RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-11

PHASE II STUDY OF PACLITAXEL AND CISPLATIN IN COMBINATION WITH SPLIT COURSE CONCOMITANT HYPERFRACTIONATED RE-IRRADIATION IN PATIENTS WITH RECURRENT SQUAMOUS CELL CANCER OF THE HEAD AND NECK

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PHASE II STUDY OF CONCOMITANT PACLITAXEL, CISPLATIN, AND CONCURRENT, SPLIT COURSE HYPERFRACTIONATED RE-IRRADIATION IN PATIENTS WITH RECURRENT SQUAMOUS CELL CANCER OF THE HEAD AND NECK

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S Radiation Therapy on weeks 1, 3, 5, and 7
60 Gy total dose in 40 fractions: 1.5 Gy/fraction twice daily (4-6 hours between fractions) x5 days.

T Treatment must begin on a Monday.

E Chemotherapy on Weeks 1, 3, 5, and 7
Cisplatin: 15 mg/m² i.v. daily x 5 days
Paclitaxel: 20 mg/m² over 1 hour x 5 days
G-CSF: See Section 7.3.1

Eligibility: (See Section 3.0 for details) (12/13/02)

- Recurrent squamous cell cancer from a primary in the head and neck (excluding nasopharynx or salivary gland tumors) or second primary within a previously irradiated field
- Uni- or bi-dimensionally measurable tumor confined to the head and neck with no distant metastases
- The patient is not a candidate for complete surgical resection
- The majority of the tumor volume ($\geq 75\%$) must have been previously treated to between 45 Gy and 75 Gy XRT completed at least 6 months prior to disease recurrence
- The entire tumor volume can be included in a treatment field without exceeding total spinal cord dose (previous and planned treatments) of 50 Gy.
- Radiation records, including simulation and portal films (if available), from the primary (previous) course of treatment must be submitted to RTOG
- Zubrod performance score 0-1
- Granulocytes $\geq 1500$ mm$^3$, platelets $\geq 100,000$ mm$^3$, bilirubin $\leq 1.5$ mg/dl, creatinine $\leq 1.5$ mg/dl
- No hypersensitivity to E. coli-derived products
- No distant metastases
- No other concurrent invasive malignancies
- No intercurrent medical illnesses that will impair patient’s tolerance of treatment or limit survival
- Signed study-specific consent form prior to study entry

Required Sample Size: 100
1. Does the patient have recurrent or second primary tumor of the upper aerodigestive tract is in an area that has been previously irradiated? 
2. Is the study site a salivary gland or nasopharyngeal tumor? 
3. Has the recurrence been pathologically confirmed and found to be squamous cell carcinoma? 
4. Did the recurrence occur \( \geq 6 \) months following radiotherapy? 
5. Is the tumor measurable? 
6. Is the recurrence confined to the head and neck area above to the clavicles? 
7. Any evidence of distant metastases? 
8. Is the patient a candidate for complete surgical resection? 
9. Has 75% or more of the current tumor area been previously irradiated to a minimum of 45 Gy and not more than 75 Gy? 
10. Can the entire tumor volume be included in treatment fields that will limit the total spinal cord dose from all courses (previous and current) to \( \leq 50 \) Gy? 
11. Any intercurrent medical condition that will impair patient's tolerance of treatment or limit survival? 
12. Has the patient received any chemotherapy for recurrent tumor? 
13. Any chemotherapy or radiation therapy within 6 months of the currently planned treatment? 
14. What is the patient's Zubrod Performance Status? 
15. What is the granulocyte count \( (mm^3) \) per 1000? 
16. What is the platelet count \( (mm^3) \) per 1000? 
17. What is the serum bilirubin \( (mg/dl) \)? 
18. What is the serum creatinine \( (mg/dl) \)? 
19. Are the LFTs more than twice your institution's upper normal range?

\[
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Institution # 
RTOG 99-11

ELIGIBILITY CHECK (6/20/01)(12/13/02)

Case # 

(6/20/01)(12/13/02)

______(Y) 20. Were all required tests done within 2 weeks prior to registration?

______(Y) 21. Is material documenting prior H&N radiotherapy available (including films, calculations, and treatment records)? (See Section 3.1.12 for requirements)

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. Treatment Start Date

17. Medical Oncologist’s Name

18. Treatment Assignment

(Y/N) 19. Is this patient going to receive IMRT?

Completed by ________________________________ Date ________________________________
1.0 INTRODUCTION

1.1 Recurrent Head and Neck Cancer

Local failure after curative intent radiation therapy alone or in combination with surgery and/or chemotherapy is still a significant problem, especially in advanced stage head and neck cancer. Fifty to 60% of patients will die as a direct consequence of locally recurrent disease. Surgical salvage is sometimes successful, but not always feasible due to disease extent or involvement of critical structures.

Chemotherapy is widely used for palliation of patients with recurrent, unresectable head and neck cancers and generally produces a less than 50% response rate and a median survival of 5-6 months. Even the best results reported from single institution trials report a complete response rate of 27% and a median survival of eight months. Clearly new approaches need to be evaluated in this poor prognostic patient population.

1.2 Re-irradiation in Recurrent Head and Neck Cancer

Re-irradiation, except for nasopharyngeal carcinoma, has not been used frequently in the past due to previous high radiation dosage and concern for limited tissue tolerance. However, local control rates up to 50% and a five-year survival of 20% are reported with external beam re-irradiation. Interstitial implantation also has been used for salvage treatment of recurrences at the primary site or in the neck with 40-60% local control and a 14% five-year survival. Hyperthermia has been added to interstitial or external modalities resulting in 40-70% complete responses. Unfortunately, the size and location of most recurrences does not allow the optimal use of interstitial therapy or hyperthermia.

Preclinical studies have attempted to evaluate normal tissue tolerance to repeated doses of radiation. It has been estimated that the amount of dose which can be given ranges from 0-40% of the initial dose. However, there is also evidence that soft tissue can tolerate a repeat dose as high as approximately 90% of the original dose if the second treatment is applied six weeks to ten months after the first. Other studies suggest that tolerance depends upon whether early or late reactions are being assessed. Tolerance is also dependent upon fraction size. The dose compensation factor for the previous irradiation varied for 6-10% for prediction of acute reactions and from 21-38% to estimate late toxicity.

The incidence of tissue necrosis following repeat irradiation varies from 0-40%. The doses used have ranged from 35 Gy to greater than 65 Gy, with the dose per fraction varying from 1.80 Gy to 2.40 Gy. Most authors conclude that doses of greater than 50 Gy are necessary to yield substantial response rates. Langlois demonstrated that a reduction in the size of the re-irradiated volume decreases the probability of complications. Re-irradiation fields greater than 70 cm² correlated with increased frequency of complications. Radiation myelitis is a major complication which must be avoided. Recent studies emphasize that fraction size as well as total dose is important in predicting the probability of the development of myelitis. If fraction sizes are kept at 1.8 - 2.0 Gy per fraction, the risk of myelitis should be less than 6%. Total re-irradiation doses of 60 Gy or greater have been given with acceptable late toxicity rates of 25% or less.

1.3 Chemoradiotherapy for Recurrent Head and Neck Cancer

In an attempt to improve local control and palliation for patients with recurrent head and neck cancer after previous full dose radiation therapy, an outpatient treatment regimen incorporating 5-fluorouracil (5-FU) and hydroxyurea (HU) with radiation has been used at the University of Alabama at Birmingham. 5-FU has single agent activity against head and neck cancer and is a radiation sensitizer. HU also has single agent activity in head and neck cancer and is a radiation sensitizer. HU may biochemically modulate 5-FU activity by depleting cellular deoxyuridine monophosphate (dUMP), thus facilitating the competitive binding of the active 5-FU metabolite, 5-fluoro deoxyuridine monophosphate (5-FdUMP), to the target enzyme thymidylate synthase. Vokes et al. have employed a similar approach using infusional 5-FU and HU which have shown encouraging results but with substantial local toxicity with a high rate of complete and overall response and a 24% long-term disease-free survival has also been reported with concomitant cisplatin, 5-FU infusion and re-irradiation.

To provide optimal radiation-chemotherapy interaction, both modalities should be given concomitantly, usually necessitating a split in the radiation therapy regimen. Although single modality split course radiation therapy is reported to be inferior to continuous course radiation therapy due to prolongation of overall treatment time and accelerated repopulation, improved local control and survival has been reported with split course radiation therapy and the addition of concomitant chemotherapy.
In the UAB series, thirty-five patients with recurrent head and neck cancer, a Karnofsky performance status of at least 50, who had received prior curative intent radiation therapy, including the site of failure, have been treated. The median age was 63 years (range 42 to 76; 28 were male and seven were female). The mean performance status at the beginning of treatment was 60 (range 50 to 90). The mean prior radiation dose to the site of recurrence was 62.8 Gy. Fourteen patients had previous chemotherapy, seven as part of their primary management, six as treatment for recurrent disease, and one in both settings. Three patients had metastatic disease outside the head and neck area. Median time from previous radiation to retreatment was 24 months (range 7 to 144 months).

Three dose variations were examined. In all regimens, treatment was given on weeks 1, 3, 5, and 7 with no therapy on weeks 2, 4 and 6. The initial eleven patients received HU 2 g by mouth 2 hours before, and 5-FU 300 mg/m² i.v. bolus 20 to 30 minutes before, single daily fraction (2.0 Gy/fraction, 40 Gy total dose) radiation therapy. The single radiation dose was 2 Gy per treatment. Significant myelosuppression was encountered in these patients, but no dose-limiting in field toxicity. The schedule was then modified for the next nine patients. Radiation therapy was given twice per day at 1.2 Gy per fractions, 6 hours apart to a total dose of 48 Gy. The dose for HU was reduced to 1.5 g. Hematologic tolerance was much improved and again severe radiation toxicity was not observed. For the last fifteen patients, the radiation dose was increased to 1.5 Gy per fraction b.i.d., 6 hours apart to a total dose of 60 Gy. The HU and 5-FU dose remained as per the second modification. Both 5-FU and HU were timed in respect to the afternoon radiation therapy. Radiation therapy was given based on a treatment planning CT scan with the goal to treat all known disease with a 2 cm margin. The preliminary results of this trial have been published and presented.40,41 A final summary is in preparation.

Twenty-six patients (69%) completed all four planned courses of combined therapy. One patient completed all courses of radiation but received only one course of chemotherapy. This patient had hepatic insufficiency unrelated to his malignancy or therapy. Three patients did not receive the fourth week of treatment because of persistent neutropenia, and one patient did not complete the fourth week because of persistent diarrhea. Four deaths occurred during treatment. Two patients expired after three courses of treatment, one with neutropenia and secondary sepsis, and a secondary with aspiration pneumonia. The third patient died secondary to carotid artery rupture. The fourth patient expired on the third day of treatment with no evidence of toxicity.

There were three grade 4 and one grade 5 hematologic toxicities all in regimens 1 and 2. The skin and mucosal toxicities were acceptable in all three regimens with no grade 4 or 5 toxicities noted. Seventeen patients lived >12 months, four of whom have developed late complications. One patient developed TIA-like symptoms 2 years post-re-treatment. It was not clear if the symptoms were secondary to perturbation of blood flow as a result of radiation fibrosis. Two patients developed esophageal strictures. The stricture in one patient was clearly out of the re-irradiate volume. This patient did, however, develop significant fibrosis of the tongue and required a gastrostomy. He died with widely metastatic lung cancer. The stricture in the second patient was located in the surgically reconstructed cervical esophagus which was within the re-irradiated volume. He, likewise, required feeding tube placement and died with progressive local disease noted at the level of stricture formation. The fourth patient developed trismus one year after re-treatment. He had received a surgical resection of recurrent disease 21 months prior to re-irradiation. The TMJ was within the re-irradiation volume. He is currently gastrostomy-dependent. The acute and late infield toxicities were not different in the three treatment groups.

Fifteen patients had a complete response. Eleven patients had a partial response. Nine patients, including the four who died during treatment are considered non-responders. The overall median survival was 10.5 months. There was no statistical difference in the median survival among the three regimens. The median survival was 12.5, 8 and 9.5 months for regimens 1, 2 and 3, respectively. Patients who had complete responses had a longer median survival compared to those who had partial responses or no response. Patients who received their initial course of radiation 24 months or more prior to the repeat course had a median survival of 15 months versus 6.5 months in patients who were retreated within one year of their initial therapy.
1.4 Rationale for the Proposed Study

Wheeler et al. mounted a phase II RTOG study (9610) evaluating this approach using concurrent split course hyperfractionated XRT, 5-fluorouracil and hydroxyurea; 86 patients were accrued. Untoward toxicity has not been observed. Vokes et al. reported the results of concurrent RT, 5-FU, and hydroxyurea in patients with locally recurrent squamous cell cancer of the head and neck, with the vast majority of patients responding, some durably disease-free.32 He later added cisplatin to the same regimen yielding responses in 13 of 17 patients, but found this approach was tolerable only with G-CSF added as well.43 Cisplatin is well recognized as a radiosensitizer42-43 and there is increasing evidence that paclitaxel has similar effects44-48 with clinical studies showing that concurrent RT and paclitaxel is feasible without compromising RT dose.38,49 Paclitaxel has proven single agent activity in SCCHN,50 in pulmonary malignancies52-54 and in esophageal cancer,54 and there is emerging evidence that prolonged or repeated infusions (e.g. 96 hours vs. ≤ 24 hours) may be more cytotoxic in preclinical cell lines, especially in pulmonary malignancies.55-57 Cisplatin, likewise, has been used standardly in each of these malignancies, both alone56,57 and in combination.58,59 In addition, as a radiosensitizer, cisplatin may be most effective when administered on a daily basis during RT60 as opposed to a more intermittent basis; in this manner, the potential for radiosensitization is maximized.

A European study of daily bolus cisplatin in conjunction with split course RT in locally advanced NSCLC proved superior to weekly RT and cisplatin and to split course RT alone,61 whereas a similar American study which evaluated cisplatin administered q 3 weeks during conventional radical thoracic RT for NSCLC failed to yield any benefit compared to RT alone.61 In addition, a SWOG study implementing cisplatin at 5 mg/m² daily weekdays continuously during radical TRT in locally advanced, unresectable NSCLC proved both tolerable and feasible in a cooperative group setting.62

Forastiere at Johns Hopkins has conducted a phase I study of RT, in conjunction with weekly cisplatin and paclitaxel62 after surgical resection of locally advanced SCCHN and demonstrated safety for this approach. To explore optimally both the cytotoxic and radiosensitizing effects of this combination, a phase I study of daily bolus cisplatin and daily one-hour paclitaxel infusion in combination with hyperfractionated, split course RT in patients with relapsed SCCHN and other aerodigestive cancers67 was conducted at Fox Chase Cancer Center. Inaugurated in 2/97, 31 patients to date have been enrolled. Although formal dose limiting toxicity61 has not observed, at top dose levels (paclitaxel 20 mg/m², daily x 5; cisplatin, 15 mg/m² daily x 5), the investigators were obligated to cycle treatment at 3-week, rather than 2-week, intervals because of delayed recovery of neutropenia. The routine use of hematopoietic growth factor during the “off week,” permitted cycle compression at 2-week intervals without dose reduction in 6 or 7 patients, avoiding undesirable treatment delays. At this dose level with G-CSF, all patients completed scheduled treatment. In addition, the use of hematopoietic growth factor resulted in a significant reduction in local mucositis, as well as reduced myelosuppression. Treatment overall has been well tolerated. Mucositis has not been dose-limiting. Durable freedom from progression has been observed in several patients,63 although definitive conclusions about long-term survival cannot be made in this phase I trial.

Hence, we will conduct this study using split course hyperfractionated radiation, in combination with daily bolus cisplatin, (15 mg/m²/d; x 5) and daily paclitaxel infusion (20 mg/m²/d/1° x 5), with growth factor (G-CSF) support days 6 through 12 of each 2-week treatment cycle.

Although data exist to show that continuous daily RT is superior to split course daily RT as primary therapy,65-67 a split course schedule in the relapsed setting enables optimal integration of chemotherapy with radiation, the dose of which is likely to be limited. In addition, evidence from retrospective studies at MGH suggests that 1.6 Gy with a split is at least as effective as continuous course radiation.69-72 Wong and Vokes and colleagues have previously shown that the addition of aggressive chemotherapy administered concurrently with radiotherapy does not compromise local control, even if it prolongs treatment to twice the usual duration of conventional RT.73 Finally, a split course schedule also allows the incorporation of hematopoietic growth factor (HGF) between cycles, avoiding the paradoxical toxicity (heightened myelosuppression) previously noted with concurrent RT and HGF.74,75 The use of HGF may ameliorate mucositis,75,76 as well as reduce myelosuppression, which would otherwise be expected to be dose limiting during this trial.
As in the previous phase II RTOG effort (RTOG 96-10), this protocol will concentrate on locally recurrent, previously irradiated squamous cell carcinoma of the head and neck, and, to a lesser extent, on second primary SCCHN. If results appear promising, we will consider a phase III study comparing this regimen to chemotherapy alone, which is standardly used in this setting.

Finally, this study will not discriminate against patients based on race or gender; nor has there been any heretofore established evidence of differential toxicity with these agents based on gender or race.

**2.0 OBJECTIVES**

2.1 To estimate the median and one-year disease-free and overall survival rates of the treated patients.
2.2 To identify and estimate the incidence rate of acute and late toxicities associated with combined chemotherapy and re-irradiation in patients with recurrent squamous cell cancer of the head and neck.
2.3 To determine the pattern of disease progression in recurrent disease patients treated with chemoradiotherapy.

**3.0 PATIENT SELECTION**

**3.1 Conditions for Patient Eligibility**

3.1.1 Patients must have pathologically confirmed recurrence (reappearance of previously cleared) squamous cell cancer primary in the upper aerodigestive tract or a second squamous cell primary (excluding nasopharynx or salivary gland tumors). Patients may have experienced more than one recurrence as long as the first recurrence occurred ≥ 6 months following the end of the prior RT.
3.1.2 The recurrence or second primary must have defined bi- or uni-dimensional measurements.
3.1.3 Recurrence or second primary must be confined to the head and neck above the clavicles (loco-regional recurrence).
3.1.4 The patient must not be a candidate for complete surgical resection.
3.1.5 The majority (≥ 75%) of the tumor volume must have been in areas previously irradiated to ≥ 45 Gy. The previous irradiation must not exceed a maximum of 75 Gy.
3.1.6 The entire tumor volume must be included in a treatment field that limits the total spinal cord dose to 50 Gy (prior RT and anticipated RT).
3.1.7 Patients must be at least 6 months from prior chemotherapy and radiation therapy.
3.1.8 Patients may have received prior chemotherapy as a component of their primary treatment, but not for recurrent disease.
3.1.9 Zubrod performance status 0-1.
3.1.10 Granulocytes ≥ 1500/mm3, platelets ≥ 100,000/mm3, serum bilirubin ≤ 1.5 mg/dl, creatinine ≤ 1.5 mg/dl within 2 weeks prior to registration.
3.1.11 LFT’s ≤ 2 x normal (SGOT/SGPT/Alkaline Phosphatase). If > 2 x normal, liver ultrasound or CT is required to exclude metastases. If negative for metastases, patients are eligible.
3.1.12 Must be able to submit previous radiation records (simulation and portal film, if available) in order to assure that cord tolerance is not exceeded. (12/13/02)
3.1.13 Patients must sign a study-specific informed consent form prior to study entry.

**3.2 Conditions for Patient Ineligibility**

3.2.1 Distant metastases.
3.2.2 Primary in the nasopharynx or the salivary gland.
3.2.3 Other concurrent invasive malignancies.
3.2.4 Prior invasive malignancy unless disease free for at least two years (prior in situ malignancies, e.g. cervix, breast, non-melanomatous skin cancer, etc. are permissible).
3.2.5 Intercurrent medical illnesses which would impair patient tolerance to therapy or limit survival.
3.2.6 Pre-existing grade ≥ 2 peripheral sensory neuropathy.
3.2.7 Patients with a hypersensitivity to E. coli-derived products.
3.2.8 Pregnant and nursing women are excluded because of the potential teratogenic effects and potential unknown effects on nursing newborns.

**4.0 PRETREATMENT EVALUATIONS**

4.1 Patient must have completed the following within 2 weeks of registration unless noted:
4.1.1 Physical examination to define measurable disease.
4.1.2 Baseline CT or MRI scan of head and neck that includes entire disease extent (within 1 month before study entry).
4.1.3 CBC with differential and platelet count.
4.1.4 Bilirubin, SGOT, SGPT, creatinine, sodium, chloride, bicarbonate, potassium, BUN, glucose, alkaline phosphatase.

4.1.4.1 Liver ultrasound or CT scan if the liver chemistries (SGOT, SGPT, bilirubin) are > 2 times normal values.

4.1.5 Chest x-ray (within 1 month prior to protocol treatment).

4.1.6 Additional studies (bone scan, barium swallow, etc.) to exclude distant metastases or second primaries as clinically indicated.

4.1.7 Information on prior radiation field(s) and dose(s) to permit assessment of eligibility (Section 3.1) and planning of current treatment field(s) (Section 6.0).

5.0 REGISTRATION PROCEDURES

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 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 following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY (6-20-01)

The allowable treatment approaches include a standard approach, a 3D-CRT approach, or an IMRT approach. Additional information is required if an IMRT treatment planning or a 3D-CRT delivery approach is used.

6.1 Dose Fractionation (6-20-01)

RT will be given as two daily fractions (1.5 Gy per fraction) separated by at least 4 hours for five consecutive days every other week for four weeks (weeks 1, 3, 5, and 7). Total dose will be 60 Gy in 40 fractions. Dose to the spinal cord must be limited to 50 Gy total (prior plus current). Decay factors are not permitted. Paclitaxel and cisplatin will be given between the b.i.d. fractions. No treatment is given on weeks 2, 4 and 6. Treatment will begin on Mondays. The exact time and date of each treatment is to be recorded. If the patient misses more than two days, i.e., four fractions, missed treatments (radiation with chemotherapy) should be made up following administration of the 4th cycle of Filgrastim (i.e., starting week 9 [day 57]). The makeup of missed treatments (≥ 3) given during week 9 will be reported on the final Treatment Summary Form (TF). Do not make up if a single date is missed. If the chemotherapy and radiation are given during the “off week”, delay the G-CSF until the day after chemoradiation. Do not give G-CSF simultaneously with RT or chemotherapy.

6.2 Physical Factors

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

6.2.2 Photon beams of ≥ 1.25 MeV and/or electron beams from 4-25 MeV are allowed.

6.2.3 Treatment distance must be ≥ 80 cm SSD or greater, or ≥ 80 cm SAD for isocentric techniques.

6.3 Localization Requirements

6.3.1 Simulation of all fields is mandatory. Patients must be reproducibly immobilized. Radio-opaque markers should be used whenever possible to delineate the extent of nodal disease, skin involvement, and any gross disease. The use of customized blocks or multileaf collimation for field shaping is strongly recommended.

6.3.2 Treatment planning CT scans are required if a 3D-CRT or an IMRT treatment approach is used. If the standard treatment approach is followed, then treatment planning CT scans are strongly recommended to facilitate accurate dosimetry. (6-20-01)

6.3.3 Beam localization films (portal films) should be obtained for all photon and electron fields.

6.3.4 Target Volume

A combination of lateral opposing fields, single fields, anterior and lateral wedge pair fields, and oblique fields may be used for the site of recurrent tumor. The treatment fields should encompass the recurrent tumor with adequate margins of at least 2.0 cm whenever possible. Margins of less than 2.0 cm is an acceptable deviation only in instances of spinal cord encroachment. Partial miss or gross tumor cut
through is an unacceptable deviation. The treatment fields should encompass the recurrent tumor defined as the Gross Tumor Volume (GTV), considered all known disease defined by clinical, radiographic or any other information available. Adequate margins of at least 2 cm should be added whenever possible. Margins less than 2.0 cm are an acceptable deviation only in instances of spinal cord encroachment.

6.3.5 Dose Calculation (6-20-01)

6.3.5.1 For a standard treatment approach, an isodose distribution in a transverse plane through the center of the target volume is required summatung all fields. If the spinal cord is in close proximity to the treatment volume, off axis isodose distributions should be performed as well. This will enable an accurate computation of the maximum and minimum dose to the spinal cord. For a 3D-CRT approach or an IMRT approach, isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the GTV and the spinal cord are required. Independent of the treatment approach, the maximum dose to the spinal cord must be indicated on the daily treatment record. The specification of the protocol target dose is in terms of a dose to a point at or near the center of the target volume.

6.3.5.2 The dose for arrangement of two or more intersecting beams should be at the intersection of the central ray of the beams.

6.3.5.3 The dose for two opposed coaxial equally weighted beams should be on the central ray at mid-separation of beams.

6.3.5.4 The dose for more complex arrangements should be at the center of the target area.

6.3.5.5 The inhomogeneity within the target volume should not exceed ± 10% of the target dose.

6.4 Evaluation Criteria

6.4.1 Dose and Fractionation

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<tr>
<td>&gt; 9%</td>
<td>&gt; 5 Days of non HFX</td>
<td>Deviation Unacceptable</td>
</tr>
</tbody>
</table>

6.5 Dose Modifications (6-20-01)

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

6.5.2 If a treatment delay for local acute toxicity is required, only the dose of chemotherapy will be modified (Section 7.5), not the total RT dose.

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

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

6.5.5 If treatment breaks unrelated to toxicity occur, e.g., department schedule, bad weather, or patient absence, the missed treatments should be made up as described in Sections 6.1 and 7.3.1.

6.5.5.1 There is a real, but relatively small risk of carotid rupture in patients whose tumors overlap the carotid artery. Most of these events have occurred in association with active tumor in this region and may not necessarily be due to adverse effects of treatment. (12/13/02)

6.6 Treatment Verification

6.6.1 For standard and 3D-CRT treatment approaches, first day port films or portal images of each field must be obtained. In addition, there must be included a set of orthogonal megavoltage images (AP and lateral) from the first approved treatment. Thereafter, weekly verification films or images or orthogonal films are required.

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

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

6.7 Dosimetry Required

6.7.1 For standard treatment approaches, an isodose distribution in a transverse plane through the center of the target volume is required summatung all fields. If the spinal cord is in close proximity to the treatment volume, off axis isodose distributions should be performed as well.
6.7.2 For 3D-CRT, isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the GTV and the spinal cord are required.

6.7.3 For IMRT, isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the GTV and the spinal cord are required. This documentation must indicate the planning system and version, e.g., Corvus, V. 3.1. Please provide a description of the treatment delivery system, e.g., IMRT compensating filter, MLC step and shoot, or dynamic tomotherapy.

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

7.1 Paclitaxel (Taxol)

7.1.1 Dose
Will be given on an outpatient or inpatient basis, initial dose of 20 mg/m²/1 hour per day x 5 on weeks 1, 3, 5, and 7; paclitaxel will be administered immediately after the first fraction of RT, and completed ≥ 3 hours prior to the second fraction.

7.1.2 Chemical Name

7.1.3 Formulation
Concentrated sterile solution, 6 mg/ml in a 5 ml vial (30 mg/vial) as well as 16.7 cc (100 mg) and 50 cc (300 mg) vials in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP 50%. The contents of the vial must be diluted before use. The intact ampules should be stored under refrigeration (2-25 °C [36-77 °F]).

7.1.4 Incompatibilities
Little is known concerning physical incompatibilities with Taxol. Based on information from other cremophor based drugs it is recommended that no other solutions be mixed with the Taxol-containing solution.

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

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

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

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

7.1.7 Toxicity
The following toxicities are anticipated: myelosuppression, myalgias and arthralgias, bradycardia and other cardiac rhythm disturbances, alopecia, stomatitis, nausea, vomiting, allergic reactions, peripheral neuropathy, CNS toxicity-seizures. Urticaria (hives, welts, wheals), hemoglobin, leukocytes (total WBC), lymphopenia, neutrophils/granulocytes (ANC/AGC), platelets, conduction abnormalities/atrioventricular block, nodal/junctional arrhythmias (SVT/atrial fibrillation/flutter), ventricular arrhythmia (PVCs/bigominy/trigeminy/ventricular tachycardia), cardiac-ischemia/infarction, hypertension, hypotension, fatigue (lethargy, malaise, asthenia), erythema multiforme, flushing, injection site reaction, nail changes, pruritis, radiation recall reaction, rash/desquamation, colitis, diarrhea, stomatitis/pharyngitis, taste disturbance, typhlitis, alkaline phosphatase, bilirubin, liver dysfunction/failure, SGOT, SGPT, infection, dizziness, lightheadedness, leukoencephalopathy associated with radiological findings, mood alteration-anxiety agitation, neuropathy-motor, neuropathy-sensory, ocular-other (scintillation scotoma), blurred vision, flashing lights/floaters, pneumonitis/pulmonary infiltrates, Stevens-Johnson Syndrome.
7.1.8 Patient Care Implications
Monitor for signs and symptoms of allergic reactions. Ensure that premedications have been given and that emergency agents are available. The patient’s blood pressure and heart rate will be monitored during the infusion (every 15 minutes during the first hour).
Asymptomatic bradycardia has been reported in up to 30% of patients. Patients with more serious arrhythmias usually have other predisposing cardiac risks.
Evaluate for nausea, which should be mild with low dose daily infusion and consider pretreatment of patients who exhibit nausea in subsequent courses.
Evaluate i.v. site regularly for signs of infiltration. It is not known whether Taxol is a vesicant, but since it interacts with microtubules (similar to vincas), care should be exercised. The vehicle Cremophor-EL is also a known vesicant in high concentrations.
Patients should be warned about arthralgia-myalgia syndromes which may occur after treatment. Acetaminophen, NSAIAAs or, if necessary, narcotics may be given for symptomatic control.

7.1.9 Supplier
Taxol is available commercially in the United States. Bristol Myers Squibb (BMS) Oncology-Canada will provide Taxol to Canadian institutions. Contact the local BMS representative. The intact ampules should be stored under refrigeration (2-25°C [36 °F - 77 °F]).

7.2 Platinol (Cisplatin)
7.2.1 Dose
15 mg/m² i.v. bolus daily x 5 days on weeks 1, 3, 5, and 7 in 500 cc ½ normal saline solution (NSS) or NSS over 30 minutes immediately following paclitaxel after 500 cc prehydration over 2 hours. Additional intravenous fluids pre- or post-cisplatin can be administered as necessary.

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

7.2.3 Formulation
Cisplatin (Platinol-AQ) is available 1 mg/mL in 50 mL and 100 mL vials and as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of Sterile Water for Injection USP, respectively.

7.2.4 Storage and Stability
The intact vials should be stored under refrigeration. However, once reconstituted, the solution should be kept at room temperature to avoid precipitation. Due to lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride containing vehicle such as D5NS, NS, or D5 1/2 NS (ppt. occurs in D5W). cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.2.5 Administration
Cisplatin should be given immediately after preparation.

7.2.6 Toxicity
Toxicity includes nausea, vomiting, anorexia, loss of taste, renal toxicity (with an elevation of BUN, creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy, allergic reactions, and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.

7.2.7 Supplier
Cisplatin is commercially available.
7.3 Filgrastim (Neupogen)

7.3.1 Dose (6-20-01)

Will be administered subcutaneously at a dose of 300 mcg SQ daily for patients ≤ 60 kg and 480 mcg SQ daily for patients > 60 kg, starting 24 hours after the end of the chemotherapy infusion (day 6), continuing through day 13 (8 days total). A total of 4 cycles of Filgrastim will be administered to correlate with each of the 4 cycles of chemotherapy/radiation. If treatment must be added (week 9) to make up missed chemotherapy/RT, additional Filgrastim must also be administered for an additional 8 days starting the day after the last dose of chemoradiation. The patient’s ANC must be at least 1500 before the next dose of chemotherapy can be administered. Filgrastim will be continued past day 13, if necessary, to achieve this goal. Note that Filgrastim must be discontinued at least 24 hours prior to the next dose of chemotherapy. If radiation/chemotherapy doses are missed due to departmental schedule or patient absence, i.e., not due to toxicity modification, the missed treatments (see Section 6.1) are given after the 4th cycle of Filgrastim. Filgrastim is not to be administered simultaneously with chemotherapy or radiation.

7.3.2 Source and Pharmacology

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

7.3.3 Formulation and Stability

G-CSF is a sterile, clear, colorless, preservative-free liquid for parenteral administration. Each single-use vial of G-CSF contains 300 micrograms/ml of filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg. The product is formulated in a 10mM sodium acetate buffer at pH 4.0, containing 5% sorbitol and 0.004% Tween 80. Both 1.0 and 1.6 ml vials are available. Store between 2 and 8° C. Do not freeze. Avoid shaking. Drug administered SQ should not be diluted and can be drawn directly from the vial and administered.

7.3.4 Route of Administration

Subcutaneously.

7.3.5 Toxicity

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

7.3.6 Supplier

Provided by Amgen.

7.3.6.1 U.S. Sites (11-16-01)

- **Supplier**: G-CSF (Filgrastim) is commercially available. However, for this study it is being supplied free-of-charge by Amgen, Inc. and is available from UintaVision. To obtain a supply of G-CSF, complete the G-CSF (Filgrastim) Drug Request Form supplied in Appendix VI, and fax or send the form to the following address:

  UintaVision, Inc./Axion, Inc.
  232 Castro Street, Suite #2
  San Francisco, CA 94114
  General Phone (800) 370-2508
  FAX (650) 745-3877

- UintaVision’s office hours are 6:30 a.m. to 1 p.m. PST; a phone message may be left at other times. Phone messages left after 1 p.m. will be returned the next business day.

- Orders received by 11:30 a.m. PST Monday through Thursday will be shipped for next day delivery. The initial shipment to each study site will be delivered by 3:30 p.m.

**G-CSF orders from USA sites only will be accepted.** Patients must be registered to the study before study drug can be obtained.
• When the study is terminated, unused drug at the site will be returned to UintaVision, Inc./Axion, Inc., with a completed Return Medication Packing Slip (Appendix VII) included to identify for which study the drug was originally shipped.

7.3.6.2 Canadian Sites
• AMGEN will require that a Reimbursement Assessment Form be completed for all patients enrolled in the trial (Appendix VIII).
• Complete and fax to Karen Arts (Amgen Canada, Inc) as well as leaving a phone message.

FAX (905) 542-3206
TEL (905) 819-5198

• **NEUPOGEN® Reimbursement:**
AMGEN will require that all reimbursement options available to the patient be explored and utilized to cover the cost of NEUPOGEN®. In the event that the patient does not have coverage for NEUPOGEN® then AMGEN Canada Inc., as a last resort, will provide NEUPOGEN® free of charge. A NEUPOGEN® Request Form must be completed and faxed to, as well as a phone message left for Karen Arts at Amgen Canada Inc (Appendix VIII). In the event that reimbursement options for a particular patient are unclear, please contact your local Amgen Canada Inc., Biopharmaceutical Specialist. If you do not know your local Biopharmaceutical Specialist, please call 1-800-665-4273 ext. 261.

• **Deductible / Co-pay:**
Amgen Canada Inc., will not be providing assistance with Co-pay or deductibles for this study. Should these issues be problematic, please contact your local Amgen Canada Inc., Biopharmaceutical Specialist for guidance with this issue.

• **Delays from Government Reimbursement Systems:**
If the patient is eligible for a reimbursement system and requires NEUPOGEN® before an approval has been granted, AMGEN Canada Inc., upon proof of submission, will supply one cycle of NEUPOGEN® free of charge in order to allow for the approval from the reimbursement body to be received.

7.4 Other Agents to be Used in Protocol

Hypersensitivity prophylaxis ½ hour prior to paclitaxel consisting of:
• Dexamethasone 10 mg i.v. pre-paclitaxel
• Diphenhydramine 50 mg i.v. pre-paclitaxel
• Cimetidine 300 mg i.v. pre-paclitaxel
• Granisetron 10 mcg/kg prior to each dose of cisplatin (or ondansetron or other 5HT3 antagonists).

Doses may be adjusted accordingly. It is suggested that anti-emetics be continued for 3-4 days after the last dose of cisplatin during each cycle. Suggested regimens include prochlorperazine, 10mg and diphenhydramine 25mg prior to meals or low-dose ondansetron, e.g. 4mg p.o. q 8 hours.

7.5 Treatment Plan/Dose Modifications

7.5.1 The doses for each patient enrolled will not be raised. The doses of both cisplatin and paclitaxel will be reduced by 25% during second and subsequent cycles for any of the following:
• Neutropenic fever (fever of ≥ 100.6 °F and grade 3 or 4 neutropenia requiring hospitalization and i.v. antibiotics)
• Delay in resuming radiation by > 1 week
• Grade 4 thrombocytopenia (<25,000) requiring platelet transfusions
• Grade 4 mucositis requiring TPN or hospitalization
• Grade 3 or 4 fatigue, which, in the opinion of the treating physician, precludes full dose therapy

7.5.2 Non-hematologic Toxicity

7.5.2.1 For grade 3 neurotoxicity or other non-hematologic, grade 4 toxicity, excluding nausea, vomiting, alopecia and fatigue, the dose of the implicated agents will be reduced by 25%, and will not be raised back to the original dose seen in the absence of subsequent grade 3 or 4 toxicity. (6-20-01)

7.5.2.2 Osteoarthralgias attributed to G-CSF (Filgrastim) and/or paclitaxel will be controlled by analgesics, and will not mandate dose reductions of G-CSF or paclitaxel.

7.5.2.3 Renal toxicity: full dose cisplatin for serum creatinine ≤ 1.5 mg/dl. Fifty percent reduction for 1.6-2.0 mg/dl at the time of retreatment. Cisplatin will be with held only for increase in creatinine > 2.0 mg/dl.
7.5.3  **Criteria for Treatment Delays**

Treatment will be delayed ≥ 1 week if either of the following exists at the time treatment is due to resume:

- Ongoing mucositis that precludes adequate hydration or intake (*not applicable to patients with G-tubes or receiving TPN*).
- Grade ≥ 2 neurotoxicity
- Failure to recover ANC to ≥ 1500/cc or platelets to ≥ 80,000/cc
- Other, ongoing, grade ≥ 3 non-hematologic toxicities (*except for alopecia*).

7.5.4  **Hypersensitivity Reactions**

If hypersensitivity reaction occurred during paclitaxel infusion, the infusion will be halted x 5-20 mins. Patients will receive hydrocortisone 150 mg i.v. and diphenhydramine 25-50 mg, and paclitaxel infusion will be resumed at slow rate initially, then gradually accelerated per nursing policy. If allergic reaction recurs, despite slowing the infusion rate, patients will receive a full 24 hours of oral steroid prophylaxis (*e.g. dexamethasone 6 mg q 6 hrs*) prior to the next day’s dose.

7.5.5  **Premedications**

The patient will be premedicated 10-30 minutes prior to paclitaxel with dexamethasone 10 mg i.v. in conjunction with diphenhydramine 50 mg i.v. and with cimetidine 300 mg i.v. or, if intolerant to cimetidine, ranitidine 50 mg i.v. Patients will receive granisetron antiemetic prophylaxis at dose of 10 mcg/kg, or other antiemetic regimens, at treating physician’s discretion, prior to cisplatin administration days 1 through 5.

7.5.6  **Carotid Rupture**

There is a real, but relatively small risk of carotid rupture in patients whose tumors overlap the carotid artery. Most of these events have occurred in association with active tumor in this region and may not necessarily be due to adverse effects of treatment. (12/13/02)

7.6  **Toxicity Reporting**

7.6.1  The revised NCI Common Toxicity Criteria (*CTC*) Version 2.0 (3/98) will be used to score chemotherapy and acute radiation (*≤ 90 days*) toxicities and can be downloaded from the CTEP home page [http://ctep.info.nih.gov](http://ctep.info.nih.gov). This study will be monitored by the Clinical Data Update System (*CDUS*) Version 1.1. Cumulative CDUS date will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol, which 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.

7.6.1.1  Any ADR which is both serious (*life threatening, fatal*) and unexpected (*phone report within 24 hours; written report within 10 days*).

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

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

7.6.1.4  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.

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

**Investigational Drug Branch**

P.O. Box 30012
Bethesda, Maryland 20824
Telephone (301) 230-2330
available 24 hours
Fax (301) 230-0159

8.0  **SURGERY**

8.1  Patients who initially respond to therapy but recur with a resectable lesion inside or outside the re-treatment field may undergo resection (*overall medical condition permitting*). The surgical report and the resection pathology report must be also submitted to RTOG. (6-20-01)

8.2  The surgical and/or reconstructive procedures employed are at the discretion of the surgeon.
Patients who have pathologically proven complete response with a non-healing major defect should be considered for debridement and repair by flap or free tissue transfer. All resected tissue must be submitted for local pathology review.

Any surgical procedure(s) and their complications must be noted in the protocol data forms.

**9.0 OTHER THERAPY**

Does not apply to this study.

**10.0 PATHOLOGY**

Does not apply to this study.

**11.0 PATIENT ASSESSMENTS**

**11.1 Study Parameters (12/13/02)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre Entry</th>
<th>Weekly</th>
<th>Monthly (d) (First Follow-up)</th>
<th>Q 4 Monthly (d) (Subsequent Follow-ups)</th>
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</thead>
<tbody>
<tr>
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<td>X</td>
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</tr>
<tr>
<td>Tumor measurements</td>
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<td>CBC with platelets, diff</td>
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<td>X(b,g)</td>
<td>X(f)</td>
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</tr>
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<td>Chemistries (b)</td>
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<td>X(c,g)</td>
<td>X(f)</td>
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</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
<td></td>
<td>X(f)</td>
<td></td>
</tr>
<tr>
<td>Head and neck CT or MRI</td>
<td>X</td>
<td></td>
<td>X(e)</td>
<td></td>
</tr>
<tr>
<td>Bone scan, barium swallow, etc.</td>
<td>X(a)</td>
<td></td>
<td>X(a)</td>
<td></td>
</tr>
<tr>
<td>Liver ultrasound or CT</td>
<td>X(i)</td>
<td></td>
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</tr>
<tr>
<td>Toxicity scoring</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. As needed to assess distant metastases or second primaries.

b. Weekly during treatment and then repeat weekly times two after last course of treatment.

c. Repeat every two weeks during treatment.

d. Follow-up evaluations will be every 3 months through year 2, every 6 months for 3 years, then annually. Also at progression/reapse, significant post-treatment toxicity, and death. (6-20-01)

e. Repeat two months after completion of therapy for response assessment, then as needed to document progression.

f. Repeat every six months after the first year.

g. CBC and chemistries must be obtained at the beginning of each treatment week. It is critical that this timing be followed. Studies obtained earlier may not fully reflect the developing hematologic toxicity. Secondly, the dose modification guidelines require that the granulocyte count be ≥ 1500/mm³. It is important that this guideline be followed.

h. Bilirubin, SGOT, SGPT, creatinine, sodium, chloride, bicarbonate, potassium, BUN, glucose, alkaline phosphatase.

i. If liver chemistries are > 2 x normal.

**11.2 Other Information**

11.2.1 Prior radiation treatment fields and doses must be documented relative to the recurrence. Previous treatment records and films must be available for submission to RTOG Headquarters. See Section 12.0.

11.2.2 After treatment completion, any late toxicity must be documented relative to all treatment fields and doses.

11.2.3 All post-treatment surgical procedures and complications must be documented.

11.2.4 All recurrences and sites of recurrence must be documented relative to the re-treatment fields(s).

11.2.5 Survival will be measured from the time treatment starts.

11.2.6 All patients will be followed for survival.

11.2.7 Intervals between each fraction of radiotherapy must be recorded in the patient record.

**11.3 Criteria for Discontinuing Therapy**

11.3.1 The development of unacceptable toxicity not amenable to dose reduction.

11.3.2 Greater than three weeks delay between treatment courses.
11.3.3 Intercurrent illness that precludes further treatment.
11.3.4 Disease progression.
11.3.5 Patient request.

11.4 Methods of Malignant Disease Evaluation

11.4.1 Measurable, bi-dimensional
Malignant disease measurable \((\text{metric system})\) in two dimensions by rulers or calipers with surface area determined by multiplying the longest diameter by the greatest perpendicular diameter \((i.e., \text{metastatic pulmonary nodules, lymph nodes and subcutaneous masses})\). Malignant disease with sharply defined borders visualized by ultrasonography or computerized axial tomography is considered measurable. Repeat studies should be performed at the same pre-therapy sites\((s)\) or malignant disease.

11.4.2 Measurable, uni-dimensional
Malignant disease measurable \((\text{metric system})\) in one dimension by ruler or calipers.

11.4.3 Non-measurable, evaluable
Malignant disease evident on clinical \((\text{physical or radiographic})\) examination, but not measurable by ruler or calipers.

11.4.3.1 Photographs should be taken prior to and after therapy to document response \((i.e., \text{skin and subcutaneous metastases, intraoral lesions})\).

11.4.3.2 Bone scans cannot be used to evaluate response.

11.4.4 Non-measurable, non-evaluable malignant disease found to be surgically unresectable, but not clinically detectable.

11.5 Objective Criteria of Response

11.5.1 All tumor measurements must be recorded in centimeters and should consist of the two longest perpendicular cross-diameters. Patients will be separately assessed for response by physical exam and by CT scan prior to and two months following completion of therapy. Both the clinical \((\text{physical exam})\) and radiographic \((\text{CT scan})\) response will be recorded on the study forms.

11.5.2 Complete response - The disappearance of all known disease determined by two assessments not less than four weeks apart.

11.5.3 Partial response - A 50% or more decrease in total tumor size of bi-dimensionally measured lesions, or in the single dimension of uni-dimensional lesions, which have been measured to determine the effect of therapy determined by two observations not less than four weeks apart. Non-measurable, evaluable lesions must have decreased in size.

11.5.4 Stable disease - A 50% decrease in total tumor measurement cannot be established nor has a 25% increase in the measurement of one or more lesions been demonstrated. In addition, there can be no appearance of new lesions.

11.5.5 Progressive disease - A 25% or more increase in the size of one or more measurable lesions, the appearance of new lesions or 50% increase in evaluable non-measurable lesions.

11.5.6 Relapse

11.5.6.1 The appearance of new lesions in previously responding patients.

11.5.6.2 The reappearance of old lesions in patients who have achieved a complete remission.

11.5.6.3 For patients in partial remission, an increase of 25% or more in the product of the diameters of any measured bi-dimensional lesion or of the single measurement of a uni-dimensional lesion or a 50% increase in evaluable, non-measurable lesions over that which was obtained at the time of maximum regression.

11.6 Completion of an Adequate Trial

11.6.1 An evaluable case must have received at least one full week of treatment and undergone tumor measurements to evaluate the patient's response status.

11.6.2 Duration of response shall be measured from the achievement of that response to the first sign of relapse.

11.6.3 All patients receiving one full cycle of XRT, cisplatin, and paclitaxel and developing toxicity or surviving four weeks will be considered evaluable for toxicity. An adequate therapeutic trial will be defined as one infusion of therapy and four weeks survival or death from tumor progression within four weeks.
12.0 DATA COLLECTION (12/13/02)  
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)  
12.1 Summary of Data Submission  

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry</td>
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<tr>
<td>Initial Evaluation Form (I1)</td>
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<tr>
<td>Pathology Report (P1)</td>
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<tr>
<td>Tumor and Nodal Diagrams (I6, I7)</td>
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<tr>
<td>Prior Radiotherapy Materials (TM)</td>
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</tr>
<tr>
<td>(Prior treatment record including calculation summary and documentation of spinal cord dose)</td>
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</tr>
<tr>
<td>Preliminary Dosimetry Information:</td>
<td>Within 1 week of start of RT</td>
</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
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<tr>
<td>Films (simulation and portal) (T3)</td>
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<tr>
<td>Calculations (T4)</td>
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<tr>
<td>Final Dosimetry Information:</td>
<td>Within 1 week of RT end</td>
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<td>Radiotherapy Form (T1)</td>
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</tr>
<tr>
<td>Daily Treatment Record (T5)</td>
<td></td>
</tr>
<tr>
<td>Isodose Distribution (T6)</td>
<td></td>
</tr>
<tr>
<td>Boost Films (simulation and portal) (T8)</td>
<td></td>
</tr>
<tr>
<td>Dose Volume Histograms (DVH) (6-20-01)</td>
<td></td>
</tr>
<tr>
<td>Treatment Form (TF)</td>
<td>After each cycle and at completion or discontinuation of chemotherapy</td>
</tr>
<tr>
<td>Initial Followup Form (FS)</td>
<td>At 4 weeks after completion of RT</td>
</tr>
<tr>
<td>Followup Form (F1)</td>
<td>q 3 months through year 2, q 6 months x 3 years, then annually; at progression/relapse and at death and upon significant post-treatment toxicity</td>
</tr>
<tr>
<td>Surgical Op Note (S2)</td>
<td>Following resection as described in Section 8.0.</td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
<td></td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable</td>
</tr>
</tbody>
</table>

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

13.0 STATISTICAL CONSIDERATIONS  
13.1 Study Endpoints  
13.1.1 To estimate overall and disease-free survival  
13.1.2 To identify and estimate the incidence rate of acute and late toxicities associated with combined chemotherapy and re-irradiation  
13.1.3 To determine the pattern of disease progression in recurrent disease patients treated with chemotherapy  
13.2 Sample size (6-20-01)  
The primary objective of this study is to estimate the one-year survival rate for patients with recurrent squamous cell cancer of the head and neck treated with paclitaxel and cisplatin in combination with split course concomitant hyperfractionated re-irradiation. In the recently closed RTOG 96-10 study, this group of patients had an estimated one-year survival rate of about 35%. Using the method of Dixon and Simon,76 a sample size of 90 evaluable patients followed over 12 months will ensure at least 80%
probability of detecting a minimum of 15% improvement in the one-year survival rate compared to this RTOG study at the 0.05 significance level (with a one-sided test). This number of patients will also allow for testing the rate of late grade 4 and 5 toxicities using the method of Blackwelder \( \gamma \) under the following conditions: \( \alpha = 0.05, \beta = 0.20, \epsilon_0 = 5\%, \Delta = 20\% \). If the patients survived 12 months, 30 patients would be required under the above conditions. Based upon the data from RTOG 96-10, the probability of surviving beyond 12 months is 35%. Using this as a projection, then 86 (=30/0.35) patients would be required. Allowing for a 10% ineligibility/inevaluability rate, the total sample size required will be 100 patients.

The protocol has been revised to allow for the addition of IMRT. The primary endpoint is survival and we will assume that IMRT will have no enhancement on efficacy. However, it is possible that IMRT may reduce toxicity. For this reason, we will report toxicity for all patients; toxicity for patients treated without IMRT, and toxicity for patients treated with IMRT.

### 13.3 Inclusion of Women and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we have considered differences in prognosis by race and gender. In an analysis of the RTOG head and neck database, we found no difference. No other study so far has indicated any significant racial or gender differences in treatment effects for recurrent head and neck cancer patients. These issues are not well studied. The study was designed to test the efficacy under the assumption of the same efficacy across the genders and across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

### 13.4 Patient Accrual

The patient accrual is projected to be a minimum of three cases per month based upon the monthly accrual for RTOG 96-10 although the rate of accrual is expected to increase since there are no efforts competing. At this rate, it will take 34 months to reach the required total accrual of 100 cases. If the average monthly accrual is less than 2 patients, the study will be re-evaluated with respect to feasibility.

### 13.5 Suspension of Accrual Due to Morbidity

If there is any fatal treatment morbidity, the event will be immediately reported to the study chairman for review. If there are three such fatal events, accrual will be suspended, and all data pertaining to the events will be reviewed by the study chairman and reported to the RTOG Data Monitoring Committee (DMC) for review. The results from this review will determine the future course of action.

### 13.6 Analyses Plans

#### 13.6.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with a projected completion date for the accrual phase, and compliance rate of treatment delivery with respect to protocol prescription;
- b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of toxicities.

Through examining the above items, the RTOG DMC and the statistician can identify problems with the execution of the study. These problems will be reported to the RTOG committee responsible for the study, and, if necessary, the RTOG Research Strategy Committee, so that corrective action can be taken.

#### 13.6.2 Analysis for Reporting the Initial Treatment Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting of institutional accrual;
- c) distribution of important prognostic baseline variables (prior radiation dose, KPS, tumor size, and location of primary);
- d) observed results with respect to the endpoints described in Section 13.1.

The estimated survival from this sample will be tested against the RTOG 96-10 trial as the historical control using a one-sample test. The one-year overall and disease-free survival estimates with 95% confidence intervals will be calculated. The incidence rate of major late toxicities will be calculated and the probabilities will be tested for clinical acceptability (\( a < 25\% \) rate of grade \( \geq 4 \) late toxicity).
REFERENCES


61. Forastiere AA. Personal communication.


APPENDIX I
RTOG 99-11

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

PHASE II STUDY OF PACLITAXEL AND CISPLATIN IN COMBINATION WITH SPLIT COURSE
CONCOMITANT HYPERFRACTIONATED RE-IRRADIATION IN PATIENTS WITH RECURRENT
SQUAMOUS CELL CANCER OF THE HEAD AND NECK

This is a clinical trial (a type of research study). Clinical trials include only patients who choose
to take part. You are being asked to take part in this study because you have previously been
treated for squamous cell cancer of the head and neck area and cancer has returned to the treated
area.

Please take your time to make your decision. Discuss it with your friends and family. The
National Cancer Institute (NCI) booklet, Taking Part in Clinical Trials: What Cancer Patients
Need to Know, is available from your doctor.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (good and bad) the drugs cisplatin,
paclitaxel and G-CSF (filgrastim) combined with additional radiation therapy to the
tumor site will have on your cancer.

This research is being done because there is currently no effective treatment for this type
of cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 100 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

• All patients will receive the following treatments:
  
  Radiation Therapy: Radiation therapy will be given every other week for four
cycles. During each cycle you will receive radiation therapy
twice a day with at least four hours between the treatments, for
five days. Each week of treatment will be followed by a nine
day rest period from radiation therapy.

  Chemotherapy: Chemotherapy drugs are used to stop the growth of your tumor
and the spread of tumor cells. You will receive the drugs
cisplatin and paclitaxel on the days you receive radiation
therapy. The drugs will be injected into a vein (intravenously)
Immediately after your first radiation treatment of the day.
Paclitaxel will be injected over a one hour period followed by
cisplatin for half an hour. Premedications will be given within 30 minutes prior to the paclitaxel to prevent allergic reactions. In addition, you will be given extra fluids intravenously to help decrease some of the side effects of these drugs.

G-CSF: G-CSF is being used in this study to speed recovery of blood counts so treatment can be given on schedule. G-CSF will be injected under your skin once each day for eight days every two weeks for four cycles. G-CSF will start the day after each cycle of chemotherapy and radiation therapy is completed and will continue for eight days. G-CSF injections will stop two days before your radiation and chemotherapy begins again. *(6-20-01)*

If you take part in this study, you will have the following tests and procedures:

• Procedures that are part of regular cancer care and may be done even if you do not join the study.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Exam</td>
<td>Prior to study entry, weekly during treatment, then at follow-up visits</td>
</tr>
<tr>
<td>Tumor Measurements</td>
<td>Prior to study entry and at follow-up visits</td>
</tr>
<tr>
<td>Blood Counts</td>
<td>Prior to study entry, weekly during treatment, every four months for one year, then every six months</td>
</tr>
<tr>
<td>Chemistries (liver &amp; kidney tests)</td>
<td>Prior to study entry, every two weeks during treatment, every four months for one year, then every six months</td>
</tr>
<tr>
<td>Chest X-Ray</td>
<td>Prior to study entry, every four months for one year, then every six months</td>
</tr>
<tr>
<td>Head &amp; Neck CT or MRI</td>
<td>Prior to study entry, two months after end of treatment, then as medically indicated.</td>
</tr>
<tr>
<td>Bone Scan, Barium Swallow, etc.</td>
<td>As medically indicated</td>
</tr>
<tr>
<td>Liver ultrasound or CT</td>
<td>As medically indicated</td>
</tr>
</tbody>
</table>

• Follow-up visits with your physician will be scheduled every 3 months through year 2, every 6 months for 3 years, then annually. *(6-20-01)*

• Standard procedures being done because you are in this study:

Blood counts, chemistries and follow-up visits may be more frequent because you are enrolled in a research study.
HOW LONG WILL I BE IN THE STUDY?

Your radiation, chemotherapy and G-CSF treatments will last for a total of about seven weeks. Follow-up visits will continue for the rest of your life according to the above schedule.

The researcher may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding or participation.

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

WHAT ARE THE RISKS OF THE STUDY?

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

Risks Associated with Radiation Therapy

Very Likely
- Sores in mouth or throat
- Temporary skin redness or peeling
- Dryness of the mouth, difficulty in swallowing
- Reduction in blood counts
- Dental cavities
- Hoarseness

Less Likely, But Serious
- Severe irritation of the esophagus (swallowing tube) or treatment area that causes swallowing difficulty and may require a feeding tube. This may last up to a year.
- Hardening or thickening of the skin in the treatment area that causes swallowing difficulty and may require a feeding tube.
- Damage to the jawbone causing bone destruction and pain that might require surgery.

Risks Associated with Chemotherapy

Cisplatin

Very Likely
- Nausea and/or vomiting
- Weakness
- Hearing loss, ringing of the ears

Less Likely
- Allergic reactions (sweating, difficulty breathing, rapid heart beat)
- Facial swelling
Numbness of the fingers and toes  
Lower blood counts  
Loss of coordination  
Involuntary movement  
Loss of taste  
Restlessness  
Blurred vision, excessive tears  
Mouth sores, difficulty swallowing  

Less Likely, But Serious  
Kidney damage  
Liver damage  
Acute leukemia  
Increased risk of bleeding, bruising or infection that could be life-threatening and require hospitalization  

Paclitaxel  
Very Likely  
Low pulse  
Loss of hair  
Skin redness or rash  
Tingling, numbness, burning pain in hands and feet  
Lower blood counts  
Gastrointestinal discomforts  

Less Likely  
Nausea and/or vomiting  
Diarrhea  
Anemia  
Skin ulcers  
Aches and pains in muscles and joints  
Allergic reactions  
Headaches  
Skin or nail darkening  
Increased reaction to radiation  

Less Likely, But Serious  
Cardiovascular changes  
Seizures  

Very Rare  
Generalized skin rash which could lead to peeling or shedding  

Risks Associated with G-CSF  
Very Likely  
Chest Pain  
Fever  
Loss of hair  
Fluid retention  
Nausea and/or vomiting  
Diarrhea  
Spleen enlargement  
Bone pain  
sites  

Less Likely  
Headache  
Rash  
Anorexia  
Constipation  
Sore throat  
Transient cardiovascular arrhythmia, hypotension  
Temporary mild swelling at injection  

Reproductive Risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Both men and women should use effective contraception while on this study. Ask your doctor about counseling and more information about preventing pregnancy. [Attach a statement about possible sterility when appropriate.] [Attach additional information about contraception, etc.]
**Bleeding Risk:** There is a real, but relatively small risk of bleeding from the main artery in the neck, the carotid artery, in patients who have tumors that overlap this artery. Most of these bleeding events have occurred in patients who have active tumor in this region and may not necessarily be due to the treatment. This bleeding risk, while rare, almost always results in the death of the patient. *(12/13/02)*

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. You should know that to date there is no standard treatment for squamous cell malignancies that have recurred in the irradiated field. We hope the information learned from this study will benefit other patients with recurrent head and neck cancer in the future.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) 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.

Another option may be to get this treatment plan at this institution or another institution even if you do not take part in the study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

**WHAT ABOUT CONFIDENTIALITY?**

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

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

**WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.
In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

**U.S. Patients:** You will receive no payment for taking part in this study, however the drug G-CSF will be provided to you at no cost by the drug company.

**Canadian Patients:** You will receive no payment for taking part in this study, however the drug G-CSF will be provided to you at no cost by the drug company if other reimbursement is not available.

**WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in head and neck cancer from the RTOG Head and Neck Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study. *(12/13/02)*

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

*This section must be completed*

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>

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)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
</table>
WHERE CAN I GET MORE INFORMATION?

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


SIGNATURE

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

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

Patient Signature (or legal Representative) ________________________________ Date __________
## APPENDIX II

### KARNOFSKY PERFORMANCE SCALE

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

### ZUBROD PERFORMANCE SCALE

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

AJCC STAGING
HEAD & NECK, 5th Edition

STAGING-PRIMARY TUMOR (T)

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

ORAL CAVITY

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

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

PHARYNX

Nasopharynx

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

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

Oropharynx

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

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

**Hypopharynx**

Pyriform fossae
Postcrioid 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: postcrioid area, pre-epiglottic tissues.
T4 Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus.

**Glottis**

True vocal cords including anterior and posterior commissures

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

**Subglottis**

T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g.trachea, or soft tissues of the neck including thyroid, esophagus*)
REGIONAL LYMPH NODES (N) Excluding Nasopharynx

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

REGIONAL LYMPH NODES (N) Nasopharynx Only

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

DISTANT METASTASIS (M)

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

STAGE GROUPING Excluding Nasopharynx STAGE GROUPING Nasopharynx

Stage 0  Tis, N0, M0  Stage 0  Tis, N0, M0
Stage I  T1, N0, M0  Stage I  T1, N0, M0
Stage II T2, N0, M0  Stage IIA T2a, N0, M0
Stage III T3, N0, M0  Stage IIB T1-T2a, N1, M0
T1-3, N1, M0  T2b, N0-1, M0
Stage IVA T4, N0-1, M0  Stage III T1-T2b, N2, M0
Any T, N2, M0  T3, N0-2, M0
Stage IVB Any T, N3, M0  Stage IVA T4, N0-2, M0
Stage IVC Any T, Any N, M1  Stage IVB Any T, N3, M0
Stage IVC Any T, Any N, M1
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
APPENDIX VI (11-16-01)

Filgrastim (G-CSF) Drug Request Form

Amgen Study No:   Group Study No: RTOG 99-11: “Phase II Study of Paclitaxel and Cisplatin in Combination with Split Course Concomitant Hyperfractionated Re-Irradiation in Patients with Recurrent Squamous Cell Cancer of the Head and Neck”

Requested by:                                        Ship To:
Pharmacist: _ _______________________________ Name: ______________________________________
Institution: ___________________________________ Address*: __________________________________
RTOG Study Number: ______________________________ * Please do not use P.O. Box numbers
(must be included)
Principal Investigator: __________________________
Phone #: ______________________________ Fax: __________________________________

<table>
<thead>
<tr>
<th>Pt. ID</th>
<th>Pt Initials (Last, First)</th>
<th># of Vials*</th>
<th>RTOG Case#</th>
<th>Starter Supply (For this pt.)</th>
<th>Re-order (For this pt.)</th>
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* Reminder: See protocol section on drug formulation for instructions regarding amounts of drug to order.

G-CSF will be shipped (refrigerated) on Monday through Thursday for next day delivery.

Orders received by 11:30 a.m. PST Monday through Thursday will be shipped the same day for next day delivery.

Date of Drug Request ______________________________ Pharmacist Signature ______________________________

Return Completed, Signed, and Dated form to:

UintaVision, Inc./Axion, Inc.
232 Castro Street, Suite #2
San Francisco, CA 94114
General Phone (800) 370-2508
FAX (650) 745-3877
APPENDIX VII (11-16-01)

RETURNED MEDICATION PACKING SLIP

Institution Name: ____________________________________________________________

Address: ____________________________________________________________________

Principal Investigator: _______________________________________________________

Amgen Study No: ___________ Group Study No: RTOG 99-11

“Phase II Study of Paclitaxel and Cisplatin in Combination with Split Course Concomitant Hyperfractionated Re-Irradiation in Patients with Recurrent Squamous Cell Cancer of the Head and Neck”

Instructions:
Per FDA requirements, please retain a copy of this completed form for your files. Drug being returned for any reason should be sent, together with this original form, to UintaVision, Inc./Axion, Inc., 232 Castro Street, Suite #2, San Francisco, CA 94114. Only drug returns are to be sent to this address, no other correspondence. Questions may be directed to (800) 370-2508, Monday through Friday 6:30 a.m. – 1:00 p.m., PST. Voice Mail is available at all other times.

Study in progress? __________ Person Shipping Drug: ____________________________

Yes No

Drug being returned by: ________________________________

Fed Ex UPS US Mail

Study completed per protocol? ____________________________

Yes No

Date: ___________ No. of cartons: ______

Research Associate's/Pharmacist's Signature: ________________________________ Date: ___________

Reason drug returned? (Please check one) ________________________________

Return receipt requested: Yes No

Fax number: ________________________________

Drug Expired

Unused drug being returned

DESCRIPTION OF RETURN SHIPMENT

<table>
<thead>
<tr>
<th>Drug Name &amp; Vial Description</th>
<th>Lot Number</th>
<th>Number of Vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>__________________________</td>
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</table>

Comments: ___________________________________________________________________

TO BE COMPLETED BY AMGEN

Returned shipment received on __________________________ and checked by: ________________ (Name)
APPENDIX VIII

NEUPOGEN® (r-metHuG-CSF) Request Form
(Canadian Participants Only)

Study Name: Phase II Study of Paclitaxel and Cisplatin in Combination with Split Course Concomitant Hyperfractionated Re-irradiation in Patients with Recurrent Squamous Cell Cancer of the Head and Neck

Study Number: RTOG 99-11
RTOG Case #

Patient Initials or Name ___________________________ Patient ID # ________________

Date of Request __________________

Physician Name ___________________________ RTOG Institution # ________________

What is the daily dose of NEUPOGEN® (in μg) being administered? _______________

Number of days that NEUPOGEN® will be administered ______________________

Have all other reimbursement options (private insurance, provincial drug plan, other drug plans) been explored for this patient? Yes ____ No __

Has a completed Reimbursement Assessment Form for NEUPOGEN® been faxed to AMGEN Canada? Yes ___ No ___

On which cycle of chemotherapy has the patient started NEUPOGEN® ______________

Date NEUPOGEN® required ______________________

Drug Delivery Address ___________________________
and contact name ___________________________

Telephone: ___________________________
Fax #: ___________________________

Please Fax this completed form to:

Karen Arts  Phone: 1-800-665-4273 ext 280
Amgen Canada, Inc.  FAX: (905) 542-3206

________________________________________________________________________

For AMGEN Internal use only

Approved by ___________________________ Date ___________________________
APPENDIX VIII

Reimbursement Assessment Form for NEUPOGEN® (r-metHuG-CSF)
(Canadian Participants Only)

THIS FORM IS TO BE COMPLETED (and faxed) UPON REGISTRATION OF THE PATIENT TO RTOG 99-11

Study Name: Phase II Study of Paclitaxel and Cisplatin in Combination with Split Course Concomitant Hyperfractionated Re-irradiation in Patients with Recurrent Squamous Cell Cancer of the Head and Neck

Study Number: RTOG 99-11

Patient Initials _____________ Patient ID # ________________

Physician Name ________________________________________

Hospital Name ________________________________________ RTOG Institution # ________

Name of Person Completing this Form ___________________________

Telephone # _________________________ Fax # _________________

1. Is the patient covered by Third Party Insurance/Private Insurance (Coverage may be through the patient’s spouse’s insurance)? Yes___ No___

2. If yes to above:
   Name of Insurance Company: __________________________________________

3. Does the insurance plan have a copay? Yes___ No___
   What is the copay percentage? _________

4. Does the insurance plan have a deductible? Yes___ No___
   What is the deductible amount? ________

5. Is the patient covered by a provincial government drug plan Yes ___ No___
   If yes, name of plan ____________________________________________

6. Is the patient covered by any other drug plan not mentioned above Yes___ No___
   If yes, name of plan ____________________________________________

Please fax this completed form to:

Karen Arts Phone 1-800-665-4273 ext 280
Amgen Canada, Inc. FAX (905) 542-3206
RTOG 99-11 is a phase II study of paclitaxel and cisplatin in combination with split course concomitant hyperfractionated re-irradiation in patients with recurrent squamous cell cancer of the head and neck. Participating institutions have inquired as to the possibility of using IMRT treatment techniques for this protocol. The NCI has expressed patient safety concerns relative to the use of IMRT treatment techniques for this group of patients. This questionnaire is designed to address those concerns.

To be able to utilize IMRT treatment techniques in this protocol, institutions are requested to perform the following three actions:

1. Complete this questionnaire.
2. Send a dry run paper copy of the dosimetry, which is based upon the assumption that a patient has been placed on this protocol and treated using IMRT techniques, to:

   Michael Gillin, Ph.D. (5/13/03)
   Chair, RTOG Medical Physics Committee
   Professor, Radiation Physics
   The University of Texas M.D. Anderson Cancer Center
   1515 Holcombe Blvd – 94
   Houston, TX 77030-4009
   (713) 745-5777
   FAX (713) 794-5272

3. Plan and treat the RTOG/RPC IMRT head and neck phantom. This phantom is available from:

   Radiological Physics Center
   UT M.D. Anderson Cancer Center
   Box 547
   1515 Holcombe Blvd.
   Houston, TX 77030
   (713) 792-3226
   FAX (713) 794-1364

The radiation dose is 60 Gy in 40 fractions, 1.5 Gy/fraction twice daily. Paragraph 6.3.4 states “The treatment fields should encompass the recurrent tumor defined as the Gross Tumor Volume (GTV), considered all known disease defined by clinical, radiographic or any other information available. Adequate margins of at least 2 cm should be added whenever possible. Margins less than 2.0 cm are an acceptable deviation only in instances of spinal cord encroachment”. This specification clearly defines the PTV.

This protocol defines a dose to a point at or near the center of the target volume, namely 1.5 Gy per fraction. This protocol limits the total dose to the spinal cord from both the prior treatment and the current treatment to 50 Gy. There are no specifications for coverage of the PTV or for maximum dose to the PTV or to unspecified tissue. It is anticipated that IMRT treatment approaches would be prescribing the dose to approximately the 80% line, with 100% being the maximum dose. When using IMRT treatment techniques, the coverage of the GTV, which is the CTV, by the 60 Gy dose surface should approach 100%. When using IMRT treatment techniques, the coverage of the PTV by the 60 Gy dose surface should be greater than 90%. It is expected that the participating institution will be sensitive to the location and the volume of doses greater than the prescription dose and will use their judgment as to the consequences of these doses and volumes.

The normal tissue volume to be contoured must include the spinal cord. The spinal cord contours will be defined as being at least 5 mm larger in the radial dimension than the spinal cord (i.e., the cord diameter on any given slice will be 10 mm larger than the cord itself).
## IMRT Questionnaire for RTOG 99-11

### I. Institution Data

<table>
<thead>
<tr>
<th>Institution Name:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>IMRT Head and Neck Oncologist</td>
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</tr>
<tr>
<td>Email</td>
<td></td>
</tr>
<tr>
<td>IMRT Head and Neck Physicist</td>
<td></td>
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<tr>
<td>Email</td>
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</tbody>
</table>

### II. IMRT Treatment Planning System

<table>
<thead>
<tr>
<th>Vendor/Software Name</th>
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</thead>
<tbody>
<tr>
<td>Software Version</td>
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</table>

### III. IMRT Treatment Delivery System

<table>
<thead>
<tr>
<th>Accelerator Vendor and Model</th>
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</thead>
<tbody>
<tr>
<td>IMRT Treatment Technique</td>
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</tr>
<tr>
<td>Compensator</td>
<td>Yes</td>
</tr>
<tr>
<td>Dynamic MLC</td>
<td>Yes</td>
</tr>
<tr>
<td>Static MLC</td>
<td>Yes</td>
</tr>
<tr>
<td>Serial Tomotherapy</td>
<td>Yes</td>
</tr>
<tr>
<td>Other (Please specify)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

### IV. IMRT Patient Specific Planning Information

1. For head and neck patients being treated with IMRT techniques at your institution, how is the spinal cord defined and how is the spinal cord planning risk volume defined?

   | Spinal cord only (Critical Structure) | Yes | No |
   | Planning Risk Volume: |  |
   | Cord is defined in radial direction | 5 mm | 10 mm |

2. What is your institution’s maximum dose/volume specification for tissues or structures outside of the PTV for head and neck patients being treated with IMRT techniques? (For example, less than 1% of the unspecified tissue can receive greater than 110% of the prescription dose).

3. What is your institution’s maximum dose/volume specification for tissues or structures inside the PTV for head and neck patients being treated with IMRT techniques? (For example, less than 10% of the PTV can receive greater than 120% of the prescription dose).

4. What immobilization system is used at your institution for IMRT Head and Neck patients? What reproducibility (3D vector) do you achieve and how do you know this?
V. IMRT Patient Specific QA

Please describe the QA process at your institution that will be performed for patients entered onto this protocol. It is expected that, at a minimum, this will include the confirmation by measurement with an ion chamber of the dose delivered to a user-defined volume.

What agreement between measured and calculated dose is required at your institution before the patient can be treated?