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Institutional clinical trial accrual volume and survival of patients with head and neck cancer

Wuthrick, et al

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0129

A PHASE III TRIAL OF CONCURRENT RADIATION AND CHEMOTHERAPY (FOLLOWED BY SURGERY FOR RESIDUAL PRIMARY/N2-3 NODAL DISEASE) FOR ADVANCED HEAD AND NECK CARCINOMAS

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A PHASE III TRIAL OF CONCURRENT RADIATION AND CHEMOTHERAPY (FOLLOWED BY SURGERY FOR RESIDUAL PRIMARY/N2-3 NODAL DISEASE) FOR ADVANCED HEAD AND NECK CARCINOMAS

SCHEMA (5/11/04)

<p>S</p> <p>T</p> <p>R</p> <p>A</p> <p>T</p> <p>I</p> <p>F</p> <p>Y</p>	<p><u>Tumor Site</u></p> <p>1. Larynx</p> <p>2. Non-larynx</p> <p><u>Nodal Stage</u></p> <p>1. N0</p> <p>2. N1 or N2a-b</p> <p>3. N2c-N3</p> <p><u>Zubrod Performance Status</u></p> <p>1. 0</p> <p>2. 1</p>	<p>R</p> <p>A</p> <p>N</p> <p>D</p> <p>O</p> <p>M</p> <p>I</p> <p>Z</p> <p>E</p>	<p><u>Arm 1:</u> Standard Fractionation (SFX): 70 Gy / 35 fx for 7 weeks plus cisplatin: 100 mg/m² on days 1, 22, and 43</p> <p><u>Arm 2:</u> Accelerated Fractionation by Concomitant Boost^a (AFX-CB): 72 Gy/42 fx for 6 weeks plus cisplatin: 100 mg/m² on days 1 and 22</p>	<p>6-8 weeks post-RT/chemo</p> <p><u>All Patients:</u> CT Scan: To reassess primary and nodal disease</p> <p>If suspicion of relapse: Directed biopsy</p>	<p><u>Selected Patients:</u></p> <p>Surgery Residual primary: Surgical removal^b</p> <p>N1/Residual Disease: Neck dissection^c</p> <p>N2-N3 Disease: Mandatory neck dissection^c</p>
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- a. See Section 6.1.3 for details
- b. See Section 8.1 and Appendix VII for details
- c. See Section 8.3 and Appendix VII for details

Eligibility: (See Section 3.0 for details) (9/30/03)

- Histologic proof of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
- Selected Stage III-IV disease (T2N2-3M0, T3-4 any N M0); patients with T1-2N1 or T1N2-3 are excluded.
- Zubrod Status 0-1.
- Patients must be ≥ 18 years of age.
- AGC ≥ 2,000/mm³, platelets ≥ 100,000/ mm³, bilirubin ≤ 1.5 mg/dl, AST or ALT ≤ 2 x upper normal, serum creatinine ≤ 1.5 mg/dl, creatinine clearance ≥ 50 ml/min, normal serum calcium.
- No clinically significant heart disease.
- No evidence of metastases.
- No prior radiation treatment to the head and neck or any prior chemotherapy.
- Patients with prior invasive malignancy and disease-free for ≥ 3 years are eligible (*simultaneous primaries are ineligible*).
- No pregnant women.
- Signed study-specific consent form prior to study entry.

Required Sample Size: 720 (5/11/04)

RTOG Institution # _____

RTOG 0129

ELIGIBILITY CHECKLIST (2/24/04)

RTOG Case # _____

(page 1 of 3)

- _____ (Y) 1. Is there histologic confirmation of squamous cell cancer of the oral cavity, oropharynx, hypopharynx, or larynx?
- _____ (Y) 2. Is the stage III or IV (*T2N2-3M0, T3-4 any N M0*)?
- _____ (N) 3. Any evidence of distant metastasis?
- _____ (N) 4. Any evidence of simultaneous cancer, i.e., more than one cancer?
- _____ (Y/N) 5. Any symptomatic coronary artery disease (*angina*) or history of myocardial infarction within the last 6 months?
_____ (Y) If patient has symptomatic angina, was the cardiac workup negative for coronary artery disease?
- _____ (N) 6. Any history of prior chemotherapy?
- _____ (N) 7. Any prior radiation therapy to the head or neck area?
- _____ (N) 8. Has there been any surgery of the primary tumor or node, except for diagnostic biopsy or nodal sampling?
- _____ (Y/N) 9. Other than nonmelanoma skin cancer, is there any history of a prior invasive malignancy?
_____ (Y) If yes, has the patient been continually cancer-free for the past 3 years?
- _____ (Y) 10. At least 18 years of age?
- _____ (≥ 2) 11. What is the absolute granulocyte count (*per mm³*)?
- _____ (≥ 100) 12. What is the platelet count (*per mm³*)?
- _____ (≤ 1.5) 13. What is the bilirubin (*mg/dl*)?
- _____ (Y) 14. Is the ALT or AST ≤ 2 times upper normal?
- _____ (≤ 1.5) 15. What is the serum creatinine (*mg/dl*)?
- _____ (≥ 50) 16. What is the on-study creatinine clearance (*ml/min*) as determined by 24 hour collection or nomogram calculation?
- _____ (Y) 17. Is the serum calcium (or corrected serum calcium) within normal range (*see Section 3.1.5*)?
- _____ (N/NA) 18. Is the patient pregnant?
- _____ (Y) 19. Does the patient have a Zubrod Status of 0-1?

(cont'd on next page)

RTOG Institution # _____

RTOG 0129

ELIGIBILITY CHECKLIST (2/24/04)

RTOG Case # _____

(page 2 of 3)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Initials (Last, First)
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Ethnic Category (*Hispanic or Latino, Not Hispanic or Latino, Unknown*)
- _____ 10. Race
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 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
- _____ (Y/N) 17. Tissue/blood kept for cancer research?
- _____ (Y/N) 18. Tissue/blood kept for medical research?
- _____ (Y/N) 19. Allow contact for future research?
- _____ 20. Medical Oncologist
- _____ 21. Tumor site: larynx vs. non-larynx.
- _____ 22. Nodal status: N0 vs. N1, N2a, N2b vs. N2c, N3
- _____ 23. Zubrod Performance Status: 0 vs. 1.

(cont'd on next page)

RTOG Institution # _____

RTOG 0129

RTOG Case # _____

ELIGIBILITY CHECKLIST (2/24/04)

(page 3 of 3)

_____ 24. Treatment Assignment

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 _____

1.0 BACKGROUND

1.1 Treatment of Advanced Head and Neck Carcinomas

The treatment of advanced head and neck squamous cell carcinomas (*HNSCC*) has been the subject of intensive investigation during the last two decades. Up to a few years ago, surgical resection, often followed by adjuvant radiotherapy, was the standard of care in most cases¹⁻⁴ despite the resulting cosmetic and functional impairment affecting quality of life (*QOL*). Results of conventionally fractionated radiotherapy as a single modality for patients with resectable and unresectable advanced *HNSCC* are rather poor in terms of local control and survival. Therefore, new fractionation regimens and the combination of radiation and chemotherapy have been studied to improve non-surgical treatment results of advanced head and neck cancers.

1.2 Altered Fractionation

Several altered fractionation regimens have been subjected to phase III testing. Multiple studies have tested hyperfractionation and various accelerated fractionation regimens and have shown positive results.⁵ RTOG 90-03 is a large randomized trial comparing standard fractionation (*SFX*) against hyperfractionation (*HFX*), accelerated fractionation with split-course (*AFX-S*), and accelerated fractionation by concomitant boost (*AFX-CB*) in the management of patients with advanced *HNSCC*. Between September 1991 and August 1997, 1113 patients were enrolled. Analysis undertaken in September of 1999 revealed that *AFX-CB* and *HFX* yielded a significantly higher local-regional control rate (*LRC*) than *SFX* ($p=0.05$) but not *AFX-S* ($p=0.67$). *AFX-CB* was associated with a higher transient grade 3 late toxicity. However, there was no difference in the incidence of persistent grade 3 or grade 4 late toxicity among the arms at one year or longer follow-up. The results of this trial reveal that tumor clonogenic proliferation during a course of radiotherapy is a major cause of radiation failure and show the existence of differential fractionation sensitivity between *HNSCC* and late responding normal tissues. Since hyperfractionation is much more cost and labor-intensive, the RTOG investigators have recommended *AFX-CB* as the new standard radiotherapy for intermediate-stage (*e.g.*, *T2* and favorable *T3, N0-1*) *HNSCC* and further clinical testing for more advanced *HNSCC* (*see below*).

1.3 Combination of Radiotherapy and Chemotherapy

Sequential radiation-chemotherapy (*most given in neo-adjuvant setting*) has been studied extensively in prospective pilot and large randomized trials.⁶⁻¹⁰ So far, a survival advantage over standard surgery has not been demonstrated, but organ preservation has been achieved in many patients. Response rates to chemotherapy are high, and a decrease in distant metastases has been demonstrated in some trials. Despite a high response rate in trials comparing neoadjuvant chemotherapy and radiation to radiation alone, improved *LRC* has not been shown.

Concurrent radiation-chemotherapy has received more attention because of the recognition that a variety of chemotherapeutic agents can enhance the effects of radiation not only through different cytotoxic mechanisms, but also by direct radiosensitization. Single agent cisplatin,¹¹⁻¹⁴ 5-fluorouracil,¹⁵⁻¹⁸ bleomycin,¹⁹ methotrexate,² mitomycin C,^{20, 21} and hydroxyurea²² have been used in combination with radiation therapy in several trials. Improvements in response rates and survival have been noted in some trials. The addition of some single agents to radiation has improved response rates at the cost of additional toxicity.^{13, 18, 22}

Combination chemotherapy has shown increased response rates in recurrent or metastatic disease compared to single agent therapy. Thus, more recent studies have applied the concept of *multi-agent chemotherapy* combined with radiation.²³ Recognizing the pitfalls of meta-analysis, there is evidence for a survival advantage in patients receiving concurrent radiation-chemotherapy (*though at the expense of increased morbidity*).²⁴ One example of a randomized study evaluating multi-agent chemotherapy and conventional radiation was done by the Northern California Oncology Group (*NCOG*) and reported by Fu et al.²⁵ Using concomitant bleomycin, methotrexate, and radiation resulted in improved relapse-free survival rates but had an incidence of severe late toxicity of 10% (*4 patients*) in patients treated with combination therapy compared to 2% (*1 patient*) of patients treated with radiation only. None of the side effects was life threatening.

Several groups have evaluated cisplatin with or without 5-FU in combination with radiation, as both agents have been found to have radiation sensitizing effects *in vitro*. Several trials have given cisplatin and 5-FU throughout radiotherapy. Taylor et al.²⁶ gave cisplatin 60 mg/m² and 5-FU 800 mg/m² in 14-day cycles with conventional radiotherapy. They demonstrated an improved freedom from recurrence in patients treated with concurrent radiation compared to sequential chemoradiation. There was, however, an increase in mucositis requiring supportive care in the concurrent group. Other trials²⁷ have given cisplatin at doses

as high as 100 mg/m² every three weeks with tolerable toxicity. Gandia et al.²⁸ treated head and neck cancer patients with cisplatin 80 mg/m² every 3 weeks for 3 cycles and 5-FU 300 mg/m²/day by continuous infusion for 7 weeks during radiotherapy to a total dose of 70 Gy given over 7 weeks with acceptable toxicity.

Investigators at the University of Chicago have investigated the concurrent administration of hydroxyurea and 5-FU with radiation therapy. This is based on established clinical activity of both agents and preclinical evidence of a synergistic interaction of the two drugs (*the ribonucleotide reductase inhibitor, hydroxyurea, depletes cells of the deoxyuridine monophosphate [dUMP] and thereby facilitates binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase*). Both agents have been shown to be radiation enhancers in preclinical and clinical settings.

Results of randomized trials testing concurrent radiation-chemotherapy are emerging. An increasing body of evidence showed that concurrent chemoradiotherapy yields a survival advantage over radiation alone.²⁹⁻³² A recently completed intergroup study randomized patients with unresectable HNSCC to radiation alone (70 Gy), radiation (70 Gy) plus cisplatin (100 mg/m² every 3 weeks x3), or split-course radiation (30 Gy + 30-40 Gy) given with the 1st and 3rd cycles of cisplatin (75 mg/m² on day 1) plus fluorouracil (1000 mg/m² on days 1-4) every 4 weeks. The two and three year actuarial survival rates were 30%-20% for radiation alone, 43%-37% for radiation and cisplatin ($p=0.016$), and 40%-29% for split-course radiation + cisplatin-fluorouracil ($p=0.13$). The grade 3 or worse toxicity, however, occurred in 53%, 86% ($p<0.0001$) and 77% ($p<0.001$), respectively.²⁹

1.4 RTOG Trials on Combined Radiation-Chemotherapy

Available data indicate that concurrent radiation and chemotherapy improves outcome of patients with local-regionally advanced HNSCC. However, there is still a need to refine the combined regimen. Questions such as which agents may be most appropriate, what is the optimal timing of drug administration, and what is the proper radiation schedule remain to be answered. Ideally, combination schedules should be based on mechanisms of radiation-drug interaction. Unfortunately, the modes of interaction for most drugs are not well understood.

RTOG has conducted three trials addressing some relevant questions mentioned above. RTOG 91-11, a phase III trial in patients with T3 and selected T4 laryngeal carcinoma, is assessing the relative efficacy of cisplatin given at days 1, 22, 43 of standard radiotherapy against neoadjuvant chemotherapy (*the VA cisplatin-fluorouracil regimen*) plus standard radiotherapy⁹ and radiation alone in preserving the larynx. The results so far show that the concurrent regimen yielded the highest larynx preservation rate, significantly higher than radiation alone; however, the differences between concurrent and neoadjuvant arms and between neoadjuvant and radiotherapy alone arms were not statistically significant.³³

RTOG 97-03, a randomized phase II trial in patients with stage III and IV disease, is evaluating different approaches to combining radiation and chemotherapy using both different agents and different timing of radiation-drug administration. The three regimens being tested are: 1) daily cisplatin-fluorouracil given during the last two weeks of the 7-week standard radiotherapy; 2) combination of fluorouracil-hydroxyurea and once-a-day radiotherapy administered every other week for a total of 13 weeks; and 3) weekly cisplatin and paclitaxel during the 7-week standard radiotherapy. Recent analysis showed that all three arms yielded higher actuarial 2-year survival rates than those of the 4-arm fractionation trial (*RTOG 90-03*), i.e., approximately 65% vs. approximately 50%. The data of the cisplatin-paclitaxel arm (*Arm 3*) were slightly more impressive than the other two arms.³⁴

Because of the positive results of RTOG 90-03 showing that concomitant boost yielded a significantly higher LRC than standard fractionation, RTOG 99-14 was designed to test the feasibility of combining AFX-CB with cisplatin. This trial completed accrual of 84 patients and preliminary results showed that mucosal toxicity is not more than what was observed with concomitant boost alone.

1.5 Rationale for this Proposed Phase III Trial

Many concurrent chemo-radiation regimens studied had been designed empirically with little biologic rationale and some had integrated altered fractionation. Consequently, after enrolling thousands of patients into randomized trials, it is still unclear which concurrent regimen should be recommended as the standard-of-care.

Selection of the Control Arm: The combination of conventional radiation (70 Gy over 7 weeks) and cisplatin (100 mg/m² given every 3 weeks) was first piloted by the RTOG (*RTOG 81-17*). Three

subsequent randomized trials showed its superiority over radiotherapy alone. The intergroup trial on advanced nasopharyngeal cancer showed that this regimen followed by adjuvant cisplatin-fluorouracil yielded significantly higher local-regional control and survival rates. As discussed above, another intergroup trial for advanced non-nasopharyngeal HNSCC also obtained a significantly higher survival rate²⁹ and RTOG 91-11 yielded an improved larynx preservation rate. Thus, this relatively simple combined therapy regimen has the best tract record and was therefore chosen as the control arm.

Selection of the Experimental Arm: Although a number of trials showed that concurrent chemo-radiation improved treatment outcome of patients with advanced HNSCC, it is unclear which of the regimens tested is most appropriate for routine use. Since the data of many randomized trials together strongly support the hypothesis that altered (*accelerated*) fractionation radiotherapy alone is superior to standard radiotherapy alone, it is logical and important to test whether this remains true in the setting of concurrent chemoradiotherapy. In addition, as there are more data using cisplatin with standard or accelerated radiotherapy than with any other drug, and in order to keep the drugs the same in both arms of this study, we have opted to use cisplatin with accelerated radiation as the "experimental" arm. This schema was successfully piloted by the RTOG (*RTOG 99-14*).

Surgery (5/11/04)

Patients who are 6-8 weeks post-chemoradiotherapy will undergo a contrast enhanced CT scan of the head and neck. A directed biopsy will be performed for patients with clinical or radiographic suspicion for persistent primary disease. If persistent tumor is conclusively identified (i.e., therapy failure), the patient will be evaluated for the feasibility of surgical salvage. If the patient is deemed operable, surgery should be performed as soon as arrangements for reconstructive procedures and logistics permit. The surgery should encompass the original primary site and disease volume. If the primary site is negative on evaluation at 6-8 weeks post-chemoradiotherapy, the patient will be observed, provided the initial neck stage was N0 or N1 and the neck is clinically and radiographically free of disease. A neck dissection will be performed for N1 patients with incomplete resolution of neck disease, for all patients initially staged N2a or N2b (*or N2c when the node is > 3cm or persists on clinical or radiographic examination following chemoradiation*), or for patients initially staged N3. Neck dissection should take place within 15 weeks after completion of chemoradiotherapy. The extent of the dissection (i.e., *nodal levels removed and non-lymphatic structures preserved*) will be at the discretion of the operating surgeon. In every case, the nodal level(s) corresponding to the pre-treatment levels of disease will be dissected.

1.6 Quality of Life

It is now well recognized that comprehensive treatment evaluation must include assessment of the patient's quality of life. In HNSCC, both the disease and its treatment have the potential to significantly impact key functions, such as eating, speaking, and socializing. Most recently, investigators have documented the effects of intensive chemoradiotherapy regimens. While these treatments minimize surgery and consequently disfigurement, they have other significant immediate, delayed and potentially long-term side effects that may profoundly influence QOL. Radiotherapy, particularly combined with radiosensitizing chemotherapy, is associated with severe mucositis, sticky saliva, pain, dry mouth, hoarseness, skin irritation and difficulties in swallowing and tasting, with many of these symptoms persisting years after treatment completion.³⁵⁻⁴¹ For example, in studies of patients on regimens similar to those used in the current protocol, List and colleagues observed that on-treatment, up to three-quarters of patients reported moderate to severe problems with dry mouth, swallowing, tasting, sticky saliva and hoarse voice. While there was some improvement in most symptoms over 12 months, there was little change in dry mouth and over a third continued to report difficulties with sticky saliva and swallowing. In addition, patients' diets remained extremely restricted with a half to three-quarters on a soft food diet at 12 months.^{39,40,42,43} Longer follow-up (*2-4 years post treatment*) of these patients suggested some continued recovery in ability to eat a full range of foods and comfort in eating with others, although a third still had significant restrictions in diet and there was little change in other QOL or symptom domains post 12 months.⁴² Recent longer term follow-up of a second cohort of patients treated with intensive chemoradiotherapy has shown virtually no change in any QOL dimension, report of symptoms or performance status from 12 to 2-4 years post-treatment completion (*List, personal communication 1/02*).

The current protocol randomizes patients to one of two concurrent chemoradiotherapy regimens. In general, previous RTOG studies using global QOL measures (e.g., *FACT-H&N*), while observing changes over time, have not found differences between therapy regimens. Given that all treatment arms are radiation based, a radiation specific QOL measure {the Head and Neck Radiotherapy Questionnaire (*HNRQ*)⁴⁴ (*Appendix VIII*) was selected as most sensitive to detect differences between groups. The HNRQ was developed to measure radiation related morbidity and quality of life from the perspective of

patients with head and neck cancer that are treated with radiation therapy. In addition, the Performance Status Scale for Head and Neck Cancer (*PSS-HN*)^{45,46} (*Appendix VII*) will be administered to assess performance/functional status and the Spitzer Quality of Life Index (*SQLI*)⁴⁷ (*Appendix IX*) to assess overall QOL for the purpose of deriving utilities.

1.7 Biomarker Study

Several biomarker studies undertaken using biopsy specimens of patients enrolled into RTOG 90-03 include p105 (*proliferation related marker*), p53, microvascular density (*MVD*), epidermal growth factor receptor (*EGFR*) expression, and cyclo-oxygenase-2 COX-2 expression. So far, quantitative EGFR immunohistochemistry (*IHC*) emerged as the most promising marker as summarized below (*unpublished data*).

Quantitative EGFR IHC was done by incubating dewaxed tumor sections with mouse monoclonal antibodies that react to the peptide backbone of the extracellular domain of the EGFR molecule (31G7, Zymed Laboratories, Inc.). The receptor expression was then scored with the SAMBA 4000 Cell Image Analysis System, without knowledge of clinical outcome, to yield mean optical density (*MOD*), staining index (*SI*), and quick score ($QS=MOD \times SI/100$). It was shown that HNSCC exhibited a wide variation in EGFR expression (*MOD*: 0.2-66.0, *SI*: 0.3-97.0, and *QS*: 0.01-69.9) with a strong correlation between MOD and SI (r^2 : 0.79). There was no correlation between EGFR expression and T-stage, N-stage, AJC stage grouping, and RTOG-RPA classes for survival and for LR control (r^2 ranged from -0.07 to 0.17). The OS and DFS rates of patients with > median MOD carcinomas were significantly lower ($p=0.0006$ and $p=0.0016$, respectively) and the LR relapse rate was significantly higher ($p=0.0031$) than those of patients with \leq median MOD cancers. However, there was no difference in the metastasis rates between the two groups ($p=0.96$). It was concluded, with the support of multivariate analysis, that EGFR expression was a strong independent prognostic determinant for overall and disease-free survival and a robust predictor for LR relapse but not for distant metastasis.

A preliminary study was also undertaken to quantify COX-2 expression by processing deparaffinized tumor slides with polyclonal COX-2 antisera (*PD-27b*, Cayman Chemical) and ABC kit. The COX-2 expression was scored using a semi-quantitative scale for stain density (SD: 0-3+) and % stained cells (% SC: 0-4+). This study (*unpublished*) showed that HNSCC had a wide range of COX-2 expression, which was not correlated with AJC stage grouping ($r^2=0.09$), RPA class for LR control ($r^2=0.02$), or RPA class for survival ($r^2=-0.03$). In contrast, COX-2 expression was found to correlate with the distant metastasis rate (0.03) but not with LR relapse or overall survival.

Based on these findings, it will be rational to test whether these markers have prognostic significance in patients receiving treatment with concurrent chemoradiation.

2.0 OBJECTIVES

- 2.1 To determine whether intensification of radiation, relative to conventional fractionation plus cisplatin in the combined therapy setting can further improve the overall survival of patients with advanced HNSCC.
- 2.2 To assess the actuarial local-regional control and disease-free rates of patients treated with the different regimens.
- 2.3 To define the acute and late toxicity of each treatment regimen.
- 2.4 To evaluate whether there are differences in patient's QOL, perception of side effects, and performance status between treatment arms.
- 2.5 To establish whether EGFR and COX-2 expressions are independent prognostic markers for patients receiving concurrent chemoradiation.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (1/31/05)

- 3.1.1 Patients with histological proof (*from the primary lesion and/or lymph nodes*) of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
- 3.1.2 Patients should have selected Stage III or IV disease (*T2N2-3M0, T3-4 any N M0*)
- 3.1.3 Patients must have Zubrod Performance Status of 0-1 (*Appendix II*).
- 3.1.4 Patients must be \geq 18 years of age.
- 3.1.5 Patients should have adequate bone marrow function defined as an absolute peripheral granulocyte count (*AGC*) of \geq 2000 cells/mm³, platelet count of \geq 100,000 cells/mm³; adequate hepatic function with

bilirubin \leq 1.5 mg/dl, AST or ALT \leq 2x the upper limit of normal; serum creatinine \leq 1.5 mg/dl, creatinine clearance \geq 50 ml/min, and normal serum calcium (or normal corrected serum calcium).

Formula for corrected calcium if albumin value is below normal range:

Corrected calcium (mg/dl) = $[4 - [\text{patient albumin (g/dl)}] \times 0.8 + \text{patient calcium (mg/dl)}$

3.1.6 Creatinine clearance (CC) \geq 50 ml/min is determined by 24 hour collection or nomogram:

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

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

3.1.7 No symptomatic coronary artery disease (*angina*) or history of myocardial infarction within the last 6 months; patients with symptomatic angina who are subsequently determined to be disease free are eligible.

3.1.8 Patients with a history of non-melanoma skin cancer, or other previous invasive malignancies from which the patient has remained continually disease free for \geq 3 years.

3.1.9 Patients must sign a study-specific informed consent form prior to study entry.

3.2 Ineligibility Criteria

3.2.1 Histology other than squamous cell carcinoma.

3.2.2 Patients with T1-2N1 or T1N2-3.

3.2.3 Evidence of metastases (*below the clavicle or distant*) by clinical or radiographic examinations.

3.2.4 Prior chemotherapy for any reason or prior radiotherapy to the head and neck region except for radioactive iodine therapy.

3.2.5 Initial surgical treatment excluding diagnostic biopsy of the primary site or nodal sampling of neck disease; radical or modified neck dissection is not permitted.

3.2.6 Patients with simultaneous primaries.

3.2.7 Pregnant women because of the embryotoxic effects of chemotherapy.

4.0 PRETREATMENT EVALUATION (1/14/04)

4.1 Complete history and physical examination.

4.2 Biopsy of primary tumor and/or fine needle aspirate/biopsy of metastatic lymph node.

4.3 Location, type, and size of all measurable lesions within 2 weeks prior to randomization must be recorded and diagrammed prior to treatment.

4.4 Quality of Life Questionnaires.

4.5 **Laboratory Studies** (*within 30 days prior to study entry*)

4.5.1 CBC with differential and platelet count

4.5.2 SMA-12, (*sodium, potassium, glucose, calcium, magnesium, BUN, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, AST or ALT*).

4.5.3 Creatinine clearance either by 24 hour collection or nomogram (*See 3.1.5*).

4.5.4 Optional: Prothrombin time (*PT*), partial thromboplastin time (*PTT*).

4.5.5 Pregnancy test as applicable.

4.6 **Radiographic Studies** (*9/30/03*)

4.6.1 Appropriate radiographic study of tumor (*CT or MRI within 8 weeks of study entry*).

4.6.2 Chest X-ray or thoracic CT scan (*within 8 weeks of study entry*).

4.6.3 Abdominal CT if abnormal LFTs are noted (must be done in the presence of elevation \geq 1.5 x ULN of alkaline phosphatase, SGOT, bilirubin, or other clinical indicator).

4.7 Optional: Panendoscopy

4.8 Dental evaluation with management according to the guidelines of Daly⁴⁸ prior to the start of radiation (*Appendix VI*).

4.9 Feeding tubes (*either Dobhoff, percutaneous endoscopic gastrostomy [PEG] or percutaneous fluoroscopic gastrostomy [PFG]*) are strongly recommended before treatment begins.

5.0 REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. 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.

6.0 RADIATION THERAPY (CALL DR. ANG WITH QUESTIONS)

6.1 Target Volume and Dose Fractionation

6.1.1 *Target Volume:* The initial target volume will have a 2-3 cm margin around gross primary and nodal disease. The boost portals will have a 1-1.5 cm margin around gross disease.

6.1.2 *Standard Fractionation:* Radiation (to both the initial target volume encompassing the gross and subclinical disease sites and the boost volume covering the primary tumor and involved nodes) will be delivered in 2 Gy per fraction, five fractions a week. The primary tumor and clinically/radiologically involved nodes will receive 70 Gy in 7 weeks and uninvolved nodes will receive 50 Gy in 5 weeks. The anterior lower neck field will be treated with 2 Gy per fraction at 3-cm depth to a total dose of 50 Gy.

6.1.3 *Concomitant Boost Regimen:* Radiation to the initial target volume encompassing the gross and subclinical disease sites will be delivered in 1.8 Gy per fraction, five fractions a week to 54 Gy in 30 fractions over 6 weeks. At 32.4 Gy/18 Fx (i.e., latter part of week 4), the boost volume covering gross tumor and clinically/radiologically involved nodes will receive boost irradiation of 1.5 Gy/Fx as second daily fraction (at least 6 h interval) for a total of 12 treatment days (18 Gy total). All treatment times must be documented on the treatment record.

The primary tumor and clinically/radiologically involved nodes will receive 72 Gy in 42 fractions over 6 weeks and uninvolved nodes will receive 54 Gy in 6 weeks. Clinically/radiologically negative posterior neck should receive a minimum dose of 50.4 Gy at 3 cm. The anterior lower neck field will be treated with 1.8 Gy per fraction at 3-cm depth to a total dose of 50.4 Gy in 28 fractions in 5.6 weeks.

6.1.4 *Technique:* Radiotherapy will commence with opposed lateral portals for the primary tumor and upper nodes and a matching anterior field for the lower neck and supraclavicular fossa. The anterior field should match the lateral fields on the skin, and should have an appropriate method to avoid overlap on the spinal cord at the junction of the fields. The inferior border of the anterior field will be 1 cm below the clavicles.

A portal reduction off the spinal cord will be made to limit the spinal cord dose to ≤ 45 Gy in all arms. Therefore, to supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include an additional electron beam of proper energy to the posterior neck, wedge pair or oblique fields. The use of IMRT is not allowed.

6.2 Physical Factors

6.2.1 Megavoltage equipment, linear accelerators, is used to provide appropriate photon energies (4-18 MV) and a wide range of electron energies (6-20 Mev). Telecobalt units can be used for irradiation of the initial large portals.

6.2.2 Treatment distances must be ≥ 80 cm SSD or SAD.

6.3 Localization Requirements

6.3.1 Portals will be simulated. Patients must be reproducibly immobilized. Shaping the radiation beam using customized cerrobend blocking or multileaf collimation is required.

6.3.2 Treatment verification (*port films*) must be done for each new field. This should be repeated at least once every two weeks and whenever any field adjustments are made.

6.3.3 Simulation films of each field, initial port films, and the calculation form will be sent to RTOG Headquarters in the first week of therapy, together with the treatment prescription for radiation therapy quality assurance review.

6.4 Dose Calculation

6.4.1 Complete isodose curves are required. Composite isodose distributions of the upper neck at the tumor center, and a copy of the treatment record indicating cumulative doses and boost field simulation and portal films must be submitted at the completion of radiotherapy.

The specification of the target dose is in terms of a dose to a point at or near the center of target volume.

The following portal arrangements are specified for photon beams:

6.4.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid separation of beams.

6.4.1.2 For arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

6.4.1.3 Other or complex treatment arrangements: at the center of the target(s) area.

6.4.1.4 The electron beam energy should be chosen such that the distal depth of the target is covered by the distal 90% of the depth dose curve. This dose should be prescribed to D_{max} .

6.4.2 Appropriate wedges and compensating filters will be used as needed to ensure dose homogeneity. The variation within the target volume should not exceed 10% of the target dose.

6.4.3 The anterior low neck/supraclavicular field dose will be specified at 3 cm depth.

6.4.4 Boost doses will be specified at the actual site(s) of gross primary and nodal disease.

- 6.4.5** Neck Dissection: If a neck dissection is planned for > 3 cm lymph nodes after radio-chemotherapy, the dose to the involved lymph nodes may be limited to 50.4-63 Gy. This information must be clearly documented in the treatment record. When there is (are) positive node (s) in the lower neck, an additional field may be necessary to deliver a supplemental dose to the positive node (s).

For all patients with clinically positive nodes greater than 6 cm, positive supraclavicular nodes, or pyriform sinus tumors that are T3 or T4 or have clinically positive nodes, a mediastinal T field may be used. The lateral limbs of the T extend to 1 cm below the clavicle and the central portion of the field extends 5 cm more inferiorly to include the upper mediastinum.

6.5 Dose Constraint, Anticipated Side Effects and Toxicities

- Time and dose modifications for radiotherapy (*in any of the two treatment arms*): treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should ideally not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for healing of severe acute toxicity reactions and/or intercurrent illness, and not for social or logistical reasons. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.
- 6.5.1** Recommended maximum dose to the spinal cord is 45 Gy regardless of the fractionation schedule.
- 6.5.2** Reversible mucositis is expected and its timing with dose and severity should be noted and graded. In very rare cases of severe grade 4 mucositis, it may be necessary to interrupt radiotherapy for a few days. However, it is prudent to limit the break to a minimum.
- 6.5.3** Also expected will be epilation and various degrees of skin reaction in the treated area.
- 6.5.4** Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of either of these should be noted, as well as whether a supplemental feeding tube was used.
- 6.5.5** Late effects include permanent xerostomia in almost all patients and occasionally persistent dysphagia. Mandibular osteoradionecrosis will occur in $\leq 5\%$ of the patients, but may be reduced by thorough dental evaluation and treatment before irradiation, which is required. Extraction of bad teeth should be carried out with conservation of restorable teeth where possible before radiotherapy. At least 10 days should be allowed for healing of gingivae post-extraction.
- 6.5.6** Amifostine and pilocarpine (*Salagen®*) are allowed as per physician discretion. If used, all details must be recorded on the data forms.
- 6.5.7** Radiation-induced myelopathy is not anticipated provided that the cervical spinal cord dose remains ≤ 45 Gy. However, special attention should be directed in followup exams to any numbness, paresthesia, or L'hermitte's signs, particularly in the first 6-12 months of followup.
- 6.6.8** RTOG Headquarters and the study chairman must be notified by telephone of all fatal and life threatening toxicities (*those \geq grade 4*).
- 6.6.9** Toxicities, and all interventions for toxicity, must be recorded on the data forms.

7.0 DRUG THERAPY (CALL DR. WHEELER WITH QUESTIONS) [5/13/03]

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual. All cases will undergo modality review by the modality study chair.

7.1 Chemotherapy Pharmaceutical Data (1/14/04)

7.1.1 Cisplatin (Cis-Diaminedichloroplatinum, DDP)

- 7.1.1.1** Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Reconstituted drug is now available from the manufacturer.
- 7.1.1.2** Storage and Preparation: The dry, unopened vials should be stored at refrigeration temperature ($+4^{\circ}\text{C}$ to $+8^{\circ}\text{C}$). Reconstitution results in a solution stable for not more than one hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.
- 7.1.1.3** Administration: Intravenous.
- 7.1.1.4** Mechanism of Action: The mechanism of action of DDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

7.1.1.5 Toxicology: The major effects in humans have been renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range (4000 to 8000 Hz), nausea and vomiting, hyperuricemia, mild to moderate anemia, peripheral neuropathy, and electrolyte abnormalities.

7.1.1.6 Supplier: Commercially available.

7.2 Chemotherapy Dose Schedule (CALL DR. WHEELER WITH QUESTIONS) [1/31/05]

7.2.1 Arm 1 – Conventional fractionation plus cisplatin.

7.2.1.1 Patients will receive cisplatin (100 mg/m²) administered intravenously on days 1, 22, and 43 of the treatment course, i.e., weekends count as days. Use the actual body weight as long as the BSA is ≤ 2.0. If the BSA is > 2.0, recalculate using the ideal weight, and use the recalculated BSA to determine the dose with no cap.

7.2.1.2 Suggested premedication: granisetron, 0.7-1.0 mg i.v. or ondansetron 32 mg i.v. will be given 30 minutes prior to cisplatin chemotherapy. A more aggressive prophylactic antiemetic regimen and any "as-needed" antiemetics may be given at the discretion of the treatment physician. Any pre-existing dehydration must be corrected prior to cisplatin administration.

7.2.1.3 **Patients must receive vigorous hydration and diuresis.** A suggested regimen is pre-hydration with a 1 liter of D5N S over 2-4 hours and mannitol 12.5 g i.v. bolus immediately prior to cisplatin. Then cisplatin 100 mg/m² in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration.

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

7.2.1.4 Dose Modifications for Cisplatin, days 22 and/or 43 (9/30/03)

7.2.1.4.1 Neutropenia may occur. If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 2000, hold treatment until ANC ≥ 2000 then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction.

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

7.2.1.4.3 Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin.

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

<u>Creatinine Clearance</u>	<u>Cisplatin Dose (5/13/03)</u>
> 50 ml/min.	100 mg/m ²
40-50 ml/min.	50 mg/m ²
< 40 ml/min.	Discontinue and notify Dr. Wheeler

(1/14/04)

*If creatinine is > 1.2, creatinine clearance must be done in order to make dose adjustment.

If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

7.2.1.4.5 Other toxicities:

- Mucositis: Grade 4 will require permanent 25% dose reduction. (See Section 6.5.2)
- Ototoxicity: For clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living that resolve prior to the next scheduled dose of cisplatin, treat at 50% dose reduction. If hearing loss or tinnitus persist at 50% dose reduction or for hearing loss requiring a hearing aid, discontinue cisplatin.

7.2.1.4.6 Chemotherapy will be delayed appropriately if treatment course is delayed (i.e. second and third courses are administered on the 22nd and 43rd day of radiation therapy). If the second and third doses are delayed more than 14 days because of hematologic or renal toxicity, that dose will be omitted. If radiation is completed before cycle 3 is due for any reason, cycle 3 should still be given up to 2 weeks after completion of radiation therapy.

7.2.2 Arm 2 – Concomitant boost plus cisplatin. (9/30/03)

7.2.2.1 Patients will receive cisplatin (100 mg/m²) administered intravenously on days 1 and 22 of the treatment course, i.e., weekends count as days.

7.2.2.2 Premedication, hydration, and dose modification are as specified in arm 1 (Section 7.2.1)

7.3 Supportive Care

- 7.3.1** Placement of a gastrostomy tube (*PEG or PFG*) before treatment begins is strongly recommended to optimize nutrition and hydration during combined therapy.
- 7.3.2** Aggressive oral and skin care, and analgesics are recommended.
- 7.3.3** The use of amifostine and pilocarpine (*Salagen®*) are not encouraged; however, if used, record all details on the TF, FS, and F1 forms.
- 7.3.4** Use of G-CSF (*Filgrastim*) or other growth factors is not anticipated for any treatment arm of this protocol. However, if the use of a growth factor is judged to be necessary in the supportive care of a patient by the treating physician, its use should be carefully documented on the TF, FS, and F1 forms.

7.4 Toxicity Reporting

- 7.4.1** (3/24/10) This study utilized the Common Toxicity Criteria (*CTC*) version 2.0 for grading of chemotherapy and acute radiation (≤ 90 days) toxicity. See Appendix V for Adverse Event Reporting Guidelines. This study will be monitored by the Clinical Data Update System (*CDUS*) version 1.1. Cumulative *CDUS* data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.
- 7.4.2** The following guidelines for reporting adverse drug reactions (*ADR's*) apply to any research protocol that uses commercial anticancer agents. The following *ADR'S* experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery:
 - 7.4.2.1** Any *ADR* which is both serious (*life-threatening [grade 4] or fatal [grade 5]*) and unexpected (*for reporting Hospitalizations, see Appendix V, Section E*);
 - 7.4.2.2** Any increased incidence of a known *ADR* which has been reported in the package insert or the literature;
 - 7.4.2.3** Any death on study if clearly related to the commercial agent(s).
 - 7.4.2.4** The *ADR* report should be documented on FDA Form 3500 (*Form 3500A is the mandatory reporting form*) and mailed or faxed to the address on the form and to the RTOG Data Management Department:

RTOG Data Management
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Phone (215) 574-3214
Fax (215) 923-1737

All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

- 7.4.3** Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management department within ten days of discovery.
- 7.4.4** Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at <http://ctep.info.nih.gov>. The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

RTOG Headquarters
AML/MDS Report
1818 Market Street, Suite 1600
Philadelphia, PA 19103

All forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

8.0 SURGERY (CALL DR. WEBER WITH QUESTIONS) [8/6/08]

- 8.1** Surgical removal (*salvage*) of the primary tumor: Directed biopsies at the site of the index lesions should not be performed in the absence of suspicion for relapse. Criteria for biopsy after chemoradiation includes a persistent mucosal abnormality or imaging studies that are suspicious for persistent or recurrent disease. Surgical removal (*salvage resection*) of the primary tumor should be performed if biopsy-proven cancer remains more than three months after completion of therapy. The nature of the surgical resection should be dictated by the extent of tumor at the initial evaluation. The operation should be conducted using accepted criteria for primary surgical treatment of the cancer.
- 8.2** Tissues for pathologic evaluation of margins should be taken from the patient (*rather than the surgical specimen itself*). However, the specimen itself should be marked at sites corresponding to the evaluated margins in order to assess sampling error in obtaining clear margins. If gross tumor remains or when no effort to remove tumor has been made, the patient will be considered to have "gross residual disease." In the absence of residual disease, if the cancer extends to within 5 mm of a surgical margin, the patient would be considered to have "close" margins.
- 8.3** Neck dissection: A planned neck dissection for patients with multiple neck nodes or with lymph nodes exceeding 3 cm in diameter (*N2a, N2b, N3*) is mandatory, regardless of the clinical and/or radiographic response (*Appendix VII*). A neck dissection is required for patients with N1 disease if a palpable or worrisome radiographic abnormality persists in the neck six weeks after completion of therapy.⁴⁹ Surgery should be performed within 2 weeks once the decision for neck dissection is made.
- 8.4** Cervical lymphadenectomy should encompass the original levels of lymph node involvement. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon.
- 8.5** The operative report must accurately and completely describe the precise location and the extent of the primary lesion and cervical lymph node metastases. Assessment of the completeness of the resection and results of intra-operative frozen section should be included. The nature of the closure should be specified (*e.g., allowed to granulate, primary closure, skin graft, local flap, regional pedicle flap, free tissue transfer*).
- 8.5.1** (5/11/04) Institutions must submit a Surgery Form (**S1**) for all patients. In addition, institutions must submit an Operative Report (**S2**), and a Surgical Pathology Report (**S5**) for patients who have surgery to the primary site and/or to regional nodes post RT/chemo (*See Section 12.1*).

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY (1/31/05, 8/6/08)

- 10.1** **RTOG Biospecimen Resource** (*for patients who have consented to participate in the tissue component of the study*)
- 10.1.1** If the patient consents to participate in the tissue component of the study, the following materials must be submitted to the RTOG Biospecimen Resource:
- 10.1.1.1** One H&E stained slide.
- 10.1.1.2** A paraffin-embedded tissue block of the tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.
- 10.1.1.3** Pathology report documenting that submitted block or slides contain tumor.
- 10.1.1.4** A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Biospecimen Resource.
- 10.1.2** Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).

10.1.3 (1/31/05, 8/6/08) Materials will be sent as follows:
Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

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

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

10.1.4 Quantitative immunohistochemical assay for EGFR and COX-2 expression and their correlation with clinical outcome will be done according to the methods used in RTOG 90-03.

10.1.5 For biomarker studies, deparaffinized slides will be stained with mouse monoclonal EGFR antisera (*Zymed Laboratories, Inc.*) or polyclonal COX-2 antisera (*PD-27b, Cayman Chemical*) and the complexes will be detected by ABC kit. The EGFR and COX-2 expressions will be measured by computerized quantitative image analysis using a SAMBA 4000 Cell Image Analysis System (*Imaging Products International Inc., Chantilly, VA*) without the knowledge of clinical data. The image analyzer consists of a Zeiss microscope with 10X, 20X, 40X objectives and a Sony 960 MD 3-chip CCD camera, interfaced with a Power Spec computer (*Micro Center Co., Houston, Texas*) equipped with a Matrox Meteor digitizer board (*Matrox Electronic Systems Ltd., Dorval, and Quebec, Canada*). Light and camera settings are standardized, resulting in average background values of 210 ± 5 (*mean \pm standard deviation; scale 0-255 from black to white*) for the red, green and blue channels. Parameters measured will be mean optical density (*MOD: the mean of optical densities measured over the labeled areas within the structure, proportional to the mean stain concentration*), and staining index (*SI: the proportion of stained area relative to the total area of the structures*).

10.2 Blood Samples (1/31/05)

10.2.1 Blood samples will be collected prior to protocol treatment for translational research to identify predictive biomarkers (*e.g., serum cytokine level, other changes resulting from the tumor*) for iatrogenic toxicity coordinated through the RTOG-TRP. Testing for germ line mutation is not permitted for this study.

10.2.2 (5/13/03, 8/6/08) Peripheral blood will be collected by venipuncture into two 12 ml Vacutainer® tubes containing ACD Solution A ("*yellow top*" tubes). A single tube will suffice if two cannot be collected. The blood should be stored at refrigerator temperature and shipped on wet ice the same day. Alternatively, the blood can be shipped and stored frozen at -20°C and shipped on dry ice. This second method allows for the collection of several samples over time; they can be shipped together thus lowering shipping costs. Specimens should be labeled with study number, case number, and institution name only. Questions regarding blood collection or shipment should be directed to the RTOG Biospecimen Resource at the University of California San Francisco. Ship by express overnight service and avoid a weekend or holiday arrival date. Blood samples will be sent as follows:

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

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

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

10.2.3 (1/31/05, 8/6/08) RTOG will reimburse submitting institutions \$300 per case for fresh or flash frozen tissue; \$200 per case for a block or core of material; \$100 per case for 10-12 slides, \$50 per case for urine, \$300 per case for complex material (blood, serum, buffy coat cells). After confirmation from the RTOG Biospecimen Resource 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.

10.2.4 Blood collection/pathology is encouraged but is not mandatory.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (1/31/05)

Assessment	Pre-Treatment	Weekly During XRT	Post all treatment					@ F/U
			@ 6-8 wks	@ 3 mos	@ 6 mos	@ 9 mos	@ 12 mos	
History/Physical	X	X	X	X	X	X	X	X
Performance Status/Weight	X	X	X	X	X	X	X	X
Endoscopy & Biopsy	X			X ^c				
Tumor Assessment	X	X	X	X	X	X	X	X ^c
CBC/platelet/differential	X ^a	X ^l						
SMA-12 (per 4.5.2)	X ^a		X ^e	X ^e	X ^e	X ^e	X ^e	
PT/PTT (optional)	X ^a							
Electrolytes, Mg ⁺⁺ , creatinine		X ^k						
Creatinine Clearance	X ^a	X ^f						
Pregnancy Test	X ^{a,d}							
CT/MRI of tumor	X ^b		X ^m		X			X ^d
CXR or thoracic CT	X ^b						X	
Panendoscopy (optional)	X							
QOL Assessments	X	X ^h		X ⁱ			X ⁱ	X ^j
Toxicity Evaluation		X	X	X	X	X	X	X
Dental Evaluation	X							
Feeding Tubes (recommended)	X							
Blood Samples	X ^g							

- a. Within 30 days of study entry
- b. (9/30/03) Within 8 weeks of study entry; if LFT's are abnormal, abdominal CT should be done (*must be done in the presence of elevation $\geq 1.5 \times$ ULN of alkaline phosphatase, SGOT, bilirubin, or other clinical indicator*)
- c. Only if clinically indicated
- d. As applicable
- e. ALT/AST, Bilirubin, Alk Phos at each followup for one year
- f. As applicable (creatinine clearance should be done as indicated in Section 7.2.1.4.4)
- g. See Section 10.2. Blood samples must be collected prior to protocol treatment, as applicable.
- h. During one of the last two weeks of treatment.
- i. QOL assessment timed from start of treatment.
- j. QOL assessments annually for years 2-5.
- k. Also, as clinically indicated.
- l. CBC should be done 3 weeks post last dose of chemotherapy.
- m. If chemotherapy is given up to 2 weeks post-XRT, CT scan is done 6-8 weeks from the last chemotherapy.

11.2 Tumor Clearance (9/30/03)

The only meaningful response for this study population is a complete response; anything less than that will be considered a treatment failure. A patient will be considered a complete response if there is no measurable tumor either on clinical or radiological examination.

11.4 Progression (P)

An estimated increase in the size of the tumor of greater than 25% or appearance of new areas of malignant disease.

11.5 Survival

Record survival from start of treatment.

11.6 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 2-week intervals, whenever possible, after completion of treatment and until their acute reactions have resolved. They will then be seen every three months for 2 years, every 6 months through year 5, then annually.

11.7 Late Effects

At each follow-up visit, note condition of tissues (*nerves, mucosa, skin, subcutaneous*) and signs of soft tissue change or bony necrosis. Record any change or abnormality in CNS and/or peripheral nervous system.

11.8 QOL Measurement (1/31/05, 4/13/05)

The quality of life 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. These instruments, described below, are included in the forms packet for the study. Additional instructions for the investigator/data manager/nurse and patient will be included with the data forms.

11.8.1 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.^{45,46} The interviewer rates the patient on each scale based on the patient's responses to targeted questions. Scores on each subscale range from 0-100, with higher scores indicating better performance. It has been demonstrated to be reliable and valid in head and neck cancer patients. The investigator/data manager/nurse will determine the score on each of the subscales by performing a clinical evaluation and unstructured interview format.

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.

Head and Neck Radiotherapy Questionnaire (HNRQ). The HNRQ was developed at McMaster University as a measure of morbidity and quality of life for clinical trials of radiation therapy in local-regionally advanced HNSCC. It consists of 25 questions (*last two questions are not counted in the total score*) about patients' experiences of radiation-related side effects (*e.g., dry mouth, throat pain, skin irritation*) and their overall well-being. Patients rate each item on a 7-point Likert type scale with 1 indicating that a given item is 'a great deal' of trouble, and 7 'not at all' troublesome. Questions relate to six domains: oral cavity (*mouth*), throat, skin, digestive function, energy and psychosocial. The questionnaire has proven sensitive to treatment effects and correlates highly with existing measures of toxicity and performance ratings.⁴⁴

Spitzer Quality of Life Index (SQLI). The SQLI is a general QOL index that covers five dimensions of quality of life (*activity, daily living, health, support of family and friends and outlook*), each rated on a 3-point scale. Lower scores reflect better performance. The five item categorical questionnaire is summed in a

Likert format, with previous reliability and validity testing. The SQLI will be used as a patient self-assessment tool.⁴⁷

Assessment Schedule. QOL instruments will be administered pre-treatment, during one of the last two weeks of the treatment, then at 3 and 12 months from start of treatment and annually in years 2-5.

11.9 Criteria for Discontinuation of Treatment

11.9.1 Patient's refusal to continue study participation.

11.9.2 Occurrence of unacceptable toxicity necessitating major modification of treatment. In this event, followup and data submission will continue according to protocol.

12.0 DATA COLLECTION (1/31/05)

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 (1/31/05)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Pathology Blocks (P2)	
Tumor and Nodal Diagram (I7)	
Treatment Form (TF) (includes pre-registration labs and initial chemotherapy treatment)	
Performance Status Scale for H&N Cancer (QP)	Within 2 weeks of study entry
H&N Radiotherapy Questionnaire (QF)	
Spitzer Quality of Life Index (PF)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
<u>Final Dosimetry Information:</u>	Within 1 week of RT end
Radiotherapy Form (T1)	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films (<i>simulation and portal</i>) (T8)	
Treatment Form (TF)	After each dose and at completion or discontinuation of chemotherapy
Initial Followup Form (FS)	At 13 weeks from start of RT
Surgery Report (S1)	At 16 weeks post-RT/chemo for all patients
Operative Report (S2)	At 16 weeks post-RT/chemo for patients who have surgery to the primary and/or to regional nodes post-RT/chemo
Surgical Pathology Report (S5) (not biopsy)	
Performance Status Scale for H&N Cancer (QP)	At one of last two weeks of treatment, then at

H&N Radiotherapy Questionnaire (QF) Spitzer Quality of Life Index (PF)	3 and 12 months from start of treatment; then annually for years 2-5
Follow-up Form (F1)	At 6-8 weeks, q 3 months for 2 years, q 6 months in years 3-5, then annually and/or at death
Autopsy Report (D3)	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary

Overall survival (*failure: death due to any cause*)

13.1.2 Secondary (5/11/04)

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

13.1.2.2 Disease-free survival (*failure: local-regional [see Section 13.1.2.1], distant metastases, second primary, or death without progression*)

13.1.2.3 Toxicity (*rates of grade ≥ 3*)

13.1.2.4 Quality of Life (*PSS-HN and HNRQ*)

13.1.2.5 Correlation of EGFR with survival and local-regional control

13.1.2.6 Correlation of COX-2 with time to distant metastases

13.2 Sample Size Determination

The primary hypothesis of this trial is that the experimental regimen (AFX-CB + CDDP) can improve overall survival when compared to the control regimen (SFX + CDDP). Secondary endpoints will include comparisons of local-regional control and disease-free survival. In addition, we will look at the effect of EGFR and COX-2 on outcome. For these analyses, patients from the 2 arms will be combined to achieve sufficient statistical power. The experimental regimen has been previously studied in RTOG 99-14, a phase II protocol. The control regimen has been studied in the prior RTOG protocol 81-17, 91-11, and has been shown to significantly improve survival when compared to radiation alone in the intergroup ECOG/SWOG phase III trial.⁵⁰

An historical comparison of data from RTOG 90-03, a study that compared various fractionation schedules, was performed to estimate the magnitude of the possible treatment effect. Patients were limited to those who would be potentially eligible for this study (i.e., Stage IV or T3N1 (Stage III) patients with squamous cell carcinomas of the oral cavity, oropharynx, or hypopharynx with KPS ≥ 70). We compared the AFX-CB arm to the SFX arm to determine the reduction in death rate associated with treating patients with AFX-CB as compared to SFX. The Cox proportional hazards model⁵¹ was used to estimate the difference while stratifying for the RTOG Recursive Partitioning Analysis (RPA) prognostic class.⁵² At 2 years, the estimated survival rates for AFX-CB and SFX were 49.46% and 42.67%, respectively. The primary endpoint of RTOG 90-03 was local-regional control; therefore, the study was not powered for the survival comparison. Thus, there were no significant differences in survival in RTOG 90-03. The estimated reduction in the death rate was approximately 20%.

With the addition of concurrent chemotherapy, which was shown to reduce the distant metastatic rate in the completed intergroup larynx preservation trial (RTOG 91-11), this study is designed to detect a minimum of 25% reduction in the death rate using the experimental regimen. This equates to an approximate 10% improvement in 2-year survival.

The statistical software EaST⁵³ for group sequential design with the O'Brien-Fleming boundary⁵⁴ was used for calculating the sample size with two planned interim tests. Three hundred nine deaths are required to detect a 25% reduction in the death rate with 80% statistical power using a 1-sided test at the 0.05 significance level. Four hundred fifty-six patients accrued over three years will be required. Adjusting by approximately 5% to allow for ineligibility and lack of data, the total sample size required will be 480 patients.

Based on data from RTOG 81-17 and the ECOG/SWOG intergroup study, we estimated the 2-year survival rate for the control arm to be 45%. It is possible that the baseline rate in this study will be higher than what was observed in these studies because of patient selection or better delivery of chemoradiation therapy itself. In addition, larynx patients are eligible for this study, which could also raise the baseline rate. If all study design constraints are kept constant other than the baseline rate, the total sample size will not change, but the total study time will be increased because it will take longer to observe the required number of events.

The maximum study duration, including follow-up requirements, under the above constraints is 4.9 years if the 2-year survival rate for the control arm is 45%. This maximum study duration will increase to 5.4 or 6 years if the 2-year survival rate for the control arm is 50% or 55%.

Quality of life will be assessed using the PSS-HN and the HNRQ. The primary endpoint will be at twelve months from start of treatment. An area under the curve (AUC) analysis will be performed to compute the average QOL observed from pretreatment to twelve months. It is estimated that at least 126 patients per arm will have analyzable QOL data for that analysis. RTOG 90-03⁵⁵ indicated that a difference of at least 7 between treatment arms was clinically meaningful for the three components of PSS-HN. Assuming a standard deviation of 18, based upon RTOG 90-03⁵⁵, then this study will have at least 86% statistical power to find a difference of 7 between average QOL. The PSS-HN has three separate scores and HNRQ has one summary score that will be examined between arms. Hommel's adjustment for type I error will be used.⁵⁶ If the scores are correlated then no adjustment will be necessary, but if the scores are independent then a maximum adjustment of 0.0125 will be made to maintain an overall significance level of 0.05. The statistical power to observe the above difference will be 71% with the maximum adjustment to the significance level.

13.3 Patient Accrual (5/11/04)

The patient accrual is projected to be about 160 cases per year based on the accrual of RTOG 91-11, RTOG 97-03, and RTOG 99-14. We expect to complete the accrual in three years. If the accrual rate is less than 100 patients per year, the study will be re-evaluated with respect to feasibility.

13.3.1 Overview and Rationale for Sample Size Increase

This trial is one of the first multi-institutional trials testing the principle that an accelerated radiation therapy (RT) fractionation scheme will improve the efficacy when given with concurrent chemotherapy as compared to standard once-daily RT with concurrent chemotherapy. When the trial was originally designed, the patient registration rate was projected at just over 13 patients per month, and so the accrual period was projected to take 3 years to test for a 25% reduction in the death rate. At that time, the study chairs and statisticians felt that a 25% reduction was realistic and ruled out a smaller difference of 20% because of the increased time added to the trial before its planned definitive analysis could be performed. There was an underlying desire to have the trial results available as soon as possible. As of January 7, 2004, 313 patients had been entered for an average of 18.1 per month over the entire study, and 23.5 per month in the last six months. The original targeted accrual goal will be completed within two years. As previously described in section 13.3, there was an estimated reduction in the death rate of approximately 20% when comparing the AFX-CB arm to the SFX arm in the altered fractionation trial, RTOG 90-03 without chemotherapy. Because of the rapid accrual, this study, RTOG 0129, now can test for that smaller reduction of 20% by entering patients for the originally projected three years. The assumption made here is that the chemotherapy will have the same effect on both fractionation schemes. This proposal has been endorsed by the RTOG Head and Neck Committee Chair and the RTOG Research Strategy Committee at the RTOG January 2004 semi-annual meeting. It was subsequently reviewed and approved by RTOG Data Monitoring Committee at its February 2004 semi-annual meeting.

The study sample size will be increased to 684 analyzable patients to detect a 20% reduction in the death rate with a 1-sided test ($\alpha = 0.05$) and 80% statistical power. Futility testing has also been added. With the drastic increase in patient accrual, the revised sample size can be accrued within the original projected accrual period of three years. The study has > 90% power to detect the original hypothesized reduction in death rate of 25%.

Adjusting by approximately 5% to allow for ineligibility and lack of data, **the revised total sample size is 720 patients.** The total study time is estimated to be between 6.45 and 7.81 years if the study is not stopped early after the interim analyses. The monthly accrual to RTOG 0129 has been 18.1 over the

entire study, and 23.5 over the last six months. The projected completion time for the patient accrual period is still three years.

13.4 Randomization

The treatment allocation scheme described by Zelen⁵⁷ will be used at randomization to balance risk factors other than treating institution. Patients will be stratified by primary site (larynx vs. non-larynx), N-stage (N0 vs. N1, N2a, N2b vs. N2c, N3), and Zubrod status (0 vs. 1). The stratification factors are based on the RTOG Recursive Partitioning Analysis.

13.5 Analysis Plan

13.5.1 *Statistical Methods*

Overall and disease-free survival will be estimated by the Kaplan-Meier method.⁵⁸ The log-rank test⁵⁹ will be used to test the experimental treatment against the control. The cumulative incidence method will be used to estimate local-regional failure rates, and the failure rates for the experimental treatment will be compared against the control using the method developed by Gray.⁶⁰ Multivariate analysis will be performed using the Cox proportional hazards model. Rates of grade ≥ 3 toxicity will be compared using Fisher's exact test.

13.5.2 *Interim Reports*

Interim reports with statistical analyses will be prepared twice each year until the initial paper reporting the treatment results has been submitted for publication. In general, these reports will contain patient accrual rate, projected completion date for accrual, compliance rate for treatment delivery with respect to the protocol prescription, distribution of important baseline prognostic variables, and the frequency and severity of toxicity. These interim reports will not contain the results from the treatment comparisons with respect to the efficacy endpoints such as overall and disease-free survival.

13.5.2.1 Rationale for Modification of Statistical Analysis Plan (8/6/08)

RTOG 0129 was opened to patient accrual on July 30, 2002. The original analysis plan called for 309 deaths to detect a 25% reduction in the death rate with 2 interim analyses after 103 and 206 deaths had been reported. The plan was based upon an estimated 2-year survival rate of 45% for the control arm and a 1-sided test at the 0.05 significance level with 80% statistical power. The survival was assumed to follow an exponential distribution; namely, that the risk of dying was constant over time. The patient accrual rate was projected to be 13 patients per month. The target sample size was 456 analyzable patients to be accrued over 3 years.

In May 2004, the protocol was amended to increase the sample size to 684 analyzable patients. This increase was made because study accrual had exceeded expectations at 23 per month and in order to detect a smaller reduction of 20% in the death rate with a 1-sided test ($\alpha = 0.05$) and 80% statistical power. The revised sample size was projected to be accrued within the original accrual period of 3 years. The analysis plan was modified to require 584 deaths to detect a 20% reduction in the death rate with 2 interim analyses after 184 and 369 deaths had been reported.

The trial was closed to new entries on June 23, 2005 with 743 patients enrolled. In January 2007, the survival result from the first interim analysis (with 192 deaths) was reported to the RTOG Data Monitoring Board (DMC). At time of this analysis, it was noted that the estimated 2-year survival rate for both arms exceeded 72%, significantly more than the projected 2-year rate of 45% for the control arm. Since no statistical boundary was crossed, the recommendation of the DMC was to continue the study as written until the second interim analysis, and the RTOG Group Chair approved this recommendation. The second interim analysis was projected to take place at 3.5 years, for the June 2010 DMC meeting.

Prior to the June 2008 DMC meeting, the timeframe of the second interim analysis was re-evaluated due to concerns about the length of time to the analysis (i.e. June 2010). With 257 deaths reported on both arms and with less than 4% of patients censored before 2 years, the 2-year survival rates still exceeded 72%, much higher than the projected rate of 45%. As noted above, when the study originally was designed, the death rate was assumed to constant over time. However, as seen Table 1 below, the yearly death rate is highest during the first year for both RTOG 0811 and 0129 but lower and similar for year 2 and subsequent years. Utilizing a death rate based upon years 2 and 3 for 0129, the timeframe for the second interim analysis was even longer, projected to take place for the January 2011 DMC meeting.

This trial is one of the first multi-institutional trials testing the principle that an accelerated radiation therapy (RT) fractionation scheme will improve the efficacy of treatment when given with concurrent chemotherapy, as compared to standard once-daily RT with concurrent chemotherapy. The radiation oncology community anxiously awaits the results from this study because accelerated RT with concurrent chemotherapy is considered to be more toxic than the standard treatment. In order to spare new patients unnecessary toxicity while awaiting the results from this study, the current protocol analysis plan will be modified to reflect the original analysis plan to detect a 25% reduction in the death rate with accelerated RT arm. Since the current number (257) of deaths appreciatively exceeds the number specified for the second analysis (206) in the original analysis plan, the second interim analysis will not be performed. Instead the final analysis will be done at first RTOG DMC meeting to take place after 309 deaths have been reported. This analysis is projected for the June 2009 DMC meeting.

13.5.3 Interim Analyses for Early Stopping (5/11/04)

Two interim treatment comparisons will be performed. The first interim analysis will take place after 103 deaths (total from both arms) have been observed; the nominal significance level for this test is 0.0011. The second interim analysis will take place after 206 deaths have been observed; the nominal significance level for this test is 0.0168. For each of these interim analyses, toxicity, treatment delivery, survival, local-regional control and disease-free survival will be reported to the RTOG Data Monitoring Committee (DMC). The boundary for early stopping (or the nominal significance level for the test) will be computed based on the observed number of deaths according to the O'Brien-Fleming alpha spending function approach. If the difference is highly significant, i.e., p-value less than the nominal level, the responsible statistician will recommend to Data Monitoring Committee that the study be written up for publication.

13.5.3.1 Due to the increase in sample size (see Section 13.3.1), the two interim tests will be performed after 184 and 369 deaths have been observed. The boundaries for each test are provided in the table below:

Number of Deaths	Nominal Critical Point	
	Reject H0	Reject H1
184	>2.867	< -0.249
369	>1.980	< 0.986

13.5.3.2 (8/6/08) There will be no second interim treatment comparison (see Section 13.5.2.1 for the revised analysis plan).

13.5.4 Initial Analysis for Reporting Treatment Results (5/11/04)

The analysis reporting the treatment results will be carried out after 309 deaths have been observed unless the criteria for early stopping are met. The survival difference between the control arm and the experimental arm will be tested using the log-rank statistic at the significance level of 0.0445 given that the two interim analyses are carried out according to Section 13.5.3. Only eligible patients will be included in this analysis. Quality of life through twelve months will be analyzed using an AUC method and comparing the AUC results using a z-test. Patients with available data will be used in the QOL analysis. Imputation for missing observations will not be used. Based on RTOG 90-03, only 4% of the QOL forms at 12 months were not completed due to multiple reasons. Thus, the cause of missing data is assumed to be random.

Quality-adjusted Survival (QAS) has its roots in Quality-Adjusted Life Years (QALY), which was developed for health care utilization. QALY incorporate societal-based utilities of health states into expected life years for a health condition. The QALY model is $QALY(h,y)$ where h is a health state and y is the years of life. In this study the endpoint of interest is quality-adjusted survival where the adjustment is based upon a patient-derived weight. In addition, there are multiple health states that will

be assessed. $WS = \int_0^T V(Q(t))dt$ where WS is a weighted survival function. $Q(t)$ is the quality-

adjusted function at time t and $V(t)$ is the length of time. In order to determine a patient's health state, it is preferable to ask the patient. The Spitzer Quality of Life Index (SQLI) produces 243 possible health states. The SQLI will be given to the patient to determine their current health state. The HNRQ will be used to provide a weight for the health state. The area under the curve (AUC) for the HNRQ will be

computed when multiple assessments are performed for one health state. The WS over the survival period can be estimated using a one-step estimator.⁶² This function is distributed as a normal function and differences can be tested using the z-test.

13.5.4.1 Due to the increase in sample size (*see Section 13.3.1*), the major analysis will now occur after 553 deaths have been observed, with a significance level of 0.0491.

13.5.4.2 (8/6/08) Due to the revised analysis plan (*see Section 13.5.2.1*), the major analysis will occur after 309 deaths have been observed, with a significance level of 0.046.

13.6 Tumor Marker Evaluation (5/11/04)

In an analysis of the standard radiation arm of RTOG 90-03, Ang, et al. showed that patients with higher expression of EGFR had significantly lower overall survival (HR=1.72, p=0.0073) and local-regional control (HR=2.02, p=0.0013).⁶³ In addition, they showed that patients with higher expression of COX-2 had significantly lower incidence of distant metastases (HR=3.16, p=0.0123) [*unpublished*].

Based on the above results, this component will test the hypotheses that: 1) EGFR overexpression, measured by mean optical density, will predict lower overall survival due to increased local-regional relapse but not higher propensity for systemic metastasis; and 2) COX-2 overexpression, measured by percent staining, will correlate with the distant metastasis rate. Quantitative immunohistochemistry will be performed according to the method used in 90-03 without knowledge of clinical outcome and the data will be forwarded to the RTOG Statistical Unit for correlation with clinical outcome.

One hundred fifty of 279 (54%) patients randomized to the standard radiation arm were analyzable for EGFR. Patients were grouped by whether their EGFR value was above or below the median value of 24.0.

One hundred fifty-four of 279 (55%) patients were analyzable for COX-2. Patients were grouped by whether their COX-2 value was 0,1,2 or 3,4. Quantitation of COX-2 expressions of tumor samples of patients enrolled in RTOG 90-03 using an image analysis system is currently ongoing. The data obtained will be taken into account in planning future analyses.

The use of COX-2 inhibitors (Celebrex™ or Vioxx™) by patients may theoretically affect the expression of COX-2 and the tumor sensitivity to treatment. These compounds, however, act predominantly by inhibiting the catalytic function of COX-2. There is no firm data indicating that such inhibitors affect the expression of COX-2. Consequently, we do not anticipate that the use of the COX-2 inhibitors at the time of biopsy would appreciably affect the outcome of immunohistochemical assays. The use of COX-2 inhibitors during the course of therapy might indeed affect tumor sensitivity to radiation and/or chemotherapy. A review of the primary medical evaluation notes of previously untreated patients with head and neck cancer from centers enrolling the largest number of patients to 0129 revealed that <10% of patients (3 out of 52) were taking COX-2 inhibitors. Consequently, the potential confounding effect of COX-2 inhibitors use is anticipated to be very small. However, we plan to prospectively collect patient data on their use and initially confirm that the frequency of patients receiving COX-2 inhibitors prior to biopsy and during treatment is low. We will not retrospectively collect these data from patients already entered into the study because the patients may be either unavailable or unreliable. If their use is much higher than expected (>25%), then the possible impact of COX-2 inhibitors on outcome will be explored in multivariate analyses.

In this study, we seek to determine if similar results are found in patients treated with chemoradiation. First, we will correlate EGFR expression with overall survival. Patients will be grouped by whether their EGFR value is above or below 24.0. The two arms will be combined to allow for sufficient statistical power. Based on 90-03, we will assume that 50% of randomized patients will be analyzable for EGFR, giving a total of 342 analyzable patients, based on the revised sample size.

The equation described by Schoenfeld⁶¹ is used to calculate statistical power:

Number of failures = $(z_{1-\alpha/2} + z_{1-\alpha})^2 / (\ln HR)^2 w (1 - w)$, where
 $z_{1-\alpha/2}$ = normal deviate for the significance level

z_1 = normal deviate for the statistical power

HR = hazard ratio comparing favorable risk group (MOD > 24.0) to unfavorable risk group (MOD ≤ 29.0)

w = prevalence rate of favorable risk group (% of patients with MOD > 24.0)

Table 1 below shows statistical power to detect hazard ratios for survival of 1.50, 1.75, and 2.00 for prevalence rates of 10%, 20%, 30%, 40%, or 50% (*24.0 was the median in 90-03, but will not necessarily be so in this study*). Based on the revised study design, the final analysis will occur after 553 deaths have been observed. If we assume that 50% of patients will be analyzable for EGFR, there will be 276 deaths observed at the time of analysis. The significance level is set at 0.05.

Table 1 Statistical Power – Survival

Prevalence	Hazard Ratio		
	1.50	1.75	2.00
10% (or 90%)	0.52	0.79	0.93
20% (or 80%)	0.76	0.96	0.99
30% (or 70%)	0.87	0.98	0.99
40% (or 60%)	0.90	0.99	0.99
50%	0.92	0.99	0.99

Next, we will correlate EGFR expression with local-regional control. Again, patients will be grouped by whether they fall above or below EGFR of 24.0. It is estimated that there will be 388 local-regional failures at the time of analysis. Again, assuming 50% will be analyzable for EGFR, there will be 194 failures observed at the time of analysis.

Table 2 below shows statistical power to detect hazard ratios for local-regional control of 1.75, 2.00, and 2.25 for prevalence rates of 10%-50%. Statistical significance is set at 0.05.

Table 2 Statistical Power – Local-Regional Control

Prevalence	Hazard Ratio		
	1.75	2.00	2.25
10% (or 90%)	0.64	0.82	0.92
20% (or 80%)	0.87	0.97	0.99
30% (or 70%)	0.94	0.99	0.99
40% (or 60%)	0.96	0.99	0.99
50%	0.97	0.99	0.99

Finally we will correlate COX-2 with incidence of distant metastases. Patients will be grouped in the following way: 0,1, or 2 vs. 3 or 4. It is estimated that there will be 211 patients with distant metastases by the time of the final analysis. Assuming 50% will be analyzable for COX-2, there will be 105 failures observed at the time of analysis.

Table 3 below shows the statistical power to detect hazard ratios for distant metastases of 1.75, 2.00, and 2.25 for prevalence rates of 10%-50%. Statistical significance is set at 0.05.

Table 3 Statistical Power – Distant Metastases

Prevalence	Hazard Ratio		
	1.75	2.00	2.25
10% (or 90%)	0.40	0.56	0.70
20% (or 80%)	0.63	0.81	0.91
30% (or 70%)	0.74	0.90	0.96
40% (or 60%)	0.80	0.93	0.98
50%	0.81	0.94	0.98

For survival, the log-rank test will be used to test for differences between the favorable and unfavorable risk groups; for local-regional control and distant metastases, Gray’s test will be used. The prognostic value as measured by hazard ratio for each tumor marker will be estimated using the Cox proportional hazards model. Also, a multivariate model will be evaluated for each endpoint, with potential covariates of age, Zubrod, T-Stage, N-Stage, AJCC Stage, primary site, and assigned treatment. A stepwise procedure

using the Cox model will be used to develop a base model for each endpoint prior to evaluating the prognostic impact of each tumor marker. Then the marker will be added to the model to test for significance. If the hypothesized cut points do not yield statistical significance, other cut points will be evaluated.

13.7 Inclusion of Women and Minorities (1/31/05)

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, we have also considered the possible interaction between race and treatments. Based on the accrual statistics from RTOG 97-03, we project that 78% of patients enrolled to this study will be men, and 22% women. In addition, we project 6% Hispanic/Latino and 94% not Hispanic/Latino, and 79% white and 21% not white. The following table lists the projected accrual for each group. Assuming no differences between the genders or ethnicities, or among the races, the statistical power for detecting the hypothesized difference is 71% for males, 31% for females, 71% for whites, 30% for non-whites, 77% for Hispanics, and 14% for non-Hispanics.

Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	7	35	42
Not Hispanic or Latino	149	529	678
Ethnic Category: Total of all subjects	156	564	720
Racial Category			
American Indian or Alaskan Native	0	8	8
Asian	3	3	6
Black or African American	29	98	127
Native Hawaiian or other Pacific Islander	0	0	0
White	124	455	579
Racial Category: Total of all subjects	156	564	720

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APPENDIX IA (2/24/04)

RTOG 0129

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE (5/11/04)

**A PHASE III TRIAL OF CONCURRENT RADIATION AND CHEMOTHERAPY
(FOLLOWED BY SURGERY FOR RESIDUAL PRIMARY/N2-3 NODAL DISEASE) FOR
ADVANCED HEAD AND NECK CARCINOMAS**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, *“Taking Part in Clinical Trials: What Cancer Patients Need To Know,”* is available from your doctor.

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

WHY IS THIS STUDY BEING DONE?

One of the standard treatment options for your type of cancer is standard radiation therapy combined with chemotherapy. The main purpose of this study is to compare this standard treatment with another method of giving radiation treatments, combined with the same chemotherapy. We will be looking at the effects (good and bad) on you and fellow participants in the study.

This research is being done because we do not know which of the radiation and chemotherapy combinations being studied may better control your cancer or have fewer side effects.

The study will also collect information about your quality of life, including how treatment affects your diet, eating in public, speech, and side effects such as dry mouth, throat pain, and skin irritation.

In addition, if you agree, biologic factors (markers) will be studied that may help to predict and treat head and neck cancer patients in the future.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY (5/11/04)

About 720 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (1/31/05)

You will be “randomized” into one of the study Arms described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will determine into which study Arm you are placed. You will have approximately a one in two chance of being placed into either Arm:

Arm 1

Radiation Therapy:	Once a day, five days a week, for 7 weeks
Chemotherapy:	Cisplatin given in the vein on days 1, 22, and 43 of radiation therapy

Arm 2

Radiation Therapy:	Once a day, five days a week, for about 3.5 weeks, then twice a day, five days a week, for 2.5 weeks
Chemotherapy:	Cisplatin given in the vein on days 1 and 22 of radiation therapy

In general, most of your treatment will be done as an outpatient at your institution. However, it is likely you will need to remain in the hospital overnight after receiving cisplatin to receive additional fluids to prevent dehydration. You may also receive additional fluids, as an outpatient, later in the week after you receive the cisplatin.

After radiation therapy and chemotherapy is completed, if your doctor finds that your cancer remains or has regrown, you will have a biopsy of the tumor and surgery to remove the tumor. If your cancer has spread to your lymph nodes, your doctor will recommend that you have surgery to remove those lymph nodes. Your doctor will describe the surgery and discuss the risks and side effects of surgery with you.

The following procedures that are part of regular cancer care and may be done even if you do not join the study:

- Physical Exam
- Blood Tests
- Chest X-ray or CT scan
- CT/MRI scan
- Endoscopy (examination of the inside of your throat)
- Biopsy
- Tumor Measurements

Standard procedures being done because you are in this study: (1/31/05)

Schedule	Procedure
Before treatment, weekly during radiation treatment, after treatment is completed at 6-8 wks then every 3 mos. for 2 years, every 6 mos. for 3 years, then annually	Physical examination
Before treatment	Dental Evaluation
Before treatment	Pregnancy test if appropriate
Weekly during radiation treatment, after treatment is completed at 6-8 wks and then every 3 mos. for 2 years, every 6 mos. for 3 years, then annually	Evaluation for Side Effects
Before treatment, weekly and as needed during radiation therapy, after treatment is completed at 6-8 wks and at 3, 6, 9, and 12 mos.	Blood Tests
Before treatment and at 12 mos. after treatment	Chest X-ray/CT scan of your chest
Before treatment, if needed, because of an unsatisfactory liver function test	CT scan of your belly area
Before treatment, after treatment is completed at 6-8 wks and at 6 mos., then as needed during follow up	CT/MRI of tumor
Strongly encouraged to make sure you get adequate nutrition during treatment, because sores inside your mouth and throat will make chewing and swallowing difficult	Insertion of feeding tube
Pretreatment, one of the last two weeks of treatment, then at 3 and 12 months from start of treatment and yearly for years 2-5. These questionnaires will take between 20-30 minutes to complete.	Quality of Life Questionnaires

HOW LONG WILL I BE IN THE STUDY? (1/31/05)

If you are randomized to Arm 1, you will receive treatment five days a week for seven weeks. If you are randomized to Arm 2, you will receive treatment five days a week for approximately six weeks. After you finish your treatment, you

will be seen for follow up at 6-8 weeks, every three months for two years, every six months for three years, then annually for the rest of your life.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

The researcher may decide to take you off this study if your disease gets worse despite the treatment, the side effects of the treatment are very serious, or new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation. The study could also be stopped early, if one Arm is found to be clearly better than the other.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects listed below. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the radiation therapy and chemotherapy are stopped, but in some cases side effects can be long-lasting or permanent.

Risks Associated with Radiation Therapy When Used in Combination With Cisplatin

Very Likely

Sores in the mouth and throat that are likely to interfere with swallowing
Temporary hair loss (of the face/chin/neck)
Tanning, redness, or blistering or peeling of skin in treatment area
Loss of teeth, or cavities in teeth, if strict dental care is not followed
Hardness and tightness of the skin and muscles of the head and neck
Dryness of the mouth or altered taste that may be permanent
Loss of appetite
Weight loss

Less Likely, But Serious

Permanent hair loss (of the face/chin/neck)
Decrease in function of thyroid gland which may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
Temporary pain or scarring around nerves in the shoulder, which could cause numbness and/or weakness
Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia
Severe damage to the jawbone and/or voice box which could require major surgery to correct or even to remove the jaw bone and/or voice box
Serious ear infections and/or hearing loss

Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”

Risks Associated with Cisplatin

Very Likely

Nausea and/or vomiting

Weakness

Hearing loss, ringing of the ears

Numbness of the fingers and toes

Lower blood counts with risk of infection or bleeding

Anemia

Loss of appetite

Weight loss

Less Likely

Allergic reactions (sweating, difficulty breathing, rapid heartbeat)

Facial swelling

Loss of taste

Muscle cramps

Loss of coordination

Involuntary movement

Restlessness

Less Likely, But Serious

Kidney damage

Liver damage

Acute leukemia

Reproductive risks: Because the radiation therapy and drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with advanced cancer of the head and neck region in the future.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) once or twice a day radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other. There may also be other treatment trials in which you could participate.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Another option may be to get the treatment plan for advanced head and neck cancer described in this study at this center or at another center even if you do not take part in the study.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (*RTOG*). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*) or its authorized representatives, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems. You may find a National Cancer Institute Guide: “Clinical Trials and Insurance Coverage – a Resource Guide” helpful in this regard. You may ask your doctor for a copy, or it is available on the world wide web at <http://www.nci.nih.gov/ClinicalTrials/insurance> (and click on printable version).

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your disease and research-related injury, you may contact:

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OHRP) suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-549-0715 (from the continental U.S. only) or 800-937-8281 Ext. 4445 (from sites outside the continental U.S.)

WHERE CAN I GET MORE INFORMATION?

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

Visit the NCI's Web sites for comprehensive clinical trials information at
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ
<http://cancernet.nci.nih.gov>.

CancerFax

Includes NCI information about cancer treatment, screening, prevention, and supportive care. To obtain a contents list, dial 301-402-5874 or 800-624-2511 from a fax machine hand set and follow the recorded instructions.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (*full study plan*).

Patient Signature (*or legal Representative*)

Date

APPENDIX IB (2/24/04)

RTOG 0129

CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

ABOUT USING TISSUE FOR RESEARCH

You have had a biopsy showing you have cancer. We would like to keep some of the tissue that is left over from that biopsy for research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer or other diseases in the future.

In addition, we would like to collect additional blood samples before starting your treatment, to be used for research looking at substances in the blood that may tell how a cancer will behave. These samples will be sent to a central office for study.

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

THINGS TO THINK ABOUT (1/14/04)

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

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us at 801-408-5626 and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue be returned to you or your designee.

You may call 801-408-5626 at a later time if you change your mind about allowing the use of your blood samples for additional tests.

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

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

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

BENEFITS

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

RISKS

The greatest risk to you is the release of information from your health records. The [treating institution/treating physician] will protect your records so that your name, address, and phone number 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”. **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call the National Cancer Institute’s Cancer Information Service at 1-800-422-6237 (1-800-4-CANCER).

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

Yes No

- 2. **My tissue 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 from [treating institution/treating physician] may contact me in the future to ask me to take part in more research.**

Yes No

Please sign your name here after your circle your answers.

Your Signature: _____ Date: _____

Signature of Doctor/Nurse: _____ Date: _____

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

0	Fully active, able to carry on all predisease activities without restriction <i>(Karnofsky 90-100).</i>
1	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 <i>(Karnofsky 70-80).</i>
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours <i>(Karnofsky 50-60).</i>
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours <i>(Karnofsky 30-40).</i>
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair <i>(Karnofsky 10-20).</i>

APPENDIX III
AJCC STAGING
HEAD & NECK, 5th Edition

STAGING-PRIMARY TUMOR (T)

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

ORAL CAVITY

- Buccal mucosa
- Lower alveolar ridge
- Upper alveolar ridge
- Retromolar gingiva (*Retromolar trigone*)
- Floor of mouth
- Hard palate
- Anterior two-thirds of the oral tongue

- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumor more than 4 cm in greatest dimension
- T4 Tumor invades adjacent structures (*e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin. Superficial erosion of bone/tooth socket by gingival primary is not sufficient to classify as T4*).

PHARYNX

Nasopharynx

- Postero-superior walls
- Lateral walls
- Inferior (*anterior*) wall, consists of the superior surface of the soft palate

- 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, or orbit.

Oropharynx

- Faucial arch including soft palate, uvula and anterior tonsillar pillar
- Glossotonsillar sulci and pharyngeal tonsils
- Base of tongue
- Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumor more than 4 cm in greatest dimension
- T4 Tumor invades adjacent structures (*e.g. pterygoid muscle[s], mandible, hard palate, deep muscle of tongue, larynx*)

Hypopharynx

Pyramidal fossae
Postcricoid region
Lateral and posterior hypopharyngeal walls

- 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.
- T4 Tumor invades adjacent structures (*e.g. thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus*).

LARYNX

Supraglottis

Suprahyoid epiglottis
Infrahyoid epiglottis
Aryepiglottic folds (*laryngeal aspect*)
Ventricular bands (*false cords*)
Arytenoids

- 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.
- T4 Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus.

Glottis

True vocal cords including anterior and posterior commissures

- T1 Tumor limited to the vocal cord(s) (*may involve anterior or posterior commissures*) with normal mobility
 - T1a Tumor limited to one vocal cord
 - T1b Tumor involves both vocal cords
- T2 Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
- T3 Tumor limited to the larynx with vocal cord fixation
- T4 Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g., trachea, soft tissues of neck including thyroid, pharynx*)

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
- T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g. trachea, or soft tissues of the neck including thyroid, esophagus*)

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 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.

REGIONAL LYMPH NODES (N) Nasopharynx Only

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa
- N3 Metastasis in a lymph node(s)
 - N3a greater than 6 cm in dimension
 - N3b in the supraclavicular fossa

DISTANT METASTASIS (M)

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

STAGE GROUPING Excluding Nasopharynx STAGE GROUPING Nasopharynx

Stage 0	Tis, N0, M0	Stage 0	Tis, N0, M0
Stage I	T1, N0, M0	Stage I	T1, N0, M0
Stage II	T2, N0, M0	Stage IIA	T2a, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0	Stage IIB	T1-T2a, N1, M0 T2b, N0-1, M0
Stage IVA	T4, N0-1, M0 Any T, N2, M0	Stage III	T1-T2b, N2, M0 T3, N0-2, M0
Stage IVB	Any T, N3, M0	Stage IVA	T4, N0-2, M0
Stage IVC	Any T, Any N, M1	Stage IVB	Any T, N3, M0
		Stage IVC	Any T, Any N, M1

RTOG/EORTC Late Radiation Morbidity Scoring Scheme					APPENDIX IV	
ORGAN TISSUE	0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	5
SKIN	None	Slight atrophy; Pigmentation change; Some hair loss	Patch atrophy; Moderate telangiectasia; Total hair loss	Marked atrophy; Gross telangiectasia	Ulceration	D
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; Slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; Field contracture > 10% linear measurement	Necrosis	E
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia; Little mucous	Marked atrophy with complete dryness; Severe telangiectasia	Ulceration	H
SALIVARY GLANDS	None	Slight dryness of mouth; Good response on stimulation	Moderate dryness of mouth; Poor response on stimulation	Complete dryness of mouth; No response on stimulation	Fibrosis	D
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadriplegia	R
BRAIN	None	Mild headache; Slight lethargy	Moderate headache; Great lethargy	Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; Coma	C
EYE	None	Asymptomatic cataract; Minor corneal ulceration or keratitis	Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma	Severe keratitis; Severe retinopathy or detachment Severe glaucoma	Panophthalmitis/Blindness	Y
LARYNX	None	Hoarseness; Slight arytenoid edema	Moderate arytenoid edema; Chondritis	Severe edema; Severe chondritis	Necrosis	R
LUNG	None	Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes	Severe respiratory insufficiency/continuous O2/Assisted ventilation	E
HEART	None	Asymptomatic or mild symptoms; Transient T wave inversion & ST Changes; Sinus tachycardia >110 (at rest)	Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS	Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities	Tamponade/Severe heart failure/Severe constrictive pericarditis	T
ESOPHAGUS	None	Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing	Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated	Severe fibrosis; Able to swallow only liquids; May have pain on swallowing Dilation required	Necrosis/Perforation Fistula	D
SMALL/LARGE INTESTINE	None	Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrhea and colic; Bowel movement >5 times daily; Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis/Perforation Fistula	T
LIVER	None	Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function	Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal	Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites	Necrosis/Hepatic coma or encephalopathy	E
KIDNEY	None	Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%; Creatinine 1.5-2.0 mg%; Creatinine clearance > 75%	Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea > 36-60mg% Creatinine clearance (50-74%)	Severe albuminuria; Severe hypertension Persistent anemia (< 10%); Severe renal failure; Urea >60 mg% Creatinine >4.0 mg% Creatinine clearance < 50%	Malignant hypotension; Uremic coma/Urea > 100%	S
BLADDER	None	Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)	Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized Telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (< 150 cc)	Necrosis/Contracted bladder (capacity < 100 cc); Severe hemorrhagic cystitis	
BONE	None	Asymptomatic; No growth retardation; Reduced bone Density	Moderate pain or tenderness; Growth retardation; Irregular bonesclerosis	Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis	Necrosis/Spontaneous fracture	
JOINT	None	Mild joint stiffness; Slight limitation of movement	Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement	Severe joint stiffness; Pain with severe limitation of movement	Necrosis/Complete fixation	

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

Definite:	The adverse event is <i>clearly related</i> to the treatment/procedure.
Probable:	The adverse event is <i>likely related</i> to the treatment/procedure.
Possible:	The adverse event <i>may be related</i> to the treatment/procedure.
Unlikely:	The adverse event is <i>doubtfully related</i> to the treatment/procedure.
Unrelated:	The adverse event is <i>clearly NOT related</i> to the treatment/procedure.

B. Grading of Adverse Events (3/24/10)

Beginning April 1, 2010, the CTEP Active Version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized to grade severity of adverse events. The CTEP Active Version of the CTCAE is identified and located on the CTEP web site at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. **When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supercede the General Guidelines.** A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.
3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

- a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.
- b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.
5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).
6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.
7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).
8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.
9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.
10. All neuro-toxicity (\geq grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

D. Adverse Event Reporting Related to Radiation Therapy (3/24/10)

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.
2. All grade 4, (CTEP’s Active Version CTCAE and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.
3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

E. Adverse Event Reporting Related to Systemic Anticancer Agents

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. Commercial Agents/Non-Investigational Agents (3/24/10)

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE¹	Hospitalization During Treatment²	Secondary AML/MDS³
FDA Form 3500 ⁴ Within 10 days	X	X	X	
NCI/CTEP Secondary AML/MDS Form within 10 days of diagnosis ⁴				X
Call RTOG within 24 hrs of event ⁶	X ⁵			

1. Any increased incidence of a known AE.
2. Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTEP's Active Version CTCAE Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
3. Reporting required during or subsequent to protocol treatment.
4. Copy to RTOG Data Management labeled: Attention: Adverse Event Report; also, send to the address on the form.
5. All grade 5 known toxicity.
6. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents

An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator's Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, <http://ctep.info.nih.gov> for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)

Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses "decentralized" notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators'

reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.

Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: **An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).**

Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

b. Expedited Reporting for Phase I Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Grade 2: Expedited report within 10 working days. Grade 3: Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of last dose of treatment with an investigational agent.	Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days. This includes deaths within 30 days of the last dose of treatment with an investigational agent.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. Expedited Reporting for Phase 2 and Phase 3 Studies

Unexpected Event		Expected Event	
Grades 2-3 Attribution: Possible, Probable or Definite	Grades 4 & 5 Regardless of Attribution	Grades 1 - 3	Grades 4 & 5 Regardless of Attribution
Expedited report within 10 working days. Grade 1: Adverse Event Expedited Reporting NOT required.	Report by phone to IDB ^{1,2} within 24 hrs. Expedited report to follow within 10 working days.	Adverse Event Expedited Reporting NOT required.	Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you're reporting an "adverse event", provide your name, institution number and a telephone number where you may be contacted.
2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

APPENDIX VI

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

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

Preirradiation Care and Procedures

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

Group 1

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

Group 2

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

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

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth which 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 carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

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

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

Hypersensitivity of Teeth

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

Infections

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

Bone Necrosis

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

APPENDIX VII

SURGICAL MANAGEMENT OF THE NECK

- I. N0: No mandatory surgical management of the neck is indicated.
- II. N1: Patients with N1 neck disease whose nodes are 3 cm or less in diameter require careful physical examination of the neck and post-treatment imaging. If there is clinical or radiographic evidence of residual neck disease, neck dissection is required. A CR must be achieved at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The planned neck dissection is performed 6-10 weeks post-treatment, if indicated. For oral cavity and oropharynx, levels I-IV will be dissected. For larynx and hypopharynx, levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon.
- III. N2A: For patients with lymph nodes between 3 and 6 cm, post-treatment physical examination and imaging studies will be obtained. Patients with a CR at the primary site are eligible for neck dissection alone at 6-10 weeks post-treatment; otherwise, surgical salvage with or without neck dissection will be necessary. For oral cavity and oropharynx, neck dissection will include levels I through IV. For larynx and hypopharynx, levels II-IV will be dissected. Level V dissection and removal of non-lymphatic structures will be at the discretion of the surgeon and dictated by the extent of residual disease in the neck.
- IV. N2B: For patients with multiple lymph nodes, post-treatment physical examination and imaging studies will be obtained. Neck dissection will be performed at 6-10 weeks post-treatment for patients with a CR at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. A neck dissection to include levels I through IV is mandatory for oral cavity and oropharynx. For larynx and hypopharynx, Levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon and dictated by the extent of residual disease in the neck.
- V. N2C: For patients with bilateral neck disease, each side of the neck will be managed separately according to the criteria above.
- VI. For patients with N3A disease, post-treatment physical examination and imaging studies will be obtained. The neck dissection will be performed at 6-10 weeks post-treatment for patients with a CR at the primary site; otherwise, surgical salvage with or without neck dissection will be necessary. The type of neck dissection will be determined by the extent of the disease. A neck dissection to include levels I through IV is mandatory for oral cavity and oropharynx. For larynx and hypopharynx, Levels II-IV will be dissected. Dissection of Level V and removal of non-lymphatic structures will be at the discretion of the surgeon and dictated by the extent of residual disease in the neck.

APPENDIX VIII

PERFORMANCE STATUS SCALE FOR HEAD & NECK CANCER PATIENTS - PSS-HN

Suggestions for Administration

These performance scales may be rated by health professionals (e.g., physicians, nurses, nutritionists) or other personnel (e.g., clerks, data managers). Ratings are determined through use of an unstructured interview format.

Normalcy of Diet

Begin by asking the patient what kinds of foods (s)he has been eating. Ask what foods are difficult to eat. Based on the patient's response, choose an item at the low end of the scale. Move up the scale giving examples of foods in each category and asking the patient if (s)he is eating those food items. Even if the patient says that (s)he eats everything, inquire about specific items beginning with 50, soft chewable foods and moving upwards. Stop at the item at, and above which the patient cannot eat. The patient then receives the score **below** that. If the patient indicates that (s)he is eating a full diet, also inquire whether (s)he needs to drink more liquids than usual with meals; eating a full diet with intake of extra fluids is scored 90.

If the patient can take foods orally, but is also using a feeding tube, score based on solid food intake and check the box provided. Also use this guideline when rating patients who can eat some foods but cannot take oral liquid.

Public Eating

Score the Public Eating scale by asking the patient where (s)he eats (in a restaurant, at home, at friends/relatives' homes, etc.) and with whom (s)he eats (always alone, with family/friends, etc). Ask patient if (s)he chooses different foods (softer, less messy, etc.) when eating with others. When was the last time the patient ate in a restaurant, cafeteria, MacDonald's, picnic, family reunion? Choose the score beside the description that best fits the patient. A patient on a restricted diet, (e.g., tube feeding, pureed foods) who does not eat in public but will join others in a public eating setting should be rated 75. Score 999 for inpatients.

Understandability of Speech

This scale is scored based on the interviewer's ability to understand the patient during conversation (in this case, based on conversation about patient's diet and social activities). Choose the score beside the description that best fits the patient. See if you can understand the patient if you are looking away while (s)he is talking.

Special Considerations for Inpatients: Administration of the PSS-HN varies somewhat for inpatients. Score the Normalcy of Diet and Understandability of Speech Scale as indicated. The Eating in Public Scale is not applicable as inpatients generally have little opportunity to eat with others or leave their hospital rooms. Inpatients receive a score of 999 on the Eating in Public Scale.

**PERFORMANCE STATUS SCALE FOR
HEAD AND NECK CANCER PATIENTS: PSS-HN**

Patient ID# / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / Date / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ / _ /

NORMALCY OF DIET / _ / _ / _ / _ /

100	Full diet (no restrictions)	100
90	Full diet (liquid assist)	
80	All meat	75
70	Raw carrots, celery	
60	Dry bread and crackers	
50	Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)	
40	Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)	
30	Pureed foods (in blender)	
20	Warm liquids	
10	Cold liquids	
0	Non-oral feeding (tube fed)	

PUBLIC EATING / _ / _ / _ / _ /

100	No restriction of place, food or companion (eats out at any opportunity)
75	No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (e.g., liquids))
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone
999	Inpatient

UNDERSTANDABILITY OF SPEECH / _ / _ / _ / _ /

100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication

List MA, Ritter-Sterr C, Lansky SB. *A Performance Status Scale for Head and Neck Cancer Patients. Cancer. 66:564-569, 1990*

APPENDIX IX (2/24/04)

HEAD & NECK RADIOTHERAPY QUESTIONNAIRE – PRE-TREATMENT

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

INSTRUCTIONS: The cover sheet is the first page of the questionnaire. The cover sheet is completed by the clinical staff and is attached to the front of the RT Questionnaire. If you are submitting a complete or partially complete questionnaire, complete cover sheet question 1. If the evaluation was missed, complete cover sheet question 2. N. B. This form is to be used for the pre-treatment assessment as well as for follow-up. This form is to be completed prior to treatment, during one of the last two weeks of the treatment, then at 3 and 12 months from start of treatment and annually for years 2-5.

1. IF ANY QUESTIONNAIRE ITEMS ARE ANSWERED, COMPLETE THIS SECTION, SIGN, DATE AND ATTACH COVER SHEET TO PRE-TREATMENT SPITZER FORM BEFORE SUBMITTING.

A. ____/____/____ DATE QUESTIONNAIRE COMPLETED BY PATIENT

B. DID THE PATIENT REQUIRE ASSISTANCE IN COMPLETING THE RADIOTHERAPY QUESTIONNAIRE?

1. No

2. Yes

_____ Who

_____ Reason

2. OMITTED SPITZER QUESTIONNAIRE. If the evaluation was not done, complete this section, sign, date, and submit to HQ.

A. REASON QUESTIONNAIRE NOT COMPLETED

1 Patient unable to complete questionnaire due to illness

2 Patient refused to complete any items. Reason for refusal _____

3 Patient (family, significant other) could not be contacted.

4 Not completed due to institution error.

5 Patient unable to complete due to language, educational or physical barrier. Explain

6 Other reason, explain _____

Name of Person Submitting Cover Sheet

Date Submitted

HEAD & NECK RADIOTHERAPY QUESTIONNAIRE

This box is to be completed by the clinical research assistant:

Pt. Serial # _____

Pt. Initials: _ _

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

INSTRUCTIONS: We are interested in some things about you and your health. Please answer all the questions yourself by circling the number that best applies to you. There are no “right” or “wrong” answers. Choose the best single response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions – if you wish them to know this information, please bring it to their attention.

1. HAVE YOU HAD ANY PAIN OR SORENESS IN YOUR MOUTH IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

2. HAVE YOU HAD DRYNESS OF YOUR SKIN, WHERE IT WAS TREATED, IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

3. HAVE YOU HAD ANY DIFFICULTY SWALLOWING IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

4. HAVE YOU FELT LOW IN ENERGY IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

This box is to be completed by the clinical research assistant:

Pt. Serial # _____

Pt. Initials: _ _

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

5. IN GENERAL, HAVE YOU FELT ANGRY, DEPRESSED OR DOWN IN THE DUMPS IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

6. HAVE YOU FELT NAUSEATED IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

7. HAVE YOU HAD ANY ITCHING OF THE SKIN, IN THE TREATED AREA IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

8. HAVE YOU HAD ANY DIFFICULTY GETTING A GOOD NIGHT'S SLEEP IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

9. HAVE YOU HAD ANY DRYNESS OF THE MOUTH IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

This box is to be completed by the clinical research assistant:

Pt. Serial # _____

Pt. Initials: _ _

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

10. HAVE YOU FELT TIRED OR FATIGUED, IN THE PAST WEEK, SUCH THAT YOU ARE PREVENTED FROM DOING SOCIAL OR RECREATIONAL ACTIVITIES?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

11. HAVE YOU HAD A SORE OR PAINFUL THROAT IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

12. HAVE YOU HAD ANY UPSET OF STOMACH IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

13. HAVE YOU FOUND YOUR SALIVA TO BE VERY STICKY IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

14. HAVE YOU HAD ANY FATIGUE OR TIREDNESS WHICH INTERFERED WITH YOUR WORK OR ROUTINE DAILY ACTIVITIES IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

This box is to be completed by the clinical research assistant:

Pt. Serial # _____

Pt. Initials: _ _

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

15. HAVE YOU HAD DIFFICULTY TASTING YOUR FOOD IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

16. HAVE YOU HAD DIFFICULTY WITH YOUR APPETITE IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

17. HAVE YOU FELT GOOD ABOUT YOURSELF IN THE PAST WEEK?

- __ 1 Yes → How OFTEN did you feel this way?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
rarely *continuously*

- 2 No

18. HAVE YOU HAD DIFFICULTY KEEPING DOWN FOODS OR LIQUIDS IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

19. HAVE YOU HAD A HOARSE VOICE IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

This box is to be completed by the clinical research assistant:

Pt. Serial # _____

Pt. Initials: _ _

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

20. HAVE YOU HAD ANY PAIN OR SORENESS OF YOUR SKIN THE TREATED AREA IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

21. HAVE YOU HAD DIFFICULTY CHEWING YOUR FOOD IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

22. DO YOU FEEL YOUR RELATIONSHIPS WITH YOUR FAMILY OR FRIENDS HAVE BEEN AFFECTED BECAUSE OF YOUR TREATMENTS IN THE PAST WEEK?

- _____ 1 No
_____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

23. ARE YOU NOW TAKING?

- _____ 1 Liquids only?
_____ 2 Liquids and soft foods only?
_____ 3 Liquids, soft foods and solid foods?

24. ARE YOU TAKING NUTRITIONAL SUPPLEMENTS LIKE ENSURE, RESOUNA OR BOOST?

- _____ 1 No
_____ 2 Yes

This box is to be completed by the clinical research assistant:

Pt. Serial # _____

Pt. Initials: _ _

RTOG Study 0129

Institution _____

Institution # _____

Patient ID# _____

25. ARE YOU BEING FED BY A STOMACH TUBE?

- _____ 1 No
- _____ 2 Yes → How TROUBLESOME was this for you?

_____ 1 _____ 2 _____ 3 _____ 4 _____ 5 _____ 6
hardly any *a great deal*

Signature of person completing form

Date

_____-_____-_____

APPENDIX X

SPITZER QUALITY OF LIFE INDEX

A. ACTIVITY

DURING THE LAST WEEK I HAVE:

2

been carrying out my normal activities, working or studying full-time, or nearly so, in usual occupation; or managing own household; or participating in unpaid voluntary activities, whether retired or not

1

been working or studying, in usual occupation or managing own household or participating in unpaid volunteer activities but requiring major assistance or significant reduction in hours worked or a sheltered situation or was on sick leave

0

not been working or studying in any capacity and not managing own household

B. DAILY LIVING

DURING THE LAST WEEK I HAVE:

2

been self-reliant in eating, washing, toileting and dressing; using public transportation or driving

1

been requiring assistance (another person or special equipment) for daily activities and transportation but performing light tasks

0

not been managing personal care nor light tasks and/or not leaving own home or institution at all

C. HEALTH

DURING THE LAST WEEK I HAVE:

2

been appearing to feel well or reporting feeling "great" most of the time

1

been lacking energy or not feeling entirely "up to par" more than just occasionally

0

been feeling very ill or "lousy", seeming weak and washed out most of the time

D. SUPPORT

DURING THE LAST WEEK I HAVE:

2

been having good relationships with others and receiving strong support from at least one family member and/or friend

1

received or perceived the support from my family and friends as being limited which may be related to my condition

0

received support infrequently or only when absolutely necessary

E. OUTLOOK

DURING THE LAST WEEK I HAVE:

2

usually been appearing calm and positive in outlook, accepting and in control of personal circumstances, including surroundings

1

sometimes been troubled because not fully in control of personal circumstances or has been having periods of obvious anxiety or depression

0

been seriously confused or very frightened or consistently anxious and depressed