrual period since activation (November 2005 to April 6, 2008) was 17.8 patients. The brisk rate of patient accrual is expected to continue. If the rate of 33 patients per month continues, the new targeted accrual goal of 945 patients will be reached in 13.5 months (or at the end of May 2009). If the average accrual decreases to 25 patients per month, the accrual phase will take 17.5 months (or at the end of September 2009).

13.6 Randomization

Patients will be stratified by primary site (larynx vs. non-larynx), Nodal stage (N0 vs. N1, N2a, N2b vs. N2c, N3), Zubrod status (0 vs. 1), use of IMRT (no vs. yes), and pre-treatment PET/CT (no vs. yes).

The first 3 stratification factors are based on prior RTOG Recursive Partitioning Analyses.^{11, 60}

The treatment allocation scheme described by Zelen⁶¹ will be used at randomization to balance risk factors other than treating institution.

13.7 Analysis Plan

13.7.1 *Statistical Methods*

(8/25/08) Overall and progression-free survival will be estimated by the Kaplan-Meier method⁶² and the log-rank test⁶³ will be used to test the experimental treatment against the control. The cumulative incidence method will be used to estimate local-regional failure rates, and the failure rates for the experimental treatment will be compared against the control using failure-specific log-rank test.⁶⁴ Multivariate analysis also will be performed using the Cox proportional hazards model with the stratifying variables (see Section 13.6) as fixed covariates. Rates of grade ≥ 3 toxicity will be compared using Fisher's exact test. For each of the three PSS-HN subscales, the frequencies of patients with scores of 50 or less will be compared between the two treatments using the z-statistic for testing binomial proportions at 3 and 12 months from start of treatment. The EQ 5D will be used to generate health utilities, which will then be used in deriving quality

adjusted survivals. The utility scores lie between 0 “Worst health state” and 1 “Best health state”. It will provide two utility scores, one of which is from five-item index score and other from visual analogue scale (VAS), and both will be used in generating separate quality adjusted survivals. The log-rank test will compare those survivals between the treatments. The correlation coefficient between the EQ 5D’s five-item score and the global FACT-G score will be computed for the patient evaluation at baseline, at one year, and at five years from start of protocol treatment.

(8/25/08) All failure times will be measured from the date of study registration to the date of failure, competing risk, or last follow-up. The following table shows how each first event will be counted for local-regional control (LRC) and progression-free survival (PFS). Anything not explicitly in the table (e.g., second primary tumor) is not considered an event and the patient will continue to be followed for failure. For overall survival, death from any cause will be considered a failure.

First Event	LRC	PFS
None	Censored	Censored
Local-regional progression or recurrence	Failure	Failure
Distant metastasis	Competing risk	Failure
Death due to study cancer or from unknown causes	Failure	Failure
Death due to any other reason	Competing risk	Failure
Salvage surgery of primary with tumor present/unknown	Failure	Failure
Salvage neck dissection with tumor present/unknown, >15 weeks from end of RT	Failure	Failure

13.7.2 Interim Analyses to Monitor Study Progress

Interim reports with statistical analyses will be prepared twice each year until the analysis reporting the primary endpoint has been presented. In general, these reports will contain:

- Patient accrual rate with a projected completion date for the accrual phase;
- Distribution of important baseline pre-treatment characteristics;
- Frequency and severity of adverse events;
- Compliance rate for treatment delivery with respect to the protocol prescription;
- Level of patient participation at each protocol-designated HRQOL evaluation time point, along with reasons for non-participation.

These interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints such as OS and DFS. The RTOG Head and Neck Steering Committee and the RTOG Data Monitoring Committee (DMC) will review this report with particular emphasis on toxicity and patient accrual.

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

13.7.3 Interim Analysis to Monitor Treatment Delivery and Early Death

Since there is limited experience with the experimental regimen, an interim analysis will be performed to assure that there is no unexpected problem with tolerability of the drugs and no decrease in the radiation therapy dose delivered. This interim analysis will occur after the first 80 patients are entered into the protocol (The data for this analysis would be available six months after the 80th patient is entered. The six-month interval would allow sufficient time for the treatment to be completed, the first two therapy toxicity assessments to be done at 4 and 8-9 weeks as specified in the protocol, and the data processed). There would be about 40 patients on the 0522 experimental arm available for analysis. Treatment delivered per protocol

prescription will be used to evaluate patient tolerability for the experimental arm (Arm 2). Tolerability will be measured by the percentage of patients who receive the following:

- Two chemotherapy cycles;
- The initial dose of cetuximab;
- At least five of the weekly cetuximab doses;
- Radiation therapy scored by the study chair as per protocol or with minor deviation.

The tolerability rate for the control arm without cetuximab (Arm 1) is approximately 82% based on two prior RTOG studies. For the 0522 experimental arm, 75% will be considered the minimum acceptable rate of tolerability. If the observed tolerability rate falls between 50% and 65%, then possible modifications to the regimen will be explored to improve the tolerability rate. If the observed rate is less than 50%, the tolerability rate will be considered unacceptably low, and a recommendation will be made to the RTOG DMC to discontinue the study. Assuming a binomial distribution with a one-sided test at the 0.05 level, the statistical power to detect at least a 25% decrease from 75% with 40 patients is 0.75.

The expected toxicity profiles for the two 0522 arms will be similar except for skin toxicity, which will be increased with C225. However, that toxicity is considered acceptable for this study and will not be used as a criterion for discontinuing the study. The rate of patients dying while on or within 30 days of discontinuation of protocol treatment (early death) will be used to monitor for possible unexpected fatal toxicities. The early death rate for the 0522 control arm regimen from two past RTOG studies is about 5%. If the early death rate is 10% higher with C225 arm, then all early deaths will be re-reviewed and modifications to the study will be considered depending on the results of this review. If the true early death rate is 5% or less, there is less than a 1% chance that the regimen will be identified as unacceptable assuming a binomial distribution with a one-sided test.

13.7.4 Significance Testing for Early Termination and Reporting (8/25/08)

Three interim treatment comparisons will be performed for the RTOG meeting immediately after 108, 217, and 325 PFS failures (total from both arms) have been reported. Toxicity, treatment delivery, PFS, and OS will be reported to the RTOG DMC. The PFS difference between the control arm and the experimental arm will be tested using the log-rank statistic at the significance level of 0.001. In addition, the conditional statistical power (CP) to observe the hypothesized treatment effect will be calculated. If any tests are significant or the CP < 0.10, the responsible statistician will recommend to the DMC that further patient accrual should be discontinued, if appropriate, and the results reported early.

13.7.5 Analysis for Reporting the Initial Treatment Results (8/25/08)

The analysis reporting the treatment results will be carried out after 434 PFS failures (or 239 on control arm) have been observed unless the criteria for early stopping are met.

The usual components of this analysis include:

- Tabulation of all cases entered, and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline pre-treatment characteristics;
- Frequency and severity of adverse events;
- Compliance rate for treatment delivery with respect to the protocol prescription;
- Observed results with respect to the study endpoints.

The difference in PFS between the control arm and the experimental arm will be tested using the log-rank statistic at the significance level of 0.0238 given that the three interim analyses are carried out and show no statistical significance. Survival distributions for treatment arms will be compared across all the primary sites and also in patients without laryngeal primary. The rationale for exclusion of laryngeal patients is that their surgical salvage rate is generally as seen in the intergroup larynx trial, RTOG 91-11.

Patients who are found to be ineligible retrospectively after protocol registration or have withdrawn their consent will be excluded from treatment analysis. Thus, only eligible patients will be included in this analysis.

(8/25/08) Subset analyses comparing the treatments within the HPV+ and the HPV- patient populations will be performed at the same time as the protocol-designated final analysis

comparing the treatment arms. With HPV- patients, the difference in PFS and OS between the control arm and the experimental arm will be tested using the log-rank statistic. However, with oropharyngeal HPV+ patients, the treatment effect on PFS and OS only will be estimated by hazard ratio with a 95% confidence interval because of the limited numbers of patients in that subset and the events expected. The subset analyses initially will be done using all patients with non-oropharyngeal primaries and with patients with oropharyngeal primaries for which the HPV status has been determined. If HPV status is missing, it will be imputed, and additional analysis will be performed to check the robustness of the results using the oropharyngeal patients with HPV determination.

13.7.6 Quality of Life and Health Utility Analysis

For each of the three PSS-HN subscales, the frequency of patients with scores of 50 or less will be estimated along with its 95% confidence interval for each treatment regimen at 3 and 12 months from start of treatment. These frequencies will be compared between the two treatments using the z-statistic for testing binomial proportions. In addition, each patient will be classified at these two time points relative to change from the baseline scores as improved, no change, or worsened. Either 20+ points increase or decrease will be considered as a change for diet and 25 points for eating and speech. The pattern of changes for each subscale at the two time points will be compared between the two treatments with Chi-square test. The distributions of the EQ-5D five-item index score for each treatment will be compared at 3 and 12 months using the non-parametric Kolmogorov-Smirnov test. The correlation coefficient between the EQ 5D's five-item and the global FACT-G score will be computed for the patient evaluation at baseline, at one year, and at five years from start of protocol treatment.

Protocol eligible patients will be included in the quality of life (QOL) analysis only if they have provided data for the QOL measurement to be analyzed. There will be no imputation for QOL missing observations. The cause of missing data is assumed to be missing completely at random. The distribution of pre-treatment characteristics, such as performance score and treatment assignment, will be compared between the patients with available QOL data and the patients without QOL data. Striking differences (e.g., > 20%) will be reported.

13.7.7 Tumor Marker Analysis

Quantitative immunohistochemistry will be performed at study chair's laboratory without knowledge of clinical outcome, and the results will be forwarded to the RTOG Statistical Unit for correlation with clinical outcome. All tumor marker analyses will occur after the analysis reporting the results from the treatment comparison. The correlation among the tumor markers' values will be computed and reported.

The patients will be initially divided into two subgroups based upon previously defined (or hypothesized) cut points one or more tumor markers, and these two groups will be referred to as favorable and unfavorable risk groups. In univariate analysis, the log-rank test will be used to test for DFS and OS differences between the favorable and unfavorable risk groups; a failure-specific log-rank test will be used for LRF.⁶⁴

Multivariate analysis will be performed using the Cox proportional hazards model for both outcomes.⁶⁵ Potential covariates evaluated for the multivariate models are assigned treatment, age, Zubrod performance status, T-stage, N-stage, and primary site. A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the tumor markers. This approach will be employed to account for as much variation as possible for each outcome before they are tested. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here. Then the tumor marker or combination of markers will be added to the model to test for significance. If the hypothesized cut points do not yield statistical significance, other cut points may be evaluated.

The analysis of one individual marker will include only patients with that marker. However, the analysis of two or more markers will include all patients with at least one determination of the five tumor makers. The assumption is made that the other tumor maker values are missing completely at random. The missing tumor values will be imputed 10 times, and the average value along with the pooled standard error associated with the parameter estimates for each tumor marker in the Cox model analysis will be reported.⁶⁶ The tumor marker study population will be compared with the patients without a value for that tumor marker to determine if there are any differences with respect to distribution of baseline variables or outcome.

13.7.8 PET/CT Analysis

13.7.8.1 Pre-Treatment PET/CT Analysis

The patients will be initially dichotomized for each of three possible prognostic variables as defined in Section 13.4. In univariate analysis, the log-rank test will be used to test for survival differences between the subdivisions for each variable and the failure-specific log-rank test will be used for local-regional failure rate.

Multivariate analysis will be performed using the Cox proportional hazards model. Potential covariates evaluated for the multivariate models are assigned treatment, age, Zubrod performance status, T-stage, N-stage, and primary site. A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the three pre-treatment PET/CT SUV_{max} variables. This approach will be employed to account for as much variation as possible for each outcome before the three PET/CT variables will be tested in the model. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here. Then three pre-treatment PET/CT variables will be added to the model to test for their significance and the one resulting in the smallest p-value < 0.05 will be considered prognostic for the endpoint. Other cut points for SUV_{max} values, which have reported as prognostic, will be also evaluated.

The patients who had pre-treatment PET/CT will be compared with the patients who did not have a pre-treatment PET/CT to determine if there are any differences with respect to distribution of baseline variables and outcome.

13.7.8.2 Post-Treatment PET/CT Analysis

For patients undergoing neck dissection, pathology will be used as our gold standard. The predictive values for FDG-PET/CT imaging along with their associated 95% confidence intervals will be calculated by clinical nodal response status (complete vs. < complete) as follows:

- Sensitivity = (TP)/(TP + FN);
- Specificity = (TN)/(TN + FP);
- Positive Predictive Value (PPV) = (TP)/(TP + FP);
- Negative Predictive Value (NPV) = (TN)/(TN + FN)

Where “TP” = true positives, or number of patients with positive nodes correctly shown to contain disease; “FP” = false positives, or number of patients with negative nodes incorrectly labeled as containing disease; “TN” = true negatives, or number of patients with negative nodes correctly shown to not contain disease; “FN” = false negatives, or number of positive nodes not detected.

As noted in Section 13.4.2, only a subset of N2-3 patients will have both the post-treatment PET/CT study and a nodal dissection. Therefore, there is a possible risk of verification bias. We plan on using a multiple imputation framework to address this bias. The Rubin (Logit) method for imputation will be utilized per recommendation by Harel and Zhou.⁶⁷ However, the final determination of the method to be used will be made after reviewing the statistical literature prior to performing the PET/CT analysis. For this analysis, information will be collected on why the post-treatment PET/CT was not performed and on why a nodal dissection was not performed

Also, the yearly nodal relapse rates will be estimated for four patient subset defined by clinical nodal response status and the post-treatment PET/CT finding (negative or positive). The nodal relapse rates between the PET/CT subgroups will be compared within each response status category

13.8 Inclusion of Women and Minorities (8/25/08)

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, a statistical analysis will be performed, as sample sizes allow, to examine possible differences by gender, race, or ethnicity. Based on the accrual statistics from ongoing trial RTOG 0129, we project that 80% of patients enrolled to this study will be men, and 20% women. With respect to race, we project 80% white and 20% not white. With respect to ethnicity, we project 5% Hispanic/Latino and 95% not Hispanic/Latino. Assuming no differences between the genders or ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference is 0.76 for males and 0.68 for whites. The statistical power for females, non-whites, and Hispanic/Latino is too low for any meaningful treatment comparison.

Projected Distribution of Gender and Minorities

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	9	38	47
Not Hispanic or Latino	180	718	898
Ethnic Category: Total of all subjects	189	756	945
Racial Category			
American Indian or Alaskan Native	1	5	6
Asian	1	5	6
Black or African American	29	116	145
Native Hawaiian or other Pacific Islander	0	3	3
White	158	627	785
Racial Category: Total of all subjects	189	756	945

REFERENCES

1. Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: Altered fractionation regimens. *The Lancet Oncology*. 3: 693-701, 2002. PMID:12424072
2. Fu KK, Pajak TF, Trotti A, et al. A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *Int J Radiat Onc Biol Phys*. 48: 7-16, 2000. PMID: 10924966
3. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol*. 21: 92-98, 2003. PMID: 12506176
4. Al-Sarraf M, LeBlance M, Shanker PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099. *J Clin Oncol*. 16: 1310-1317, 1998. PMID: 9552031
5. Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *NEJM*. 349: 2091-2098, 2003. PMID: 14645636
6. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: Comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J Radiat Onc Biol Phys*. 55: 93-98, 2003. PMID: 12504040
7. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: A randomized multicenter study. *J Clin Oncol*. 16:1318-1324, 1998. PMID: 9552032
8. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *NEJM*. 338: 1798-1804, 1998. PMID: 9632446
9. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: A prospective randomized trial. *J Clin Oncol*. 18: 1458-1464, 2000. PMID: 10735893
10. Bernier J, Dommenege C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *NEJM*. 350: 1945-1952, 2004. PMID: 15128894
11. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *NEJM*. 350: 1937-1944, 2004. PMID: 15128893
12. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves loco-regional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *J Clin Oncol*. In press.
13. Wee J, Tan EH, Tai BC, et al. Phase III randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with AJCC/UICC (1997) stage 3 and 4 nasopharyngeal cancer of the endemic variety. Annual Meeting Proceedings of the ASCO Meeting. 23: 487, 2004.
14. Bachaud J-M, Cohen-Jonathan E, Alzieu C, et al. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: Final report of a randomized trial. *Int J Radiat Onc Biol Phys*. 36: 999-1004, 1996. PMID: 8985019
15. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Research*. 62: 7350-7356, 2002. PMID: 12499279

REFERENCES (Continued)

16. Ang KK, Andratschke NH, Milas L. Epidermal growth factor receptor and response of head-and-neck carcinoma to therapy. *Int J Radiat Onc Biol Phys.* 58: 959-965, 2004. PMID: 14967456
17. Mendelsohn J, Baselga J. Status of Epidermal Growth Factor Receptor Antagonists in the Biology and Treatment of Cancer. *J Clin Oncol.* 21: 2787-2799, 2003. PMID: 12860957
18. Harari PM, Huang S-M. Combining EGFR inhibitors with radiation or chemotherapy: Will preclinical studies predict clinical results? *Int J Radiat Onc Biol Phys.* 58: 976-983, 2004. PMID: 14967459
19. Bonner JA, Giralt J, Harari PM, et al. Cetuximab prolongs survival in patients with locoregionally advanced squamous cell carcinoma of head and neck: A phase III study of high dose radiation therapy with or without cetuximab. *Proceedings of the American Society of Clinical Oncology.* 23: 488, 2004.
20. Weber R, Berkey B, Forastiere A, et al. Outcome of salvage total laryngectomy following organ preservation therapy: The Radiation Therapy Oncology Group trial 91-11. *Arch Otolary H & N Surg.* 129:44-49, 2003. PMID 12525193
21. Ang KK, Harris J, Garden AS, et al. Concomitant boost radiation plus concomitant cisplatin for advanced head and neck carcinomas: A phase II trials of the Radiation Therapy Oncology Group (RTOG 99-14). *J Clin Oncol.* In press.
22. David Pfister, personal communication.
23. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomized controlled trial. *Lancet.* 362(9388): 933-40, 2003. Erratum in: *Lancet.* 362(9395):1588. PMID: 14511925
24. Cooper J, Farnum N, Asbell S, et al. Recursive partitioning analysis of 2,105 patients treated in RTOG studies of head and neck cancer. *Cancer.* 77: 1905-1911, 1996. PMID: 8646692
25. Vermeersch H, Loose D, Ham H, et al. Nuclear medicine imaging for the assessment of primary and recurrent head and neck carcinoma using routinely available tracers. *Eur J Nucl Med Mol Imaging.* 30:1689-1700, 2003. PMID 14576949
26. Antoch G, Saoudi N, Kuehl H, et al. Accuracy of whole-body dual-modality fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: Comparison with CT and PET. *J Clin Oncol.* 22:4357-4368,2004. PMID 15514377
27. Schwartz DL, Rajendran J, Yueh B, et al. FDG-PET prediction of head and neck squamous cell cancer outcomes. *Arch Otolaryngol Head Neck Surg.* 130:1361-1367,2004. PMID 15611393
28. Minn H, Lapela M, Klemi PJ, et al. Prediction of survival with fluorine-18-fluoro-deoxyglucose and PET in head and neck cancer. *J Nucl Med.* 38:1907-1911, 1997. PMID 9430467
29. Brun E, Kjellen E, Tennvall J, et al. FDG PET studies during treatment: prediction of therapy outcome in head and neck squamous cell carcinoma. *Head Neck.* 24:127-135,2002. PMID 11891942
30. Yao M, Graham MM, Hoffman HT, et al. The role of post-radiation therapy FDG PET in prediction of necessity for post-radiation therapy neck dissection in locally advanced head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys.* 59:1001-1010,2004;. PMID 15234033
31. Kostakoglu L, Goldsmith SJ. PET in the assessment of therapy response in patients with carcinoma of the head and neck and of the esophagus. *J Nucl Med.* 45:56-68, 2004. PMID 14734674
32. Huguenin PU, Taussky D, Moe K, et al. Quality of life in patients cured from a carcinoma of the head and neck by radiotherapy: the importance of the target volume. *Int J Radiat Oncol Biol Phys.* 45:47-52, 1999.

REFERENCES (Continued)

33. de Graeff A, de Leeuw JR, Ros WJ, et al. A prospective study on quality of life of patients with cancer of the oral cavity or oropharynx treated with surgery with or without radiotherapy. *Oral Oncol.* 35:27-32, 1999.
34. de Graeff A, de Leeuw RJ, Ros WJ, et al. A prospective study on quality of life of laryngeal cancer patients treated with radiotherapy. *Head Neck.* 21:291-6, 1999.
35. Epstein JB, Emerton S, Kolbinson DA, et al. Quality of life and oral function following radiotherapy for head and neck cancer. *Head Neck.* 21:1-11, 1999.
36. List MA, Haraf D, Hagerman D, et al. Two-four years post chemoradiotherapy (CT/XRT) for stage IV head and neck cancer (HNC): How are our patients doing? *Amer Soc of Clin Onc.* 391a, 1999.
37. List MA, Siston A, Haraf D, et al. Quality of life and performance in advanced head and neck cancer patients on concomitant chemoradiotherapy: A prospective examination. *J Clin Oncol.* 17:1020-8, 1999.
38. List MA, Mumby P, Haraf D, et al. Performance and quality of life outcome in patients completing concomitant chemoradiotherapy protocols for head and neck cancer. *Qual Life Res.* 6:274-84, 1997.
39. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. *Cancer.* 66: 564-9, 1990. PMID: 2364368
40. Vokes EE, Kies MS, Haraf DJ, et al. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer. *J Clin Oncol.* 18:1652-61, 2000.
41. List M, Haraf D, Stracks J, et al. Quality of life (QOL)/performance in head & neck Cancer (HNC): Comparison between paclitaxel-based (P-CT/XRT) and cisplatin-based (C-CT/XRT) concomitant chemoradiotherapy regimens. *Amer Soc of Clin Onc.* 412,2000.
42. List M, personal communication.
43. List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale: A study of utility and validity. *Cancer.* 77: 2294-301, 1996. PMID: 8635098
44. Cella, D.F., et al., The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*, 1993. 11(3): p. 570-9.
45. D'Antonio, L.L., et al., Quality of life and functional status measures in patients with head and neck cancer. *Arch Otolaryngol Head Neck Surg*, 1996. 122(5): p. 482-7.
46. Glick HA, Polsky D, Willke RJ, et al. A comparison of preference assessment instruments used in a clinical trial: Responses to the visual analog scale from the EuroQol EQ-5D and the Health Utilities Index. *Med Decis Making.* 19: 265-275, 1999. PMID: 10424833
47. Johnson JA, Coons SJ. Comparison of the EQ-5D and SF-12 in an adult U.S. sample. *Qual Life Res.* 7: 155-166, 1998. PMID: 952349
48. Johnson JA, Coons SJ, Ergo A, et al. Valuation of EuroQol (EQ-5D) health states in an adult U.S. sample. *Pharmacoeconomics.* 13: 421-433, 1998. PMID: 9523497
49. Johnson JA, Ohinmaa A, Murti B, et al. Comparison of Finnish and U.S.-based visual analog scale valuations of the EQ-5D measure. *Med Decis Making.* 20:281-289, 2000. PMID: 10929850
50. Trippoli S, Vaiani M, Lucioni C, et al. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life study group of the master 2 project in pharmacoeconomics. *Pharmacoeconomics.* 19: 855-863, 2001. PMID: 11596837

REFERENCES (Continued) [2/23/11]

51. Schulz MW, Chen J, Woo HH, et al. A comparison of techniques for eliciting patient preferences in patients with benign prostatic hyperplasia. *J Urol*. 168: 155-159, 2002. PMID: 12050512
52. Badia X, Herdman M, Kind P. The influence of ill-health experience on the valuation of health. *Pharmacoeconomics*. 13: 687-696, 1998. PMID: 10179704
53. Wu AW, Jacobson KL, Frick KD, et al. Validity and responsiveness of the EuroQol as a measure of health-related quality of life in people enrolled in an AIDS clinical trial. *Qual Life Res*. 11: 273-282, 2002. PMID: 12074264
54. Lakatos, E. Sample size determination in clinical trials with time-dependent rates of losses and noncompliance. *Controlled Clin Trials*. 7:189-199, 1986. PMID: 3802834
55. Michiels S, et al. Surrogate endpoints for overall survival (OS) in head and neck squamous cell carcinoma (HNSCC) using individual data of 23,737 patients. *J Clin Oncol*. 25: Abstract 6035, 2007.
56. Mellin H. Human papillomavirus (HPV) DNA in tonsillar cancer: clinical correlates, risk of relapse, and survival. *Int J Cancer*. 89: 300-304, 2000.
57. Schwartz S, Yueh B, Mcdougall J, Daling J, Schwartz S. Human papillomavirus infection and survival in oral squamous cell cancer: A population-based study. *Otol Head Neck Surg*. 125:1-9, 2001.
58. Pajak, TF. RTOG Senior Statistician. Personal communication, 2008.
59. Schoenfeld D. The asymptotic properties of nonparametric tests for comparing survival distributions. *Biometrika*. 68: 316-319, 1981.
60. Cooper, J., Berkey B, Marcial V, Lee DJ, Fu KK. Validation of the RTOG recursive partitioning classification for head and neck tumors. *Head and Neck J* 23(8): 669-677, 2001.
61. Zelen M. The randomization and stratification of patients to clinical trials. *J Chron Dis*. 27: 365-375, 1994. PMID: 4612056
62. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Amer Stat Assoc*. 53: 457-481, 1958.
63. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*. 5: 163-170, 1966. PMID: 5910392
64. Prentice RL, Kalbfleisch JD, Peterson AV, Flournoy N, Farewell VT, Breslow NE. The analysis of failure times in the presence of competing risks. *Biometrics*. 34: 541-554, 1978.
65. Cox DR. Regression models and life tables. *J Royal Stat Soc. Series B*, 34:187-229, 1972.
66. Allison PA. *Missing Data*. Thousand Oaks, Ca: SAGE Publications; 2002.
67. Harel O, Zhou X-H. Multiple imputation for correcting verification bias. *UW Biostatistics Working Paper Series* [series online]. 2005; paper 252. Available at: <http://www.bepress.com/uwbiostat/paper252>.
68. Ang KK, Harris J, Wheeler R, et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. *NEJM*. [epub 2010 June 7].

APPENDIX I

RTOG 0522

A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin Versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) [Followed by Surgery for Selected Patients] for Stage III and IV Head and Neck Carcinomas

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have advanced head and neck cancer.

Why is this study being done? (6/1/06)

The purpose of this study is to compare the effects, good and/or bad, of radiation therapy and chemotherapy (cisplatin) with radiation therapy, chemotherapy, and cetuximab (C225) on you and your advanced head and neck cancer to find out which is better. In this study, you will get either radiation and cisplatin or radiation, cisplatin, and C225.

C225 was approved in 2004 as a treatment for patients with colorectal cancer, and when this study began, C225 was an experimental treatment for patients with head and neck cancer. In 2006, the FDA approved C225 for the treatment of head and neck cancer. C225 may delay or prevent tumor growth by blocking certain cellular chemical pathways that lead to tumor development.

In addition, some patients in this study will have a combination of a PET (Positron Emission Tomography) and CT (Computed Tomography) scan (explained below). For those patients, this study will see if PET/CT is a good way to find out the effect of treatment on their cancer.

How many people will take part in the study? (8/25/08)

About 945 people will take part in this study.

What will happen if I take part in this research study? (10/17/13)

Before you begin the study, you will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination by several doctors
- One of the following:
 - Chest x-ray
 - Or CT (Computed Tomography) scan of your chest: A study using x-rays to look at one part of your body
 - Or the combination of a PET (Positron Emission Tomography) and CT scan of your body ; A PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body.

- CT scan or an MRI (Magnetic Resonance Imaging) of your head and neck or a PET/CT scan of your body (MRI: Imaging using a strong magnetic field to look at one part of your body)
- Tests of your heart function: One of two common tests of heart function will be used to make sure that your heart can handle the stress of fluid loads given with chemotherapy: a Multiple Gated Image Acquisition scan (MUGA) or an echocardiogram.
 - A MUGA scan is performed by injecting a small amount of radioactive substance mixed with your own blood. A camera records the path of the radioactive tracer like a movie, and computer analysis estimates the efficiency of the heart in pumping blood.
 - An echocardiogram accomplishes the same analysis by using sound waves bounced off the walls of the heart using a small instrument held against the chest wall.
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
- For women able to have children, a pregnancy test
- If your study doctor recommends:
 - A dental evaluation before receiving radiation
 - A hearing test
 - An evaluation of your diet and ability to chew and swallow to see if a feeding tube is needed

(8/25/08) If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures **during the study**. They are part of regular cancer care.

- Physical examination by your several doctors
- Evaluation of your weight and ability to carry out daily activities
- Blood tests every week and every third week during treatment (about 7 times); about 2-3 teaspoons of blood will be taken from your vein
- Evaluation of any side effects you may be having
- An evaluation of your diet and ability to chew and swallow to see if a feeding tube is needed

You will need these tests and procedures in follow-up visits. They are being done to see how you and your cancer was affected by the treatment you received.

At 4 weeks after treatment

- Evaluation of your weight and ability to carry out daily activities
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having

At 8-9 weeks after treatment

- A physical examination
- For patients with remaining large tumors, a CT scan or MRI of the head and neck; these patients may also have a PET/CT scan.

At 6, 9, and 12 months from the start of treatment

- A physical examination
- Evaluation of your weight and your ability to carry out your daily activities
- Evaluation of any side effects you may be having
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)

Every 3 months for year 2, every 6 months for years 3-5, then annually:

- A physical examination
- Blood tests (about 2-3 teaspoons of blood will be taken from your vein)

At 6 months for year 1, then annually:

- Chest x-ray or CT scan of the chest or PET/CT scan of your body

At 6 months after treatment, then annually for 5 years:

- CT scan or MRI of your head and neck or PET/CT scan of your body

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

If you are in Group 1 (often called "Arm 1"), you will receive radiation therapy and chemotherapy (cisplatin).

All patients will receive radiation therapy for 6 weeks. Each radiation treatment will take about 30 minutes. There are several ways to receive radiation therapy in this study. Your study doctor will discuss with you how your radiation therapy will be given:

- You may receive radiation therapy once a day, Monday through Friday, for about 3 ½ weeks and then twice a day, Monday through Friday, for the remaining 2 ½ weeks. There will be at least 6 hours between the two daily treatments.
- Or you may receive radiation therapy once a day for four days of the week (Monday through Thursday) and twice a day on the fifth day (Friday) for 6 weeks. When given twice a day on the fifth day, there will be at least 6 hours between treatments.
- Or you may receive radiation therapy once a day, Monday through Saturday for 6 weeks.

All patients also will receive chemotherapy (cisplatin), through the vein, on days 1 and 22 of treatment. This will take 60 minutes. Some patients may stay overnight in the hospital after each chemotherapy treatment to receive medicines to replace body fluids. Your study doctor will discuss this with you.

If you are in group 2 (often called "Arm 2"), you will receive cetuximab (C225), radiation therapy, and chemotherapy (cisplatin).

Before your first dose of C225, you will be given some medicine through your vein to prevent an allergic reaction to C225. Then you will be given the first dose of C225 through your vein for approximately two hours. You will not receive chemotherapy or radiation therapy on the day you receive the first dose of C225.

Your blood pressure and overall physical condition will be closely monitored while you receive C225 and for at least one hour afterwards. If you have a severe allergic reaction to the first dose of C225 or any later doses, the study doctor will treat you for the reaction, and you may not receive further C225 on this study. You and the study doctor can discuss other treatments that you can receive off study.

If you tolerate the first dose of C225 well, the following week you will begin receiving C225 before radiation therapy and chemotherapy. You will receive C225 once a week for 7 weeks.

All patients will receive radiation therapy for 6 weeks. Each radiation treatment will take about 30 minutes. There are several ways to receive radiation therapy in this study. Your study doctor will discuss with you how your radiation therapy will be given:

- You may receive radiation therapy once a day, Monday through Friday, for about 3 ½ weeks and then twice a day, Monday through Friday, for the remaining 2 ½ weeks. There will be at least 6 hours between the two daily treatments.
- Or you may receive radiation therapy once a day for four days of the week (Monday through Thursday) and twice a day on the fifth day (Friday) for 6 weeks. When given twice a day on the fifth day, there will be at least 6 hours between treatments.
- Or you may receive radiation therapy once a day, Monday through Saturday for 6 weeks.

All patients also will receive chemotherapy (cisplatin), through the vein, on days 1 and 22 of treatment. This will take 60 minutes. Some patients may stay overnight in the hospital after each chemotherapy treatment to receive medicines to replace body fluids. Your study doctor will discuss this with you.

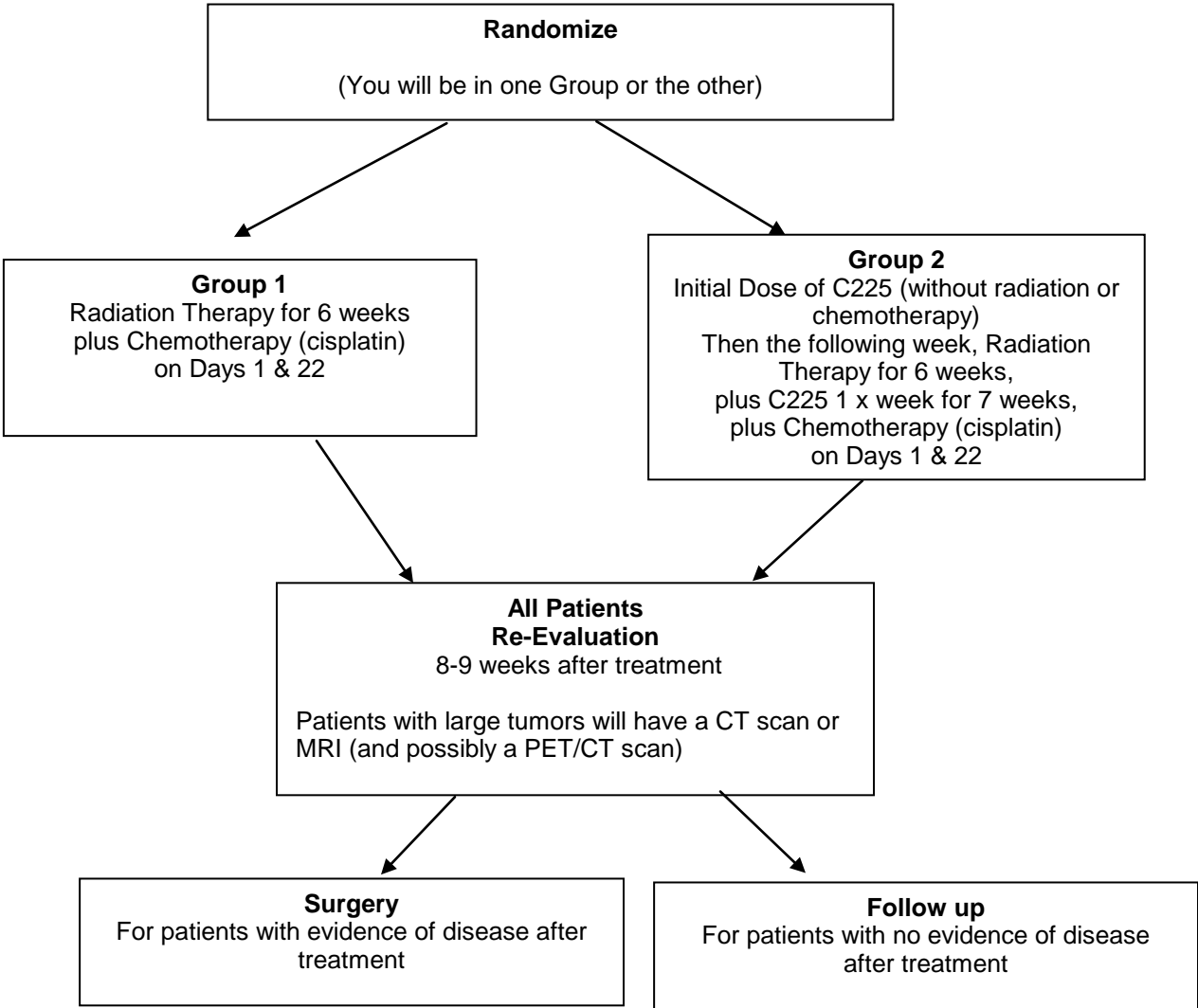
Both Groups: Evaluation of Treatment

Eight to nine weeks after treatment, patients with large tumors will have a CT scan or MRI of the head and neck (and may have an additional PET/CT scan) to evaluate the effect of treatment on their cancer.

Patients with remaining large tumors after treatment will have surgery to remove the cancer, if it is found that surgery can be done to remove the remaining cancer. The study doctor and surgeon will discuss the need for this re-evaluation and surgery with you.

Study Plan (6/1/06)

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the study? (8/17/11)

If you are in Group 1, you will receive treatment for about 6 weeks. If you are in Group 2, you will receive treatment for about 7 weeks. Patients with remaining large tumors after treatment will have surgery 9-10 weeks after treatment, if it is found that surgery can be done to remove the remaining cancer.

After you are finished with treatment, the study doctor will ask you to visit the office for follow-up exams at 8-9 weeks after treatment, 6, 9, and 12 months from the start of treatment, every 3 months in year 2, every 6 months in years 3-5, then annually.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so that any risks from the radiation therapy, chemotherapy, or C225 (if you receive C225) can be evaluated by the study doctor. Another reason to tell the study doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop radiation therapy, chemotherapy, or C225 (if you receive C225). In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects include:

Combining cisplatin with radiation to the head and neck can increase the effectiveness of radiation therapy on your cancer, but also can increase the side effects of radiation on normal tissue in treatment area. In addition, receiving a combination of cisplatin with radiation can result in the side effects described below being more likely or more severe.

Risks Associated with Radiation to the Head and Neck

Very Likely

- Sores in the mouth and/or throat which can be painful and make it very difficult to chew and or swallow foods
- Mouth dryness or changes in taste and/or smell that may be permanent
- Thick saliva
- Hoarseness
- Tanning or redness of the skin in the head and neck area being treated with radiation
- Ear pain and/or pressure
- Fatigue
- Weight loss
- Permanent hair loss in the area treated with radiation
- Loss of teeth, or cavities in the teeth, if strict dental care is not followed and/or hypersensitivity of teeth

Less Likely, But Serious

- Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
- Serious damage to the spinal cord, nerves in the neck, jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening
- Temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness
- Breathing problems
- Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia.
- Serious ear infections and/or hearing loss
- Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”
- Permanent hair loss (of the face/chin/neck)

Risks Associated with PET/CT scans

A PET/CT scan involves exposure to a low dose of radiation from an injection of a radioactive substance (a tracer). The risk from this level of radiation exposure is about 60% of the allowable annual dose for radiation workers (such as an x-ray technician) and is small when compared with other everyday risks. Ask the study doctor if you would like more information about radiation exposure.

Less Likely

- Discomfort from lying still on an enclosed scanning table
- Bruising or bleeding at the site of the injection of the tracer
- Infection at the injection site

Rare but Serious

- An allergic reaction to the radioactive substance

Risks Associated with cisplatin (6/1/06)

Very Likely

- Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
- Anemia
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
- Generalized loss of strength
- Hearing loss, ringing in the ears
- Loss of muscle or nerve function that may cause weakness or numbness in your hands and feet
- Loss of appetite and weight loss
- Low magnesium in the blood, which could result in muscle cramps and/or weakness
- Low calcium in the blood
- Kidney damage

Less Likely

- Allergic reactions (sweating, difficulty breathing, rapid heartbeat)
- Muscle cramps or spasm
- Facial swelling
- Loss of taste
- Loss of coordination
- Involuntary movement
- Restlessness
- Loss of hair, which is temporary
- Blood clots
- Low blood pressure

Less Likely, But Serious

- Seizures
- A severe allergic reaction, which could be life threatening
- Decrease in the kidneys' ability to handle the body's waste, which may be permanent
- Calcium or potassium levels so low that it may affect heart function
- Decrease in liver function
- Another cancer called acute leukemia
- A condition called hemolytic uremic syndrome that involves decreased red blood cells and platelets, fever, and kidney failure

Risks Associated with Cetuximab (C225) [8/25/08]

Very Likely

- Weakness
- Headache
- Fever
- Dry skin
- Localized acne-like skin reactions, rash, itching

- Low calcium in the blood
- Low magnesium in the blood, which could result in muscle cramps and/or weakness

Less Likely

- Inflammation under fingernails and/or toenails, which can last for several months after C225 is stopped
- Mouth sores
- Nausea and/or vomiting
- Diarrhea
- Constipation
- Upset stomach
- Reduced appetite, which could lead to weight loss
- Stomach pain
- Chills
- Dehydration
- Trouble sleeping
- Tiredness and/or sluggishness
- Feeling depressed
- Muscle aches
- Joint or back pain
- Build up of fluid in ankles, feet, and/or legs
- Shortness of breath
- Cough
- Hair loss
- Inflammation of the lining of the eye

Less Likely, But Serious

- Reduced blood counts, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily; this lowering of blood counts can lead to need for treatment with antibiotics, transfusions, or hospitalization if severe.
- Calcium or potassium levels so low that it may affect heart function
- Blood clots within a blood vessel in the lungs, legs, pelvis, or other places
- Kidney failure, which could lead to being hospitalized, or rarely, to death

Rare

- Changes in blood tests that check how your liver is working

Rare, But Serious

- Scarring of lung tissue, which could be life threatening or lead to death
- Heart attack
- Blood clots outside of the lungs, legs, and pelvis

Possible allergic reactions to Cetuximab

Cetuximab also may cause allergic reactions such as hives, itching, and/or skin rash. Some patients have had allergic reactions with the first dose of cetuximab, but some patients have had reactions with later doses. The allergic reactions also can be severe, involving shortness of breath, wheezing, difficulty swallowing, lightheadedness, very low blood pressure, and rarely, heart attack and/or death.

Your condition will be closely monitored during doses of cetuximab and for at least one hour afterwards. If you have a severe reaction, your doctor will treat you for the reaction, and you will not receive further treatment on this study. If you have a delayed severe reaction after receiving cetuximab, you must immediately tell your doctor.

Risks Associated with Cisplatin, Cetuximab (C225), and Radiation Therapy

The combination of cetuximab with chemotherapy and radiation therapy could increase the likelihood and/or severity of the side effects of chemotherapy and radiation therapy. The combination also could increase the risk of heart damage, including heart attack, abnormal heart rhythms, and/or heart failure, which could lead to death.

Risks Associated with Neck Surgery

Patients with remaining large tumors after treatment will have surgery to remove the cancer, if it is found that surgery can be done to remove the remaining cancer. The study doctor and surgeon will discuss the need for

surgery with you. You will need to review and sign a separate permission form from your doctor/hospital for this surgery.

The serious risks of surgery are infection, bleeding, poor healing of the skin and/or muscles in the neck, clots in the legs and/or lung, pneumonia, heart attack stroke, and/or death.

These risks may be more likely or severe for people in this study than for someone having neck surgery without having had chemotherapy and/or radiation therapy before surgery.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs and scans in this study can affect an unborn baby. Women who are able to have children will have a pregnancy test before beginning treatment. Women should not breastfeed a baby while on this study and for at least 60 days after the last study treatment. It is important you understand that you need to use birth control while on this study and for at least 60 days after the last study treatment. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. There is a risk of not being able to have children in the future due to the chemotherapy. If you think that you may want to have children in the future, discuss this with the study doctor.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope radiation therapy, chemotherapy, and C225 (if you receive C225) may keep your head and neck cancer from growing, there is no proof of this yet. We do know that the information from this study will help doctors learn more about these therapies as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study? (6/1/06)

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Receiving cetuximab without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private? (1/26/16)

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Records of your progress and medical images while on this study will be kept in confidential form at _____(institution) and in computers at NRG Oncology and the ECOG-ACRIN Medical Research Foundation, Inc. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- NRG Oncology
- ECOG-ACRIN Medical Research Foundation, Inc.
- Qualified representatives of Eli Lilly and Company or its local affiliate, marketer and distributor of cetuximab
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide patients and doctors greater access to cancer trials
- Other qualified researchers studying new methods to analyze your medical images; at this time it is not known what type of studies these might be. Your name and any other information that identifies you will not be provided to these researchers.

Research studies may be conducted on aspects of the data and medical images collected during this study. At this time, it is not known what type of studies may be conducted. These studies may affect patient care or future studies of a medical or non-medical nature.

What are the costs of taking part in this study? (1/26/16)

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Eli Lilly and Company or its local affiliate is supplying cetuximab (C225) at no cost to you. However, you or your health plan may need to pay for costs of the supplies for drug administration and personnel who give you the cetuximab.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study? (6/1/06)

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

A Data Safety Monitoring Board will be meeting regularly to monitor safety and other data related to this study. The Board may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [**Only applies to sites using the CIRB.*]

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in any of these additional studies.

You can say “yes” or “no” to each of the following studies. Please mark your choice for each study.

Quality of Life Study (8/25/08)

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of Life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to complete 2 questionnaires. In addition, you will be asked some questions about what you are able to eat at home and in public and how clear your speech is.

You will complete one of the questionnaires and answer the questions at your first visit, during the 5-6th week of treatment, at 3 and 12 months from the start of treatment, then annually for years 2-5. It takes about 5-10 minutes to fill out the questionnaire and about 5-10 minutes to answer the questions.

You will be asked to complete the other questionnaire at your first visit and then annually in years 1 and 5. It takes about 5-10 minutes to fill out this questionnaire.

If any questions make you feel uncomfortable, talk with your study doctor or nurse about skipping those questions and not giving an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the 2 questionnaires and answer some questions. You may change your mind about participating at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the 2 Quality of Life Questionnaires and answer some questions about my speech and my eating abilities.

YES

NO

Use of Tissue and Blood for Research

About Using Tissue and Blood for Research (8/17/11)

You will have or have had a biopsy (or surgery) to see if you have cancer. Your doctor will remove or has removed some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If your tumor comes back after you complete study treatment, we would like to keep some of that tumor tissue as well. If you agree to allow us to keep your tissue, it will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "Providing your Tissue for Research" to learn more about tissue research. This information sheet is available to all at the following web site:
<http://www.cancer.gov/clinicaltrials/resources/providing-tissue.pdf>.

In addition, you will have blood tests before you start treatment. We would like to keep about one tablespoon of your blood for future research.

Your tissue and blood may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue and blood for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue or blood. Then any tissue or blood that remains will no longer be used for research and will be returned to the submitting institution.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue or blood is used for genetic research (about diseases that are passed on in families). Even if your tissue and blood is used for this kind of research, the results will not be put in your health records. Your tissue and blood will be used only for research and will not be sold. The research done with your tissue and blood may help to develop new products in the future.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My tissue and blood may be kept for use in research to learn about, prevent, or treat cancer.

Yes No

2. My tissue and blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to take part in more research.

Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).
5	Death (Karnofsky 0).

APPENDIX III

AJCC STAGING SYSTEM, 6th Edition HEAD & NECK

STAGING-PRIMARY TUMOR (T)

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

PHARYNX

Nasopharynx

- T1 Tumor confined to the nasopharynx
- T2 Tumor extends to soft tissues of oropharynx and/or nasal fossa
 - T2a without parapharyngeal extension
 - T2b with parapharyngeal extension
- T3 Tumor invades bony structures and/or paranasal sinuses
- T4 Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space.

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.

Hypopharynx

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

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.

APPENDIX III (Continued)

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.

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

APPENDIX III (Continued)

STAGE GROUPING Excluding Nasopharynx

Stage 0	T _{is} , 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

STAGE GROUPING Nasopharynx

Stage 0	T _{is} , N0, M0
Stage I	T1, N0, M0
Stage IIA	T2a, N0, M0
Stage IIB	T1-T2a, N1, M0 T2b, N0-1, M0
Stage III	T1-T2b, N2, M0 T3, N0-2, M0
Stage IVA	T4, N0-2, M0
Stage IVB	Any T, N3, M0
Stage IVC	Any T, Any N, M1

APPENDIX IV (8/25/08)

SURGICAL MANAGEMENT OF THE NECK

N0: No mandatory surgical management of the neck is indicated.

N1: Patients with N1 neck disease whose nodes are 3 cm or less in diameter require careful physical examination of the neck and post-treatment imaging. If there is clinical or radiographic evidence of residual neck disease at 8-9 weeks post-treatment, neck dissection is required. A CR must be achieved at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The neck dissection is performed 8-11 weeks post-treatment, if indicated. Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed *en bloc*. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary, the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as “nodal clusters.” These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix V.

N2A: For patients with lymph nodes between 3 and 6 cm, post-treatment physical examination and imaging studies will be obtained. For patients with a CR at the primary site, neck dissection alone is optional at 8-9 weeks post-treatment; otherwise, surgical salvage with or without neck dissection will be necessary. Neck dissection is mandatory for patients with clinical or radiographic evidence for persistent disease in the neck at 8-9 weeks post-treatment. A CR must be achieved at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The neck dissection is performed 8-11 weeks post-treatment, if indicated. Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed *en bloc*. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary, the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as “nodal clusters.” These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix V.

N2B: For patients with multiple lymph nodes, post-treatment physical examination and imaging studies will be obtained. For patients with a clinical and radiographic complete response in the neck, cervical lymphadenectomy is optional. For patients with clinical or radiographic evidence for residual neck disease at 8-9 weeks post-treatment, neck dissection is mandatory and will be performed at 8-9 weeks post-treatment for patients with a CR at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. A CR must be achieved at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The neck dissection is performed 8-11 weeks post-treatment, if indicated. Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed *en bloc*. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary, the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

APPENDIX IV (Continued) [8/25/08]

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as “nodal clusters.” These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix V.

N2C: For patients with bilateral neck disease, each side of the neck will be managed separately according to the criteria above.

For patients with N3A disease, post-treatment physical examination and imaging studies will be obtained. If a CR is obtained in the neck, cervical lymphadenectomy is optional. For patients with a clinical or radiographic finding of residual neck disease at 8-9 weeks post-treatment, the neck dissection will be performed at 8-9 weeks post-treatment for patients with a CR at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. A CR must be achieved at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The neck dissection is performed 8-11 weeks post-treatment, if indicated. Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed *en bloc*. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary, the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as “nodal clusters.” These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix V.

APPENDIX V

Cervical Lymph Node Dissection: Documentation and Processing of the Specimen

Operative report

The surgeon will document the preoperative clinical examination and radiographic findings in reference to the presence or absence of primary and nodal disease. The operative report will describe the lymph node levels dissected and removed for pathologic examination. The non-lymphatic structures removed at the time of neck dissection also should be included in the operative report.

Processing the neck dissection specimen

Upon completion of the neck dissection, the surgeon will divide the specimen into nodal levels and submit each level in a separate container. Accompanying documentation for each specimen container will include the patient case number, the side or sides of the neck dissected, and lymph node level.

APPENDIX VI

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 VI (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 post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX VII (8/17/11)

RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

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



Step 1

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



Step 2

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

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



Step 3

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

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

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

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

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens or Trackable shipments
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

APPENDIX VII (8/17/11)

RTOG BLOOD COLLECTION KIT INSTRUCTIONS

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

Kit contents:

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

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

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

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

Process:

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

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

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

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

Process:

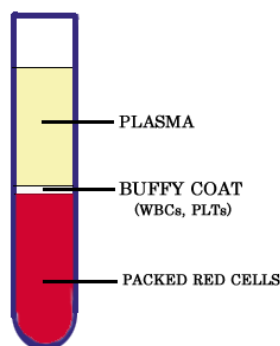
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature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

(continued on next page)

APPENDIX VII

RTOG BLOOD COLLECTION KIT INSTRUCTIONS (continued)



(C) Whole Blood for DNA (if requested): Purple Top EDTA tube #2

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected..Label them with the RTOG study and case number, collection date/time, 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 ml blood into as many cryovials as are necessary for the blood collected (3 to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on STF.

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 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 RTOG 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 VII

RTOG 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 RTOG@ucsf.edu or call (415)476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens

RTOG Biospecimen Resource

University of California San Francisco

1657 Scott Street, Room 223

San Francisco, CA 94115

For questions, call 415-476-RTOG (7864) or e-mail: RTOG@ucsf.edu

APPENDIX VIII (1/26/16)

CTSU LOGISTICS

ADDRESS AND CONTACT INFORMATION FOR RTOG-0522

To submit site registration documents:	For patient enrollments:	Submit study data directly to NRG Oncology unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 900 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19103 Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
<u>For patient eligibility questions:</u> Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214. <u>For treatment-related questions:</u> Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.		
<u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at: http://members.ctsu.org		

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at <http://members.ctsu.org>

All forms and documents associated with this study can be downloaded from the RTOG-0522 Web page on the CTSU registered member Web site (<http://members.ctsu.org>). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS.

APPENDIX VIII (Continued)

Requirements for RTOG-0522 site registration:

- **All patients MUST be treated with either 3DCRT or IMRT on this trial and all institutions must be pre-credentialed.** Credentialing requirements for 3DCRT are outlined in Section 5.1 of the protocol and on the ITC web site at <http://itc.wustl.edu>. Credentialing requirements are outlined in Section 5.2 and on the IMRT Advanced Technology Consortium (ATC) web site at <http://atc.wustl.edu>. Submission of digital data to the Image-Guided Therapy Center (ITC) requires advanced request for an FTP account with the ITC (itc@castor.wustl.edu). The ITC will notify the registering institution when that institution is eligible to enter patients on study. The status of the credentialing review will be reflected on the RSS Site Registration Status screen <http://members.ctsu.org/rss/>
- All subjects will be eligible for PET/CT imaging analysis. Pre-treatment FDG-PET/CT scan is highly recommended for all patients. Each site must send at least one test case to the PET Core Lab for evaluation **prior to the enrollment of that site's first patient.** Application and instructions for test case submission can be found on the ACRIN web site at <http://www.acrin.org/petcorelab.html>
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

Note: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Pre-study requirements for patient enrollment on RTOG-0522

- **Allow adequate time (7-10 days) for processing of initial drug shipment request before contacting the CTSU to randomize your first patient.**
- Request initial specimen collection/shipping kits from LDS Hospital per Appendix VII.
- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- Baseline QOL forms completed prior to treatment start.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG-0522 Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG within the confines of RTOG's registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

APPENDIX VIII (Continued)

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0522 web page located on the CTSU registered member Web site (<http://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU. See the Special Materials or Substudies section below for submission of dosimetry data.
3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.
4. Please affix the RTOG study/case label to all source documentation and redact the patient's name.

SPECIAL MATERIALS OR SUBSTUDIES

Radiation Therapy (section 6.0)

Dosimetry data for 3DCRT and IMRT must be submitted to the Image-Guided Therapy Center (ITC), either by digital transmission using the ITC-assigned FTP account or tape submission (contact ITC for acceptable tape types and format). Hard copy materials accompanying digital data should also be sent directly to the ITC. See section 12.2 for a complete inventory of dosimetry items to be submitted.

Tissue/Specimen Submission – optional but highly recommended (section 10.0)

1. With patient's consent, tumor tissue and blood will be collected. Submit specimens, pathology report, and RTOG Specimen Transmittal Form to the RTOG Tissue Bank at LDS Hospital.
2. See protocol section 10.0 for detailed instructions on collection kits, preparation, and shipment of samples. All reports must include the protocol number and patient's case number (or RTOG label attached). Surgical pathology numbers and information must not be removed from the report; however, the patient's name and/or other identifying information should be redacted. Do not send specimens, forms, reports, or transmittals to the CTSU.
3. CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.3 of the protocol. Payments will be made in accordance with RTOG's pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.

PET Evaluations (sections 5.3 and 12.3)

A pre-treatment PET/CT scan is highly recommended for all patients on study. A post-treatment FDG-PET/CT scan is recommended 8-9 weeks after completion of therapy. Sites must submit at least one test case to the PET Core Lab for evaluation prior to enrollment of their first patient. See protocol sections 5.3 and 12.3 and the ACRIN web site (<http://www.acrin.org/petcorelab.html>) for details.

SERIOUS ADVERSE EVENT (SAE) REPORTING

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (<http://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG-0522 web page.
3. Do not send adverse event reports to the CTSU.

APPENDIX VIII (Continued)

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via AdEERS within 30 days of AML/MDS diagnosis.

DRUG PROCUREMENT (Section 7.0)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in section 7 of the protocol.
2. You may navigate to the drug forms on the CTSU Members' Web Site by selecting Pharmacy Forms from the document center drop down list on the rtog-0522 web page.
3. Commercial agent: cisplatin
4. Investigational agent: cetuximab - supplied free of charge by the manufacturer to patients on study.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.