RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-15

PHASE II MULTI-INSTITUTIONAL TRIAL OF TARGETED SUPRADOSE CISPLATIN CHEMORADIATION FOR STAGE IV SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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INDEX

Schema

Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Eligibility

4.0 Pretreatment Evaluation

5.0 Registration

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Interventional Radiology

10.0 Pathology

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Karnofsky Performance Status
Appendix III - Staging System
Appendix IV - Toxicity Criteria
Appendix V - Adverse Reaction Reporting
Appendix VI - Management of Dental Problems in Irradiated Patients
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SCHEMA

R  Sites  R  DDP 150 mg/m² IA bolus/sodium thiosulfate IV
1. Oral Cavity  days 1, 8, 15, 22 with concomitant radiotherapy
E 2. Oropharynx  E 2 Gy once a day to 70 Gy total dose in 7 weeks
C 3. Hypopharynx  G
4. Larynx  O
R
I
S
D
T
E
R

Eligibility (See Section 3.0 for details)

- Squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx
- Stage IV disease comprised of only T4 N0-3 M0 lesions
- Karnofsky ≥ 60
- Age ≥ 18
- No distant metastases
- No prior chemotherapy or radiation therapy to the head or neck
- ANC ≥ 2000, platelets ≥ 100,000, and calculated or 24 hour creatinine clearance > 50
- Protocol treatment must begin ≤ 8 weeks after biopsy
- No prior (≤ 5 years) or concurrent malignancies
- No pregnant or lactating women
- Study-specific consent form

Required Sample Size: 60

Institution # ________________
1. Does the patient have a biopsy proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx?
2. Is this a recurrent tumor?
3. What is the T classification of the tumor?
4. Is there any evidence of distant metastatic disease?
5. Has the patient received any surgery, other than biopsy, to the study site?
6. Has the patient had any previous radiation therapy to the head or neck?
7. Has the patient received any previous chemotherapy for any reason?
8. Are lab tests within parameters specified in Section 3.1.7 and 3.2.3 of the protocol?
9. Has the patient had any other malignancies within the past five years other than basal or squamous cell of the skin?
10. Will the protocol treatment begin within 8 weeks of the biopsy?
11. What is the patient's age?
12. What is the patient's Karnofsky performance status?
13. Has the patient signed a study-specific consent form?

The following questions will be asked at registration:

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

(continued on next page)
RTOG 96-15  ELIGIBILITY CHECK (2/2/98)
Case # ________________  (page 2 of 2)

____________________  Patient's Name
____________________  Verifying Physician
____________________  Patient ID #
____________________  Referring Institution # (if different)
____________________  Medical Oncologist
____________________  Site of Primary Tumor
____________________  Birthdate
____________________  Sex
____________________  Race
____________________  Social Security Number
____________________  Zip Code (9 digit if available)
____________________  Method of Payment
____________________  Will any component of the patient’s care be given at a military or VA facility?
____________________  Treatment Start Date
____________________  Treatment Assignment

Completed by ______________________________ Date __________________________
1.0 INTRODUCTION

1.1 Head and Neck Cancer

1.1.1 Head and Neck Cancer

These malignancies represent a group of epidermoid tumors that arise from the epithelium lining the mouth, pharynx, and larynx. They are common, and it is estimated that in excess of 42,000 new head and neck cancers will be diagnosed in the United States in 1994. Three modalities of therapy have established roles in the treatment of carcinoma of the head and neck: chemotherapy, radiation therapy (XRT), and surgery. The choice of modality depends upon many factors such as the site and extent of the primary lesion, the likelihood of complete surgical resection, the presence of lymph node metastases, etc. In general, smaller lesions (stage T1-T2) are effectively treated either by surgical excision or irradiation whereas more advanced disease (stage III-IV) is best treated with combined surgery and XRT. However, even when surgery and XRT are used together, only a small fraction of patients with advanced regional disease are cured. The subsequent morbidity related to extensive surgical extirpations is also a major problem among survivors. Clearly there is a need to change the therapeutic strategy for patients with advanced head and neck cancer with more effective approaches employing non-surgical modalities.

1.1.2 Chemotherapy for Head and Neck Cancer

The drug cisplatin (DDP) has played a major role in the chemotherapy for some solid tumors. It has proven efficacy in the treatment of testicular carcinoma and as well has major effects on ovarian, breast, and head and neck carcinomas. In chemotherapy trials for head and neck tumors, the highest response rates seen to date have been with cisplatin-based combinations such as the Wayne State regimen and the Dana Farber program. A 93% overall response rate reported by the Wayne State group using cisplatin (100 mg/m^2) and 5 fluorouracil (5000 mg/m^2) every 3 weeks and the 65% complete response rate reported by the Dana Farber group using cisplatin (125 mg/m^2), 5 FU (4000 mg/m^2), and leucovorin (500 mg/m^2) every 3 weeks, are comparable with the high chemotherapy response rates seen for lymphoreticular malignancies and testicular carcinoma. However, as promising as this may appear, the improved survival rates achieved with chemotherapy for other chemosensitive organ specific malignancies have yet to be demonstrated in head and neck cancer.

1.1.3 DDP Resistance

Rapidly acquired drug resistance may be a major component contributing to the perplexing problem of failure to improve survival with chemotherapy in head and neck cancer. There is substantial laboratory and clinical evidence that tumors initially responding to cytotoxic agents become resistant, thus rendering the tumor non-responsive to subsequent drug exposures. Both in vitro and in vivo, resistance to DDP develops rapidly, and clinically significant degrees of resistance are present after as few as 4 exposures to the drug. In a 3-dimensional culture system, Graham et al. reported rapid acquisition of DDP-resistance not detected in monolayer cultures. This implies a physiologic mechanism of adaptation operative at the multicellular level as well as the mechanisms outlined by others. Human cell lines selected for DDP resistance in vitro demonstrate low level cross-resistance to XRT, and patients who have failed DDP chemotherapy are usually unresponsive to XRT and vice versa. The development of DDP resistance is thought to be due to the selection for and overgrowth of drug-resistant cells that arise through spontaneous somatic mutation. Determination of DDP sensitivity in vitro on tumor samples or cell lines obtained before and after treatment of patients with DDP indicate that the level of resistance that emerges in vivo is only modest, in the range of 1.5-3.0-fold. This is consistent with levels of resistance produced in experimental animals by clinically relevant DDP dose schedules. It is a general characteristic of resistance to DDP and the alkylating agents that it is very difficult to select for resistance levels of greater than 10-fold. In humans it is possible to double the therapeutic dose with increased but acceptable toxicity. Unfortunately, cisplatin doses above this are highly toxic to other organs, particularly the kidney. Using the pharmacokinetic trick of simultaneous intravenous infusion of a neutralizing agent and regional administration of cisplatin, it is possible to infuse doses of cisplatin directly into targeted regions of the head and neck approaching amounts that are 10 times the standard doses.

1.1.4 High DDP Dose Strategies

In cancer chemotherapeutics, there is evidence that drug resistance can be overcome by increasing drug dosage. However, a practical limitation to this strategy is toxicity to normal cells. Prior to the use of
hydration and diuresis, cisplatin doses exceeding 50 mg/m$^2$ frequently caused nephrotoxicity. Thus the results of early clinical trials with cisplatin using relatively low doses showed only modest response rates. After hydration was instituted, allowing cisplatin to be used in doses as high as 125 mg/m$^2$, better response rates were observed. Dose limiting toxicity beyond this amount continued to be renal and gastrointestinal (severe nausea and vomiting). To date, clinical trials using cisplatin in doses above this level have not been practical because of excessive toxicity.

1.1.5 High Dose Intensity Versus High Dose

Dose intensity is the amount of drug delivered per unit time expressed as mg/m$^2$/week, regardless of drug scheduling. Calculations are based on the amount of drug scheduled to be given (planned dose intensity) or the amount actually administered (received dose intensity). The latter reflects dose reductions and scheduling delays usually caused by toxicity.\(^{18}\) Dose intensity can be calculated for combination chemotherapy regimens as well, assuming that the drugs are equivalent in activity and that there are no significant interactions between the drugs. There is substantial evidence to indicate that cisplatin high dose intensity has beneficial effects, independent of dosage and total dose, on certain organ site-specific tumors. In 10 chemotherapy trials for ovarian cancer, a tumor known to be sensitive to cisplatin, Hryniuk retrospectively analyzed the response rate relative to planned dose intensity and found a clear-cut relationship when cisplatin was used either as a first line of treatment or as salvage therapy in patients failing alkylating agents.\(^{19}\) The slope of the response curve derived from this analysis was found to be sufficiently steep enough to indicate a 10% improvement in response for every increase of 4 mg/m$^2$/week of dose intensity. Furthermore, the dose response curve did not reach a plateau at 50 mg/m$^2$/week, indicating that supradose therapy would likely result in even higher response rates if this was possible. In a randomized trial for advanced testicular cancer, high dose intensity cisplatin therapy provided a better response rate and longer survival.\(^{20}\) Retrospective dose intensity measurements from trials of vincristine or mitoxantrone against breast cancer\(^{21,22}\) of etoposide against small cell lung cancer,\(^{23}\) of fluorouracil against colorectal cancer,\(^{24}\) have all shown positive correlations with response rate.

Although head and neck cancer is considered to be a DDP-responsive tumor, there have been few formal comparisons of high versus low dose IV regimens. In a study using high dose cisplatin (200 mg/m$^2$ q 4 weeks), a high response rate (72 %) was achieved in a group of 22 patients, 16 of whom had recurrent disease (16/22).\(^{25}\) Haines et al treated 51 patients (Stage III-IV disease) with 187.5-200 mg/m$^2$ of cisplatin and 60 U/m$^2$ of bleomycin q 4 weeks resulting in an overall response of 69 % (CR 24 %, PR 45 %).\(^{26}\) Kish et al. reported a 90 % response rate (CR 45 %) in 11 patients treated with cisplatin 150-200 mg/m$^2$ and 5-FU 1000 mg/m$^2$ q 3 weeks.\(^{27}\) These authors concluded that the higher dose schedule showed no added benefit for response whereas toxicity was greater. However, when evaluating these findings it is important to underscore the difference between high dose and high dose intensity. In all of these previous head and neck studies, the maximum dose intensity of the cisplatin schedule was 66.7 mg/m$^2$/week, equivalent to 2-3 fold the standard dose.

Clinically it is possible to deliver higher concentrations of DDP through pharmacologic and technical manipulations. One strategy is through intra-arterial (IA) delivery. The relative advantage ($R_t$) of IA infusion (relative to IV infusion of the same dose and schedule) is defined by the equation: $R_t = 1 + (\text{plasma clearance/tumor plasma flow})$. The greater the plasma clearance of the drug and the smaller the tumor plasma flow, the greater the advantage of injecting the drug by the IA route. All of the advantage of an IA infusion occurs with the first pass of the drug through the tumor bed, since once the drug has reached the venous circulation, subsequent tumor exposure due to recirculation will be equivalent whether the drug entered the systemic circulation via an IA or and IV injection.\(^{28}\) Figure 1 shows how for DDP $R_t$ varies as a function of tumor plasma flow and clearance. Note the extraordinarily high $R_t$ values that can be obtained with low flow arteries.
Figure 1. $R_t$ for IA DDP as a function of tumor plasma flow ($Q$). The 3 curves depict the relationship for clearances of 200, 1000, and 2500 ml/min.

In order to increase $R_t$, one must either decrease tumor plasma flow or increase plasma clearance.$^{29}$ The former can be accomplished by giving the IA injection into as small an artery as possible. In the case of DDP, the latter can be accomplished by using the neutralizing agent thiosulfate.$^{16}$ Thiosulfate reacts covalently with DDP to produce a complex that is still soluble but is totally devoid of either toxicity or antitumor activity.$^{20}$ When this neutralization occurs in the plasma it effectively increases the "clearance" of DDP. The extent of reaction is a function of the concentration of both agents.$^{20}$ Thiosulfate is not a very potent neutralizing agent, and molar thiosulfate/DDP ratios in excess of 10 are required before the reaction is fast enough to contribute significantly to the clearance of DDP.$^{31}$ Thiosulfate itself is very non-toxic and doses in excess of 72 g can be given acutely, which is well above that needed to provide effective DDP neutralization. Thiosulfate has been used extensively at the University of California, San Diego in conjunction with IP chemotherapy for ovarian carcinoma,$^{16,32}$ and pharmacokinetic studies have demonstrated an additional important feature of its use.$^{33}$ Thiosulfate is extensively (>25-fold) concentrated in the urine, and this provides excellent protection against DDP-induced nephrotoxicity$^{34}$ which is the dose-limiting toxicity of DDP. When the kidneys are protected against the toxicity of DDP, either with thiosulfate$^{35}$ or with large volumes of saline,$^{36}$ the rest of the body will tolerate a doubling of DDP exposure. Thus, the ability of thiosulfate to selectively protect the kidneys reduces the requirement for DDP neutralization by thiosulfate in the plasma.

The head and neck region is particularly well suited for regional chemotherapy. Most patients who present with advanced carcinomas of the upper aerodigestive tract do not have demonstrable distant metastases. Furthermore, approximately one half of the patients have large, bulky lesions confined to one anatomical site such as the tongue, pharyngeal wall, nasal cavity and paranasal sinuses or larynx. Although many of these patients may have metastases to the regional cervical lymph nodes, it is usually uncontrolled tumor within the primary site which presents an immediate threat to life. The blood supply to these tumors is primarily derived from branches of the external carotid artery. Significant technical advances in angiography now permit repeated safe super-selective micro-catheterization of the dominant nutrient artery using a coaxial approach, which serves to decrease blood flow and further increase $R_t$.$^{37}$

The feasibility of selective IA DDP infusion for head and neck tumors has been established, and a number of studies of IA DDP have been reported.$^{38-40}$ Too often the fundamental pharmacologic principles of IA therapy have been ignored and response rates and survival have not been convincingly superior to those obtained with IV DDP. Enthusiasm for IA chemotherapy in head and neck cancer has also been dampened by technical problems related to the placement of infusion catheters.$^{41}$ Most studies involved percutaneous catheterization of the external carotid with or without implantable infusion pumps and indwelling catheters, and this was problematic because of infection and thrombosis. Significant technical advances in vascular radiology techniques now permit safe repetitive super-selective catheterization of the smaller nutrient arteries of the tumor.$^{17,40,42}$
1.1.6 DDP-based Chemoradiation

There are many interactions between radiation and chemotherapeutic agents when used concomitantly that theoretically could be more active than the effects of sequential use. The mechanisms are based on differential activity of drug and radiation against specific tumor cell subpopulations such as hypoxic cells,\textsuperscript{43} pH differences in tumor cells,\textsuperscript{44} cell cycle phase distribution patterns,\textsuperscript{45} or mechanical factors such as reduced tumor bulk leading to improved drug delivery and reoxygenation of hypoxic cells. Other mechanisms may require direct interactions between the drug and radiotherapy and include inhibition of repair of radiation damage, cell cycle synchronization, or the elimination of inherent resistance to drug or radiation as single agents.\textsuperscript{46-48}

Cisplatin has been well studied as a radiation sensitizer. Zak and Drobnik first described enhanced radiation cytotoxicity in the presence of cisplatin in a murine tumor.\textsuperscript{49} It was later demonstrated that radiation cytotoxicity could be enhanced with cisplatin in mammalian cells.\textsuperscript{50} Other chemotherapy agents including 5-FU, mitomycin, and hydroxyurea are also capable of enhancing the cytotoxic effects of radiation.\textsuperscript{50} Several chemoradiation trials have been conducted in patients with previously untreated head and neck cancer using cisplatin alone;\textsuperscript{51-54} cisplatin\textsuperscript{55-58} and 5-FU; and other combinations.\textsuperscript{50} In 8 single institutional studies totaling 359 patients, the average complete response to concomitant therapy was 67.5\% and the range was 47-84\%.\textsuperscript{50-56, 57, 58} The highest response rate was 84\%, reported in 27 patients with nasopharyngeal carcinoma, a site-specific tumor with high sensitivity to radiotherapy.\textsuperscript{58} There have been very few randomized studies with DDP-based chemoradiation. An earlier Head and Neck Intergroup Trial comparing radiation therapy with radiation therapy and simultaneous low-dose DDP (20 mg/m\textsuperscript{2} weekly) in patients with inoperable tumors, failed to demonstrate a survival advantage.\textsuperscript{59} However, a more recent report with a higher cisplatin dose indicated an improved survival when cisplatin was added to postoperative radiation therapy in patients with resectable disease and extracapsular spread.\textsuperscript{60}

Despite the encouraging results of phase II and III trials, DDP-based chemoradiation protocols for advanced head and neck cancer are characteristically toxic. In 3 studies, the average rate of severe mucositis was 36.6\% (range: 28-53\%).\textsuperscript{51,52,55} Consequently, interruptions in radiation schedules and incomplete chemotherapy and/or radiotherapy are frequent. This inability to consistently administer the complete protocol to patients is deleterious to the overall goal of improving survival and underscores the importance for developing new approaches intended to circumvent this problem.

1.1.7 Preliminary Studies

At the University of California, San Diego, Cancer Center and subsequently at the University of Tennessee, Memphis, a new approach has been piloted to treat patients with advanced head and neck malignancies employing the pharmacologic principles and techniques described above. Capitalizing on the DDP-neutralizing agent sodium thiosulfate and its pharmacokinetic properties, we were able to deliver enormous concentrations of cisplatin directly into large head and neck tumors through a targeted IA approach. In a phase I study, we determined that cisplatin could be safely administered to patients with advanced and recurrent head and neck cancer at a dose intensity of 150 mg/m\textsuperscript{2}/week.\textsuperscript{61} This dose intensity is at least 5-fold greater than conventional cisplatin chemotherapy regimens. In a second phase, we have added a second therapeutic modality, concomitant radiotherapy, to the supradose cisplatin infusion strategy. In a phase II pilot study, referred to as the RADPLAT protocol, we have treated 29 patients between 1991-1993 with stage IV head and neck cancer at UCSD achieving a complete response rate in 95\% of patients.\textsuperscript{62, 63} The regimen (IA DDP 150/mg/m\textsuperscript{2} and concurrent sodium thiosulfate 9 gm IV bolus followed with 12 gm over 12 hours, weekly X 4; and concomitant irradiation 180-200 cGy/fraction X 35 over 7 weeks) was very well tolerated. An additional 60 patients were treated at UT Memphis between 1992-95 and a similar high response rate was found.\textsuperscript{64} The most recent anlaysis\textsuperscript{65} of 85 consecutive patients from both centers followed for 18-66 months (median 30 months), indicates a 5 year overall and disease-related survival of 40\% and 58\% respectively using Kaplan-Meier projected plots. The rate of disease control above the clavicle was 88\%. Twenty one patients have developed recurrent disease: 4 within the primary site; 3 within the regional lymphatics; and 14 in distant sites. The amount of mucositis toxicity was relatively low with 23 patients (28\%) having grade III and only 2 patients (2\%) having grade IV. There were 18 grade III/IV chemotoxicity events including 9 gastrointestinal, 7 hematologic, 7 neurologic toxicities and 1 vascular. Six of the 7 neurologic toxicities were CNS following an intra-arterial procedure. Three of these patients had a complete recovery whereas 3 had residual
deficits, none of which were severely incapacitating. 87% of patients were able to receive all 4 cycles of chemotherapy, whereas 11% received 3 cycles and 2% received less than 3.

The RADPLAT program uses a 4 min IA infusion of DDP in 1 mg/ml of normal saline, and concurrent IV bolus administration of thiosulfate at 9 g/m². During the brief interval of the rapid IA infusion, the tumor is exposed to an extraordinarily high DDP concentration (approximately 250 times higher than peak plasma concentration following standard IV dosing). Because of the very high DDP/thiosulfate concentration ratio in the tumor bed, and the slow rate of reaction between DDP and thiosulfate, little neutralization of DDP is expected in the tumor. However, once the DDP passes through the tumor and reaches the plasma, it is diluted into the blood volume, and its concentration falls relative to the high concentration of thiosulfate in the plasma. Thus neutralization is favored, and this effectively increases the plasma clearance. Assuming that the concentration of DDP in the tumor capillaries is one eighth of the infused concentration during the 4 min injection, and that the thiosulfate concentration in the tumor is equivalent to the peak plasma concentration produced by 9 g/m² injection (approx. 2.2 mM), the thiosulfate to DDP ratio in the tumor would be just 10:1, a ratio associated with a DDP neutralization half-life of 60 min. On the other hand, the ratio in the plasma shortly after injection would be expected to be >250:1, a value associated with a neutralization half-life of just 3.7 min. Thus, the tumor will receive a very brief exposure to an extremely high concentration of DDP, and the exposure of the systemic circulation to active DDP will be reduced.

Although initiated at UCSD by the principal investigator, the HIAPLAT concept has also been used by a Japanese group in the treatment of hepatocellular carcinomas. In this study DDP 120 mg/m² was given IA via the hepatic artery concurrently with thiosulfate 9 g/m² IV. It was possible to give 4 weekly doses with minimal systemic toxicity (480 mg/m²/mo), and 5/11 patients (45%) achieved a partial response.

2.0 OBJECTIVES
2.1 To determine the percentage of patients for whom a complete course of therapy can be administered using targeted supradose DDP chemoradiation (RADPLAT program) in a multi-institutional setting for the purpose of expanding the availability of the protocol to patients with advanced head and neck cancer.
2.2 To determine the partial and complete response rate of the RADPLAT program conducted in a multi-institutional setting under rigorous quality control guidelines.
2.3 To determine the incidence of adverse events
2.4 To define the rate of disease-free survival and overall survival.
2.5 To determine the incidence and pattern of recurrence
2.6 To document quality of life measured by disease-specific instruments

3.0 PATIENT SELECTION
3.1 Eligibility Criteria
3.1.1 Biopsy-proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
3.1.2 Stage IV disease comprised only of T4 N0-3, M0 lesions.
3.1.3 No previous radiation therapy to the head or neck; no prior chemotherapy for any reason.
3.1.4 No evidence of distant metastatic disease.
3.1.5 Age ≥ 18.
3.1.6 Karnofsky performance status of ≥ 60.
3.1.7 ANC ≥ 2000, platelets ≥ 100,000, calculated or 24 hour creatinine clearance > 50.
3.1.8 Signed study-specific informed consent form.
3.1.9 Protocol treatment must begin ≤ 8 weeks of biopsy.
3.1.10 No other malignancies (except basal or squamous cell of the skin) within the past five years.

3.2 Ineligibility Criteria (2/2/98)
3.2.1 Recurrent tumors
3.2.2 Previous or concurrent head and neck primaries.
3.2.3 Imaging studies performed > one month preregistration; laboratory studies > 2 weeks preregistration.
3.2.4 Prior surgery to study site other than biopsy.
3.2.5 Pregnant or lactating women.
3.2.6 Lip, nasopharynx, or salivary gland lesions.
3.2.7 Patients who, because of their medical status, are not candidates for proposed protocol treatment.
4.0 PRETREATMENT EVALUATIONS
4.1 Complete history and physical exam with an assessment of the patient's performance, weight and dental status. Presurgical diagrams of the primary and any nodal metastases must be submitted. Quality of Life assessments must be done prior to the start of any protocol treatment. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth when possible. If an extraction site in the mandible has to be included in the treatment field, 10-14 days should be allowed for healing before initiation of radiation therapy.

4.2 Laboratory Studies (within 2 weeks preregistration)
4.2.1 Hemoglobin, CBC, differential and platelets.
4.2.2 SGOT or SGPT, alkaline phosphatase, LDH, magnesium, BUN, creatinine/creatinine clearance.
4.2.3 Creatinine clearance may be determined by nomogram as long as the creatinine is not changing rapidly; otherwise determine 24 hour urine collection. Nomogram to calculate creatinine clearance is:

\[ \text{CrCL Male} = \frac{(140 - \text{age}) \times \text{wt. in kg}}{(\text{SCr})(72)} \]

\[ \text{CrCL Female} = 0.85 \times (\text{CrCl male}) \]

4.3 Required Imaging Studies (within one month preregistration)
4.3.1 Chest x-ray or thoracic CT.
4.3.2 CT of liver only if liver enzymes are elevated > 1.5 times normal.
4.3.3 Diagnostic CT or MRI of the head and neck.

4.4 Other Tests
4.4.1 Audiogram within one month preregistration

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. Patients may also be registered by computer modem, 24 hours a day, 7 days a week. 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
- Head and Neck Surgeon’s Name
- Medical Oncologist's Name
- Radiation Oncologist’s Name
- Interventional Radiologist’s Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY PARAMETERS
6.1 Physical Factors
6.1.1 Equipment: linear accelerators with appropriate photon and electron energies for supplemental boosting to the nodes or Cobalt 60 machines must be used.
6.1.2 Photon energies of 1.25 to 6 MV and/or appropriate electron energies for boosting the nodes are allowed. Photon energies > 6 MV may be utilized in dual energy beam arrangements only if one beam is ≤ 6 MV.
6.1.3 Minimum treatment distance must be ≥ 80 cm SSD (or SAD for isocentric techniques).

6.2 Localization Requirements
6.2.1 Simulation: Simulation of all fields is mandatory. Patients must be reproducibly immobilized. Radio-opaque markers should be used to delineate the extent of nodal disease and whenever possible, the primary tumor. The use of customized blocks to shape the treatment fields is highly recommended. Simulation films of each field, initial portal films, and the calculation form should be sent to RTOG Headquarters in the first week of therapy together with the treatment prescription for radiation therapy quality assurance review.
6.2.2 **Verification**: Beam portal films must be obtained for each field. Portal films must be repeated when any field adjustments are made and at least every two weeks during treatment. Portal films of each field must be submitted to RTOG Headquarters.

6.2.3 **Electron fields** utilized for supplemental nodal boosting must be verified by either portal verification, simulation or Polaroid films. Copies of the method selected and verification shall be submitted to RTOG Headquarters.

6.3 **Radiation Dose**

6.3.1 Treatment to the primary tumor and upper neck will be given at 2 Gy/fraction, once a day, five days a week to a total dose of 70 Gy/35 fractions/7 weeks. Fields must be reduced to exclude the spinal cord at 40 Gy with dose calculated in the central plane. The entire neck must be radiated to a dose of at least 50 Gy (even in N0 stage) at anatomical levels of lymph nodes usually 2-4 cm below the skin surface. Clinically positive neck nodes should also receive a dose of 70 Gy/35 fractions given continuously in 7 weeks. An electron beam should be used to supplement the dose to the posterior neck after the spinal cord has been shielded. Hence, the total dose to the primary tumor and clinically positive nodes will be 70 Gy/35 continuous fractions/7 weeks.

The anterior lower neck will be treated at 2 Gy/fraction once a day (3 cm depth) to a total dose of 50 Gy/25 continuous fractions in 5 weeks. The maximal dose to the spinal cord should not exceed 44 Gy as determined by a separate off axis point dose calculation.

6.4 **Target Volume Irradiation Portals and Radiation Doses**

6.4.1 A combination of lateral opposing fields are recommended for the treatment of the primary tumor site and upper neck. A single anterior A-P field will be used to treat the lower neck below the fields of the primary tumor/upper neck. When there are positive nodes in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive nodes. All fields must be treated on each treatment session. The upper and lower fields should be matched using a “three dimensional” technique (i.e., appropriate rotation of the treatment table and appropriate angulation of the collimator). However, if such a three dimensional match is not possible, the upper neck and supraclavicular fields may be abutted at the skin. In the latter case, a block $\geq 2$ cm should be placed either in the lower lateral position in the upper neck fields or in the midline or the anterior supraclavicular field (whichever is appropriate and does not block tumor) to shield the areas of potential overlap of diverging beams over the spinal cord.

6.4.2 **Upper Neck Primary Volume**

The primary treatment fields should encompass the primary tumor and/or suspected lymph node disease in the upper neck using a shrinking field technique as follows:

6.4.2.1 The initial target volume should include the primary tumor, positive nodes with a 3 cm margin and the next echelon of uninvolved lymphatic nodal drainage sites to a dose of 50 Gy. Included in the initial target volume is the first field reduction occurring off the spinal cord at 40 Gy.

6.4.2.2 The second field reduction will occur at 50 Gy with the new target volume encompassing only the primary tumor site and involved nodal disease with a 2.0 cm margin.

6.4.2.3 The third and final field reduction will occur at 60 Gy with the new target volume encompassing the primary tumor and known areas of nodal disease with a 1.0 cm margin.

6.4.2.4 As a general rule, both ipsilateral and contralateral posterior cervical nodal chain and the adjacent echelon of uninvolved lymphatic nodal drainage sites will be treated to a dose of 50 Gy.

6.4.3 **Lower Neck Volume**

6.4.3.1 A single anterior lower neck field will be used to treat the lower neck and the supraclavicular fossae. When there is (are) positive node(s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node(s).

6.4.3.2 The lower border of the lower neck field will be just below the clavicle with appropriate margins as used in Section 6.4.2 when there are positive nodes in the supraclavicular fossa. The lateral borders of the lower neck field will extend to the intersection of the sternocleidomastoid muscle and the clavicle.

6.4.3.3 For all patients with clinically positive nodes greater than 6 cm or with clinically positive supraclavicular nodes, a mediastinal T field may be used. The lateral limbs of the T field will extend below the clavicle with margins and the central portion of the field extends 5 cm more inferiorly to include the upper mediastinum.

6.4.4 **Boost Doses**
Additional boost doses may be given through reduced fields to persistent primary tumor and/or clinically positive nodes or to compensate for significant interruptions in radiation therapy treatments (i.e., \( \geq 57 \) elapsed days). The additional boost dose should not exceed 6.0 Gy.

### 6.5 Dose Calculations

#### 6.5.1 Photon Beam Portal Arrangements

The following portal arrangements require dose specifications as follows:

- **6.5.1.1** For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.
- **6.5.1.2** For arrangement of two 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 clinical target volume (Note: there may be several target volumes).
- **6.5.1.4** For a single anterior AP lower neck field, the prescribed dose will be delivered at a depth of 3.0 cm as determined by an off-axis "supraclavicular point". When AP/PA fields are used to treat the lower neck, the dose shall be prescribed at the mid-separation of the two beams along the central ray.
- **6.5.1.5** Complete isodose curves are required. Variation within the planning target volume is not to exceed +/-5% of the target dose. Lithium fluoride dosimetry may be used as a further check on tumor dose.

#### 6.5.2 Electron Beam Dose Specifications

- **6.5.2.1** The target dose shall be prescribed at the depth of maximum dose.
- **6.5.2.2** The energy and field size shall be chosen so that target volume is encompassed within 90% of the prescribed dose.

### 6.6 Time and Dose Modifications

Treatment interruptions are strongly discouraged. Treatment breaks must be clearly indicated in the treatment record when they occur. If the total treatment interruptions exceed five treatment days, the case will be considered a major protocol deviation.

### 6.7 Expected Side Effects and Toxicities

- **6.7.1** The maximum dose to the spinal cord is 44 Gy.
- **6.7.2** Reversible mucositis, epilation, and various degrees of skin reactions in the treatment area are expected. Side effects within 90 days of the treatment start should be graded according to the Acute Radiation Morbidity Scoring Scale. Radiation effects persisting beyond or appearing after the first 90 days are measured on the Late Effects Scale.
- **6.7.3** Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of either of these should be noted especially if supplemental feeding (tube) is required.
- **6.7.4** Late effects may include xerostomia and occasionally persistent dysphagia. Mandibular osteoradionecrosis will rarely occur if pretreatment dental evaluation is conducted prior to radiation therapy treatment. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth when possible. If an extraction site in the mandible has to be included in the field, 10 to 14 days should be allowed for healing before the initiation of radiation therapy treatments.

### 6.8 Protocol Compliance

<table>
<thead>
<tr>
<th>Target Volume (1.0 cm margin)</th>
<th>Target Volume (2.0 cm margin)</th>
<th>Target Volume (3.0 cm margin)</th>
<th>Total Dose Midplane Isocenter</th>
<th>Elapsed Days</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 0.5 cm (1.0 - 1.5 cm)</td>
<td>± 0.5 cm (1.5 - 2.5)</td>
<td>± 0.5 cm (2.5 - 3.5)</td>
<td>≤ 5 %</td>
<td>47-56</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>1.0 - 2.0 cm</td>
<td>± 1.0 cm (1.0 - 3.0)</td>
<td>± 1.0 cm (2.0 - 4.0)</td>
<td>&gt; 5 - 10%</td>
<td>57-63</td>
<td>Variation, Acceptable</td>
</tr>
<tr>
<td>&lt; 1.0 cm or &gt; 2.0 cm</td>
<td>&gt; ± 1.0 cm (&lt; 1.0 or &gt; 3.0)</td>
<td>&gt; ± 1.0 cm (&lt; 2.0 or &gt; 4.0)</td>
<td>&gt; 10%</td>
<td>≥ 64</td>
<td>Deviation, Unacceptable</td>
</tr>
</tbody>
</table>

### 7.0 DRUG THERAPY

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

#### 7.1 Treatment Plan

- **7.1.1** All patients will receive four courses of cisplatin one week apart on days 1, 8, 15, and 22 concurrent with radiotherapy.
One course of chemotherapy will consist of intra-arterial cisplatin \((150\text{mg/m}^2)\) given over 3-5 minutes, maximum dose for each course is 300 mg.

Chemotherapy will be repeated every week on days 1, 8, 15 and 22 with RT (provided there is recovery from toxicity) for a total of four courses.

### Cisplatin

**Formulation**: Vial containing 10 mg, 50 mg, or 100 mg, cisplatin with 10 mg and 9 mg sodium chloride.

**Storage**: Refrigeration.

**Preparation**: Vial diluted to concentration of 1 mg/ml of appropriate solution according to pharmaceutical company directions.

**Administration**: Drug should be given immediately after preparation.

**Pharmacology and Pharmokinetics**: The dominant mode of action appears to be the inhibition of incorporation of DNA precursors although protein and RNA synthesis are also inhibited. Cross-linking of DNA has also been shown. Plasma levels of Cisplatin decay in a biphasic mode with an initial half-life of 25-49 minutes and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 45% of the radioactivity excreted in the first five days. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and standard alkylating agents. Also, there appears to be potentiation of other anti-tumor agents by cisplatin in tissue culture, animal tumor models and in early human work. Studies have shown that cisplatin has no cell-cycle dependency and that cytotoxicity of this agent is similar in all stages of the cell cycle.

**Toxicity**: Toxicity includes nausea, vomiting, renal toxicity (with elevation of BUN, creatinine and impairment of endogenous creatinine clearance), ototoxicity (with hearing loss which initially is in the high frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with an abnormal or obstructed urinary excretory tract. Myelosuppression, often with delayed erythrosuppression, is expected. The nadir white cell and platelet counts occur at about two weeks with recovery generally at about three weeks after initiation of therapy. Peripheral neuropathy has been reported in a few cases where long-term cisplatin was used in combination with other forms of therapy. Paralysis, myopathy, weakness, and seizures may occur.

**Supplier**: Commercially available

### Administration Guidelines (5/12/98)

The below mentioned pre-and post-hydrations are recommended; hydration may be administered according to investigator option. Document infusion start and stop times. Times must also be recorded on the Data Forms.

**Dexamethasone**: 4mg IV or P.O. will be started the evening prior to treatment, and continued every 6 hours until the morning following the procedure. No taper is necessary. The dexamethasone has been found to decrease the incidence and severity of facial edema after the cisplatin infusion.

**Pre-treatment IV Hydration**: One liter of D5 ½ NS containing 20 mEq KCl and 2 gm MgSO4 over the two hours immediately prior to treatment.

**Cisplatin**: The cisplatin dose is to be dissolved in a solution of 1 mg/ml normal saline and administered intra-arterially through an automated pump at the rate of 1-2 ml/second.

**Thiosulfate**: 9 g/m² in 200 ml distilled water is to be given IV push over 15-20 minutes, concurrently with IA cisplatin. This is to be followed by 12 g/m² thiosulfate IV continuous infusion over 6 hours (the 12 g/m² should be dissolved in 1 liter of distilled water and infused at 167 ml/hr).

**Post-treatment Hydration**: Following completion of the sodium thiosulfate infusion, the patient should receive 1 liter D5 ½ NS containing 20 Meq KCl and 2 gm MgSO4 over the next 6 hours (167 ml/hr).

**Antiemetics** may be administered according to investigator option.

**Accurate measurement of fluid intake and output after cisplatin administration is necessary, with additional i.v. fluid to match any emesis or excess urinary output.**

**Dose Modifications** (labs may be obtained day before cisplatin treatment day)

**Neutropenia** may occur. If on the day of scheduled treatment with cisplatin, the absolute neutrophil count (ANC) is < 1800, hold treatment until ANC ≥ 1800 then treat at 100% dose.

**Thrombocytopenia** may occur. If on the day of scheduled treatment with cisplatin the platelet count is < 75,000 hold treatment until platelets are ≥ 75,000 then treat at 100% dose.
7.4.3 Neurotoxicity: If any signs of paralysis, moderate myopathy, moderate weakness, seizure or peripheral neuropathy (≥ grade 2) occur, withhold treatment and contact Dr. Robbins or Dr. Christian. Document contact on Data Forms.

7.4.4 Renal Toxicity: Cisplatin should be administered on the scheduled day of treatment using the following guidelines.  
Creatinine ≤ 1.2 and/or creatinine clearance ≥ 50 ml/min: DDP 150/mg/m².  
Creatinine > 1.2 and creatinine clearance < 50 ml/min: withhold DDP until creatinine ≤ 1.2 and creatinine clearance > 50 ml/min.  
* If creatinine is > 1.2, creatinine clearance (calculated or 24 hour) must be done in order to determine whether to administer DDP or delay infusion.

7.4.5 If cisplatin needs to be held for > 2 weeks, the cisplatin should be discontinued and radiation therapy continued per protocol.

7.4.6 If radiation therapy should finish before all four courses of cisplatin are given, the remaining courses of cisplatin should not be given.

7.4.7 If there is progression of disease during study treatment, protocol treatment should be discontinued and patient should have surgery if disease is resectable. See Section 8.0.

7.5 Adverse Drug Reaction Reporting

7.5.1 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, and RTOG Data Management within ten working days:

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

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

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

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

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

Investigational Drug Branch  
P.O. Box 30012  
Bethesda, MD 20824  
(301) 230-230, available 24 hours  
(fax) (301) 230-0159

Also send a copy to RTOG Headquarters.

7.5.3 Death from any cause while the patient is receiving protocol treatment, or up to 30 days after the last protocol treatment, as well as any death related to protocol treatment, must be reported to RTOG Headquarters within ten days of discovery.

8.0 SURGERY

8.1 Primary Site

Patients who have persistent disease in the primary site at 8 weeks after the end of XRT, will undergo salvage surgery if the lesion is considered to be resectable.

8.2 Neck Dissection

All patients with clinical or radiological evidence of persistent nodal disease at 8 weeks will undergo salvage neck dissection. The type of neck dissection performed (radical, modified radical, selective) will be at the discretion of the surgeon. Patients who presented with N2-3 disease who have no clinical evidence of residual adenopathy following completion of radiotherapy and chemotherapy will not undergo neck dissection.

8.3 Operative Report

The dictated operative report must accurately and completely describe the precise location and extent of the primary lesion and clinical metastases including level of nodes resected and number positive at each level. An assessment of the completeness of the resection and the results of intraoperative frozen sections should
be included. A copy of the operative report must be submitted with the post-operative form. In addition, some judgment as to the extent and the amount of gross tumor left behind must be made.

9.0 INTERVENTIONAL RADIOLOGY

9.1 Intra-Arterial Catheterization

9.1.1 The procedure will be performed by an interventional radiologist in the angiography suite of the participating hospital. The initial procedure will be done on day 1 immediately following the first fractionation of radiotherapy.

9.1.2 The interventionalist should review the patient's record for history of previous strokes and/or carotid artery disease. History of other vascular disease, graft surgery, and contrast allergy should also be reviewed.

9.1.3 A focused review of the records should be done for serum creatinine, creatinine clearance, CBC, and coagulation values. Physical evaluation will include femoral pulses and carotid bruit.

9.1.4 Review patient's CT and/or MRI to delineate vascular territory of involvement. Priority for selection of targeted vessels should be based on the location of the primary lesion and not the nodal disease. Determine whether the infusion should be unilateral versus bilateral and estimate the proportion of the infusate to be delivered based on the volume of disease supplied through each of the targeted arteries.

9.2 Angiography

9.2.1 Sedation: use routine medications (e.g. Versed, fentanyl, stadol, etc)

9.2.2 Transfemoral Cervical Carotid Arteriogram: 4 vessel study. Perform AP and lateral views to evaluate vascular anatomy and atherosclerotic disease (anticoagulate if significant)

9.2.3 Catheters:
- Selective: 5F; Headhunter; Newton: Straight with sideholes
- Microcatheters: tracker-18; 325; Venture II

9.2.4 Selective Embolization:
- evaluate size of vessels prior to embolization
- avoid direct infusion of superficial temporal artery to minimize alopecia
- consider embolizing occipital and superficial temporal arteries to improve distribution to target vessels

9.2.5 Cisplatin Infusion Rates:
- test infusion with contrast prior to chemoinfusion
- test for 3 second infusion (diastole-systole)
- rates routinely 3-4 cc/sec ECA
- super-selective infusions @ 0.5-1 cc/sec
- IV thiosulfate infused throughout IA infusion and started 2-3 min prior to chemoinfusion

9.2.6 Spasm:
- infusion rates change with degree of spasm
- will need to reevaluate rates at each treatment cycle
- nitropaste 1/2-1" to CW to decrease spasm
- spasm increases with infusion cycles and total radiation

9.2.7 Post-Infusion Evaluation:
- femoral puncture site
- lab values
- associated angiographic complications

10.0 PATHOLOGY

A central pathology review is not planned for this study.

11.0 PATIENT ASSESSMENTS (5/12/98)

11.1 Study Parameters

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pre Tx</th>
<th>1 Wk</th>
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<th>3 Wks</th>
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<td>Tumor Measurement (by ENT)</td>
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<tr>
<td>Toxicity Notation</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
CBC and differential, platelets   X  X  X  X  X^e
Hemoglobin   X
Audiogram   X
Dental Evaluation   X
Pregnancy Test   X^d
Assessment  Pre Tx  1 Wk  2 Wks  3 Wks  4 Wks  13 Wks  F/U
Biopsy   X
BUN, Creatinine^a   X  X  X  X  X
SGOT or SGPT, Alkaline Phos, Magnesium, Bilirubin, LDH^b   X
CT or MRI of H&N   X
CXR or thoracic CT   X  X^c
Quality of Life   X  X

a. Or creatinine clearance (24 hour or calculated)
b. CT of liver if elevated > 1.5 x normal.
c. Chest X-ray/Thoracic CT will be performed q 6 months through year 3.
d. As applicable.
e. To continue during RT.

11.2 Follow-up assessments are to be reported at 13 weeks, then every three months during the first year following treatment, then every 6 months for the next two years, and annually after the third year. The following will be evaluated:

11.2.1 Primary tumor site
11.2.2 Regional nodes
11.2.3 Metastatic visceral spread
11.2.4 Treatment complications
11.2.5 Confirmation by radiographs or biopsy is preferable and agreement by two physicians of different specialties is advisable.

11.3 Additional treatment should be reported and details of management are at the discretion of physicians managing the case.

11.4 Quality of Life Assessments

11.4.1 Three questionnaires will be used. Among the three questionnaires, four domains of QOL and ten symptom-specific items will be measured and evaluated.

11.4.1.1 The first questionnaire developed by Cellâ€™s is the Functional Assessment of Cancer Therapy for Head and Neck (FACT-H&N). The F.A.C.T.-H&N (Version 2-modified) is a 43 item inventory. Of the 43 items, 28 are summarized into five subtest scores representing the different domains of QOL being measured (physical, social, emotional well-being, contentment and relationship with doctor). In addition, five of the 43 items ask patients to rate the importance of each subtest with respect to their QOL. The remaining nine items under the sixth subtest (Additional Concerns) are site specific for head and neck cancer patients (eg., swallowing, dry mouth, etc.). The inventory produces five scores, one for each domain (subtest) and one total score incorporating the site specific items.

11.4.1.2 The second questionnaire was developed by Dr. Weymüller et al. of the University of Washington, Seattle (UW). This questionnaire like Cellâ€™s was designed to be specific to head and neck patients. The UW QOL questionnaire was tested on 75 H & N patients. The questionnaire was compared to two established tools, the Karnofsky, and the Sickness Impact Profile (SIP), for validity, acceptability, reliability and responsiveness. The overall results demonstrated the UW H & N tool to be equivalent to the Karnofsky and SIP for validity, reliability, responsiveness, and was the preferred test format for 97% of the tested patients.

The selection of the UW QOL tool is to complement Dr. Cella’s FACT H&N, particularly in reference to specific symptom-related effects (saliva, eating, taste and speech) of each treatment modalities. The scale consists of ten symptom-specific categories each describing important daily living dysfunctions/limitations of H & N cancer or its treatments. Each category has five possible item choices. The highest level or “normal” is scored 100 points, while the lowest (or greatest) dysfunction is scored 0 points. The options in between are in multiples of 25. The patient is asked to
circle the statement which best describes their current status. The total score is 1000 points. The total score is then divided by 10 to obtain a final range of 0-100. Thus, the higher the score the greater the QOL, and conversely, the lower score demonstrates a decreased QOL.

11.4.1.3 The Mini Mental Status Exam will be used to assess competence of the subject. This is a standardized tool to assess mental status at the time of sickness and at protocol entry. It will be given at the pretreatment interview by the research associate or designee.

11.4.2 The data manager will read the written instruction to patients and inform them of the frequency with which the questionnaire(s) will be administered. Data managers, family members or significant other may assist the patients in completing the questionnaire(s) being careful not to influence their responses. Any assistance given should be noted on the front of the questionnaire(s) by data managers (ie., "pt. too weak, I read and circled responses"). Review all completed questionnaire(s) at the time of administration for completeness and ensure that each item has only one response. Every attempt should be made to see that the QOL questionnaire(s) are obtained according to schedule. This may require obtaining the information by phone or mail. It is critical that the questionnaire(s) following the treatment modalities be obtained in order to assess acute symptomatology. It is anticipated that the semi-annual follow-ups will become more difficult to obtain as length of time following treatment increases. However, these measurements are very critical as they will provide "change over time" end points that are critical to the analysis of this QOL study.

11.4.3 Both questionnaires are used in the current intergroup protocol that tests laryngeal preservation, RTOG 91-11, thus it may be possible to make QOL comparisons between protocols.

12.0 DATA COLLECTION (2/2/98)
(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 1 week of study entry</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td>Within 2 wks of study entry</td>
</tr>
<tr>
<td>Staging Diagrams (I6, I7)</td>
<td></td>
</tr>
<tr>
<td>Pre-Rx FACT: H&amp;N Form (FA)</td>
<td></td>
</tr>
<tr>
<td>Pre-Rx Symptom Scale (PQ)</td>
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</tr>
<tr>
<td>Diagnostic Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Preliminary Dosimetry Information: Pre-RX Mini Mental Status Exam (MS)</td>
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</tr>
<tr>
<td>RT Prescription (Protocol Treatment Form) (T2)</td>
<td>Within 1 week of start of RT</td>
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<tr>
<td>Films (simulation and portal) (T3)</td>
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<tr>
<td>Calculations (T4)</td>
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</tr>
<tr>
<td>Interim Report (F9)</td>
<td>Within 1 week of each chemotherapy cycle</td>
</tr>
<tr>
<td>Radiotherapy Form (T1)</td>
<td>Within 1 week of RT end</td>
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<tr>
<td>Final Dosimetry Information:</td>
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<tr>
<td>Daily Treatment Record (T5)</td>
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<tr>
<td>Isodose Distribution (T6)</td>
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<tr>
<td>Boost Films (simulation and portal) (T8)</td>
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<tr>
<td>Follow-up Form (F1)</td>
<td>At 13 weeks, then every 3 months through year 1; then q 6 mos through year 3; yearly thereafter, and at progression/relapse and at death (F1 only)</td>
</tr>
<tr>
<td>H&amp;N Form (QF)</td>
<td></td>
</tr>
<tr>
<td>Symptom Scale Followup (QL)</td>
<td></td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Introduction (2/2/98)

The trial is designed to determine if the treatment program can be successfully performed by other institutions. The treatment delivery for a particular patient will be classified as “successful” if the individual received at least three of the four weekly IA courses of chemotherapy, radiation to the primary within 5% of the prescribed total dose, and the elapsed treatment time was not prolonged more than seven days. In the UCSD pilot study of 29 patients, 27 (93%) had “successfully” completed the protocol treatment. So a 90% successful completion rate is hypothesized for this protocol.

U. T. Memphis and UCSD oncology programs have previously utilized the protocol treatment whereas other institutions have not. The former two institutions will be referred as "experienced" institutions and others as "non-experienced". As to the question of transporting this treatment to the "non-experienced" institutions, a subset analysis of treatment delivery will be done for them. Recognizing that there may be a "learning curve" phenomenon at these institutions, the first two patients receiving the treatment will be initially excluded from the initial estimate for successful treatment delivery. A secondary estimate will be done on all the patients treated at these new institutions. If the initial estimate for successful treatment delivery of the patients in the “in-experienced” institutions is 80% or higher, then the treatment program will be considered transportable.

As it is secondary objective, the trial will also confirm the high complete response rate observed in the pilot study and its toxicity rate. In the 24 patients evaluable for response, 23 (96%) achieved a complete response as confirmed by biopsy. The acute toxicity rate of grade 4 (life-threatening) and grade 5 (fatal) will also be used as an indicator of patient tolerance. Grade III-IV mucosal toxicity occurred in 12/29 (41%) patients but none of them required breaks in their radiotherapy because of toxicity.

13.2 Sample Size Considerations (2/2/98)

A total of sixty patients will be accrued to the trial, ideally equally from each institution. It is expected to take one year to accrue them. About forty patients patients will be entered from the "non-experienced" institution to assess treatment transportability. The initial estimate will be based on all patients entered from these institutions excluding the first two patients from each institution. So with a sample size of 32 (= 40 - 8) evaluable patients, we would have a 97% one sided confidence interval with a lower bound of 80% around a hypothesized 90% rate for successful treatment delivery. In other words, we have a 3% chance of observing an 80% or less rate for treatment delivery if the successful delivery rate is truly 90%. The secondary estimate will be based on all patients from the “in-experienced” institutions thus increasing the sample size to 40 patients. With that sample size, we have a 98% one sided confidence interval with a lower bound of 80% around a hypothesized 90% rate.

All eligible patients who start the protocol treatment will be evaluable for response analysis. Only patients achieving a complete response at three months post completion of treatment will be considered a success. All other patients will be classified as a failure. With the sample size of 60 patients, the standard error associated with the estimated rates for complete response would be, at most, 6.5% assuming binomial distribution.

Toxicities occurring within the first 90 days from the start of therapy will be considered to be acute. All eligible patients who start the protocol treatment will be evaluable for toxicity analysis. Of particular interest are grade 4 (life threatening) and grade 5 (fatal) toxicities. With a sample size of 60, the probability of observing severe toxicity is 0.70, 0.95 and 0.998 respectively for true complication rates of 0.02, 0.05, and 0.10.
All eligible patients who start the protocol treatment will be evaluable for survival analysis. Death from any cause will be considered a failure. With the sample size of 60 patients, the standard error associated with the estimated rates for survival at two years would be at most 6.5% assuming binomial distribution.

The sample size of 60 patients will provide statistical power of 99% and a significance level of 95% for detecting a correlation of r= 0.5 or greater between the average change in any quality of life domain and significant treatment morbidity. This level of power and significance are the same for the correlation between quality of life and disease status. If compliance is less than 100%, then there will be a reduction in statistical power. If at least 30 participate, then the power will be at least 82% to detect the above specified level of correlation.

### 13.5 Analyses Plans

#### 13.5.1 Interim Analyses

Interim reports with statistical analyses are prepared every 6 months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

a. the patient accrual rate with a projected completion date for the accrual phase;

b. the quality of submitted data with respect to timeliness, completeness, and accuracy;

c. compliance rate of treatment delivery with respect to the protocol prescription;

d. the frequencies and severity of the toxicities.

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

The final analysis will be performed one year after the last patient has been entered in the study. It will include:

a. tabulation of all cases entered, and any excluded from the analyses with reasons for exclusion;

b. institutional accrual;

c. distribution of the important prognostic baseline variables

d. observed results with respect to treatment delivery, complete response rate, toxicity, and survival. These endpoint points will be estimated with binomial distribution along with a two sided 95% confidence interval. If the estimated rate of “successful” treatment delivery is equal or greater than .80, then the treatment program is established as transportable. Further subgroup analysis would not be undertaken because of the small sizes involved in each subgroup.

e. QOL analyses (The Fact-H and N results will be analyzed both as one total score and subscores. They will also be correlated with toxicity and response.)

### 13.6 Inclusion of Women and Minorities

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into inoperable head and neck trials failed to show any treatment interaction with gender. No information about race was collected in the RTOG Registry study and treatment studies prior to 1990. The SEER data suggest a difference in outcome by race. In a retrospective analysis, no difference in outcome by race for patients treated for laryngeal cancer at a single institution was reported. The RTOG Special Population Committee is unaware of any other published data on patients with clinically localized head and neck cancer. Since there are no publications found to support a possible interaction between different radiation therapy schedule and either gender or race, the sample size will remain the same. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

In an ongoing 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 are male and 20% female. Then we have a 95% one sided confidence interval with a lower bound of .80 around the hypothesized 90% “successful” treatment delivery rate for male and with a lower bound of .65 around the hypothesized 90% delivery rate for female.

In an ongoing study RTOG 90-03, 73% (754/1038) of the patients were white and 27% were non-whites. 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 .78 around the hypothesized 90% delivery rate for male and with a lower bound of .52 around the hypothesized 90% delivery rate for female.
REFERENCES


11. Skipper, H.E. A review and more quantitative analysis of the results of many internally controlled combination chemotherapy trials carried out over the past 15 years (L1210 leukemia and P388 leukemia). Southern Research Inst., monograph #2, 1979.


APPENDIX I

RTOG 96-15

Phase II Multi-Institutional Trial Of Targeted Supradose Cisplatin Chemoradiation
for Stage IV Squamous Cell Carcinoma
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. 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

My physicians are conducting a research study to find out whether the chemotherapy administered directly into the artery
feeding my head and neck cancer may improve the survival and disease control. They will enter six patients from this
institution. I have been asked to take part because I have an advanced head and neck cancer, and the chances for successful
treatment by usual methods are only fair.

DESCRIPTION OF PROCEDURES

If I agree to be in this study the following will take place:

1. I will be admitted to the hospital and, under local anesthesia, a catheter (plastic tube) will be inserted into the artery in my
groin. It will be directed upwards into the head and neck region in order to study the blood supply to my cancer.

2. Cisplatin will be quickly put through the catheter in order to saturate the tumor with the drug. Sodium thiosulfate will also
be given intravenously with and after the cisplatin. Following this, the catheter will be removed. I will be discharged from
the hospital approximately two days later.

3. This treatment will be repeated every week and continued only as long as it appears to be benefiting me. There will be a
maximum of four treatments.

4. Beginning on the same day I receive my first dose of cisplatin, I will also receive daily treatments of radiation. The area of
radiation will cover the cancer and its pathways of spread to the head and neck region. There will be one daily treatment,
a few minutes each, for 7 weeks (Monday to Friday).

5. A CT and/or MRI examination will be done before treatment and will be repeated after I finish my treatment.

6. A small blood specimen will be taken each week prior to receiving chemotherapy to check on my blood counts.

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. Participation in
this study may involve some added risks or discomforts. These include:

1. Blood clots of the arteries in the neck or head region, which may cause stroke or other serious injuries including death.

2. The puncture site in the groin may cause a hematoma (painful lump of blood in the tissue) during or after the procedure.
   This risk is slightly higher when the same artery is punctured 2 weeks later. The placement of the catheter during this
   procedure may also cause my blood vessels to become blocked (thrombosis), plaque on the artery walls to become
dislocated, and spasm of the arteries in the upper part of the head or neck. Such events may cause a stroke, nerve damage in the neck or head region, and death of soft tissue.

3. Cisplatin (Platinol) may cause nausea, vomiting, weakness, hearing loss or ringing of the ears. 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 (sweating, difficulty breathing, and rapid heart beat), and numbness and tingling in fingers and toes. Rarely, the drug causes restlessness, facial swelling, loss of coordination, involuntary movement, liver damage, loss of taste, spasm, muscle cramps, or acute leukemia.

4. There are no risks associated with the use of sodium thiosulfate.

5. The radiotherapy will cause inflammation in my mouth and throat (mucositis) which if severe, may result in difficulty swallowing. This will heal upon completion of therapy. I may also have some excessive redness overlying the skin of my neck and if severe, may cause the tissue to breakdown. This will go away following completion of therapy. However, firmness of the tissue in the field of radiation sometimes develops and may be permanent.

My physician will be checking me closely to see if any of these side effects are occurring. Routine tests will be done 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.

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.

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 investigator in charge at ____________________________. In addition, I may contact ____________________________ at ____________________________ 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.

__________________________
Patient Signature *(or Legal Representative)*

__________________________
Date
# APPENDIX II

**KARNOFSKY PERFORMANCE SCALE**

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

Eligible Patients & 1988 American Joint Commission AJC Staging

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Tumor that cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>TIS</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Greatest diameter of primary tumor ≤ 2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>Greatest diameter of primary tumor &gt; 2 - ≤ 4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Greatest diameter of primary tumor more than 4 cm</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures (e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin).</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Tumor that cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>TIS</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 2 cm or less in greatest diameter</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor greater than 2 cm, but not greater than 4 cm in greatest diameter</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor greater than 4 cm in greatest diameter</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures (e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin).</td>
</tr>
</tbody>
</table>

**Nasopharynx (Ineligible for this study)**

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>TIS</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to one subsite of nasopharynx</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades more than one subsite of nasopharynx</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades nasal cavity and/or oropharynx</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades nasal cavity and/or cranial nerve(s)</td>
</tr>
</tbody>
</table>
**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  
Epiglottis (both lingual and laryngeal aspects)  
Suprahyoid epiglottis  
Infrahyoid epiglottis  
Aryepiglottic folds  

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 commissures  

TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
TIS Carcinoma in situ  
T1 Tumor limited to vocal cord(s) (may involve anterior or posterior commissures) with normal mobility  
T1a Tumor limited to one vocal cord  
T1b Tumor involves both vocal cords  
T2 Tumor extends to supraglottis and/or subglottis and or with impaired vocal cord mobility  
T3 Tumor limited to the larynx with vocal cord fixation  
T4 Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., oropharynx, 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 subgottis  
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. oropharynx, soft tissues of the neck)

**Nodal Involvement (N)**

NX  Nodes cannot be assessed  
N0  No clinically positive node  
N1  Single clinically positive ipsilateral node 3 cm or less in diameter.  
N2  Single clinically positive ipsilateral node more than 3 cm, but not more than 6 cm in diameter  
or multiple clinically positive ipsilateral or bilateral or contralateral nodes, none more than 6 cm in diameter.  
N2a  Single clinically positive ipsilateral node more than 3 cm, but not more than 6 cm in diameter.  
N2b  Multiple clinically positive ipsilateral nodes, none more than 6 cm in diameter.  
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 supersede the General Guidelines.**

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

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

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

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must 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.
  
- 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 alvelor 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 molded 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.