RADIATION THERAPY ONCOLOGY GROUP

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 Chairs (Continued on next page)

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

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

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

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

Principal Investigator/Radiation Oncology
Kian Ang, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Suite 97
Houston, TX 77030
713-563-2300/FAX 713-563-2331
kianang@mdanderson.org

Radiation Oncology Co-Chair, U.S.
David Rosenthal, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Suite 97
Houston, TX 77030
713-563-2300/FAX 713-794-5573
dirosenthal@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

PET Co-Chair
David Schwartz, MD
MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
713-563-2381/FAX 713-563-2331
docdls@mdanderson.org

Activation Date: November 22, 2005

Closure Date: March 3, 2009

Update Date: September 1, 2009

Version Date: February 23, 2011
Includes Amendments 1-6
(Broadcast: 3/2/11)

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0522

Study Chairs (Continued) [9-1-09]

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
Wayne State Univ. College of Medicine
540 E. Canfield Rd./1212 Scott Hall
Detroit, MI 48201
313-966-2274/FAX 313-966-9400
akonski@med.wayne.edu

Senior Statistician
Qiang Zhang, PhD
Radiation Therapy Oncology Group/ACR
1818 Market Street, Suite 1600
Philadelphia, PA 19103
215-574-3197/FAX 215-928-0153
ezhang@acr-arrs.org

RTOG Headquarters/Department of Statistics
215-574-3189/1-800-227-5463, ext. 4189

This study is supported by the NCI Cancer Trials Support Unit (CTSU) [2/14/07]

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each 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 RTOG Headquarters.

INDEX (6/1/06)

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 - Study Agent Shipment Form
Appendix IX - CTSU Logistics

RADIATION THERAPY ONCOLOGY GROUP

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-**	**Selected Patients**
	2. Non-Larynx			**Treatment**	
			[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) ≥ 1,800 cells/mm3
- Platelets ≥ 100,000 cells/mm3
- Hemoglobin ≥ 8.0 g/dl
- Bilirubin ≤ 1.5 mg/dl
- AST or ALT ≤ 2x the upper limit of normal
- Serum creatinine ≤ 1.5 mg/dl
- Creatinine clearance (CC) ≥ 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 that 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)

_____(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)

_____ 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)

_____(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 trials[3-9] 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/m^2, 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/m^2 over 5 consecutive days or 4 doses of 25 mg/m^2 over 4 sequential days during weeks 1, 4, and 7[12-13], weekly doses of 50 mg during the 7-9 weeks course of postoperative radiotherapy[14], or 6 mg/m^2/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/m^2 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/m^2, 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 (EFGR) 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 reaction [19] 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–alpha.(Erbitux® 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 (Erbitux® 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/m^2. Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m^2 as the dose increased from 20 to 200 mg/m^2, and at doses >200 mg/m^2, 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/m^2.

Following a 2-hour infusion of 400 mg/m^2 of cetuximab, the maximum mean serum concentration (Cmax) was 199 µg/mL (range: 70-380 µg/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m^2 produced a mean Cmax of 168 µg/mL (range120-170 µg/mL). Following the recommended dose regimen (400 mg/m^2 initial dose/250 mg/m^2 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 µg/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 immunosorbant 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 (Erbitux® 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/m 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).

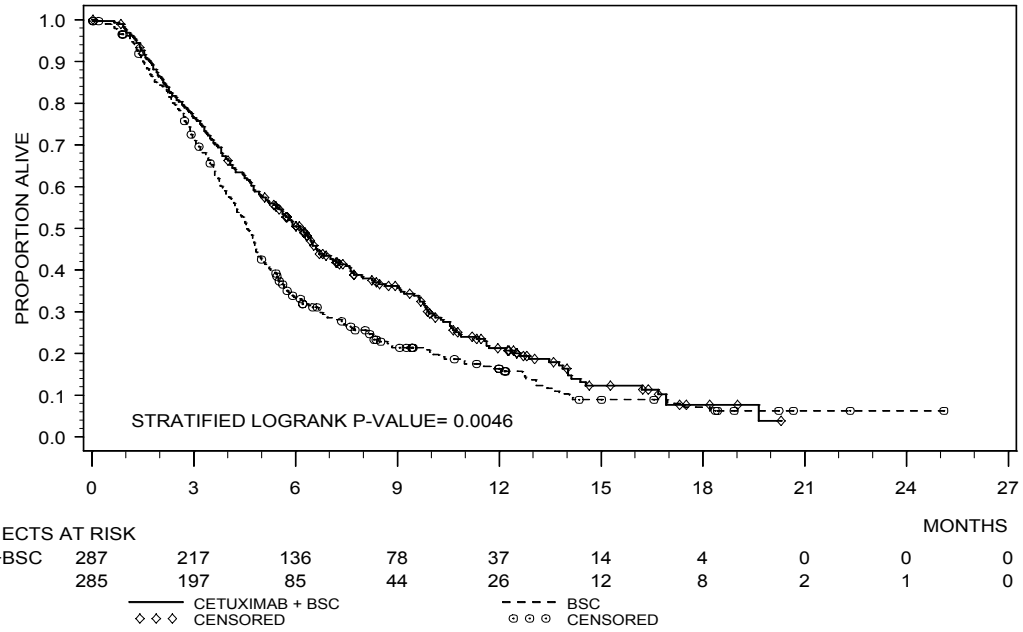
1.4.4 *Colorectal Cancer: Randomized, Controlled Trials*

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



GROUP	# DEAD / # RANDOMIZED	MEDIAN (95% CI)	HAZARD RATIO (95.00% CI)
CETUXIMAB + BSC	222/287	6.14 (5.36 - 6.70)	
BSC	234/285	4.57 (4.21 - 4.86)	
CETUXIMAB + BSC OVER BSC			0.77 (0.64 - 0.92)

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).3 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 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/m^2 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/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 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 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 pharmDxTM 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 pharmDxTM 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 (8/25/08)

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/m^2 initial dose, followed by 250 mg/m^2 weekly). Patients received a median of 8 infusions (range 1–11).

Incidence of Selected Adverse Events (≥10%) in Patients with Locoregionally Advanced SCCHN

	Cetuximab plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
Body System	Grades 1 – 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
Preferred Term	% 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				
Acneform 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] Acneform 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/m^2 weekly).

Incidence of Selected Adverse Events Occurring in ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux® Monotherapy				
	Erbitux® plus BSC (n=288)		**BSC alone (n=274)**	
Body System	**Any Grades[2]**	**Grades 3 and 4**	**Any Grades**	**Grades 3 and 4**
Preferred Term	**% 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 ≥10% of Patients with Advanced Colorectal Carcinoma[1] Treated with Erbitux® Monotherapy				
	Erbitux® plus BSC (n=288)		BSC alone (n=274)	
Body System	Any Grades[2]	Grades 3 and 4	Any Grades	Grades 3 and 4
Preferred Term	% 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 acneform 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 acneform 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 acneform rash, skin drying and fissuring, paronychial inflammation, and infectious sequelae (for example S. aureus sepsis, abscess formation, cellulitis, blepharitis, cheilitis) occurred in patients receiving cetuximab therapy. Acneform rash occurred in 76–88% of 1373 patients receiving cetuximab in clinical trials.1 Severe acneform rash occurred in 1–17 % of patients.

Acneform 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/m^2) in patients with locally advanced SCCHN (Erbitux® 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 classes [24] (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 al[25]) 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 al[28] showed that >median primary FDG SUV predicted for advanced clinical stage and poor overall disease survival. Brun, et al[29] 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 access 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 al[30] 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}>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 (≤ 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 (8/25/08)

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) ≥ 1,800 cells/mm^3 based upon CBC/differential obtained within 2 weeks prior to registration on study;

3.1.6.2 Platelets ≥ 100,000 cells/mm^3 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 ≤ 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:

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

CCr female = 0.85 x (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 Patients participating in 0522 also are eligible for and are strongly encouraged to participate in RTOG 0514, the Head and Neck tissue banking protocol.

3.1.12 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 (6/1/06)

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.

5.4.3 For the initial shipment of Cetuximab:

A Word version of the initial shipment form for this study is available on the RTOG web site, www.rtog.org, next to the protocol. **U.S. and Canadian institutions** must complete this form electronically and email the form to RTOG_BMS@phila.acr.org as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax the form in Appendix VIII to 215-574-0300 **only** if the RTOG web site is unavailable). Allow adequate processing time (7-10 days) before calling to randomize your first patient. Required regulatory documents (see Sections 5.4.1 and 54.2) must be received before drug can be shipped. See Appendix VIII for the procedure for resupply requests.

5.5 Registration

5.5.1 *Online Registration*

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 at http://www.rtog.org/members/webreg.html(bottom right corner of the screen), 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 ≥ 110% of the prescribed dose;
- No more than 1% of any PTV_{HD} or PTV_{ED} should receive ≤ 93% of the prescribed dose;
- No more than 1% or 1 cc of the tissue outside the PTVs should receive ≥ 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 ≥. 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. CTV_1 represents GTV plus a margin of generally 1 cm and CTV_2 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 CTV_1. 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 CTV_1 and CTV_2 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 CTV_1. No more than 5% of the non-target tissue can receive greater than the dose to CTV_1.

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.

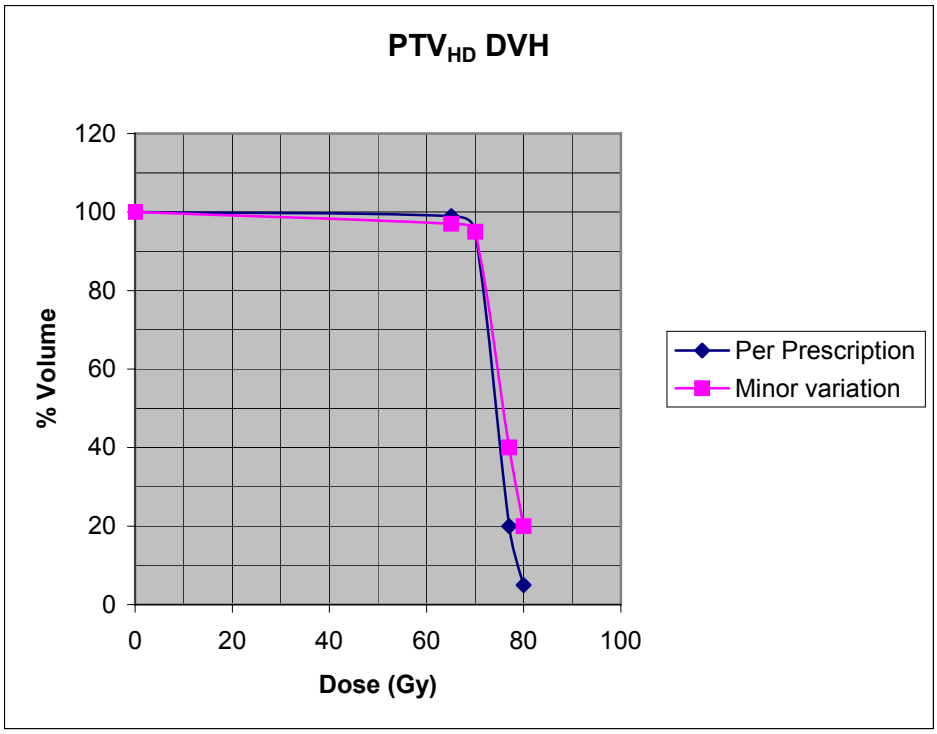
A region of "minor deviation" is also defined in the figure as the DVH represented by the square symbols. Deviations of this magnitude are not desirable, but will be deemed acceptable. That is, a DVH with at least 97% of the volume receiving 64 Gy is acceptable as a minor deviation. Additionally, as a minor deviation for the overdose region, as much as 40% of the $\underline{PTV_{HD}}$ volume can receive 76 Gy and up to 20% of this volume can receive 79 Gy. DVHs for the $\underline{PTV_{HD}}$ 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 ^{18}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 ^{18}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) (µCi/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.