RADIATION THERAPY ONCOLOGY GROUP

RTOG 0421

A PHASE III TRIAL FOR LOCALLY RECURRENT, PREVIOUSLY IRRADIATED
HEAD AND NECK CANCER: CONCURRENT RE-IRRADIATION
AND CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE

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

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at http://members.ctsu.org

- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.

- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.

- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.

- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.
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RTOG 0421
**Patient Population:** (See Section 3.0 for Eligibility) [9/19/06]
Pathologically confirmed squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx, larynx, or recurrent neck metastases with unknown primary; Patients who are potential candidates for complete surgical resection are ineligible for this protocol unless they refuse surgery or surgery is felt not to be in the patient’s best interest by the treating physicians.

**Required Sample Size:** 240
1. Does the patient have a histologically or cytologically confirmed diagnosis of recurrent or second primary SCC of the oral cavity, oropharynx, hypopharynx, larynx, or recurrent neck metastases with unknown primary?

2. Was a biopsy of the primary tumor and/or fine needle aspirate/biopsy of metastatic lymph node done prior to registration?

3. Is there measurable disease?

4. Is the patient surgically inoperable or if operable did they refuse surgery or is surgery felt not to be in the patient’s best interest by the treating physicians?

5. If the patient had a previous surgical resection, is the patient \( \geq 3 \) months post-surgery with completely healed wounds, with no signs of carotid exposure?

6. Did the patient have previous irradiation 45-75 Gy to > 75% of the present tumor volume?

7. Will the Radiation Oncologist be able to re-irradiate without exceeding the lifetime spinal cord dose of 54 Gy?

8. Did the present recurrence occur > 6 months from the end of prior radiation treatment? Or, if more than one recurrence, was the first recurrence > 6 months following the end of radiation treatment?

9. Is the patient at least 6 months post prior radiation therapy and chemotherapy (including targeted agents)?

10. Did the patient have a thorough physical assessment (with close attention to the carotids) and Medical Oncology and Radiation Oncology examinations within 8 weeks of registration?

11. Were Chest CT and CT/MRI of tumor site performed within 4 weeks prior to registration?

12. Is the Zubrod performance status 0-1?

13. Is the patient at least 18 years of age?

14. Are the lab parameters and bone marrow function within the ranges specified in Sections 3.1.12.1-3.1.12.3?

15. Was the bilirubin < 1.5 mg/dl and AST or ALT < 2 x the upper limit of normal within 2 weeks prior to registration?

16. Were abnormal LFTs noted (> 1.5 x upper limit of normal alkaline phosphatase, AST or bilirubin)?

17. Was the patient’s creatinine clearance > 50 ml/min within 2 weeks prior to registration determined by 24 hour collection or by Cockcroft-Gault formula?

(Continued on next page)
18. Was the serum calcium or corrected serum calcium < 11.5 within 2 weeks prior to registration? 

19. If the patient is a female of child bearing potential, was a pregnancy test done 2 weeks prior to registration? 

20. Is the patient pregnant or lactating? 

21. Does the patient agree to use a medically effective means of birth control throughout participation in the treatment phase of the study, including at least 30 days following the last day of treatment? 

22. Has the patient signed a study-specific informed consent? 

23. Are there distant metastases? 

24. Does the patient have a history of invasive malignancy other than head and neck, except non-melanomatous skin cancer? 

If yes, has this patient been disease free for a minimum of 3 years? 

25. Does the patient have a primary tumor of the nasopharynx or salivary gland? 

26. Did the patient receive chemotherapy (including targeted agents) for recurrent SCHNN? (Prior chemotherapy is permitted for the original primary tumor; see Section 3.2.2) 

27. Does the patient have symptomatic and or uncontrolled cardiac disease (New York Heart Association Classification III or IV)? 

28. Does the patient have a circumferential tumor involvement of the carotid sheath by imaging study? 

If yes, was a prophylactic carotid stent placed prior to study entry? 

29. Does the patient have acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration? 

30. Does the patient have chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization within 6 months of registration or precluding study therapy at the time of registration? 

31. Does the patient have hepatic insufficiency resulting in clinical jaundice and/or coagulation defects (see Section 3.2.5.5)? 

32. Does the patient have acquired immune deficiency syndrome (see Section 3.2.5.6 for details)?
33. Does the patient have a prior allergic reaction to *E. coli* derived product?

34. Does the patient have a pre-existing grade > 2 peripheral sensory neuropathy?

35. Has the patient had intolerable hypersensitivity reactions to paclitaxel or cisplatin?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist (above) been completed?

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

13. Zip Code (U.S. Residents)

14. Patient’s Insurance Status

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

16. Treatment Start Date

17. Randomization date: This date will be populated automatically.

18. Medical Oncologist’s Name

(Continued on next page)
RTOG Institution # ___
RTOG 0421 ELIGIBILITY CHECKLIST (9/19/06)
Case # ____________________________ (page 4 of 4)

______ (Y/N) 19. Blood kept for cancer research?
______ (Y/N) 20. Blood kept for medical research?
______ (Y/N) 21. Allow contact for future research?
______ (N/Y)  22. Did the patient agree to participate in the Quality of Life component of the study?
______ (NA/N/Y) 23. Is the patient’s health care covered at least in part by Medicare (and therefore, will Medicare data be used for health utility research in this study)?

__________ If yes, provide the patient’s social security number.

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. 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 ____________________________

RTOG 0421
1.0 INTRODUCTION

1.1 Recurrent Head and Neck Cancer

Over 40,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) are diagnosed each year in the United States.\(^1\) Approximately two thirds of patients are diagnosed at an advanced stage of disease such that surgery alone is either not curative or is not technically feasible. For the majority of these patients with unresectable locally advanced disease, radiation is employed as the primary treatment modality with curative intent. Radiation is also commonly used in the post-operative setting for patients with high-risk factors for recurrent disease.\(^2\)\(^-\)\(^3\) Unfortunately, the likelihood of treatment failure for patients with locally advanced SCCHN remains unacceptably high. For example, while patients with T1 glottic cancers have only approximately 10% risk of local-regional failure,\(^4\) those with T3-4 hypopharyngeal tumors have 70% or higher risk of local-regional failure with radiation alone and 30-50% risk of local-regional failure with total laryngopharyngectomy.\(^5\)

The predominant pattern of failure for SCCHN patients is to locoregional disease sites.\(^6\) In addition, the cause of death for the majority of head and neck cancer patients is due to locoregional disease rather than to metastatic disease. When locoregional failure occurs, the optimal therapy is surgical salvage. The feasibility of surgical resection is highly dependent upon the anatomic site and extent of disease. The clinical scenario is further complicated because many of these patients also have received prior definitive radiotherapy which traditionally precludes the use of additional radiation. Consequently, chemotherapy is the only remaining treatment option for this group of patients.

1.2 Chemotherapy for Recurrent Head and Neck Cancer

Chemotherapy alone is considered the standard of care treatment option for optimal performance status patients who have metastatic or recurrent SCCHN — including those patients with unresectable, previously irradiated disease. No single chemotherapy regimen has proven to be superior or standard for this disease. Cisplatin/5-FU is a commonly used regimen that in large randomized trials has demonstrated higher response rates, but not improved survival, compared to single agent chemotherapy.\(^7\)\(^-\)\(^9\) Investigators have examined taxane/cisplatin combination regimens in hopes of demonstrating improved efficacy.\(^8\)\(^,\)\(^9\) Head to head comparisons of such regimens in large multicenter randomized trials have not shown superiority of any one regimen with respect to survival.\(^7\)\(^,\)\(^10\) Median length of survival in these trials ranges from 7 to 9 months, while long-term survival rates are poor — 5 to 10%.\(^2\)\(^,\)\(^10\)

Little published data exists regarding the efficacy of chemotherapy in the subgroup of SCCHN patients who have been previously irradiated and have locoregional (non-metastatic) disease. A recent secondary analysis by Argiris of ECOG chemotherapy trials (E1393 and E1395) demonstrated that prior radiation is an independent, unfavorable prognostic factor of overall survival.\(^11\) Further analysis of this compiled data indicates that the rate of two-year survival for previously irradiated locoregional (non-metastatic) patients is only 10.5%.\(^12\)

1.3 Re-Irradiation

Re-irradiation of the head and neck after previous full course radiotherapy generally has been considered contraindicated. This is due to the risk, real or perceived, of severe, uncontrollable radiation complications such as fistulae, carotid rupture, osteoradionecrosis, soft tissue necrosis, and radiation neuropathy. Lack of enthusiasm for re-irradiation also is based on the assumption that if radiation was not initially successful, then “salvage” irradiation is unlikely to be of benefit. This concept has been reinforced by research that demonstrated in vitro radioresistance of tumor cell lines derived from patients with recurrent, previously irradiated SCCHN.\(^13\) However, these hypothetical concerns and observations from in vitro studies have not deterred researchers from attempting to overcome these potential obstacles.

Investigators have utilized preclinical animal models to demonstrate tissue tolerance to re-irradiation.\(^14\)\(^-\)\(^16\) In skin and mucosal epithelium, tolerance and latency to manifestations of acute reactions decrease with shortened intervals between first and subsequent exposure to radiation. Extensive experimentation on spinal cord tissue tolerance to re-irradiation indicates that cumulative doses equivalent to 65-68 Gy, in 2 Gy fractions, appear to be well tolerated, if the first course does not exceed 45 Gy.\(^16\) Published reports of human spinal cord re-irradiation substantiate this assertion.\(^17\)\(^-\)\(^21\)
Several human clinical studies have challenged the principle that high-dose, conventional external beam re-irradiation is contraindicated. Recognizing the potential problem of “in-field” radio-resistant tumor clones as well as “out-of-field” tumor micrometastasis, clinical trials of re-irradiation have utilized radiosensitizing concurrent chemotherapy. Most of the reported trials also have employed hyperfractionated split course radiotherapy in an attempt to maximize antitumor effects and minimize normal tissue effects of radiotherapy. These trials have reported local-regional control rates approaching 40% with acceptable acute and late toxicity.22-26 One of the largest experiences is from the University of Chicago, where sequential studies have been done combining altered fractionation radiotherapy with various chemotherapeutic agents.27 In an early report using 5-Fluorouracil/hydroxyurea +/- cisplatin, the five-year survival rate was 14.6%; more recent studies utilizing paclitaxel suggest that median and two-year survival rates have improved.28 Researchers at the University of Alabama also reported results demonstrating the feasibility of this approach.27 RTOG 96-10 was the first multi-institutional study to test the feasibility and efficacy of re-irradiation for head and neck cancer in the cooperative group setting.30 In this trial, treatment was given in 4 weekly cycles (Monday through Friday), each separated by 1 week of rest, consisting of twice daily radiation (1.5 Gy) for a total dose of 60 Gy. Chemotherapy was administered daily during radiation and consisted of hydroxyurea (1.5g) and bolus 5-FU (300mg/m²). Eighty-three patients were evaluated for response. Two deaths occurred due to non-thrombocytopenic tumor hemorrhage. Four patients died of causes unrelated to treatment. Grade 3 or 4 mucositis occurred in 17% and 6% of patients, respectively. Grade 3 or 4 hematologic toxicity occurred in 17% and 14% of patients, respectively. Median overall survival was 8.8 months and estimated one- and two-year survival rate were 41.7% and 16.9%, respectively.

RTOG 99-11 succeeded RTOG 96-10 and sought to incorporate drugs that demonstrated greater systemic activity against SCCHN and potentially more potent radiosensitizing properties.25 Paclitaxel (20 mg/m²) and cisplatin (15 mg/m²) were given on each radiotherapy day (in between the RT fractions). G-CSF was administered 24 hours after the completion of each of the 4 treatment weeks (i.e., at the end of weeks 1, 3, 5, and 7) to prevent neutropenic fever/sepsis. The radiation regimen was identical to that used in RTOG 96-10, although IMRT was permissible. There were 7 deaths (7%) associated with protocol therapy. Worst grade 3 and 4 acute non-hematologic toxicity occurred in 48% and 23% of patients, while worst grade 3 and 4 acute hematologic toxicity occurred in 24% and 20% of patients, respectively. Preliminary analysis of this study indicates that the estimated two-year survival (25.2%) exceeds that observed in RTOG 96-10.12, 30, 31 Moreover, this data also appears significantly better than the data from the matched patient subgroup treated with chemotherapy alone on ECOG studies, E1393 and E1395, who potentially would have been eligible for re-irradiation; two-year survival for this group was 10.5%. Having completed two consecutive multi-institutional cooperative group studies concurrent chemotherapy and re-irradiation for SCCHN, the feasibility of re-irradiation is now firmly established. Whether re-irradiation and concurrent chemotherapy prolongs survival compared to chemotherapy alone without resulting in significant long-term toxicity is a profound and unanswered question.

1.4 Rationale for a Phase III Comparison of Re-Irradiation Versus Chemotherapy Alone

Determination as to whether re-irradiation is superior or not compared to chemotherapy alone may have a profound impact upon future generations of SCCHN patients. Presently, for the vast majority of SCCHN patients with previously irradiated, locoregional recurrent disease, chemotherapy alone is the only active treatment offered. Yet, if re-irradiation is in fact superior, adopting this therapy as the community standard could translate to hundreds of lives saved each year. Comparison of survival data from re-irradiation trials with historical chemotherapy alone series, suggests that re-irradiation is superior. However, an analysis such as this introduces a number of biases that confound the accuracy of this conclusion. First, patients in re-irradiation trials generally have been rigorously staged to rule out distant metastases, while historically matched subsets from chemotherapy-alone studies may not have been as rigorously evaluated. In addition, patients in re-irradiation trials may be more highly motivated, compliant, and willing to accept treatment toxicity than the typical head and neck cancer patient. Finally, most re-irradiation series limit eligibility to patients who have had a relatively long disease-free interval since prior irradiation (usually a minimum of 6 months), which may predict for more indolent disease.
Only a randomized trial can rule out the strong possibility that selection bias accounts for the improved outcome in re-irradiation series compared with chemotherapy-alone trials. Furthermore, if there is a confirmed survival benefit to re-irradiation, only a randomized trial can estimate the magnitude of this benefit and examine whether added toxicity is worth the benefit. This magnitude of benefit would have to be carefully weighed against the toxicity results of re-irradiation before re-irradiation becomes an accepted community standard for this patient population.

1.5 Quality of Life and Functional Assessment

For patients with advanced disease whose life expectancy is reduced and for whom there is no cure, relief of physical symptoms and maintenance of function become primary objectives of medical intervention. Advanced, recurrent or refractory head and neck cancer is associated with a range of symptoms and impairments, including mouth and/or throat pain, impairments in swallowing, eating and/or speaking, problems breathing, and fatigue. As with most treatments for this population, the regimens in this proposal are multimodal, extremely aggressive, and confer considerable toxicity in addition to disease-related symptoms as well as potentially very significant long-term impairment in functioning. Clearly, when offering patients a treatment that has minimal potential for cure, it is critical to evaluate patients’ report of their side effects and quality of life (QOL). In selecting measures for the current study, the following issues were taken in consideration:

a. The assessments should be quickly administered and/or easy to complete to minimize the burden to a group of patients who will likely be older and quite sick;
b. Items should be included that capture the most frequent symptoms and side effects associated with recurrent head and neck cancer and the proposed regimens.

1.5.1 Quality of Life Measurement

The QOL component of this study will include three measures, two to be completed by the patient and the third completed by the investigator/data manager/nurse participant. QOL instruments will be administered pre-treatment and at 3, 6, 12, 24, and 36 months from start of treatment.

1.5.1.1 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.32-34 The investigator/data manager/nurse participant 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.

- 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.

Additional information is collected about feeding tube status, dentition, and presence or absence of a tracheostomy. Note: This assessment currently is not available in languages other than English and will be administered only to patients fluent in comprehending and speaking English.

1.5.1.2 Functional Assessment of Cancer Therapy — Head & Neck Symptom Index-10 (FHNSI-10)

While there are questionnaires that have been developed and tested to assess cancer-specific symptoms, the symptom questions have been nested within larger multidimensional
QOL questionnaires. A consequence of this approach to measurement is that the disease symptoms of most interest are embedded in larger, longer questionnaires and cannot readily be aggregated into clinically relevant, responsive symptom indices. Recently, David Cella and colleagues developed a brief Functional Assessment of Cancer Therapy – Head & Neck Symptom Index-10 (FHNSI-10), a more symptom-focused index specifically for use with patients with advanced and/or recurrent/refractory head and neck cancer. Disease-related symptoms and concerns from the FACT-H&N were presented to 65 experts in treating advanced head and neck cancer. These experts then selected the five most important symptoms/concerns to assess in treating advanced head and neck cancer. The ten items included in the FHNSI-10 represent those items endorsed by 20% or more of the medical experts. They are scored on a five-point scale from 0 (not at all) to 4 (very much). This index is currently being validated in a multi-institutional study; results will be available by the onset of the current study. Note: This assessment currently is not available in languages other than English and will be administered only to patients fluent in reading and writing English.

1.5.1.3 Multi-Attribute Health Utility Measurement Using the EuroQol (EQ-5D)
Although developed in Europe, the EQ-5D has been used in the United States and Canada. The EQ-5D is a method for obtaining valuations of HRQOL. It also can be used as an adjustment to survival and in cost-utility analysis. It is a two-part questionnaire that the patient can complete in approximately 5 minutes. The first part of the EQ-5D consists of five items covering five 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 (the scale measures approximately 20 cm). 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". Either the index score or the VAS score can be used in the quality adjusted survival analysis, or enter the cost-utility equation, depending on the health state(s) of interest. Quality adjusted survival is the weighted sum of different time in different health states added up to a total quality-adjusted survival time \[ U = \text{sum of quality (q) of K health states times the duration (s) spent in each health state.}]^{42}

There are no published reports of use of the EQ-5D in the evaluation of patients with locally recurrent head and neck disease; 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. Note: The EQ-5D has been translated into multiple languages; these translations are available from the EuroQol web site at http://www.euroqol.org.}

2.0 OBJECTIVES
2.1 Primary Objective
To determine whether re-irradiation plus concurrent chemotherapy improves overall survival of patients with previously irradiated, non-metastatic, locally recurrent or new primary squamous cell carcinoma of the head and neck (SCCHN) as compared to conventional chemotherapy alone.

2.2 Secondary Objectives
2.2.1 To compare the progression-free survival (PFS) between the two approaches
2.2.2 To assess the toxicity of each treatment regimen
2.2.3 To evaluate whether differences in patients’ quality of life and functional/performance status are associated with a treatment program
2.2.4 To compare the quality adjusted survival between the two approaches
3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (9/19/06)

3.1.1 Pathologically (histologically or cytologically) confirmed diagnosis of recurrent or second primary squamous cell carcinoma (SCC) of the oral cavity, oropharynx, hypopharynx, larynx, or recurrent neck metastases with unknown primary; this includes histologic variants of SCC such as spindle cell carcinoma, poorly differentiated keratin-positive carcinoma, and lymphoepithelioma;

3.1.2 Biopsy of primary tumor and/or fine needle aspirate/biopsy of metastatic lymph node is required prior to registration;

3.1.3 Measurable disease is required;

3.1.4 Patients with measurable recurrent disease after attempted surgical resection are eligible if they are ≥ 3 months post-surgery, have completely healed wounds, and meet all other eligibility criteria. Patients must not have any signs of carotid exposure.

3.1.5 Patients must have had prior radiation for head and neck SCC with > 75% of the present tumor volume in areas that have been previously irradiated to at least 45 Gy but not exceeding 75 Gy;

3.1.6 Prior radiotherapy data and anatomical location of gross tumor volume such that the Radiation Oncologist will have the ability to successfully re-irradiate without exceeding lifetime spinal cord dose of 54 Gy; this will be based upon physical examination plus a diagnostic and/or radiotherapy treatment planning CT and/or MRI scan done within 4 weeks prior to registration (see Section 3.1.9.3)

3.1.7 The time from prior radiation therapy to first recurrence must be > 6 months; patients may have experienced more than one recurrence as long as the first recurrence occurred > 6 months following the end of the prior radiation treatment;

3.1.8 At registration, patients must be at least 6 months post-radiation therapy or chemotherapy (or targeted agents, such as EGFR inhibitors);

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

3.1.9.1 History/physical examination (with close attention to the carotids; also see Section 4.2.2) and medical oncology and radiation oncology examination to confirm study eligibility requirements within 4 weeks prior to registration;

3.1.9.2 Chest CT scan within 4 weeks prior to registration; patients with equivocal pulmonary nodules that are < 1 cm, that cannot be safely biopsied, or that are negative on PET imaging are eligible;

3.1.9.3 Imaging (CT or MRI) of tumor site within 4 weeks prior to registration (PET/CT not acceptable as baseline unless CT portion of PET is contrast enhanced and is interpretable);

3.1.10 Zubrod Performance Status 0-1;

3.1.11 Age ≥ 18;

3.1.12 Adequate bone marrow function and laboratory parameters, defined as follows:

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

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

3.1.12.3 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);

3.1.13 Adequate hepatic function with bilirubin < 1.5 mg/dl, AST or ALT < 2 x the upper limit of normal within 2 weeks prior to registration;

3.1.14 Abdominal CT, if abnormal LFTs are noted (must be done in presence of > 1.5 x upper limit of normal of alkaline phosphatase, AST, bilirubin, or other clinical indicator);

3.1.15 Adequate renal function, defined as follows:

3.1.15.1 Creatinine clearance > 50 ml/min within 2 weeks prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

\[
\text{CrCl male} = \frac{[(140 - \text{age}) \times \text{wt in kg}]}{[(\text{sCR}) \times (72)]}
\]

\[
\text{CrCl female} = 0.85 \times (\text{CrCl male})
\]

3.1.16 Serum calcium or corrected serum calcium < 11.5 within 2 weeks prior to registration; the formula for corrected calcium if albumin valued 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);

3.1.17 Pregnancy test within 2 weeks prior to registration for women of childbearing potential;
3.1.18 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 30 days following the last study treatment);
3.1.19 Patient must sign study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (9/19/06)
3.2.1 Distant metastases;
3.2.2 Prior invasive malignancy other than head and neck (except non-melanomatous skin cancer), unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, of the oral cavity, or of the cervix are all permissible);
3.2.3 Original or new primary in the nasopharynx or salivary gland;
3.2.4 Prior systemic chemotherapy (including targeted agents such as EGFR inhibitors) for recurrent SCCHN; note: adjuvant, neoadjuvant, and/or concurrent chemotherapy with radiation for initial head and neck cancer treatment are permitted. In addition, prior use of COX-2 inhibitors or retinoids for chemoprevention is permitted.
3.2.5 Severe, active co-morbidity, defined as follows:
3.2.5.1 Symptomatic and/or uncontrolled cardiac disease, New York Heart Association Classification III or IV (see Appendix II);
3.2.5.2 Circumferential tumor involvement of the carotid sheath by imaging study, unless prophylactic carotid stent is placed prior to study entry;
3.2.5.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
3.2.5.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness precluding study therapy at the time of registration;
3.2.5.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that coagulation parameters are not required for entry into this protocol.
3.2.5.6 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.
3.2.6 Women who are pregnant or breast feeding, as treatment involves unforeseeable risks to the participant, embryo, fetus, or nursing infant; women with a positive pregnancy test on enrollment or prior to study drug administration;
3.2.7 Prior allergic reaction to \text{E. coli}-derived product;
3.2.8 Pre-existing grade > 2 peripheral sensory neuropathy.
3.2.9 Intolerable hypersensitivity reactions to paclitaxel or cisplatin.

4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT
(In addition to the mandatory pre-testing for eligibility in Section 3.0)
Note: The evaluations/interventions listed below should be done prior to the patient starting any protocol treatment (but may be done subsequent to the patient enrollment). In the unlikely event that results of any of these tests raise questions about the patient’s eligibility for this study, please contact RTOG HQ immediately, (215) 5743189.

4.1 Additional Mandatory Pre-treatment Evaluations/Interventions (9/19/06)
See Section 11.1; note that failure to perform one or more of these tests may result in assessment of a protocol violation.
4.1.1 Assessment of weight and nutritional status to ensure adequate nutritional status, defined as caloric intake $\geq$ 1500 kcal/day (may be via oral intake, gastrostomy, jejunostomy, etc) within 3 weeks prior to registration;
4.1.2 Location, type, and size of all measurable lesions within 4 weeks prior to registration; these must be recorded and diagrammed prior to treatment;
4.1.3 Dental evaluation for patients on Arm 1 prior to the start of radiation therapy, with management according to the guidelines of Daly 45 (see Appendix IV).
4.2 Additional Highly Recommended Pre-treatment Evaluations/Interventions
Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial, but not mandatory.
4.2.1 Quality of Life Questionnaires;
4.2.2 Carotid artery assessment (e.g., Doppler ultrasound, CT angiogram, or MR angiogram);
4.2.3 Panendoscopy;
4.2.4 Speech/swallowing assessment, with or without barium swallow;
4.2.5 Blood for banking (See Section 10.0).

5.0 REGISTRATION PROCEDURES

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](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 ATC. *(9/19/06)*

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](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/](http://rpc.mdanderson.org/rpc/) by selecting “Credentialing” and “RTOG”.

5.2 Registration

5.2.1 Online Registration

Online (versus Dial-in) registration is mandatory for this study. 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://69.5.4.33/c01](http://69.5.4.33/c01)).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

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

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

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

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

6.0 RADIATION THERAPY

Treatment must begin within 7-10 days of registration. (9/19/06)

NOTE: 3D radiotherapy planning is MANDATORY. IMRT is permitted for this study. Additional information is required if an IMRT treatment planning approach is used (see Section 5.1).

6.1 Dose Specifications

6.1.1 Radiation therapy will be given as two daily fractions (1.5 Gy per fraction) separated by a minimum of 4 hours (6 hours is recommended), five consecutive days every other week for four weeks (weeks 1, 3, 5, and 7). Total dose will be 60 Gy in 40 fractions. Treatment will begin on Mondays. Paclitaxel and cisplatin will be given between the b.i.d. fractions. No treatment is given on weeks 2, 4, and 6. The exact time and date of each treatment is to be recorded.

6.2 Technical Factors

NOTE: 3D radiotherapy planning is MANDATORY. IMRT is permitted for this study. Additional information is required if an IMRT treatment planning approach is used (see Section 5.1).

6.2.1 Linear accelerators with appropriate photon and electron energies for supplemental boosting must be used.

6.2.2 Photon beams of ≥ 4 MV and/or electron beams from 4-25 MeV are allowed.

6.2.3 Treatment distance must be ≥ 80 cm SAD for isocentric techniques.

6.3 Localization, Simulation, and Immobilization

6.3.1 Immobilization

Head and neck immobilization device(s) must be utilized. A thermoplastic head mask is recommended. If the treatment volume includes the lower neck, immobilization should include the shoulders as well (e.g., combination head and shoulder mask). If the target volume includes oral tongue, a form of tongue immobilization also is recommended.

6.3.2 Treatment Planning CT Scan

A treatment planning CT scan is mandatory. CT scan thickness should be 0.5 cm or smaller (preferably 0.3 cm) through the treatment volume. Intravenous contrast is recommended in patients who do not have a contraindication to it. MRI and/or PET scans with image fusion also may be helpful in treatment planning, particularly if these scans can be performed with the same immobilization device as was used for the planning CT scan.

6.3.3 Volume Definitions

6.3.3.1 Gross Tumor Volume (GTV): This is the region of interest that is known to contain gross cancer. This will include all gross tumor as based upon the planning CT scan. This also may include areas that appear “normal” by the planning CT scan but are known to harbor cancer based on the MRI, PET, physical examination, endoscopy, etc.

6.3.3.2 PTV: This includes the GTV plus a margin to compensate for various uncertainties, such as systematic treatment setup variables, organ motion, and organ displacement (e.g., laryngeal motion). A minimum of 5 mm around the GTV is required in all directions, except where the GTV is immediately adjacent to the spinal cord or brainstem (in which case, the margin from GTV to PTV may be as small as 1 mm). The recommended margin from GTV to PTV where the spinal cord or brainstem is not a concern is 15 mm (1.5 cm).

6.3.3.3 Spinal Cord: The spinal cord will be defined based upon CT scan. A spinal cord “planning” volume (PRV) also will be defined by adding a symmetrical margin of at least 0.5 cm in all dimensions around the cord.

6.3.3.4 Brainstem: The brainstem will be defined based upon the CT scan. A brainstem “planning” volume (PRV) also will be defined by adding a symmetrical margin of at least 0.5 cm in all directions around the brainstem.
6.3.3.5 **Larynx**: The larynx will be defined as the portion of the larynx from the top of the thyroid cartilage to the bottom of the cricoid cartilage that does not include any portion of the PTV. No additional margin will be added around the larynx.

6.4 **Treatment Planning/Target Volumes**

**NOTE**: 3D radiotherapy planning is MANDATORY. IMRT is permitted for this study. Additional information is required if an IMRT treatment planning approach is used (see Section 5.1).

For standard treatment approaches, an isodose distribution in a transverse plane through the center of the target volume is required summing all fields. If the spinal cord is in close proximity to the treatment volume, off axis isodose distributions should be performed as well.

6.4.1 **Treatment Planning/Target Volume for 3D Non-IMRT**

Any combination of radiotherapy beams that meet the constraints of Section 6.5 is allowed. The prescription dose (1.5 Gy bid) may be prescribed to the isocenter (100%) for an isocentric technique. Alternatively, the treating Radiation Oncologist may “re-normalize” the prescription dose (1.5 Gy bid) to an isodose curve that represents between 95% and 100% of the isocenter dose, as long as the maximum dose to the patient does not exceed 110% of the isocenter dose.

6.4.2 **Treatment Planning/Target Volume for IMRT**

Any IMRT technique (e.g., step and shoot, tomotherapy) may be used to administer radiotherapy (minimum PTV dose should be 90% of the prescription dose and 95% of the PTV should receive the prescription dose). Hot spots to a volume of tissue > 1 cc should not exceed 110%. Hot spots between 110% and 115% will be considered a minor variation and hot spots > 115% will be considered a major variation.

6.5 **Critical Structures for All Treatment Approaches**

6.5.1 **Treatment Planning Constraints**: For critical normal tissue structures (spinal cord and brainstem), consideration must be given to the patient’s previous radiotherapy doses.

6.5.1.1 **Spinal Cord PRV** (see Section 6.3.3.2 for definition): The lifetime spinal cord dose at any point must not exceed 54 Gy. Thus, if a patient received a homogenous dose to the spinal cord of 45 Gy in the past, the current radiotherapy fields must not contribute more than 9 Gy to the spinal cord at any point.

6.5.1.2 **Brainstem PRV** (see Section 6.3.3.4 for definition): The lifetime brainstem dose at any point must not exceed 60 Gy. Thus, if a patient received a homogeneous dose to the brainstem of 48 Gy in the past, the current radiotherapy fields must not contribute more than 12 Gy to the brainstem at any point.

6.5.1.3 **Larynx** (see Section 6.3.3.5 for definition): There are no specific requirements for larynx dose, but if it is not grossly involved with or immediately adjacent to tumor, the dose should be kept as low as reasonably possible.

6.6 **Documentation Requirements**

6.6.1 For all treatment approaches, first day port films or portal images of each field must be obtained. In addition, there must be included a set of orthogonal megavoltage images (AP and lateral) from the first approved treatment. Thereafter, weekly verification films or images or orthogonal films are required.

6.6.2 For all forms of IMRT dose delivery, orthogonal films that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films.

6.6.3 For all delivery techniques, except those that use a source of radiation that rotates during treatment, e.g., tomotherapy or IMAT, the intensity pattern for each gantry orientation shall be documented on a separate film. These films should NOT include the patient’s anatomy.

6.6.4 For all treatment approaches, dose volume histograms (DVH) for the GTV, PTV, cord, cord PRV, brainstem, brainstem PRV, larynx, mandible, and non-PTV tissue must be obtained.

6.7 **Compliance Criteria (9/19/06)**

**Note**: For IMRT, dose compliance requires that 95% of the PTV receives a dose that is not lower than the prescribed dose by the amount stated in the table below. The maximum dose in the PTV must not exceed 115% of the prescribed dose.

<table>
<thead>
<tr>
<th>Total Dose Variation</th>
<th>Fractionation</th>
<th>Overall Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4%</td>
<td>&lt; 2 Days of non HFX</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>&gt; 4% to &lt; 9%</td>
<td>3-5 Days of non HFX</td>
<td>Variation Acceptable</td>
</tr>
<tr>
<td>&gt; 9%</td>
<td>&gt; 5 Days of non HFX</td>
<td>Deviation Unacceptable</td>
</tr>
</tbody>
</table>
6.7.1 *Missed Treatments*
If the patient misses more than two days, i.e., four fractions, missed treatments (radiation with chemotherapy) should be made up following administration of the fourth cycle of Filgrastim (i.e., starting week 9 [day 57]. The makeup of missed treatments given during week 9 will be reported on the final Treatment Summary Form (TF). Do not make up treatment if a single date is missed. If the chemotherapy and radiation are given during the “off week”, delay the G-CSF until the day after chemoradiation. Do not give G-CSF simultaneously with RT or chemotherapy.

6.8 **R.T. Quality Assurance Reviews (9/19/06)**
The Radiation Oncology Co-Chair, Dr. Machtay, will perform an RT Quality Assurance Review after complete data for the first 30 cases enrolled has been received at RTOG Headquarters. Dr. Machtay will perform the next review after complete data for each additional 30 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. These reviews will be ongoing and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters. IMRT RT Quality Assurance reviews will be remotely performed by the ITC (see Section 12.2).

6.9 **Radiation Toxicity**
Reversible radiation mucositis is expected to develop in the majority of patients treated on Arm 1. This will commonly manifest as grades 1-3 in severity. In those rare cases of grade 4 mucositis, radiation can be interrupted (see Section 6.9.1). Other common radiation toxicities include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, hypoguesia, dysgeusia, dysphagia, and skin erythema and desquamation within the treatment fields. If a feeding tube is placed for nutritional supplementation, this should be recorded. Less common long-term radiation 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 IV), and cervical myelopathy (< 5% with restriction of spinal cord dose to < 54 Gy).

6.9.1 Acute local toxicity (skin and mucosa) must be ≤ grade 2 at the beginning of each treatment week. If toxicity is > grade 2, treatment may be held up to two weeks until ≤ grade 2 is attained. Chemotherapy should be held until radiation treatment is resumed. Patients who cannot resume treatment within two weeks will be removed from study. These patients must be followed for survival.

6.9.2 If a treatment delay for local acute toxicity is required, only the dose of chemotherapy will be modified (Section 7.10), not the total radiation dose.

6.9.3 If treatment delay is required for chemotherapy toxicity, radiation treatment will also be held until both can be resumed.

6.9.4 Treatment breaks must be clearly indicated in the treatment record.

6.9.5 If treatment breaks unrelated to toxicity occur, e.g., department schedule, bad weather, or patient absence, the missed treatments should be made up as described in Sections 6.7.1 and 7.10.1.4.

6.10 **Radiation Adverse Event Reporting**
All acute and late adverse events from radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. A copy of the CTCAE can be downloaded from the CTEP home page ([http://ctep.info.nih.gov](http://ctep.info.nih.gov)). See Section 7.13 for Adverse Event Reporting.

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.

Treatment must begin within 7-10 days of registration. (9/19/06)

7.1 **Treatment Plan**
7.1.1 **Arm 1: Re-Irradiation plus Concurrent Chemotherapy**
7.1.1.1 Paclitaxel, 20 mg/m² i.v., over 1 hour per day x 5 days on weeks 1, 3, 5, and 7; paclitaxel will be administered immediately after the first fraction of radiation treatment, and completed ≥ 3 hours prior to the second fraction.
7.1.1.2 Premedicate with diphenhydramine, 25 mg i.v., dexamethasone, 20 mg i.v., and cimetidine, 300 mg i.v., or equivalent.

7.1.1.3 Cisplatin, 15 mg/m² i.v. bolus, daily x 5 days on weeks 1, 3, 5, and 7 in 500 cc ½ normal saline solution (NSS) or NSS over 30 minutes immediately following paclitaxel after 500 cc prehydration over 2 hours.

7.1.1.4 Additional intravenous fluids pre- or post-cisplatin can be administered as necessary at the discretion of the treating physician.

7.1.1.5 Filgrastim, 300 mcg s.q. (for patients ≤ 60 kg), or 480 mcg s.q. (for patients > 60 kg) once daily for a total of 8 doses (Saturday through Saturday) on weeks 2, 4, 6, and 8 — weeks when patients are not receiving chemoradiation. The filgrastim should start 24 hours after the end of the chemotherapy infusion (on the Saturday following Friday’s chemoradiation). If treatment must be added (week 9) to make up missed chemotherapy/radiation, additional Filgrastim must also be administered for an additional 8 days starting the day after the last dose of chemoradiation. The patient’s ANC must be at least 1500 before the next dose of chemotherapy can be administered. Filgrastim will be continued past day 13, if necessary, to achieve this goal. **NOTE:** Filgrastim must be discontinued at least 24 hours prior to the next dose of chemotherapy. If radiation/chemotherapy doses are missed due to departmental schedule or patient absence, i.e., not due to toxicity modification, the missed treatments (see Section 6.7.1) are given after the fourth cycle of Filgrastim. Filgrastim is not to be administered simultaneously with chemotherapy or radiation.

7.1.2 Arm 2: Chemotherapy Alone (4/27/05)
The treating physician may select any one of the following three regimens:

**(NOTE:** Patients must have an ANC > 1500 cells/mm³ and platelets > 100,000 cells/mm³ on Day 1 of each cycle. Otherwise, hold chemotherapy and obtain weekly CBC, differential, and platelet count. Treat with dose modifications, if indicated, based on nadir toxicity of previous cycle.)

7.1.2.1 Cisplatin* and 5-Fluorouracil
Repeat cycle every 21 days; see Section 7.1.2.4 for details of duration. Dosing based upon actual body weight.

- Patients should be hydrated with 1-2 liters of fluid i.v. or p.o. in the 24 hours prior to and post cisplatin.
- **Patient must receive vigorous hydration and monitoring of fluid status for 24 hours after cisplatin.** A suggested regimen is hydration with 1000 ml NS i.v. over 2-4 hours prior to cisplatin. Mannitol, 12.5 gm i.v. bolus, immediately prior to or admixed with cisplatin. Hydrate with additional 1000 ml NS over 2-4 following cisplatin administration.
- Cisplatin, 100mg/m² in 500 ml NS is administered over 1 to 2 hours, day 1.
- Suggested premedication for cisplatin: granisetron, 0.7-1.0 mg i.v., ondansetron, 0.15 mg/kg, aprepitant, or palonosetron 0.25 mg i.v. plus dexamethasone, 20mg i.v. More aggressive anti-emetic prophylactic treatment may be given at the discretion of the treating physician.
- 5-Fluorouracil, 1000 mg/ m²/day will be administered as a continuous infusion, daily on day 1-4 (96 hours);
- Repeat cycles may be given every 28 days if necessary in order to meet pre-chemotherapy parameters.

7.1.2.2 Cisplatin* and Paclitaxel
Repeat cycle every 21 days; see Section 7.1.2.4 for details of duration. Dosing based upon actual body weight.

- Patients should be hydrated with 1-2 liters of fluid i.v., or p.o. in the 24 hours prior to and post cisplatin.
- **Patient must receive vigorous hydration and monitoring of fluid status for 24 hours after cisplatin.** A suggested regimen is hydration with 1000 ml NS i.v. over 2-4 hours prior to cisplatin. Mannitol, 12.5 gm i.v. bolus, immediately prior to or admixed with cisplatin. Hydrate with additional 1000 ml NS over 2-4 following cisplatin administration.
- Cisplatin, 75 mg/m² in 500 ml NS is administered over 1 to 2 hours, day 1.
- Suggested premedication for cisplatin: granisetron, 0.7-1.0 mg i.v., ondansetron, 0.15 mg/kg, aprepitant, or palonosetron 0.25 mg i.v. plus dexamethasone, 20mg i.v. More aggressive anti-emetic prophylactic treatment may be given at the discretion of the treating physician.
- Paclitaxel, 175 mg/ m² will be administered as a 3-hour intravenous infusion, day 1.
Prior to paclitaxel premedicate with diphenhydramine, 25 mg i.v., dexamethasone, 20 mg i.v., and cimetidine, 300 mg i.v., or equivalent.

7.1.2.3 Cisplatin* and Docetaxel (9/19/06)

Repeat cycle every 21 days; see Section 7.1.2.4 for details of duration.

Dosing based upon actual body weight.

- Patients should be hydrated with 1-2 liters of fluid i.v., or p.o. in the 24 hours prior to and post cisplatin.
- **Patient must receive vigorous hydration and monitoring of fluid status for 24 hours after cisplatin.** A suggested regimen is hydration with 1000 ml NS i.v. over 2-4 hours prior to cisplatin. Mannitol, 12.5 gm i.v bolus, immediately prior to or admixed with cisplatin. Hydrate with additional 1000 ml NS over 2-4 following cisplatin administration.
- Cisplatin, 75 mg/m² in 500 ml NS is administered over 1 to 2 hours, day 1.
- Suggested premedication for cisplatin: granisetron, 0.7-1.0 mg i.v., ondansetron, 0.15 mg/kg, or palonosetron 0.25 mg i.v. plus dexamethasone 20mg i.v. More aggressive anti-emetic prophylactic treatment may be given at the discretion of the treating physician.
- Docetaxel, 75 mg/m² over 1 hour, day 1, following administration of cisplatin
- Prior to docetaxel premedicate with dexamethasone, 8 mg p.o. every 12 hours for 5 doses starting 24 hours prior to the docetaxel infusion, continuing the day of the docetaxel infusion and finishing the day after the docetaxel infusion.

**Caution:** Docetaxel is a moderate to significant inhibitor of the CYP3A4 enzyme. There are many prescribed medications, over the counter agents, food, alternative therapies, and herbs which are inducers or inhibitors of CYP34A and which, if taken concomitantly with docetaxel, may significantly alter the patient's metabolizing of docetaxel. Patients should discontinue use of potential inducers or inhibitors of CYP34A at least 14 days prior to administration of docetaxel and throughout docetaxel administration. Sites should refer to the most current package insert for information concerning inducers and inhibitors of CYP34A.

**Note:** Carboplatin will be substituted for cisplatin only for specific conditions as described in Section 7.8.2. For details of administration, see Section 7.7.

7.1.2.4 Duration of Treatment with Chemotherapy Alone

**NOTE:** Patients will be assessed after every 2 cycles of chemotherapy. Assessment of objective response will be determined by Response Evaluation Criteria in Solid Tumors (RECIST) [see Section 11.4].

- A minimum of 6 cycles of chemotherapy are recommended. The only patients for whom less than 6 cycles should be considered are those achieving a Complete Response (CR), those who progress, and/or those who develop unacceptable toxicity.
- Patients achieving a CR may discontinue treatment 2 cycles after CR is documented at the discretion of the treating physician (a total of 4 cycles minimum).
- Patients achieving a Partial Response (PR) will receive treatment until a CR or Progressive Disease (PD) occurs.
- Patients achieving no better than Stable Disease (SD) may discontinue treatment after 6 cycles.
- Patients with PD will discontinue treatment.
- Patients who develop unacceptable toxicity from treatment may be removed from study treatment at any time.
- Patients may be removed from treatment at the discretion of the treating physician.
- Patients removed from study treatment will be followed until death.

7.2 Paclitaxel

7.2.1 Other Names

Taxol®

7.2.2 Formulation

Concentrated sterile solution, 6 mg/ml in a 5 ml vial (30 mg/vial) as well as 16.7 cc (100 mg) and 50 cc (300 mg) vials in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP 50%. The contents of the vial must be diluted before use. For further information, see package insert.
Incompatibilities
Little is known concerning physical incompatibilities with paclitaxel. Based on information from other cremophor based drugs it is recommended that no other solutions be mixed with the paclitaxel-containing solution.

Solution Preparation
Paclitaxel concentrations from 0.3 mg/ml to 1.2 mg/ml can be obtained by diluting the vial solution with proper volumes of either 0.9% sodium chloride or 5% dextrose in water. Solutions of paclitaxel diluted to these concentrations are both chemically and physically stable for at least 27 hours. All solutions exhibit a slight haze, which is common to all products containing non-ionic surfactants. Paclitaxel must be prepared in glass or polyolefin containers and administered with non-PVC tubing and connector sets; Abbott also manufactures an IVEX HIP filter, which is acceptable for use with paclitaxel.

Note: A small number of fibers within acceptable levels of USP particular matter tests for LVP have been observed; hence, in-line filtration is necessary with all paclitaxel infusions. Solutions exhibiting excessive particulate formation should not be used. Analysis of in-line filtered solutions using IVEX-2 (Abbott) 0.2 micron filters showed no appreciable loss of potency.

Caution: PVC bags and sets should be avoided due to appreciable leaching of DEHP.

Administration
Intravenous; must be filtered. In-line filtration with a 0.2 micron filter should be used with all paclitaxel infusions. Avoid infiltration; unknown whether paclitaxel is a vesicant, but Cremophor EL vehicle can cause tissue damage.

Adverse Events
The following toxicities are anticipated:
- Hematologic: Myelosuppression (hemoglobin, leukocytes [total WBC], lymphopenia, neutrophils/granulocytes [ANC/AGC], platelets), infection;
- Gastrointestinal: Nausea, vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, colitis, liver dysfunction/failure (alkaline phosphatase, bilirubin, SGOT, SGPT);
- Cardiovascular: Dizziness, lightheadedness, hypertension, hypotension, bradycardia and other cardiac rhythm disturbances, nodal/junctional arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmia (PVCs/bigominy/trigeminy/ventricular tachycardia), conduction abnormalities/atrioventricular block, cardiac-ischemia/infarction;
- Pulmonary: Pneumonitis/pulmonary infiltrates, radiation recall reaction;
- Neurologic: Mood alteration (anxiety, agitation), fatigue (lethargy, malaise, asthenia), CNS toxicity (seizures, blurred vision, flashing lights/floaters, scintillation scotoma), neuropathy-motor, neuropathy-sensory (taste disturbance), peripheral neuropathy, leukoencephalopathy associated with radiological findings;
- Dermatologic: Alopecia, rash/desquamation, injection site reaction, nail changes, erythema multiforme;
- Allergic: Flushing, pruritus, urticaria (hives, welts, wheals), Stevens-Johnson Syndrome;
- Other: Myalgias and arthralgias

Patient Implication
Monitor for signs and symptoms of allergic reactions. Ensure that premedications have been given and that emergency agents are available. The patient’s blood pressure and heart rate will be monitored during the infusion (every 15 minutes during the first hour). Asymptomatic bradycardia has been reported in up to 30% of patients. Patients with more serious arrhythmias usually have other predisposing cardiac risks. Evaluate for nausea, which should be mild with low dose daily infusion and consider pretreatment of patients who exhibit nausea in subsequent courses. Evaluate i.v. site regularly for signs of infiltration. It is not known whether paclitaxel is a vesicant, but since it interacts with microtubules (similar to vincas), care should be exercised. The vehicle Cremophor-EL is also a known vesicant in high concentrations. Patients should be warned about arthralgia-myalgia syndromes, which may occur after treatment. Acetaminophen, NSAIDs or, if necessary, narcotics may be given for symptomatic control.

Storage
The intact vials should be stored under refrigeration (20-25°C [68-77°F]).
7.2.9 Supply
Paclitaxel is available commercially in the United States.

7.3 Cisplatin

7.3.1 Other Names
Platinol-AQ, cisdiaminedichloroplatinum (II), CDDP, DDP, DACP, cis-platinum, platinum.

7.3.2 Pharmacology and Pharmacokinetics
The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 50 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 45% of the radioactivity excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

7.3.3 Formulation
Cisplatin is available 1 mg/mL in 50 mL and 100 mL vials. For further information, see package insert.

7.3.4 Administration
Cisplatin is usually administered by slow \textit{i.v.} infusion over 30 minutes or longer. Cisplatin also has been given intra-arterially, intraperitoneally, and intravesicularly.

7.3.5 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

7.3.6 Storage and Stability
The intact vials should be stored at 15-25° C. DO NOT refrigerate. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5 1/2 NS (ppt. occurs in D5W). Note: Verify shelf life once diluted. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.3.7 Supply
Cisplatin is commercially available.

7.4 Filgrastim (G-CSF)

7.4.1 Source and Pharmacology
G-CSF is a recombinant human granulocyte colony stimulating factor produced by recombinant DNA technology in Escherichia coli. G-CSF is a lineage-specific colony stimulating factor with selectivity for the neutrophil lineage. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis except for the addition of an N-terminal methionine necessary for expression in E. coli. Because G-CSF is produced in \textit{E. coli} the product is non-glycosylated and thus differs from G-CSF isolated from a human cell.

7.4.2 Formulation
G-CSF is a sterile, clear, colorless, preservative-free liquid for parenteral administration. Each single-use vial of G-CSF contains 300 micrograms/mL of filgrastim at a specific activity of 1.0 + 0.6 x 10^8 U/mg. The product is formulated in a 10mM sodium acetate buffer at pH 4.0, containing 5% sorbitol and 0.004% Tween 80. Both 1.0 and 1.6 ml vials are available. For further information, see package insert.
7.4.3 **Administration**

Administer subcutaneously.

7.4.4 **Adverse Events**

The predominant toxicity attributable to G-CSF is mild medullary bone pain. Splenomegaly and mild alopecia have also occurred. Mild transient swelling at injection sites can occur. Spontaneously reversible mild to moderate elevations in uric acid, lactate dehydrogenase, and alkaline phosphatase have occurred.

7.4.5 **Storage**

Store between 2 and 8°C. Do not freeze. Avoid shaking. Drug administered SQ should not be diluted and can be drawn directly from the vial and administered.

7.4.6 **Supply**

G-CSF is commercially available.

7.5 **5-Fluorouracil**

7.5.1 **Other Names**

5-FU, Adrucil, Efudex.

7.5.2 **Formulation**

Available in 500 mg/10 mL ampules and vials, and 1 gm/20 ml. Stable for prolonged periods of time at room temperature, if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. For further information, see package insert.

7.5.3 **Administration**

May be administered via the following: i.v. push, i.v. continuous infusion, arterial infusion, intracavitary, intraperitoneally, topically, or orally mixed in water, grape juice, or carbonated beverage.

7.5.4 **Adverse Events**

The following toxicities are anticipated:

- Hematologic: Leukopenia, thrombocytopenia, anemia (can be dose limiting, less common with continuous infusion);
- Dermatologic: Dermatitis, nail changes, hyperpigmentation, Hand-Foot Syndrome with protracted infusions, alopecia;
- Gastrointestinal: Nausea, vomiting, anorexia, diarrhea (can be dose limiting); mucositis (more common with 5-day infusion, occasionally dose limiting); severe, cholera-like diarrhea which can be fatal when given with leucovorin;
- Neurologic: Cerebellar Syndrome (headache and cerebellar ataxia);
- Cardiac: Angina, noted with continuous infusion;
- Ophthalmic: Eye irritation, nasal discharge, watering of eyes, blurred vision.

7.5.5 **Drug Interactions**

7.5.5.1 Cimetidine: Because cimetidine can decrease the clearance of 5-FU, patients should not enter on this study until the cimetidine is discontinued. Ranitidine or a drug from another anti-ulcer class can be substituted for cimetidine, as necessary.

7.5.5.2 Allopurinol: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

7.5.6 **Storage**

Stable for prolonged periods of time at room temperature, if protected from light. Inspect for precipitate; if apparent, agitate vial vigorously or gently heat to not greater than 140°F in a water bath. Do not allow to freeze.

7.5.7 **Supply**

Commercially available.

7.6 **Docetaxel**

7.6.1 **Other Names**

Taxotere, RP 56976, NSC #628503.

7.6.2 **Formulation**

Available in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in water for injection) vial. The
following strengths are available: a 20 mg or an 80 mg concentrate for infusion. For further information, see package insert.

7.6.3 Incompatibilities
PVC-Containing intravenous bags and administration sets with DEHP (di-2-ethylhexyl phthalate). No further information available.

7.6.4 Preparation

7.6.4.1 Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

7.6.4.2 Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

7.6.4.3 Docetaxel for Injection
Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the docetaxel for Injection Concentrate and the diluent vials contain an overfill.

A. Preparation of the Initial Diluted Solution
1. Gather the appropriate number of vials of docetaxel for Injection Concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.
3. Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4. The initial diluted docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process. The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

B. Preparation of the Final Dilution for Infusion
1. Aseptically withdraw the required amount of initial diluted docetaxel solution (10mg docetaxel/mL) with a calibrated syringe and inject into an infusion bag or bottle of either 0.9% Sodium Chloride solution or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74mg/mL. Thoroughly mix the infusion by manual rotation.
2. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection, initial diluted solution, or final dilution for infusion is not clear or appears to have precipitation, these should be discarded. The final docetaxel dilution for infusion should be administered intravenously as per protocol under ambient room temperature and lighting conditions.

7.6.5 Administration
Docetaxel will be administered as a sixty-minute infusion in saline or D5W through an administration set that does not contain phthalate plasticizers along the fluid pathway that is connected to the patient’s vascular access catheter.

7.6.6 Adverse Events
The following toxicities are anticipated:
- Hematologic: Dose-related neutropenia, leukopenia, thrombocytopenia, anemia;
- Gastrointestinal: Nausea and vomiting, diarrhea, oral mucositis;
- Neurologic: Reversible dysesthesia or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures;
• Allergic: Local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea);
• Dermatologic: Alopecia, desquamation following localized pruriginous maculopapular eruption skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), nail changes;
• Hepatic: Increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction;
• Cardiac: Arrhythmias;
• Pulmonary: Dyspnea with restrictive pulmonary syndrome;
• Other: Asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral phlebitis, fluid retention syndrome (i.e. peripheral edema, ascites, pleural and pericardial effusions)

7.6.7 Storage and Stability
Store between 2 and 25°C (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product. Docetaxel is stored at 4ºC and should be protected from light. The solvent vials may be stored at room temperature or at 4ºC. Taxotere infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable for 4 hours. Fully prepared Taxotere® infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 4 hours (including the administration time).

7.6.8 Supply
Docetaxel is commercially available in the U.S. However, when used in combination as directed by this protocol, the agents are classified as an “unapproved use of an agent” and, by definition, are considered investigational. While this combination is not currently approved by the FDA, the use in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2(b).

Note: Docetaxel (Taxotere®) is not commercially available to Canadian institutions. RTOG Headquarters will notify Canadian sites once a supply of Taxotere® has been established and is available.

7.7 Carboplatin

Note: Carboplatin will be substituted for cisplatin only for specific conditions as described in Section 7.8.2.

7.7.1 Other Names
CBDCA, Paraplatin, JM-8.

7.7.2 Incompatibilities
Forms a precipitate when in contact with aluminum.

7.7.3 Preparation
Add 5, 15, or 45 ml sterile water, normal saline, or 5% dextrose to the 50, 150, or 450 mg vial, respectively. The resulting solution contains 10 mg/ml. The desired dose is further diluted, usually in 5% dextrose. For further information, see package insert.

7.7.4 Dose and Administration
AUC of 6, using the total mg dose: [(CrCl + 25) 6 = total mg dose]. Use estimated creatinine clearance as described in Section 3.1.15.1 Administration is usually by continuous intravenous infusion over 15 minutes or more. Carboplatin infusion should follow paclitaxel or docetaxel infusion.

7.7.5 Nursing Considerations
• Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30.
• Premedicate with antiemetics; evaluate effectiveness.
• Monitor fluid status; maintain adequate hydration.
• Assess skin/mucous membranes.
• Assess for signs of peripheral neuropathy: coordination, sensory loss.

7.7.6 Adverse Events
• Hematologic: Thrombocytopenia, neutropenia, leukopenia, more pronounced in patients with compromised renal function and heavily pretreated patients; may be cumulative.
• Gastrointestinal: Nausea and vomiting (less severe than with cisplatin); treatable with moderate doses of antiemetics.
• Dermatologic: Rash, urticaria.
• Hepatic: Abnormal liver function tests; usually reversible with standard doses.
• Neurologic: Rarely peripheral neuropathy.
• Renal: Elevations in serum creatinine, BUN; electrolyte loss (Na, Mg, K, Ca).
• Other: Pain, asthenia.

7.7 Storage and Stability
Intact vials are stored at room temperature protected from light. The reconstituted solution is stable for at least 24 hours. When further diluted in glass or polyvinyl plastic to a concentration of 500 mg/ml, solutions have the following stability: In normal saline, 8 hours at 25°C, 24 hours at 5°C; in 5% dextrose (when reconstituted in sterile water), 24 hours at 5 or 25°C.

7.8 Supply
Commercially available in 50, 150, and 450 mg vials.

NOTE: Refer to the commercial package labeling for full prescribing information.

7.8.1 Pharmacology
Both filgrastim and pegfilgrastim are colony-stimulating factors that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function show that filgrastim and pegfilgrastim have the same mechanism of action. Pegfilgrastim has reduced renal clearance and prolonged persistence in vivo compared with filgrastim.

7.8.2 Formulation
Neulasta™ (pegfilgrastim) is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. Filgrastim is obtained from the bacterial fermentation of a strain of E. coli bearing a genetically engineered plasmid containing the human G-CSF gene. Neulasta™ is supplied in 0.6-ml pre-filled single-dose syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

7.8.3 Administration
The pegfilgrastim will be injected subcutaneously into rotating sites on the abdomen, arms, and legs. Pegfilgrastim should be visually inspected for discoloration and particulate matter before administration. Pegfilgrastim should not be administered if discoloration or particulates are observed. Pegfilgrastim can be self-administered by the patient. Each patient or a designated caregiver will be instructed by the nursing staff in the proper method for the antiseptic subcutaneous administration of pegfilgrastim. Prior to administration at home, these skills must be competently demonstrated by the patient or caregiver. Patients/caregivers will also receive written instruction concerning medication storage (refrigeration).

7.8.4 Storage
Neulasta™ should be stored refrigerated at 2° to 8° C (36° to 46° F); syringes should be kept in their carton and protected from the light until time of use. Shaking should be avoided. Before injection, Neulasta™ may be allowed to reach room temperature for a maximum of 48 hours but should be protected from the light. Neulasta™ left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta™ should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta™ should be discarded.

7.8.5 Adverse Events
Neulasta™ is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, pegfilgrastim, filgrastim, or any other component of the product. Drugs such as lithium may potentiate the release of neutrophils; patients who are taking lithium should have more frequent monitoring of their neutrophil counts. The predominant toxicity attributed to Neulasta™ in clinical trials was medullary bone pain of mild to moderate severity. Other adverse experiences included nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and neutropenic fever. Leukocytosis (WBC > 100 x 10^9/L) was observed in less than 1% of subjects. A rare case of hypoxia was also observed. Reversible elevations in LDH, alkaline phosphatase, and uric acid were also observed.

7.8.6 Supply
Neulasta™ is commercially available.
7.9 GM-CSF (9/19/06)

NOTE: Refer to the commercial package labeling for full prescribing information.

7.9.1 Other Names
Sargramostim, rhu GM-CSF, Leukine, NSC #613795

7.9.2 Mode of Action
GM-CSF stimulates granulocyte and macrophage production by bone marrow hematoprogenitor cells and activates mature neutrophils and monocytes.

7.9.3 Formulation
Leukine Liquid is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500mcg/mL) in a vial. Lyophilized Leukine is a sterile, white, preservative-free powder (250mcg) that requires reconstitution with 1 mL Sterile Water for Injection, USP or 1 mL Bacteriostatic Water for Injection, USP.

7.9.4 Storage and Stability
Leukine Liquid may be stored for up to 20 days at 2-8°C once the vial has been entered. Discard any remaining solution after 20 days. Lyophilized Leukine (250 mcg) should be reconstituted aseptically with 1.0 mL of diluent (see below). The contents of vials reconstituted with different diluents should not be mixed together.

Sterile Water for Injection, USP (without preservative): Leukine vials contain no antibacterial preservative, and therefore, solutions prepared with Sterile Water for Injection, USP should be administered as soon as possible and within 6 hours following reconstitution and/or dilution for IV infusion. The vial should not be re-entered or reused. Do not save any unused portion for administration more than 6 hours following reconstitution. Leukine should be used for SC injection without further dilution. Dilution for IV infusion should be performed in 0.9% Sodium Chloride Injection, USP. If the final concentration of Leukine is below 10 mcg/mL, Albumin (Human) at a final concentration of 0.1% should be added to the saline to prevent adsorption to the components of the drug delivery system. To obtain a final concentration of 0.1% Albumin (Human), add 1 mg Albumin (Human) per 1 mL 0.9% Sodium Chloride Injection, USP (e.g., use 1 mL 5% Albumin [Human] in 50 mL 0.9% Sodium Chloride Injection, USP). An in-line membrane filter should NOT be used for intravenous infusion of Leukine.

7.9.5 Route of Administration/Dosing
The recommended dose of GM-CSF is 250 mcg/m²/day, given subcutaneously or as a two-hour IV infusion. In order to avoid potential complications of excessive leukocytosis, a CBC with differential is recommended twice per week during treatment with GM-CSF.

7.9.6 Adverse Events
- Dermatology/Skin: Local erythema, rash.
- Gastrointestinal: Diarrhea, anorexia, nausea, vomiting, abnormal taste.
- Neurology: Confusion, neuropathies.
- Pulmonary: Dyspnea (due to fluid retention and capillary leak syndrome), pleuritis.
- Cardiovascular: Cardiac arrhythmias, atrial fibrillation, pericarditis.
- Pain: Headache, arthralgias, bone pain, abdominal pain, chest pain, myalgia.
- Coagulation: Partial thromboplastin time (PTT), Prothrombin time (PT), thromboembolic phenomena.
- Constitutional: Fever, flu-like syndrome (chills, rigors, myalgias), fatigue, malaise, asthenia, hypersensitivity.
- Renal/Genitourinary: Renal failure.

7.9.7 Supply
GM-CSF is commercially available.

7.10 Dose Modifications
7.10.1 Arm 1: Re-Irradiation plus Concurrent Chemotherapy
7.10.1.1 Dose Levels: Concurrent Paclitaxel/Cisplatin
The doses for each patient enrolled will not be raised.

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Dose Level -1</th>
<th>Dose Level -2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>20 mg/m²</td>
<td>15 mg/m²</td>
<td>10 mg/m²</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>15 mg/m²</td>
<td>12 mg/m²</td>
<td>7.5 mg/m²</td>
</tr>
</tbody>
</table>
7.10.1.2 Hematologic Toxicity: Concurrent Paclitaxel/Cisplatin Dose Modifications

Note: Also see Section 7.10.1.4 regarding criteria for treatment delay.

<table>
<thead>
<tr>
<th>NCI CTCAE Toxicity Grade (CTCAE v. 3.0)</th>
<th>Paclitaxel Dose at Start of subsequent Cycles of Therapy</th>
<th>Cisplatin Dose at Start of subsequent Cycles of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (1500-1999/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>2 (1000-1499/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>3 (500-999/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>4 (&lt;500/mm³)</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
<tr>
<td>Neutropenic Fever</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&gt;75,000/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>2 (50,000 – 74,999/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>3 (25,000 – 49,999/mm³)</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>4 (&lt;25,000/mm³)</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
</tbody>
</table>

7.10.1.3 Non-Hematologic Toxicity: Concurrent Paclitaxel/Cisplatin Dose Modifications

<table>
<thead>
<tr>
<th>NCI CTCAE Toxicity Grade (CTCAE v. 3.0)</th>
<th>Paclitaxel Dose at Start of subsequent Cycles of Therapy</th>
<th>Cisplatin Dose at Start of subsequent Cycles of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Calculated Creatinine Clearancea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50 mL/min</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>&lt; 50 mL/min, &gt; 25 mg/dL</td>
<td>Maintain dose level</td>
<td>Decrease by 2 dose levels</td>
</tr>
<tr>
<td>&lt; 25 mL/min</td>
<td>Maintain dose level</td>
<td>Hold drug until &gt;25 mg/dL, resume at dose level -2</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
<tr>
<td>Fatigue (Asthenia) &gt; Grade 3</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
<tr>
<td>Other Non-hematologic Toxicitiesb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; Grade 3</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
<tr>
<td>Delay in Resuming Radiation by &gt;1 week</td>
<td>Decrease by 1 dose level</td>
<td>Decrease by 1 dose level</td>
</tr>
</tbody>
</table>

a. Use Cockcroft-Gault formula (Section 3.1.15.1) to estimate creatinine clearance;
b. Excluding nausea, vomiting, and/or arthralgias attributable to growth factors and alopecia
c. See Section 7.10.1.4 below.

7.10.1.4 Criteria for Treatment Delay

Treatment will be delayed ≥ 1 week if any of the following exist at the time that treatment is scheduled to resume:
- Ongoing mucositis that precludes adequate hydration or intake (not applicable to patients with G-tubes or those receiving TPN);
- Grade 2 neurotoxicity;
- Failure to recover ANC to > 1500/cc or platelets to > 80,000/cc;
- Other ongoing > grade 3 nonhematologic toxicities (with the exception of alopecia).

7.10.1.5 Hypersensitivity Reactions

- If mild hypersensitivity reaction (e.g., mild flushing, rash, pruritus) occurs during paclitaxel infusion, the infusion will be halted for 5-20 minutes. Patients will receive hydrocortisone 150 mg i.v. and diphenhydramine 25-50 mg, and the paclitaxel infusion will be resumed at slow rate initially, then gradually accelerated per institutional process. If allergic reaction recurs, despite slowing the infusion rate, patients will receive a full 24 hours of oral steroid prophylaxis (e.g. dexamethasone 6 mg q 6 hrs) prior to the next day’s dose.
• If moderate anaphylaxis (e.g., moderate rash, flushing, mild dyspnea, chest discomfort) occurs, **stop infusion**. Give intravenous diphenhydramine 20-25 mg and intravenous dexamethasone 10 mg. Resume drug infusion after recovery of symptoms at a low rate, 20 ml/hr for 15 minutes, then 50 ml/hr for 15 minutes, then if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop drug infusion. The patient will go off treatment and will be followed per protocol. Report as an adverse event.

• If severe, life-threatening anaphylaxis (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria) occurs, **stop infusion**. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. The patient will go off treatment and will be followed per protocol. Report as an adverse event.

7.10.2 **Arm 2: Chemotherapy Alone Dose Modifications (9/19/06)**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Cisplatin</th>
<th>5-FU</th>
<th>Paclitaxel</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia Grade 4 b</td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia Grade 4</td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50 mL/min</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50 mL/min</td>
<td>Substitute carboplatin c</td>
<td>Maintain dose level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic Bradycardia</td>
<td>Maintain dose level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic arrhythmia</td>
<td>Maintain dose level</td>
<td>Maintain dose level</td>
<td>Stop infusion*. Remove from study treatment.</td>
<td>Maintain dose level</td>
</tr>
<tr>
<td>Chest pain, symptomatic hypotension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, Vomiting</td>
<td>No dose modifications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucositis Grade 2</td>
<td>Maintain dose level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade ≥ 3</td>
<td>Maintain dose level</td>
<td>80% of previous calculated dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>See Section 7.10.2.1 below</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>Maintain dose level d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>See footnotes d &amp; e</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>See footnote f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Grade 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maintain dose level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Substitute carboplatin</td>
<td>See footnote g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Substitute carboplatin</td>
<td>See footnote h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Remove from study treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other Non-Hematologic Toxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. Patients must have ANC > 1500/µl and platelets > 100,000/µl on Day 1; otherwise, hold chemotherapy and obtain weekly CBC, differential and platelet count. Resume treatment with dose modifications if indicated based on nadir toxicity of previous cycle;
b. Grade 4 Neutropenia (< 500/uL) persisting longer than 5 days;
c. Carboplatin, AUC 6; use formula for calculating dose in mg = 6 x (estimated creatinine clearance + 25). Use Cockcroft-Gault formula (Section 3.1.15.1) to estimate creatinine clearance using lab values immediately prior to cycle that is due (9/19/06);
d. Patients who had a mild hypersensitivity reaction (mild flushing, rash, pruritus) will be supervised, but drug infusion will be completed and no further treatment is necessary;
e. Moderate anaphylaxis (e.g., moderate rash, flushing, mild dyspnea, chest discomfort): Stop infusion. Give intravenous diphenhydramine 20-25 mg and intravenous dexamethasone 10 mg. Resume drug infusion after recovery of symptoms at a low rate, 20 ml/hr for 15 minutes, then 50 ml/hr for 15 minutes, then if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop drug infusion. The patient will go off treatment and will be followed per protocol. Report as an adverse event;
f. Severe life threatening anaphylaxis (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilatation therapy, generalized urticaria): Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. The patient will go off treatment and will be followed per protocol. Report as an adverse event;
g. For grade 2 motor sensory neurotoxicity, maintain paclitaxel at 100% dose. If after one cycle neuropathy does not improve, then decrease paclitaxel to 80%;
h. Grade 3 (impairment of function): The patient may be taken off treatment for reason of toxicity at the discretion of the treating physician based on severity of functional loss. For grade 3 toxicity, decrease to paclitaxel to 80% of previous dose;
i. Patients with severe sensorineural hearing loss may substitute carboplatin AUC = 6, if the hearing loss occurs at baseline or during the course of treatment.

7.10.2.1 Docetaxel and Paclitaxel Dose Modifications for Hepatic Toxicity
In case of liver function test abnormalities the treatment modifications outlined below will apply. No more than two dose reductions are allowed.

<table>
<thead>
<tr>
<th>ALK PHOS</th>
<th>≤ ULN</th>
<th>&gt; 1x but ≤ 1.5x</th>
<th>&gt;1.5x but ≤ 5x</th>
<th>&gt; 5x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ ULN</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>HOLD*</td>
</tr>
<tr>
<td>&gt; 1x but ≤ 2.5x</td>
<td>Full Dose</td>
<td>Full Dose</td>
<td>80% of previous calculated dose</td>
<td>HOLD*</td>
</tr>
<tr>
<td>&gt; 2.5x but ≤5x</td>
<td>Full Dose</td>
<td>80% of previous calculated dose</td>
<td>HOLD*</td>
<td>HOLD*</td>
</tr>
<tr>
<td>&gt; 5x ULN</td>
<td>HOLD*</td>
<td>HOLD*</td>
<td>HOLD*</td>
<td>HOLD*</td>
</tr>
</tbody>
</table>

*Hold until recovered, maximum 21 days, then re-treat at a one dose level reduction. “Recovered” is defined as meeting the study baseline eligibility criteria.

Bilirubin: Docetaxel should not be administered to patients with serum total bilirubin >ULN. If serum total bilirubin is >ULN on treatment day, hold docetaxel until serum total bilirubin is > ULN (maximum 21 days), then re-treat at a reduced dose level.

7.11 Criteria for Removal From Protocol Treatment (9/19/06)
- Progression of disease;
- Symptomatic deterioration;
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flow sheet, and RTOG Headquarters data management must be notified;
- The patient may withdraw from the protocol treatment/follow up assessments at any time for any reason. The site should make every effort to provide survival information.
- The patient may withdraw their consent at any time. The institution must notify RTOG Headquarters Data Management about this in writing, and follow the guidelines set forth in the RTOG procedure manual.
- For Arm1: Greater than 3 weeks delay between treatment courses.

7.12 Modality Review
The Principal Investigator, Dr. Wong, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: per
protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review, or, incomplete chemotherapy. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Principal Investigator, Dr. Wong, will perform a Quality Assurance Review after complete data for the first 30 cases enrolled has been received at RTOG Headquarters. Dr. Wong will perform the next review after complete data for each additional 30 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.

7.13 Adverse Events (9/19/06)

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.cancer.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 in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site (https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (http://www.rtog.org/members/toxicity/main.html) for this information.

7.13.1 Adverse Event (AE) Reporting — RTOG AE PHONE: 215-717-2762; 800-227-5463 ext. 4189 (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 next section], further reporting may be required. Reporting AEs only fulfills Data Management reporting requirements.

7.13.2 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, 800-227-5463 ext. 4189; 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 or if being faxed to NCI, 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, when 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.

7.13.3 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.cancer.gov/forms/index.html. 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 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>
## 7.13.4 AdEERS Expedited Reporting Requirements

Phase 2 and 3 Trials Utilizing Commercially Available Agents: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days of the Last Dose of the Commercially Available Agents in this Study

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5</th>
<th>Grades 4 &amp; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected with Hospitalization</td>
<td>Expected with Hospitalization</td>
<td>Unexpected</td>
<td>Expected</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>
<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>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Possible</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>24-Hour; 5 Calendar Days</td>
</tr>
<tr>
<td>Probable</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</td>
</tr>
<tr>
<td>Definite</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>Not Required</td>
<td>10 Calendar Days</td>
<td>10 Calendar Days</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 agents under a non-CTEP IND require reporting as follows:

- AdEERS 24-hour notification 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.

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

---

### Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing Agents under a Non-CTEP IND:

Docetaxel is commercially available in the U.S. However, when used in combination as directed by this protocol, the agents are classified as an “unapproved use of an agent” and, by definition, are considered investigational. While this combination is not currently approved by the FDA, the use in this protocol is exempt from the requirements of an IND as described under Title 21 CFR 312.2(b).

### 8.0 SURGERY

**Note:** Surgery is not part of protocol treatment for either arm but may be considered in the following circumstances in patients who have completed protocol treatment:
8.1 Patients who have pathologically proven complete response (CR) with a non-healing major defect should be considered for debridement and repair by flap or free tissue transfer. All resected tissue must be submitted for institutional pathology review.

8.2 Patients who initially respond to therapy but who recur with a resectable lesion inside or outside the re-treatment field may undergo resection (overall medical condition permitting). When such a resection is performed, reconstruction should be with regional flap or free tissue transfer.

8.3 The surgical report and the resection pathology report must be submitted to RTOG Headquarters (see Section 12.1).

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy (9/19/06)

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. If amifostine is administered, the site should document it on the Treatment Summary (TF) form.

9.1.1 Patients with disease progression in either arm will discontinue protocol treatment immediately. For patients randomized to chemotherapy alone (Arm 2) who progress locally, the use of re-irradiation, either alone or with chemotherapy as administered in Arm 1, is permitted and encouraged, as long as the patient continues to have good performance status and agrees to re-irradiation. The use of concurrent chemotherapy is left to the discretion of the treating physician. If concurrent chemotherapy is given, treating physicians are urged to use one of the schedules/doses employed in Arm 1 of this study (see Section 7.1.2).

9.1.2 Use of growth factors (e.g., Neulasta, G-CSF, or GM-CSF) for patients on Arm 2 is permitted but not encouraged.

9.2 Prohibited Therapy

9.2.1 If Patients are receiving 5-FU, cimetidine and allopurinol are not permitted (See Section 7.5.5).

10.0 SPECIMEN SUBMISSION (9/19/06)

For patients who have consented to participate in the specimen component of the study (See Appendix I)

NOTE: Sites participating in RTOG 0421 AND RTOG 0514, the Head and Neck Cancer Tissue/Specimen Bank: Consult RTOG 0514 for details of specimen collection and reimbursement and follow the 0514 specimen submission instructions versus the instructions below. Sites can access RTOG 0514 at http://www.rtog.org/members/protocols/0514/0514.pdf

Sites participating in RTOG 0421 only should follow the instructions below.

10.1 RTOG Tissue Bank

The RTOG Tissue Bank at LDS Hospital in Utah acquires and maintains high quality specimens from RTOG trials. Tissue/serum is preserved through careful storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue/serum. The RTOG Tissue Bank provides tissue/serum specimens to investigators for translational research studies. Translational research studies may, for instance, correlate clinical outcome data with research findings such as DNA damage, repair genes, and microtubule genes. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Rationale for Blood Sample Collection

Blood specimens will be collected prior to protocol treatment for translational studies utilizing DNA, RNA, and protein in this unique but limited study population of previously irradiated patients with only locally recurrent disease. The specimens will be stored in the RTOG Tissue Bank to allow future researchers to conduct such analyses. These translational studies may provide useful biologic information pertinent to assessment of predictive biomarkers. For example, SNP genotyping of metabolizing enzymes may be useful to assess pharmacogenetic associations with particular drugs. Expression studies may be conducted to examine if specific candidate genes are predictive of favorable outcome.
10.3 Specimen Collection

A Specimen Collection/Shipping Kit with instructions and all required supplies can be obtained from the RTOG Tissue Bank (see Appendix V).

10.3.1 Collecting Serum, Plasma, and Buffy Coat Cells (9/19/06)

Sites will collect blood prior to initiation of therapy. Fifteen ml of blood will be collected from each patient in one 5 ml red top tube for serum, and either two 5 ml tubes or one 10 ml purple top tube (with EDTA) for plasma and cellular analyses.

The red top tube should be allowed to clot for 30 minutes at room temperature, and then be spun down in a standard clinical centrifuge at ~2500 RPM at 4º C for 10 minutes. The supernatant (serum) should be collected in 1 ml aliquot cryovials and then frozen at -80º C before shipment on dry ice. Use cryovial tubes in the Tissue Bank kit labeled “Serum”. All tubes must be labeled with the patient case number and protocol number (0421) or attach the RTOG label.

EDTA tubes should be spun in a standard clinical centrifuge at ~2500 RPM at 4º C for 10 minutes. 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(s) should be kept on ice until centrifuging is done.

Collect the supernatant (plasma) from the EDTA tubes, aliquot and freeze the plasma in the three (3) 1ml cryovials supplied in the Tissue Bank kit and clearly label as “Plasma”. All tubes must be labeled with the patient case number and protocol number (0421) or attach the RTOG label. The plasma samples need to be frozen at -80º C before shipment on dry ice.

After the plasma has been removed, carefully remove the buffy coat layer and place it into the three cryovials supplied in the Tissue Bank kit and clearly label as “Buffy Coat”. All tubes must be labeled with the patient case number and protocol number (0421) or attach the RTOG label. The buffy coat layers should be shipped frozen when mailed to the Tissue Bank. A visual description of the buffy coat can be viewed in Appendix V.

10.3.2 A Specimen Transmittal Form clearly stating that a blood specimen is being submitted for the RTOG Tissue Bank must be provided in order for the case to be evaluable for the Tissue Bank. The form can be accessed at http://www.rtog.org/pdf_forms.html?members/forms=specimen.pdf; no password required. The form must include the protocol number (0421) and the patient’s case number (or attach the RTOG label), date of collection, and method of storage (for example, stored at -20° C).

10.4 Specimen Shipping

10.4.1 Shipping Serum, Plasma, and Buffy Coat Cells (9/19/06)

Cryo tubes with serum, plasma, or the buffy coat cells must be wrapped in an absorbable material (i.e., paper towels) and placed in an airtight plastic freezer bag (i.e., resealable bag). Pack frozen specimens in the supplied (or other) heavy grade Styrofoam box with dry ice (4–5 pounds minimum). Seal the box with plastic tape. All pertinent paperwork as described in Sections 10.3.2 should be placed in a plastic bag, sealed tightly and taped to the outside top of the Styrofoam box. Serum, plasma or buffy coat specimens requiring specific infectious precautions should be indicated clearly, with the specific source of infectious concern listed, if known. Pack the Styrofoam shipping container in a cardboard box and mark the box “Biohazard.” Serum, plasma or buffy coat specimens for patients on this study may be sent in batches, if it is within 30 days of collection. Frozen specimens must be sent by overnight express to the RTOG Tissue Bank. NOTE: Specimens should be sent only Monday through Wednesday. Saturday deliveries will not be accepted.

Samples that are received thawed will be discarded and a notification will be sent immediately to the Principal Investigator and Clinical Research Associate of the submitting institution. A subsequent specimen obtained as close as possible to the original planned collection date should be submitted.

10.4.2 (9/19/06) Submit materials (as described in Section 10.3) to:
10.5 Reimbursement (9/19/06)
RTOG will reimburse submitting institutions $300 per case for buffy coat samples, $200 per case for serum/plasma. 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.

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

10.6.1 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.

10.6.2 Specimens for banking will be stored for an indefinite period of time. 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 (9/19/06)

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Pre-Study Entry</th>
<th>Weekly During XRT</th>
<th>Prior to Each Cycle (Arm 2)</th>
<th>Every Two Cycles (Arm 2)</th>
<th>@ 3 mos</th>
<th>@ 6 mos</th>
<th>@ 9 mos</th>
<th>@ 12 mos</th>
<th>@F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy of tumor/met. node</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>History/Physical</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
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<td>Physical assessment of carotids</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Performance Status/Weight</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nutritional Evaluation</td>
<td>X</td>
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<tr>
<td>CBC/Diff/Platelet</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>Bilirubin, AST/ALT, alkaline phosphatase</td>
<td>X</td>
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<tr>
<td>Corrected serum calcium</td>
<td>X</td>
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<tr>
<td>Creatinine clearance</td>
<td>X\textsuperscript{ij}</td>
<td>X\textsuperscript{k}</td>
<td>X\textsuperscript{k}</td>
<td></td>
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<tr>
<td>Chemistries: Na, K, Cl, HCO\textsubscript{3}, BUN, Glucose, Creatinine\textsuperscript{k}</td>
<td>X</td>
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<td></td>
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<tr>
<td>Pregnancy Test</td>
<td>X\textsuperscript{d}</td>
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<tr>
<td>CT/MRI Tumor</td>
<td>X\textsuperscript{c}</td>
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<tr>
<td>Procedure</td>
<td>Frequency</td>
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<tr>
<td>Chest CT</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Abdominal CT</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Dental Evaluation</td>
<td>X&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Medical &amp; Radiation Oncology Exams</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Abdominal CT</td>
<td>X&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Dental Evaluation</td>
<td>X&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Medical &amp; Radiation Oncology Exams</td>
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<tr>
<td>Tumor Measurements</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Toxicity Assessment</td>
<td>X</td>
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<tr>
<td>QOL assessments: PSS-HN; FHNSI-10; EQ-5D</td>
<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Doppler, CTA, or MRA</td>
<td>X&lt;sup&gt;i&lt;/sup&gt;</td>
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<tr>
<td>Panendoscopy</td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
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<tr>
<td>Speech/swallow assessment</td>
<td>X&lt;sup&gt;j&lt;/sup&gt;</td>
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<tr>
<td>Blood for banking</td>
<td>X&lt;sup&gt;l&lt;/sup&gt;</td>
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</tbody>
</table>

**a.** Within 4 weeks prior to registration;

**b.** Within 2 weeks prior to registration;

**c.** Within 4 weeks of registration; Use of PET/CT is not acceptable for baseline unless CT portion of PET is contrast enhanced and is interpretable.

**d.** Tumor assessment for patients on Arm 1;

**e.** As indicated to confirm clinical suspicion of distant metastases;

**f.** Must be done in presence of > 1.5 x upper limit of normal of alkaline phosphatase, SGOT, bilirubin, or other clinical indicator;

**g.** Prior to the start of radiation therapy for patients on Arm 1;

**h.** At 24 and 36 months

**i.** Use Cockcroft-Gault formula, Section 3.1.15.1;

**j.** Highly recommended but not mandatory;

**k.** Use creatinine to calculate creatinine clearance;

**l.** Follow-up exams by the Medical and/or Radiation Oncologists are to evaluate tumor response and for toxicity assessment.

**m.** After the 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> cycles, etc. Use same modality for follow up as was used for baseline.

### 11.2 Evaluation

Local reaction of skin and mucous membranes should be scored at least weekly during and after therapy until clearance. Patients will be evaluated at two-week intervals whenever possible, after completion of treatment, and until their acute reactions have resolved. Patients then will be seen every three months for 2 years, every six months for the following 3 years, then annually.

### 11.3 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination including endoscopy. The same imaging modality must be used throughout the study to measure disease.

### 11.3.1 CT and MRI

CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions.

### 11.4 Measurement of Response

**11.4.1 Response Evaluation Criteria in Solid Tumors (RECIST)**


Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

- **Measurable disease** - the presence of at least one measurable lesion; If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques.

**Response Criteria: Evaluation of target lesions**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Disappearance of all target lesions no less than 4 weeks after the criteria for response are first met.</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD no less than 4 weeks after the criteria for response are first met.</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.</td>
</tr>
<tr>
<td>Stable Disease (SD)</td>
<td>Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started. Measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 8 weeks).</td>
</tr>
</tbody>
</table>

*Measurement of nontarget lesions is not applicable to this study.

11.4.2 **Symptomatic Deterioration**

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration.

11.5 **Evaluation of Patient’s Best Overall Response**

11.5.1 The best overall response is the best response recorded from registration until disease progression/recurrence, taking as reference for progressive disease the smallest measurements recorded since registration.

11.5.1.1 To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

11.5.1.2 To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than eight weeks).

11.5.2 **First Documentation of Response**

The time between initiation of therapy and first documentation of PR or CR.

11.5.3 **Confirmation of Response**

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed **no less than four weeks** after the criteria for response are first met.

11.5.4 **Duration of Response**

Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since treatment started.

11.5.4.1 **Duration of Overall Complete Response**

The period measured from the time measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

11.5.4.2 **Duration of Stable Disease**

A measurement from registration until the criteria for disease progression is met, taking as reference the smallest measurements recorded since registration. To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than eight weeks).
11.6 **Discontinuation of Protocol Treatment (9/19/06)**
Protocol treatment may be discontinued for the following:
- Progression of disease;
- Symptomatic deterioration;
- Unacceptable toxicity to the patient (at the discretion of the treating physician) — Reasons for removal must be clearly documented on the appropriate case report form/flow sheet, and RTOG Headquarters data management must be notified.

11.7 **Survival**
Survival will be measured from the date of entry on study.

11.8 **Progression-free survival**
This interval will be measured from the date of entry on the study to the first occurrence of the following: new metastatic lesions or objective tumor progression, new primary tumor, or death.

11.9 **Quality of Life Assessments**
11.9.1 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: This assessment currently is not available in languages other than English. The assessment should be administered only to patients fluent in comprehending and speaking English.

11.9.2 The brief Functional Assessment of Cancer Therapy – Head & Neck Symptom Index-10 (FHNSI-10) is a symptom-focused index specifically for use with patients with advanced and/or recurrent/refractory head and neck cancer. The patient can complete the index in approximately 5 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: This assessment currently is not available in languages other than English. The assessment should be administered only to patients fluent in reading and writing English.

11.9.3 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>Performance Status Scale for H &amp;N Cancer (PSS-HN)</td>
<td></td>
</tr>
<tr>
<td>[QP]</td>
<td></td>
</tr>
<tr>
<td>H &amp; N Symptom Index-10 (FHNSI-10) [SS]</td>
<td></td>
</tr>
<tr>
<td>Health Utility Measurement (EQ-5D) [HP]</td>
<td></td>
</tr>
</tbody>
</table>
**For ALL RT Approaches:**
Tumor and Nodal Diagrams (I6, I7)
Prior Radiotherapy Materials (TM) [Prior treatment record, including calculation summary and documentation of spinal cord dose.]

**Preliminary Dosimetry Information for non-IMRT Approaches** (For IMRT, See Section 12.2)
- RT Prescription (Protocol Treatment Form) [T2]
- Films (simulation, DRR’s, and portal) [T3]
- Calculations (T4)
- Planning CT and Report (C1, C3)

**Final Dosimetry Information for non-IMRT Approaches** (For IMRT, See Section 12.2)
- Within 1 week of start of RT
- Radiotherapy Form (T1)
- Daily Treatment Record (T5)
- Isodose Distribution (T6)
- Boost Films (simulation and portal) [T8]
- Dose Volume Histograms (DVH) *Required in color*

**T1** Treatment Form
**T2** RT Prescription
**T3** Films
**T4** Calculations
**T5** Daily Treatment Record
**T6** Isodose Distribution
**T7** Planning CT and Report
**T8** Boost Films
**T9** Dose Volume Histograms

**AE** Daily Treatment Record
**TF** Treatment Form
**SS** H & N Symptom Index-10 (FHNSI-10)
**HP** Health Utility Measurement
**QP** Performance Status Scale for H & N Cancer

**Follow-up Form** Every 3 months for first 2 years, q 6 months for years 3-5, then annually, and at death

**Adverse Event Form** With the first two F1 forms, then as necessary

*Radiotherapy records (and films, if available) of prior treatment to the head and neck must be submitted. All prior material must be recorded on the transmittal form. Credit will not be given until every item has been submitted (simulation and portal films should be submitted, if available; all other records are mandatory). If a prior isodose summation was not done, this must be clearly noted on the transmittal form.

**12.2 Summary of Dosimetry Data Submission for IMRT (Submit to ITC; see Section 12.2.1)**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
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</thead>
<tbody>
<tr>
<td>Preliminary Dosimetry Information (9/19/06)</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>†Digital Data Submission Form (DDSI)</td>
<td></td>
</tr>
<tr>
<td>CT data, critical normal structures, all GTV, CTV, and PTV contours</td>
<td></td>
</tr>
<tr>
<td>Simulation films and/or digital film images for all initial treatment fields and orthogonal set up pair</td>
<td></td>
</tr>
<tr>
<td>First day port films (or digital images) of all initial treatment fields and orthogonal set up pair</td>
<td></td>
</tr>
<tr>
<td>Digital beam geometry for initial and boost beam sets</td>
<td></td>
</tr>
</tbody>
</table>

**S2** Operative Report
**S5** Surgical Pathology Report

**S5** Surgical Pathology Report

**QP** Performance Status Scale for H & N Cancer

**SS** H & N Symptom Index-10 (FHNSI-10)

**HP** Health Utility Measurement

**F1** Follow-up Form

**F2** Follow-up Form

**AE** Adverse Event Form** (AE) With the first two F1 forms, then as necessary
Doses for initial and boost sets of concurrent treated beams
Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan
Hard copy isodose distributions for total dose plan as described in QA guidelines

**Final Dosimetry Information**

Within 1 week of RT end

Radiotherapy Form (T1) [copy to HQ and ITC]
Daily Treatment Record
Simulation films and/or digital film images (or digital images) of all boost treatment fields and orthogonal set up pair
First day port films of all boost treatment fields and orthogonal set up pair
Modified digital patient data as required through consultation with Image Guided Therapy QA Center

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

Hard copies 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 Primary Endpoint

Survival (Failure: Death due to any cause)

#### 13.2 Secondary Endpoints

- Progression-free survival (Failure: Disease progression per RECIST criteria — at least a 20% increase in the sum of the LD of target lesions, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions — or new primary tumor or death)
- Rates of Grade 5 toxicity
- Quality of life at 3 months (assessing the immediate [acute] side effects of treatment)
- Quality of life at 6, 12, 24, and 36 months (assessing the late side effects of treatment)
- Quality adjusted survival = (sum of quality $q_i$ of health states $K_i$) x the duration $s_i$ spent in each health state)

The primary hypothesis of this trial is that the addition of re-irradiation to paclitaxel and cisplatin can increase overall survival when compared to combination chemotherapy alone in patients with local-regionally recurrent (or with new head and neck primary) squamous cell cancer of the head and neck. Secondary endpoints will include comparisons of progression-free survival, toxicity, and quality of life. This experimental regimen has been previously studied in the phase II protocol RTOG 99-11. Survival results for combination chemotherapy alone in the proposed study population have not been reported in the literature. However, a retrospective analysis of 2 large ECOG trials of chemotherapy (1393/1395) in patients with recurrent head and neck cancer was undertaken. The analysis was limited to patients who had received prior irradiation and had
a local-regional recurrence without distant metastases. The assumption was made that they
could have been re-irradiated and their survival experience will approximate the regimen of
chemotherapy alone in this study. The table below summarizes the yearly survival rates of the
two patient groups (chemotherapy alone and chemotherapy plus re-irradiation) along with RTOG
96-10, which was the RTOG's initial phase II trial of re-irradiation.

Table 1. Historical Survival Rates

<table>
<thead>
<tr>
<th></th>
<th>ECOG 1393/1395</th>
<th>RTOG 99-11</th>
<th>RTOG 96-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead/Total</td>
<td>120/124</td>
<td>69/99</td>
<td>73/83</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>8.0</td>
<td>12.4</td>
<td>8.8</td>
</tr>
<tr>
<td>1-year rate</td>
<td>29.0%</td>
<td>51.7%</td>
<td>41.7%</td>
</tr>
<tr>
<td>2-year rate</td>
<td>10.5%</td>
<td>24.6%</td>
<td>16.9%</td>
</tr>
<tr>
<td>3-year rate</td>
<td>4.4%</td>
<td>NA *</td>
<td>7.7% #</td>
</tr>
<tr>
<td>4-year rate</td>
<td>3.5%</td>
<td>NA *</td>
<td>5.8% #</td>
</tr>
<tr>
<td>5-year rate</td>
<td>2.7%</td>
<td>NA *</td>
<td>5.8% #</td>
</tr>
</tbody>
</table>

* NA = not available
* only 4 patients at risk
# only 3 patients at risk

13.3 Sample Size

13.3.1 Sample Size Derivation

For RTOG 99-11, there was approximately a 50% death rate in each of the first two years; therefore, for planning purposes, we will assume a yearly death rate of 50% for the experimental arm. For the combined ECOG trials, the death rates for the first three years were 71%, 65%, and 60%, respectively. For planning purposes, we will assume a yearly death rate of 65% for the control arm. These correspond to yearly hazards of 1.040 and 0.693 for the control and experimental arms, respectively. This would translate into a 33.3% reduction in hazard or an increase in median survival from 8 to 12 months. Because the re-irradiation containing regimen will be associated with more severe toxicity, it would take a large survival benefit such as the proposed reduction to warrant its future use.

The statistical software EaST 46 was used for calculating the sample size with three planned interim tests. A spending function interpolated by EaST was utilized with a .001 nominal significance level at each interim test. Two hundred fourteen deaths are required to detect a 33.3% reduction in the death rate with 80% statistical power using a one-sided test at the 0.025 significance level; 228 total analyzable patients will be required. Adjusting by approximately 5% to allow for ineligibility and lack of data, the total sample size required will be 240 patients.

13.4 Randomization

The treatment allocation scheme described by Zelen47 will be used as it balances patient factors other than treating institution. There will be no stratification factors used in this study. Analyses of the previous two RTOG re-irradiation trials failed to identify any prognostic factor for survival.

13.5 Patient Accrual

The patient accrual to the past two RTOG re-irradiation trials was 36 cases per year. Because institutions from other cooperative groups will be able to participate in this trial, it is projected the annual accrual rate will be increased to 48 per year. At this rate, it will take approximately 66 months to reach the target accrual assuming that there will be very little accrual during first 6 months while institutions are obtaining IRB approval. The study statistician will recommend to the Data Safety Monitoring Committee (DSMC) that the trial be discontinued if accrual is less than 3 per month after 18 months. This stopping rule will be evaluated for a six-month period following study activation, between months 12 to 18.
13.6 **Analysis Plan**

13.6.1 **Statistical Methods**

Overall and progression-free survival will be estimated by the Kaplan-Meier method. The log-rank test will be used to test the experimental treatment against the control. Multivariate analysis will be performed using the Cox proportional hazards model. Rates of Grade 5 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. For the FHNSI-10 Index, the mean total score will be compared between the two treatments as well as the mean score for the FHNSI-10 Index with additional symptoms derived by the investigators for this patient population. The EQ 5D will be used to generate health utilities, which will then be used in deriving quality adjusted survivals. The utility scores lie between 0 “Worst health state” and 1 “Best health state”. It will provide two utility scores, one of which is from 5-item index score and other from visual analogue scale (VAS), and both will be used in generating separate quality adjusted survivals. The log rank test will compare those survivals between the treatments.

13.6.2 **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:

- The patient accrual rate with a projected completion date for the accrual phase
- Distribution of important pretreatment patient characteristics
- Frequency and severity of toxicity
- Compliance rate of treatment delivery with respect to the protocol prescription

These interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints such as overall and progression-free survival.

This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13.6.3 **Interim Analyses for Early Stopping**

Three interim treatment comparisons will be performed at the RTOG meeting immediately after the 64th, the 107th, and the 149th deaths (total from both arms) have been reported. Toxicity, treatment delivery, and overall survival will be reported to the RTOG Data Monitoring Committee (DMC). The survival 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 of tests are significant or the CP < 0.15, the responsible statistician will recommend to the Data Monitoring Committee that further patient accrual should be discontinued if appropriate and the results reported early.

13.6.4 **Analysis and Reporting of Initial Treatment Results**

The analysis reporting the treatment results will be carried out after 213 deaths have been observed unless the criteria for early stopping are met. The usual components of this analysis are:

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

The survival difference between the control arm and the experimental arm will be tested using the log-rank statistic at a significance level of .0242 in order to preserve a significant level of 0.025 for study.

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.
Protocol eligible patients will be included in 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 at random. The distribution of pretreatment 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 Inclusion of 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 the prior re-irradiation trials, RTOG 96-10 and RTOG 99-11, we project that 75% of patients enrolled to this study will be men and 25% women. These two prior trials only collected racial data, with “Hispanic” specified as a race along with “Caucasian”, “Black”, etc. Since only one patient on each phase II trial was coded as “Hispanic”, we felt that we could project 90% white and 10% not white from these study data. However, there were no prior ethnicity data available. Therefore, we requested feedback from the RTOG Head and Neck Committee about the expected level of Hispanic/Latino participation in this phase III trial. Based upon the Committee's feedback, we project that 12 (5%) of the 0421 protocol entries will be Hispanic/Latino. Assuming no differences between the genders or ethnicities, or among the races, the statistical power for detecting the hypothesized treatment difference is 0.67 for males and 0.70 for whites. The statistical power for females and for non-whites is too low for any meaningful treatment comparison.

### Gender and Minority Accrual Estimates

<table>
<thead>
<tr>
<th>Ethnic Category</th>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
<td>Males</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>3</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>57</td>
<td>171</td>
<td>228</td>
<td></td>
</tr>
<tr>
<td>Ethnic Category: Total of all subjects</td>
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<td>180</td>
<td>240</td>
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</tr>
<tr>
<td>Racial Category</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
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<td>Asian</td>
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<tr>
<td>Black or African American</td>
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<tr>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>54</td>
<td>162</td>
<td>216</td>
<td></td>
</tr>
<tr>
<td>Racial Category: Total of all subjects</td>
<td>60</td>
<td>180</td>
<td>240</td>
<td></td>
</tr>
</tbody>
</table>
References


12. Li Y. ECOG Headquarters. Personal communication.


References (Continued)


References (Continued)


APPENDIX I

RTOG 0421

Informed Consent Template for Cancer Treatment Trials (English Language)

A PHASE III TRIAL FOR LocALLY RECURRENT, PREVIOUSLY IRRADIATED HEAD AND NECK CANCER: CONCURRENT RE-IRRADIATION AND CHEMOTHERAPY VERSUS CHEMOTHERAPY ALONE

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 head and neck cancer for which you have previously received radiation therapy and for which you cannot undergo surgery.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of re-irradiation and chemotherapy with chemotherapy alone on you and your head and neck cancer to find out which is better. In this study, you will receive either the re-irradiation and chemotherapy or chemotherapy alone.

How many people will take part in the study?

About 240 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.

- A physical exam
- An evaluation of your weight and of how many calories you are receiving each day
- Blood tests
- CT (Computed Tomography) scan of your chest; a CT scan is a study using x-rays to look at one part of your body
- CT scan or MRI (Magnetic Resonance Imaging) of your tumor; an MRI is imaging using a strong magnetic field to look at one part of your body
- CT scan of your abdominal area, if advised by your study doctor
- Biopsy of your tumor
- For women able to have children, a pregnancy test
- For patients receiving re-irradiation, a dental evaluation before receiving radiation
- A x-ray exam of the blood flow in the arteries in your neck, if advised by your study doctor
- If advised by your study doctor, an exam of the lining of your digestive tract; this involves putting a tube into your mouth and down your swallowing tube into the stomach and intestines to see the lining.
- An evaluation of your speech and/or swallowing, if advised by your study doctor

During the study, 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. They are part of regular cancer care.
• A physical exam
• Blood tests

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

For patients receiving chemotherapy alone,

Before each cycle of chemotherapy:
• A physical exam by your study doctor and by a Medical Oncologist
• Blood tests

Every 2 cycles of chemotherapy: (9/19/06)
• A CT scan or MRI of your tumor
• You will be seen by your Medical and/or Radiation Oncologist.

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 3 months from start of treatment:
• For patients receiving re-irradiation, a CT scan or MRI of your tumor

Every 3 months for 2 years, every 6 months for 3 years, then annually:
• A physical exam by your study doctor and by a Medical Oncologist
• Blood tests
• A CT scan or MRI of your tumor, if advised by your study doctor
• A Chest CT scan, if advised by your study doctor
• A CT scan of your abdomen, if advised by your study doctor

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 study doctor can choose the group you will be in. You will have an equal chance of being placed in either group.

If you are in Group 1 (often called “Arm 1”), you will receive radiation therapy and chemotherapy every other week for 4 cycles (during weeks 1, 3, 5, and 7).

You will receive radiation therapy twice a day, Monday through Friday, every other week. Each radiation treatment will take about 5-10 minutes, and there will be at least 4 hours between the two daily treatments.

Between the radiation treatments each day, you will receive two chemotherapy drugs, paclitaxel and cisplatin, through your vein. Receiving the paclitaxel takes about one hour, and receiving the cisplatin takes about 30 minutes.

During weeks 2, 4, 6, and 8, you will not receive radiation or chemotherapy. Since chemotherapy drugs can decrease your white blood cells that fight infection, you will be given G-CSF, a drug to help your body make white blood cells. You will receive an injection of G-CSF under your skin once a day for 8 days, Saturday through Saturday, during each of the four weeks.

If you are in Group 2 (often called "Arm 2"), you will receive chemotherapy alone. Your study doctor and you will discuss the 3 types of chemotherapy available in this study and decide which chemotherapy is best for you. Each of the 3 treatments available includes a standard chemotherapy drug, cisplatin, which is given through your vein over about an hour. You also will receive fluids through your vein before and after each chemotherapy treatment.

Cisplatin will be given with one of the following drugs: 5-fluoruracil (also called 5-FU), paclitaxel, or docetaxel. If you receive 5-FU, it will be given through your vein over 4 days (96 hours) after the cisplatin,
either as an inpatient or an outpatient. If you receive paclitaxel, it will be given through your vein over 3 hours, just prior to the cisplatin. If you receive docetaxel, it will be given through your vein over 1 hour, just prior to the cisplatin.

You will receive chemotherapy once every 3-4 weeks (1 cycle length), and your study doctor will examine you after every 2 cycles of chemotherapy. If your cancer is responding to the chemotherapy or remains stable (does not grow), then you will continue receiving chemotherapy for as long as it continues to help you (for at least 9 weeks and possibly for 18 weeks or longer).

If your cancer worsens, you and your study doctor will discuss other treatments, which can include re-irradiation with chemotherapy as given in Group 1 (as long as there are no new cancers in areas other than your current cancer).

Both groups: When you are finished having treatment, you will be seen in follow-up visits every 3 months for 2 years, every 6 months for 3 years, then yearly.

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?

Group 1 patients will receive treatment for about 8 weeks. Group 2 patients will receive treatment for at least 9 weeks and possibly for 18 weeks or more, if there is no evidence of cancer growth.

After you are finished treatment, the study doctor will ask you to visit the office for follow-up exams for at least every 3 months for 2 years, every 6 months for 3 years, then yearly.

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 any risks from the re-irradiation and/or chemotherapy can be evaluated by your study doctor. Another reason to tell your 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 most likely will 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.

The combination of chemotherapy and radiation that some patients will receive in this study may result in more serious side effects or unexpected side effects than result in receiving either of these treatments alone. Many side effects go away soon after you stop receiving radiation and/or chemotherapy. 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.

**For patients in Group 1, Risks Associated With Re-irradiation**

** Likely **
- Sores in mouth or throat
- Temporary loss of taste
- Temporary skin redness or peeling in the treated area
- Dryness of the mouth
- Hoarseness
- Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding
- Dental cavities

**Less Likely, But Serious **
- Severe irritation of the esophagus (swallowing tube) or treatment area that causes swallowing difficulty and may require a feeding tube; this may last up to a year or may be permanent.
- Damage to the nerves that control the diaphragm, which could cause paralysis of the diaphragm and could be life threatening
- Hardening or thickening of the skin in the treatment area that causes swallowing difficulty and may require a feeding tube, which may be permanent
- Wounds that drain and/or won’t heal and/or abnormal holes that connect two or more parts of the body, such as a hole between the windpipe and the swallowing tube; these can lead to infection, pain, or other problems that can be life threatening.
- Bleeding from the blood vessels that carry blood to the brain, which could cause a stroke or could be life threatening
- Serious damage to the jawbone or other bones in the head or neck that can lead to infection, bleeding, and/or pain; this sometimes requires surgery.
- Nerve damage within the head and neck that can cause weakness, numbness, or pain in the muscles of the face, neck, throat, arm(s), and/or hand(s); sometimes this damage can be permanent.

**Risks Associated With Chemotherapy**

**Cisplatin**

**Likely**
- Tiredness and/or general weakness
- Nausea and/or vomiting
• Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding
• Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
• Decrease in platelets, the cells in the blood that help blood clot normally
• Loss of appetite and/or weight loss
• Ringing in the ears and/or hearing loss

**Less Likely**
• Decrease in the kidneys’ ability to handle the body’s waste, which may be permanent
• Changes in electrolytes, which may result in tiredness, cramps, and/or numbness and tingling
• Involuntary movements, restlessness, muscle cramps, and/or loss of coordination
• Numbness and tingling in the fingers, hands, toes, and feet

**Rare**
• Hair loss
• Loss of taste
• Changes in vision
• Seizures
• Loss of muscle or nerve function, which may result in weakness
• Allergic reactions, which can involve flushing, difficulty breathing, irregular heartbeat, low blood pressure, and can even be life threatening
• Another cancer called acute leukemia

**5-FU (5-Fluorouracil)**

**Likely**
• Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding
• Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
• Loss of appetite
• Nausea and/or vomiting
• Diarrhea with cramping or bleeding
• Skin rash
• Fatigue
• Headaches
• Hair loss, which is temporary
• Mouth sores
• Sore throat

**Less Likely**
• Confusion
• Eye irritation, watering of eyes, and/or runny nose
• Redness, tenderness, peeling, and/or tingling of the palms and soles of feet
• Increased sensitivity to sunlight
• Darkening of the skin, nails, or veins
• Loss of coordination or balance

**Less Likely, But Serious**
• Damage to the heart or spasm of the heart’s blood vessels that can cause chest pain
• Inflammation of the liver, which may result in yellowing of skin and eyes, tiredness, and/or pain on upper right of the stomach area
• Infection at the catheter entry site

**Paclitaxel**

**Likely**
• Hair loss
• Tingling, numbness, burning pain in hands and feet
• Lower blood counts during treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
• Inflammation of the lining of the mouth
• Skin redness or rash

Less Likely
• Nausea and/or vomiting
• Diarrhea
• Changes in finger or toe nails
• Inflammation of the lining of the throat and/or intestines
• Tiredness
• Blurred vision and/or the feeling of seeing flashing lights
• Flushing
• Dizziness and/or lightheadedness
• Tenderness, hardness, or itching of the skin; rarely, blistering of the skin
• Pain in muscles and joints
• Changes in mood: being anxious or agitated

Less Likely, But Serious
• Reaction to paclitaxel, resulting in injury to the skin, lung, and/or lining of the digestive tract in the chest area that has received radiation
• Cardiovascular changes, such as low or high blood pressure, speeding up or slowing of heartbeat, a blockage of blood flow to the heart, and/or heart attack
• Seizures
• Allergic reactions, which could involve sweating, itching, hives, difficulty breathing, lightheadedness, and/or rapid heartbeat
• Severe inflammation of the small and large intestines
• Severe rash called Stevens-Johnson Syndrome, which can cause fever and red sores in your mouth and eyes
• Changes in liver enzymes in the blood, which may mean damage to the liver that could lead to being hospitalized, or rarely, to death

Docetaxel (9/19/06)
Likely
• Decrease in white blood cell count, which may increase the risk of infection, decreased healing, and/or bleeding
• Decrease in red blood cell count, which may result in anemia, tiredness, and/or shortness of breath
• Tiredness and/or general weakness
• Unusual sleepiness
• Nausea and/or vomiting
• Mouth sores
• Diarrhea
• Loss of appetite, change in taste, and/or weight loss
• Loss of hair
• Headache
• Bloating and fluid retention in the hands, feet, and/or ankles
• Shortness of breath
• Muscle or joint pain
• Changes in the nails
• Inflammation of the eyes
• Numbness in fingers and in feeling

Less Likely
• Rash, redness and/or swelling of the skin
- Allergic reactions, which may involve rash, itching, fever, swelling, chills, or low back pain and which also can involve flushing, shortness of breath, and changes in blood pressure
- Inflammation of veins
- Irregular heartbeat
- Decrease in platelets, the cells in the blood that help blood clot normally
- Seizures
- Liver inflammation, which may result in yellowing of skin and eyes, tiredness, and/or pain on upper right of the stomach area
- Increased fluid around the lung and heart
- Swelling of feet

**Rare but serious**
- Lung inflammation, which may involve shortness of breath, cough, and/or fever
- Death

Some prescribed or over the counter medicines, herbal products, and/or foods may affect how your body handles docetaxel. If you participate in this study, you should talk to the study doctor about this. If the study doctor feels it is in your best interests, he/she may recommend that you stop taking certain medicines or herbals or stop eating certain foods before and during treatment with docetaxel.

Chemotherapy drugs can decrease your white blood cells that fight infection. To help prevent infections, you will be given G-CSF, a drug to help your body make white blood cells.

**Risks Associated with G-CSF or GM-CSF (9/19/06)**

**Likely**
- Bone pain

**Less Likely**
- Hair loss
- Headache
- Dizziness
- Confusion
- Difficulty sleeping
- Skin rash
- Fever and/or chills
- Nausea and/or vomiting
- Loss of appetite, change in taste, and/or weight loss
- Indigestion and/or stomach pain
- Tiredness and/or general weakness
- Diarrhea or constipation
- Mouth sores and/or sore throat
- Swelling of feet and/or legs due to increased fluid
- Muscle and/or joint pain
- Speeding up or slowing of heartbeat
- Chest pain due to inflammation of the lining of the heart
- Low blood pressure
- Larger than normal spleen (the spleen makes blood cells); you may have pain in the upper abdomen
- Temporary mild swelling at injection sites

**Rare**
- Low oxygen levels in the blood
- Changes in liver enzymes in the blood, which may mean liver damage
- Shortness of breath due to water accumulation in the lungs
- Low blood levels of albumin, which may cause increased fluid in the limbs
- Decrease in the kidney’s ability to handle the body’s waste
• Increased risk for blood clots, which could lead to stroke or blood clot in the lungs that could be life threatening

**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. Pregnancy testing for women who can have children is required. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. 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. Some of the drugs used in the study may make you unable to have children in the future.

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 a combination of re-irradiation and chemotherapy will result in better control of your head and neck cancer compared to chemotherapy alone, there is no proof of this yet. We do know that the information from this study will help doctors learn more about re-irradiation and chemotherapy as treatments 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 study 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
• 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

**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.
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 study 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? (9/19/06)

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

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.

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

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 at your first visit and at 3, 6, 12, 24, and 36 months from start of treatment. It takes about 5-10 minutes to fill out each questionnaire. 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. Answering those questions will take about 5-10 minutes.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this study, the only thing you will be asked to do is fill out the three questionnaires. You may change your mind about completing the questionnaires 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 two Quality of Life Questionnaires and to answer questions from a third evaluation.

YES  NO

**About Using Blood for Research**

We would like to send a small amount of your blood to a central office for future research. About 3 teaspoons of your blood will be drawn before treatment. These samples of your blood will be sent to the central office and may be used to learn more about cancer and other diseases.

Your blood may be helpful for research. The research that may be done with your blood 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 blood will not be given to you or your study doctor. These reports will not be put in your health record. The research will not have an effect on your care. 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

**Things to Think About**

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

If you decide now that your 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 blood. Then any blood that remains will no longer be used for research.
In the future, people who do research may need to know more about your health. While (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 blood is used for genetic research (about diseases that are passed on in families). Even if your blood is used for this kind of research, the results will not be put in your health records.

Your blood will be used only for research and will not be sold. The research done with your blood may help to develop new products in the future.

Benefits

The benefits of research using blood 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 study 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 blood may be kept for use in research to learn about, prevent, or treat cancer.
   
   Yes  No

2. My 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>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>90</td>
<td>Normal activity with effort; some sign or symptoms of disease</td>
<td>80</td>
<td>Cares for self; unable to carry on normal activity or do active work</td>
</tr>
<tr>
<td>80</td>
<td>Requires occasional assistance, but is able to care for most personal needs</td>
<td>70</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>70</td>
<td>Requires considerable assistance and frequent medical care</td>
<td>60</td>
<td>Requires special care and assistance</td>
</tr>
<tr>
<td>60</td>
<td>Severe; unable to carry on normal activity or do active work</td>
<td>50</td>
<td>Severe; hospitalization is indicated, although death not imminent</td>
</tr>
<tr>
<td>50</td>
<td>Moribund; fatal processes progressing rapidly</td>
<td>40</td>
<td>Very sick; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>40</td>
<td>Moribund; fatal processes progressing rapidly</td>
<td>30</td>
<td>Semi-dead; hospitalization necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>30</td>
<td>Semi-dead; hospitalization necessary; active support treatment is necessary</td>
<td>20</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 out 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 any self-care. Totally confined to bed or chair (Karnofsky 10-20).</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

NEW YORK HEART ASSOCIATION CLASS DEFINITIONS

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Cardiac Symptoms</th>
<th>Limitations</th>
<th>Need for Additional Rest*</th>
<th>Physical Ability to Work**</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Full Time</td>
</tr>
<tr>
<td>II</td>
<td>Only moderate</td>
<td>Slight</td>
<td>Usually only slight or occasional</td>
<td>Usually full time</td>
</tr>
<tr>
<td>III</td>
<td>Defined, with less than ordinary activity</td>
<td>Marked</td>
<td>Usually moderate</td>
<td>Usually part time</td>
</tr>
<tr>
<td>IV</td>
<td>May be present even at rest, &amp; any activity increases discomfort</td>
<td>Extreme</td>
<td>Marked</td>
<td>Unable to work</td>
</tr>
</tbody>
</table>

*To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.
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)
AJCC STAGING SYSTEM, 6th Edition
HEAD & NECK

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>
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<th>Stage</th>
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<td>T1-3, N1, M0</td>
<td></td>
<td>T2b, N0-1, M0</td>
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<td>Stage IVA</td>
<td>T4a, N0-2, M0</td>
<td></td>
<td>Stage III</td>
</tr>
<tr>
<td></td>
<td>Any T, N2, M0</td>
<td></td>
<td>T3, N0-2, M0</td>
</tr>
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<td>Stage IVB</td>
<td>T4b, Any N, MO</td>
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<td>Stage IVA</td>
</tr>
<tr>
<td></td>
<td>Any T, N3, M0</td>
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<td>Stage IVB</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T, Any N, M1</td>
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<td>Stage IVC</td>
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### STAGE GROUPING Nasopharynx

<table>
<thead>
<tr>
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<tr>
<td>Stage I</td>
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</tr>
<tr>
<td>Stage II</td>
<td>T2a, N0, M0</td>
</tr>
<tr>
<td>Stage II</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>
</tbody>
</table>
APPENDIX IV

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients
Goals for a dental care program include:

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

Pre-irradiation Care and Procedures
The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

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

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

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

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

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

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

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

Preventive Program
The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by
the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by:
1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of
fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and
tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth
guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp.,
both of which are available through local dental supply. This material is moulded 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
caries 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 V (9/19/06)

SPECIMEN COLLECTION/SHIPPING KIT PROCEDURE

Participating institutions can request initial specimen collection/shipping kits from LDS Hospital by calling or e-mailing the RTOG Tissue Bank. When a site ships a kit to the RTOG Tissue Bank, a replacement kit will be sent to the site upon request. EVERY SPECIMEN MUST BE LABELED WITH THE PROTOCOL NUMBER (0421) AND PATIENT CASE NUMBER.

LDS Hospital
RTOG/E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
(801) 408-5626; (801) 408-2035
FAX (801) 408-5020
holly.goold@intermountainmail.org; justin.bryner@intermountainmail.org

BLOOD COLLECTION KIT INSTRUCTIONS

Instructions for use of serum, plasma, or buffy coat collection kit:

This kit includes:
- Ten (10) 1ml cryovials
- Biohazard bags
- Absorbent shipping material
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Pre-paid shipping label(s)

Serum:
- Using four (4) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “serum”.

Process:
1. Allow one 5ml red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
3. Aliquot a minimum of 0.5 ml serum into each of the four 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as “serum”.
4. Place cryovials into biohazard bag.
5. Store serum at –80°C Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Plasma:
- Using three (3) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

Process:
1. Centrifuge specimen within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully pipette and aliquot a minimum of 0.5ml plasma into each of the 1ml cryovials labeled with the RTOG study and case numbers, collection date and time, and clearly mark specimens as “plasma”.
4. Place cryovials into biohazard bag.
5. Store plasma at a minimum –80°C Celsius until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.
APPENDIX V (Continued) [9/19/06]

Buffy coat:

For a visual explanation of Buffy coat, please refer to diagram below.

- Using three (3) or more 1ml cryovials, label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “buffy coat”.

Process:
1. Centrifuge EDTA (purple top) tube within one hour of collection in a standard clinical centrifuge at ~2500 RPM at 4°C Celsius for 10 minutes.
2. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
3. Carefully remove plasma close to the buffy coat and set plasma aside (can be used to send plasma samples – see above instructions).
4. Remove the buffy coat cells carefully and place into the 1ml cryovials labeled “buffy coat” (it is okay if a few packed red cells are inadvertently collected in the process). Clearly mark the tubes with date and time of collection.
5. Place cryovials into biohazard bag.
6. Store buffy coat samples frozen until ready to ship.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED.

Shipping/Mailing:
- Include all RTOG paperwork in pocket of biohazard bag.
- Ship specimens overnight Monday-Thursday. Avoid shipping on a weekend or around a holiday.
- Place frozen specimens and the absorbent shipping material in the Styrofoam cooler and fill with dry ice (if appropriate; double-check temperature sample shipping temperature). Ship ambient specimens in a separate envelope/cooler. Place Styrofoam coolers into outer cardboard box, and attach shipping label to outer cardboard box.
- **Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag.**
- For Questions regarding collection/shipping please contact the Tissue Bank by phone (801) 408-5626 or (801) 408-2035; Fax at (801) 408-5020; Email holly.goold@intermountainmail.org or justin.bryner@intermountainmail.org
APPENDIX VI  (2/14/07)

CTSU LOGISTICS

ADDRESS AND CONTACT INFORMATION FOR RTOG-0421

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the RTOG unless otherwise specified in the protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office</td>
<td>CTSU Patient Registration</td>
<td>RTOG Headquarters</td>
</tr>
<tr>
<td>1818 Market Street, Suite 1100</td>
<td>Voice Mail – 1-888-462-3009</td>
<td>1818 Market Street, Suite 1600</td>
</tr>
<tr>
<td>Philadelphia, PA 19103</td>
<td>Fax – 1-888-691-8039</td>
<td>Philadelphia, PA 19103</td>
</tr>
<tr>
<td>Phone - 1-888-823-5923</td>
<td>Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday (excluding holidays)</td>
<td>Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
<tr>
<td>Fax – 215-569-0206</td>
<td>[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></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.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at: http://members.ctsu.org

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

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

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. All forms and documents associated with this study can be downloaded from the RTOG-0421 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.
APPENDIX VI (Continued)

Requirements for RTOG-0421 site registration:

- 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.)

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 institute when that institution is eligible to enter patients on study. The status of the credentialing review will be reflected on the RSS Site Registration Status screen http://ctsumembers.westat.com/RSS_site_reg_status.asp

Pre-study requirements for patient enrollment on RTOG-0421 (9/19/06)

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- Request initial specimen collection/shipping kits from LDS Hospital per Appendix V.
- All baseline laboratory tests and prestudy evaluations performed.
- Patient completes baseline QOL forms 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. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG-0421 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 are reviewed for completeness, 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.

Protocol therapy must begin within 7-10 days of registration.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG-0421 web page located on the CTSU registered member Web site (http://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU. See the Special Materials or Substudies section below for submission of dosimetry data.

3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the RTOG.

4. Please affix the RTOG study/case label to all source documentation and redact the patient’s name.
APPENDIX VI (Continued)

SPECIAL MATERIALS OR SUBSTUDIES

Quality of Life (protocol section 1.5):
QOL assessments will be performed pre-treatment and at 3, 6, 12, 24, and 36 months from start of treatment. Two measures will be completed by the patient (FHNSI-10 and EQ-5D) and one measure will be completed by the clinician (PSS-HN). Follow instructions outlined in the protocol and send forms to RTOG; do not send forms to the CTSU.

Radiation Therapy (protocol section 6.0):
• Dosimetry data must be submitted to the Image-Guided Therapy Center (ITC), either by digital transmission using the ITC-assigned FTP account, tape submission (contact ITC for acceptable tape types and format) or hard copy. Hard copy materials accompanying digital data should also be sent directly to the ITC. See section 12.0 for a complete inventory of dosimetry items to be submitted. Send all forms to RTOG; do not send forms to the CTSU.

Modality Review (protocol section 7.10):
• A Quality Assurance Review will be conducted by the study PI after complete data are received on the first 30 cases.
• A Chemotherapy Assurance Review will be performed by the study PI to assess protocol compliance. Sites will receive a listing once a year outlining compliance for each case reviewed during that year.

Specimen Submission - optional (protocol section 10.0):
• With patient’s consent, blood specimens will be collected then banked at the RTOG Tissue Bank at LDS Hospital. See protocol section 10.0 and Appendix V for details on requesting shipping kits, specimen collection, preparation, and submission. An RTOG Specimen Transmittal Form must accompany specimens in order for the case to be considered evaluable by the RTOG Tissue Bank. 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. All forms should be submitted to RTOG; do not send forms to the CTSU.
• CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.5 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.

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 website at http://ctsumembers.westat.com. CTSU investigators are responsible for reporting serious adverse events via AdEERS in accordance with RTOG guidelines in section 7.11 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 section 7.2 for detailed instructions on drug procurement, formulation, storage, administration, and potential toxicities.

Commercial agents:
Arm 1 - cisplatin, paclitaxel, filgrastim
Arm 2 – cisplatin (or carboplatin) and at the physician’s discretion either 5-fluorouracil, paclitaxel or docetaxel
APPENDIX VI (Continued)

REGULATORY AND MONITORING

Study Audit

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

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

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

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

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

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

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

Clinical Data Update System (CDUS) Monitoring

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