RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-03

A RANDOMIZED PHASE II TRIAL OF CONCURRENT RADIATION AND CHEMOTHERAPY FOR ADVANCED SQUAMOUS CELL CARCINOMAS OF THE HEAD AND NECK

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SCHEMA

S  R  Arm 1: 70 Gy/7 weeks plus daily cisplatin and 5-FU during the last 10 days of XRT
T  KPS  A  Arm 2: 70 Gy/13 weeks plus daily hydroxyurea and 5-FU (all therapies given every other week)
R  2. 70-80  N
A  D  Arm 3: 70 Gy/7 weeks plus weekly cisplatin and paclitaxel
T  O
I  M
F  I
Y  Z
E

Eligibility: (See Section 3.0 for details)

- Histologic proof of squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx
- Stage III-IV disease (T3-4, N1-3, M0)
- KPS ≥ 70, ≥ 18 years old
- AGC ≥ 2000, platelets ≥ 100,000, bilirubin ≤ 1.5
- SGOT or SGPT ≤ 2 x upper normal, creatinine clearance ≥ 50.
- No clinically significant heart disease
- No prior treatment to the study site
- Patients with prior malignancy ≥ 5 years ago are eligible (simultaneous primaries are ineligible)
- Signed study-specific consent form

Required Sample Size: 111 + 108 = 219 (9/8/98)
Institution # __________
RTOG 97-03 ELIGIBILITY CHECK (9/8/98)
Case # __________ (page 1 of 2)

(Y) 1. Is there histologic confirmation of squamous cell cancer of the oral cavity, oropharynx or hypopharynx?

(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 (see Section 3.1.8 for descriptions)?

(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 non melanoma skin cancer, is there any history of a prior malignancy?

_____ (Y) If yes, has the patient been continually cancer free for the past 5 years?

(≥18) 11. What is the patient's age?

(≥2) 12. What is the on-study total granulocyte count (per mm³)?

(≥100) 13. What is the study platelet count (per mm³).

(≤1.5) 14. What is the on-study bilirubin (mg%)?

(Y) 15. Is the SGOT or SGPT ≤ 2 times upper normal?

(≤1.5) 16. What is the study serum creatinine (mg%)?

(≥50) 17. What is the on-study creatinine clearance (ml/min) as determined by 24 hour collection or nomogram calculation (specify which was used)?

(continued on page 2)
18. Is the serum calcium within normal range (without intervention)?
19. Is the patient pregnant?
20. Has a study specific informed consent been signed?

The following questions will be asked at randomization

1. Has the study-specific Eligibility Checklist (above) been completed?
2. Is the patient eligible for this study?

Patient’s Name
Verifying Physician
Patient ID #
Referring Institution # (if different)
Karnofsky Performance Status? (≥ 70)
Medical Oncologist
Birthdate
Sex
Race
Social Security Number
Zip Code (9 digit if available)
Method of Payment
Will the patient receive any care at a VA or military facility?
Treatment Start Date
Treatment Assignment

Completed by ____________________________  Date ____________________________
1.0 BACKGROUND

1.1 General Background

Surgical resection of advanced resectable stage III and IV squamous cell carcinomas of the head and neck, often followed by adjuvant radiotherapy, is the current standard of care in most cases, though this is often at the expense of function. Results of conventionally fractionated radiation treatment, often used as a single modality for patients with unresectable disease, are less satisfying with frequent local failures, and poor survival rates. 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 investigated various aggressively fractionated regimens with positive results. While there have been positive studies suggesting a therapeutic gain with the use of more aggressive fractionation schedules, local control remains a significant problem in patients with advanced T3 and T4 disease.

A second avenue pursued to improve results of non-surgical treatment of advanced head and neck cancers has been to add chemotherapy to radiation. Two options for combining chemotherapy to radiation are to add it in an adjuvant setting (before or after radiation), or to deliver it concomitantly. The former option has been studied extensively in prospective pilot and large randomized trials. A survival advantage over standard surgery has not been demonstrated, but organ preservation in many has been achieved. 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 local control 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 administration of chemotherapy and radiation. Various chemotherapeutic agents have been used concurrently with radiotherapy. Single agent cisplatin, 5-fluorouracil, bleomycin, methotrexate, mitomycin C and hydroxyurea 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. In a small randomized trial of 5-FU and radiation by Lo et al. “major” complications were seen in 5 of 33 patients treated with drug compared to 0 of 33 patients treated with radiation alone. In a large pilot study performed by the RTOG addressing concomitant cisplatin and radiation, Marcial et al. reported grade > 3 late toxicity developing in 15% of their patients. The most common toxicities included necrosis, fibrosis and dental caries. Only one case of necrosis was life-threatening and no cases were fatal. Stefani et al. found an increase in acute toxicity of patients receiving hydroxyurea in addition to radiation compared to radiation only controls.

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 multiagent chemotherapy combined with radiation. Recognizing the pitfalls of meta-analysis, a recent study evaluating combination radiation and chemotherapy has suggested a survival advantage in patients receiving combined treatment (at the expense of increased morbidity). One example of a randomized study evaluating multiagent chemotherapy and conventionally fractionated radiation was done by the NCOG and reported by Fu et al. 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 were life threatening.

Several groups have evaluated cisplatin and 5-FU in combination with radiation, as this combination is among the most active in the management of recurrent or metastatic disease. Additionally, this regimen has significant activity when used as induction therapy in locally advanced disease. Both agents have been found to have radiation sensitizing effects in vitro, as well as in several patient studies. Several trials have given cisplatin and 5-FU throughout radiotherapy. Taylor et al. gave cisplatin 60mg/m² and 5-FU 800mg/m² every 14 days cycled with conventionally fractionated radiotherapy. They have demonstrated an improved freedom from recurrence rate 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 trials have given cisplatin at doses as high as 100 mg/m² every three weeks.
with tolerable toxicity. Gandia et al. 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.

Other groups have investigated different combinations of drugs, looking at agents that not only have cytotoxic activity in head and neck cancers by themselves, but have radiosensitizing capabilities as well. Researchers at the University of Chicago have investigated the concurrent administration of 5-FU and hydroxyurea with radiation therapy. This is based on the single agent activity of both agents in head and neck cancer, and preclinical observations suggesting a synergistic interaction of the two drugs (hydroxyurea is a ribonucleotide reductase inhibitor and depletes cells of the deoxyuridine monophosphate (dUMP) which 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. 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.

The Eastern Cooperative Oncology Group (ECOG) completed a phase II evaluation of paclitaxel 250 mg/m² every 21 days in patients with recurrent head and neck cancer. A 40% (12/30) response rate was observed, establishing paclitaxel as an active new agent for the treatment of this disease. There is preclinical data suggesting that paclitaxel is a cell cycle selective radiosensitizer. Phase I studies testing various schedules are in progress. This effect is dependent on paclitaxel concentration and the fraction of cells in the G2 or M phase of the cell cycle. The concentration of paclitaxel required in vitro to stabilize microtubules can be achieved in vivo as demonstrated in pharmacokinetic and phase I trials determining steady state paclitaxel plasma levels. Mitotic arrest has been demonstrated in tissues from esophagus, stomach, intestine, liver, skin and bone marrow within 11 days of receiving paclitaxel.

Available data suggest that concurrent radiation and multiagent chemotherapy may improve survival for patients with locoregionally advanced squamous cell cancers of the head and neck. However, this general strategy has led to multiple approaches. Questions remain to which agents may be the most appropriate. In addition, the right timing of each modality which have different delivery schedules is unresolved. Should each modality be given as it traditionally is delivered, i.e. cycle the chemotherapy every 3-4 weeks and deliver a continuous course of radiation 5 days per week for 7 weeks? Or should one of the modalities be given as the other modality is given, i.e. cycle the radiation with the chemotherapy, or "fractionate" the chemotherapy and deliver it daily with the radiation. Ideally, combination schedules should be based on mechanisms of drug-radiation interaction. Unfortunately, the modes of interaction for most drugs are not well understood. This study will evaluate 3 different approaches of combined radiation and chemotherapy, evaluating both different chemotherapeutic agents as well as different timing strategies.

1.2.1 Specific Approaches

The first approach evaluates a course of conventionally fractionated high dose radiation (70 Gy delivered once daily for 7 weeks) combined with cisplatin and 5-FU. During standard radiation of head and neck cancers, patients are initially treated not only to their primary lesion, but electively to regional sites of potential spread. The radiation volume tends to be large, but these sites are treated for a shorter period of time, and to lower doses, as the aim is to control sites of potential subclinical disease. Following achievement of these doses to subclinical sites, the radiation fields are reduced in size to encompass only sites of gross disease. These fields are then taken to the final dose, and are referred to as the "boost" fields, as the gross disease is "boosted" to the higher dose. Thus standard fractionation is done sequentially, first treating a large volume of clinical and potential subclinical disease, followed by continued treatment to the clinical disease. The "concomitant boost" radiotherapy concept was to treat the large volume and smaller "boost" volume at the same time. A randomized study demonstrated that
the optimal time to deliver the boost was during the last 2 weeks of treatment. Local-regional control rates (2-year) were approximately 13% higher when the boost was delivered at the end of the therapy schedule compared to a boost at the beginning of the schedule or distributed throughout the radiation course. A plausible explanation for these improved results with the boost delivered concomitantly at the end of treatment is that during a course of radiation as tumors respond to therapy and shrink more clonogens are recruited to repopulate the tumor. This phenomenon is referred to as accelerated repopulation. Rapidly proliferating cells may be more susceptible for damage by radiation through net radiosensitization (cell cycle redistribution and division delay). Based on the above rationale, chemotherapy will be delivered concomitantly at the end of treatment to give an increased intensity of treatment during the phase of radiation when more treatment is needed, as well as during the phase when the tumor is most likely to be sensitive to chemotherapy. Besides this potential therapeutic effect, the drugs given during the boost portion of radiation, when the treated volume is smaller, exposing smaller volumes of normal tissues to the toxic effects of the two modalities. By avoiding chemotherapy throughout the majority of the radiation period, toxicity should be minimized and the full program should be completed without interruption. A dose searching phase I study performed at M.D. Anderson Cancer Center has established 400mg/m$^2$ 5-FU and 10mg/m$^2$ of cisplatin as the maximally tolerated doses of drugs given during the 10 day boost of radiation.

1.2.2
The second approach to be investigated is a combination of 5-FU, hydroxyurea, and radiation therapy (FHX) administered every other week. This was initially explored in patients with recurrent disease. In this setting, high response and encouraging locoregional control rates were observed. Subsequent studies investigated this regimen in patients with stage II and III disease. In this group of patients, a local control rate exceeding 90% (without use of surgery) was observed. Patients with stage IV disease were treated with induction chemotherapy followed by FHX. Here, similar encouraging locoregional control and survival data have been reported.

Overall, the experience in the University of Chicago Network suggests high locoregional control rates when administering 5-FU and hydroxyurea with concurrent radiation therapy to patients with advanced head and neck cancer. Of note, these response and survival data were observed despite utilization of "protracted" chemoradiotherapy in that both drugs and radiation therapy were administered every other week only. These observations emphasize the need to evaluate concomitant chemoradiotherapy regimens "as a whole", in addition to considering optimization of administration of the respective single modalities involved.

1.2.3 The third approach is the administration of weekly paclitaxel and cisplatin to improve local regional control and survival. Because of its unique intracellular target and resulting mechanism of action, paclitaxel is an attractive alternative to 5-fluorouracil-based chemotherapy for use in the treatment of HNSCC. Clinical trials of paclitaxel as single agent and in combination with cisplatin in patients with HNSCC have also demonstrated significant clinical activity. In vitro studies demonstrate that paclitaxel is a potent radiation sensitizer. Paclitaxel and cisplatin are synergistic and both lead to radiation enhancement.

In vitro studies have demonstrated that radiation therapy and chemotherapy cause cell death by triggering apoptosis, or programmed cell death. Many of the genes/gene products which are either pro-apoptotic (such as p53) or anti-apoptotic (such as bcl-2) are abnormal in malignant cells. As a complete molecular progression model of HNSCC has recently been described, relationships between frequent areas of chromosomal loss/gene mutation and response to chemotherapy can be prospectively studied in patients who are treated uniformly.

A phase I trial of weekly paclitaxel/cisplatin chemotherapy given as a radiation-sensitizing regimen concomitant with post-operative radiation therapy in patients with high-risk HNSCC has also been performed at Johns Hopkins University. This trial demonstrated that paclitaxel, 30 mg/m$^2$ could be given weekly, either alone or in combination with weekly cisplatin, 20 mg/m$^2$, during a postoperative course of radiation therapy (60 Gy/6 weeks by once daily fractions). Nineteen patients were treated at three dose levels. Observed toxicities (RTOG criteria) included mucositis, dysphagia/odynophagia, skin toxicity, and nausea/vomiting. Grade 4 mucositis was the dose-limiting toxicity, occurring in 2/5 patients treated with weekly paclitaxel, 45 mg/m$^2$ (the highest dose studied). Over all dose levels, no
grade 4 hematologic toxicities were encountered, and only 12/112 weeks of radiation therapy were delayed due to mucositis or hematologic toxicity.

2.0 OBJECTIVES
2.1 To determine patient tolerance to each regimen.
2.2 To determine the feasibility of treatment delivery and the acute and late toxicities associated with each regimen.
2.3 To determine the overall survival and disease free survival of patients with advanced squamous cell carcinomas of the head and neck treated with three different combinations of chemotherapy and high dose radiation.
2.4 To determine the time to local, regional, and distant failure of each regimen.

3.0 PATIENT SELECTION (9/8/98)
3.1 Conditions for Patient Eligibility
3.1.1 Patients with histological proof (from the primary lesion and/or lymph nodes) of squamous cell carcinoma of the oral cavity, oropharynx, or hypopharynx.
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 Karnofsky performance status of ≥ 70 (Appendix II).
3.1.4 Age ≥ 18 years.
3.1.5 No distant metastatic disease.
3.1.6 Patients should have adequate bone marrow function defined as an absolute peripheral granulocyte count (AGC) of ≥ 2000 cells/mm³, platelet count of ≥ 100,000 cells/mm³, adequate hepatic function with bilirubin ≤ 1.5 mg%, serum creatinine ≤ 1.5 mg %, SGOT or SGPT ≤ 2 x the upper limit of normal, normal serum calcium (without intervention).
3.1.7 Creatinine clearance ≥ 50 ml/min determined by 24 hour collection or nomogram:
   \[
   \text{CrCl male} = \frac{(140 - \text{age}) \times (\text{wt. as kg})}{\text{Serum Cr}} \times 72
   \]
   \[
   \text{CrCl female} = 0.85 \times (\text{CrCl male})
   \]
3.1.8 No clinically significant heart disease.
3.1.8.1 No significant ventricular arrhythmia requiring medication with antiarrhythmics.
3.1.8.2 No symptomatic coronary artery disease (angina).
3.1.8.3 No myocardial infarction within the last 6 months.
3.1.8.4 No second or third degree heart block or bundle branch block or clinically significant conduction system abnormality.
3.1.9 Patients must sign a study-specific informed consent form.
3.2 Ineligibility Criteria (9/8/98)
3.2.1 Histology other than squamous cell carcinoma.
3.2.2 Evidence of metastases (below the clavicle or distant) by clinical or radiographic means.
3.2.3 Prior chemotherapy for any reason or prior radiotherapy to the head and neck.
3.2.4 Initial surgical treatment excluding diagnostic biopsy of the primary site or neck disease is not permitted.
3.2.5 Patients with simultaneous primaries.
3.2.6 Serum creatinine > 1.5, AGC < 2000, platelets < 100,000, liver function tests > 2 times upper limit of normal.
3.2.7 Pregnant women are ineligible because of the embryotoxic effects of chemotherapy.
3.2.8 Patients with a history of non-melanoma skin cancer, or other previous malignancies treated 5 years or more prior the current tumor from which the patient has remained continually disease free are eligible.

4.0 PRETREATMENT EVALUATION
4.1 Complete history and physical examination.
4.2 Biopsy of primary tumor and/or biopsy or fine needle aspirate 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 (9/8/98)
4.4.1 CBC with differential and platelet count
4.4.2 SMA-12, (sodium, potassium, glucose, calcium, magnesium, BUN, creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, SGPT or SGOT, and LDH), electrolytes.
4.4.3 Prothrombin time (PT) partial thromboplastin time (PTT), optional.
4.4.4 Creatinine clearance.

4.5 Radiographic Studies (9/8/98)
4.5.1 Appropriate radiographic study of tumor.
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 Panendoscopy, optional.
4.7 Standard 12-lead electrocardiogram (pre tx for patients randomized to Arm 3).
4.8 Dental evaluation with management according to the guidelines of Daly42 prior to the start of radiation (Appendix VII).
4.9 Feeding tubes (either Dobhoff, PEG or 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 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
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY
6.1 Dose Fractionation
6.1.1 Arm 1 standard fractionation:
The first day of radiation should be on the Moday of week 1. All treatment will be at 2 Gy per day. Uninvolved subclinical sites will receive 50 Gy/25 fractions. Fields will be reduced to limit the spinal cord to \( \leq 44 \) Gy. Fields will be reduced a second time after 50 Gy to treat gross disease only an additional 20 Gy/10 fractions at 2 Gy per fraction (with the concomitant chemotherapy) to a final dose of 70 Gy. Treatment will be continuous, 5 days per week for 7 consecutive weeks.

6.1.2 Arm 2 standard fractionation:
The first day of radiation should be on the Moday of week 1. All treatment will be at 2 Gy per day. Uninvolved subclinical sites will receive 50 Gy / 25 fractions. Fields will be reduced to limit the spinal cord to \( \leq 44 \) Gy. Fields will be reduced a second time after 50 Gy to treat gross disease only an additional 20 Gy /10 fractions at 2 Gy per fraction to a final dose of 70 Gy. Treatment will be delivered 5 days/week. Treatment will be given with the delivery of chemotherapy. After each 5 days of therapy there will be 9 days of break. Treatment is delivered every other week for a total of 13 weeks.

6.1.3 Arm 3 standard fractionation:
The first day of radiation should be on the Moday of week 1. All treatment will be at 2 Gy per day. Uninvolved subclinical sites will receive 50 Gy / 25 fractions. Fields will be reduced to limit the spinal cord to \( \leq 44 \) Gy. Fields will be reduced a second time after 50 Gy to treat gross disease only an additional 20 Gy / 10 fractions at 2 Gy per fraction to a final dose of 70 Gy. Treatment will be continuous, 5 days per week for 7 consecutive weeks.

6.1.4 Boost Doses:
Additional boost doses may be given through reduced fields to persistent primary tumor and or clinically positive nodes. The boost dose should not exceed 5.0 Gy for each of the study arms.

6.1.5 The anterior low neck field will be treated at 2 Gy per fraction to 3 cm depth, once daily to a total dose of 44 Gy / 22 fxs. Patients on Arm 2 will receive treatment to the low neck only on days when receiving planned radiation and chemotherapy.

6.2 Physical Factors
6.2.1 Megavoltage equipment, either linear accelerators or $^{60}$Cobalt 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 All fields will be simulated. Patients must be reproducibly immobilized. Shaping the radiation beam using customized cerrobend blocking or multileaf collimation is required.

6.3.2 Treatment verification must be done with portal imaging for each new field, 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 (defined below). 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.

All fields will start with a 2-3 cm margin around gross primary and nodal disease. A reduction off the spinal cord to limit it to $\leq 44$ Gy is mandatory for all arms. A second reduction specific for each arm will be made off subclinical sites. These reduced fields will have a 1 - 1.5 cm margin around gross disease.

6.5 Dose Calculation

6.5.1 Complete isodose curves are required. Cumulative isodose distributions 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 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.

6.5.2 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.

6.6 Anticipated Side Effects and Toxicities

6.6.1 Suggested maximum dose to the spinal cord is 44.0 Gy/22 fx/4.5 weeks.

6.6.2 Reversible mucositis is expected and its timing with dose and severity should be noted and graded according to the RTOG Acute Radiation Morbidity criteria for mucous membrane.

6.6.3 Also expected will be epilation of treated areas and various degrees of skin reaction in the treated area. These should be graded according to the RTOG Acute Radiation Morbidity Criteria for skin.

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 5% or less of the patients, but may be reduced by thorough dental evaluation and treatment before irradiation, which is required. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth where possible. At least 10 days should be allowed for healing of gingivae post-extraction.

6.6.6 Radiation-induced myelopathy should not occur providing cervical spinal cord dose remains below 44 Gy in 22 fractions in 4.5 weeks. However, special attention should be directed in follow-up exams to any numbness, paraesthesia, or Lhermitte's signs, particularly in the first 6-12 months of follow-up.

6.6.7 Adverse Reaction Reporting RTOG Headquarters and the study chairman must be notified by telephone of all fatal and life threatening toxicities (those $\geq$ grade 4). See RTOG Toxicity Reporting guidelines for details.

6.6.8 Toxicities $\geq$ grade 3 that are not dependent on laboratory results must be described on the data forms.

7.0 DRUG THERAPY

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: The dry, unopened vials should be stored at refrigeration temperature (4°C to 8°C). Reconstitution results in a solution which is stable for not more than 1 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 interstrand 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 man 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. (9/8/98)

7.1.1.6 Supplier: Commercially available.

7.1.2 5-Fluorouracil (5-FU)

7.1.2.1 Formulation: 500 mg ampules containing 50 mg/cc. The synthesis of 5-FU was described by Heidelberger et al. in 1957 and, as indicated by its name, is one of the halogenated pyrimidines.

7.1.2.2 Storage: Room temperature.

7.1.2.3 Administration: Intravenous.

7.1.2.4 Mechanism of Action: 5-FU is considered to act primarily as an inhibitor of thymidylate synthetase.

7.1.2.5 Toxicology: Side effects reported from the use of 5-FU include (in decreasing order of frequency) anorexia, nausea and vomiting, diarrhea, mucositis, myelosuppression (white count, platelet count), skin changes, alopecia and cardiac consisting of arrhythmias and coronary artery spasm. Severe toxicity is encountered relatively infrequently with the weekly regimen.

7.1.2.6 Supplier: Commercially available.

7.1.3 Hydroxyurea:

7.1.3.1 Hydroxyurea is commercially available as 500 mg capsules. It is stored at room temperature and will be administered orally. Common side effects include myelosuppression (mainly leukopenia), nausea, vomiting, diarrhea or constipation and stomatitis.

7.1.3.2 It may aggravate the inflammation of mucous membranes secondary to irradiation. Less common side effects include dysuria or impairment of renal tubular function as well as rare neurologic disturbances, e.g., headache, dizziness, disorientation, hallucination and convulsion.

7.1.4 Paclitaxel

7.1.4.1 Formulation: A concentrated sterile solution, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylene castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents will be diluted just prior to clinical use.

7.1.4.2 Storage: The intact vials should be stored at 2-25° Celsius (36°-77° Fahrenheit) and retained in the original package in order to protect from light. Freezing does not adversely affect the concentrate. Upon refrigeration components in the paclitaxal vial may precipitate, but will redissolve upon reaching room temperature with little or no agitation. There is no impact on product quality under these conditions. If the solution remains cloudy or if an insoluble precipitate is noted, the vial should be discarded.

7.1.4.3 Administration: Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used. Taxol should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns.

7.1.4.4 Solution Preparation: Paclitaxel for injection concentrate must be diluted prior to infusion, in 0.9% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer's Injection, USP to a final concentration of 0.3 to 1.2 mg/ml. the solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°) and room lighting conditions. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of
the solution through IV tubing containing an in-line (0.22 micron) filter. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers.

7.1.5 Toxicology: The dose limiting toxicities and MTD of paclitaxel administered on a variety of schedules to patients with solid neoplasms were previously evaluated in phase I trials. In these studies, paclitaxel was infused over 1, 3, 6, and 24 h, but severe acute reactions, characterized by bronchospasm, hypotension, stridor, tachy- and bradyarrhythmias, and death, resulted in the temporary discontinuation of all trials. These reactions were attributed to paclitaxel’s Cremophor vehicle, since identical reactions were observed with other drugs formulated with it and when the vehicle alone was administered to animals. Since a higher incidence of these acute reactions was observed with shorter durations of infusion, studies that used shorter infusions were permanently discontinued, and trials that evaluated longer infusion durations (24 h) were resumed using antiallergic pre-medications consisting of corticosteroids, H₁ and H₂ histamine antagonists. These modifications were associated with a marked reduction in the incidence of acute reactions. Neutropenia was the major dose-limiting toxicity for paclitaxel in phase I solid tumor trials. In addition, a sensory neuropathy, characterized by a glove-and-sock distribution of numbness and paresthesias, was observed at higher doses. Nausea and vomiting, myalgias, mucositis, total-body alopecia, diarrhea, and phlebitis were also observed. The MTD and recommended phase II doses of paclitaxel administered as a 6-h infusion were 265 and 212 mg/m², respectively, and 275 and 250 mg/m², respectively, as a 24-h infusion.

7.1.4.6 Commercially available as Taxol®.

7.2 Chemotherapy Dose Schedule

7.2.1 Arm 1 - General Concept (call Dr. Garden with questions):
Chemotherapy consisting of cisplatin i.v. 10 mg/m² daily and 5-FU 400 mg/m² i.v. continuous infusion over 24 hours daily will be delivered on the final 10 treatment days of radiation (weeks 6 and 7).

7.2.1.1 Cisplatin Administration: Cisplatin will be given in 500 ml of NS with mannitol 12.5 grams over one hour on days 1-5 of the sixth and seventh weeks of radiotherapy.

7.2.1.2 5-Fluorouracil Administration: A continuous infusion 400 mg/m²/day of 5-FU diluted in one liter of normal saline will be given by continuous infusion daily for 5 days (120 hours of infusion time) beginning on day 1 and completing on day 5 of the sixth week and repeated on days 1-5 of the seventh week of radiotherapy. Total accumulated dose over 10 days of treatment with 5-FU in 4000 mg/m².

7.2.1.3 Criteria for Instituting Chemotherapy
• No indication for holding radiation therapy.
• Laboratories must meet the pre-randomization limits stated in Section 3.1.6.

7.2.2 Arm 2 - General Concept (call Dr. Vokes with questions):
5-FU 800 mg/m²/day (120 hours), hydroxyurea 1 gm p.o. q 12 hrs x 6 days (11 doses, first dose to be given Sunday evening) p.o. b.i.d and radiotherapy will be delivered concurrently in seven “14 day cycles” consisting of 5 days of therapy and 9 days of break.

7.2.2.1 Hydroxyurea: Start hydroxyurea Sunday p.m. 1.0 gm, p.o. q 12 hours x 6 days (11 doses per cycle. While the actual time of administration of HU and radiotherapy may vary from patient to patient, one daily dose of HU will precede radiotherapy at a constant of 2 hr (peak serum levels.) Hydroxyurea may be given through the feeding tube if necessary.

7.2.2.2 5-FU: Start continuous infusion of 5-fluorouracil at 800 mg/m²/day x 5 days Monday-Friday. Start Monday a.m. before XRT (120 hours total infusion time). Radiation therapy to be administered daily x 5 days.

7.2.2.3 Completion of Cycle
Day 6-14: No therapy
Cycle length: 14 days (repeat every other week until completion of radiotherapy) for a total of 7 cycles.

7.2.2.4 Dose Modifications
Dose modifications will proceed according to the toxicities observed on the previous cycle.

Mucositis, dermatitis, diarrhea:
Grade 2-3 mucositis is anticipated to occur following each cycle of therapy. It generally will peak during days 8-12 and will not be resolved by day 14. Dose reduction will be performed only in patients having grade 4 mucositis at time of chemotherapy administration. For grade 4 mucositis, dermatitis, or diarrhea on previous cycle, decrease 5-FU to 600 mg/m²/day x 5. A decrease of 5-FU to < 600 mg/m² may result in inferior treatment outcome and should be
avoided. Instead, nutritional support, pain management, skin care and other means of supportive care should be optimized.

**Myelosuppression on day 1-5:**
For WBC count between 2000/µl-2500/µl or platelet count between 50,000/µl-74,000/µl on day 1 of each treatment: decrease hydroxyurea to 500 mg p.o. b.i.d.
For WBC count <2000/µl or platelet count < 50,000/µl on day 1 of each treatment: No hydroxyurea to be given. Continue radiotherapy at 5-FU at full doses.

Cycles of concomitant chemoradiotherapy will be postponed by one week only for persistent unresolved grade 4 toxicity that cannot be handled by aggressive supportive care.

7.2.3 **Arm 3 - General Concept** *(call Dr. Forastiere with questions)*: *(9/8/98)*
Concomitant weekly chemotherapy/radiation therapy with paclitaxel 30 mg/m² given before the start of radiation therapy *(day 1)*, and cisplatin 20 mg/m² to start day 2. Subsequent chemotherapy will be given weekly before the start of the day's radiation therapy. Chemotherapy will be held during any radiation interruptions. Ideally, RT would start on a Monday with paclitaxel administered each Monday and cisplatin administered each Tuesday. However, if this is not feasible, chemotherapy can be started on Tuesday, Wednesday or Thursday, as long as paclitaxel and cisplatin are administered on 2 successive days starting week 1 of RT and repeated on the same days weekly for 7 weeks.

7.2.3.1 **Chemotherapy Regimens During Radiation Therapy**
a. **Starting doses**
   - Paclitaxel, 30 mg/m² over 3 hours on day 1, every seven days.
   - Cisplatin, 20 mg/m² over 2 hours on day 2, every seven days.

7.2.3.2 **Criteria for Weekly Chemotherapy**
a. No indication to hold radiation therapy.
b. To receive paclitaxel, the patient must meet all of the following:
   i. Absolute neutrophil count ≥ 1000/µl
   ii. Platelets ≥ 75,000/µl
If these parameters are not met, continue RT and delay paclitaxel and cisplatin by one week.
c. To receive cisplatin, the patient must meet all the following:
   i. Absolute neutrophil count ≥ 1000/µl, platelets ≥ 75,000/µl.
   ii. Stable serum Cr or Cr Cl ≥ 50 mg/min. Determine CrCL if the serum creatinine is higher than at the previous determination.
If these parameters are not met, continue RT and paclitaxel *(if parameters in Section 7.2.3.2b are met)*. Hold cisplatin for one week.

7.2.3.3 **Modifications to Weekly Chemotherapy** should the patient encounter the following toxicities:
a. **Grade 4 mucositis *(RTOG scale)***
b. Development of hematologic toxicity requiring a chemotherapy delay > 7 treatment days.
c. Toxicity which requires a delay in radiation therapy > 10 treatment days in total. First episode of above toxicities—discontinue cisplatin and continue RT with weekly paclitaxel 30 mg/m². Second episode—discontinue paclitaxel, continue RT only.

7.2.3.4 **Administration of Paclitaxel**
a. Premedication will be given.
   i. Dexamethasone, 20 mg po 12 and 6 hours before chemotherapy.
   ii. Diphenhydramine 50 mg IV and ranitidine 50 mg IV 30 minutes before chemotherapy.
b. After premedication, paclitaxel will be given as a 3 hour continuous infusion, diluted in 500 cc of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Paclitaxel will be administered via an infusion control and device *(pump)* using non-PVC tubing, connectors, and bags/bottles. A 0.22 micron in-line filter will be used. Nothing else will be infused through the line where paclitaxel is being administered. Paclitaxel may be administered using peripheral i.v. infusion.

7.2.3.5 **Administration of Cisplatin**
a. Suggested premedication: granisetron, 0.7-1.0 mg IV or ondansetron 32 mg IV 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.
b. Cisplatin *(at the appropriate dose)* will be diluted in 0.9% Sodium Chloride Injection, USP to a volume of 1 liter and infused over 2 hours. Any pre-existing dehydration must be corrected prior
to cisplatin administration. No further pre/post cisplatin hydration will be necessary. Cisplatin may be administered using peripheral i.v. infusion.

7.2.3.6 Supportive Care
   a. Placement of a gastrostomy tube (PEG) before treatment begins is strongly recommended to optimize nutrition and hydration during chemo-radiation.
   b. Aggressive oral and skin care, and analgesics are recommended.

7.3 G-CSF
   Use of G-CSF (Filgrastrim) or other growth factors is not anticipated for any treatment arm of this protocol. However, if the use of a growth factor is judged to be necessary in the supportive care of a patient by the treating physician, its use should be carefully documented on the flow sheets. G-CSF should not be administered during an actual infusion of 5-FU.

7.4 Adverse Drug Reaction Reporting
   7.4.1 The following guidelines for reporting adverse drug reactions (ADR’s) apply to any research protocol which uses commercial anticancer agents. The following ADR’s 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 ten 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 of 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 FDA Form 3500 (Appendix V) and mailed to the address on the form, RTOG Data Management Department, and to:
      Investigational Drug Branch
      P.O. Box 30012
      Bethesda, MD 20824
      (301) 230-2330, available 24 hours
      (fax) (301) 230-0159
   7.4.3 Death from any cause while the patient is receiving protocol treatment, or up to 30 days after the last protocol treatment, must be reported to RTOG Headquarters Data Management department within ten days of discovery.

8.0 SURGERY (call Dr. Ridge 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 worrisome clinical features. Surgical removal (salvage resection) of the primary tumor should be performed if biopsy-proven cancer remains at least six weeks after completion of radiotherapy. 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 Neck dissection: A planned neck dissection for patients with multiple neck nodes or with lymph nodes exceeding three 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 radiotherapy ends. Surgery should be performed within 2 weeks.
   8.3 Cervical lymphadenectomy should be comprehensive rather than selective. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle will be at the discretion of the surgeon.
   8.4 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).

9.0 OTHER THERAPY
   Not applicable to this study.
10.0 PATHOLOGY
10.1 Central pathology review will not be required for the study.
10.2 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.

11.0 PATIENT ASSESSMENTS
11.1 Study Parameters *(9/8/98)*

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<th>Assessment</th>
<th>Pre Treatment</th>
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</table>

a. Arm 1 - Weekly starting week 5
   Arm 2 - CBC/plt/diff weekly; electrolytes, creatinine every other week
   Arm 3 - Weekly
b. Only if clinically indicated
c. As applicable
d. To be performed preTX if patient is randomized to Arm 3.
e. SGOT or SGPT, LDH, bilirubin, and alkaline phosphatase at each followup for one year.

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 before therapy, 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 size of diseased areas. This should be confirmed by at least two investigators evaluating independently, or photographs or x-rays should be submitted to Dr. Garden for confirmation.
• 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 4 weeks after the 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 (9/8/98).
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 The development of unacceptable toxicity that would necessitate discontinuing or modifying the treatment.
11.7.3 Followup and data submission will continue according to protocol.

12.0 DATA COLLECTION
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)
12.1 Summary of Data Submission (9/8/98)

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<tr>
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<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 wks of study entry</td>
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<td>Pathology Report (P1)</td>
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<td>Tumor and Nodal Diagrams (I6, I7)</td>
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<td>Chemotherapy Flowsheets (M1)</td>
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<td>(Includes pre-registration labs and initial chemotherapy treatment [except Option1])</td>
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<td>Boost Films (simulation and portal) (T8)</td>
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</table>
Chemotherapy Flowsheets (M1)

At completion or discontinuation of chemotherapy

Follow-up Form (F1)

q 3 months through year 2, q 6 months x 3 years, then at progression/relapse and at death and upon significant post-treatment toxicity

Autopsy Report (D3)

As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints (9/8/98)

13.1.1 To determine the feasibility and tolerance.

13.1.2 To determine the frequency of major (≥ grade 4) acute toxicities.

13.1.3 To determine the tumor clearance rate, where tumor clearance is defined as absence of all visible and palpable disease 4-6 weeks after completion of treatment. (The primary site and nodal disease will be scored separately.)

13.1.4 To determine the frequency of major (≥ grade 4) late toxicities associated with combined chemotherapy.

**Background for Original**

Patient tolerance of these three treatment schedules is the major question. Two indicators of tolerance are the major acute toxicity rate and the percentage of patients able to complete the treatment according to the protocol prescription. Ability to complete protocol treatment, either per protocol or with minor deviation without prolonged elapsed delays (≥ 14 days), will be used as the principal end-point in this study. Previous analyses of the combined standard RT arms of RTOG 79-13 and 79-15 show elapsed treatment days to be an important component of compliance. Patients with prolonged treatment had significantly shorter local control and survival both in univariate and multivariate analyses. Approximately 69% of the RTOG 79-13/79-15 patients received treatment per protocol or with minor deviation without prolonged elapsed treatment delays. In the next phase III study RTOG 85-27, 82% of patients assigned to the standard RT arm received treatment per protocol or with minor deviation without prolonged elapsed treatment delays. Based on these results, a treatment regimen will be considered tolerable if 75% of the eligible patients successfully complete it. All grade 5 (fatal) toxicities must be reported immediately to the headquarters data manager responsible for the study who, in turn, will notify the study chairman and the study statistician. There will be early stopping rules for excessive fatal toxicities.

**Background for Revision**

The preliminary analysis of data (7/98) suggests that all three treatments were feasible and tolerable with acute toxicities. When this study was designed, the projected month accrual rate was 6.7 cases. However, in the first seven months of 1998, the average monthly accrual was 12.1 which was 81% over the projected. Because of this, the RTOG Research Strategy Committee reviewed and approved the proposal from the Head and Neck Committee to increase the sample size in order to obtain an estimate of the major late (> grade 4) effects at one year.

In the first completed RTOG chemoradiation study, the estimated one-year rate for late (> grade 4) effects was 4.8% with no fatal toxicities. By four years, the estimated rate for late (> grade 4) effects was 12.5% with no fatal toxicities. So a rate of 5% for late RT related grade 4 (not including hematologic) or 5 (fatal) would be deem acceptable in this population but, if it is ≥ 17%, it would be clinically unacceptable. The sample size was revised to rule out such a high rate for each arm.

13.2 Sample Size (9/8/98)

13.2.1 Thirty-three evaluable patients will be required on each arm of this study. With a sample size of 33 evaluable patients we have a 95% one-sided confidence interval with lower bound of 62.5% around a hypothesized 75% tolerance. In other words, we have a 5% chance of accepting the treatment for further study if the true patient tolerance is 62.5% or lower.

With this sample size, the standard error associated with the one year estimated rates for either local control or survival would be at most 10%.

If an additional 12% of the sample is added to guard against ineligible or unevaluable (no data) cases, then the target total accrual for this study will be 111 = (3 [33 + 4]) patients.

13.2.2 Thirty-three patients who survive 12 months will be required on each arm of this study to estimate major late effect at one year. The sample size was calculated using the normal approximation to
binomial distribution with correction for continuity.\textsuperscript{50} With this sample size, we have a 95\% one-sided confidence interval with upper bound of 17\% around the hypothesized 5\% major (≥ grade 4) late toxicity. In other words, we have a 5\% chance of accepting the treatment for further study if the true major late effect is greater than .17. Past RTOG studies in this patient population had the median of one year. Thus \(66 = \frac{33}{.50}\) evaluable patients would have to be entered in order to obtain at least 33 patients for the late effect analysis at one year.

With 66 evaluable patients, the standard error associated with tumor clearance rate and with the one year estimated rates for either local control or survival would be at most 6.1\%.

Guarding against a loss up to 10\% due to ineligibility and inevaluable data, the targeted sample size was increased to 73 patients for each arm. The revised targeted sample size for the study is 219 patients.

13.3 Patient Accrual (9/8/98)

13.3.1 Between March 1995 and February 1997, 399 patients were entered into the RTOG 90-03. Based upon this, the accrual rate to this study is projected at five 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 24 months. If the average monthly rate is less than three cases, the study will be re-evaluated with respect to feasibility.

13.3.2 As of August 1, 1998, 110 patients were entered into the protocol. Using a month accrual of 12 patients, the remaining accrual is projected to be completed in 10 months.

13.4 Randomization Scheme

Patients will be randomized to one of three combined modality schedules in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen\textsuperscript{47} will be used because it balances patient factors other than institution. Based upon analyses of past RTOG inoperable head and neck studies, T-stage, N-stage, primary site, and initial Karnofsky performance score proved to be significant factors independently predictive of primary tumor response.\textsuperscript{48} Analysis of the completed RTOG 85-27 found KPS to be most significant. It will be used as stratifying variables and divided into two categories 90-100 vs. < 90.

13.5 Early Stopping Rules for Unacceptable Toxicity (9/8/98)

The unacceptable toxicity is defined as grade 5 (fatal) toxicity due to chemotherapy and radiation therapy. The following early stopping rules are proposed to test the null hypothesis that the proportion of unacceptable toxicity is less than or equal to 5\% with significance level 0.05. We will reject the null hypothesis if we observe, in each arm, more than

- 2 fatal toxicities (grade 5) out of the first 11 evaluable patients, or
- 3 fatal toxicities (grade 5) out of the first 22 evaluable patients; or
- 4 fatal toxicities (grade 5) out of the first 33 evaluable patients; or
- 7 fatal toxicities (grade 5) out of the first 66 evaluable patients.

If we observe the specified number or fewer of fatal toxicities at the designated time, the trial shall proceed as planned. On the other hand, if we observe more toxicities than that specified, we shall conclude that the proportion of unacceptable fatal toxicity is greater than 5\%. After reviewing toxicity data, appropriate actions shall be recommended by study chair, disease chair and statisticians to the RTOG Data Monitoring Committee and the Research Strategy Committee for their approval.

Note that the boundary above is set in such a way that the probability that the observed number of fatal toxicity exceeds the boundary is 0.05 if the true toxicity rate is 5\%; the probability is 0.42 if the true toxicity rate is 10\%; the probability is 0.83 if the true toxicity rate is 15\%; the probability is 0.97 if the true toxicity rate is 20\%.

13.6 Analysis Plan

13.6.1 Interim Reports

Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about patient 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 toxicity due to chemotherapy and radiation therapy.

13.6.2 Analysis for Reporting the Initial Treatment Results

13.6.2.1 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 from the analyses with the reasons for exclusion; institutional accrual; distribution of the important prognostic baseline 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
small sizes involved in each subgroup. There will not be a sufficient number of patients to compare the efficacy of the three treatment program.

13.6.2.2

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 to three treatment regimens under the assumption of the same tolerance rate across the genders and the across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

In study RTOG 90-03, 81% (843/1038) of the patients were males and 19% were females. For planning purposes, we assume that 80% entered into this protocol will be male and 20% female. Then we have a 95% one sided confidence interval with a lower bound of .61 around the hypothesized 75% tolerance for male and with a lower bound of .58 around the hypothesized 75% tolerance for female.

In an ongoing study RTOG 90-03, 73% (754/1038) of the patients were white and 27% were non-white. For planning purposes, we assume that 70% entered into this protocol are white and 30% non-white. Then we have a 95% one sided confidence interval with a lower bound of .60 around the hypothesized 75% tolerance for male and with a lower bound of .52 around the hypothesized 75% tolerance for female.

The interim analysis will include a tabulation of all cases by gender and racial categories. The analysis for reporting the initial treatment results will include 95% confidence intervals for treatment tolerance and response.
REFERENCES


* Added 9/8/98
APPENDIX I

RTOG 97-03

A Randomized Phase II Trial of Concurrent Radiation and Chemotherapy for Advanced Squamous Cell Carcinomas of the Head and Neck

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so I have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits, and alternatives involved. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I have been told I have a cancer in the region of my head and/or neck. Standard treatment often involves surgery with radiation, radiation alone, or chemotherapy (drugs) followed by radiation. To enhance the likelihood of controlling my type of cancer as well as possibly avoid the functional loss that would result from surgery, the Radiation Therapy Oncology Group (RTOG) is conducting a research trial studying treatment with the combination of chemotherapy and radiation. While combining radiation and chemotherapy together may improve cancer control rates, it also may increase the likelihood and duration of side effects. This study is comparing three different approaches to combining chemotherapy and radiation. The approaches are different both in drugs being given, and in the timing of the drugs and radiation. The purpose of this study is to determine which of the three combination regimens is most effective in treating cancers in the head and neck region and to monitor the side effects of these three treatment regimens.

DESCRIPTION OF PROCEDURES (9/8/98)

This study involves at random (by chance) assignment to one of three treatment arms. It is not clear at the present time which of the three regimens is better. For this reason the therapy which is to be offered to me will be based upon a the method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the three regimens by computer. The chance of my receiving one of the three therapies is approximately equal. I will be assigned to one of the following three treatments:

Treatment 1: I will receive radiation (RT) once a day, five days a week, for seven weeks. I will also have chemotherapy which will consist of cisplatin (by i.v. over one hour) on days 1-5 of weeks six and seven of RT (total 10 times) plus i.v. 5-FU continuously (in patient or outpatient) over five days also in weeks six and seven.

Treatment 2: I will receive RT once a day, five days a week every other week. I will also have chemotherapy during my RT: i.v. 5-FU continuously over each five days of RT plus hydroxyrea (by mouth) two times a day (every 12 hours) with the first pill to be taken on a Sunday night. I will take my morning pill two hours before my RT treatments. The total treatment will be 13 weeks from start to end.

Treatment 3: I will receive RT once a day, five days a week, for seven weeks. Once a week, I will have chemotherapy which will consist of i.v. paclitaxel over three hours on the first day of each week plus i.v. cisplatin over two hours on the second day of each week.

If my physician thinks that I cannot eat enough during treatment to keep up my strength, I may need a feeding tube. My physician will be checking my progress during and at the end of treatment then at regular intervals after that (every 3 months for two years, every 6 months for three years, then yearly).

RISKS AND DISCOMFORTS
Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

**Radiation Therapy:** Possible side effects include sore throat, temporary hair loss (sometimes permanent) and tanning or redness of the skin in the treatment area. Also, possible destruction of some teeth which can be prevented by strict dental care during therapy. Guidelines for dental care are available from my physician. More serious, but less frequent, is a decrease in function of the thyroid gland which can be combated with the use of oral thyroid medication. Uncommon side effects include a temporary pain, or scarring around nerves in the shoulder which could cause numbness and/or weakness. Dryness of the mouth or altered taste may be permanent.

**Cisplatin (Platinol)** may cause nausea, vomiting, weakness, hearing loss, ringing of the ears, and numbness of the fingers and toes. It can also cause damage to the kidneys; I will be given extra amounts of fluids and other medications to lessen the risk of kidney injury. It can lower the blood counts and the levels of calcium and magnesium in my blood. It is possible that I may become anemic and require transfusion. Other less common side effects include allergic reactions such as sweating, difficulty breathing, and rapid heart beat. Rarely the drug causes restlessness, facial swelling, loss of coordination, involuntary movement, liver damage, loss of taste, spasm, muscle cramps, or acute leukemia.

5-Fluorouracil (5-FU) can cause diarrhea, a metal taste in the mouth, dry skin, dry nose, and watery eyes. The drug can cause soreness or painful ulcers of the mouth and throat. Loss of hair may result. The drug may cause thinning of the skin, nail changes, redness or darkening of the skin, rash, and increased sensitivity to the sun. 5-FU may cause headaches which continue after treatment is stopped. Rarely, the drug can cause reversible unsteadiness upon walking, dizziness, and slurred speech. It has also rarely been associated with heart attack.

**Paclitaxel (Taxol)** commonly causes a lowering of blood counts which could lead to an increased risk of infection, weakness and fatigue, or bleeding complications. I might need treatment with antibiotics, require hospitalization, and need transfusions if these problems are severe. Other possible side effects include nausea, mouth sores, hair loss, muscle aches, joint pains, visual loss, and fatigue. There is the possibility of skin irritation should paclitaxel leak from my vein into the surrounding skin. Rarely paclitaxel can cause a severe allergic reaction resulting in the development of a rash, difficulty breathing, and low blood pressure. Medication will be given prior to treatment in an effort to prevent this type of reaction. If I am treated with a high dosage or for a prolonged period, I may experience numbness of the hands and feet. Taxol can occasionally cause a slowing of the heart rhythm, or an irregular heart rhythm, but only rarely does it cause symptoms that I would notice. In addition, paclitaxel may increase any radiation risks as listed above.

**Hydroxyurea** may lower blood counts, or cause nausea, vomiting, diarrhea or constipation, or sore mouth. Less frequently, it may cause difficulty in urination, headache, dizziness, disorientation, hallucinations, or convulsions.

This study may be harmful to an unborn child. There is insufficient medical information to see whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. The results will be made available to the study participant prior to the initiation of this study.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood tests will be done weekly during my treatment to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

**CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the inve: ___________________________. In addition, I may contact ________
for information regarding patients' rights in research studies.

**BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

**ALTERNATIVES**

Alternatives which could be considered in my case include radiation therapy performed off-study either alone or with chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain procedures related to this protocol. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

**VOLUNTARY PARTICIPATION**

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

**CONFIDENTIALITY**

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.
### 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>

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22
APPENDIX III


AJC STAGING-Primary Tumor (T)

Oral Cavity

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

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor ≤ 2 cm in greatest dimension
T2 Tumor > 2 - ≤ 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).

PHARYNX

Oropharynx

Faucial arch including soft palate, uvula and anterior tonsillar pillar
Tonsillar fossa and tonsil
Base of tongue including glossoepiglottic and pharyngoepiglottic folds
Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

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

Nasopharynx

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

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to one subsite of nasopharynx
T2 Tumor invades more than one subsite of nasopharynx
T3 Tumor invades nasal cavity and/or oropharynx
T4 Tumor invades skull and/or cranial nerve(s)
Hypopharynx

Pyriform sinus
Postcricoid area
Posterior hypopharyngeal wall

TX Tumor that cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to one subsite of hypopharynx.
T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, without fixation of hemilarynx.
T3 Tumor invades more than one subsite of hypopharynx or an adjacent site, with fixation of hemilarynx.
T4 Tumor invades adjacent structures (e.g. cartilage or soft tissues of neck).

LARYNX

Supraglottis

Ventricular bands (false cords)
Arytenoids
Suprhyoid epiglottis (both lingual and laryngeal aspects)
Infrahoid epiglottis
Arytenoepiglottic folds (laryngeal aspect)

TX Tumor that cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to one subsite of supraglottis with normal mobility.
T2 Tumor invades more than one subsite of supraglottic or glottis with normal vocal cord morbidity.
T3 Tumor limited to larynx with vocal cord fixation and/or extension to involve postcricoid area, medial wall of pyriform sinus, or pre-epiglottic tissues.
T4 Massive tumor extending beyond the larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage.

Glottis

True vocal cords including anterior and posterior comissures

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior comissures) 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., oropharynx, or soft tissues of neck)

Subglottis

TX Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis  Carcinoma in situ
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., to the oropharynx, or soft tissues of the neck)

Nodal Involvement (N)

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 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 a multiple ipsilateral nodes, none more than 6 cm in greatest dimension.
   N2c  Bilateral or contralateral lymph node more than 6 cm in greatest dimension.
N3  Metastases in a lymph node more than 6 cm in greatest dimension.

Stage Groupings

Stage I  - T1, N0, M0
Stage II - T2, N0, M0
Stage III - T3, N0, M0
   T1-3, N1, M0
Stage IV - T4, N0-1, M0
   T1-4, N2-3, M0
   Any T, or 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 supercede 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 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**
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.