RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-03

A RANDOMIZED PHASE III TRIAL TO ASSESS THE EFFECT OF ERYTHROPOIETIN ON LOCAL-REGIONAL CONTROL IN ANEMIC PATIENTS TREATED WITH RADIOTHERAPY FOR CARCINOMA OF THE HEAD AND NECK

Study Chairs

Radiation Oncology

Mitchell Machtay, M.D
Department of Radiation Oncology
Jefferson Medical College
111 S. 11th Street
Philadelphia, PA 19107
(215) 955-6702
FAX (215) 955-0412
Mitchell.Machtay@mail.tju.edu

Matthew B. Parliament, M.D.
(780) 432-8517
FAX *(780)* 432-8380
matthew.parliament@CancerBoard.ab.ca

Medical Oncology

Diane Hershock, M.D.
(215) 614-1858
FAX *(215)* 662-2432
hershock@xrt.upenn.edu

Activation Date: **June 30, 2000**

Update Date: **September 2, 2003**

Version Date: **August 3, 2004 (Broadcast 8/16/04)**
Includes Revisions 1- 6

Closure Date: **November 19, 2003**

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SCHEMA (8/26/02)

STRATIFY

Stage
1. I/II
2. III/IVwithout chemotherapy
3. III/IVwith chemotherapy

Hemoglobin Level
1. 9.0 to < 11.5
2. 11.5 – 13.5

Gender
1. Male
2. Female

RANDOMIZE

ARM 1: Radiotherapy*
66-72 Gy

ARM 2: Radiotherapy*
66-72 Gy
plus

Erythropoietin 40,000 IU SQ
qwk *(Begin 7-10 days pre-XRT)*

*** XRT dose 66-72 Gy depends on stage:**

- T1N0 cancers will receive 2 Gy once daily to 66 Gy in 33 fractions. T1N0 tumors will be treated to 66 Gy in 2 Gy once daily fractions. A "boost" dose of up to 4 Gy in 2 Gy once daily fractions is allowed for slowly responding disease.
- T2N0 cancers will receive 2 Gy once daily to 70 Gy in 35 fractions.
- Stage III/IV cancers will receive "concomitant boost" accelerated fractionation technique to 72 Gy/6 weeks with or without single-agent cisplatin *(See Section 7.4)* OR standard fractionation RT (70 Gy/7 weeks) + weekly low dose platinum-based chemotherapy *(See Section 9.0).*

Eligibility: *(See Section 3.0 for details)* **(8/26/02)**

- Histologically-confirmed squamous cell carcinoma of the head and neck, including carcinoma arising from the oral cavity, oropharynx, larynx, and hypopharynx *(carcinomas of the nasopharynx, nasal cavity/paranasal sinuses or salivary glands are excluded).*
- Planned treatment with definitive irradiation
- No evidence of distant metastases
- Anemia, defined as hemoglobin ≤ 13.5 for men and ≤ 12.5 for women; severe anemia < 9.0 is not eligible.
- Prior transfusion is acceptable, but no anticipated need for transfusion during RT.
- No unstable angina, malignant hypertension or other poorly controlled cardiac illness
- No prior head/neck irradiation; no prior chemotherapy
- Zubrod performance status 0-2
- If the patient is to receive concurrent chemotherapy *(cisplatin)* with accelerated XRT, serum creatinine, creatinine clearance, absolute neutrophil count *(ANC)*, and platelet count must be as specified in Sections 3.1.7 and 3.1.8.
- If stage III or IV, the ability to come for twice-daily radiation treatments or the ability to receive standard fractionation XRT + chemotherapy as per Section 9.0
- No women of child bearing potential except with a no rmal Beta-HcG test and use of contraception
- No prior erythropoietin therapy or recent use *(< 4 weeks)* or planned use of cytokine therapy
- No other malignancies except for carcinoma *in situ*, non-melanomatous skin cancer, or prior malignancies unless disease free > 3 years
- No history of congenital or acquired immunodeficiency or AIDS
- Signed study-specific informed consent prior to randomization.

Required Sample Size: 372 **CASE CREDIT: 2** **9/28/01**

Institution # _____

RTOG 99-03 **ELIGIBILITY CHECK (8/26/02)**

Case # _____ ***(page 1 of 2)***

_____(Y) 1. Does the patient have histologically-confirmed squamous cell carcinoma of the head & neck *(as detailed in Section 3.1.1)*?

_____(N) 2. Does the patient have any distant metastases?

_____(Y) 3. Is definitive radiotherapy planned in continuous course per Section 3.1.3?

_____(Y) 4. Is the patient's hemoglobin ≤ 13.5 for men or ≤ 12.5 for women?

_____(Y/N) 5. If stage III or IV, is the patient able and willing to come for twice-daily RT during the last 2 ½ weeks of therapy?
_____(Y) If no, is the patient able and willing to receive standard fractionation RT with concurrent chemotherapy as per Section 9.0?

_____(Y/N) 6. If stage III or IV, will the patient receive concurrent cisplatin chemotherapy as per Section 7.5?
_____(Y) If yes, are serum creatinine, calculated clearance, ANC, and platelet count as specified in Sections 3.1.7 and 3.1.8?

_____(Y) 7. Zubrod performance status 0-2?

_____(N) 8. Any active infection requiring IV antibiotics, or unexplained fever?

_____(N) 9. Malignant or poorly controlled hypertension as defined in Section 3.2.5?

_____(Y/NA) 10. If the woman is of child-bearing potential, did she have a normal beta-HcG test and use medically acceptable contraception?

_____(N) 11. Does the patient have carcinoma *in situ* without an identifiable invasive component of disease?

_____(Y) 12. If the patient was surgically explored, is there gross residual disease remaining?

_____(N) 13. Has the patient used *(< 4 weeks)* or plan to use other cytokine therapy?

_____(N) 14. Is hemoglobin of < 9.0 due to causes other than chronic disease?

_____(N) 15. Any prior head and neck irradiation, or prior or concurrent chemotherapy?

_____(N) 16. Prior erythropoietin therapy?

_____(N) 17. Is the patient entered on any other RTOG head and neck protocols?

_____(N) 18. Does the patient have unstable angina or any other cardiac conditions listed under Section 3.2.10?

_____(N) 19. Does the patient have a known sensitivity to mammalian cell derived products or to human albumin?

(continued on next page)

Institution # _____

RTOG 99-03 **ELIGIBILITY CHECK (9/28/01, 1/15/02)**

Case # _____ ***(page 2 of 2)***

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 Name

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Social Security Number

_____ 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. Specify T Stage.

_____ 17. Specify N Stage.

_____ 18. Specify hemoglobin *(9.0 to < 11.5 or 11.5-13.5).*

_____ 19. Gender *(for stratification, see Schema)*

_____ 20. Specify Stage Group *(I/II, III/IV without chemotherapy, or III/IV with chemotherapy)*

_____ 21. Erythropoietin Start Date

_____ 22. RT Treatment Start Date

_____ 23. Treatment Assignment

_____(Y/N) 24. IMRT?

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 INTRODUCTION:

1.1 Background (7/13/01)

This study is based on the hypothesis that anemia is detrimental to the chance for local-regional control with radiotherapy, perhaps by contributing to tumor hypoxia. Numerous retrospective series, including a recent secondary analysis of RTOG 85-27, have shown worse local-regional control and/or survival in anemic patients, though evidence of a cause and effect relationship is lacking. Erythropoietin *(Procrit®/Eprex®,Ortho-Biotech)* appears to significantly improve hemoglobin levels in anemic cancer patients and thus offers the ability to test the above hypotheses.

1.2 Hypoxia, Hemoglobin, and Radiotherapy Background (9/28/01, 8/26/02)

It has long been presumed that a major reason for the failure of radiotherapy to control many cancers is due to tumor hypoxia.[1] It is well known that *in vitro* studies of radiosensitivity for most cell lines demonstrate an oxygen enhancement ratio of approximately 2.5-3.5; this means that the dose of radiation required to kill a given amount of cells is about three times higher under hypoxic conditions *($pO2 \leq 3$ mmHg)* than under normal aerobic conditions. Such levels of hypoxia have in fact been demonstrated clinically in human tumors.[2,3]

Seriously damaging to the theory of hypoxia as a major factor-influencing outcome is the fact that trials of agents expected to combat hypoxia have mostly been negative. The earliest series of studies reported by the Radiation Therapy Oncology Group *(RTOG)* used the drug misonidazole, which has definite ability to radiosensitize hypoxic cells in preclinical studies. Randomized trials of this drug in carcinoma of the cervix and head and neck showed no suggestion of any benefit.[4,5] More recently the RTOG reported the results of a randomized trial on a newer generation hypoxic cell sensitizer, etanidazole, in advanced head and neck cancer. Again, this drug showed no clinical benefit.[6] Trials using neutron irradiation, which overcomes hypoxic cell radioresistance, have been similarly discouraging, occasionally showing increased response rates and/or local-regional control, but with an increase in complication rates[7].

As summarized by Brown, several hypotheses exist to explain the failure of hypoxic cell radiosensitizers in the clinic. These include: 1) Toxicity of the radiosensitizers prevents their use at optimal radiosensitizing dosages; 2) The adverse effect of tumor hypoxia is partly corrected by fractionation in radiotherapy; and 3) Not all tumors in clinical trials have hypoxia.[8]

Available evidence would suggest the Hypotheses 2 and 3 are only partly true, while there is no question that the toxicity of the radiosensitizers limits their clinical utility *(Hypothesis 1)*. A better test of the theory of hypoxia would be to use an agent that has minimal or no toxicity, thus allowing maximal dosages to be given.

It has been suggested that a relatively simple method of increasing the oxygen delivery to tumor cells would be to increase the hemoglobin level within the circulation. Several studies in carcinoma of the cervix and head and neck have shown a negative effect of anemia on local control in patients treated with radiotherapy.[9,10] Of course this does not imply a cause and effect relationship. However, Bush reported the results of a randomized trial in patients with cervix cancer, comparing the use of elective transfusions during radiotherapy to keep the hemoglobin level > 12.5 vs. standard therapy, which was to only transfuse if the hemoglobin fell below 10. This study showed a statistically significant increase in pelvic control among patients randomized to the "transfusion" arm.[11] It is important to note that while analysis was performed in an intent -to-treat fashion, not all of the patients in the "transfusion" arm actually received transfusions, while some of the patients in the control arm did receive transfusions.

This study has not been reproduced for several reasons, including the wide interest in studies of hypoxic cell radiosensitizers, combined chemoradiotherapy, and other treatment modifiers in the 1980's. Perhaps most importantly, though, was the increased awareness of the iatrogenic complications of blood transfusions, most notably AIDS and hepatitis. In most current clinical trials of radiotherapy, there is no mention of guidelines for transfusion.

Recently, the growth factor erythropoietin *(Epoetin alfa)* has been synthesized in the laboratory and is now commercially available. This drug has shown considerable efficacy and minimal toxicity in the treatment of anemia related to chronic renal failure. More recently, it has shown efficacy in the treatment of anemia resulting from chemotherapy.[12] The use of Epoetin alfa during radiotherapy or combined chemoirradiation has been less extensively tested. However, several randomized studies in patients receiving radiotherapy

have shown a significant increase in hemoglobin compared to controls.[13, 14] These studies have been small and do not address the question of whether the obvious improvement in hemoglobin seen with Epoetin alfa results in an improvement in tumor local control. Given the fact that not all tumors have significant hypoxia, one would expect a large number of patients to be required to determine if an improvement in hemoglobin results in improved outcome.

The Radiation Therapy Oncology Group recently analyzed 521 patients treated as part of RTOG 85-27 *(a randomized study of XRT with vs. without etanidazole)* with respect to anemia, as reported by Lee et al.[15] Patients with anemia *(defined as hemoglobin <14.5 for men and < 13.0 for women)* had significantly worse overall survival *(p=.0003)*. A trend was noticed with respect to local-regional control, with anemic patients having a worse outcome *(p=.065)*. Of note, there was also a trend toward fewer late complications in anemic patients *(p=.054)*; it is unclear whether this could reflect hypoxia in normal tissues as well as tumor or whether this finding was an artifactual result of anemic patients having shorter survival and thus less time to develop late complications.

Given RTOG's long history of studying hypoxia as a clinically significant barrier to radiocurability and its recent demonstration of a relationship between anemia and outcome, it is logical that the next step would be a large scale intervention study to overcome anemia. At this time it would appear that erythropoietin is the safest and most effective way to do this in patients undergoing radiotherapy.

This study will utilize different radiotherapy fractionation schemata depending upon stage and whether or not concurrent chemotherapy *(cisplatin)* is to be used. Stage I/II patients will be treated with conventional fractionation *(2 Gy per day)* to 66-70 Gy, without chemotherapy. Stage III/IV patients will be treated more aggressively, with accelerated "concomitant boost" radiotherapy +/- concurrent cisplatin chemotherapy. The concomitant boost accelerated radiotherapy schema is based on pilot data from the M.D. Anderson Hospital,[16] as well as preliminary data from RTOG's large scale randomized trial *(RTOG 90-03)*,[17] a study in which eligibility was limited to stage III/IV disease. In this trial, patients treated with the accelerated concomitant boost regimen had improved local-regional control compared with conventional *(2 Gy/day to a total dose of 70 Gy in 35 fractions)* radiotherapy.

Since the completion of RTOG 90-03, however, there have been increasing data supporting the efficacy of concurrent chemotherapy with radiotherapy as superior to radiotherapy alone. This has manifested in survival as well as local-regional control. Notable studies include randomized data from the Eastern Cooperative Oncology Group[18] as well as trials from other groups reporting improved survival for Stage III/IV head/neck cancer treated with concurrent chemoradiotherapy compared with conventional radiotherapy.[19-20] Based on these and other recent data, it can no longer be considered appropriate to deny patients the option of concurrent chemotherapy if they meet chemotherapy eligibility criteria and desire chemotherapy. There are fewer data studying the combination of accelerated radiotherapy with concurrent chemotherapy. However, several institutional pilot studies have demonstrated the feasibility of combining accelerated radiotherapy with chemotherapy. The RTOG recently completed a multicenter phase II trial *(RTOG 99-14)* combining accelerated concomitant boost radiotherapy with two cycles of concurrent cisplatin. The study completed successful accrual in a very short time period and is currently undergoing analysis. Several larger trials from Europe have reported on the feasibility of combining accelerated radiotherapy with concurrent chemotherapy, including one trial which suggested improved tumor control with concurrent chemotherapy/accelerated radiotherapy versus accelerated radiotherapy alone.[21] The combination of accelerated radiotherapy plus chemotherapy has been shown to be feasible in the United States, as well. [22]

In light of these recent data, which were not available when this study was first written, the current study will allow *(though not mandate)* patients with Stage III/IV SCCHN who are receiving accelerated XRT to also receive concurrent cisplatin x 2 cycles *(as per RTOG 99-14)*. The dose of cisplatin in this study will be reduced in comparison to RTOG 99-14 *(from 100 mg/m2 per cycle to 80 mg/m2 per cycle*), in an effort to minimize the fluid/electrolyte problems associated with high dose cisplatin in patients receiving accelerated fractionation XRT. Patients with Stage III/IV SCCHN also may receive standard fractionation XRT *(70 Gy/7 weeks)* with concurrent chemotherapy. There are several well-validated regimens of concurrent chemoradiotherapy when standard fractionation XRT is used: two of the recommended regimens for this study involve weekly low dose platinum/paclitaxel. Low dose platinum/paclitaxel was studied in RTOG 97-03 with acceptable toxicity and very encouraging results.[23] Similar data with similar

regimens have been reported by groups at Johns Hopkins University,[24] Brown University,[25] and the University of Maryland.[26] A regimen of single agent cisplatin is recommended for those sites without access to paclitaxel or for patients who have a contraindication to paclitaxel. This regimen was validated in the study by Bachaud.[27].

There are fewer data on the relationship between anemia and local control in the setting of patients treated with both radiotherapy and chemotherapy. One prospective but non-randomized European study showed that anemia was associated with inferior pathologic response and local control in patients treated with chemoradiotherapy plus surgery.[28] These authors also showed that rhEpo could reverse anemia and was associated with a statistically significantly better pathologic response rate and local control than in historical control patients. The magnitude of the difference in outcome between anemic patients and non-anemic patients seen in that study was similar to that observed in studies of XRT alone.

1.3 QOL Background ***(3/5/04)*** Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data; see Section 13.2.

Fatigue is one of the most common problems for patients receiving treatment for cancer.[29-32] Many studies document the existence of a fatigue syndrome related to treatment with radiation therapy and that it is not specific to disease type or radiation treatment site.[31] Fatigue may be attributed to the side effects of the various treatment modalities or it can be a direct result of the disease process.[33] It is not clear why patients undergoing radiation therapy have fatigue. It has been suggested that fatigue may be related to weight loss, negative mood, pain, or length of treatment.[34] Anemia occurs frequently in patients with cancer, and fatigue, as well as other cancer-related symptoms that may have a significant effect on a patient's quality of life.[32, 35,36]

Many methods and tools for the measurement of fatigue have been reported in the literature.[31] For this study we have chosen the Fatigue Symptom Inventory *(FQ)*, a 14-item self-report measure that is designed to measure the intensity, frequency, and daily pattern of fatigue as well as its impact on quality of life.[29] All items *(except those measuring daily pattern of fatigue and number of days of fatigue)* are rated along 11-point scales *(0=Not at all fatigued; 10=As fatigued as I could be)*. Daily pattern of fatigue is rated along a 5-point scale *(0=Not at all fatigued; 4=No consistent pattern of fatigue)*, while number of days ranges from 0 to 7 in the past week.

Quality of life measurement is a multidimensional construct including physical, social, functional and emotional dimensions.[37-39] We have chosen QOL-RTI*(H&N)*[38-40] as a QOL measure for this study. The QOL-RTI is a general tool which assesses components of physical function *(nine questions)*, emotion *(seven)*, family/socioeconomics *(six)*, and overall QOL *(three)*, along with the H&N specific companion module which contains 14 questions related to pain *(two)*, appearance *(one)*, speech *(one)*, chewing and swallowing *(five)*, mucous and saliva *(three)*, taste *(one)*, and cough *(one)*.[40] The QOL-RTI *(H&N)* is also set up in an 11point scale and is a patient completed subjective measure.

In addition to the two measurements described above, the brief List Performance Status Scale *(PF)* and the Quality of Life Linear Analog Scale Assessment *(LAS)* will be used. The LAS scale has been used in large-scale studies of erythropoietin in cancer patients receiving chemotherapy.[55] QOL studies have been used in many previous RTOG head and neck studies and QOL studies from other academic centers. The PF is relatively straightforward to perform and focuses on the lifestyle implications of the most common and relevant acute and late morbidity from radiotherapy.

2.0 OBJECTIVES (9/28/01)

2.1 The primary purpose of this trial is to test whether erythropoietin given during radiation or chemoradiation will improve the local-regional control rate in squamous cell carcinoma of the head and neck treated with definitive radiation or chemoradiation. Its secondary purpose is to test whether erythropoietin will improve survival and to identify patterns in first failure.

2.2 This study will test for a significant increase *(>1.5 gm)* in the hemoglobin level between the baseline value and the value at 28 days after starting erythropoietin among patients randomized to Arm 2.

2.3 Other secondary objectives will include toxicity and quality of life. ***(3/5/04)*** Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data; see Section 13.2.

3.0 ELIGIBILITY

3.1 Conditions for Patient Eligibility (8/26/02)

3.1.1 Histologically-confirmed invasive squamous cell carcinoma of the head and neck, including carcinoma arising from the oral cavity, oropharynx, larynx and hypopharynx *(carcinomas of the nasopharynx, nasal cavity/paranasal sinuses or salivary glands are excluded).*

3.1.2 No distant metastatic disease.

3.1.3 Plan for definitive radiotherapy**,** in continuous course**.** Patients who have been surgically explored with gross residual disease remaining are eligible. Patients who have undergone neck dissection with or without biopsy of the primary tumor but have not had radical surgery for the primary tumor will also be eligible.

3.1.4 Anemia, defined as hemoglobin $\leq$ 13.5 for men and $\leq$ 12.5 for women. Any single hemoglobin measurement that is < 13.5 *(< 12.5 for females)* is acceptable for eligibility, as long as it is obtained prior to registration. Transfusion prior to randomization is acceptable but there should be no anticipated need for transfusion during therapy.

3.1.5 If stage III or IV, the ability and willingness to come for twice-daily radiation treatments for the last 2 ½ weeks of therapy.

3.1.6 Zubrod performance status 0-2.

3.1.7 If the patient is to receive concurrent chemotherapy *(cisplatin)* along with accelerated fractionation XRT, serum creatinine must be $\leq$ 1.5 mg/ml and creatinine clearance must be $\geq$ 50 ml/min determined by 24-hour collection or nomogram within 3 weeks of registration.

For Males:

$$\text{Creatinine clearance } (mL/min) = \frac{(140\text{-age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}$$

For Females:

$$\text{Creatinine clearance } (mL/min) = 0.85 \times \frac{(140\text{-age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}$$

3.1.8 If the patient is to receive concurrent chemotherapy *(e.g., cisplatin as per Section 7.4, or other chemotherapy as per Section 9.0),* patients must have adequate hematologic reserve, including absolute neutrophil count *(ANC)* $\geq$ 2000 cells/mm^3 and platelet count $\geq$ 100,000 cells/mm^3 within 1 week of registration.

3.1.9 All laboratory studies must be completed as specified in Section 4.0.

3.1.10 Signed study-specific informed consent form.

3.2 Conditions for Patient Ineligibility (9/28/01)

3.2.1 Histology other than squamous cell carcinoma.

3.2.2 Carcinoma *in situ (protocol site)* without an identifiable invasive component of disease.

3.2.3 Women of childbearing potential except with a normal Beta-HcG pregnancy test and use of a medically acceptable form of contraception. There are no adequate studies of erythropoietin in pregnant women or nursing women. This study thus involves unpredictable and potentially adverse risks to the participant and to the embryo/fetus or nursing infant. There is the possibility that erythropoietin as given in this study may be teratogenic, both to oocytes and spermatogonia. In addition, radiotherapy as given in this protocol may also be teratogenic. Patients *(both men and women)* who are sexually active and of reproductive potential must therefore practice medically appropriate contraception.

3.2.4 Active infection requiring i.v. antibiotics or unexplained fever.

3.2.5 Malignant or poorly controlled hypertension, defined as symptomatic hypertension or diastolic blood pressure $\geq$ 100 despite antihypertensive medication.

3.2.6 AIDS or other history of congenital or acquired immunodeficiency. HIV test is not required for enrollment.

3.2.6.1 Patients with HIV and/or AIDS appear to have significantly enhanced mucosal reaction to radiation therapy. The increased mucosal reactions could result in radiotherapy interruptions which could significantly lower local regional control.

3.2.7 Recent *(<4 weeks)* use or planned use of other cytokine therapy *(e.g. G-CSF, interleukins, interferons, etc.)*

3.2.8 Severe anemia defined as hemoglobin < 9.0 *(transfusion prior to enrollment to achieve hemoglobin ≥ 9.0 is acceptable)*.

3.2.9 Anemia confirmed to be due to causes other than anemia of chronic disease *(e.g. iron-deficiency anemia)*.

3.2.10 Unstable angina or other poorly controlled cardiac disease or other acute/subacute illness that would make the need for transfusion likely.

3.2.11 Prior head and neck irradiation; prior chemotherapy.

3.2.12 Prior erythropoietin therapy.

3.2.13 Other malignancies except for carcinoma *in situ*, non-melanomatous skin cancer, or prior malignancies unless disease free > 3 years.

3.2.14 Patients entered onto other RTOG head and neck protocols.

3.2.15 Known hypersensitivity to mammalian cell-derived products or to human albumin.

4. 0 PRETREATMENT EVALUATION

4.1 History and Physical Examination including tumor diagrams and dental evaluation.

4.2 Laboratory Studies (8/26/02)

4.2.1 CBC, differential, platelets *(for baseline, must be done within 1 week of registration. Note that any hemoglobin level [<13.5; < 12.5 for females] is acceptable for eligibility; see Section 3.1.4)*

4.2.2 Reticulocyte count *(within 3 weeks)*

4.2.3 B-12 and folate levels *(within 3 weeks)*

4.2.4 Fe, Ferritin [*and/or transferrin levels*], *(within 3 weeks)*

4.2.5 Chemistry 11 panel *(Sodium, Potassium, Chloride, C02, BUN, Serum Creatinine [24 hr. or calculated creatinine clearance are acceptable], Glucose, Calcium, Bilirubin, Alkaline Phosphatase, SGOT (or SGPT) [within 3 weeks]*.

4.2.6 Pregnancy test *(beta HcG)* prior to study entry for women of childbearing potential.

4.2.7 If the patient is to receive concurrent chemotherapy *(cisplatin)*, a creatinine clearance and absolute neutrophil count *(ANC)* must be done *(See Sections 3.1.7 and 3.1.8).*

4.3 Radiographic Studies

4.3.1 CXR or Chest CT Scan *(within 6 weeks prior to registration)*

4.3.2 CT *(or MRI)* of the head and neck with the exception of T1-2 glottic cancer *(within 4 weeks of registration).* The use of radiation therapy "treatment planning" CT is acceptable.

4.4 Baseline Quality of Life *(3/5/04)* Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data; see Section 13.2.

4.4.1 Baseline evaluations must be performed prior to the start of any protocol treatment.

5.0 REGISTRATION PROCEDURES (7/13/01, 9/2/03)

5.1 Each institution must submit a Study Agent Shipment Form *(Appendix VI)* to the CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case (the shipment form is only submitted once). Allow adequate processing *time (7-10 days)* before calling to register your first case. **Canadian institutions must also submit all the regulatory documents itemized in Section 7.1.6.7.**

5.2 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 am to 5:00 pm 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

6.1 Dose/Fractionation (8/26/02)

NOTE: The dose/fractionation scheme to be used will depend on the tumor stage. In all cases, radiotherapy will be a continuous course, without any planned breaks.

6.1.1 *Stage I or II (T1N0 or T2N0) tumors*: T1N0 tumors will be treated to 66 Gy in 2 Gy once daily fractions *(33 fractions).* A "boost" dose of up to 4 Gy in 2 Gy once daily fractions is allowed for slowly

responding disease. All T2N0 tumors will be treated to 70 Gy in 2 Gy once daily fractions *(35 fractions)*.

6.1.2 *Stage III or IV (T3/4 or N+)*: Patients receiving concurrent chemotherapy as per Section 9.0 will receive standard fractionation XRT as per Section 6.1.1 *(70 Gy in once-daily fractions of 2 Gy)*. The "concomitant boost" accelerated fractionation schema will be used if the patient is being treated with XRT alone, or if the patient is being treated with any chemotherapy regimen other than as described in Section 7.4 *(single agent cisplatin weeks 1 and 4)*. The technique for concomitant boost accelerated radiotherapy *(if used)* is as follows:

6.1.2.1 Initial "large" volume: This volume *(incorporating the primary tumor and elective lymph node areas)* will be treated in 1.8 Gy q.d. fractionation to a total dose of 54 Gy *(with spinal cord limited to 45 Gy)* over a total of 30 treatment days *(6 weeks)*. The dose to the supraclavicular fossa in an uninvolved hemineck*(s)* may be limited to 50.4 Gy. After a dose of 32.4 Gy/18 Fx/3 ½ weeks, the concomitant boost will begin *(See Section 6.1.2.2)*.

6.1.2.2 Concomitant "boost" volume: This volume *(incorporating gross primary and gross nodal disease)* will begin treatment when the dose to the "large" volume reaches 32.4 Gy *(after 18 fractions)*. This "boost" volume will be treated in 1.5 Gy q.d. fractionation on the same days as the continuing treatment to the "large" volume. These two treatments must be given at least 6 hours apart *(treatment times must be recorded)*. The "boost" volume will be treated for 12 treatment days, for a total dose of 18 Gy. Including the contribution from the "large" field, therefore, the total dose to gross disease will be 72 Gy in 6 weeks. Exception: In patients with positive nodes in whom post-XRT neck dissection is definitely planned, the dose to the involved nodes may be limited to 60-66 Gy. The dose to the primary tumor must still be 72 Gy. Electrons may be used to supplement the dose to clinically positive lymph nodes.

6.2 Equipment Requirements

Treatment must be given with megavoltage equipment *(linear accelerator or ^{60}Co therapy)*. Minimum treatment distance is 80 SSD or 100 SAD. Simulation of all fields is required. Field shaping using customized alloy blocking or multileaf collimation is required. Portal films of all fields *(except electron fields)* must be performed prior to starting treatment.

6.3 Field arrangements

Field arrangements will be at the discretion of the treating physician. It is anticipated that most patients will be treated with "standard" three-field technique to the comprehensive neck plus primary site followed by shrinking-field conedowns, although there are notable exceptions *(e.g. early glottic cancer)*. The policy on "elective" lymph nodal coverage is as follows:

6.3.1 *Oral Cavity*: The bilateral submandibular and upper and mid jugular nodes will be treated to a minimum of 46 Gy in all cases. Lower jugular nodal irradiation to 46 Gy is recommended in all cases. For N0 cases, irradiation of the posterior cervical chain is not mandatory.

6.3.2 *Oropharynx-well lateralized primary lesion*: For T3-4 or N+ lesions, comprehensive bilateral nodal irradiation *(including retropharyngeal nodes at the base of skull)* to a minimum of 50.4 Gy is mandatory. For T1-2N0 well-lateralized lesions, nodal irradiation may be limited to the ipsilateral nodal regions.

6.3.3 *Oropharynx-midline lesions:* Comprehensive bilateral nodal irradiation *(including retropharyngeal nodes)* is required for all stages.

6.3.4 *Glottis:* For T3-4 N0 lesions, bilateral nodal irradiation of the upper, mid, and lower jugular nodes is mandatory. For N+ lesions, the posterior cervical nodes should also be irradiated. For T1-2N0 lesions, elective nodal irradiation is not required.

6.3.5 *Supraglottic Larynx*: For T3-4 or N+ lesions, bilateral nodal irradiation of the upper/mid/lower jugular nodes and posterior chains is required. For T1-2N0 lesions, irradiation of the posterior cervical chain is not required. For involvement of the pyriform sinus or oropharynx, the field must extend superiorly to the base of skull.

6.3.6 *Hypopharynx*: Comprehensive bilateral nodal irradiation *(including retropharyngeal nodes)* is required for all stages.

6.4 Dose Calculation

6.4.1 *Daily Fractions*

6.4.1.1 Opposed lateral fields: On the central ray at mid-separation of beams, with the exception of the treatment of T1-2 glottic cancer, in which *(due to the use of a small field size)*, the dose may be renormalized to the 95-99% isodose curve.

6.4.1.2 Anterior low neck/supraclavicular fields: If treated anterior only, prescription will be to a depth of 3 cm below the skin surface.

6.4.1.3 Other arrangements of 2 or more beams: At the intersection of the central ray of the beams.

6.4.2 *Isodose Plans*: A minimum of one isodose plan will be generated through the center of the target volume, with cumulative isodose distributions plotted.

6.4.3 *Dose Homogeneity*: Variation within the target volume should not exceed 10% of the specified target dose. Wedges and/or compensators may be needed to achieve this. For targets close to the skin surface *(e.g. anterior commissure or superficial nodes)*, bolus material should be placed on the skin when using 6MV or greater energies.

6.5 Normal Tissue Considerations

Suggested maximum dose to any portion of the spinal cord is 45 Gy. It may be necessary to consider the dose to the spinal cord from posterior electron fields, particularly if the patient has a thin neck and/or relatively high electron energies are used.

6.6 Time and Dose Modifications

Treatment breaks are strongly discouraged. Mucositis should be actively supported with a analgesics, topical anesthetics, enteral feedings and/or intravenous fluids. **The use of amifostine is not allowed.** Treatment breaks must be clearly indicated in the treatment record. Treatment breaks, if necessary, should not exceed one week *(5 days)* and should be allowed only for healing of severe mucositis. If treatment interruptions exceed five treatment days total, the case will be considered a protocol deviation.

6.7 Protocol Compliance

Score	Total Dose to Gross Disease	Spinal Cord Dose	XRT Elapsed Time
Per Protocol	≤ 5%	≤ 47 Gy	≤ 49 days
Minor Variation	5-10%	47-50 Gy	50-57 days
Major Deviation	> 10%	> 50 Gy	> 57 days

7.0 DRUG THERAPY *(ALSO SEE SECTION 9.0, "OTHER THERAPY')*

Institutional participation in chemotherapy studies must be in accordance with the medical oncology quality control guidelines stated in the RTOG procedures manual.

7.1 Erythropoietin *(Epoetin alfa, Procrit®/Eprex®, Ortho Biotech)* (7/13/01)

7.1.1 *Formulation/Supply*

Erythropoietin will be supplied by Ortho Biotech. See Section 7.1.6 for distribution procedures. The vials should be stored at 2° to 8° Centigrade *(36° to 46° F)*. Do not freeze or shake.

7.1.2 *Administration*

Patients randomized to receive Epoetin alfa *(Arm 2)* will receive 40,000 IU given subcutaneously once per week. Patients should be encouraged to take iron supplementation *(See Section 7.2)*. Treatment with Epoetin alfa will begin 7 to 10 days prior to the start of radiotherapy. It is anticipated that the patient will have just received their second dose of Epoetin alfa upon starting XRT. Treatment will be administered in the radiation oncology clinic or medical oncologist's office. Patients will continue Epoetin alfa injections on a weekly basis until the completion of radiotherapy. It is anticipated that a total of 8 or 9 doses of Epoetin alfa will be given *(8-9 weeks)*, after which point, Epoetin alfa will be discontinued. However, if radiotherapy is interrupted *(e.g. for mucositis)*, Epoetin alfa will still be given during the break*(s)* thus some patients may receive more than 9 doses. Stage III or IV patients *(who receive an accelerated fractionation schema)* will generally receive one less dose of Epoetin alfa than Stage I and II patients.

7.1.3 *Dose Modifications* **(8/26/02)**

Epoetin alfa will be discontinued temporarily if/when hemoglobin rises to ≥ 16 *(≥ 14 for females)* and restarted if/when it drops to ≤ 13.5 *(≤ 12 for females)* Hemoglobin will be checked weekly; if/when hemoglobin drops to ≤ 13.5, Epoetin alfa will be restarted at 30,000 IU per week.

If the patient's hemoglobin fails to increase by ≥ 1 g/dl above baseline level after the fourth Epoetin alfa injection, the dose of Epoetin alfa will be increased to 60,000 IU subcutaneously once per week.

7.1.4 *Toxicity* **(8/26/02)**

Erythropoietin is generally well tolerated. The most frequent side effects are hypertension, headache, rash, malaise, fever, diarrhea, arthralgias, and nausea/vomiting and is contraindicated in patients with malignant or poorly controlled hypertension. Other side effects may include allergic reactions with hives, rash, red eyes, chills, shortness of breath, increased heart rate or hypotension. There have been case reports of hypertensive encephalopathy and seizures in patients compared with controls and seizures in patients receiving Epoetin alfa for chronic kidney disease compared with controls. Polycythemia may occur if hemoglobin is not carefully monitored *(See Section 7.1.3)*. One study in patients who were undergoing open heart surgery and receiving Procrit®/Eprex® suggested that these patients *(with severe heart disease)* may have a higher risk of life-threatening or even fatal blood clots than patients who did not receive Procrit®/Eprex®. However, the percentage of Epoetin alfa treated patients who died in this

study was comparable to that reported in the literature for patients undergoing cardiac surgery who were not treated with Epoetin alfa.

There have been post-marketing reports of rare occurrences of pure red cell aplasia *(PRCA)* associated with antibody formation against erythropoietin in chronic renal failure patients. This paradoxical effect has been associated with neutralizing anti-erythropoietin antibodies. Most of these cases have occurred with Eprex®, an erythropoietin formulation which is marketed outside of the U.S., as described in a *New England Journal of Medicine* article.[56] Most of the patients affected with this problem were taking erythropoietin for a a median duration of 11 months (range 1-92 months). However, it is possible for any formulation of erythropoietin to induce antibodies, and rarely, PRCA. If a patient develops significantly worsening anemia during study or in follow up that is not attributable to other causes, consideration should be given to the possibility of anti-erythropoietin antibodies and/or PRCA. Treatment with Epoetin alfa must be discontinued immediately. Patients should not be switched to another erythropoietin, and a full investigation *(including bone marrow examinations)* should be conducted.

7.1.5 *Protocol Compliance*

Score	**EPO Treatment**
Per Protocol	2 doses before start of XRT and at least 5 doses during XRT
Minor Variation	1 dose before XRT and at least 5 doses during XRT or 2 doses before XRT and 3-4 doses during XRT
Major Deviation	0 doses of EPO before start of XRT or < 3 doses during XRT

7.1.6 *General Distribution Procedures* **(7/13/01, 8/26/02, 9/2/03)**

7.1.6.1 Erythropoietin will be supplied and distributed by Ortho Biotech. Each institution must submit a Study Agent Shipment Form *(Appendix VI)* to CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the Study Agent Shipment Form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case. Upon receipt of the Study Agent Shipment Form, RTOG will forward a supply of yellow study-specific product labels to the person responsible for the study agent.

7.1.6.2 Non-patient specific supplies will be shipped to the institution for each patient randomized to Arm 2. All study drug supplies will be stored securely until the time of administration. Affix the yellow labels from RTOG on all shipments upon receipt and store at 2° to 8° Centigrade *(36° to 46° F)*. Erythropoietin shipped to the sites for RTOG 99-03 must be used only for this study.

7.1.6.3 All study drug supplies will be accompanied by accountability and shipping documents which must be maintained by the Investigator or designee *(e.g., study pharmacist, study nurses, etc.)*. These records will be available for inspection, and a copy will be supplied to Ortho Biotech on request. Information recorded on these accountability and shipping documents will include lot numbers, quantity received and to whom dispensed. Lot numbers must be recorded on the case report forms.

7.1.6.4 After all study patients have completed protocol treatment at the site, the Investigator will return all remaining supplies as per Section 7.1.6.5.

7.1.6.5 Any/all damaged, suspect and/or unused drug must be returned for destruction. Sites must not destroy drug on site. To return damaged, suspect, or unused drug, contact RTOG Headquarters *(fax 215-574-0300)* for an Ortho Biotech Supply Return/Destruction Form. All returns must be accompanied by this form. For questions concerning study drug/shipments, contact Paul Stoffel, Ortho Biotech, *(908)* 541-4582 *(U.S. sites)* or Kara Lee McWatters, *(416)* 382-4911 *(Canadian sites).*

- U.S. Institutions should return study drug to:

Director of Clinical Supplies
(RTOG 99-03 for destruction)
RW Johnson PRI
Welsh and McKean Roads
Spring House, PA 19477-0776

- Canadian institutions should return study drug to:

Paula Abbott
Clinical Supplies Unit
(RTOG 99-03 for destruction)
Janssen-Ortho Inc.
19 Greenbelt Drive
Toronto, Ontario
Canada M3C 1L9
***(416)* 449-9444**

7.1.6.6 The erythropoietin supplied for this study will not be used for any purpose other than for this study or administered other than as described in this protocol.

7.1.6.7 **Shipments to Canada**

Ortho Biotech *(a division of Janssen-Ortho Inc.)* will ship erythropoietin *(Eprex®)* from its corporate office in Toronto, Ontario to participating institutions after RTOG notification. The following documents must be on file with Ortho Biotech:

- Ethics committee approval letter clearly identified with Protocol title, study-specific Consent form, version dated, and signed and dated Research Ethics Board *(REB)* Attestation form;
- Ethics Committee composition *(current);*
- Updated investigator's list with trial coordinators and pharmacist's name;
- Investigational staff documents: Qualified Investigators Undertaking *(QUI)* form *(Principal Investigator only),* current CV with signature and date, and Investigator Financial Disclosure forms for all investigational staff: physicians, coordinators and pharmacist.

The above must be sent as a complete package to:

Karalee McWatters
Ortho Biotech Canada
19 Green Belt Drive
Toronto, Ontario
M3C 1L9
Toll free#: 1-800-387-8781, EXT. 4911
Phone: (416) 382-4911
FAX: (416) 382-4914

7.2 Iron Supplementation

Erythropoietin will be less effective, or ineffective, in the absence of sufficient iron stores. Patients randomized to Erythropoietin should therefore be encouraged to take iron supplementation.

7.2.1 *Recommended Iron Supplementation*

The goal is to deliver 180 mg of elemental iron per day. Therefore, consider prescribing a commercially available form of iron supplementation in which the iron is delivered as a polysaccharide-iron complex *(e.g., Niferex®)* in order to minimize gastrointestinal effects.

7.2.2 *Alternative*

Alternatively, patients may take Ferrous Sulfate 300 mg t.i.d., in tablet or elixir form, though gastric intolerance and constipation are more likely and may greatly limit compliance.

7.2.3 *Administration of Iron Supplementation*

Ideally, iron supplements should be given on an empty stomach and/or with ascorbic acid to maximize absorption. Note: The administration of antacids *(as are commonly used as part of "Magic Mouthwash" solutions)* may interfere with iron absorption and thus should not be used within 2 hours of iron administration.

7.2.4 *Monitoring of Serum Iron Levels* **(8/26/02)**

Serum iron and ferritin levels and/or transferrin levels should be checked every three weeks in patients randomized to receive Epoetin alfa *(See Section 11.1)*.

7.2.5 *Iron Supplementation in the "Control" Arm*

Patients in the control arm *(Arm 1)* will not be given iron supplementation.

7.3 Study Guidelines on Transfusion

7.3.1 Red blood cell transfusion is generally discouraged after registration though it is recognized that in this population, transfusions may be necessary. Patients who are transfused prior to enrollment are eligible. Patients who receive a transfusion*(s)* during treatment will still be considered to be on-study. It is ultimately up to individual physician discretion whether or not to transfuse his/her patient. It is expected that transfusions would be less likely in the Epoetin treatment arm, though patients in either arm may require transfusions. If a patient has been randomized to Epoetin and requires transfusion, Epoetin alfa will be continued. **(8/27/01)**

7.3.2 The general guidelines for transfusion are as follows:

- Acute bleeding with signs of hypovolemia.
- Anemia in the presence of unstable angina, myocardial infarction, severe congestive heart failure, sepsis, stroke or other condition in which oxygen delivery must be improved for a potentially life threatening process.
- Patients with known cardiovascular disease in whom the hemoglobin level falls below 8.0.

7.3.3 The need for transfusion and documentation of the reason*(s)* for transfusion should be reported to the study chair within seven days after transfusion and must be recorded on the RTOG data forms.

7.4 Cisplatin (8/26/02)

7.4.1 Cisplatin chemotherapy may be given concurrently with accelerated radiotherapy for patients with Stage III/IV disease. If this is planned, it must be disclosed at the time of registering the patient *(See Section 3 and Eligibility Checklist).*

7.4.2 If cisplatin chemotherapy + accelerated radiotherapy is given, it will be given according to the following schedule:

Day 1 of radiotherapy: Cisplatin 80 mg/m2 IV.

Day 22 of radiotherapy: Cisplatin 80 mg/m2 IV *(see Section 7.4.4)*

7.4.3 Suggested Pre-medication/hydration/administration regimen for cisplatin:

- Granisetron 0.7-1 mg I.V., ondansetron 32 mg I.V. *(or comparable high potency anti-emetic)* 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 treating physician.
- Any pre-existing dehydration must be corrected prior to cisplatin administrations. **All patients must receive vigorous hydration and diuresis.** A suggested regimen is pre-hydration of 1 liter D5 ½ NS over 2-4 hours.
- Mannitol 12.5g *i.v*. bolus immediately prior to cisplatin.
- Cisplatin 80 mg/m2 in 500 ml NS over 1-2 hours will then be given, with post-hydration administered as clinically indicated.
- In addition to the hydration mentioned above, it is **strongly recommended** that patients receive at least 1000 ml *(or more*) *i.v.* hydration in the 24 hours after cisplatin administration in order to prevent dehydration, particularly since patients are likely to have fluid/electrolyte problems due to head/neck tumor and/or radiation mucositis. This may require overnight hospitalization because of dehydration issues.

7.4.4 Dose modifications for Day 22 Cisplatin

7.4.4.1 Neutropenia may occur. If on the day of scheduled treatment with cisplatin the absolute neutrophil count *(ANC)* is < 1000, hold treatment until ANC > 1000, and then treat at 100% dose.

7.4.4.2 Thrombocytopenia may occur. If on the day of scheduled treatment with cisplatin the platelet count is ≥ 75,000, the patient may receive cisplatin at cycle 2.

7.4.4.3 Neurotoxicity: If any signs of paralysis, moderate myopathy, moderate weakness, seizure, or peripheral neuropathy occur, discontinue cisplatin.

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

Creatinine Clearance	Cisplatin Dose
> 50 ml/min.	80 mg/m^2
40-50 ml/min	60 mg/m^2
< 40 ml/min.	Discontinue cisplatin

7.4.4.5 Mucositis: If XRT is held on Day 22 because of mucositis or other local toxicity, hold cisplatin until XRT is resumed. Decrease cisplatin dose to 60 mg/m^2.

7.5 Toxicity Reporting

7.5.1 The revised NCI Common Toxicity Criteria *(CTC)* Version 2.0 will be used to score all chemotherapy and acute radiation *(≤ 90 days)* toxicities associated with this protocol. Radiation toxicities appearing or persisting beyond 90 days from start of protocol treatment will be evaluated using the RTOG Late Radiation Morbidity Scoring Scheme in Appendix IV. The CTC version 2.0 and the CTC search tool are available on the CTEP home page ***(http://ctep.info.nih.gov)***. All appropriate treatment areas should have access to a copy of the CTC. The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent*(s)* should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.

7.5.1.1 Any ADR which is both serious *(life threatening, fatal)* and unexpected.

7.5.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.5.1.3 Any death on study if clearly related to the commercial agent*(s)*.

7.5.1.4 Acute myeloid leukemia *(AML)*. The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.

7.5.2 The ADR report should be documented on Form FDA 3500 and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
***(301)* 230-2330**
available 24 hours

7.5.3 *Special Reporting for this Study* *(fax 215/928-0153)* **(7/13/01)**

7.5.3.1 All grade ≥ 3 **nonhematologic** toxicities *(except grade 3 radiation mucositis or dermatitis)* must be reported to RTOG within 24 hours.

7.5.3.2 All grade ≥ 4 **hematologic** toxicities must be reported to RTOG within 24 hours.

7.5.3.3 Note: Include relationship of adverse events to Procrit®/Eprex® administration when reporting these events on Med Watch 3500.

7.5.3.4 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

7.5.4 *CDUS Reporting*

This study will be monitored by the Clinical Data Update System *(CDUS)* version 1.X. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

7.5.5 *Investigational Agents*

Reporting information is described in Appendix V.

7.5.6 **Additional Reporting (7/13/01)**

- The RTOG will notify Ortho Biotech and the Therapeutic Products Programme *(TPP)* of Health Canada of any events occurring in RTOG 99-03 which are defined as serious, unlabelled or unlisted *(do not currently appear in the Product Monographs for Procrit® or Eprex®)* and considered by the reporting investigator to be probably or possibly related to the administration of Procrit® or Eprex®. The timeframe for reporting of such events from receipt of notification by the site is seven *(7)* calendar days for deaths and life-threatening events and fifteen *(15)* calendar days for all other events. In addition, the RTOG will inform all participating investigators of all serious, unlabelled and associated events reported to TPP in a timely fashion and request that local Institutional Review Boards/Ethics Committees be notified of the same.
- Canadian investigators will also report serious and unexpected adverse events to:

1) Adverse Drug Reaction Reporting Unit
Continuing Assessment Division
Bureau of Licensed Product Assessment
A/L 0201C2
Ottawa, Ontario K1A 1B9
FAX 613-957-0335
ATT: Eprex Report – Control #071296
File # 9427-R1206-21C

2) Bureau of Biologics and Radiopharmaceuticals
FAX 613-957-0364
ATT: Eprex Report – Control #071296
File # 9427-R1206-21C

3) Karalee McWatters/Atul Dave
FAX 416-382-4914
ATT: Eprex Report – Control #071296
File # 9427-R1206-21C

8.0 SURGERY

8.1 Patients with N2-3 disease at presentation are encouraged to undergo post-radiotherapy neck dissection 4-6 weeks after the completion of radiotherapy if their primary tumor is controlled, regardless of the response to radiotherapy. Patients with N1 disease may also undergo post-radiotherapy neck dissection if there is suspicion of residual carcinoma or if the neck node dose was ≤ 66 Gy. In these settings, the neck dissection will not be considered a "salvage operation" nor will the patient be considered to have had a local-regional failure for statistical purposes. Other surgical procedures will be considered salvage operations and are at the discretion of the treating physicians.

9.0 OTHER THERAPY (8/26/02)

9.1 Patients with stage III/IV disease will receive accelerated fractionated XRT +/- single-agent cisplatin *(See Section 7.4)* **OR** standard XRT + concurrent chemotherapy.

If the patient is treated with standard XRT + concurrent chemotherapy, the patient's hematologic function must be adequate *(per Section 3.1.8*), and the patient must have adequate renal function *(a creatinine level of ≤ 2.0 mg/ml)*. In addition, the concurrent chemotherapy regimen with standard XRT must be one of the following:

- Weekly cisplatin, 20 mg/m^2, and paclitaxel, 30 mg/m^2
- Weekly carboplatin, AUC=1, and paclitaxel, 30 mg/ m^2
- Weekly cisplatin, 30 mg/ m^2, without paclitaxel

9.2 Amifostine use is not allowed; all other supportive medications for mucositis and other side effects of treatment are allowed and encouraged.

10.0 PATHOLOGY

10.1 RTOG Tissue Bank

10.1.1 Patients entered on this study should also participate in the RTOG Tissue Bank.

10.1.2 The following must be provided:

10.1.2.1 One paraffin block of tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

10.1.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.3 A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.

10.1.3 RTOG will reimburse pathologists from submitting institutions $100. per case if proper materials are submitted *(reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement)*.

10.1.4 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)*.

10.1.5 ***(8/3/04)*** Materials will be sent to:

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

11. 0 PATIENT ASSESSMENT

11.1 Patient Assessment Table *(3/5/04)*

Assessment	Pre-Rx	During XRT	Post-Rx
H & P including blood pressure	X	Weekly	X[a]
Tumor Diagrams	X		as applicable
CBC, Diff, Platelets	X	Weekly	2 and 4 weeks post-Rx
Chemistry 11 Panel[d]	X	X[c]	X[c]
Reticulocytes, Iron/Ferritin studies, and/or Transferrin levels	X	q 3 weeks *(Epoetin alfa arm only)*	X[c]
B-12 and folate levels	X		
Beta HcG *(women of childbearing age)*	X		
CXR	X	X[c]	yearly
CT/MRI Head and Neck[e]	X	X[c]	X[b,f]
Dental Eval	X		
EUA/Bx	X	X[c]	X[c]
Chest CT	X[c]	X[c]	X[c]
Bone Scan	X[c]	X[c]	X[c]
Assessment of Toxicity	X	Weekly	X[a]
Serum creatinine; Creatinine clearance *(24 hr. or calculated);* ANC[g]	X	X[h]	

a. Follow-up examinations after completion of all therapy will be 3 mo x 2 year, then q 6mo x 3 years. After 5 years the patient should be followed annually.
b. It is recommended, but not required, that patients have a "baseline" CT or MRI at 6-8 weeks after completion of all therapy and then q 6-12 mo.
c. If clinically indicated.
d. Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Glucose, Calcium, Bilirubin, Alkaline Phosphatase, SGOT or SGPT
e. With the exception of T1-2 glottic cancer
f. Every effort should be made to obtain histologic confirmation of suspected local residual or recurrent disease.
g. For patients receiving concurrent chemotherapy
h. See Section 11.3.6 for schedule.

11.2 History/Physical Examination

11.2.1 Patients will be examined weekly during radiotherapy, including assessment of side effects of Epoetin alfa and radiotherapy and, where relevant, response to treatment. Blood pressure must be obtained at each treatment visit.

11.2.2 Patients will be seen two weeks and four weeks after completion of radiotherapy.

11.2.3 Patients will then be seen every three months for two years *(patient may alternate visits between radiation oncologist and surgeon)*; every 6 months the third through fifth years; then annually.

11.3 Laboratory (9/28/01)

11.3.1 Baseline CBC and other laboratory studies will be obtained prior to starting Epoetin alfa *(See Section 4.0)*.

11.3.2 CBC will be obtained on the day of or the day prior to the start of radiotherapy.

11.3.3 CBC will be performed weekly during radiotherapy before each dose of Epoetin alfa. CBC will also be performed weekly in the non-Epoetin alfa patients.

11.3.4 CBC will be obtained at two weeks and four weeks after completion of radiotherapy. Subsequently CBC will be obtained only as needed, except for patients receiving concurrent chemotherapy *(See Section 11.3.6).*

11.3.5 In the Epoetin alpha arm only, reticulocyte and iron testing will be performed the first week and then q3 weeks during radiotherapy *(total of 3)* to confirm adequate iron stores.

11.3.6 Patients receiving concurrent chemotherapy will have post-cycle CBC within 4 weeks of completion of chemotherapy; creatinine will be drawn immediately prior to each cycle of chemotherapy and two weeks after the 2nd cycle of chemotherapy.

11.4 Radiographic

11.4.1 Tests will be performed only as needed during radiotherapy.

11.4.2 CXR will be performed at yearly intervals.

11.4.3 It is recommended *(though not mandatory)* that follow-up CT *(or MRI)* scan of the treated area will be obtained at 6-12 month intervals.

11.4.4 Other radiographic testing will be on an as needed basis.

11.5 Pathologic

11.5.1 Attempts should be made to document local-regional control with biopsy, particularly where clinical examination and/or radiographic studies are equivocal. It is, however, recognized that this is not always feasible, and thus is optional.

11.6 Assessment of Toxicity (9/28/01)

11.6.1 *Toxicity from Epoetin*

Toxicity from Epoetin alfa is expected to be mild *(See Section 7.1.4)*. Side effects may include fever, rash, malaise, headache, arthralgias, diarrhea, elevated blood pressure and nausea/vomiting. Toxicity will be monitored according to the Common Toxicity Criteria *(CTC)*.

11.6.2 *Toxicity from Radiotherapy*

Toxicity from radiotherapy will be related primarily to acute effects on the mucous membranes, salivary glands, and skin. It is not expected that radiotherapy toxicity will be different with or without Epoetin alfa. Radiotherapy toxicity will be monitored as per the CTC and RTOG/EORTC late morbidity scales.

11.6.3 *Toxicity from Chemotherapy (Cisplatin)*

Common side effects of cisplatin include nausea and/or vomiting, weakness, and ringing in the ears and/or hearing loss. Cisplatin can cause allergic reactions *(sweating, difficulty breathing, rapid heartbeat)*. Neutopenia, thrombocytopenia, neurotoxicity, or renal toxicity may occur *(See Section 7.4.4)*. Toxicity will be monitored as per the CTC.

11.7 Quality of Life *(QOL)* Assessments *(3/5/04)* Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data; see Section 13.2.

Quality of life *(QOL)* assessments will consist of the QOL-RTI *(H&N),* the Fatigue Symptom Inventory *(FSI [FQ]),* the List Performance Status Scale *(PF)*,[50] and the QOL Linear Analog Scale Assessment *(LAS [L4])*. The QOL-RTI, FSI, and List scales have been used in previous RTOG head and neck studies and in QOL studies in other academic centers. The LAS scale has been used in large-scale studies of erythropoietin in cancer patients receiving chemotherapy.[57] The List Scale is relatively straightforward to perform and focuses on the lifestyle implications of the most common and relevant acute and late morbidities of radiotherapy. The assessments will be administered at baseline *(prior to beginning protocol treatment)*, at the end *(during the last week of treatment)* of radiotherapy, 4 weeks after treatment, and then every six months for two years.

12.0 DATA COLLECTION *(8/3/04)*

Data should be submitted to:

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

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Pathology Slides/Blocks **(P2)** Tumor and Nodal Diagrams **(I6, I7)**	Within 2 weeks of study entry
Preliminary Dosimetry Information: RT Prescription *(Protocol Treatment Form)* **(T2)** Films *(simulation and portal)* **(T3)** Calculations **(T4)**	Within 1 week of start of RT
Final Dosimetry Information: Radiotherapy Form **(T1)** Daily Treatment Record **(T5)** Isodose Distribution **(T6)**	Within 1 week of RT end

Boost Films *(simulation and portal)* **(T8)**	
Treatment Form **(TF)** Interim Follow-up Form **(FS)**	Four weeks after XRT
Follow-up Form **(F1)**	q 3 months in years 1 and 2
Long-Term Follow-up Form **(FF)**	q 6 months in years 3-5; annually beginning at year 5 unless any of the following events occur: change in tumor status, new toxicity, an increase in an existing toxicity grade, new cancer therapy or agent, or at death. For any of these events, the F1 Form must be submitted.
Autopsy Report **(D3)**	As applicable

12.2 Patients Receiving Concurrent Chemotherapy *(Cisplatin)*

All chemotherapy-related effects and laboratory data, including the required pretreatment, interim, and post-chemotherapy results, must be recorded on the Treatment Form **(TF)**.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints *(8/3/04)*

13.1.1 Local-regional failure is the primary endpoint. *(Failure: persistent or recurrent disease in the primary tumor or regional nodes).*

13.1.1.1 Local-regional progression-free survival *(Failure: local-regional failure or death in absence of local-regional failure).*

13.1.2 Overall survival *(Failure: death due to any cause)*

13.1.3 Patterns of first failure

13.1.4 Frequency of major *(≥ grade 4)* toxicity

13.1.5 The difference *(> 1.5 gm)* in hemoglobin levels between the baseline value and the value at 28 days after starting erythropoietin in patients randomized to Arm 2.

(3/5/04) The endpoints below no longer apply. No statistical analysis will be done of any collected QOL data; see Section 13.2

13.1.6 Fatigue Symptom Inventory *(FSI)* scores

13.1.7 Quality of life - radiation therapy instrument *(QOL-RTI[H&N])* scores

13.1.8 List Performance Status Scale for head and neck scores

13.1.9 Linear Analog Scale Assessment scores

13.2 Study Closure and Revision of Analyses Plans *(8/3/04)*

On September 26, 2003, the RTOG suspended accrual to RTOG 99-03 in response to information received from Ortho Biotech (the company that manufactures Procrit®) about a possible association between epoetin alfa and higher than expected risk of thrombolic events. Subsequent to the accrual suspension, on October 18, 2003, *Lancet* published the results from a randomized trial in Europe that was similar in design to RTOG 99-03. The European study showed that the patients randomized to receive epoetin beta had a statistically significant increase in the hemoglobin level and significantly worse local-regional progression free survival and overall survival rates compared with the control population. The interim analysis of RTOG 99-03 did not show any statistically significant differences in local-regional control or survival between the two arms; however, there was a non-significant trend toward poorer outcome with the epoetin alfa arm. Based on all of the above information, the RTOG Data Monitoring Committee *(DMC)* recommended that RTOG 99-03 be permanently closed to accrual, and the Group Chair *(Dr. Walter Curran)* concurred. The trial was permanently closed to patient accrual on November 19, 2003. A total of 148 patients were entered.

With enrollment discontinued at 40% of the 372 targeted sample size, statistical analysis of the Quality of Life *(QOL)* data will not yield meaningful information because of the loss in statistical power.

Consequently, all future collection of QOL data will be discontinued. No statistical analysis of any QOL data already collected will be performed for the same reason. The protocol has been revised to indicate this.

The analyses plans of efficacy for this trial have revised in light of the European trial. That trial's primary endpoint was locoregional progression-free survival. The trial found that locoregional progression-free survival was poorer with epoetin beta than with placebo *(adjusted relative risk 1·62 [95% CI 1·22–2·14]; p=0·0008)* in all patients. In the subset of 74 patients treated definitively, a similar result was reported. *(p = 0.006)*. That endpoint has been added to RTOG 99-03. The Kaplan Meier, logrank test and Cox model also will be utilized in the analysis of the locoregional failure endpoint and the locoregional progression-free survival endpoint, so the results of the European trial and RTOG 99-03 can be compared.

(8/3/04) When the study was designed during 1999, there were no data to suggest that the addition of erythropoietin to radiation +/- chemotherapy may adversely affect local-regional control or survival. A one-sided test for a possible positive treatment effect was utilized in the original study design. However, in the European trial referred to above, there is now the possibility that there may be an unfavorable effect with erythropoietin. Therefore, two-sided tests will now be necessary for evaluating the erythropoietin treatment in 99-03.

13.3 Required Sample Size

13.3.1 *Treatment*

The baseline data used to generate the sample size calculations came from RTOG 76-19,[6] RTOG 85-27,[6] and the data reported by Princess Margaret Hospital.[37] In RTOG 85-27, anemic *(males ≤ 13.5, females ≤ 12.5)* stage III/IV patients were found to have a 2-year locoregional failure rate of 73%. Princess Margaret reported a 5-year locoregional control rate of 81% among T1/T2 patients, with most failures occurring within the first two years and patients in the lowest quartile of pretreatment hemoglobin experiencing the highest failure rate. In the RTOG Head and Neck registry study *(RTOG 76-19)*, stage I/II patients similarly had a two-year locoregional failure rate of 19%. Pretreatment hemoglobin was not collected in RTOG 76-19, so as a baseline failure rate estimate of anemic stage I/II patients, an assumption was made that one-quarter of patients on RTOG 76-19 would have been classified anemic. As such, for the purposes of estimating sample size, anemic stage I/II patients were treated as having a 26.5% two-year rate.

As anemic patients of all stages and sites are eligible for this protocol, a composite binomial failure rate will be estimated based upon potential mixes of stages. Additionally, as some patients are expected to die within two years without recurring, the sample size will be adjusted. In RTOG 85-27 Stage III/IV patients were found to have a 20% two-year rate of death without failure; from RTOG 76-19, stage I/II patients experienced a 12% two-year rate. These estimates, in conjunction with projected mixes of I/II and III/IV patients, were used in calculating the sample sizes below. An additional 10% increase in total sample size was made to account for patient ineligibility and loss. Various sample sizes were calculated with a fixed $\alpha = 0.05$ *(type I error)*, with statistical power $1 - \beta$ *(type II error)* at either 80% or 85%, either a one-sided or two-sided test, and with an anticipated treatment effect of either 33% or 25% reduction in locoregional *failure rate.*

13.3.1.1 **(9/28/01)** The protocol has been revised to include the option of chemoradiation in stage III-IV patients. A retrospective study in Austria has shown Erythropoietin to have a positive effect on both locoregional control and overall survival in oral cavity and oropharynx patients treated with preoperative chemoradiation.[23] In patients with pre-treatment HGB < 14.5, locoregional control for the patients treated with Erythropoietin was 95% at two years compared to 72% for patients not treated with Erythropoietin. In addition, two-year overall survival for the Erythropoietin group was 88%, compared to 60% for the group that did not receive Erythropoietin. The definition of anemia used in RTOG 99-03 was not based upon the 14.5 value. Rather it was defined as ≤ 13.5 for men and ≤ 12.5 for women. The patients from the completed chemoradiation trial, RTOG 97-03, were used for estimating the sample size of anemic patients needed for this revision of RTOG 99-03. Ideally, such patients from the RTOG 99-14 study should be used, but two-year data are unavailable at this time. In RTOG 97-03, patients were randomized to three chemoradiation regimens but were combined for this analysis. The two-year locoregional failure rate was 52.2%. In addition, 10.3% died within two years without locoregional failure. Based on this data, there are three distinct groups with different failure rates for this study: stage I/II patients *(who will not be eligible to receive chemotherapy)*, stage III/IV patients who do not receive chemotherapy, and stage III/IV patients who receive chemotherapy.

Stage	2-year locoregional failure	2-year death without failure
Stage I/II	26.5%	12.0%
Stage III/IV no chemotherapy	73.0%	20.0%
Stage III/IV chemotherapy	52.2%	10.3%

Since all stages are eligible for this protocol, a composite binomial failure rate will be estimated based upon the distribution of stage and chemotherapy use. For example, if each group represents 1/3 of patients entered, the failure rate would be 0.33*0.265 + 0.33*0.73 + 0.33*0.522 = 0.50. The study still seeks to detect a 33% reduction in the failure rate. In this example, that would be an improvement from 50% locoregional failure to 33.3% locoregional failure. The sample size will not be adjusted at this time. When 150 patients have been entered on the study, the distribution of stage and chemotherapy use will be calculated, and the sample size will be adjusted so as to ensure adequate statistical power to detect a 33% reduction in the failure rate.

13.3.2 *Overall Survival*

Anemic stage III/IV patients in RTOG 85-27 had a hazard rate of 0.658 for survival *(median survival of 1.05 years),* and the hazard ratio between normal and anemic patients was 0.662. The stage I/II patients in RTOG 96-19 had a median survival of 7.85 years. With our assumption that 25% of those patients would be anemic and that the risk ratio between normal and anemic would be the same as that from RTOG 8527, a hazard rate of 0.118 was estimated for anemic stage I/II patients. This would translate to a hazard rate of 0.388 for anemic patients in this study under the assumption of a 50/50 distribution among stage I/II and III/IV patients. We want to test if EPO also reduces the overall survival hazard rate. Using type I error of 0.05 *(one-sided)* and initial sample size of 372 calculated for primary endpoint, the estimated statistical powers are given in the table below with various hazard reduction rates and years of followup. Exponential distribution is assumed for survival distribution function in calculations.

Table of Estimated Powers *(%)* with the sample size of 372				
	Years of Follow-up			
Hazard rate reduction in	2	3	4	5
25%	60	70	75	79
30%	76	85	89	92
35%	87	94	96	97

This study has adequate power to detect moderate hazard reduction *(≥ 30%)* for overall survival.

	20% Stage I/II *80% Stage III/IV*			*50% Stage I/II* *50% Stage III/IV*			*80% Stage I/II* *20% Stage III/IV*		
33% Reduction	Power	One-sided	Two-sided	Power	One-sided	Two-sided	Power	One-sided	Two-sided
	85%	240	285	85%	372	446	85%	603	722
	80%	213	255	80%	328	397	80%	533	644
25% Reduction	Power	One-sided	Two-sided	Power	One-sided	Two-sided	Power	One-sided	Two-sided
	85%	409	490	85%	649	778	85%	1046	1257
	80%	362	438	80%	573	695	80%	922	1119

The initially targeted sample size for this protocol will be 372. More early stage patients are expected to be entered into the study. Unless an adjustment is made in the sample size, statistical power may be substantially reduced. To guard against this occurrence, the patient population will be examined as to the distribution of stage and primary site after the first 100 patients are entered into the protocol. At that time, the sample size will be adjusted so as ensure the appropriate power to detect a treatment effect of 33%. No statistical testing will be performed at the time that sample size is reconsidered.

13.3.2.1 **(9/28/01)** Anemic patients in RTOG 97-03 had two-year survival of 53.7%. This equates to an exponential hazard rate of 0.311. Again, a composite rate will be calculated. Using the example above in which each group represents 1/3 of the total patients entered, the composite hazard rate is 0.362. As stated above, when 150 patients have been entered and the distributions of the 3 groups have been determined, the statistical powers for detecting a difference in overall survival will be recomputed.

13.3.3 *Quality of Life (QOL)* ***(3/5/04)*** Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data; see Section 13.2.

The FSI and QOL-RTI *(H&N)* will be assessed according to the schedule in Section 11.7. For purposes of examining statistical power, we will consider the difference in the average FSI and the average QOL-RTI *(H&N)* scores between the two treatment arms four weeks after the completion of radiation therapy. A recent head and neck, study RTOG 90-03, evaluated QOL. The compliance rate there with the four week QOL assessment post treatment was approximately 75% in the eligible patients who were alive. We will assume a similar compliance rate in this study. After further adjusting for ineligibility and early death, the available sample size is projected to be 242 patients *(65% of 372)*.

Hann et al.[24] reported that the average scores of the FSI indicators *(except Most Fatigue)* in breast cancer patients during treatment ranged from 2.0 to 4.1 with standard deviations *(SD)* between 2.1 to 2.8. The corresponding average scores in healthy women group were about 35% smaller than those in breast cancer group and ranged from 1.3 to 2.1 with SD between 1.4 and 2.4. We will assume that anemic head and neck cancer patients will have at least 15% higher average FSI scores than do breast cancer patients. We hypothesize that Erythropoietin *(EPO)* will lower the average FSI indicator scores by 20%. Using alpha level of 0.05 *(one sided)* and SD of 2, the statistical powers with various FSI scores are listed in table below.

Average FSI Indicator Score						
RT only arm	2.3	2.8	3.3	3.8	4.3	4.8
RT + Epo arm *(20% reduction)*	1.84	2.24	2.64	3.04	3.44	3.84
Power *(%)*	55	70	81	90	95	98

The statistical power for the average FSI scores of at least 3.3 for RT only is adequate.

The QOL-RTI *(H&N)* has two components, a general score and a specific head and neck score. At the end of treatment, Trotti et al. reported that the average general score was 5.8 *(SD 0.799)* and the average head and neck score was 4.2 *(SD 1.727)*.[35] Using a sample size of 242, alpha level of 0.05 *(two sided)* and power of 0.80, this study will able to detect the difference of QOL-RTI *(H&N)* scores between two treatment arms for as small as 0.6, i.e. a 15% change.

When the sample size for treatment comparison is reconsidered after 100 patients accrued, the statistical powers for FSI and QOL-RTI *(H&N)* will also be re-evaluated.

13.4 Patient Accrual

The annual patient accrual rate for RTOG 85-27 was approximately nine per month. Given that the distribution of anemic versus normal hemoglobin patients in that study was very nearly equal, we assume that the accrual of stage III/IV patients to this protocol would be approximately half of that figure. It is anticipated that stage I/II patients will enter at at least the same pace. Thus an annual accrual rate approximately 110 is expected. Patient accrual will be carefully assessed prior to each semi-annual meeting. If the accrual drops below 60 per year *(allowing for a six-month startup time)*, the feasibility of continuing will be carefully reviewed.

13.5 Randomization and Stratification

The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.[38] The stratifying variables will be stage *(I/II vs. III/IV)*, pretreatment hemoglobin level *(9.0 to < 11.5 vs. 11.5-13.5)*, and gender.

13.5.1 **(9/28/01)** With the revision to allow Stage III-IV patients the option of receiving chemotherapy, the Stage III-IV patients will be further stratified by chemotherapy use *(yes vs. no)*.

13.6 Analysis Plan for Treatment Test (7/13/01)

13.6.1 Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about patient accrual rate *(including the projected completion date for the accrual phase)*, data quality, compliance rate of the treatment delivery, distributions of the important prognostic baseline variables, and frequency and severity of toxicities by treatment arms. The reports will not contain any results of the treatment comparisons with respect to the efficacy endpoints. *(locoregional failure, overall survival).* Toxicity report will usually consist of three tables with patients who experienced a grade 4 or 5 *(fatal)* toxicity listed individually in a footnote. The first table gives the frequency and the severity of the individual acute toxicities by treatment arm as well as the frequency of the worst reported acute toxicity in each patient. The second table gives the frequency and the severity of individual late toxicity by treatment arm as well as the frequency of the worst reported late toxicity in each patient. The third table will give the frequency of most severe acute or late toxicity observed in a patient by treatment arm. The study chairs as well as the head and neck disease committee chair reviews the toxicity report to ensure the treatment acceptability for the patient population under test. In addition, the RTOG Data Monitoring Committee, whose members do not participate in RTOG studies, performs a similar review. If the treatment is judged to be intolerable or unsafe, modifications to it will be then considered and approved by the RTOG research strategy committee and then sent to National Cancer Institute and the corporate sponsor. Formal statistical comparisons of toxicity rates will be done only at the two interim analyses to test for early termination of the study and at final analysis for reporting the results via abstract and manuscript.

13.6.2 Two interim analyses of the primary efficacy endpoints to test early termination of the study have been planned. There are three possible courses of action: 1) continue study as is; 2) terminate patient accrual; or 3) modify the study. These two interim analyses will be performed when one-third and two-thirds of the total required sample size has been followed for potentially two years. At the first and second

interim analyses, the boundary of the test statistic is 2.89 *(p=0.0019)* and 2.00 *(p=0.022)* respectively *(O'Brien-Fleming approach)*. If an early stopping rule is met, the study statistician would recommend to the DMC that randomization is discontinued and the study be immediately written up for publication.
In addition, the frequencies of patients with either acute or late grade 4 or 5 toxicities will be compared between the two treatments using the z-statistic for testing binomial proportions.
If patient accrual were stopped after first interim analysis, approximately 90% of originally planned sample size would be available for analysis with assumed annual accrual rate. Then the treatment effect on fatigue and QOL could be assessed with similar statistical power as if the originally planned sample size was available.

13.6.3 ***(3/5/04)*** Collection of QOL data is discontinued. There will be no statistical analysis of any collected QOL data; see Section 13.2.

The major treatment analysis will take place after a positive significance test in either of the first two time points specified in Section 13.5.2 or after all the patients have been entered on the study and have potentially been followed for at least two years. If the two early significance tests do not satisfy the early termination criteria, the critical value for "final" analysis will be 1.66 *(p=0.048)* to preserve an overall alpha level of 0.05 for the study. It will include a tabulation of all cases entered, and those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, distribution of FSI, QOL-RTI *(H&N)* and PSS scores at baseline, and observed results with respect to the endpoints mentioned in Section 13.1. All eligible patients randomized will be included in the comparison by assigned treatment arm in the analysis. The cumulative incidence[39] will be used to estimate yearly rates of local-regional failure because it adjusts for patients dying without such a failure. The primary hypothesis of treatment benefit for local regional disease control will be tested using the statistic which Gray[40] developed for comparing cumulative incidence rates. Additional analyses of the treatment benefit will be done employing the methodology described in Fine and Gray's paper, " A proportional hazards model for the subdistribution of a competing risk".[46] The first model evaluating treatment will include disease stage, sex, and pretreatment hemoglobin. These have been shown to be highly significant in previous analyses of RTOG head and neck database and were selected as stratifying variables in this trial. Additional analyses of treatment benefit on local regional disease will include modifying factors such as age, race, and other patient characteristics. They will also use Fine and Gray's approach. The Kaplan Meier[47] will be used to estimate the yearly survival rates. The secondary hypothesis of treatment benefit for survival will be tested using the log rank statistic.[48] Additional treatment comparisons on overall survival will be analyzed in similar fashion as local regional disease except that the Cox proportional hazard model[49] will be employed. The treatment comparisons on the patterns of treatment failures and the toxicity will use the z-statistic for testing binomial proportions. The average FSI scores and QOL-RTI *(H&N)* scores will be tested using t-statistics between two arms, and will be modeled by General Linear Model *(GLM)*[50] to assess treatment effect after adjusting stratification factors. The distribution of scores between two treatment arms will be compared using Cochran-Armitage test.[51] The correlation among three QOL scores will be tested using Pearson correlation coefficient.[52-53] In addition, Random Effects Model[54] will be used to explore the treatment effect to QOL over time.
The compliance rate with QOL assessments is projected to be at 75% and is considered to be moderate. To detect and to adjust for possible bias introduced by that compliance rate, we will investigate the differences in compliance rates between two treatment arms, and the differences in performance outcomes other than QOL between the compliance and the non-compliance patients. The Zubrod performance score at four weeks post radiation therapy would be an example of such outcome. Methods in analyzing QOL scores to adjust bias will be utilized then if bias is discovered.

The student's T statistic will be used to test if the difference in mean hemoglobin levels between the baseline values and the values at 28 days after starting erythropoietin in patients randomized to Arm 2 is greater than 1.5 gm. It will also be used to test if there is a difference in mean hemoglobin levels for the values at 28 days between the two treatment arms.

13.6.3.1 ***(3/5/04)*** There will be three analyses performed to report the results. The RTOG DMC recommended the preliminary toxicity results from the trial be reported as soon as possible. Analysis will be performed for an abstract submission to the 2004 ASTRO meeting. At that time, 100 patients will have potentially been followed for one year, and 36 patients for two years. After all the patients have potentially been followed for at least two years, a second analysis for the manuscript reporting the initial results will be begun in September 2005. The original primary endpoint of the trial was locoregional failure rate. Based upon prior RTOG studies, over 90% of the patients, who failed local-regionally will have failed in first two years. After all the patients have potentially been followed for

at least five years, a third analysis for the manuscript reporting the long term results especially survival will be begun in September 2008.

Each analysis will include a tabulation of all cases entered, those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints in Section 13.1. All randomized, eligible patients will be included in the comparison by assigned treatment arm. The cumulative incidence[39] will be used to estimate yearly rates of local-regional failure because it adjusts for patients dying without such a failure. The primary hypothesis of treatment benefit for local-regional disease control will be tested using the statistic which Gray[40] developed for comparing cumulative incidence rates. The Kaplan Meier[47] will be used to estimate the yearly rates, and log rank statistic[48] will test for difference. The Cox proportional hazard model[49] will be employed to estimate the hazard ratio and its 95% confidence interval associated with treatments for each endpoint with the stratifying variables included as fixed covariates. The treatment comparisons on the patterns of treatment failures and the toxicity will use the z-statistic for testing binomial proportions (grades 3, 4, and 5 versus 0, 1, and 2).

The student's T statistic will be used to test if the difference in mean hemoglobin levels between the baseline values and the values at 28 days after starting erythropoietin in patients randomized to Arm 2 is greater than 1.5 gm. The proportion of patients randomized to Arm 2 having an increase of the hemoglobin by greater than 1.5 gm will be estimated with its associated 95% confidence interval. It will also be used to test if there is a difference in mean hemoglobin levels for the values at 28 days between the two treatment arms.

(8/3/04) The original study design specified a one-sided test for a possible positive treatment effect. However, in light of the European trial results, there is now the possibility that there may be an unfavorable effect with erythropoietin seen on either local-regional control or survival. Therefore, two-sided tests will now be utilized to evaluate the erythropoietin treatment in 99-03.

13.7 Race and Gender Considerations

In conformance with the National Institute of Health *(NIH)* Revitalization Act of 1993 with regarding to inclusion of women and minority in clinical research, we have considered differences in prognosis by race and gender. No study has indicated gender, races or their interaction effect to treatment outcomes. This study is designed to test the efficacy under the assumption of the same efficacy across the gender and across the races. The interim analysis will include a tabulation of all cases by gender and racial categories. Statistical analyses will be performed to examine the possible treatment outcome differences between the genders or/and among the races at the end of this study. The projected gender and races accruals are listed below:

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	1	10	4	0	60	0	75
Male	3	3	60	17	0	212	2	297
Total	3	4	70	21	0	272	2	372

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APPENDIX I

RTOG 99-03

A RANDOMIZED PHAASE III TRIAL TO ASSESS THE EFFECT OF ERYTHROPOIETIN ON LOCAL-REGIONAL CONTROL IN ANEMIC PATIENTS TREATED WITH RADIOTHERAPY FOR CARCINOMA OF THE HEAD AND NECK

SAMPLE CONSENT FOR RESEARCH STUDY

THERE IS A RESEARCH STUDY ABOUT YOUR CONDITION AND ITS TREATMENT. THIS CONSENT FORM WILL TELL YOU ABOUT THIS STUDY AND HOW THE TREATMENT MAY OR MAY NOT HELP YOU.

IT IS IMPORTANT THAT YOU READ AND UNDERSTAND THIS FORM, THE STUDY AND THE TREATMENT BEFORE YOU DECIDE TO BE PART OF THIS STUDY. IF YOU HAVE ANY QUESTIONS ABOUT THIS STUDY, THE TREATMENT OR HOW IT WILL AFFECT YOU, PLEASE ASK YOUR DOCTOR.

RESEARCH STUDY

You have the right to know about the procedures used in this research study and the risks, benefits and alternatives to the treatment in this study. You should know and understand the treatment proposed in this study, how it will be given, how the treatment may help you, how the treatment may harm you, and the choices available to you. This form will tell you about the study, the benefits, the risks and the alternatives so you can decide whether to be a part of this research study.

PURPOSE OF THIS STUDY (7/13/01)

Your diagnosis is carcinoma *(cancer)* arising from the head and neck, such as the lining of the mouth or throat. Treatment with radiation therapy has been recommended. You have been asked to participate in a clinical trial using the drug erythropoietin *(Procrit®/Eprex®)* together with your radiation therapy. This drug is used to increase the number of red blood cells in the blood, thus treating the anemia *(low red blood cell count)* that often occurs in people with cancer. Currently, Procrit®/Eprex® is approved to be given three times a week to treat anemic cancer patients receiving chemotherapy. Once weekly dosing is investigational and is not approved by the U.S. Food and Drug Administration or the Therapeutic Products Programme (TPP) of Health and Welfare Canada. The purpose of this clinical trial is to determine if Procrit®/Eprex® will improve the chance of eliminating your cancer with radiation therapy. This study will also evaluate how the side effects of treatment and your disease affect you.

Three hundred and seventy-two patients will be enrolled at participating centers in the United States and Canada. Approximately fifty subjects will be enrolled at Canadian sites.

DESCRIPTION OF PROCEDURES

The treatment you will be given will be one of two treatment methods. You will be assigned to one or the other treatment method by chance *(at random)*. Although both treatments may be good, it is not known right now which of the two methods of treatment is better. The treatment you get will be assigned by a computerized selection process. Your doctor will call a statistical office where a computer will assign you to one of the two treatment methods. Your chance of receiving one of the two treatments is approximately equal. You will be assigned to one of the following:

Treatment 1 (8/26/02)
You will receive daily radiation treatments (*Monday through Friday)*. If you have a relatively "small" cancer *(Stage I or II)*, you will receive one radiation treatment per day for 6 to 7 weeks.

If you have a relatively "larger" cancer *(Stage III or IV)*, you and your doctor will decide whether you will be treated with radiation alone or radiation plus chemotherapy. You will have one of the following treatments:

- If you are going to have radiation therapy alone, you will receive one radiation treatment per day for 3 ½ weeks and then two radiation treatments per day *(six hours apart)* for 2 ½ weeks for a total of 6 weeks — this is known as "accelerated" radiation therapy.

- If you are going to have accelerated radiation and cisplatin chemotherapy, you will receive one radiation treatment per day for 3 ½ weeks and then two radiation treatments per day *(six hours apart)* for 2 ½ weeks for a total of 6 weeks. You also will receive two injections *(into a vein in the arm)* of the chemotherapy drug cisplatin on Days 1 and 22 of radiation therapy. Each time you receive a dose of cisplatin, you will also receive several hours of intravenous *(injected into a vein in the arm)* fluids and medications to decrease the side effects of cisplatin. On the day after cisplatin *(or for several days, if necessary)*, you may be given an additional several hours of intravenous *(injected into a vein in the arm)* fluids and medications to decrease the side effects of cisplatin. It will take about 1 to 2 hours to then give you the cisplatin. Each cisplatin treatment on each of these two days will take a total of about 6 hours. This treatment may be done as an inpatient or outpatient.
- If you are not going to have accelerated radiation therapy, you will receive one radiation treatment per day for 7 weeks, along with chemotherapy as determined by your doctor and you.

Treatment 2 (8/26/02)
You will receive daily radiation treatments (*Monday through Friday).* If you have a relatively "small" cancer *(Stage I or II)*, you will receive one radiation treatment per day for 6 to 7 weeks.

If you have a relatively "larger" cancer *(Stage III or IV)*, you and your doctor will decide whether you will be treated with radiation alone or radiation plus chemotherapy. You will have one of the following treatments:

- If you are going to have radiation therapy alone, you will receive one radiation treatment per day for 3 ½ weeks and then two radiation treatments per day *(six hours apart)* for 2 ½ weeks for a total of 6 weeks — this is known as "accelerated" radiation therapy.
- If you are going to have accelerated radiation therapy and cisplatin chemotherapy, you will receive one radiation treatment per day for 3 ½ weeks and then two radiation treatments per day *(six hours apart)* for 2 ½ weeks for a total of 6 weeks. You also will receive two injections *(into a vein in the arm*) of the chemotherapy drug cisplatin on Days 1 and 22 of radiation therapy. Each time you receive a dose of cisplatin, you will also receive several hours of intravenous *(injected into a vein in the arm)* fluids and medications to decrease the side effects of cisplatin. On the day after cisplatin *(or for several days, if necessary),* you may be given an additional several hours of intravenous *(injected into a vein in the arm)* fluids and medications to decrease the side effects of cisplatin. It will take about 1 to 2 hours to then give you the cisplatin. Each cisplatin treatment on each of these two days will take a total of about 6 hours. This treatment may be done as an inpatient or outpatient.
- If you are not going to have accelerated radiation therapy, you will receive one radiation treatment per day for 7 weeks, along with chemotherapy as determined by your doctor and you.

In addition, you will receive an injection of erythropoietin *(Procrit®Eprex®)* 40,000 units under your skin once per week beginning one week before you start the radiation. These injections will be given once per week until the end of radiation treatments for a total of approximately 8 to 9 injections. If your red blood cell count has not risen very much after four weeks, the dose of the drug will be increased to 60,000 units per week. This may require two separate injections under the skin each week. The injections will be given in the Radiation Oncology or Medical Oncology Clinic. In order to improve the chance of increasing your blood counts, you will also be asked to take iron pills *(or liquid)* several times a day until the completion of radiation treatments. If your radiation therapy is delayed, you will continue to receive injections of Procrit®/Eprex®.

Whether or not you are assigned to receive erythropoietin, you will be asked to have some blood tests. Before starting treatment you will have blood tests taken from a vein in your arm *(about two tablespoonful)*. If you have been assigned to take erythropoietin, you will have another blood test just before starting radiotherapy. You will also have a blood test once per week during radiation treatments *(about one teaspoon)*. After the completion of radiation treatments you will have a blood test at two and four weeks after treatment.

After radiation treatments are completed you will return for follow-up visits at least every three months for two years, then at least once every six months for three years, and then at least once a year. At some visits *(twice per year)* you will have x-rays of your chest and neck performed.

As of [broadcast date here] collection of QOL data is discontinued. See Section 13.2.One of the purposes of this study is to look at the side effects of your treatment and how they and your cancer affect you. You will be asked to complete a few questionnaires which describe your day-to-day activities, and overall sense of well being. You will complete these questionnaires just before you start treatment, twice during your radiation treatment, then when you come in for follow-up with your doctor.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. This tissue may be sent to a central office for review and research investigation associated with this protocol.

RISKS AND DISCOMFORTS (8/26/02)

Cancer treatments, whether given in a research study or in the ordinary practice of medicine, may often hurt or harm you *(side effects)*. The treatment used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Radiation Therapy to the Head and Neck: Radiation therapy almost always causes sores in the mouth and/or throat, which can be painful and make it very difficult to chew and or swallow foods. Other common side effects include mouth dryness, changes in taste and/or smell, thick mucus *(phlegm)*, hoarseness, cough, skin redness and/or rash *(in the head and neck)*, sinus/ear pain and/or pressure, fatigue, and lowering of the blood counts *(which can lower resistance to infection and/or promote easy bleeding or bruising)*. Radiation therapy can cause problems with the thyroid gland which may require taking lifelong thyroid hormone pills.

Rarely, radiation therapy can cause serious damage and/or infection of the jawbone, voice box, skin, blood vessels, nerves, or other parts of the head and neck. These radiation complications may require a major operation to correct and can rarely even be life threatening or fatal.

Risks Associated with Chemotherapy (Cisplatin) with accelerated radiotherapy: These risks only apply if you have a "larger" cancer *(Stage III or IV)* and if you and your doctor decide that adding two large doses of cisplatin chemotherapy to accelerated radiation therapy would be in your best interest. Common side effects of cisplatin include nausea and/or vomiting, weakness, ringing in the ears, hearing loss, numbness of the fingers and toes, lower blood counts, and anemia. Cisplatin can cause allergic reactions *(such as sweating, difficulty breathing, or rapid heartbeat*), facial swelling, loss of coordination, involuntary movement, loss of taste, and/or restlessness. Less likely, but serious risks include muscle cramps, spasm, kidney damage, liver damage, and acute leukemia.

Erythropoietin (Procrit®Eprex®): The possible side effects, risks and/or discomforts that may be experienced by patients receiving Procrit®/Eprex® include an allergic reaction with possible fever, hives, chills, shortness of breath, an increase in heart rate, or an increase or decrease in blood pressure. Other side effects may include rash, red eyes, and a chilly, flu-like syndrome after injection. Also, temporary pain at the site of the injections may occur. There is the risk that placing a needle*(s)* under the skin *(to give Procrit®/Eprex®)* could cause infection, bleeding, pain, or bruising.

Sometimes patients with chronic *(long-standing, severe)* kidney disease who are receiving Procrit®/Eprex®, can get very high blood pressure. This can cause problems with the brain function similar to a stroke *(hypertensive encephalopathy)* and/or seizures *(convulsions)*. This risk may be lowered by not allowing the blood count to rise up too quickly or too high. Rarely, patients without kidney disease have developed very high blood pressure and/or seizures which may be related to Procrit®/Eprex®. Your blood pressure will be checked at least once per week while you are receiving treatment in this study.

Seizures have occurred in AIDS patients treated with Procrit®/Eprex® but these have occurred in the context of central nervous system illness such as cerebral lymphoma *(brain cancer)*, and are probably unrelated to Procrit®/Eprex® therapy. No seizures have been seen in normal volunteers or surgical patients treated with Procrit®/Eprex®. Seizures in cancer patients treated with Procrit®/Eprex® have rarely occurred and have been related to central nervous system illness or possibly high blood pressure.

Results of one surgical study in cardiac patients suggested that patients with cardiac disease undergoing surgically bypass procedures and receiving Procrit®/Eprex® therapy might be at a higher risk for fatal thrombotic/vascular events *(clots in the blood vessels)* than patients who did not receive Procrit®/Eprex®. However, the percent of Procrit®/Eprex®-treated patients who died in this study was comparable to that reported in the literature for patients undergoing cardiac surgery who were not treated with Procrit®/Eprex®.

Rarely, the use of Procrit®/Eprex® can result in the body forming immune reactions *(antibodies)* against Procrit®/Eprex®.

Although taking Procrit®/Eprex® is expected to increase the number of red blood cells, in some rare instances, patients with chronic kidney disease have had a severe decrease in red blood cells. This side effect, called pure red cell aplasia (PRCA) has been reported in patients after months to years of treatment with Procrit® or Eprex®. PRCA can be very serious and can require blood transfusions, even after treatment with Procrit®/Eprex® is stopped. Severe anemia such as this can cause serious weakness, fatigue, trouble breathing, heart problems or even be life-threatening. This uncommon problem has been reported more often with Eprex® than with Procrit® or other forms of erythropoietin.

Antibodies against Procrit®/Eprex® have been found in most of the patients who reported the development of PRCA, but it has not been proved that these antibodies are the cause of PRCA. Some patients, who have never been treated with Procrit®/Eprex®, develop antibodies to hormone produced by their own kidneys.

There is no standard treatment for PRCA, other than to maintain acceptable levels of red blood cells with transfusions. About half of the patients who develop PRCA improve with or without treatment. If you have or develop antibodies against Procrit®/Eprex® without a decrease in red blood cells, it is not clear whether or not you need any treatment. Your doctor will discuss treatment options with you.

In addition to the above, there is the possibility of a previously unknown side effect or complication occurring with the use of Procrit®/Eprex®.

Iron: Iron pills or liquid can cause upset stomach, nausea, heartburn, and/or constipation in some people. This may be helped by switching to a different form of iron preparation.

Blood Drawing: Risks of blood drawing include pain, bruising, bleeding, or, very rarely, infection at the site of the blood draw.

Your physician will be checking you closely for these side effects. Side effects usually disappear after the treatment is stopped. In the meantime, your doctor may prescribe medication to keep these side effects under control.

Pregnancy Issues: This study may be harmful to an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman of childbearing age and have not been surgically sterilized *(tubal ligation or hysterectomy),* you must have a pregnancy test before enrolling in this study. You must use adequate birth control measures to prevent pregnancy while participating in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on this study, you must tell your doctor immediately.

COSTS (7/13/01)

If you are assigned to receive the drug erythropoietin, the drug will be supplied free of charge by the company that makes it *(Ortho Biotech).* Routine blood tests and scans will be done to evaluate the effects of treatment. There may also be laboratory testing and procedures required by this study for research purposes. These additional tests may increase your medical bills although the impact will be dependent on your insurance company. If injury occurs as a result of this research, treatment will be available. The use of medication to help control side effects could result in added costs. This institution is not financially responsible for the treatment of side effects caused by the study treatment. You will not be reimbursed for medical care other than what your insurance carrier or provincial healthcare may provide. You will not be paid for your participation in this research study.

CONTACT PERSONS
(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:
(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

_____	_____
Name	Telephone Number

ALTERNATIVES

Other treatments that could be considered for your condition may include the following: *(1)* 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.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. You should discuss your condition and the expected outcome with your doctor. Your doctor will be available to answer any questions. You are encouraged to ask your doctor any questions you have about this research study and the choices of treatment available to you. If you have any questions at all, please ask your doctor.

If your disease becomes worse, if side effects become very severe, or if developments occur that indicate the research study is not in your best interest, the treatment would be stopped. Further treatment would be discussed at that time.

BENEFITS

It is not known whether the treatment you will be given in this research study will help your condition more than the standard treatment for this disease would. The information from this study may also help others by providing information about your type of cancer and its response to treatment. The information will be used scientifically. A possible personal benefit of this research study may be a decrease in the size of your tumor and a longer survival. None of these possible benefits is certain or guaranteed.

VOLUNTARY PARTICIPATION

You do not have to take part in this research study. You are free to withdraw or withhold your consent from taking part in this research study at any time. If you refuse to participate, there will be no penalty or loss of benefits. You may seek care from a doctor of your choice at any time. If you do not take part in this study or if you withdraw from the study, you will continue to receive care.

CONFIDENTIALITY (7/13/01)

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).*** The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration ***(FDA),*** the National Cancer Institute ***(NCI),*** qualified representatives of the drug company *(Ortho Biotech),* and other groups or organizations that have a role in this study may have access to medical records that contain your identity. However, no information by which you can be identified will be released or published.

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.

Patient Signature *(or legal Representative)* Date

Investigator Signature *(Canada)* Date

TISSUE AND BLOOD TESTING *(RTOG 99-03)*

I agree to the use of my tissues/other samples for additional research studies.

☐ Yes ☐ No

Patient Signature *(or Legal Representative)* Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

APPENDIX III

AJCC STAGING
HEAD & NECK, 5th Edition

STAGING-PRIMARY TUMOR *(T)*

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T*is* 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. pyterygoid muscle[s], mandible, hard palate, deep muscle of tongue, larynx)*

Hypopharynx

Pyriform 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
Aryeepiglottic 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 0	T*is*, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0
Stage IVA	T4, N0-1, M0 Any T, N2, M0
Stage IVB	Any T, N3, M0
Stage IVC	Any T, Any N, M1

STAGE GROUPING Nasopharynx

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

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff *(215/574-3214)* within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol *(FAX #215/928-0153).*

4. The Group Chairman in consultation with the Study Chairman 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.

5. For those incidents requiring telephone reporting to the National Cancer Institute *(NCI)*, Investigational Drug Branch *(IDB)* or Food and Drug Administration *(FDA)*, the Principal Investigator should first call RTOG *(as outlined above)* unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group *(in the case of RTOG-coordinated intergroup studies)* must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities *(grade 5)* resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening *(grade 4)* toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

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

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

i. Any fatal *(grade 5)* or life threatening *(grade 4)* adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.

ii. Unknown adverse reactions *(≥ grade 2)* resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.

iii. All neurotoxicities *(≥ grade 3)* from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch *(IDB)*
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent.	As above
- All life threatening *(grade 4)* events which may be due to agent.	As above
- First occurrence of any toxicity *(regardless of grade)*.	Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. *Phase II, III Studies Utilizing Investigational Agents*

- All fatal *(grade 5)* and life threatening *(grade 4)* known adverse reactions due to investigational agent.	Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within 10 working days with a copy to IDB. *(Grade 4 myelosuppression not reported to IDB)*
- All fatal *(grade 5)* and life threatening *(grade 4)* unknown adverse reactions resulting from or suspected to be related to investigational agent.	Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.	**Report **in writing** to RTOG Headquarters and IDB within 10 working days.

****** See attached *(if applicable to this study)* NCI Adverse Drug Reaction Reporting Form

D. CANADIAN REPORTING PROCEDURE

Canadian investigators will also report serious and unexpected events to:

1) Adverse Drug Reaction Reporting Unit
Continuing Assessment Division
Bureau of Licensed Product Assessment
A/L 0201C2
Ottawa, Ontario K1A 1B9
FAX 613-957-0335
ATT: Eprex Report – Control #071296
File # 9427-R1206-21C

2) Bureau of Biologics and Radiopharmaceuticals
FAX 613-957-0364
ATT: Eprex Report – Control #071296
File # 9427-R1206-21C

3) Karalee McWatters/Atul Dave
FAX 416-382-4914
ATT: Eprex Report – Control #071296
File # 9427-R1206-21C

APPENDIX VI, (9/2/03)

RTOG 99-03

STUDY AGENT (ERYTHROPOIETIN) SHIPMENT FORM

Erythropoietin will be shipped only to institutions who have identified a single individual associated with the investigational drug unit of the institution. Each institution must submit this form to the CTSU Regulatory Office (215-579-0206) as soon as the individual responsible for the study agent has been identified. **Canadian Institutions must submit the this form and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300).** This must be done prior to registration of the institution's first case. Allow adequate processing time *(7-10 days)* before calling to randomize your first patient. Canadian centers must also submit the regulatory documents listed in Section 7.1.6.7 directly to OrthoBiotech.

SHIP TO:

Name: _____ *(ATT: RTOG 99-03 Supply)*

Address: _____
(no P.O. addresses)

_____

_____

_____

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

Investigator *(PI)* Signature _____ Date:_____

Investigator Name *(Print)* _____

Investigator NCI # _____

Send Completed Form to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX 215-569-0206

RTOG Headquarters Approval _____ Date: _____