

RADIATION THERAPY ONCOLOGY GROUP

RTOG 99-14

A PHASE II TRIAL OF CONCOMITANT BOOST RADIATION AND CONCURRENT CISPLATIN FOR ADVANCED HEAD AND NECK CARCINOMAS

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SCHEMA

R		R	72 Gy / 42 fxs / 6 weeks (AFX-CB*) plus cisplatin (100 mg/m ²) on
E		E	days 1 and 22 (week 1 and week 3, before initiation of twice a day
C	<u>Zubrod Status</u>	G	irradiation).
O	Zero (0), or	I	* <u>Accelerated Fractionation with Concomitant Boost:</u>
R	One (1)	S	
D		T	a. <u>Large Field:</u>
		E	32.4 Gy/18 fx/3 ½ weeks
		R	1.8 Gy/fx/day, 5 days/week
			b. <u>Concomitant Boost:</u>
			1.5 Gy/fx/day to boost field for 18.0 Gy/12 fx > 6 hours after large
			field treatment
			Large Field Treatment to receive 21.6 Gy/12 fx, 1.8/fx
			c. <u>Total Dose:</u>
			72.0 Gy/42 fx/6 weeks

Eligibility: (See Section 3.0 for details)

- Histologic proof of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx
- Stage III-IV disease (T3-4, N1-3, M0)
- Zubrod status 0-1
- AGC ≥ 2000, platelets ≥ 100,000, bilirubin ≤ 1.5, serum creatinine ≤ 1.5 mg %
- SGOT or SGPT ≤ 2 x upper normal, creatinine clearance ≥ 50 ml/min.
- No clinically significant heart disease
- No prior radiation treatment to the head and neck or any prior chemotherapy
- Patients with prior malignancy ≥3 years ago are eligible (*simultaneous primaries are ineligible*)
- Signed study-specific consent form prior to study entry

Required Sample Size: 56

(8/25/00)

Institution # _____

RTOG 99-14

Case # _____

ELIGIBILITY CHECKLIST (8/25/00)

(page 1 of 2)

- _____(Y) 1. Is there histologic confirmation of squamous cell cancer of the oral cavity, oropharynx, hypopharynx, or larynx?
- _____(Y) 2. Is the stage III or IV? (*N+*: any T; *N0*: T3-4; M0)
- _____(N) 3. Any evidence of distant metastasis?
- _____(N) 4. Any evidence of simultaneous cancer, i.e., more than one cancer?
- _____(Y) 5. Is the patient's life expectancy at least 6 months?
- _____(N) 6. Any evidence of clinically significant heart disease?
- _____(N) 7. Any history of prior chemotherapy?
- _____(N) 8. Any prior radiation therapy to the head or neck area?
- _____(N) 9. Except for diagnostic biopsy, has there been any surgery of the primary tumor or nodes?
- _____(Y/N) 10. Other than nonmelanoma skin cancer, is there any history of a prior malignancy?
_____(Y) If yes, has the patient been continually cancer free for the past 3 years?
- _____(≥ 2) 11. What is the on-study total granulocyte count (*per mm³*)
- _____(≥ 100) 12. What is the study platelet count (*per mm³*).
- _____(≤ 1.5) 13. What is the on-study bilirubin (*mg%*)?
- _____(Y) 14. Is the SGOT or SGPT ≤ 2 times upper normal?
- _____(≤ 1.5) 15. What is the study serum creatinine (*mg%*)?
- _____(≥ 50) 16. What is the on-study creatinine clearance (*ml/min*) as determined by 24 hour collection or nomogram calculation (*specify which was used*)?
- _____(Y) 17. Is the serum calcium within normal range (*without intervention*)?
- _____(N/NA) 18. Is the patient pregnant?

(cont'd on next page)

Institution # _____

RTOG 99-14

Case # _____

ELIGIBILITY CHECKLIST (8/25/00)

(page 2 of 2)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____ (Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____ (Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Medical Oncologist's Name
- _____ 18. Zubrod Status (*0-1*)
- _____ 19. Treatment Assignment

Completed by _____

Date _____

1.0 BACKGROUND

1.1 Radiotherapy

Surgical resection of advanced resectable stage III and IV head and neck squamous cell carcinomas (*HNSCC*), often followed by adjuvant radiotherapy, is the current standard of care in most cases¹⁻⁴ though this is often associated with cosmetic and functional impairment affecting quality of life. Results of conventionally fractionated radiotherapy as a single modality for patients with resectable and unresectable advanced HNSCC are rather poor in terms of local control and survival. Several approaches have been used to improve non-surgical results of treatment of advanced head and neck cancers. One approach is to use altered fractionated radiation as the sole modality. Multiple studies have tested hyperfractionation and various accelerated fractionation regimens with positive results.⁵

1.2 RTOG Phase III Trial on Altered Fractionation

RTOG 90-03 is a large randomized trial comparing standard fractionation (*SFX*) against hyperfractionation (*HFX*), accelerated fractionation with split-course (*AFX-S*), and accelerated fractionation by concomitant boost (*AFX-CB*) in the management of patients with advanced HNSCC. Between September 1991 and August 1997, 1113 patients were enrolled. Analysis undertaken in September of 1999 revealed that *AFX-CB* and *HFX* yielded a significantly higher local-regional control rate (*LRC*) than *SFX* ($p=0.05$) but not *AFX-S* ($p=0.67$). *AFX-CB* was associated with a higher transient grade 3 late toxicity. However, there was no difference in the incidence of persistent grade 3 or grade 4 late toxicity among the arms at one year or longer follow-up. The results of this trial reveal that tumor clonogen proliferation during a course of radiotherapy is a major cause of radiation failure. The Head and Neck Committee decided to develop a novel combined therapy regimen based on the *AFX-CB* regimen because of its logistic convenience.

1.3 Combination of Radiotherapy and Chemotherapy

A second strategy pursued to improve results of non-surgical treatment of advanced HNSCC has been to add chemotherapy to radiation. With this approach, chemotherapy can be delivered sequentially, i.e., before (*neoadjuvant*) or after (*adjuvant*) radiation or concurrently with radiation. *Sequential radiation-chemotherapy* has been studied extensively in prospective pilot and large randomized trials.⁶⁻¹⁰ So far, a survival advantage over standard surgery has not been demonstrated, but organ preservation has been achieved in many patients. Response rates to chemotherapy are high, and a decrease in distant metastases has been demonstrated in some trials. Despite a high response rate in trials comparing neoadjuvant chemotherapy and radiation to radiation alone, improved *LRC* has not been shown.

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

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

Several groups have evaluated cisplatin with or without 5-FU in combination with radiation, as both agents have been found to have radiation sensitizing effects *in vitro*. Several trials have given cisplatin and 5-FU throughout radiotherapy. Taylor et al.²⁶ gave cisplatin 60mg/m² and 5-FU 800mg/m² in 14-day cycles with conventional radiotherapy. They demonstrated an improved freedom from recurrence in patients treated with concurrent radiation compared to sequential chemoradiation. There was however an increase in mucositis requiring supportive care in the concurrent group. Other trials²⁷ have given cisplatin at doses as high as 100 mg/m² every three weeks with tolerable toxicity. Gandia et al.²⁸ treated head and neck cancer patients with cisplatin 80mg/m² every 3 weeks for 3 cycles and 5-FU 300mg/m²/day by continuous infusion for 7 weeks during radiotherapy to a total dose of 70 Gy given over 7 weeks with acceptable toxicity.

Investigators at the University of Chicago have investigated the concurrent administration of hydroxyurea and 5-FU with radiation therapy. This is based on established clinical activity of both agents and preclinical evidence of a

synergistic interaction of the two drugs (*the ribonucleotide reductase inhibitor hydroxyurea depletes cells of the deoxyuridine monophosphate (dUMP) and thereby facilitates binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase*). Both agents have been shown to be radiation enhancers in preclinical and clinical settings.

More recently, paclitaxel has generated interest as it has shown in vitro radiosensitization, and has clinically been investigated with radiation both as a single agent and in combination with cisplatin. Paclitaxel (*Taxol*), a novel diterpene compound, isolated from the bark of the pacific yew *Taxus brevifolia*, binds to tubulin and induces the formation of stable microtubules. This results in blocking cells in the G2 or M phase of the cell cycle.²⁹ In phase II trials paclitaxel has been shown to be active in ovary, lung, breast and head and neck cancer. At Johns Hopkins University, and elsewhere, paclitaxel has been studied extensively. Myelosuppression is the primary toxicity, specifically neutropenia. Neurotoxicity is dose limiting when single agent doses exceed 250 mg/m². Mucositis is an uncommon toxicity of paclitaxel in doses less than 300 mg/m².³⁰

1.4 RTOG Trials on Combined Radiation-Chemotherapy

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

Two ongoing RTOG trials address some relevant questions mentioned above. RTOG 91-11, a phase III trial in patients with T3 and selected T4 laryngeal carcinoma, is assessing the relative efficacy of cisplatin given at days 1, 22, 43 of standard radiotherapy against neoadjuvant chemotherapy (*the VA cisplatin-fluorouracil regimen*) plus standard radiotherapy⁹ and radiation alone in preserving larynx. RTOG 97-03, a randomized phase II trial in patients with stage III & IV disease, is evaluating different approaches of combining radiation and chemotherapy using both different agents and different timing of radiation-drug administration. The three regimens being tested are: 1) daily cisplatin-fluorouracil given during the last two weeks of the 7-week standard radiotherapy; 2) combination of fluorouracil-hydroxyurea and once-a-day radiotherapy administered every other week for a total of 13 weeks; and 3) weekly cisplatin and paclitaxel during the 7-week standard radiotherapy. These two trials are projected to complete patient accrual in 6-12 months but the final tumor control and toxicity data will not be available for at least 2 additional years.

Objective of the Proposed Study: This trial builds on the results of RTOG 90-03 showing that accelerated fractionation by concomitant boost (*AFX-CB*) yielded a significantly higher LRC than standard fractionation without increasing the persistent grade 3-4 toxicity. The primary objective of the present study is to test the feasibility of combining AFX-CB with cytotoxic or biologic agents selected preferentially based on mechanisms of action/interaction.

1.5 Rationale and Preliminary Data of Proposed Combined Regimen

- 1.5.1** This regimen consists of combination of AFX-CB with cisplatin. Cisplatin has been shown to enhance radiation response though the exact mechanisms are not well understood. RTOG has studied and is testing combinations of standard radiotherapy with cisplatin in advanced HNSCC (*e.g., RTOG 81-17, RTOG 91-11*). It is thus desirable to assess the feasibility of combining AFX-CB with cisplatin. This arm is considered the closest to the potential new standard treatment. The 6-week overall duration of AFX-CB provides the opportunity for administration of two doses of cisplatin concurrently with radiotherapy. To minimize potential interference with normal tissue cellular repair of sublethal radiation injury, cisplatin will be given on days 1 and 22, i.e., before initiation of twice daily irradiation.

2.0 OBJECTIVES

- 2.1** To determine the rate of local-regional recurrence at one year.
2.2 To determine the feasibility of treatment delivery, patient tolerance, acute and late toxicities.
2.3 To determine the overall survival, disease-free survival, and distant relapse rates of patients with relatively advanced HNSCC treated with this regimen.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (8/25/00)

- 3.1.1** Patients with histological proof (*from the primary lesion and/or lymph nodes*) of squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
3.1.2 Patients should have Stage III or IV disease (*M0*) (*Appendix III*).

- 3.1.3 Patients must have a life expectancy of at least 6 months and a Zubrod performance status of 0-1 (*Appendix II*).
- 3.1.4 No distant metastatic disease.
- 3.1.5 Patients should have adequate bone marrow function defined as an absolute peripheral granulocyte count (AGC) of ≥ 2000 cells/mm³, platelet count of $\geq 100,000$ cells/mm³, adequate hepatic function with bilirubin ≤ 1.5 mg%, serum creatinine ≤ 1.5 mg %, creatinine clearance ≥ 50 ml/min, SGOT or SGPT $\leq 2x$ the upper limit of normal, and normal serum calcium (*without intervention*).
- 3.1.6 Creatinine clearance ≥ 50 ml/min determined by 24-h collection or nomogram:

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

$$\text{CrCl female} = 0.85 \times (\text{CrCl male})$$
- 3.1.7 No symptomatic coronary artery disease (*angina*) or myocardial infarction within the last 6 months.
- 3.1.8 Patients with a history of non-melanoma skin cancer, or other previous malignancies from which the patient has remained continually disease free for ≥ 3 years are eligible.
- 3.1.9 Patients must sign a study-specific informed consent form prior to study entry.

3.2 Ineligibility Criteria

- 3.2.1 Histology other than squamous cell carcinoma.
- 3.2.2 Evidence of metastases (*below the clavicle or distant*) by clinical or radiographic examinations.
- 3.2.3 Prior chemotherapy for any reason or prior radiotherapy to the head and neck region.
- 3.2.4 Initial surgical treatment excluding diagnostic biopsy of the primary site or neck disease.
- 3.2.5 Patients with simultaneous primaries.
- 3.2.6 Pregnant women because of the embryotoxic effects of chemotherapy.

4.0 PRETREATMENT EVALUATION

- 4.1 Complete history and physical examination.
- 4.2 Biopsy of primary tumor and/or fine needle aspirate/biopsy of metastatic lymph node.
- 4.3 Location, type, and size of all measurable lesions within 2 weeks prior to randomization must be recorded and diagrammed prior to treatment.
- 4.4 **Laboratory studies** (*within 30 days prior to study entry*)
 - 4.4.1 CBC with differential and platelet count
 - 4.4.2 SMA-12, (*sodium, potassium, glucose, calcium, magnesium, BUN, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, SGPT or SGOT, and LDH*).
 - 4.4.3 Creatinine clearance.
 - 4.4.4 Optional: Prothrombin time (*PT*), partial thromboplastin time (*PTT*).
- 4.5 **Radiographic Studies**
 - 4.5.1 Appropriate radiographic study of tumor (*CT or MRI*).
 - 4.5.2 Chest X-ray or thoracic CT scan (*within 8 weeks of study enrollment*).
 - 4.5.3 Abdominal CT if abnormal LFT's are noted.
- 4.6 Optional: Panendoscopy
- 4.7 Dental evaluation with management according to the guidelines of Daly³¹ prior to the start of radiation (*Appendix VI*).
- 4.8 Feeding tubes (*either Dobhoff, percutaneous endoscopic gastrostomy [PEG] or percutaneous fluoroscopic gastrostomy [PFG]*) are strongly recommended before treatment begins.

5.0 REGISTRATION PROCEDURES

- 5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY

6.1 Dose Fractionation

- 6.1.1 Radiotherapy will be given according to the concomitant boost regimen. The initial target volume encompassing primary tumor and upper neck nodes will receive 1.8 Gy per fraction, five fractions a week to 54 Gy in 30 fractions over 6 weeks to the primary tumor and upper neck nodes. At 32.4 Gy/18 Fx (*i.e., latter part of week 4*), the boost target volume covering gross tumor and clinically/radiologically involved nodes will receive boost irradiation of 1.5

Gy/Fx as second daily fraction (*at least 6 h interval*) for a total of 12 treatment days. The use of IMRT is not allowed.

6.1.2 The primary treatment fields must be reduced off the spinal cord at 45 Gy.

6.1.3 Clinically/radiologically involved nodes should receive a minimum dose of 72 Gy, 42 fractions in 6 weeks. Clinically/radiologically negative posterior neck should receive a minimum dose of 50.4 Gy at 3 cm. To supplement the dose to clinically positive/negative nodes, the posterior neck may be treated with electron beams of appropriate energies. The anterior lower neck field will be treated with 1.8 Gy per fraction at 3 cm depth to a total dose of 50.4 Gy in 28 fractions in 5.6 weeks. All treatment times must be documented on the treatment record.

6.2 Physical Factors

6.2.1 Megavoltage equipment, either linear accelerators or ⁶⁰Cobalt units will be used to provide appropriate photon energies (*1-18 MV*) and a wide range of electron energies (*6-20 Mev*).

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

6.3 Localization Requirements

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

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

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

6.4 Target Volume

6.4.1 The primary tumor and known or suspected lymph node disease will be treated with either lateral-opposed fields or several beam-directed fields with a margin. All fields will start with a 2-3 cm margin around gross primary and nodal disease. A reduction off the spinal cord to limit its dose to ≤ 45 Gy is mandatory. These reduced fields will have a 1-1.5 cm margin around gross disease. A single anterior field will be used to treat the neck and supraclavicular fossa below the fields encompassing the primary tumors. This field should match the lateral fields on the skin, and should have an appropriate method to avoid overlap on the spinal cord at the junction of the fields. The inferior border of this field will be 1 cm below the clavicles.

6.5 Dose Calculation

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

The specification of the target dose is in terms of a dose to a point at or near the center of target volume. The following portal arrangements are specified for photon beams:

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

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

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

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

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

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

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

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

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

6.6 Dose Constraint, Anticipated Side Effects and Toxicities

6.6.1 Suggested maximum dose to the spinal cord is 45 Gy/25 fx/5 weeks.

6.6.2 Reversible mucositis is expected and its timing with dose and severity should be noted and graded.

6.6.3 Also expected will be epilation of treated areas and various degrees of skin reaction in the treated area.

6.6.4 Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of either of these should be noted, as well as whether a supplemental feeding tube was used.

6.6.5 Late effects include permanent xerostomia in almost all patients and occasionally persistent dysphagia. Mandibular osteoradionecrosis will occur in $\leq 5\%$ of the patients, but may be reduced by thorough dental evaluation and treatment before irradiation, which is required. Extraction of bad teeth should be carried out with conservation of

restorable teeth where possible before radiotherapy. At least 10 days should be allowed for healing of gingivae post-extraction.

- 6.6.6 The use of amifostine and pilocarpine (*Salagen®*) are not encouraged; however, if used, record all details on the data forms.
- 6.6.7 Radiation-induced myelopathy is not anticipated providing cervical spinal cord dose remains ≤ 45 Gy in 25 fractions in 5 weeks. However, special attention should be directed in follow-up exams to any numbness, paresthesia, or L'hermitte's signs, particularly in the first 6-12 months of follow-up.
- 6.6.8 RTOG Headquarters and the study chairman must be notified by telephone of all fatal and life threatening toxicities (*those \geq grade 4*).
- 6.6.9 Toxicities, and all interventions for toxicity, must be described on the data forms.

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 Chemotherapy Pharmaceutical Data

7.1.1 Cisplatin (Cis-Diaminedichloroplatinum, DDP)

- 7.1.1.1 Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5.
- 7.1.1.2 Storage and Preparation: The dry, unopened vials should be stored at refrigeration temperature ($+4^{\circ}\text{C}$ to $+8^{\circ}\text{C}$). Reconstitution results in a solution stable for not more than one hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.
- 7.1.1.3 Administration: Intravenous.
- 7.1.1.4 Mechanism of Action: The mechanism of action of DDP has not been clearly elucidated. However, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.
- 7.1.1.5 Toxicology: The major effects in human have been renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range (*4000 to 8000 Hz*), nausea and vomiting, hyperuricemia, mild to moderate anemia, peripheral neuropathy, and electrolyte abnormalities.
- 7.1.1.6 Supplier: Commercially available.

7.2 Cisplatin Dose Schedule (8/25/00)

Mucosal and hematologic toxicity will be monitored closely by the Study Chair and RTOG Headquarters staff. Appropriate modifications will be made as outlined in Section 13.3.

- 7.2.1 Patients will receive cisplatin (100 mg/m^2) administered intravenously on days 1 and 22.
- 7.2.1.1 Suggested premedication: granisetron, 0.7-1.0 mg i.v. or ondansetron 32 mg i.v. will be given 30 minutes prior to cisplatin chemotherapy. A more aggressive prophylactic antiemetic regimen and any "as-needed" antiemetics may be given at the discretion of the treatment physician. Any pre-existing dehydration must be corrected prior to cisplatin administration.
- 7.2.1.2 Patients should receive vigorous hydration and diuresis. A suggested regimen is pre-hydration with a 1 l of D5NS over 2-4 hours. Mannitol 12.5 g i.v. bolus immediately prior to cisplatin. Cisplatin 100 mg/m^2 in 500 ml NS over 1-2 hours with post-hydration as clinically indicated.
- 7.2.2 Dose Modifications for day 22 Cisplatin
- 7.2.2.1 Neutropenia may occur. If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1000 , hold treatment until $\text{ANC} > 1000$ then treat at 100% dose.
- 7.2.2.2 Thrombocytopenia may occur. If on the day of scheduled treatment with cisplatin the platelet count is $< 75,000$ hold treatment until platelets are $\geq 75,000$ then treat at 100% dose.
- 7.2.2.3 Neurotoxicity: If any signs of paralysis, moderate myopathy, moderate weakness, seizure or peripheral neuropathy occur, discontinue cisplatin.
- 7.2.2.4 Renal Toxicity: Cisplatin should be administered on the scheduled day of treatment using the following guidelines.

<u>Creatinine Clearance</u>	<u>Cisplatin Dose</u>
$> 50\text{ ml/min.}$	100 mg/m^2
$40\text{-}50\text{ ml/min.}$	75 mg/m^2
$< 40\text{ ml/min.}$	Discontinue and notify Dr. Forastiere

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

7.2.3 If RT is held as day 22 because of mucositis, hold cisplatin until RT is resumed.

7.3 Supportive Care

7.3.1 Placement of a gastrostomy tube (*PEG or PFG*) before treatment begins is strongly recommended to optimize nutrition and hydration during combined therapy.

7.3.2 Aggressive oral and skin care, and analgesics are recommended.

7.3.3 The use of amifostine and pilocarpine (*Salagen®*) are not encouraged; however, if used, record all details on the data forms.

7.4 Toxicity Reporting

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

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

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

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

7.4.1.4 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.

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

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

7.4.3 Special Reporting for this Study (fax 215/928-0153)

7.4.3.1 **All grade ≥ 3 nonhematologic toxicities (except grade 3 radiation mucositis or dermatitis) must be reported to RTOG within 24 hours and followed by a written report.**

7.4.3.2 **All grade ≥ 4 hematologic toxicities and grade ≥ 4 mucositis must be reported to RTOG within 24 hours and followed by a written report.**

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

7.4.4 CDUS Reporting

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

8.0 SURGERY (CALL DR. WEBER WITH QUESTIONS)

8.1 Surgical removal (*salvage*) of the primary tumor: Directed biopsies at the site of the index lesions should not be performed in the absence of suspicion for relapse. Surgical removal (*salvage resection*) of the primary tumor should be performed if biopsy-proven cancer remains more than three months after completion of therapy. The nature of the surgical resection should be dictated by the extent of tumor at the initial evaluation. The operation should be conducted using accepted criteria for primary surgical treatment of the cancer.

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

8.3 Neck dissection: A planned neck dissection for patients with multiple neck nodes or with lymph nodes exceeding 3 cm in diameter (*N2a, N2b, N3*) is not required. A neck dissection is allowed if there has been complete clinical and/or radiographic response of *N2a, N2b, or N3* nodes. A neck dissection is required if a palpable or worrisome radiographic abnormality persists in the neck six weeks after completion of therapy.³² Surgery should be performed within 2 weeks once the decision for neck dissection is made.

- 8.4** Cervical lymphadenectomy should encompass the original levels of lymph node involvement. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle will be at the discretion of the surgeon.
- 8.5** The operative report must accurately and completely describe the precise location and the extent of the primary lesion and cervical lymph node metastases. Assessment of the completeness of the resection and results of intra-operative frozen section should be included. The nature of the closure should be specified (*e.g., allowed to granulate, primary closure, skin graft, local flap, regional pedicle flap, free tissue transfer*). **(8/25/00)**

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

10.1 Tumor Specimens (8/25/00)

- 10.1.1** Paraffin-embedded (*50-100 μ m thick*) blocks of pre-treatment tumor biopsy specimens will be collected for future correlative biomarker studies (*e.g., proliferation markers, EGFR overexpression, etc.*) to be coordinated through the RTOG Translational Research Program (*TRP*). Ten to 15 unstained slides may be sent instead of blocks.
- 10.1.2** Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.
- 10.1.3** Pathology report documenting that submitted block or slides contain tumor.
- 10.1.4** A Pathology Submission Form must be included and must clearly state that it is being submitted for the RTOG Tissue Bank.
- 10.1.5** RTOG will reimburse pathologists from submitting institutions \$100. per case if proper materials are submitted (*reimbursement is handled through an invoice submitted to RTOG Administration, ATT: Path Reimbursement*).
- 10.1.6** Patient consent form should give the Pathology Department authority and responsibility to comply with this request (*pathology blocks belong to the patient from whom tissue has been removed*).
- 10.1.7** Materials will be sent to:

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

10.2 Blood Samples (8/25/00)

- 10.2.1** Blood samples will be collected prior to protocol treatment for translational research to identify predictive biomarkers (*e.g., serum cytokine level, genetic pattern.*) for iatrogenic toxicity coordinated through the RTOG TRP.
- 10.2.2** Peripheral blood will be collected by venipuncture into two 12-ml draw Vacutainer tubes containing ACD Solution A ("*yellow top*" tubes). A single tube will suffice if two cannot be collected. The blood should be stored at refrigerator temperature and shipped on wet ice the same day. Alternatively, the blood can be shipped and stored frozen at -20°C and shipped on dry ice. This second method allows for the collection of several samples over time and shipped together thus lowering shipping costs. Specimens should be labeled with study number, case number and institution name only. Questions regarding blood collection or shipment should be directed to Drs. Weil and Story Ship by express overnight service and avoid a weekend or holiday arrival date. Blood samples will be sent to:

**Drs. Michael Weil and Michael Story
Department of Radiation Oncology
M.D. Anderson Cancer Center
1515 Holcombe Blvd, Room Y3.5823
Houston, TX 77030
(713) 792-3424**

10.2.3 Blood collection is encouraged but is not mandatory.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (8/25/00)

Assessment	Pre Treatment	Weekly During XRT	@ 4 wks	@ 3 mos	@ 6 mos	@ 12 mos	@ F/U
History/Physical	X	X	X	X	X	X	X
Performance Status/Weight	X	X	X	X	X	X	X
CBC/platelet/differential counts	X	X ^a					
Serum Creatinine, BUN	X	X ^a					
Creatinine Clearance	X		X ^e				
SMA-12 (<i>per 4.4.2</i>); PT/PTT (<i>optional</i>)	X		X ^d	X ^d	X ^d	X ^d	
CXR or CT	X					X	
Pregnancy Test	X ^c						
Toxicity Evaluation		X	X	X	X	X	X
Tumor Measurements	X	X	X	X	X	X	X ^b
Endoscopy & Biopsy	X			X ^b			
Dental Evaluation	X						
Blood Samples	X ^f						

- CBC/plt/diff weekly; electrolytes, Mg⁺⁺, creatinine every other week
- Only if clinically indicated
- As applicable
- See Section 12.1.
- Prior to second dose of cisplatin
- See Section 10.2. Blood samples must be collected prior to protocol treatment, as applicable.

11.2 Acute Reactions

Local reaction of skin and mucous membranes should be scored at least weekly during radiotherapy and post therapy until clearance.

11.3 Tumor Clearance

Response of tumor should be documented weekly during therapy and at each follow-up. Documentation of tumor should include caliper or ruler measurements, measuring longest measurement and at right angles to it, by inspection and palpation.

11.3.1 Response Criteria for Measurable Lesions

- Complete Response (CR)** - Complete disappearance of measurable and palpable disease.
- Partial Response (PR)** - Tumor shrinkage greater than 50% of the product of the perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (*excluding regional nodes*) or without appearance of new areas of malignant disease within the treated volume.
- Minor Response (MR)** - Tumor shrinkage greater than 25% but less than 50% of the product of the perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (*excluding regional nodes*) or without appearance of new areas of malignant disease within the treated volume.
- No change (NC)** - Up to 25% growth or 25% shrinkage of the product of perpendicular diameters of the two largest dimensions without increase in size of any other area of known malignant disease (*excluding regional nodes*) or without appearance of new areas of malignant disease within the treated volume.
- Progression (P)** - Growth of tumor greater than 25% of the product of the perpendicular diameters of the two largest dimensions.

11.3.2 Response Criteria for Evaluable, Non-Measurable Lesions

- Complete Response (CR)** - Complete disappearance of known disease
- Partial Response (PR)** - A definite decrease in tumor size. This should be confirmed by at least two investigators evaluating independently, or photographs or x-rays should be submitted for review.

- Minor Response (MR) - Not applicable
- No Change (NC) - Insufficient regression of lesion to meet criteria above and no new areas of malignant disease.
- Progression (P) - An estimated increase in the size of the tumor of greater than 25% or appearance of new areas of malignant disease.

11.4 Survival

Record survival from start of treatment

11.5 Evaluation After Treatment

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

11.6 Late Effects

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

11.7 Criteria for Discontinuation of Treatment:

11.7.1 Patient's refusal to continue study participation.

11.7.2 Occurrence of unacceptable toxicity necessitating major modification of treatment. In this event, follow-up and data submission will continue according to protocol.

12.0 DATA COLLECTION (8/25/00)

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Pathology Blocks (P2)	
Tumor and Nodal Diagrams (I6, I7)	
Treatment Form (TF)	
<i>(includes pre-registration labs and initial chemotherapy treatment)</i>	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
<u>Final Dosimetry Information:</u>	Within 1 week of RT end
Radiotherapy Form (T1)	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Boost Films (<i>simulation and portal</i>) (T8)	
Treatment Form (TF)	At completion or discontinuation of
systemic therapy	
Initial Followup Form (FS)	At 4 weeks post RT
Follow-up Form (F1)	q 3 months through year 2, q 6 months in year 3.
Long Term Followup Form (FF)	q 6 months x 2 years, then annually unless any of the following events occur: Change in tumor status, a new toxicity, an increase in severity of an existing toxicity, new cancer therapy or agent,

or at death. If any one or more of these events occur, the longer F1 Form must be submitted.

Autopsy Report (D3)

As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

- 13.1.1 To estimate the one-year local-regional control rate
- 13.1.2 To determine the frequency of major (\geq grade 4) mucositis or leukopenia
- 13.1.3 To determine the frequency of acute and late toxicities
- 13.1.4 To estimate the overall survival, disease free survival, and distant relapse rates.

13.2 Sample Size

The one-year local-regional control rate for the accelerated fractionation arm with concomitant boost arm of RTOG 90-03 was approximately 52%. We project a relative improvement of 33%, for a one-year local-regional control rate of 70%. With 50 evaluable patients, we have a one-sided 95% confidence interval around the hypothesized rate of 70% with a lower bound of 59%. This lower bound still corresponds to a relative improvement of greater than 13%. The treatment will be accepted for further study if the lower bound is \geq 59%. In other words, we have a 5% chance of accepting the treatment for further study if the one-year local-regional control rate is less than 59%. If an additional 10% of the sample is added to guard against ineligible or inevaluable (*no data*) cases, **then the target total accrual for this study will be 56 patients.**

13.3 Drug Modifications For Unacceptable Toxicity

The drug schedule has been tested in Phase I trials with standard radiation, but has not been formally tested with the proposed radiation schedule. So the treatment will be monitored for excessive toxicity using the method of Fleming.³³ The toxicities that will be monitored are grade 4 mucositis and grade 4 leukopenia. These side effects when encountered are anticipated to occur during or within 2 weeks after completion of treatment. The frequency of grade 4 mucositis/leukopenia on the accelerated fractionation with concomitant boost arm of RTOG 90-03 was about 6%. Modifications to the drug dose will be made if the expected grade 4 mucositis/leukopenia rate is greater than 15%. Therefore, if any of the following boundaries of grade 4 mucositis/leukopenia is exceeded, the second dose of cisplatin will be deleted.

Number of Patients with Grade 4 Mucositis or Leukopenia	Total Number Evaluable
4	5
4	10
5	20
5	30
6	50

If the true toxicity rate is 15%, the probability of exceeding the boundary is greater than 75%. If the true toxicity rate is 20%, the probability of exceeding the boundary is greater than 96%. If there is any fatal treatment morbidity, it will be immediately reviewed by the study chair, followed by a conference call with all study chairs to determine if a dose modification is warranted. If there are two such fatal treatment morbidities, accrual will be immediately suspended pending review by the study chairs.

13.4 Patient Accrual

Between July 1997 and June 1999, 241 patients were entered into the RTOG 97-03. Based upon this, the accrual rate to this study is projected at ten cases per month. Allowing time for IRB approvals and other logistical issues to be resolved at the institutional level, the accrual is projected to be completed in 7 months. If the average monthly rate is less than 3.0 cases, the study will be re-evaluated with respect to feasibility.

13.5 Analysis Plan

13.5.1 Interim Reports

Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about accrual rate with projected completion date, pretreatment characteristics of patients accrued, quality of submitted data with respect to timeliness, completeness, and accuracy, compliance rate of treatment delivery with respect to the protocol prescription, the frequencies and severity of iatrogenic toxicity.

13.5.2 Analysis for Reporting the Initial Treatment Results

- 13.5.2.1 This major analysis will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are: patients excluded from the analyses with their reasons for exclusion; institutional accrual; distribution of the important baseline prognostic variables, patient accrual rate with projected completion date, observed results with respect to the endpoints described in Section 13.1. Further subgroup analysis will not be undertaken because of the relatively small sample size.

13.5.2.2

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 the two possible interactions (*treatment by race and treatment by gender*). The study was designed to evaluate the tolerance of the treatment regimen under the assumption of the same tolerance rate 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.

In RTOG 97-03, 79% (191/241) of the patients were male and 21% were female. For planning purposes, we assume 80% of patients entered into this protocol will be male and 20% female. Then for males we have a 93% one-sided confidence interval with a lower bound of 59% around the hypothesized 70% local-regional control rate and a 77% confidence interval for females. Also, for males we have a 95% confidence interval with a lower bound of 58% around the hypothesized 70%, and a 95% confidence interval with a lower bound of 46% for females.

Seventy-five percent of patients on RTOG 97-03 were white, and 25% were non-white. Thus we assume 75% of patients entered into this protocol will be white and 25% will be non-white. Then for whites we have a 92% one-sided confidence interval with a lower bound of 59% around the hypothesized 70% local-regional control rate, and an 80% confidence interval for non-whites. Also, for whites we have a 95% confidence interval with a lower bound of 51% around the hypothesized 70%, and a 95% confidence interval with a lower bound of 49% for non-whites. The following table gives the expected number of patients in each race and gender group.

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Female	0	0	2	1	0	8	0	11
Male	1	1	7	2	0	33	1	45
Total	1	1	9	3	0	41	1	56

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APPENDIX I

RTOG 99-14

CONSENT FOR RESEARCH STUDY (8/25/00)

STUDY TITLE

A PHASE II TRIAL OF CONCOMITANT BOOST RADIATION AND CONCURRENT CISPLATIN FOR ADVANCED HEAD AND NECK CARCINOMAS

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

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to find out what effects (both good and bad) this combination of radiation therapy and chemotherapy has on advanced cancer of the head and neck region.

This research is being done because while surgery is the current standard of care for people with advanced cancer of the head and/or neck, it is also often associated with cosmetic and functional impairment affecting quality of life. We want to find a treatment that is as effective as surgery but provides a better quality of life.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 56 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

All patients will receive:

Radiation Therapy: Once a day, five days a week, for 3.5 weeks, then
Twice a day, five days a week, for 2.5 weeks

Chemotherapy: Cisplatin administered intravenously once during week 1 and once during week 3

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.

- Physical Exam
- Blood Counts
- Chest X-ray or CT scan
- SGOT/Bilirubin (liver function tests)
- Endoscopy & Biopsy

Tumor Measurements

- Standard procedures being done because you are in this study.
 - Dental Evaluation
 - Toxicity Evaluation
 - Insertion of feeding tube if you are unable to eat enough during treatment to maintain your weight/strength
 - Biopsy material will be sent to a central repository for future study and analysis

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

HOW LONG WILL I BE IN THE STUDY?

You will receive treatment five days a week for six weeks. After you finish your treatment you will be seen by your doctor once every three months for two years, then once every six months for three years and after that once a year for the rest of your life.

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

If you do not complete the prescribed treatment you will still have regular checkups with your doctor for the rest of your life unless you choose to remove yourself from the study. You will have these checkups once every three months for two years, then once every six months for three years and then once a year after that.

The researcher may decide to take you off this study if your disease gets worse despite the treatment, the side effects of the treatment are too dangerous for you, or new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but accrual to the study may be stopped early due to lack of funding or participation.

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 therapy 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

- Sore throat
- Temporary hair loss
- Tanning or redness of skin in treatment area
- Loss of teeth if strict dental care is not followed

Less Likely, But Serious

- Permanent hair loss
- Decrease in function of thyroid gland
- Temporary pain or scarring around nerves in the shoulder which could cause numbness and/or weakness
- Dryness of the mouth or altered taste that may be permanent

Risks Associated with Chemotherapy (Cisplatin)

Very Likely

- Nausea and/or vomiting
- Weakness
- Hearing loss, ringing of the ears
- Numbness of the fingers and toes
- Lower blood counts
- Anemia

Less Likely

- Allergic reactions (sweating, difficulty breathing, rapid heart beat)
- Facial swelling
- Loss of coordination
- Involuntary movement
- Loss of taste
- Restlessness

Less Likely, But Serious

- Kidney damage
- Liver damage
- Acute leukemia
- Spasm
- Muscle cramps

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

[Attach additional information about contraception, etc.]

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

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

WHAT OTHER OPTIONS ARE THERE?

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

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

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

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

WHAT ABOUT CONFIDENTIALITY?

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

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*), qualified representatives of applicable drug manufacturers, 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.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

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

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

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

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

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

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

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

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

TISSUE AND BLOOD TESTING (RTOG 99-14)

I agree to the use of my tissue and blood samples for future correlative studies related to my cancer. If I do not agree, I will still be able to participate in the treatment part of this study.

Yes No

Patient Signature (*or legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

APPENDIX III

AJCC STAGING HEAD & NECK, 5th Edition

STAGING-PRIMARY TUMOR (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T_{is} Carcinoma *in situ*

ORAL CAVITY

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

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

PHARYNX

Nasopharynx

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

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

Oropharynx

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

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

Hypopharynx

- Pyriform fossae

Postcricoid region
Lateral and posterior hypopharyngeal walls

- T1 Tumor limited to one subsite of hypopharynx and 2 cm or less in greatest dimension.
- T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx.
- T3 Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx.
- T4 Tumor invades adjacent structures (*e.g. thyroid/cricoid cartilage, carotid artery, soft tissues of neck, prevertebral fascia/muscles, thyroid and/or esophagus*).

LARYNX

Supraglottis

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

- T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
- T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (*e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus*) without fixation of the larynx.
- T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues.
- T4 Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus.

Glottis

True vocal cords including anterior and posterior commissures

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

Subglottis

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

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

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

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.

N3 Metastases in a lymph node more than 6 cm in greatest dimension.

REGIONAL LYMPH NODES (N) Nasopharynx Only

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa

N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa

N3 Metastasis in a lymph node(s)

N3a greater than 6 cm in dimension

N3b in the supraclavicular fossa

DISTANT METASTASIS (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

STAGE GROUPING Excluding Nasopharynx STAGE GROUPING Nasopharynx

Stage 0 Tis, N0, M0

Stage I T1, N0, M0

Stage II T2, N0, M0

Stage III T3, N0, M0
T1-3, N1, M0

Stage IVA T4, N0-1, M0
Any T, N2, M0

Stage IVB Any T, N3, M0

Stage IVC Any T, Any N, M1

Stage 0 Tis, N0, M0

Stage I T1, N0, M0

Stage IIA T2a, N0, M0

Stage IIB T1-T2a, N1, M0
T2b, N0-1, M0

Stage III T1-T2b, N2, M0
T3, N0-2, M0

Stage IVA T4, N0-2, M0

Stage IVB Any T, N3, M0

Stage IVC Any T, Any N, M1

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *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 (\geq *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
MANAGEMENT OF DENTAL PROBLEMS
IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

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

Preirradiation Care and Procedures

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

Group 1

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

Group 2

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

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

Group 3

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

Group 4

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

Extraction of Teeth

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

Causative Factors

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

Preventive Program

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

Results

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

Failure to Control Decay

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

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

Hypersensitivity of Teeth

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

Infections

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

Bone Necrosis

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