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
1029 Walnut St., #1014
Philadelphia, PA 19107
215-923-9131/FAX 215-955-1965
rita.Axelrod@Jefferson.edu

Medical Oncology Co-Chair
Eric Sherman, MD
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
215-214-1663/FAX 215-214-1632
eric.Sherman@fccc.edu

Radiation Oncology Co-Chair
Kian Ang, MD
MD Anderson Cancer Center
1515 Holcombe Blvd., Suite 97
Houston, TX 77030
713-563-2331/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
713-563-2353/FAX 713-794-5573
dironsenthal@mail.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

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

PET Co-Chair
David Schwartz, MD
MD Anderson Cancer Center
1515 Holcombe Blvd.
Houston, TX 77030
713-563-2353/FAX 713-563-2331
docdls@mdanderson.org

Version Date: September 14, 2005

Patient enrollments from institutions that are not aligned with RTOG will be conducted via the NCI Cancer Trials Support Unit (CTSU), and all data should be sent to CTSU Data Operations unless otherwise specified in the CTSU logistics (Appendix IX).
This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
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
2. Non-Larynx

Nodal Status

S 1. N0
T 2. N1, N2a, N2b
R 3. N2c, N3

Arm 1
Accelerated Fractionation by Concomitant Boost (AFX-CB) or IMRT plus cisplatin

Arm 2
Accelerated Fractionation by Concomitant Boost (AFX-CB) or IMRT plus cisplatin plus cetuximab

Reassessment
Required CT scan or MRI for N2-N3c and N1-N2c patients

Selected Patients
 Persistent nodal disease, but Complete response of primary

Dissection:
These patients also can receive post-treatment PET/CT scan
For details of surgery for primary, see Section 8.0

Use of IMRT
1. No
2. Yes

Pre-Treatment PET/CT
1. No
2. Yes

Pre-Treatment PET/CT
1. No
2. Yes

a. See Section 5.1 and 5.2 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 shall be included.

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: 720

RTOG 0522
1. Does the patient have a histologically proven (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx?  
2. Does the patient have selected stage III or IV disease (T2N2-3M0, T3-4 any N M0)?  
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?  
4. Was a Chest x-ray, Chest CT scan, or PET/CT scan completed within 6 weeks prior to registration?  
5. Was a CT scan or MRI of head and neck, or PET/CT scan completed within 6 weeks prior to registration?  
6. Was the left ejection fraction determined by ECHO and/or MUGA technique within 12 weeks of registration?  
7. Is the Zubrod 0-1?  
8. Is the patient at least 18 years of age?  
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  
   - Electrolytes, Mg++ within normal range  
   - Serum calcium, corrected serum calcium, or ionized calcium within normal range  
10. For women of childbearing potential, was a pregnancy test completed within 2 weeks of registration?  
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)?  
12. Is there a history of prior invasive malignancy (other than non-melanomatous skin cancer)?  
   - If yes, has the patient been disease free for greater than three years?  
13. Has the patient had prior systemic chemotherapy for the study cancer?  
14. Has the patient had prior radiotherapy to the region of study cancer that would result in overlap of radiation therapy fields?
RTOG Institution # __
RTOG 0522 ELIGIBILITY CHECKLIST
Case # __________ (page 2 of 3)

____(N) 15. Is the primary tumor site oral cavity, nasopharynx, sinuses, or salivary gland?
____(N) 16. Has the patient had initial surgical treatment other than the diagnostic biopsy of the primary site or nodal sampling of neck disease?
____(N) 17. Does the patient have any of the severe comorbid conditions listed in Section 3.2.6 that would exclude him/her from participation?
____(N) 18. Has the patient had a prior allergic reaction to the study drugs involved in this protocol?
____(N) 19. Has the patient had prior therapy that specifically and directly targets the EGFR pathway?
____(Y) 20. Has the patient signed a study-specific consent form?

The following questions will be asked at Study Registration:

______________ 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]
______________ 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

(Continued on the next page)

RTOG 0522
14. Patient’s Insurance Status

15. Will any component of the patient’s care be given at a military or VA facility?

16. Treatment Start Date

17. Medical Oncologist

18. Tissue/Blood kept for cancer research? (Y/N)

19. Tissue/Blood kept for medical research? (Y/N)

20. Allow contact for future research? (Y/N)

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 use of IMRT (No vs. Yes)

25. Specify pre-treatment PET/CT (No vs. Yes)

26. Treatment Assignment

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 regimes were designed and subjected to phase III testing. Collectively, clinical trials revealed that hyperfractionation and various accelerated fractionation regimes improved local-regional control (LRC) and in some trials, also survival. 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. 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 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. In earlier trials, cisplatin was given in a dose of 100 mg/m², administered during weeks 1, 4, and 7 of radiotherapy (approximately a third of patients were not able to tolerate the last dose). The systemic and mucosal toxicities of such a high-dose, intermittent cisplatin regimen can be severe. There are now four trials showing LRC and/or survival benefit of alternative cisplatin regimens, i.e., 5 doses of 20 mg/m² over 5 consecutive days or 4 doses of 25 mg/m² over 4 sequential days during weeks 1, 4, and 7, weekly doses of 50 mg during the 7-9 weeks course of postoperative radiotherapy, or 6 mg/m²/day, 5 days a week during the 7 weeks course of radiotherapy. Taken together, the available data suggest that a cumulative cisplatin dose of 200 mg/m² given either every 3 weeks, weekly, or daily during the course of radiotherapy yields therapeutic benefit.

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

1.2 Proposed Trial: Rationale and Design

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

Progress in the understanding of tumor biology has opened an exciting new era for research. For example, as summarized in several recent publications, 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). 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 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 Clinically Relevant Adverse Events Related to Cetuximab (C225)

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

A total of 90.3% of the patients reported adverse events (AEs). Approximately two-thirds (64.8%) of patients reported at least one Grade 3 or 4 event. Cetuximab-related AEs were observed in 1,817 patients (85.4%). The most common composite groupings of adverse events deemed related to C225 as reported by investigators in all C225 trials (N = 1,817) include acneform rash (76.2%), acne-like rash (72.4%), fatigue/malaise/lethargy (30.1%), nausea/vomiting (24%), mucositis/stomatitis (17.5%), infusion-related symptoms (15.6%), diarrhea (15.4%), and hypersensitivity reaction (5.3%).

The development of acute interstitial pneumonitis in patients treated with EGFR-targeted agents has recently been described (Investigator Brochure; see Section 7.3.1 of the protocol to obtain a copy).

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

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

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

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

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

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.
Data in patients with advanced colorectal carcinoma in the tables below are based on the experience of 354 patients treated with cetuximab plus irinotecan and 420 patients treated with cetuximab monotherapy.

### Incidence of Adverse Events (≥ 10%) in Patients with Advanced Colorectal Carcinoma

<table>
<thead>
<tr>
<th>Body System</th>
<th>Cetuximab plus Irinotecan (n=354)</th>
<th>Cetuximab Monotherapy (n=420)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grades 1 - 4</td>
<td>Grades 3 and 4</td>
</tr>
<tr>
<td><strong>Body as a Whole</strong></td>
<td>% of Patients</td>
<td>% of Patients</td>
</tr>
<tr>
<td>Asthenia/Malaise b</td>
<td>73</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>Fever c</td>
<td>34</td>
<td>4</td>
</tr>
<tr>
<td>Pain</td>
<td>23</td>
<td>6</td>
</tr>
<tr>
<td>Infusion Reaction d</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Back Pain</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>72</td>
<td>22</td>
</tr>
<tr>
<td>Nausea</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>41</td>
<td>7</td>
</tr>
<tr>
<td>Anorexia</td>
<td>36</td>
<td>4</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>2</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td><strong>Hematic/Lymphatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>25</td>
<td>17</td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td><strong>Metabolic/Nutritional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Loss</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea c</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Cough Increased</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin/Appendages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acneform Rash e</td>
<td>88</td>
<td>14</td>
</tr>
<tr>
<td>Alopecia</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Skin Disorder</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Nail Disorder</td>
<td>12</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>14</td>
<td>1</td>
</tr>
</tbody>
</table>

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

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

c Includes cases reported as infusion reaction.

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

Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis.”
1.3.1 Acne-Like Rash
In clinical studies of cetuximab, dermatologic toxicities, including acneform rash, skin drying and fissuring, and inflammatory and infectious sequelae (e.g., blepharitis, cheilitis, cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneform rash was reported in 89% (686/774) of all treated patients, and was severe (grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including S. aureus sepsis and abscesses requiring incision and drainage were reported. Non-suppurative acneform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 68% (14% grade 3) of patients receiving cetuximab plus irinotecan and in 90% (8% grade 3) of patients receiving cetuximab monotherapy. Acneform rash most commonly occurred on the face, upper chest, and back but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (e.g., blepharitis, cellulitis, cyst). Two cases of S. aureus sepsis were reported. The onset of acneform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

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

1.3.3 Infusion Reactions
In clinical trials, severe, potentially fatal infusion reactions were reported, one leading to death (see Section 1.3). These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving cetuximab plus irinotecan and 19% of patients receiving cetuximab monotherapy. A 20-mg test dose was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions.

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

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

1.4 Biomarker Studies
1.4.1 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, 90-03.15 This work revealed no correlation between EGFR expression and T-stage, N-stage, AJCC stage grouping, and RPA classes (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.

1.4.2 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 downstream 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 downstream signaling pathways, i.e., PI-3K/AKT.

1.5 Positron Emission Tomography (PET) and CT Imaging

1.5.1 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 radion tracer for cancer has been [F-18] fluorodeoxyglucose (FDG-PET). Neoplastic cells exploit anaerobic glycolysis more than surrounding normal tissues, due to intracellular signaling abnormalities, high metabolic rate, and poor vascular supply. FDG is converted within these cells to 2-deoxyglucose-6-phosphate, which cannot be utilized by the glycolytic pathway and becomes trapped within the cells.

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

Several clinical studies suggest that highly elevated baseline FDG uptake by primary HNSCC, quantified as the standardized uptake value (SUV), predicts for worse prognosis.27 Schwartz, et al at the University of Washington showed in a cohort of 54 patients that greater than median primary tumor FDG-PET SUV was associated with inferior local control and disease free survival. In thirty-seven patients, Minn, et al28 showed that >median primary FDG SUV predicted for advanced clinical stage and poor overall disease survival. Brun, et al29 obtained FDG-PET images in 47 patients treated with definitive radiotherapy. They found that >median baseline primary tumor FDG SUV predicted for inferior response to radiotherapy, local disease control, and overall survival. Systematic study of FDG-PET in this phase III setting will permit large-scale, multi-institutional validation of these findings.
In previous cooperative group trials, systematic use of planned neck dissection surgery following radiotherapy was generally recommended for patients having N2-3 disease at diagnosis. However, due to lack of controlled studies, no consensus could be reached as to whether patients presenting with N2-3 disease that regresses completely at 6-10 weeks after completion of radio-chemotherapy would benefit from planned neck dissection. Proponents of planned neck dissection argue that nodal relapse is difficult to salvage and uncontrolled neck disease causes morbidity. Opponents of planned neck dissection contend that the neck dissection specimens of complete responders rarely harbor microscopic residual tumor and that isolated nodal relapse rate is low without surgery. Since the cost of neck dissection is not negligible and the procedure is associated with moderate morbidity, it is prudent to assess its need in a prospective trial.

An objective of this trial is to assess the role of FDG-PET/CT scans in determining the overall clinical outcomes and the need for nodal dissection. Few data exist to document the ability of FDG-PET/CT to accurately assess disease status immediately following radiation treatment. One small series examined the accuracy of post-radiotherapy FDG-PET (without CT) for neck assessment prior to planned neck dissection. Yao, et al. 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. 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.

1.5.2 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.

1.6 Quality of Life Evaluation and Health Utilities

1.6.1 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. 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. 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. 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.

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).

1.6.2 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. 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.

1.6.3 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. 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.

1.6.4 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. 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. 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. 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. 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.

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

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

2.2 Secondary Objectives

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 toxicities;
- Quality of life and health utilities;

2.2.2 Correlate the expression of EGFR and its downstream 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 disease-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

3.1.1 Histologically proven (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx;

3.1.2 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

3.1.2.1 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;

3.1.2.2 Chest x-ray (or Chest CT scan or PET/CT scan) within 6 weeks prior to registration; see Section 11.4 for details of PET scans.

3.1.2.3 CT scan or MRI of head and neck or PET/CT scan within 6 weeks prior to registration; see Section 11.4 for details of PET scans.

3.1.2.4 Left ejection fraction determined by ECHO and/or MUGA technique within 12 weeks of registration;

3.1.3 Zubrod Performance Status 0-1;

3.1.4 Adequate bone marrow function, defined as follows:

3.1.4.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study;

3.1.4.2 Platelets ≥ 100,000 cells/mm³ based upon CBC/differential obtained within 2 weeks prior to registration on study;

3.1.4.3 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.)

3.1.5 Adequate hepatic function, defined as follows:

3.1.5.1 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.

3.1.5.2 AST or ALT ≤ 2x the upper limit of normal within 2 weeks prior to registration on study;

3.1.6 Adequate renal function, defined as follows:

3.1.6.1 Serum creatinine ≤ 1.5 mg/dl within 2 weeks prior to registration

3.1.6.2 Creatinine clearance (CC) ≥ 50 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

\[
CCr = \left(\frac{[140 – \text{age}] \times \text{(wt in kg)}}{[\text{Serum Cr mg/dl}] \times (72)}\right)
\]

3.1.9 Electrolytes (Sodium, potassium, bicarbonate, chloride, BUN, glucose, phosphorus), Mg++ within normal range within 2 weeks prior to registration;

3.1.10 Serum calcium or ionized calcium within normal range within 2 weeks prior to registration; the formula for corrected calcium if albumin value is below normal range is as follows:

Corrected calcium (mg/dl) = (4 - [patient’s albumin (g/dl)]) x 0.8 + (patient’s measured calcium [mg/dl])

3.1.11 Pregnancy test within 2 weeks prior to registration for women of childbearing potential;

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

3.1.13 Patients participating in 0522 are also eligible for and are strongly encouraged to participate in RTOG 0514, the Head and Neck tissue banking protocol.

3.1.14 Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except non-melanomatus skin cancer) unless disease free for a minimum of 3 years;

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

3.2.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.4 Primary site of tumor of oral cavity, nasopharynx, sinuses, or salivary glands;
3.2.5 Initial surgical treatment, excluding diagnostic biopsy of the primary site or nodal sampling of neck disease; radical or modified neck dissection is not permitted.
3.2.6 Severe, active co-morbidity, defined as follows:
3.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization in past 6 months;
3.2.6.2 Left Ventricular Ejection Fraction < 45%;
3.2.6.3 Transmural myocardial infarction within the last 6 months;
3.2.6.4 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
3.2.6.5 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
3.2.6.6 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.
3.2.6.7 Any uncontrolled condition, which in the opinion of the investigator, would interfere in the safe and timely completion of study procedures;
3.2.7 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.
3.2.8 Prior allergic reaction to the study drug(s) involved in this protocol;
3.2.9 Prior therapy that specifically and directly targets the EGFR pathway.

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
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 11.4 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

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 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.

Institutions that have been certified by the ATC to participate in RTOG head and neck-specific studies (e.g., RTOG 0022 or RTOG 0225) may enroll patients on this study without further credentialing by the ITC.

Institutions that have not been certified by the ATC to participate in head and neck-specific IMRT studies (e.g., RTOG 0022 or RTOG 0225) MUST apply for IMRT certification as described in Sections 5.1.1-5.1.3.
5.1.1 IMRT Certification Process (For institutions not previously certified for RTOG head and neck – specific IMRT studies)

5.1.1.1 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.

5.1.1.2 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).

5.1.1.3 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”.

5.2 Preregistration Requirements for Cetuximab

5.2.1 U.S. sites must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution’s first case:
- IRB approval letter;
- IRB assurance number.

5.2.2 Canadian sites must fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution’s first case:
- IRB approval letter;
- IRB assurance number;
- Health Canada’s TPD Forms.

5.2.3 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 (email address to be added) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution’s first case. (Fax 215-574-0300 only if unable to email). Allow adequate processing time (7-10 days) before calling to randomize your first patient. Required regulatory documents (see Sections 5.2.1 and 5.2.2) must be received before drug can be shipped. See Appendix VIII for the procedure for resupply requests.

5.3 Registration

5.3.1 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 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 (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

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 preregistration 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.

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

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 (PTV1) will thus receive 72 Gy in 42 fractions over 6 weeks, and uninvolved upper neck nodes (PTV2) will receive 54 Gy in 6 weeks.

6.1.1.2 When desired, PTVint can receive a total dose of 63 Gy, i.e., by delivering 9 fractions of 1.5 Gy to PTVint before making a second cone down to PTV1.

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 (PTV1) will receive 2 Gy per fractions and subclinical disease sites (PTV2) 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, CTVi 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 PTV1 is covered with the prescription dose of 70 Gy. Additionally:
- No more than 20% of the PTV1 should receive ≥ 110% of the prescribed dose;
- No more than 1% of any PTV1 or PTV2 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 PTV1.

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 included in the CT scan.

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

6.4.2 Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

6.4.3 Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV1 represents GTV plus a margin of generally 1 cm and CTV2 represents GTV with a margin of about 2 cm and nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g., 59-63 Gy) to a volume (CTVint) that is slightly larger than CTV. 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 website: http://www.rtog.org/hnatlas/main.html).

6.4.4 Planning Target Volume (PTV1 and PTV2) represents an additional margin around CTV1 and CTV2 to compensate for the variability of treatment set up and internal organ motion. A minimum margin of 0.5 mm 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

0522
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

6.5.1 Spinal cord: 45 Gy or not more than 1 cc of the Planning Target Volume (PTV), exceeding 50 Gy.

6.5.2 Parotid glands: When using IMRT, the objective is to limit the mean dose to at least one gland to $\leq 26$ 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, a 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 $\leq 60$ Gy in patients with level IV node(s).

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

6.6 Documentation Requirements

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

6.6.2 Weekly verification or orthogonal images are required.

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

6.7 Compliance Criteria

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

Plan normalization should provide coverage of 95% of the volume of the PTV of the GTV (PTV1) with the prescribed dose of 69.96 Gy. No more than 1% of the volume of the PTV1 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 PTV1 volume can receive 76 Gy and up to 20% of this volume can receive 79 Gy. DVHs for the PTV1 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.

<table>
<thead>
<tr>
<th>Overall Evaluation</th>
<th>Radiotherapy Prolongation*</th>
<th>Total Dose Variation 3-D RT</th>
<th>Dose Variation IMRT**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol</td>
<td>$\leq 5$ days</td>
<td>$\leq 4%$ deviation from prescribed dose</td>
<td>See parameters in the figure and table below</td>
</tr>
<tr>
<td>Minor Variation (Acceptable)</td>
<td>6-10 days</td>
<td>$&gt; 4%$ to $\leq 9%$</td>
<td>See parameters in the figure and table below</td>
</tr>
<tr>
<td>Major Deviations (Unacceptable)</td>
<td>$&gt; 10$ days</td>
<td>$&gt; 9%$</td>
<td>Deviations greater than presented in the figure/table below</td>
</tr>
</tbody>
</table>

*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 receiving ≥ 110% of the prescribed dose and no more than 1% of any PTV1 and PTV2 receiving ≤ 93% of the prescribed dose.

### PTV1 DVH

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Per Prescription</th>
<th>Minor variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>70</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>77</td>
<td>20%</td>
<td>40%</td>
</tr>
<tr>
<td>80</td>
<td>5%</td>
<td>20%</td>
</tr>
</tbody>
</table>

6.8 **R.T. Quality Assurance Reviews**

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 perform an RT Quality Assurance Review after complete data for the first 25 cases enrolled have been received at RTOG Headquarters. Drs. Ang, Rosenthal, and Nguyen-Tân will perform reviews on subsequent blocks of 25 cases after complete data for these cases have been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled have been received at RTOG Headquarters, whichever occurs first. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters. IMRT cases will be reviewed via the remote review tool.

6.9 **Radiation Toxicity**

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatoryregs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

Grade 3-4 therapy-induced mucositis and/or dysphagia, which is enhanced by cisplatin, is 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 toxicities
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 toxicities include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation toxicities 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.

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

7.1 Treatment

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

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

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

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

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

- For acute nausea and vomiting, premedication should include a 5-HT3 antagonist, such as granisetron 1 mg iv, ondansetron, up to 32 mg iv, or palonosetron, 0.25 mg iv; plus a corticosteroid, such as dexamethasone, up to 20 mg iv. Palonosetron has a longer half life (40h) than the first generation 5HT3 antagonists.

- Delayed nausea and vomiting may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone.

- The NK-1 antagonist, aprepitant (125 mg po), may be added for prevention of delayed emesis on the day of chemotherapy administration and for two consecutive days thereafter (80, 80), with a corticosteroid, such as dexamethasone on days 1, 2, and 3. Dexamethasone should be reduced on day 1 to 12 mg and delivered at up to 8 mg twice daily thereafter for up to 4 days total.

- Delayed emesis (greater than 24 hours after chemotherapy administration) also may be managed by the addition of corticosteroids for two to three days (often at 8 mg per dose). Oral metoclopramide may be given at doses of 20 to 40 mg, two to four times per day. However, adults may develop akathisia or dystonic reaction.

- Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Potential delayed nausea regimens (starting the day after chemotherapy) include:

1. Aprepitant 125 mg po must be given before cisplatin, followed by aprepitant, 80 mg po daily x 2 days thereafter, with dexamethasone 8 mg po twice daily x 3 days; 5HT3 antagonist (e.g., granisetron, ondansetron) for 3 days, only if palonosetron was not given prior to chemotherapy; metoclopramide 0.5 mg/kg (usually 20-40mg) qid x 2-4 days; dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4mg bid x 2 days.

2. Emend (aprepitant) 80 mg daily x 2 days (Emend 125 mg must be given before cisplatin); dexamethasone 8mg po daily x 3 days; 5HT3 antagonist (e.g., granisetron, ondansetron) for 3 days, only if palonosetron was not given prior to chemotherapy; metoclopramide 0.5 mg/kg (usually 20-40 mg) qid x 2-4 days; dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4mg bid x 2 days, beginning day after chemotherapy.

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

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

7.1.2 Dose Modifications for Cisplatin, Day 22

7.1.2.1 Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction.

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

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

7.1.2.4 Renal Toxicity: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50 ml/min.</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>40-50 ml/min.</td>
<td>50 mg/m²</td>
</tr>
<tr>
<td>&lt; 40 ml/min.</td>
<td>Discontinue and notify Drs. Axelrod or Sherman</td>
</tr>
</tbody>
</table>

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

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

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

7.1.3 Arm 2: Cetuximab (With Concurrent RT and Cisplatin)

7.1.3.1 Initial Dose: Patients on Arm 2 will receive an initial dose of cetuximab (C225), 400 mg/m², intravenously (i.v.) over 120 minutes. No chemotherapy or radiation will be given this day, and the 400 mg/m² initial dose of cetuximab will precede the first 250 mg/m² dose of cetuximab and the first radiation treatment by at least 5 days. The infusion rate of cetuximab must never exceed 5 mL/min.

Weeks 1-7 (concurrent with RT and cisplatin): Patients on Arm 2 will receive cetuximab, 250 mg/m², intravenously (i.v.) over 60 minutes prior to radiation therapy and cisplatin. The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week on Monday or Tuesday for a total of 7 doses (patients receive cetuximab for a total of 8 weeks, including the initial dose).

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

The medical staff must closely observe patients for treatment-related adverse events, especially infusion reactions (see Section 1.3.3) during the cetuximab infusion and during a post-infusion observation hour. For the initial cetuximab infusion, vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be monitored prior to the administration of cetuximab, a half hour into the infusion, at the completion of the infusion, and 60 minutes post the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. In the event that a patient experiences an infusion reaction, see Section 7.4.4 for proper management.

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

### 7.2 Cisplatin (Cis-Diamminedichloroplatinum, DDP)

Refer to package insert for additional information.

#### 7.2.1 Formulation:
Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection is now available from the manufacturer.

#### 7.2.2 Mechanism of Action:
The mechanism of action of DDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

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

#### 7.2.4 Administration: Intravenous.

#### 7.2.5 Adverse Events
The following toxicities are anticipated:

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

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

#### 7.2.7 Supply: Commercially available.

### 7.3 Cetuximab (C225) [IND exempt]

0522 RTOG
7.3.1 **Formulation**
Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant. For more information on this agent, refer to the FDA approved Package Insert. To obtain a copy of the C225 Investigator Brochure or Package Insert, please contact Bristol-Myers Squibb (BMS) via Allison Hunt at (609) 897-3637 or allison.hunt@bms.com or Randy Gardner-McQuade at (609) 897-3922 or randy.gardner-mcquade@bms.com.

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

7.3.3 **Preparation and Administration**
Cetuximab must not be administered as an IV push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

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

Cetuximab can be administered via infusion pump or syringe pump.

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

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

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

7.3.4 **Adverse Events**
Following the cetuximab infusion, a one-hour observation period is recommended.

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

7.3.5 Storage Requirements/Stability
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2°C to 8°C (36°F to 46°F) and up to 6 hours at controlled room temperature (20°C to 25°C; 68°F to 77°F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2°C to 8°C. Discard any unused portion of the vial.

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

7.3.7 Drug Ordering and Accountability
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 (email address to be added) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution’s first case. (Fax 215-574-0300 only if unable to email). Allow adequate processing time (7-10 days) before calling to randomize your first patient. Required regulatory documents (see Sections 5.2.1 and 5.2.2) must be received before drug can be shipped. See Appendix VIII for the procedure for resupply requests.

Quantities of any size may be ordered (sites should keep in mind that 7-9 vials are needed for an initial dose, and 4-6 vials are needed for weekly maintenance doses, dependent on patient’s BSA). A suggested initial shipment is 20 vials. Allow 5 business days for shipment of drug from receipt of the C225 (Cetuximab) Clinical Supply Shipment Request form at BMS. The Drug Supply is available on the RTOG web site, www.rtog.org, next to the protocol.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery to the site Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Note: BMS will not ship drug the day prior to or following Thanksgiving and will not ship drug between Christmas Eve and New Year’s Day. It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for RTOG 0522 be utilized for this study. To help segregate product for RTOG 0522 from other investigational or marketed product, stickers with the protocol number (0522) will be provided and should be affixed to the front of the outer carton above the company name so as not to obscure any other marking.

Inside each shipping container will be a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping. This unit will be attached to an information card. The LCD display will show OK (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alarms have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing list. For questions regarding drug requisitioning, contact Bristol-Myers Squibb at 800-743-9224.

7.3.8 Handling and Dispensing of Investigational Product

0522
Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

7.3.9 Drug Destruction and Return
Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to the BMS for disposal. At the completion of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed, including dates and quantities. If approved procedures for destruction are not in place and/or for questions regarding cetuximab destruction, please contact BMS at 800-743-9224 or cetuximab.drug@bms.com.

7.4 Cetuximab Dose Modifications

7.4.1 Cetuximab Dose Levels

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Dose Level –1</th>
<th>Dose Level –2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab (C225)</td>
<td>400 mg/m² (week 1 only)</td>
<td>200 mg/m² (weekly)</td>
<td>150 mg/m² (weekly)</td>
</tr>
</tbody>
</table>

7.4.1 Cetuximab Dose Modifications for Hematologic Toxicities
Cetuximab will not be dose reduced or held for hematologic toxicities, such as neutropenia, neutropenic fever, or thrombocytopenia.
### 7.4.3  Cetuximab Dose Modifications for Non-Hematologic Toxicity

<table>
<thead>
<tr>
<th>NCI CTCAE Toxicity Grade (CTCAE v. 3.0)</th>
<th>Cetuximab Dose a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal-Calculated Creatinine Clearance</td>
<td></td>
</tr>
<tr>
<td>≥ 50 mL/min</td>
<td>Maintain dose levels</td>
</tr>
<tr>
<td>&lt; 50 mL/min</td>
<td>Maintain dose levels</td>
</tr>
<tr>
<td>Fatigue (Asthenia) ≥ Grade 3</td>
<td>Maintain dose levels</td>
</tr>
<tr>
<td>Nausea/Vomiting ≤ Grade 2 with maximal medical management</td>
<td>Maintain dose levels</td>
</tr>
<tr>
<td>≤ Grade 3 with maximal medical management</td>
<td>Hold drug until ≤ grade 2</td>
</tr>
<tr>
<td>Other non-hematologic Toxicities b, c</td>
<td></td>
</tr>
<tr>
<td>Grade 4 (in the RT field, or possibly related to cetuximab, or likely to be exacerbated by continuation of cetuximab)</td>
<td>Hold drug until ≤ grade 3</td>
</tr>
<tr>
<td>Grades 2-4 (out of RT field that does not reverse to Grade 1 at time of treatment, or unrelated to cetuximab, or unlikely to be exacerbated by continuation of cetuximab)</td>
<td>Maintain dose levels</td>
</tr>
</tbody>
</table>

aDose levels are relative to the previous dose. Dose reductions of C225 below the –2 dose level will not be allowed. In any case of C225 treatment delay, there will be no re-loading infusion, and all subsequent treatment will be at the assigned dose level.
bWith the exception of infusion reaction or acne-like rash (rash/desquamation);
cFor depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician.
### Cetuximab Infusion Reaction Management

<table>
<thead>
<tr>
<th>CTCAE v. 3.0 Toxicity Grade</th>
<th>Treatment Guidelines*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Slow the infusion rate for cetuximab by 50% and consider administering prophylactic antihistamine medications for subsequent doses. For mild or moderate infusion reactions manifesting only as delayed drug fever, maintain the cetuximab dose and infusion rate. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Slow the infusion rate for cetuximab by 50% and consider administering prophylactic antihistamine medications for subsequent doses. For mild or moderate infusion reactions manifesting only as delayed drug fever, maintain the cetuximab dose and infusion rate. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Severe infusion reactions, characterized by symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension, require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Severe infusion reactions, characterized by anaphylaxis, require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.</td>
</tr>
</tbody>
</table>

*Study Therapy Retreatment Following Infusion Reactions:* Once a C225 infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second infusion reaction with the slower infusion rate, the infusion should be stopped, and the subject should receive no further C225 treatment. If a subject experiences a Grade 3 or 4 infusion reaction at any time, the subject should receive no further C225 treatment. If there is any question as to whether an observed reaction is an infusion reaction of Grades 1-4, the Study Chair or Medical Oncology Co-Chairs should be contacted immediately to discuss and grade the reaction.

### Cetuximab Special Instructions

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

#### Management of Cetuximab Infusion Reactions

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

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

Cetuximab should be immediately and permanently discontinued in patients who experience severe (grade 3 or 4) infusion reactions.
In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

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

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

### 7.4.5.3 Cetuximab-related Rash

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

  **NOTE**: Rash intensity (i.e., the size and number of papules or the level of discomfort and extent of erythema) may be an important consideration. However, the absolute number of lesions, without associated physical discomfort, does not necessarily constitute a basis for a dose reduction or delay. Rash considered “intolerable” (because of pain, itching, or appearance) or that has failed to respond to symptomatic management may be considered grade 3 and thus prompt dose reduction or delay of cetuximab. The **clinical judgment of the treating physician is critical to grading and will ultimately dictate dose modification**.

- **Acute Skin Changes (Acute = From start of treatment to 3 months after completion of treatment)**
  - Rash Occurring Outside of the Radiation Field: Should be graded using the following CTCAE v. 3.0 terms. A rash complicated by secondary infection or cellulitis should be graded per additional CTCAE terms.

<table>
<thead>
<tr>
<th>Rash/desquamation*</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus/itching*</td>
<td>Mild of localized</td>
<td>Intense or widespread</td>
<td>Intense or widespread and interfering with ADL</td>
<td></td>
</tr>
<tr>
<td>Rash/desquamation*</td>
<td>Macular or papular eruption or erythema without associated symptoms</td>
<td>Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering &lt; 50% of body surface area (BSA)</td>
<td>Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering &gt; 50% BSA</td>
<td>Generalized, exfoliative, ulcerative, or bullous dermatitis</td>
</tr>
<tr>
<td>Rash/acro/acroform</td>
<td>Intervention not indicated</td>
<td>Intervention indicated</td>
<td>Associated with pain; disfigurement, ulceration, or desquamation</td>
<td></td>
</tr>
<tr>
<td>Nail changes*</td>
<td>Discoloration; ridging (koilonychias); pitting</td>
<td>Partial or complete loss of nail(s); pain in nail bed(s)</td>
<td>Interfering with ADL</td>
<td></td>
</tr>
</tbody>
</table>

Rash Occurring Inside the Radiation Field: Acute radiation dermatitis may be exacerbated by cetuximab or chemotherapy. The severity of such rash should be graded using the CTCAE v. 3.0 criteria for radiation dermatitis (table below).

<table>
<thead>
<tr>
<th>Rash: dermatitis associated with radiation</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faint erythema or dry desquamation</td>
<td>Moderate to brisk erythema, patchy moist desquamation, mostly confined to skin folds and creases; moderate edema</td>
<td>Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion</td>
<td>Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site</td>
<td></td>
</tr>
</tbody>
</table>

Late Skin Changes (Late = Changes present ≥ 3 months from completion of treatment): A potential late change of interest is consequential scarring/pock marking in or out of the radiation field. This may be reported by using the MedDRA code, “Dermatologic injury, ‘other’”, with the following protocol-specific grading scale as guidance:

- Grade 1: Mild (seen only on close inspection)
- Grade 2: Moderate (scarring, intervention or cosmetic coverage/intervention indicated)
- Grade 3: Severe (significant disfigurement, deep scarring, or ulceration)
- Grade 4: Deep cratering/scarring, skin necrosis, or disabling

Cetuximab Dose Modification Guidelines for Dermatologic Changes

<table>
<thead>
<tr>
<th>Cetuximab</th>
<th>Outcome</th>
<th>Cetuximab Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
<td>Improvement to ≤ Grade 2; No Improvement; remains grade 3</td>
</tr>
<tr>
<td>2nd occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
<td>Improvement to ≤ Grade 2; No Improvement; remains grade 3</td>
</tr>
<tr>
<td>3rd occurrence</td>
<td>Delay infusion 1 to 2 weeks</td>
<td>Improvement to ≤ Grade 2; No Improvement; remains grade 3</td>
</tr>
<tr>
<td>4th occurrence</td>
<td>Discontinue cetuximab</td>
<td></td>
</tr>
</tbody>
</table>

7.5 Modality Review
The Medical Oncology Co-Chairs, Rita Axelrod, MD and Eric Sherman, MD, will perform a Drug Therapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: per protocol; variation acceptable (Minor); variation acceptable (NOS); deviation unacceptable; not evaluable for chemotherapy review; or incomplete.

7.5.1 Cetuximab Dose Modifications

- 1st occurrence: Delay infusion 1 to 2 weeks
- 2nd occurrence: Delay infusion 1 to 2 weeks
- 3rd occurrence: Delay infusion 1 to 2 weeks
- 4th occurrence: Discontinue cetuximab

- Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneiform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

- If a patient experiences severe acneiform rash, cetuximab treatment adjustments should be made according to the table below. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

- Deleted: Skin Toxicity

- Deleted: Grade 3 Acneiform Rash

- Deleted: Chemotherapy
chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chairs, Rita Axelrod, MD and Eric Sherman, MD, will jointly perform a Quality Assurance Review after complete data for the first 25 cases enrolled have been received at RTOG Headquarters. Drs. Axelrod and Sherman will alternate performing reviews on subsequent blocks of 25 patients after the complete data for these cases becomes available at RTOG Headquarters. This schedule may be modified during the trial in light of preliminary results. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.6 Adverse Events

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). The CTEP home page also can be accessed from the RTOG web page at http://www.rtog.org/regulatory/regs.html. All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

All adverse events (AEs) as defined below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined below will be reported using either the FDA MedWatch Report or AdEERS. The RTOG Data Manager will tell the site which type of report to use for each study. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

7.6.1 Adverse Events (AEs) — RTOG AE PHONE: 215-717-2762 (available 24 Hours/Day)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported via AdEERS. Use the patient’s case number as the patient ID when reporting via AdEERS. AEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1). NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

7.6.2 Serious Adverse Events (SAEs) All SAEs that fit any one of the criteria in the SAE definition below must be reported to RTOG (SAE PHONE: 215-717-2762, available 24 hours/day) within 24 hours of discovery of the event.

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

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

Outside of regular business hours (8:30-5:00 EST), leave a message that includes the study/case numbers and the caller's contact information. A Data Manager will return the call the next business day requesting details of the event and also will inform the caller which type of report is required for that study (5 or 10 day AdEERS). The required report must be completed in AdEERS within 5 or 10 calendar days of the initial phone report, as directed by the
Data Manager taking the call. SAEs reported using AdEERS also must be reported on the AE case report form (see Section 12.1).

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported to RTOG via the AE/SAE telephone line within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, where applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system.

Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.6.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at http://ctep.info.nih.gov. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification (RTOG study/case numbers). This form will take the place of the FDA Form 3500 (MedWatch) or a report via the AdEERS system and must be faxed to the Investigational Drug Branch, FAX 301-230-0159, and mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.

<table>
<thead>
<tr>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
</tr>
</tbody>
</table>
7.7 AdEERS Expedited Reporting Requirements

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

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5¹</th>
<th>Grades 4 &amp; 5²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Unlikely</td>
<td>Not Required</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
</tr>
</tbody>
</table>

¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows:
- AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via email to [Group] AE Coordinator for agents in non-CTEP IND studies) followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
- AdEERS 10 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

³ Please see exceptions below under section entitled “Additional Instructions or Exceptions.”

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. “On study” is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:
Not applicable to this study.

8.0 SURGERY

8.1 Neck Dissection

The following patients will be assessed 8-9 weeks post-treatment with CT scan or MRI: All patients with N2a, N2b, and N3 disease and patients with ≤3 cm nodes on one side (N1) or both sides (a subset of N2c) with questionable neck findings. A post-treatment PET/CT scan (in addition to the required CT or MRI) is optional (see Section 4.1.6). NOTE: PET/CT is
investigational in this study; therefore, PET/CT findings should not affect the decision of neck dissection.

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

**For Patients Undergoing a Neck Dissection**

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

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

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

**8.2 Surgical Removal (Salvage) of the Primary Tumor**

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

Tissues for pathologic evaluation of margins should be taken from the patient (rather than the surgical specimen itself). However, the specimen itself should be marked at sites corresponding to the evaluated margins in order to assess sampling error in obtaining clear margins. If gross tumor remains or when no effort to remove tumor has been made, the patient will be considered to have "gross residual disease." In the absence of residual disease, if the cancer extends to within 5 mm of a surgical margin, the patient would be considered to have "close" margins.

**8.3 Surgical Quality Assurance Reviews**

The Surgical Oncology Co-Chair, Randal Weber, MD, will perform a Quality Assurance Review of patients undergoing neck dissection or salvage surgery after complete data for the first 25 cases enrolled has been received at RTOG Headquarters. Dr. Weber will perform the next review after complete data for the next 50 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.
9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy
All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. The use of amifostine and pilocarpine is discouraged in light of the overlapping toxicity profile with cetuximab and possible impact on the endpoints. If amifostine or pilocarpine is administered, it should be documented on the Treatment Form (TF) and the Follow-up Form (F1).

9.2 Non-permitted Supportive Therapy

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

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

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

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

10.1 Biomarker Studies

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

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

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

10.1.2 Hypotheses
The primary hypothesis is that EGFR expression level measured by image analysis based quantitative immunohistochemical assay predicts for local-regional control and survival (i.e., higher EGFR expression predicts for lower local-regional control and poorer survival), in patients receiving radiation-cisplatin regimen. The secondary hypothesis is that the effect of EGFR overexpression is mediated predominantly by one of its four down-stream signaling pathways, i.e., PI-3K/AKT. Previously published assay and correlative analysis methods will be used to test these hypotheses.
10.2 Specimen Collection for Translational Research and Tissue Banking

The following must be provided in order for the case to be evaluable for the Tissue Bank:

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

10.2.2 A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Tissue Bank (see Appendix VII). If both of these tissue types are unavailable, 15 unstained slides may be submitted; however, submission of unstained slides is strongly discouraged, as these slides are not useful for all translational research and present shipping and storage difficulties for pathology departments. Block or core (or slides) must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

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

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

10.2.5 Peripheral blood will be collected before initiation of treatment by venipuncture into two tubes: a plain 13 x 75 mm Vacutainer® tube from which serum can be extracted, and a 2 x 10 mm Vacutainer® tube containing acid-citrate-dextrose (ACD) solution from which leukocytes can be extracted. When received at the RTOG Tissue Bank, the serum will be aliquoted and frozen, and whole blood will be mixed with sterile DMSO to a final volume of 10% and frozen.

Specimens should be sent with a Specimen Transmittal Form documenting the date of collection of the serum; the RTOG protocol number, the patient’s case number, and method of storage, for example, stored at -20° C, must be included. Questions regarding blood collection or shipment should be directed to LDS Hospital, Department of Pathology (see contact information below). Ship by express overnight service, avoid a weekend or holiday arrival date, and DO NOT ship on Friday. Sites must notify the Tissue Bank by phone or email of expected arrival of peripheral blood.

10.2.5 Submit materials for Translational Research and Tissue Banking to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
holly.goold@ihc.com

10.3 Reimbursement

RTOG will reimburse submitting institutions $300 per case for fresh or flash frozen tissue; $200 per case for a block or core of material; or $100 per case for slides, serum, or leukocyte collection. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution’s summary report with the institution’s regular case reimbursement.

10.4 Confidentiality/Storage

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

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

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

## 11.0 PATIENT ASSESSMENTS

### 11.1 Study Parameters

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study Entry</th>
<th>Weekly During Treatment</th>
<th>From End of Treatment</th>
<th>From Start of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 Weeks</td>
<td>8-9 Weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 Mos</td>
<td>9 Mos</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 Mos</td>
<td>Follow Up*</td>
</tr>
<tr>
<td>Evaluations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete history/physical</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zubrod, weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>ECHO or MUGA</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Oncology Exam</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol-specific</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Eval, including mucosal assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dent evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutritional evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR or thoracic CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/MRI of tumor/primary site</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET/CT scan</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Diff, Platelets</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes, Mg++</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bilirubin, AST or ALT, Serum creatinine</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium or corrected serum calcium</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue/blood for TRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of Life Assessments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSS-HN</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>FACT-H&amp;N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Within 4 weeks prior to registration;
b) Within 12 weeks prior to registration;
c) Not required but highly recommended (see Section 4.2);
d) Within 6 weeks prior to registration;
e) Within 2 weeks prior to registration; Electrolytes: Sodium, potassium, bicarbonate, chloride, BUN, glucose, and phosphorus;
f) For women of childbearing potential, within 2 weeks prior to registration;
g) Primary tumor tissue and peripheral blood, taken before the initiation of treatment (see Section 10.2);
h) PSS-HN and EQ-5D will be administered pretreatment, during one of the last 2 weeks of treatment, at 3
and 12 months from start of treatment, then annually for years 2-5; FACT-HN will be administered
pretreatment, and annually in years 1 and 5;
i) Every 3 weeks, prior to chemotherapy (cisplatin) cycle;
j) Weekly and within 24 hours of receiving chemotherapy;
k) In follow up, CXR or thoracic CT scan or PET scan will be done at 6 months (+/- 1 month) in year 1, then annually.

L) In follow up, CT scan/MRI of the head and neck (plus optional PET/CT) will be done 8-9 weeks after completion of radiation for all N2a-b and N3 patients and for selected N1-N2c patients (see Section 8.1 for details) and then at 6 months in year 1, then annually. If special circumstances (e.g., patient unable to lie supine) prevent routine imaging, evaluation of the primary site may be done by visual inspection (e.g., visual endoscopy).

m) Creatinine only.

n) Follow up will be at 8-9 weeks post-treatment and at 6, 9, and 12 months from start of treatment for year 1, every 3 months for year 2, every 6 months for years 3-5, and then annually.

### 11.2 Evaluation During and Post-Treatment

#### 11.2.1 Protocol-Specific Adverse Event Evaluation

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>AE term</th>
<th>Ref page in CTCAE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Dysphagia (difficulty swallowing)</td>
<td>21</td>
</tr>
<tr>
<td>Pulmonary/Upper Respiratory</td>
<td>Edema, larynx (includes need for tracheostomy)</td>
<td>57</td>
</tr>
<tr>
<td>Gastrointestinal*</td>
<td>Dysphagia (difficulty swallowing)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis (clinical exam) [specify oral cavity, pharynx, or larynx primary site]</td>
<td>24</td>
</tr>
<tr>
<td>Dermatology/Skin*</td>
<td>Rash [desquamation [face (out of field), trunk, extremities] , ]</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Rash: dermatis associated with radiation- [Select radiation (radiation dermatitis may be exacerbated by C225, but in-field skin changes are graded using the radiation scale)]</td>
<td>15</td>
</tr>
<tr>
<td>Neurology</td>
<td>Neuropathy: sensory</td>
<td>50</td>
</tr>
<tr>
<td>Pulmonary/Upper Respiratory</td>
<td>Edema, larynx (includes need for tracheostomy)</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dysphagia (difficulty swallowing)</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Mucositis/stomatitis (clinical exam) [specify oral cavity, pharynx, or larynx primary site]</td>
<td>24</td>
</tr>
<tr>
<td>Dermatology/Skin</td>
<td>Rash [desquamation [for late effects/scarring out of RT field – face, trunk, or extremities] , ]</td>
<td>15</td>
</tr>
</tbody>
</table>

Additional: rate

Deleted: hard coded

Formatted: Font: Bold

Deleted: .

Deleted: The reference pages listed below are from t

Deleted: Font: Bold

Deleted: .

Deleted: In place of the CTCAE spiral bound book, you may use the

Deleted: provided by

Deleted: on our

Deleted: .

Deleted: s

Deleted: Targeted

Deleted: -

Deleted: Mucositis/stomatitis (clinical exam)- pharynx

Deleted: 24

Deleted: Mucositis/stomatitis (functional/symptomatic)- oral cavity

Deleted: 24

Deleted: Mucositis/stomatitis (functional/symptomatic)- pharynx

Deleted: 24

Deleted: :

Deleted: provided

Deleted: acne/acneiform [in RT field]

Deleted: Rash: acne/acneiform [out of RT field]

Deleted: Mucositis/stomatitis (clinical exam)- pharynx

Deleted: 24

Deleted: Mucositis/stomatitis (functional/symptomatic)- oral cavity

Deleted: 24

Deleted: Mucositis/stomatitis (functional/symptomatic)- pharynx

Deleted: 24

Deleted: :

Deleted: acne/acneiform [in RT field]

Deleted: Rash: acne/acneiform [out of RT field]

Deleted: Mucositis/stomatitis (clinical exam)- pharynx

Deleted: 24

Deleted: Mucositis/stomatitis (functional/symptomatic)- oral cavity

Deleted: 24

Deleted: Mucositis/stomatitis (functional/symptomatic)- pharynx

Deleted: 24

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

11.2.2 In addition to protocol-specific AEs (AE terms provided on protocol-specific forms), additional AEs experienced during treatment and in follow up must be documented on Adverse Event (AE) form. When reporting additional AEs, please refrain from using the 'Other, Specify' mechanism. This should be the exception, not the rule in the rare event that a suitable CTCAE term cannot be found. If this is absolutely necessary, the investigator must make a note to this affect in the source documentation. See section 12.1 for submission schedule.

11.2.3 For patients without a feeding tube, a nutritional evaluation based on acute reactions and Zubrod status should be done weekly during treatment. Status of feeding tube and placement/removal of a tracheostomy should be documented on the Follow-up Form (F1).

11.2.4 Whenever possible, patients will be evaluated at two-week intervals after completion of treatment until their acute reactions have resolved.

11.2.5 Assessment for possible neck dissection should take place 8-9 weeks after completion of treatment, and dissection should take place within 2 weeks once the decision for neck dissection is made.

11.2.6 Treatment for recurrence depends on the site of relapse and is at the discretion of the treating physician.

11.3 Measurement of Response

11.3.1 Tumor Clearance

Since the primary endpoint of this study is disease-free survival, and the major secondary endpoint is local-regional control, the only meaningful response for this study population is a complete response; anything less will be considered a treatment failure. A patient will be considered to have complete response if there is no measurable or palpable tumor either on clinical or radiographic (CT scan or MRI) examination.

PET/CT scans will not be used in determining a patient's response to treatment for purposes of evaluating efficacy endpoints such as disease-free survival. The primary tumor and regional nodes will be evaluated and reported separately. Patients that have non-protocol radiation to the primary tumor or regional nodes or chemotherapy prior to achieving complete response will be considered a treatment failure.

11.3.2 Local or Regional Relapse

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

11.3.3 Local or Regional Progression

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

11.3.4 Distant Metastasis

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

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

11.3.6 Discontinuation of Protocol Treatment
Protocol treatment may be discontinued for any of the following reasons:
- Progression of disease;
- Unacceptable toxicity [at the discretion of the treating physician(s)];
- Patient refusal;
- Patient's withdrawal of consent; the treating institution must notify RTOG Headquarters Data Management about this in writing and follow the guidelines set forth in the RTOG procedure manual. Data for patients that withdraw consent will not be used for any analysis.

11.3.7 Discontinuation of Follow-Up Assessments
Follow-up assessments may be discontinued for either of the following reasons:
- Patient refusal;
- Patient's withdrawal of consent; the treating institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual. Data for patients that withdraw consent will not be used for any analysis.

11.4 FDG-PET/CT Imaging
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 (in addition to the required CT scan or MRI) 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.

11.4.1 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.

The PET Core Lab will collect at least one test case from each site prior to enrollment of their first patient to evaluate and resolve issues associated with image transfer capabilities and image set compatibility.

The application and instructions for submitting a single test case can be found 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. The form can be sent via email or fax 215-923-1737. For further information, contact the PET Core Laboratory at 215-574-3244.

11.4.2 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.

11.4.3 FDG Injection
A dose of 10-20 mCi of 18FDG 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 18FDG 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.

11.4.4 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.

11.4.5 Assessment at 8-9 Weeks Post-Treatment

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: 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.

11.4.6 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.

11.4.7 Image Submission to PET Core Laboratory

All images to be collected from PET/CT are to be in DICOM digital format. Films will not be accepted for this study. The PET Core Lab can provide software that allows for electronic transmission of images to the IMC that have been scrubbed of all participant identifiers. Please contact Tim Welsh for instructions at 215-717-2754. 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 specifically to your 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 before the images are transferred. If using ACRIN software, header scrubbing is accomplished automatically. For further information on the scrubbing of pertinent patient information, contact the PET Core Laboratory at 215-717-2754 or at 215-574-3244.

11.5 Quality of Life Assessments

11.5.1 The Performance Status Scale for Head and Neck Cancer (PSS-HN) consists of assessment of three functions (subscales): Normalcy of Diet, Eating in Public, and Understandability of Speech. The site research nurse or clinical research associate (CRA) will administer the PSS-HN. Interviewers are encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. The interviewer rates the patient on each scale based on the patient's responses to targeted questions. The PSS-HN takes approximately 5 minutes to complete. Note: The PSS-HN has been translated into 12 languages and is available to institutions at no charge. Contact Dr. List, the QOL Co-Chair, for these translations.
11.5.2 *Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N)* is a multidimensional, QOL instrument specifically designed and validated for use with HNC patients that the patient can complete in 5-10 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. Note: The FACT-H&N has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at [http://www.facit.org/translation/licensure.aspx](http://www.facit.org/translation/licensure.aspx).

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

Data should be submitted to:

RTOG Headquarters  
1818 Market Street, Suite 1600  
Philadelphia, PA 19103

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

12.1 **Summary of Data Submission**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Slides/Blocks (P2)</td>
<td></td>
</tr>
<tr>
<td>Performance Status Scale for H &amp;N Cancer (PSS-HN) [QP]</td>
<td></td>
</tr>
<tr>
<td>Functional Assessment of Cancer Treatment (FACT-H&amp;N) [FA]</td>
<td></td>
</tr>
<tr>
<td>Health Utility Measurement (EQ-5D) [HP]</td>
<td></td>
</tr>
<tr>
<td>Nodal Diagram (I7)</td>
<td></td>
</tr>
<tr>
<td>*PET Assessment Form (IM)</td>
<td></td>
</tr>
<tr>
<td>*If participating in PET component of study.</td>
<td></td>
</tr>
</tbody>
</table>

Preliminary Dosimetry Information for 3D-CRT Approach

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

Final Dosimetry Information for 3D-CRT Approach

For digital submission, See Section 12.2

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Form (TF)</td>
<td>At completion or discontinuation of systemic treatment</td>
</tr>
<tr>
<td>Adverse Event Form (AE)</td>
<td></td>
</tr>
<tr>
<td>Surgical Form (S1)</td>
<td>At 9 months from start of treatment (or earlier, if surgery occurs prior to 9 months from start of treatment)</td>
</tr>
<tr>
<td>Surgical Operative Report (S2)</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Performance Status Scale for H &amp;N Cancer (PSS-HN) [QP]</td>
<td>At completion or discontinuation of systemic treatment, at 4 weeks post-systemic treatment, at 12 months from the start of systemic treatment, then annually for years 2-5</td>
</tr>
<tr>
<td>Health Utility Measurement (EQ-5D) [HP]</td>
<td></td>
</tr>
</tbody>
</table>

*PET Assessment Form (IM)                                           | At 8 weeks post-systemic therapy                                     |
*If participating in PET component of study.                        |                                                                     |

Follow-up Form (F1)                                                 | At 10 weeks post-treatment and at 6, 9, and 12 months from the start of treatment, every 3 months for 1 year, every 6 months for the next 2 years, then annually and at death. |
Adverse Event Form (AE)  As needed
### 12.2 Summary of Dosimetry Digital Data Submission (Submit to ITC; see Section 12.2.1)

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preliminary Dosimetry Information</strong></td>
<td></td>
</tr>
<tr>
<td>†Digital Data Submission Form (T2)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>CT data, critical normal structures, all GTV, CTV, and PTV contours (C1, C3)</td>
<td></td>
</tr>
<tr>
<td>Simulation films and/or digital film images for all initial treatment fields and orthogonal setup pair</td>
<td></td>
</tr>
<tr>
<td>First day port films (or digital images) of all initial treatment fields and orthogonal setup pair</td>
<td></td>
</tr>
<tr>
<td>Digital beam geometry for initial and boost beam sets</td>
<td></td>
</tr>
<tr>
<td>Doses for initial and boost sets of concurrent treated beams</td>
<td></td>
</tr>
<tr>
<td>Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan (DV)</td>
<td></td>
</tr>
<tr>
<td>Hard copy isodose distributions for total dose plan as described in QA guidelines†</td>
<td>(T6)</td>
</tr>
<tr>
<td><strong>Final Dosimetry Information</strong></td>
<td>Within 1 week of RT end</td>
</tr>
<tr>
<td>Radiotherapy Form (T1) [copy to HQ and ITC]</td>
<td></td>
</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Simulation films and/or digital film images (or digital images) of all boost treatment fields and orthogonal setup pair (T8)</td>
<td></td>
</tr>
<tr>
<td>First day port films of all boost treatment fields and orthogonal setup pair (T8)</td>
<td></td>
</tr>
<tr>
<td>Modified digital patient data as required through consultation with Image Guided Therapy QA Center</td>
<td></td>
</tr>
</tbody>
</table>

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

### 12.2.1 Digital Data Submission to ITC

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

For tape submission: Please contact the ITC about acceptable tape types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63110
314-747-5415
FAX 314-747-5423
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
Disease-free survival (Failure: local-regional [see Section 13.1.2.2] distant metastases, second primary, or death without progression);

13.1.2 Secondary Endpoints

13.1.2.1 Overall survival (Failure: death due to any cause);

13.1.2.2 Local-regional control (Failure in primary: persistent or recurrent disease; failure in regional nodes: persistent disease, if not cleared by surgery; or recurrent disease);

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

13.1.2.4 Other toxicity (Rates of ≥ grade 3);

13.1.2.5 Protocol treatment delivery;

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

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

13.1.2.8 Quality of life (FACT-G);

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

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

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

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

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Projected RTOG 0522 AFX-CB + cisplatin</th>
<th>RTOG 99-14 AFX-CB + cisplatin</th>
<th>RTOG 90-03 AFX-CB</th>
<th>RTOG 91-11 SFX + cisplatin</th>
<th>RTOG 91-11 SFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40.0% (20%)</td>
<td>39.4%</td>
<td>52.2%</td>
<td>27.9%</td>
<td>44.3%</td>
</tr>
<tr>
<td>2</td>
<td>12.0%</td>
<td>11.5%</td>
<td>15.1%</td>
<td>15.7%</td>
<td>21.4%</td>
</tr>
<tr>
<td>3</td>
<td>12.0%</td>
<td>NA</td>
<td>15.2%</td>
<td>16.9%</td>
<td>12.6%</td>
</tr>
<tr>
<td>4</td>
<td>7.5%</td>
<td>NA</td>
<td>10.5%</td>
<td>20.7%</td>
<td>16.7%</td>
</tr>
<tr>
<td>5</td>
<td>7.5%</td>
<td>NA</td>
<td>8.1%</td>
<td>9.1%</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Projected RTOG 0522 AFX-CB + cisplatin</th>
<th>RTOG 99-14 AFX-CB + cisplatin</th>
<th>RTOG 90-03 AFX-CB</th>
<th>RTOG 91-11 SFX + cisplatin</th>
<th>RTOG 91-11 SFX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20.0% (20%)</td>
<td>19.5%</td>
<td>32.0%</td>
<td>14.5%</td>
<td>12.3%</td>
</tr>
<tr>
<td>2</td>
<td>12.0%</td>
<td>12.2%</td>
<td>26.8%</td>
<td>13.3%</td>
<td>14.5%</td>
</tr>
<tr>
<td>3</td>
<td>12.0%</td>
<td>NA</td>
<td>16.3%</td>
<td>8.3%</td>
<td>14.2%</td>
</tr>
<tr>
<td>4</td>
<td>12.0%</td>
<td>NA</td>
<td>11.5%</td>
<td>11.3%</td>
<td>10.1%</td>
</tr>
<tr>
<td>5</td>
<td>12.0%</td>
<td>NA</td>
<td>8.8%</td>
<td>10.3%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>
RTOG 90-03 tested three altered fractionation radiation schedules without chemotherapy in locally advanced head and neck cancer (including laryngeal primary sites) against standard once-daily radiation (SFX). One of the altered fractionation schedules (AFX with concomitant boost during the last 12 days) is used on both arms in this study. RTOG 91-11 tested two regimens for laryngeal preservation: standard once-a-day radiation (SFX) and SFX + concurrent cisplatin. RTOG 99-14 was a phase II trial evaluating AFX-CB + concurrent cisplatin.

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

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

13.3 Tumor Markers: Background and Statistical Power Considerations

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

For planning purposes, it is assumed that the patient accrual will not be discontinued in the trial before reaching its target. Based on RTOG 0129, it is projected that 60% of randomized patients will be analyzable for tumor marker evaluation, giving a total of 410 analyzable patients or 205 per arm.

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

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

\[
\text{Number of failures} = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2}{(\ln HR)^2 w (1 - w)}
\]

where \(z_{1-\alpha/2}\) is normal deviate for the significance level.
z_{1-\beta} = normal deviate for the statistical power
HR = hazard ratio comparing favorable risk group (low EGFR values) to unfavorable risk group (high EGFR values)
w = prevalence rate of risk group

Table 3 below shows statistical power to detect hazard ratios for survival of 1.50, 1.75, and 2.00 for prevalence rates of 40%, or 50%, or 60%. The proposed analysis will be done when there are at least 105 deaths on the cetuximab arm with tumor marker determination. The significance level was set at 0.05. As seen in the table, there will be good power to detect a hazard ratio of 1.75, which was seen in RTOG 90-03 for OS.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.50</td>
</tr>
<tr>
<td>40% (or 60%)</td>
<td>0.53</td>
</tr>
<tr>
<td>50%</td>
<td>0.54</td>
</tr>
</tbody>
</table>

13.4 **PET/CT Evaluation: Background and Statistical Power Considerations**

Pre-treatment PET/CT scans have been incorporated in the staging work up of head and neck cancer patients in an increasing number of centers. Controversy persists as to whether patients presenting with N2-3 disease that regresses completely at 8-9 weeks after completion of radio-chemotherapy would benefit from neck dissection. This study component is designed to assess the possible prognostic value of pre-treatment PET/CT scan for local-regional failure (LRF) and OS and also the value of PET/CT done after completion of treatment to determine the need for neck dissection in patients initially presenting with N2-3 disease (with the exception of bilateral nodes, N2c, all measuring < 3 cm) by estimating the predicted true negative value. The specific hypotheses to be tested are:

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

13.4.1 **Statistical Power for Pre-Treatment PET/CT Scan Analysis**

It should be noted that patients and institutions could initially decline to participate in the PET/CT component in this study and still participate in the treatment comparison, which is its primary efficacy question. Assuming that 75% of 681 eligible patients will have a pre-treatment scan done, there would be 514 patients available for analysis. This PET/CT analysis will be done after the analysis for reporting the treatment efficacy results that will be performed with the protocol required 387 disease-free survival (DFS) failures. Approximately 300 DFS failures, 200 deaths, and 150 local-regional failures are anticipated. The equation described by Schoenfeld\(^5\) was used to calculate the statistical powers reported in Tables 4-6 with a significance level of 0.05. Two of the three variables evaluated as possible prognostic variables are based on the median value for the FDG SUV_{max} values associated with the primary and nodal disease respectively. The third variable is based upon patients having both their FDG SUV_{max} values (primary and nodal disease) above their respective median. Thus, the percentage of patients satisfying this requirement theoretically can vary from 50% to 0%.
Table 4 below shows statistical power to detect hazard ratios for DFS of 1.50, 1.75, 2.00, and 2.25 for various divisions of patient population, i.e., one group with 10%, 20%, 30%, 40%, or 50%.

<table>
<thead>
<tr>
<th>% in one group</th>
<th>Hazard Ratio</th>
<th>1.50</th>
<th>1.75</th>
<th>2.00</th>
<th>2.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10 (or 0.90)</td>
<td></td>
<td>0.55</td>
<td>0.82</td>
<td>0.94</td>
<td>0.98</td>
</tr>
<tr>
<td>0.20 (or 0.80)</td>
<td></td>
<td>0.80</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>0.30 (or 0.70)</td>
<td></td>
<td>0.89</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>0.40 (or 0.60)</td>
<td></td>
<td>0.93</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>0.50</td>
<td></td>
<td>0.93</td>
<td>0.99</td>
<td>0.99</td>
<td>0.99</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>% in one group</th>
<th>Hazard Ratio</th>
<th>1.50</th>
<th>1.75</th>
<th>2.00</th>
<th>2.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10 (or 0.90)</td>
<td></td>
<td>0.40</td>
<td>0.66</td>
<td>0.83</td>
<td>0.93</td>
</tr>
<tr>
<td>0.20 (or 0.80)</td>
<td></td>
<td>0.63</td>
<td>0.88</td>
<td>0.97</td>
<td>0.99</td>
</tr>
<tr>
<td>0.30 (or 0.70)</td>
<td></td>
<td>0.74</td>
<td>0.95</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>% in one group</td>
<td>Hazard Ratio</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.50</td>
<td>1.75</td>
<td>2.00</td>
<td>2.25</td>
<td></td>
</tr>
<tr>
<td>0.70)</td>
<td>0.80</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>0.40 (or 0.60)</td>
<td>0.81</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>0.81</td>
<td>0.97</td>
<td>0.99</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

Table 6 below shows statistical power to detect hazard ratios for LRC of 1.50, 1.75, 2.00, and 2.25 for various divisions of patient population, i.e., one group with 10%, 20%, 30%, 40%, or 50%.
Table 6: Local-Regional Control (LRC) — Statistical Power with 150 Events and 5% Alpha

<table>
<thead>
<tr>
<th>% in one group</th>
<th>Hazard Ratio</th>
<th>1.50</th>
<th>1.75</th>
<th>2.00</th>
<th>2.25</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10 (or 0.90)</td>
<td>0.31</td>
<td>0.53</td>
<td>0.72</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>0.20 (or 0.80)</td>
<td>0.51</td>
<td>0.78</td>
<td>0.72</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>0.30 (or 0.70)</td>
<td>0.62</td>
<td>0.88</td>
<td>0.92</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>0.40 (or 0.60)</td>
<td>0.68</td>
<td>0.91</td>
<td>0.97</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>0.50</td>
<td>0.69</td>
<td>0.92</td>
<td>0.98</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

In summary, the statistical power is sufficiently high to detect a hazard ratio of at least 1.50 for DFS and OS and at least 1.75 for LRC.

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

It should be noted that patients and institutions could decline to have the second PET/CT scan performed. Based upon the current 0129 trial, it is estimated that 460 (67%) patients enrolled on this protocol will have clinical N2-3 disease. It is projected that 50% of N2-3 patients will have a post-treatment PET/CT because of lack of insurance coverage and further, because of the protocol requirement of a combined PET/CT scanner (see Section 11.4). Thus, potentially there would be 230 patients available for correlating PET/CT findings with nodal disease status post-treatment. The protocol calls for N2-3 patients with less than complete clinical nodal response to undergo neck dissection while it is optional for patients with complete clinical nodal response. The rate of neck dissection in patients with less than complete clinical nodal response is projected to be 90% while the rate in patients with complete clinical nodal response is 50%. Because of a possible selection bias in the clinical complete responders going to neck dissection, the correlation of PET/CT findings with pathologic response will be done not only in all patients but also within these two clinical nodal response subsets. Based upon previous RTOG studies, the projected clinical complete nodal response rate is 50%. Using the projected estimates, there will be approximately 58 patients with a clinical nodal complete response available to correlate PET/CT findings with pathologic response and 104 patients with less than clinical nodal complete response. In addition, since not all patients who had a post-treatment PET/CT evaluation will undergo neck dissection, the two-year nodal relapse rates will be estimated and compared by post-treatment PET/CT finding (negative and positive) within the nodal response subset. The only results available for post-treatment PET/CT scan come from relatively small institutional series and may not provide a reliable estimate of the percentage of patients with negative PET/CT scan. Our best estimate would be 40% negative post-treatment PET/CT scan rate. Of particular interest will be clinical nodal complete responders who have a negative PET/CT. Based upon the assumptions, there will be 23 such patients available to correlate with pathologic nodal response and 46 available to estimate the two-year nodal relapse rate.

13.5 Patient Accrual

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

13.6 Randomization

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

The first 3 stratification factors are based on prior RTOG Recursive Partitioning Analyses.11,56

The treatment allocation scheme described by Zelen67 will be used at randomization to balance
risk factors other than treating institution.

13.7 Analysis Plan

13.7.1 Statistical Methods

Overall and disease-free survival will be estimated by the Kaplan-Meier method58 and the log-
rank test59 will be used to test the experimental treatment against the control. The cumulative
incidence method will be used to estimate local-regional failure rates, and the failure rates for
the experimental treatment will be compared against the control using failure-specific log-rank
test.60 Multivariate analysis also will be performed using the Cox proportional hazards model
with the stratifying variables (see Section 13.6) as fixed covariates. Rates of grade ≥3 toxicity
will be compared using Fisher’s exact test. For each of the three PSS-HN subscales, the
frequencies of patients with scores of 50 or less will be compared between the two treatments
using the z-statistic for testing binomial proportions at 3 and 12 months from start of treatment.
The EQ 5D will be used to generate health utilities, which will then be used in deriving quality
adjusted survivals. The log-rank test will compare those survivals between the treatments. The
correlation coefficient between the EQ 5D’s five-item score and the global FACT-G score will
be computed for the patient evaluation at baseline, at one year, and at five years from start of
protocol treatment.

Local-regional control will be measured from the date of randomization to the date of first local
or regional relapse. A patient must achieve a complete response of both the primary tumor and
regional nodes before any local-regional relapse/progression or non-protocol therapy in order
to be considered in local-regional control. Complete response of the primary tumor only can be
achieved through protocol chemoradiation therapy. Complete response of the regional nodes
also can be achieved through salvage “neck dissection” surgery following the completion of
protocol chemoradiation therapy. Patients with persistent local or regional disease will be
considered a failure at day 1. For non-failures, the last follow-up date reported will be used.

Disease-free survival will be measured from the date of randomization to the date of first local,
regional, or distant relapse, second primary neoplasm, or death. However, patients with
persistent local or regional disease will be considered a failure at day 1. For non-failures, the
last follow-up date reported alive will be used.

Overall survival will be measured from the date of randomization to the date of death or
otherwise, the last follow-up date reported alive.

13.7.2 Interim Analyses to Monitor Study Progress

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

- Patient accrual rate with a projected completion date for the accrual phase;
- Distribution of important baseline pre-treatment characteristics;
- Frequency and severity of adverse events;
- Compliance rate for treatment delivery with respect to the protocol prescription;
- Level of patient participation at each protocol-designated HRQOL evaluation time point,
  along with reasons for non-participation.
These interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints such as OS and DFS. The RTOG Head and Neck Steering Committee and the RTOG Data Monitoring Committee (DMC) will review this report with particular emphasis on toxicity and patient accrual.

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

13.7.3 Interim Analysis to Monitor Treatment Delivery and Early Death

Since there is limited experience with the experimental regimen, an interim analysis will be performed to assure that there is no unexpected problem with tolerability of the drugs and no decrease in the radiation therapy dose delivered. This interim analysis will occur after the first 80 patients are entered into the protocol (The data for this analysis would be available six months after the 80th patient is entered. The six-month interval would allow sufficient time for the treatment to be completed, the first two therapy toxicity assessments to be done at 4 and 8–9 weeks as specified in the protocol, and the data processed). There would be about 40 patients on the 0522 experimental arm available for analysis. Treatment delivered per protocol prescription will be used to evaluate patient tolerability for the experimental arm (Arm 2).

Tolerability will be measured by the percentage of patients who receive the following:
- Two chemotherapy cycles;
- The initial dose of cetuximab;
- At least five of the weekly cetuximab doses;
- Radiation therapy scored by the study chair as per protocol or with minor deviation.

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

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

13.7.4 Significance Testing for Early Termination and Reporting

Three interim treatment comparisons will be performed for the RTOG meeting immediately after 98, 196, and 294 DFS failures (total from both arms) have been reported. Toxicity, treatment delivery, DFS, and OS will be reported to the RTOG DMC. The DFS difference between the control arm and the experimental arm will be tested using the log-rank statistic at the significance level of 0.001. In addition, the conditional statistical power (CP) to observe the hypothesized treatment effect will be calculated. If any tests are significant or the CP < 0.10, the responsible statistician will recommend to the DMC that further patient accrual should be discontinued, if appropriate, and the results reported early.

13.7.5 Analysis for Reporting the Initial Treatment Results

The analysis reporting the treatment results will be carried out after 392 DFS failures (or 214 on control arm) have been observed unless the criteria for early stopping are met.

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

The difference in DFS between the control arm and the experimental arm will be tested using the log-rank statistic at the significance level of 0.0238 given that the three interim analyses are carried out and show no statistical significance.

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

**13.7.6 Quality of Life and Health Utility Analysis**

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

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

**13.7.7 Tumor Marker Analysis**

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

The patients will be initially divided into two subgroups based upon previously defined (or hypothesized) cut points one or more tumor markers, and these two groups will be referred to as favorable and unfavorable risk groups. In univariate analysis, the log-rank test will be used to test for DFS and OS differences between the favorable and unfavorable risk groups; a failure-specific log-rank test will be used for LRF. Multivariate analysis will be performed using the Cox proportional hazards model for both outcomes. Potential covariates evaluated for the multivariate models are assigned treatment, age, Zubrod performance status, T-stage, N-stage, and primary site. A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the tumor markers. This approach will be employed to account for as much variation as possible for each outcome before they are tested. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here. Then the tumor marker or combination of markers will be added to the model to test for significance. If the hypothesized cut points do not yield statistical significance, other cut points may be evaluated.

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

13.7.8.1 Pre-Treatment PET/CT Analysis

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

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

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

13.7.8.2 Post-Treatment PET/CT Analysis

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

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

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

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

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

13.8 Inclusion of Women and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, a statistical analysis will be performed, as sample sizes allow, to examine possible differences by gender, race, or ethnicity. Based on the accrual statistics from ongoing trial RTOG 0129, we project that 80% of patients enrolled to this study will be men, and 20% women. With respect to race, we project 80% white and 20% not white. With respect to ethnicity, we project 5% Hispanic/Latino and 95% not Hispanic/Latino. Assuming no differences between the genders or ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference is 0.71 for males.
and 0.71 for whites. The statistical power for females, non-whites, and Hispanic/Latino is too low for any meaningful treatment comparison.

### Gender and Minority Accrual Estimates

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>7</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>137</td>
</tr>
<tr>
<td><strong>Ethnic Category: Total of all subjects</strong></td>
<td>144</td>
</tr>
<tr>
<td>Racial Category</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>1</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>Black or African American</td>
<td>22</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>120</td>
</tr>
<tr>
<td><strong>Racial Category: Total of all subjects</strong></td>
<td>144</td>
</tr>
</tbody>
</table>
REFERENCES


REFERENCES (Continued)


22. David Pfister, personal communication.


REFERENCES (Continued)


42. List M, personal communication.


REFERENCES (Continued)


APPENDIX I
RTOG 0522

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

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

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

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of radiation therapy and chemotherapy (cisplatin) with radiation therapy, chemotherapy, and cetuximab (C225) on you and your advanced head and neck cancer to find out which is better. In this study, you will get either radiation and cisplatin, or radiation, cisplatin, and C225. You will not get both.

C225 was approved in 2004 as a treatment for patients with colorectal cancer, but it is an experimental treatment for patients with head and neck cancer. C225 may delay or prevent tumor growth by blocking certain cellular chemical pathways that lead to tumor development.

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

How many people will take part in the study?

About 720 people will take part in this study.

What will happen if I take part in this research study?

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

- Physical examination by several doctors
- One of the following:
  - Chest x-ray
  - Or CT (Computed Tomography) scan of your chest: A study using x-rays to look at one part of your body
  - Or the combination of a PET (Positron Emission Tomography) and CT scan of your body: A PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer’s signal as it travels through your body.
• CT scan or an MRI (Magnetic Resonance Imaging) of your head and neck or a PET/CT scan of your body (MRI: Imaging using a strong magnetic field to look at one part of your body)
• Tests of your heart function: This may be done by injecting a low-dose radioactive substance (a tracer) into your vein. A camera records the tracer as it flows through your heart, showing your heart’s function. Another option is to use sound waves from a machine that looks like a microphone and that is passed across your chest to test heart function.
• Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
• For women able to have children, a pregnancy test
• If your study doctor recommends:
  > A dental evaluation before receiving radiation
  > A hearing test
  > An evaluation of your diet and ability to chew and swallow to see if a feeding tube is needed

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures during the study. They are part of regular cancer care.
• Physical examination by your several doctors
• Evaluation of your weight and ability to carry out daily activities
• Blood tests every week during treatment (about 7 times): about 2-3 teaspoons of blood will be taken from your vein
• Evaluation of any side effects you may be having
• An evaluation of your diet and ability to chew and swallow to see if a feeding tube is needed

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

At 4 weeks after treatment
• Evaluation of your weight and ability to carry out daily activities
• Blood tests (about 2-3 teaspoons of blood will be taken from your vein)
• Evaluation of any side effects you may be having

At 8-9 weeks after treatment
• For patients with remaining large tumors, a CT scan or MRI of the head and neck; these patients may also have a PET/CT scan.

At 6, 9, and 12 months from the start of treatment
• Evaluation of your weight and your ability to carry out your daily activities
• Blood tests (about 2-3 teaspoons of blood will be taken from your vein)

Every 3 months for year 2, every 6 months for years 3-5, then annually:
• A physical examination
• Blood tests (about 2-3 teaspoons of blood will be taken from your vein)

At 6 months for year 1, then annually:
• Chest x-ray or CT scan of the chest or PET/CT scan of your body

At 6 months after treatment, then annually:
• CT scan or MRI of your head and neck or PET/CT scan of your body

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

If you are in Group 1 (often called “Arm 1”), you will receive radiation therapy and chemotherapy (cisplatin).
All patients will receive radiation therapy for 6 weeks. Each radiation treatment will take about 30 minutes.

There are several ways to receive radiation therapy in this study. Your study doctor will discuss with you how your radiation therapy will be given:

- You may receive radiation therapy once a day, Monday through Friday, for about 3 1/2 weeks and then twice a day, Monday through Friday, for the remaining 2 1/2 weeks. There will be at least 6 hours between the two daily treatments.
- Or you may receive radiation therapy once a day for four days of the week (Monday through Thursday) and twice a day on the fifth day (Friday) for 6 weeks. When given twice a day on the fifth day, there will be at least 6 hours between treatments.
- Or you may receive radiation therapy once a day, Monday through Saturday for 6 weeks.

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

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

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

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

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

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

- You may receive radiation therapy once a day, Monday through Friday, for about 3 1/2 weeks and then twice a day, Monday through Friday, for the remaining 2 1/2 weeks. There will be at least 6 hours between the two daily treatments.
- Or you may receive radiation therapy once a day for four days of the week (Monday through Thursday) and twice a day on the fifth day (Friday) for 6 weeks. When given twice a day on the fifth day, there will be at least 6 hours between treatments.
- Or you may receive radiation therapy once a day, Monday through Saturday for 6 weeks.

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

Both Groups: Evaluation of Treatment

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

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

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

How long will I be in the study?

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

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

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.
It is important to tell the study doctor if you are thinking about stopping so that any risks from the radiation therapy, chemotherapy, or C225 (if you receive C225) can be evaluated by the study doctor. Another reason to tell the study doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

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

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

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

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

Risks and side effects include:

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

Risks Associated with Radiation to the Head and Neck

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

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

Risks Associated with cisplatin

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

Less Likely
• Low magnesium in the body
• Low calcium in the body (It is unlikely that the calcium level will be low enough to affect heart function)
• Low potassium in the body (It is unlikely that the potassium level will be low enough to affect heart function)
• Kidney damage

Less Likely, But Serious
• Allergic reactions (sweating, difficulty breathing, rapid heartbeat)
• Muscle cramps or spasm
• Facial swelling
• Loss of taste
• Loss of coordination
• Involuntary movement

Restlessness
• Loss of hair, which is temporary
• Blood clots
• Low blood pressure

Risks Associated with Cetuximab (C225)

Very Likely
• Weakness
• Headache
• Fever
• Dry skin
• Localized acne-like skin reactions, rash, itching
• Low magnesium in the blood, which could result in muscle cramps and/or weakness

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

- Reduced white blood cell count which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily; this lowering of blood counts can lead to need for treatment with antibiotics, transfusions, or hospitalization if severe.
- Blood clots within a blood vessel in the lungs, legs, or pelvis
- Kidney failure, which could lead to being hospitalized, or rarely, to death

Rare

- Scarring of lung tissue, which could be life threatening or lead to death

Possible allergic reactions to Cetuximab

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

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

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

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

Risks Associated with Neck Surgery

Patients with remaining large tumors after treatment will have surgery to remove the cancer, if it is found that surgery can be done to remove the remaining cancer. The study doctor and surgeon will discuss the need for surgery with you. You will need to review and sign a separate permission form from your doctor/hospital for this surgery.

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

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

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

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

Are there benefits to taking part in the study?

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

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

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

Will my medical information be kept private?

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

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- The Radiation Therapy Oncology Group
- Qualified representatives of Bristol-Myers Squibb, makers of cetuximab (C225)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide patients and doctors greater access to cancer trials
- Other qualified researchers studying new methods to analyze your medical images; at this time it is not known what type of studies these might be. Your name and any other information that identifies you will not be provided to these researchers.

What are the costs of taking part in this study?

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

Bristol-Myers Squibb is supplying cetuximab (C225) at no cost to you. However, you or your health plan may need to pay for costs of the supplies for drug administration and personnel who give you the cetuximab.

If, during the study, cetuximab becomes approved for use in your cancer, you and/or your health plan may have to pay for drug needed to complete this study.

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

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

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.
What happens if I am injured because I took part in this study?

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

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

What are my rights if I take part in this study?

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

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

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

Who can answer my questions about the study?

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

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

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

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

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

Quality of Life Study

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

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.
You will be asked to complete 2 questionnaires. In addition, you will be asked some questions about what you are able to eat at home and in public and how clear your speech is.

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

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

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

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

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

Please circle your answer.

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

YES  NO

Use of Tissue and Blood for Research

About Using Tissue and Blood for Research

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

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called “How is Tissue Used for Research” to learn more about tissue research. This information sheet is available to all at the following web site: http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf

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

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

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

Things to Think About

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

RTOG 0522
If you decide now that your tissue and blood can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue or blood. Then any tissue or blood that remains will no longer be used for research and will be returned to the submitting institution.

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

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

Benefits

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

Risks

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

Making Your Choice

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

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

1. My tissue and blood may be kept for use in research to learn about, prevent, or treat cancer.  
   Yes  No

2. My tissue and blood may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).  
   Yes  No

3. Someone may contact me in the future to ask me to take part in more research.  
   Yes  No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/
- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/
You will get a copy of this form. If you want more information about this study, ask your study doctor.
Signature

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

Participant ________________________________

Date _____________________________________
## APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

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

### ZUBROD PERFORMANCE SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours (Karnofsky 50-60).</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on self-care. Totally confined to bed or (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death (Karnofsky 0).</td>
</tr>
</tbody>
</table>
APPENDIX III
AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

STAGING-PRIMARY TUMOR (T)

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

PHARYNX

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

Oropharynx
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4a Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
T4b Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

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

LARYNX

Supraglottis
T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.
T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.
APPENDIX III (Continued)

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

Subglottis
T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
  T4a Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
  T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

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

DISTANT METASTASIS (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
### STAGE GROUPING  Excluding Nasopharynx

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2, N0, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td></td>
<td>T1-3, N1, M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a, N0-2, M0</td>
</tr>
<tr>
<td></td>
<td>Any T, N2, M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b, Any N, MO</td>
</tr>
<tr>
<td></td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>

### STAGE GROUPING  Nasopharynx

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tis, N0, M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1, N0, M0</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2a, N0, M0</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T1-T2a, N1, M0</td>
</tr>
<tr>
<td></td>
<td>T2b, N0-1, M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1-T2b, N2, M0</td>
</tr>
<tr>
<td></td>
<td>T3, N0-2, M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4, N0-2, M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>
APPENDIX IV
SURGICAL MANAGEMENT OF THE NECK

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

N1: Patients with N1 neck disease whose nodes are 3 cm or less in diameter require careful physical examination of the neck and post-treatment imaging. If there is clinical or radiographic evidence of residual neck disease at 8-9 weeks post-treatment, neck dissection is required. A CR must be achieved at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The neck dissection is performed 8-11 weeks post-treatment, if indicated. For oropharynx, levels I-IV will be dissected. For larynx and hypopharynx, levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon.

N2A: For patients with lymph nodes between 3 and 6 cm, post-treatment physical examination and imaging studies will be obtained. For patients with a CR at the primary site, neck dissection alone is optional at 8-9 weeks post-treatment; otherwise, surgical salvage with or without neck dissection will be necessary. Neck dissection is mandatory for patients with clinical or radiographic evidence for persistent disease in the neck at 8-9 weeks post-treatment. For oropharynx, neck dissection will include levels I through IV. For larynx and hypopharynx, levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon.

N2B: For patients with multiple lymph nodes, post-treatment physical examination and imaging studies will be obtained. For patients with a clinical and radiographic complete response in the neck, cervical lymphadenectomy is optional. For patients with clinical or radiographic evidence for residual neck disease at 8-9 weeks post-treatment, neck dissection is mandatory and will be performed at 8-9 weeks post-treatment for patients with a CR at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. A neck dissection to include levels I through IV is mandatory for oropharynx. For larynx and hypopharynx, Levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon and dictated by the extent of residual disease in the neck.

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

For patients with N3A disease, post-treatment physical examination and imaging studies will be obtained. If a CR is obtained in the neck, cervical lymphadenectomy is optional. For patients with a clinical or radiographic finding of residual neck disease at 8-9 weeks post-treatment, the neck dissection will be performed at 8-9 weeks post-treatment for patients with a CR at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The type of neck dissection will be determined by the extent of the disease. A neck dissection to include levels I through IV is mandatory for oropharynx. For larynx and hypopharynx, Levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon and dictated by the extent of residual disease in the neck.

Selective neck dissection is encouraged. Synchronous bilateral neck dissection is not to be performed. For patients requiring bilateral radical neck dissections, the cervical lymphadenectomy should be staged with a minimum of six weeks between procedures.
APPENDIX V
Cervical Lymph Node Dissection: Documentation and Processing of the Specimen

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

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

Goals for a dental care program include:

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

Pre-irradiation Care and Procedures

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

**Group 1**
Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

**Group 2**
Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

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

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

**Group 4**
Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

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

Causative Factors

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

Preventive Program

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

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

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

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

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

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

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

SPECIMEN COLLECTION/SHIPPING KIT PROCEDURE

Participating institutions can request initial specimen collection/shipping kits from LDS Hospital by calling or e-mailing Holly Goold (contact information below). Each site will receive two kits with pre-paid Fed-Ex shipping attached. When a site ships a kit to the RTOG Tissue Bank, a replacement kit will be sent to the site. EVERY SPECIMEN MUST BE LABELED WITH THE PROTOCOL NUMBER (0522) AND PATIENT CASE NUMBER.

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626
FAX (801) 408-5020
holly.goold@ihc.com

Contents of Tissue Procurement Kit:
- Underpads (Chux) 17.5” x 24”
- Biohazard wipes 4” x 4”
- Labeling marker
- Sterile disposable forceps
- Sterile disposable scalpels with 22 blade
- Ten 1ml cryovials
- Five 5ml cryovials
- Biohazard bags
- Absorbant shipping material
- Cardboard shipping (outer) box
- Styrofoam (inner) box
- Pre-paid Fed-Ex shipping label

Preparation of Serum:
- Use the four 1 ml cryovials labeled “serum”.
- Label the cryovials with the procedure date and the patient’s case number and protocol number (0522) or use RTOG labels.

Process:
- Allow one 5ml red top tube to clot for 30 minutes at room temperature.
- Spin down at 800-10,000 rpm for 10 minutes in a refrigerated centrifuge.
- Aliquot into the four labeled, 1ml cryovials.
- Place cryovials into biohazard bag.
- Label the bag with the patient’s case number and protocol number (0522) or use RTOG labels.
- Store at –80 Celsius until ready to mail.

Preparation of Buffy coat and Plasma:
- Use the three 1ml cryovials labeled “buffy coat”, and label the cryovials with the procedure date and the patient’s case number and protocol number (0522) or use RTOG labels.
- Use the three 1ml cryovials labeled “plasma” and label the cryovials with the procedure date and the patient’s case number and protocol number (0522) or use RTOG labels.
APPENDIX VII (Continued)

Process:
- Spin EDTA (purple top) tube at 800-1000 in a refrigerated centrifuge within one hour of collection.
- If the interval between specimen collection and processing is anticipated to be greater than one hour, then the tube should be kept on ice until centrifuging is done.
- Remove the buffy coat white blood cells carefully and place into the 1ml cryovials labeled “buffy coat”.
- Store at a minimum –20 Celsius until shipped.
- Aliquot plasma into the 1ml cryovials labeled “plasma”.
- Place cryovials into biohazard bag.
- Label the bag with the patient’s case number and protocol number (0522) or use RTOG labels.
- Store at a minimum –20 Celsius until shipped.

Shipping:
- Include all RTOG paperwork in pocket of biohazard bag.
- Place all specimens and the absorbent shipping material in Styrofoam cooler lined with outer box, filled with dry ice.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.
- Notify Holly Goold at LDS Hospital (contact information above) before you send specimens via Fed-ex using the pre-paid shipping label.
C225 (Cetuximab) CLINICAL SUPPLY SHIPMENT REQUEST TO INVESTIGATIONAL SITE

Cetuximab will be shipped only to institutions that have identified a single individual for receipt of shipment.

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.

NOTE: The initial shipment form must be processed before the institution is approved to receive drug. In addition, required regulatory documents (see Sections 5.2.1 and 5.2.2) must be received before drug can be shipped. Institutions should allow adequate time (7-10 days) for form processing before calling to register the first case. Patient registration, not submission of the SASF, triggers the initial drug shipment.

For Resupply Requests, a Word version of the resupply 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 this form to cetuximab.drug@bms.com. Note: The email address is different for the initial shipment form and the re-supply shipment form. For questions, call 800-743-9224.

U.S. and Canadian institutions must complete the initial shipment and resupply shipment forms electronically if the RTOG web site is available. The shipment forms have been included in the protocol (see next page) for use only if the RTOG web site is unavailable. Fax the form(s) to 215-574-0300. Forms must be legible.
**CETUXIMAB (ERBITUX)™ REQUEST for INITIAL DRUG SHIPMENT**

Attention Site: All the information requested on this form is required before drug can be shipped by BMS. Please complete the form electronically using the tab key to improve legibility. Handwritten or illegible forms will delay processing and shipment.

<table>
<thead>
<tr>
<th>BMS / ImClone Protocol Number:</th>
<th>CA225223</th>
<th>RTOG Protocol Number:</th>
<th>0522</th>
<th>RTOG Site Number:</th>
<th>55011</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG Protocol Number:</td>
<td>0522</td>
<td>CTEP NCI Code:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group Affiliation:</td>
<td>RTOG</td>
<td>IND Holder:</td>
<td>NA</td>
<td>IND Exempt:</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Investigator:</td>
<td></td>
<td>Sub-Investigator:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Contact (Research Nurse / Study Coordinator / Research Pharmacist):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name:</td>
<td></td>
<td>Title:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
<td>Email:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator Address (please include contact information):</td>
<td>Ship Supplies To (If Different From Investigator Address):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institution Name:</td>
<td></td>
<td>Institution Name:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Address:</td>
<td></td>
<td>Address:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City, State Zip:</td>
<td></td>
<td>City, State Zip:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
<td>Telephone:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Email:</td>
<td></td>
<td>Email:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Date Requested: (DD/MM/YYYY)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Study Drug:** CETUXIMAB (ERBITUX)™

**Strength / Dose:** 100 mg

**Quantity of Supplies to be Shipped:**
- Shipment must be in multiples of 4

**Shipment Must Reach Destination By:**
- (DD/MM/YYYY - Deliveries are not made on Monday)

Provision of an assigned patient ID number serves as assurance that all required documentation for this site have been received, reviewed as complete, and acceptable.

Shipment Time frames & Limitations: Allow 5 business days for shipment of drug from the date of registration of the patient. Shipments will be made on Monday through Thursday for delivery to sites on Tuesday through Friday. There will be no weekend or holiday delivery of drugs. There will be no shipments between December 24th and January 2nd.
**CETUXIMAB (ERBITUX)™ REQUEST for RESUPPLY**

Attention Site: All the information requested on this form is required before drug can be shipped by BMS. Please complete the form electronically using the tab key to improve legibility. Handwritten or illegible forms will delay processing and shipment.

<table>
<thead>
<tr>
<th>BMS / ImClone Protocol Number:</th>
<th>CA225223</th>
<th>RTOG Site Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG Protocol Number:</td>
<td>0522</td>
<td>CTEP NCI Code:</td>
</tr>
<tr>
<td>Group Affiliation: RTOG</td>
<td></td>
<td>IND Holder: NA</td>
</tr>
<tr>
<td>IND Exempt: Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Investigator:</td>
<td></td>
<td>Sub-Investigator:</td>
</tr>
<tr>
<td>Secondary Contact [Research Nurse / Study Coordinator / Research Pharmacist]:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name:</td>
<td></td>
<td>Title:</td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
<td>Email:</td>
</tr>
<tr>
<td>Investigator Address (please include contact information):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Institution Name:</td>
<td></td>
<td>Address:</td>
</tr>
<tr>
<td>City, State Zip:</td>
<td></td>
<td>City, State Zip:</td>
</tr>
<tr>
<td>Telephone:</td>
<td></td>
<td>Email:</td>
</tr>
<tr>
<td>Date Requested: (DD/MM/YYYY)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Drug: CETUXIMAB (ERBITUX)™</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength / Dose: 100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quantity of Supplies to be Shipped:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Vials Requested:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shipment Must Reach Destination By: (DD/MM/YYYY - Deliveries are made on Monday)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Open Text If Needed For Site Use

Provision of an assigned patient ID number serves as assurance that all required documentation for this site have been received, reviewed as complete, and acceptable.

Shipment Time frames & Limitations: Allow 5 business days for shipment of drug from the date of registration of the patient. Shipments will be made on Monday through Thursday for delivery to sites on Tuesday through Friday. There will be no weekend or holiday delivery of drugs. There will be no shipments between December 24th and January 2nd.

**PLEASE FORWARD THIS DOCUMENT TO CETUXIMAB DRUG SUPPLY (cetuximab.drug@bms.com) FOR SHIPMENT REQUEST INITIATION**

(FAX: 609-252-7856 ONLY if unable to email)
### ADDRESS AND CONTACT INFORMATION FOR RTOG-0522

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrolments:</th>
<th>To mail study forms or data:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206</td>
<td>CTSU Data Operations Center Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 [For CTSU patient enrollments that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]</td>
<td>Westat CTSU Data Operations Center 1441 W. Montgomery Avenue Rockville, MD 20850-2062</td>
</tr>
</tbody>
</table>

**For patient eligibility questions:**
Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214.

**For treatment-related questions:**
Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page.

The option remains to contact CTSU Help Desk for assistance in obtaining a response from the Group.

**All other questions (including forms-specific questions) should be communicated by phone or e-mail to the CTSU Help Desk at:**
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org
The CTSU Registered Member Web site is located at [http://members.ctsu.org](http://members.ctsu.org)

---

### CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

#### REGISTRATION/RANDOMIZATION

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

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the RTOG-0522 Web page on the CTSU registered member Web site (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

**Requirements for RTOG-0522 site registration:**
- The treating physician must determine the radiation therapy technique (3D-CRT vs. IMRT) prior to the site registering the patient

---

88 RTOG 0522
APPENDIX IX (Continued)

- Additional credentialing requirements for sites using an IMRT Treatment Approach are outlined in Section 5.1 of the protocol and on the Advanced Technology Consortium (ATC) web site at http://atc.wustl.edu. Submission of digital data to the Image-Guided Therapy Center (ITC) requires advanced request for an FTP account with the ITC (itc@castor.wustl.edu). The ITC will notify the registering institution when that request is eligible to enter patients on study. The status of the credentialing review will be reflected on the RSS Site Registration Status screen http://members.ctsu.com/RSSAll subjects will be eligible for PET/CT imaging analysis. Pre-treatment FDG-PET/CT scan is highly recommended for all patients. Each site must send at least one test case to the PET Core Lab for evaluation prior to the enrollment of that site’s first patient. Application and instructions for test case submission can be found on the ACRIN web site at http://www.acrin.org/petcorelab.html.

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Radiation Therapy Facility Inventory Form (Radiation therapy facilities must participate in the RPC monitoring program to participate in studies sponsored by the CTSU.)

Pre-study requirements for patient enrollment on RTOG-0522

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

CTSU Procedures for Patient Enrollment

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

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

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 7:00 p.m. Eastern time, Monday through Friday (excluding holidays). The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check the forms for completeness and followup with the site to resolve any discrepancies. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact RTOG to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site via a confirmation e-mail or fax, followed by a data submission calendar and case specific labels with the patient ID number.

DATA SUBMISSION

All case report forms (CRFs) and other documents associated with this study must be downloaded from the RTOG-0522 Web page located on the CTSU registered member Web site (http://members.ctsu.org). CTSU investigators must use the current version of the protocol-specific RTOG-0522 forms and adhere to the RTOG-0522 schedule for data submission per protocol Section 12. CRFs and associated reports must be submitted in the following manner:

- Patient enrollment CRFs should be faxed to the CTSU according to the instructions in the CTSU patient enrollment procedures section of this Appendix.
- See the Special Materials or Substudies section below for submission of dosimetry data. The Treatment Summary Form (TF) and Radiotherapy Form (T1) are considered CRFs and should be sent to the CTSU Data Operations Center for forwarding to RTOG.

0522
APPENDIX IX (Continued)

- See the Special Materials or Substudies section below for submission of tissue and blood specimens. A completed RTOG Specimen Transmittal Form must accompany each submission and CTSU should be copied on this form for tracking purposes.
- Original and amended CRFs (including QOL forms), surgical and operative reports, and responses to query and delinquency letters must be mailed directly to the CTSU Data Operations Center accompanied by a properly completed CTSU Data Transmittal Form; the CTSU will forward all data submissions to the RTOG. Please affix the RTOG study/case label to all source documentation and redact the patient’s name.

A CTSU Data Transmittal Form must accompany all data submissions to the CTSU. Data submitted with an improperly completed CTSU Data Transmittal Form or without a CTSU Data Transmittal Form will be returned to the site for corrective action without being processed. An RTOG study/case label should be affixed to all case report forms and source documentation. The CTSU Data Transmittal Form may only be used for transmission of post-enrollment case report forms and reports. Do not use this form to submit site registration or patient enrollment documentation.

Mail original and amended post-enrollment CRFs, reports, and responses to query and delinquency to: Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD  20850-2062

SPECIAL MATERIALS OR SUBSTUDIES

Radiation Therapy (protocol section 6.0):
Radiotherapy may be delivered with 3D-CRT or IMRT techniques; however the chosen modality must be used for the entire course of treatment. The RTOG highly recommends digital submission of dosimetry information to the Image-Guided Therapy Center (ITC). See protocol section 12.0 for a complete inventory of dosimetry items to be submitted. Sites unable to submit digitally should contact RTOG Headquarters, RTQA Department at 215-574-3219. A completed Digital Data Submission Form (T2) or Dosimetry Transmittal Form must accompany all digital and hard copy submissions. The Treatment Summary Form (TF) and Radiotherapy Form (T1) are considered CRFs and should be sent to the CTSU Data Operations Center for forwarding to RTOG.

Modality Review (protocol section 7.5):
A Chemotherapy Assurance Review and Quality Assurance Review will be conducted by the Medical Oncology Co-Chairs.

Specimen Collection (protocol section 10.0):
- With patient’s consent, RTOG highly recommends that tissue and blood be collected and submitted to the RTOG Tissue Bank at LDS Hospital for the purpose of conducting biomarker studies and banking for future research. See protocol section 10.0 and Appendix VII for details on requesting shipping kits, specimen collection, preparation, and submission. An RTOG Specimen Transmittal Form must accompany all blood and tissue specimens and a pathology report must accompany all tissue specimens in order for the case to be considered evaluable by the RTOG Tissue Bank. The RTOG Specimen Transmittal Form is available for download from the RTOG-0522 Web page of the CTSU Member Web site. A copy of the RTOG Specimen Transmittal Form and pathology report should also be sent to the CTSU Data Operations Center along with a completed CTSU Data Transmittal Form. All reports must include the protocol number and patient’s case number (or RTOG label attached). The patient’s name and/or other identifying information should be redacted.
- CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.3 of the protocol. Payments will be made in accordance with RTOG’s pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.
**APPENDIX IX (Continued)**

**PET Evaluations for Analysis of Study Objectives (protocol section 11.4):**
A pre-treatment PET/CT scan is highly recommended for all patients on study. A post-treatment FDG-PET/CT scan is recommended 8-9 weeks after completion of therapy. Sites must submit at least one test case to the PET Core Lab for evaluation prior to enrollment of their first patient. See protocol section 11.4 and the ACRIN web site (http://www.acrin.org/petcorelab.html) for details.

**Quality of Life (protocol section 11.5):**
QOL assessments will be administered according to the schedule in protocol section 11.1. Two measures will be completed by the patient (FACT-H&N and EQ-5D) and one measure will be completed by the clinician (PSS-HN). Completed assessments are submitted to the CTSU for forwarding to RTOG.

**ADVERSE EVENT (AE) REPORTING**
Your local Investigational Review Board must be informed of all reportable serious adverse events.

This study will utilize the CTCAE version 3.0 for toxicity and Adverse Event reporting. A hyperlink to the CTEP home page that contains CTCAE information is available on the CTSU web site at http://members.ctsu.org/adeers_drug_info.asp. CTSU investigators are responsible for reporting serious adverse events via AdEERS in accordance with RTOG guidelines in section 7.6 of the protocol. Do not copy CTSU Data Operations Center on serious adverse event reports.

**Secondary AML/MDS reporting:**
CTSU investigators will submit the NCI Secondary AML/MDS Report Form and supporting documentation to the CTSU. Once received, the CTSU will send this information to RTOG, and RTOG will forward it on to the NCI.

**DRUG PROCUREMENT:**
CTSU investigators should refer to the Drug Therapy section 7.0 for detailed instructions on drug procurement, formulation, storage, administration, and potential toxicities.

**Investigational agent: cetuximab** – supplied free of charge by the manufacturer to patients on study.

- **Initial supply:** Download the initial shipment form located under the pharmacy forms section of the RTOG-0522 page of the CTSU Member Web site. Complete and submit via email to the address provided in Appendix VIII of the protocol. Allow adequate time for processing (7-10 days) before contacting CTSU to randomize your first patient.
- **Resupply:** Download the resupply shipment form located under the pharmacy forms section of the RTOG-0522 page of the CTSU Member Web site. Complete and submit via email to cetuximab.drug@bms.com.

**REGULATORY AND MONITORING**

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

Responsibility for assignment of the audit will be determined by the site’s primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.
Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

**Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the informed consent section of this protocol document; however, authorization for the release of Protected Health Information is considered separate and distinct from the Informed Consent process for participation in this clinical trial.

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

**Clinical Data Update System (CDUS) Monitoring**

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