RADIATION THERAPY ONCOLOGY GROUP

RTOG H-0024

PHASE II TRIAL OF EARLY POSTOPERATIVE PACLITAXEL FOLLOWED BY PACLITAXEL AND CISPLATIN CONCURRENT WITH RADIATION THERAPY FOR RESECTED, HIGH-RISK SQUAMOUS CARCINOMA OF THE HEAD AND NECK

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Surgical Status at Study Entry***
- E 1. Surgery completed prior to registration
- G
- I 2. Surgery to be performed after registration
- T
- R

Local Therapy***
- None
- XRT*
- XRT
- XRT
- XRT
- XRT

Paclitaxel (mg/m²)**
- 80
- 80
- 80
- None
- None
- None
- 30
- 30
- 30

Cisplatin (mg/m²)**
- None
- None
- None
- None
- None
- None
- 20
- 20
- 20

* If the start of radiation therapy is scheduled to be on a Friday, weekend, or holiday, treatment should be deferred to the next business day.

** If one of the 3 scheduled early post-op chemotherapy treatment days falls on a weekend or holiday, treatment may be deferred to the next business day. Concurrent paclitaxel and cisplatin should be given on Monday, Tuesday, Wednesday, if possible. Thursday or Friday is less desirable as the goal is to maximize drug-XRT interaction. The schedule must be kept so that patients receive all 3 cycles of paclitaxel/cisplatin concurrent with XRT.

*** Patients may be registered either preoperatively if the patient has clinically evident advanced neck disease, or after surgery (See Section 3.1). Protocol chemotherapy must begin 7-14 days from date of surgery.

Eligibility: (See Section 3.0 for details)
- Any stage III or IV squamous carcinoma of the head and neck with gross total resection requiring postoperative XRT for high-risk factors (See Section 3.1.1.1) OR planned surgery (See Section 3.1.1.2)
- No evidence of distant metastases
- Zubrod Score 0 and 1
- WBC ≥ 3,000; platelets ≥ 100,000
- Creatinine, total bilirubin and AST or ALT ≤ 1.5 X institutional upper limit of normal
- Adequate nutritional status, as determined by the treating physicians in conjunction with consultation with clinical nutritionists as indicated
- No prior chemotherapy or head and neck irradiation
- No prior malignancy unless disease free for ≥ 3 years
- No active cardiac disease
- No history of severe COPD requiring ≥ 3 hospitalizations over past year
- No pregnant or nursing women due to the embryotoxic effects of chemotherapy
- No pre-existing ≥ grade 2 peripheral neurotoxicity

Required Sample Size: 60
1. What is the stage?

2. Has histologically proven squamous cell cancer of the oral cavity, oropharynx, larynx or hypopharynx been confirmed?

3. Is there a complete gross total resection?
   - (Y) If yes, are one of the risk factors listed in Section 3.1.1.1 present?

4. Is the complete gross total resection planned within the next 14 days (for pre-op registrations)?

5. Is there evidence of distant metastasis?

6. What is the Zubrod score?

7. Are lab values within ranges specified in Section 3.1.5 and 3.1.6?

8. Have all pre-treatment evaluations been performed within the timelines specified in Section 4.1?

9. Does the patient have a significant wound infection, fistula, or major wound dehiscence?

10. Any prior head and neck irradiation or chemotherapy?
    - (Y) If yes, is it within the parameters of Section 3.2.7?

11. Does the patient have unstable angina or any other cardiac conditions listed under Section 3.2.8 and 3.2.9?

12. Was the patient hospitalized three or more times for COPD complications?

13. If female, is patient non-pregnant and non-lactating?

14. Does the patient have ≥ grade 2 peripheral toxicity?

(continued on next page)
The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?
2. Has the Eligibility Checklist (above) been completed? *(Y)*
3. Is the patient eligible for this study? *(Y)*
4. Date the study-specific Consent Form was signed? *(must be prior to study entry)*
5. Patient’s Name
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
11. Gender
12. Patient’s Country of Residence
13. Zip Code
14. Patient’s Insurance Status
15. Will any component of the patient’s care be given at a military or VA facility? *(Y/N)*
16. Has the patient already undergone definitive surgery? *(Y/N)*
   ______ If yes, provide date of surgery ________________
   ____________________
   Provide chemotherapy start date
   ______________________________________________________
   ____________________ *(must be 7-14 days from date of surgery)*
   ______ If no, provide planned date of surgery ________________
   ____________________ *(must be within the next 14 days)*
17. Treatment Assignment

Completed by ___________________________ Date ___________________________
1.0 INTRODUCTION

1.1 Background

The standard treatment for locally advanced but resectable squamous cell carcinoma of the head and neck (SCCHN) is surgery combined with post-operative (post-op) radiation therapy (XRT). Cytoreductive events, including chemotherapy and XRT, are thought to trigger regrowth of surviving tumor clonogens, which might compromise tumor control. It also has been suggested that surgical resection might have a similar effect on any remaining clonogens. Patterns of failure analyses suggest that at least some patients who have undergone resections of their cancers do, in fact, harbor residual tumor clonogens, which must be addressed in order to prevent recurrence regardless of their proliferative rate.

Patterns of failure analysis for patients with advanced oropharyngeal carcinoma treated with surgery and post-op XRT at the University of Pennsylvania reveal first failure with isolated locoregional recurrence in 29% and isolated distant metastases in 28% at 2-year median follow up. These are consistent with other reports in the literature, and highlight the need for both improved locoregional and systemic control in order to have a significant impact on cause-specific survival.

This protocol is designed to address the problems of post-op repopulation of remaining clonogens and systemic micrometastases in patients treated with surgery and post-op XRT for locally advanced SCCHN by the selective addition of chemotherapy agents. The ultimate goal of this approach is to improve cancer control.

1.2 Accelerated Repopulation

Three sources of data suggest that remaining tumor clonogens during XRT regenerate more rapidly as a result of radiation-induced cellular depopulation:

1. Time to recurrence analyses
2. Comparison of split-vs.-continuous course XRT
3. Analysis of tumor control doses as a function of time as corrected for fraction size

Based on these analyses, it is postulated that clonogen repopulation accelerates approximately 28 days after the initiation of XRT. This problem has been addressed in clinical trials with gross disease by delivering planned XRT more rapidly, “accelerated radiation therapy,” and has led to an approximate 15% improvement in tumor control.

There may be an even more complex cell kinetic interaction as a result of surgery and post-op XRT. It has been suggested that tumor cell depopulation resulting from surgical resection may also trigger accelerated repopulation. While there is no direct data about rates of such repopulation, the problem of residual tumor clonogens is highlighted by the following data:

1. A retrospective analysis that the intervals from surgery to the start of XRT, and the total “package time” from the day of surgery to the completion of post-op XRT for SCCHN affect tumor control. An analysis of 214 consecutive patients treated at the University of Pennsylvania reveals a significant reduction in local control when the treatment package time exceeds 100 days.
2. A retrospective analysis of patients with stage IV SCCHN including nodal disease > 3cm treated with neck dissection followed by XRT to the primary and both sides of the neck, revealed that a delay in the initiation of XRT greater than 14 days significantly decreased survival.

These data suggest that 1) delays at varying times during post-op treatment may have relatively different impact on tumor control, and 2) there may be critical tumor kinetic time windows representing potential therapeutic targets. The magnitude of proliferative factors at the cellular level may have a bi-modal distribution during post-operative XRT for SCCHN. Proliferative factors might peak in the early post-op period, and then again towards the end of XRT.

The problem of accelerated post-operative repopulation of tumor clonogens can be addressed in at least 4 ways:

1. Early initiation of effective postoperative treatment (XRT and/or chemotherapy)
2. Completion of post-op XRT as quickly as possible (early initiation ± accelerated fractionation; no treatment breaks)
3. The addition of an effective preoperative cytotoxic regimen (multiple log cell kill)
4. A radiosensitizer with post-op XRT to address the greater potential clonogen burden.

There is concern that the healing of surgical wounds might be impaired if XRT were started too soon. Postoperative XRT is generally started once surgical wounds are thought to be adequately healed. XRT has been started as soon as 2 weeks following neck dissection alone, and well tolerated. Typically at least 3-4 weeks are allowed for healing if there is resection of a mucosal primary through external skin incisions. There are practical difficulties in starting XRT early after surgery in terms of patient comfort, mobility and neck swelling, and ability to tolerate mouthpieces and immobilization masks. Practicalities in scheduling radiotherapy simulation and treatment planning process may cause additional delays. RTOG protocol 95-01 allowed a time window for XRT to begin between 2 and 8 weeks post-operatively.

Induction chemotherapy prior to XRT may be associated with a decrease in the rate of distant metastases, but there has been no improvement in locoregional control or overall survival. There is, thus, no established role for neoadjuvant chemotherapy in locally advanced SCCHN. It has been suggested that clonogen depopulation resulting from chemotherapy may also result in accelerated repopulation. Active chemotherapy agents lead to a decrease in the size of a tumor mass, and reduction in the number of clonogens. If the remaining clonogens are dividing very rapidly (fast kinetics), however, the "biologic equivalent size" of the smaller residual tumor mass may equal or exceed that of the pre-chemotherapy mass; i.e., "smaller tumors may be leaner but meaner."10

INT 0034 randomized patients with resected high-risk SCCHN to receive immediate post-op XRT versus a delay of 4 months with interposed 3 cycles of cis-platinum/5-fluorouracil chemotherapy. There was no difference in locoregional control, disease-free or actuarial survival at 4 years. It is important to note, however, that:

- The chemotherapy arm did no worse in local control or survival, despite a 4 month delay to the starting of radiation therapy.
- Chemotherapy did not compromise delivery of subsequent XRT.
- Chemotherapy resulted in benefit by significant reduction in regional nodal recurrences and distant metastases.

These data suggest that the chemotherapy was active in suppressing additional tumor clonogen regrowth.

Adjuvant chemotherapy (following surgery or XRT) has been shown to decrease distant metastases in several studies, including the Head and Neck Contracts Study. This also has not translated to improvement in survival. These data suggest that adjuvant chemotherapy, either before or after XRT, may alter the patterns of failure by improving systemic control, but has no impact on local control or survival.

There is mounting data that concurrent chemoradiation as definitive treatment may improve local control and survival for some patients with cancers of the upper aerodigestive tract. This includes esophageal cancer (RTOG 85-01),13 nasopharyngeal carcinoma (INT 0099),14 and a randomized trial of hyperfractionated XRT ± chemotherapy for SCCHN (Brizel).15 Additionally, Bachaud et al. reported a trial of standard post-operative XRT ± DDP at 50mg/w with the chemoradiation arm resulting in improved locoregional control.16

Single institution trials have shown benefit to concurrent post-op chemoradiation for high-risk patients. This was evaluated in a large multi-institution trial. Recently closed for accrual RTOG protocol 95-01 randomized patients with high-risk SCCHN to post-op XRT ± 3 cycles of concurrent cis-platinum 100mg/m² on days 1, 22 and 43.

1.3 Effect of Radiation and Chemotherapy on Wound Healing
There are four phases to wound healing:17

1. Inflammatory phase: Platelets adhere to exposed collagen forming a plug, the coagulation cascades are activated generating fibrin and the two combine to form a clot; multiple cytokines and other proliferative factors are released.
2. Migratory phase: Inflammatory cells, fibroblasts and other mesenchymal cells migrate to the wound, and angiogenesis begins.
3. **Proliferative phase:** *(starts about 5 days)* The wound epithelializes, new vessels form, fibroblasts proliferate, and tensile strength increases as collagen is organized with and glycosaminoglycans; collagen content plateaus at 3 weeks.

4. **Scar remodeling:** Collagen cross-linking matures, and capillaries coalesce to form larger vessels.

The effects of XRT on wound healing are time, dose and fraction size dependent. Radiation has been showed to affect all phases of wound healing. Fibroblast proliferation is important to tensile strength. If XRT is applied within 48 hours of wounding, fibroblast incorporation of tritiated thymidine decreases. Early XRT decreases rodent cutaneous wound breaking strength, but there was no decrease in tensile strength if the wound was irradiated 7 days post-wounding. There is little clinical data, but wound complications are significantly less frequent if after loading brachytherapy catheters are loaded >72 hours after open intraoperative placement.

There are multiple animal studies on chemotherapy effects on wound healing; however, this does not seem to translate to clinically significant wound disruption with breakdown, infection or fistulization. Neutropenia related to chemotherapy may affect rates of wound infection, but does not affect ultimate tensile strength. If chemotherapy is delayed for 4-7 days post-wounding, there is no decrease tensile strength.

There is significant precedent for excellent tolerance of early post-op chemotherapy:

1. Starting within 24 hours of curative colon resection in a prospective controlled trial. There was no difference in wound complications as compared to patients receiving chemotherapy >30 days post-op.
2. There is no increase in wound complications for patients receiving early, < 7 days, as compared to delayed multi-agent platinum-based chemotherapy following primary cytoreductive surgery, including bowel anastomoses, for epithelial ovarian cancer. It is now common practice for paclitaxel-based chemotherapy to begin 4-5 days post-op.

### 1.4 Paclitaxel

Paclitaxel is perhaps the most active single agent for SCCHN. Specifically, there is no evidence that paclitaxel impairs wound healing. Paclitaxel has been used extensively with concurrent XRT. Both laboratory and clinical data suggest that more frequent exposure to paclitaxel may be an optimal dose-schedule for direct tumor cytotoxicity, radiosensitization, inducing apoptosis, and inhibiting angiogenesis. Weekly administration of paclitaxel may maintain serum levels above 0.01 µmol/L the concentration associated with *in vitro* radiosensitization, apoptosis and inhibition of angiogenesis, but below the 0.05 µmol/L concentration associated with neutropenia.

Paclitaxel has been shown to have a maximum tolerated dose of 30mg/m²/w when given with concurrent post-op XRT for SCCHN. Severe mucositis was the dose-limiting toxicity at doses ≥ 45mg/m²/w. The standard weekly dose of paclitaxel given alone is 80mg/m²/w. It has been given in cycles to include 3 weeks of treatment, 1 week off. This dose-schedule is extremely well tolerated with no significant neutropenia and no neuropathy. Doses >100mg/m²/w did lead to more pronounced myelosuppression, but no significant neuropathy.

### 1.5 Cisplatin

Cisplatin is the chemotherapy agent with which there is the most experience with concurrent use with radiation therapy as a sensitizer, and is highly active against squamous carcinoma of the head and neck. When used alone, it is given three times during a seven-week course of radiotherapy at a dose of 100mg/m². It can be given on a weekly schedule during radiotherapy at 50mg/w. Cisplatin has been combined with paclitaxel during radiotherapy, because of activity and lack of overlapping toxicities; specifically it does not cause significant mucositis. When combined with weekly paclitaxel at 30mg/m², cisplatin is well tolerated at 20mg/m² weekly, and adds no additional toxicity to the paclitaxel. The sequence is critical. Taxol should precede Cisplatin; otherwise there is risk for antagonism.

### 1.6 Goal

To address the problems of repopulation of surviving tumor clonogens following resection of high-risk SCCHN and systemic micrometastases in patients with resected high-risk head and neck cancers who require post-op XRT. We propose to:
1. Deliver weekly paclitaxel starting post-op by day 14 after early phases of wound healing are established with the goal of inhibiting proliferation of subclinical locoregional and systemic clonogens
2. Deliver weekly paclitaxel and cisplatin concurrent with XRT as radiosensitizers
3. Evaluate the efficacy of this regimen as indicated by time to failure

2.0 PURPOSE
2.1 Primary Purpose
To determine the feasibility of this treatment regimen, specifically the percentage of patients who can complete the combined treatment program.

2.2 Secondary Purposes
2.2.1 To estimate the disease-free survival (DFS) of this regimen.
2.2.2 To determine the acute and chronic toxicity of this regimen.
2.2.3 To determine overall survival and patterns of failure of this regimen.

3.0 ELIGIBILITY
3.1 Eligibility Criteria
3.1.1 AJCC stage III or IV squamous cell of the head and neck, meeting one of the following:
3.1.1.1 Gross total resection completed, with one or more of the following risk factors:
   - Multiple pathologically-proven lymph node metastases;
   - One or more lymph nodes with extracapsular extension of tumor;
   - Positive margin(s) of resection, including mucosal margins and/or soft tissue or deep margins of resection.
3.1.1.2 Gross total resection not completed yet but planned within the next 14 days, with anticipation of needing postoperative XRT for one of the following:
   - Multiple pathologically-proven lymph node metastases;
   - Multiple clinically/radiologically-evident lymph nodes ≥ 1.5 cm;
   - Single clinically/radiologically-evident lymph node ≥ 3 cm.
3.1.2 Site of tumor origin in the oral cavity, oropharynx, larynx, or hypopharynx
3.1.3 No evidence of distant metastases
3.1.4 Zubrod Score 0 and 1
3.1.5 WBC ≥ 3,000; platelets ≥ 100,000
3.1.6 Creatinine, total bilirubin and AST or ALT ≤ 1.5 x institutional upper limit of normal
3.1.7 Adequate nutritional status, as determined by the treating physicians in conjunction with consultation with clinical nutritionists, as indicated
3.1.8 Patients must sign a study-specific consent form prior to registration.

3.2 Ineligibility Criteria
3.2.1 Significant wound infection, fistula, major wound dehiscence
3.2.2 Nasopharyngeal cancer
3.2.3 Paranasal sinus carcinoma
3.2.4 T3N0 glottic cancer
3.2.5 Less than gross total resection or patients requiring staged surgery
3.2.6 Prior head and neck irradiation or chemotherapy
3.2.7 Prior malignancy except under the following circumstances:
   - Disease free for minimum of 3 years;
   - Low-risk non-melanomatous skin cancer;
   - Carcinoma in situ (breast, cervix, bladder, etc.);
   - Stage T1-2, low-to-moderate grade prostate cancer.
3.2.8 Active cardiac disease defined as: unstable angina, MI in the last 6 months (unless successfully treated with CABG or PTCA), uncontrolled arrhythmia
3.2.9 Second or third degree heart-block or other clinically significant conduction system abnormality, unless pacemaker is in place
3.2.10 Severe COPD requiring ≥ 3 hospitalizations over the past year
3.2.11 Pregnant or nursing women due to the embryotoxic effects of chemotherapy
3.2.12 Pre-existing ≥ grade 2 peripheral neurotoxicity
4.0 PRE-TREATMENT EVALUATIONS

4.1 Mandatory Evaluations Prior to Registration

4.1.1 History and physical examination to be done within three weeks prior to registration

4.1.2 Examination under anesthesia/Biopsy within three weeks prior to registration for patients who have not yet had gross total resection

4.1.3 CBC to be done within two weeks prior to registration

4.1.4 Chemistry battery to include BUN, creatinine, liver function tests, to be done within four weeks prior to registration

4.1.5 CXR to be done within eight weeks prior to registration

4.2 Mandatory Evaluations Prior to Surgery/Chemotherapy

4.2.1 Dental Evaluation: dental extractions with alveoplasty and primary closure ideally should be done prior to the time of surgery; Healing after dental extractions generally requires about two weeks before XRT is started (See Appendix VI).

4.2.2 Medical oncology evaluation to evaluate medical contraindications, including cardiac, prior to chemotherapy

4.3 Other Evaluations

4.3.1 Pre-operative CT or MRI of the neck for clinical staging

4.3.2 Chest/abdominal CT and bone scan, as clinically indicated

4.3.3 Nutritional Evaluation: Prophylactic placement of a gastrostomy (PEG) tube is highly recommended for all patients

4.3.4 Pregnancy test as applicable

5.0 REGISTRATION PROCEDURES

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

6.0 RADIATION THERAPY

6.1 Radiation Dose

6.1.1 Radiation therapy should begin no earlier than post-op day (POD) 28 (study day 22) and no later than POD 42. Do not start radiation if there is major fistula/wound dehiscence until significantly healed. Must be cleared surgically to start. Once daily (2 Gy/d) radiation therapy is given to a total minimum dose of 58 Gy and maximum dose of 64 Gy to involved areas, over 5.5 - 6.5 weeks. If POD 42 falls on a Thursday, Friday, weekend, or holiday, then XRT must be deferred to the next business day (unless the patient is treated over the weekend/holiday) so that the patient receives at least three consecutive early RT fractions before a two-day non-work day interruption.

6.1.2 Spinal Cord

The dose to any point within the spinal cord should not exceed 45 Gy. Spinal cord dose must be clearly documented. Spinal cord blocks should be inserted into all fields at a dose of 40-44 Gy to achieve this goal.

6.1.3 Primary Tumor Bed

Final dose (using shrinking field technique): Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors (Section 3.0).

6.1.4 Neck Lymph Nodal Bed

Final dose (using shrinking field technique): Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors (Section 3.0).

6.1.5 Contralateral and other unoperated lymph node regions (Levels 1-5, and for pharyngeal cancers, the retropharyngeal lymph node region): 50 Gy minimum dose.

6.2 Treatment Planning

All fields must be designed on a simulator. Immobilization with a mask is strongly recommended. Bite blocks to displace the tongue, palate, or mandible may also be helpful. 3-Dimensional planning is not required, although the use of CT-planning (CT with the patient in the treatment position) for the final conedown dosimetry is required. Computerized 2-dimensional plans with isodose distributions at a minimum of two levels (at isocenter and at least one other level) are required.

6.3 Field Arrangements
6.3.1 It is expected that most patients will be treated with conventional comprehensive radiotherapy technique, including opposed lateral fields to the primary tumor bed and upper cervical lymph nodes, matched on to an anterior low neck supraclavicular field. The decision on the “site” of the match is left to the individual investigator, with the requirement that the match point not be within 2 cm of gross tumor.

6.3.2 For relatively superiorly located tumors, it is acceptable to utilize a “high” match at a level 1-2 cm below the hyoid bone, in order to minimize irradiation of the larynx. With this technique, the larynx may be shielded in the low neck supraclavicular field. When using the “high-match” technique in the setting of adenopathy, it should be remembered that there may be underdosing of relatively posteriorly located lymph nodes. Treatment of the low neck supraclavicular field AP-PA or conedowns of the low neck field may be necessary to comply with Section 6.1.4.

6.4 Dosimetry

6.4.1 Opposed Lateral Fields
For opposed lateral fields the prescription dose will be delivered to the midplane in the center of the treatment field, or an isodose line more appropriately encompassing the treatment volume.

6.4.2 Low/Neck Field
For the low/neck supraclavicular field, the prescription dose will be delivered to a depth of 3 cm. With a “high match,” this may result in a relative underdose of the posterior cervical nodal chain and field and/or prescription adjustments may be necessary (See Section 6.1.3 and 6.1.4).

6.4.3 Conedowns
Conedowns to areas of prior gross disease may be performed using opposed laterals with “shrinking field” technique, or may be performed with other techniques for lateralized lesions (tonsil), such as a wedge pair or ipsilateral mixed photon-electron beam technique. More complex “conformal” plans are also acceptable. Guidelines for conedowns are as follows:

6.4.3.1 For any plan other than shrinking field opposed laterals, CT-planned dosimetry is strongly recommended.

6.4.3.2 The conedown plan must encompass the gross tumor volume within the prescription isodose curve.

6.4.3.3 The maximum acceptable “hot spot” on the plan is 10%, with a strong recommendation to keep the maximum “hot spot” below 5%.

6.4.3.4 The maximum spinal cord dose (Section 6.1.2) must be ≤45 Gy.

6.5 Protocol Compliance Criteria

<table>
<thead>
<tr>
<th>Score</th>
<th>Target Volume</th>
<th>Spinal Cord Dose</th>
<th>XRT Elapsed Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Protocol</td>
<td>≤ 5%</td>
<td>≤ 47 Gy</td>
<td>47-56 days</td>
</tr>
<tr>
<td>Minor Variation</td>
<td>5-10%</td>
<td>47-50 Gy</td>
<td>57-63 days</td>
</tr>
<tr>
<td>Major Deviation</td>
<td>&gt; 10%</td>
<td>&gt; 50 Gy</td>
<td>≥ 64 days</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 Schema

7.1.1 Patients undergo gross total surgical resection of high-risk, squamous carcinoma of the head and neck prior to receiving study treatment. (Surgery may be before or after study registration; see Section 3.1.) Early post-op paclitaxel is given weekly for three weeks starting between post-op day (POD) 7 and post-op day 14 (study day 1). Study Day 1 is defined as the first day that the patient receives the first dose of chemotherapy. See Section 7.2. Paclitaxel and Cisplatin are given concurrently with XRT weekly for three weeks starting POD 56 (study day 43). See Section 7.3.

7.1.2 If POD 14 falls on a weekend or holiday, the early post-op chemotherapy may be deferred to the next business day. The day the chemotherapy is given is defined as the first study day.

7.1.3 Concurrent weekly chemotherapy should be given on Monday-Thursday, so that XRT is given that day and at least the next day before a weekend break. Chemotherapy administration on Monday, Tuesday or Wednesday is preferred.

7.1.4 Compliance Guidelines for Start of Chemotherapy
- 7-14 days post-op: per protocol
- 15-18 days post-op: minor variation
- > 18 days post-op: major deviation

7.2 Early Postoperative Chemotherapy
7.2.1 To begin between postoperative day 7 and postoperative day 14 (Study Day #1), using the following drug/schedule:

Cycle 1 is given between postoperative day (POD) 7 and POD 14, this represents “Study Day #1.” Paclitaxel 80 mg/m² i.v. will be administered as a ONE (1) hour continuous infusion.

7.2.1.1 Premedications for paclitaxel will include:
1. Dexamethasone 10 mg i.v. 30-60 minutes prior to paclitaxel infusion.  
2. Cimetidine 300 mg i.v. or Ranitidine 50 mg i.v. 30-60 minutes prior to paclitaxel infusion.  
3. Diphenhydramine 25 mg i.v. 30-60 minutes prior to paclitaxel infusion.  

If institutions have similar pre-medication protocols, with minor deviation, this is acceptable.

7.2.2 The patient will be reassessed for toxicity weekly for further cycles. Cycles 2 and 3 of perioperative chemotherapy will be given at the same dose level and schedule as Cycle 1, to be given at seven day intervals.

7.2.3 Dose/Schedule Modifications for Early Post-op Cycles 2 and 3 (study days 8 and 15)

If a patient develops febrile neutropenia (defined as fever ≥ 38.2 and ANC < 500) during any cycle, the following dose adjustment will be used for subsequent cycles:

Paclitaxel: 60 mg/m² (G-CSF may be given at the discretion of the treating physician if there were an episode of febrile neutropenia requiring dose reduction of paclitaxel.)

7.2.4 Modifications Based on CBC Parameters on Day of Treatment

ANC ≥ 1,500 and platelets 75,000: Dose as previous cycle.
ANC 1,000-1,499 and/or platelets 50,000-74,999: paclitaxel dose = 60 mg/m².
ANC < 1,000 and/or platelets < 50,000: withhold paclitaxel

7.2.5 Dose Modification for Non-hematologic and Non-mucosal Toxicity (Use Non-RT Toxicity Criteria)

7.2.5.1 Dose modification for non-hematologic toxicity:
   Grade 2-dose as previous cycle
   Grade 3-discontinue paclitaxel

7.2.5.2 Dose modification for mucosal toxicity (stomatitis/pharyngitis):
   Grade 3 (painful erythema, edema, or ulcers requiring i.v. hydration): dose as previous cycle
   Grade 4 (severe ulceration or requires parenteral or external nutritional support or prophylactic intubation): discontinue paclitaxel

7.3 Chemotherapy Concurrent with Radiation Therapy (3/1/04)

7.3.1 The first 3 weeks of radiotherapy are given without chemotherapy. Paclitaxel and Cisplatin will then be given once weekly for 3 weekly infusions with radiotherapy.

Paclitaxel Dose

Paclitaxel will always be dosed prior to Cisplatin and given once per week on Study Days #43, 50, and 57 (corresponding to PODs approximately 50-57, 57-64, and 64-71) during radiotherapy (Monday, Tuesday, Wednesday, or Thursday) at a dose of 30 mg/m² i.v. over one hour. Pre-medications will be given as described in Section 7.2.

Cisplatin Dose

Cisplatin will be given after Paclitaxel once weekly on Study Days 43, 50, and 57. Cisplatin will be given at a dose of 20mg/m² as an i.v. infusion.

Administration Guidelines for Cisplatin

At the time of hospital admission: Pre-hydration should be given to correct any pre-existing dehydration prior to the administration of the Cisplatin. Cisplatin should be mixed in 1 liter of saline and infused over 1-3 hours. Antiemetics may be administered according to investigator option.

7.3.2 Dose Schedule Modification for Concurrent Chemotherapy with Radiation

7.3.2.1 Modifications for Paclitaxel

If a patient develops febrile neutropenia (defined as fever ≥ 38.2 and ANC < 500) during any cycle, the following dose adjustment will be used for subsequent cycles:

Paclitaxel: 20 mg/m² (G-CSF may be given at the discretion of the treating physician if there were an episode of febrile neutropenia requiring dose reduction of paclitaxel.)

7.3.2.2 Modifications of Paclitaxel and Cisplatin for Mucosal Toxicity (Use Toxicity Criteria for Mucositis Due to RT)

If mucositis grade 3 (confluent pseudomembranous reaction; contiguous patches generally > 1.5 cm in diameter) persists for 2 weeks; hold further chemotherapy until resolves to ≤ grade 2, but continue radiation.
If in earlier than the last week of radiation, mucositis grade 3 persists for a third week despite holding chemotherapy (i.e. grade mucositis ≥ 14 days), then hold both chemo and radiation until resolves to ≤ grade 2.

If mucositis grade 4 (necrosis or deep viceration; may include bleeding not induced by minor trauma or abrasion): stop radiation and chemotherapy until resolves to ≤ grade 2 then resume radiation, discontinue chemotherapy and notify Study Chair.

If skin reaction ≥ grade 4: hold radiation and chemotherapy until resolves to ≤ grade 2.

7.3.2.3 Neurotoxicity and Renal Toxicity:
For any ≥ grade 2 neurotoxicity or renal toxicity discontinue chemotherapy and notify Study Chair.

7.3.2.4 There will be no chemotherapy dose reduction concurrent with radiation.

7.4 Paclitaxel (Taxol)

7.4.1 Formulation: Paclitaxel is a natural product with antitumor activity. The chemical name paclitaxel is 5ß,20-Epoxy-1,2? hexahydrox ytax-11-en 9-one 4, 10 diacetate 2- benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel is a white to off-white crystalline powder with the empirical formula C47H51NO14 and a molecular weight of 853.9. It is extremely lipophilic and melts at around 216-217°C. Paclitaxel (Taxol(r)) for Injection Concentrate is a clear colorless to slightly yellow viscous solution. It is supplied as a solution in a nonaqueous infusion. Paclitaxel is available in 30 mg (5mL) vials. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor (r) EL (polyoxyethylated castor oil) and 49.7% 9 (v/v) dehydrated alcohol, USP.

7.4.2 Preparation: Taxol should be diluted to a final concentration of 0.3 to 1.2 mg/mL in either 0.9% sodium chloride or 5% dextrose. The diluted Taxol solution will show a slight haziness that is proportional to the concentration of drug and the time elapsed since preparation. A solution that exhibits excessive particulate formation should be discarded. The Taxol solution must be prepared in glass, polypropylene, or polyolefin due to the leaching of diethylhexylphthalate (DEHP) plasticizer when polyvinyl chloride bags are used. Non-PVC tubing and connectors, such as those which are polyethylene lined, must be used during administration of Taxol. In-line filtration should be done using a hydrophilic, microporous filter of pore size not greater that 0.22 microns (e.g., IVEX-HP and IVEX-II, Abbot).

7.4.3 Administration: Paclitaxel will be administered as a ONE (1)-hr. continuous infusion. Premedications for paclitaxel will include:
1. Dexamethasone 10 mg i.v. 30-60 minutes prior to paclitaxel infusion.
2. Cimetidine 300 mg i.v. or Ranitidine 50 mg i.v. 30-60 minutes prior to paclitaxel infusion.
3. Diphenhydramine 25 mg i.v. 30-60 minutes prior to paclitaxel infusion.

7.4.4 Storage: Unopened vials of paclitaxel for Injection Concentrate are stable until the date indicated on the package when stored at 2°-25°C (36°-77° F). Refrigeration is not required for shipping provided the temperature falls within this range. Freezing does not adversely affect the concentrate. Solutions for infusion which are prepared as recommended are stable at ambient temperature and lighting for up to 27 hours.

7.4.5 Adverse Effects:
- **Hematologic**: Myelosuppression
- **Gastrointestinal**: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase) hepatic necrosis, hepatic necrosis.
- **Heart**: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness.
- **Neurological**: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma.
- **Allergy**: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis.
- **Other**: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), radiation recall reaction.

7.4.6 Supplier: Paclitaxel is commercially available.

7.5 Cisplatin

7.5.1 Formulation: Cisplatin injection is a clear, colorless solution and contains hydrochloric acid and/or sodium hydroxide to adjust pH and sodium chloride. The commercially available injection has a pH of 3.7 – 6, an osmolality of about 285 – 286 mOsm/kg. And contains a sodium chloride concentration of 0.9%.
7.5.2 **Preparation:** Cisplatin injection should be diluted in 2L of 5% dextrose and 0.33 or 0.45% sodium chloride injection containing 18.75g of mannitol per liter (i.e., 37.5g in 2 L) and infused i.v. over 6-8 hours.

7.5.3 **Administration:** Drug should be given as an intravenous infusion over 1-2 hours. Various other methods of dilution and/or rates of administration are used, and the clinician should consult published protocols for information related specific regimens, i.v. infusions over 15 minutes to 2 hours are commonly employed and have been used with minimal adverse renal effects. While Cisplatin has been administered by rapid i.v. injection (e.g., over 1-5 minutes) such rapid administration may be associated with increased nephrotoxicity or ototoxicity compared with slower i.v. infusion of the drug.

7.5.4 **Storage:** Injection should be stored at 15-25°C and refrigeration avoided (since precipitation of the drug may occur); however, if Cisplatin injection is inadvertently refrigerated, the precipitate dissolves; the manufacturer states that the chemical or physical stability of the injection is not affected. When stored under recommended conditions, commercially available Cisplatin injection is stable for 17 months following the date of manufacture; Cisplatin injection remaining in the amber vial following initial entry is stable for 28 days when protected from light or for 7 days when stored under fluorescent room light.

7.5.5 **Adverse Effects:** includes nausea, vomiting, alopecia, decreased Mg and Ca, elevated SGOT and SGPT, anorexia, 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 erythrocytosis, 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 and acute myeloid leukemia have been reported in a few cases where long-term cisplatin was used in combination with other forms of therapy.

7.5.6 **Supplier:** Cisplatin is commercially available.

7.6 **Hypersensitivity Reactions**
The treatment of mild/moderate hypersensitivity (moderate rash/flushing, mild dyspnea/ chest discomfort) will be as follows: Stop paclitaxel infusion. Continuous bedside monitoring of vital signs must begin. Give i.v. diphenhydramine 25 mg and i.v. decadron 10 mg. When symptoms resolve, resume paclitaxel infusion at a low rate (20 mg/hr x 15 minutes). If no further symptoms develop after 15 minutes, paclitaxel infusion at the full rate may resume. If symptoms recur, paclitaxel will be stopped and the patient will not receive any additional paclitaxel.

If a patient develops severe hypersensitivity reaction (hypotension requiring pressors, anaphylaxis, respiratory distress requiring bronchodilators, generalized angioedema or urticaria), paclitaxel will be stopped and continuous bedside monitoring of vital signs must begin. Give i.v. diphenhydramine and decadron as above. Epinephrine and/or bronchodilators may be given as needed. The patient may not receive re-challenge with paclitaxel.

7.7 **Colony Stimulating Factors**
Not allowed during chemoradiotherapy unless required for neutropenic fever during chemoradiotherapy, in which case radiotherapy must be held along with chemotherapy until at least 48 hours after the last dose of G-CSF.

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

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

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

7.8.1.3 Any death on study if clearly related to the commercial agent(s).
7.8.1.4 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.

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

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

7.8.3 Death from any cause while the patient is receiving protocol treatment, or up to 30 days after the last protocol treatment, must be reported to RTOG Headquarters Data Management department by telephone, (215) 574-3214, within ten days of discovery.

8.0 SURGERY
Patients may be registered either preoperatively if the patient has clinically evident advanced neck disease, or after surgery (See Section 3.1). Protocol chemotherapy must begin 7-14 days from date of surgery. Patients registered preoperatively who subsequently do not have gross total resection will be removed from study after all required documentation has been submitted to RTOG Data Management (See Section 12.2).

9.0 OTHER THERAPY
Not applicable to this study.

10.0 PATHOLOGY

10.1 Tumor Specimens
10.1.1 Paraffin-embedded (50-100 µm thick) blocks of pre-treatment tumor biopsy specimens will be collected for future correlative biomarker studies (e.g., proliferation markers, EGFR overexpression, etc.) to be coordinated through the RTOG Translational Research Program (TRP). Ten to 15 unstained slides may be sent instead of blocks.

10.1.2 Block/slides must be clearly labeled with the pathology identification number that agrees with the pathology report.

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

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

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

10.1.6 Patient consent form should give the Pathology Department authority and responsibility to comply with this request (pathology blocks belong to the patient from whom tissue has been removed).

10.1.7 Materials will be sent to:

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

11.1 Study Parameters

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pre-Study Entry</th>
<th>During early post-op chemo</th>
<th>Reassessment (Section 11.2)</th>
<th>During XRT</th>
<th>Post Rx</th>
</tr>
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<tbody>
<tr>
<td>History &amp; physical</td>
<td>X</td>
<td>weekly</td>
<td>X</td>
<td>weekly</td>
<td>X^a</td>
</tr>
<tr>
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<td>weekly</td>
<td>X</td>
<td>weekly</td>
<td>X^c</td>
</tr>
<tr>
<td>Chemistries</td>
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<td>weekly</td>
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<td>X^c</td>
<td>X</td>
<td>X^c</td>
<td>X^g</td>
</tr>
<tr>
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<td>X^c</td>
<td>X^g</td>
<td>X^c</td>
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<tr>
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<td>X</td>
<td>X^c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT/MRI Neck</td>
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<td>X^c</td>
<td>X^c</td>
<td>X^c</td>
<td>X^b</td>
</tr>
<tr>
<td>Chest/abdominal CT and bone scan</td>
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<td>X^c</td>
<td>X^c</td>
<td>X^c</td>
<td></td>
</tr>
<tr>
<td>Nutritional Eval/Gastrostomy</td>
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<td>X^c</td>
<td>X^c</td>
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</tr>
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<td>Beta HCG (women of childbearing age)</td>
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<td>X^c</td>
<td>X^c</td>
<td>X^c</td>
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</tbody>
</table>

a. Follow-up complete head and neck clinical examinations by the head and neck surgeon and/or radiation oncologist after completion of all therapy will be q 3mos from end of treatment x 2 years, then q 6mos. x 3 years, then annually.
b. Patients should have a “baseline” CT or MRI at 8-10 weeks after completion of all therapy and then only as clinically indicated.
c. Only if clinically indicated
d. Nutritional evaluation prior to all treatment is mandatory; Gastrostomy placement is highly recommended for all patients.
e. Examination under anesthesia may be necessary to evaluate for recurrence if clinical exam is equivocal; Biopsy is to be performed only if recurrence is suspected (See Section 11.2).
f. Biopsy is mandatory to confirm recurrence
g. Dental evaluation ideally should be done prior to time of surgery; See Appendix VI regarding guidelines for management of dental problems in patients with head and neck cancer.
h. Preoperatively for clinical staging
i. Prior to initiation of chemotherapy
j. Chemistries to include BUN, creatinine, liver function tests

11.2 Re-evaluation (Re-assessment)

Re-evaluation will be performed weekly during early post-op chemotherapy by the surgeon to evaluate for local mucosal and surgical wound toxicity, and the medical oncologist to evaluate for systemic toxicity. Patients will be seen weekly by the radiation oncologist during XRT. Patients will be seen by the medical oncologist prior to each cycle of chemotherapy.

It is the goal that patients complete XRT according to schedule and without unnecessary delays. If there is concern that additional chemotherapy toxicity may compromise the XRT schedule, then management should be discussed with the study chair, and concurrent chemotherapy and possibly radiation may need to be held for one or more cycles per Sections 7.2 and 7.3. The study chair should be notified if chemotherapy will be discontinued for recurrent significant allergic reaction per Section 7.6.

After treatment, follow up will consist of office head and neck examination per schedule and, as indicated, CT and/or MRI. If a recurrence is suspected, CT or MRI, CXR and biopsy of the lesion should be performed. When recurrence is suspected but office examination and CT/MRI are equivocal, examination under anesthesia or PET scan may be helpful. Examination under anesthesia and/or biopsy are to be performed only to exclude recurrence.

11.3 Response Criteria/Outcome Definitions (3/1/04)

11.3.1 Response Criteria

11.3.1.1 (NED): No evidence of disease; All patients must have no measurable tumor following surgery.
11.3.1.2 **Local-Regional Relapse:** Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; Biopsy confirmation is necessary.

11.3.1.3 **Distant Relapse:** Clear evidence of distant metastases (lung, bone, brain, etc.); Biopsy is recommended where possible. A solitary lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

11.3.1.4 **Second Primary Neoplasm:** A new cancer developing within or outside of the field of original treatment; Cancer re-appearing within the treatment field will be reviewed among the members of the Center for Head and Neck Cancer for determination of whether it represents a local recurrence of the index cancer or a new primary. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

11.3.1.5 **Disease-free survival (DFS):** Duration for which the patient is without evidence for local-regional or distant relapse, second primary, or death.

11.4 **Discontinuation of Protocol Treatment**

11.4.1 The protocol treatment can be discontinued if:
1. A toxicity develops which, in the opinion of the investigator, precludes further therapy;
2. The investigator, for safety reasons, considers it to be in the best interest of the patient that they be withdrawn;
3. Disease progression occurs;
4. The patient withdraws consent;
5. The patient becomes pregnant.

The date and reason for discontinuation must be noted on the appropriate forms. Every effort should be made to complete the appropriate assessments.

12.0 **DATA COLLECTION**

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

12.1 **Summary of Data Submission**

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of calendar base date</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
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</tr>
<tr>
<td>Pathology Report (P1)</td>
<td></td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
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</tr>
<tr>
<td>Surgery Form (S1)*</td>
<td></td>
</tr>
<tr>
<td>Surgical Operative Report (S2)*</td>
<td></td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)*</td>
<td>(*Within 3 weeks after surgery if after study entry)</td>
</tr>
</tbody>
</table>

**Preliminary Dosimetry Information:**

- RT Prescription *(Protocol Treatment Form)* (T2)
- Films *(simulation and portal)* (T3)
- Calculations (T4)

**Final Dosimetry Information:**

- Radiotherapy Form (T1)
- Daily Treatment Record (T5)
- Isodose Distribution (T6)
- Boost Films *(simulation and portal)* (T8)

**Initial Followup Form (FS):**
90 days after RT; include all acute treatment toxicities

**Treatment Summary (TF):**
At completion of post-op chemo and at completion of concurrent chemotherapy
Followup Form (F1) Every 3 months from end of treatment for 2 years; q 6 months x 3 years. Also at progression/relapse and at death.

Long Term Follow-up Form (FF) Yearly after 5 years in place of the F1 form, as applicable. See FF Form for instructions.

Autopsy Report (D3) As applicable

12.2 Patients registered preoperatively who subsequently do not undergo gross total resection or who do not subsequently begin protocol treatment will be removed from study after the appropriate documentation has been submitted to RTOG Data Management, including I1, S1, S2, and S5. In addition, the reason for no treatment must be recorded on forms T1 and TF.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Patient tolerance of the treatment regimen

13.1.2 Frequency of grade 5 and acute non-hematologic grade 4 toxicity

13.1.3 Frequency of other acute and late toxicity

13.1.4 Local-regional control (Failure: disease progression in the primary or regional nodes)

13.1.5 Disease-free survival (Failure: disease progression, second primary, or death)

13.1.6 Overall Survival (Failure: death to any cause)

13.2 Sample Size

13.2.1 Overview (3/1/04)

The protocol tests whether single agent chemotherapy can be safely started 7-14 days postoperatively. When the study was designed, it was not clear whether the consent to the study and registration should be obtained pre-operatively or postoperatively. Therefore, the protocol allows for both. The frequency of the preoperative and the postoperative registration will be used to determine if one is more feasible across the group-wide setting than the other. The primary endpoint is patient tolerance to the protocol treatment regimen. Tolerability will be defined as receiving \( \geq 90\% \) of the protocol radiation dose, all 3 early cycles of Paclitaxel and at least 2 of the 3 late cycles of Paclitaxel/Cisplatin and starting chemotherapy no later than postoperative day 18. In the intergroup study, RTOG 95-01, a chemoradiation program with Cisplatin and 5-FU was evaluated in similar patients with high-risk, resectable tumors. Seventy-nine percent of the 179 evaluable patients in RTOG 95-01 received within 10\% of the protocol radiation dose and at least 2 doses of Cisplatin. Based on this, the treatment will be considered tolerable if 75\% of the eligible patients tolerate (as described above) the treatment regimen. The regimen will also be monitored for excessive acute toxicity, defined as acute non-hematologic grade 4 toxicity or any grade 5 toxicity. In RTOG 9501, 13\% of the evaluable patients experienced the above toxicity, and 2 (2\%) treatment-related deaths were reported. For this study, we will assume a baseline rate of 15\%, with a rate of acute toxicity > 30\% being considered unacceptable.

13.2.2 Sample Size Derivation (3/1/04)

To calculate sample size, we estimate that 15\% of patients will experience acute toxicity as described above. A toxicity rate of 30\% is set as the highest acceptable rate. Fleming’s One-Stage Multiple Testing Procedure\(^28\) is utilized here. We chose Type I error of 0.10 and Type II error of 0.10 (i.e. 90\% statistical power). The higher Type I error rate is chosen so that we may increase the statistical power without increasing the sample size significantly. We are more concerned with a false negative decision (i.e. failing to detect the increase in toxicity if it exists) then we are with a false positive decision (i.e. deciding the new regimen is more toxic when in fact it is not). Forty-nine analyzable patients will be needed.

With a sample size of 49 patients, we have a \( \geq 95\% \) (two-sided) confidence interval around a hypothesized 75\% tolerance rate with margin of error \( \leq 12.1\% \).

Overall survival will be compared with RTOG 95-01 (both arms will be combined since there was no survival advantage shown with chemoradiation) as the historical control as described by Dixon.\(^29\) With
49 evaluable patients, we can detect an absolute improvement $\geq 17.7\%$ in overall survival at 2 years with 80% statistical power at the 5% significance level.

If an additional 15% of the sample is added to guard against ineligible or inevaluable (no data) cases, then the target total accrual for this study will be 60 patients.

13.3 Toxicity Monitoring (3/1/04)
The regimen will also be monitored for excessive acute toxicity, defined as acute nonhematologic Grade 4 toxicity or any Grade 5 toxicity. In RTOG 9501, 13% of the evaluable patients experienced the above toxicity, and 2 (2%) treatment-related deaths were reported. We wish to ensure that this treatment is tolerable and does not significantly increase acute toxicity. If at any time the following boundaries are crossed, all data pertaining to the events will be reviewed by the study chairs and a recommendation will be made to the RTOG Research Strategy Committee for their consideration. For example, if there are 6 patients with toxicity reported in the first 10 patients, the study will immediately undergo special review. Note that these are the first 10 patients entered (and eligible) consecutively onto the trial. It is not the first 10 patients for whom we have data.

<table>
<thead>
<tr>
<th>Number of patients with toxicity</th>
<th>Total Number Evaluable</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
</tr>
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<td>30</td>
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<td>10</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
</tr>
</tbody>
</table>

13.4 Patient Accrual
Based on accrual from RTOG institutions to RTOG 95-01, patient accrual is projected to be 5 patients per month. At this rate, it will take approximately 12 months to reach the target accrual. If the average monthly accrual is less than 2 cases, the study will be re-evaluated with respect to feasibility.

13.5 Analysis Plan
13.5.1 Interim Reports
Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about:
- patient accrual rate with a projected completion date for the accrual phase;
- distribution of pretreatment characteristics of patients accrued;
- quality of submitted data with respect to timeliness, completeness, and accuracy;
- compliance rate of treatment delivery with respect to the protocol description;
- frequency and severity of toxicities.

13.5.2 Analysis and Reporting of Initial Treatment Results
The analysis to report the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 6 months. The emphasis of this analysis will be on treatment tolerance and acute toxicity. The usual components of this analysis are:
- patients excluded from the analyses with their reasons for exclusion;
- institutional accrual;
- distribution of the important baseline prognostic variables;
- patient accrual rate;
- observed results with respect to the endpoints described in Section 13.1.

The rates of tolerance and toxicity will be estimated along with 95% confidence intervals. So if the estimated tolerance is less than 63, we will reject a 75% tolerance rate.

13.5.3 Analysis and Reporting of Final Treatment Results
The analysis to report the final results of treatment will be undertaken when each patient has been potentially followed for a minimum of 2 years. The emphasis of this analysis will be on locoregional control, and disease-free and overall survival. The usual components of this analysis are:
- patients excluded from the analyses with their reasons for exclusion;
- institutional accrual;
- distribution of the important baseline prognostic variables;
• patient accrual rate;
• observed results with respect to the endpoints described in Section 13.1.

Local-regional control will be estimated using the method of cumulative incidence, as this accounts for non-administrative censoring (i.e., death without local-regional failure). Disease-free and overall survival will be calculated by the Kaplan-Meier method. All failure time variables will be measured by the time interval from the date of registration to the date of the first failure. The one and two-year rates of local-regional control, disease-free and overall survival will be estimated along with 95% confidence intervals. Overall survival will be compared to the results from RTOG 95-01.

13.6 Inclusion of Women and Minorities

In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered the two possible interactions (treatment by race and treatment by gender). The study was designed to evaluate the treatment tolerance rate under the assumption of the same rates across the genders and across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races.

13.6.1 Gender

In RTOG 95-01, 84% of the patients eligible for this trial were male, and 16% were female. So for planning purposes, we assume 85% of patients entered into this protocol will be male, and 15% female.

13.6.2 Race

In RTOG 95-01, 74% of the patients eligible for this trial were white, and 26% were non-white. So for planning purposes, we assume 75% of patients entered into this protocol will be white, and 25% non-white.

For males we have a 92% confidence interval (two-sided) with margin of error ≤ 12.1% around the hypothesized 75% tolerance rate, and a 54% confidence interval for females. Also, for males we have a 95% confidence interval with margin of error ≤ 13.1% around the hypothesized 75% toxicity rate, and a 95% confidence interval with margin of error ≤ 32.1% for females.

For whites we have a 91% confidence interval (two-sided) with margin of error ≤ 12.1% around the hypothesized 75% toxicity rate, and a 66% confidence interval for non-whites. Also, for whites we have a 95% confidence interval with margin of error ≤ 14.0% around the hypothesized 75% toxicity rate, and a 95% confidence interval with margin of error ≤ 24.5% for non-whites.

The following table gives the expected number of patients in each race and gender group:

<table>
<thead>
<tr>
<th></th>
<th>American Indian or Alaskan Native</th>
<th>Asian</th>
<th>Black or African American</th>
<th>Hispanic or Latino</th>
<th>Native Hawaiian or Pacific Islander</th>
<th>White</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Male</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>38</td>
<td>1</td>
<td>51</td>
</tr>
<tr>
<td>Total</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>45</td>
<td>1</td>
<td>60</td>
</tr>
</tbody>
</table>
REFERENCES


APPENDIX I
RTOG H-0024

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

PHASE II TRAIL OF EARLY POSTOPERATIVE PACLITAXEL FOLLOWED BY PACLITAXEL AND CISPLATIN CONCURRENT WITH RADIATION THERAPY FOR RESECTED, HIGH-RISK SQUAMOUS CARCINOMA OF THE HEAD AND NECK

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

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

WHY IS THIS STUDY BEING DONE?

The usual treatment in head and neck cancer is surgery under general anesthesia followed by radiation therapy. In this study, the chemotherapy drug, Paclitaxel, also will be given after surgery and before radiation therapy. Then radiation will be combined with the chemotherapy drugs Paclitaxel and Cisplatin. The study will gather information about the effects (good and bad) this combination of chemotherapy and radiation has on you and your cancer.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 60 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, you will have the following treatment:

Chemotherapy: You will receive chemotherapy using the drug Paclitaxel (Taxol) once a week for 3 weeks. The
first dose is scheduled to be given about two weeks after surgery. Paclitaxel will be injected into a vein in your arm (intravenously) and will take about one hour. Your chemotherapy treatment will be given as an outpatient at your institution, unless you are still in the hospital for other reasons.

**Chemotherapy and Radiation Therapy:**
After you complete the chemotherapy listed above, you will receive chemotherapy and radiation treatments together.

**Radiation:**
About 5 weeks after your surgery, you will receive radiation treatments once a day, five days a week for 5 ½ to 7 weeks, depending on your cancer. Your treatments will be aimed at the prior location of the tumor on your head and neck. All radiation therapy will be given as an outpatient at your institution.

**Chemotherapy:**
Starting the third week of radiation therapy, you will receive the chemotherapy drugs Paclitaxel and Cisplatin, once a week until the end of radiation. These will be injected into a vein in your arm (intravenously) over approximately four to five hours. Your chemotherapy treatments will be given as an outpatient at your institution.

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

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to Study Entry</td>
<td>Physical exam with a history</td>
</tr>
<tr>
<td></td>
<td>Biopsy under anesthesia (if you have not yet had surgery)</td>
</tr>
<tr>
<td></td>
<td>Chest x-ray</td>
</tr>
<tr>
<td></td>
<td>Blood tests</td>
</tr>
<tr>
<td></td>
<td>Evaluation of your teeth</td>
</tr>
<tr>
<td></td>
<td>Bone scan (if necessary)</td>
</tr>
<tr>
<td></td>
<td>CT Scan of the chest and/or stomach (if necessary)</td>
</tr>
</tbody>
</table>

**Nutritional evaluation:**
It is expected that it may be very hard for you to eat normally during treatment. It may be necessary to place a feeding tube through your skin directly into your stomach to give you liquid nutrition during treatment. If necessary, this tube is put in during a 45-minute procedure for which you will be given sedation.
Pregnancy test (as applicable)

**During Chemotherapy Treatment**
Weekly
Physical exam
Blood tests

If necessary to check for side effects or your cancer
Chest x-ray
CT Scan of the neck
CT Scan of the chest and/or stomach
Evaluation of your teeth
Bone scan
Nutritional evaluation

**During Chemotherapy and Radiation Treatment**
Weekly
Physical exam
Blood tests

If necessary to check for side effects or your cancer
Chest x-ray
CT Scan of the neck
CT Scan of the chest and/or stomach
Evaluation of your teeth
Bone scan
Nutritional evaluation

**At Follow-up Visits**
Physical exam
Blood tests (if necessary)
Chest x-ray (every 6 months)
Evaluation of your teeth
CT Scan of the neck (8 to 10 weeks after completing all treatment)
CT Scan of the chest and/or stomach (if necessary)
Nutritional evaluation
Biopsy (if necessary, to check for cancer)

Follow-up visits with your physician will be scheduled every three months from the end of your treatment for 2 years, then every 6 months for 3 years, and then annually for the rest of your life.

Also, at the time of your diagnosis by biopsy, all or some of your tumor was removed. As is usually done, this tissue went to the hospital’s pathology department for routine testing and diagnosis. After that process was complete, the remaining tumor samples were stored in the pathology department. You are being asked for permission to use the
remainder of the tumor samples for additional tests. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense.

The tissue will be sent to a central office for review and for future research into biologic factors and inherited traits (genes) that may help to predict head and neck cancer as early as possible.

**HOW LONG WILL I BE IN THE STUDY?**

This study treatment will take approximately three months to complete. Follow-up visits will continue for the rest of your life according to the schedule above.

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

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

**WHAT ARE THE RISKS OF THE STUDY?**

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

**Risks Associated with Radiation Therapy to the Head and Neck**

*Very Likely*
- Decrease in blood counts, which can lead to a risk of infection and bleeding
- Sores in the mouth and/or throat which can be painful and make it very difficult to chew and or swallow foods
- Mouth dryness
- Changes in taste and/or smell
- Thick mucus
- Hoarseness
- Cough
- Tanning or redness of the skin in the head and neck area being treated
- Ear pain and/or pressure
Fatigue
Hair loss
Loss of teeth

Less Likely, But Serious
Thyroid gland dysfunction, which may require taking lifelong thyroid hormone pills.
Serious damage or infection of the jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening
Breathing problems
Permanent use of the feeding tube because you are unable to swallow

Risks Associated with Paclitaxel

Very Likely
Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
Hair loss
Fatigue
Mouth sores
Muscle aches and/or joint pains
Nausea and/or vomiting
Numbness or tingling in the hands or feet

Less Likely, But Serious
Allergic reaction, which can cause difficulty breathing, irregular heartbeat, low blood pressure, and even be life threatening
Changes in vision
Decrease in blood pressure
Severe rash called Stevens-Johnson syndrome which can cause fever and red sores in your mouth and eyes

Risks Associated with Cisplatin

Very Likely
Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
Loss of appetite and/or taste; metallic taste in your mouth
Nausea and/or vomiting
Fatigue

Less Likely
Ringing in the ears
Muscle cramps or spasm
Loss of coordination
Loss of muscle or nerve function which may cause weakness or
numbness in your hands and feet

Less Likely, But Serious
- Decrease in the kidneys’ ability to handle the body’s waste, which may be permanent
- Hearing loss
- Allergic reactions which can cause difficulty breathing, fast heartbeat, and sweating
- Facial swelling
- Decrease in liver function
- Another cancer called Acute Leukemia

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with head and neck cancer in the future. Treatment with radiation and chemotherapy may keep your cancer from regrowing or spreading, but this benefit is not guaranteed.

WHAT OTHER OPTIONS ARE THERE?

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

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

Another option may be to get this treatment with Paclitaxel, Cisplatin, and radiation therapy at this center even if you do not take part in the study.

Please talk to your regular doctor about these and other options.
WHAT ABOUT CONFIDENTIALITY?

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

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

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

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

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.
WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
(This section must be completed)

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

________________________________________________________________________
Name                                               Telephone Number

For information about this study, you may contact:

________________________________________________________________________
Name                                               Telephone Number

For information about your rights as a research subject, you may contact:
(OHReP suggests that this person not be the investigator or anyone else directly involved with the research)

________________________________________________________________________
Name                                               Telephone Number

WHERE CAN I GET MORE INFORMATION?

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

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

SIGNATURE

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

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

__________________________________________  ________________
Patient Signature (or legal Representative)       Date
TISSUE AND BLOOD TESTING  *(RTOG H-0024)*

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

☐ Yes  ☐ No

Patient Signature *(or legal Representative)*  ___________________ Date ___________________
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

STAGING-PRIMARY TUMOR (T)

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

ORAL CAVITY

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

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

PHARYNX

Nasopharynx

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

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

Oropharynx

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

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

Pyriform fossae  
Postcricoid region  
Lateral and posterior hypopharyngeal walls

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

**LARYNX**

**Supraglottis**

Suprahypoid epiglottis  
Infrahypoid epiglottis  
Aryepiglottic folds (laryngeal aspect)  
Ventricular bands (false cords)  
Arytenoids

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

**Glottis**

True vocal cords including anterior and posterior commissures

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

**Subglottis**

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

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

REGIONAL LYMPH NODES (N) Nasopharynx Only

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

DISTANT METASTASIS (M)

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

STAGE GROUPING  Excluding Nasopharynx STAGE GROUPING  Nasopharynx

Stage 0  T\textit{is}, N0, M0                     Stage 0  T\textit{is}, N0, M0
Stage I  T1, N0, M0                           Stage I  T1, N0, M0
Stage II T2, N0, M0                           Stage IIA T2a, N0, M0
Stage III T3, N0, M0                          Stage IIB T1-T2a, N1, M0
 T1-3, N1, M0                                T2b, N0-1, M0
Stage IVA T4, N0-1, M0                       Stage III T1-T2b, N2, M0
 Any T, N2, M0                               T3, N0-2, M0
Stage IVB Any T, N3, M0                      Stage IVA T4, N0-2, M0
Stage IVC Any T, Any N, M1
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

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

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

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

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

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

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

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

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

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

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

**Commercial and Non-Investigational Agents**

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

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

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

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

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

**Investigational Agents**

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

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

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.
  **A written report to follow within 10 working days.**
- All deaths within 30 days of termination of the agent.
  As above

- All life threatening (grade 4) events which may be due to agent.
  As above

- First occurrence of any toxicity (regardless of grade).
  Report by phone within 24 hours to IDB drug monitor and RTOG Headquarters.
  **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

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

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.
  Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.
  **A written report to follow within 10 working days.

- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.
  **Report in writing to RTOG Headquarters and IDB within 10 working days.

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

MANAGEMENT OF DENTAL PROBLEMS
IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients
Goals for a dental care program include:

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

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

Group 1
Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2
Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

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

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

Group 4
Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

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

Causative Factors
The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.
Preventive Program
The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrode unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is moulded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

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

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

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

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

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

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