RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-01

PHASE III INTERGROUP TRIAL OF SURGERY FOLLOWED BY
(1) RADIOTHERAPY VS. (2) RADIOCHEMOTHERAPY
FOR RESECTABLE HIGH RISK SQUAMOUS CELL CARCINOMA
OF THE HEAD AND NECK

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RADIATION THERAPY ONCOLOGY GROUP

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PHASE III INTERGROUP TRIAL of SURGERY FOLLOWED BY
(1) RADIOTHERAPY VS. (2) RADIOCHEMOTHERAPY
FOR RESECTABLE HIGH RISK SQUAMOUS CELL CARCINOMA
OF THE HEAD AND NECK

SCHEMA

SURGERY S Age
T 1. < 70
R 2. ≥ 70
A
T Risk Category*
I 1. Positive Margins
F 2. High Risk (≥ 2 positive nodes
Y or extranodal capsular spread)

R Arm 1
A RT - 60 Gy in 6 weeks (2 Gy once a day, 5 x a week)
N
D
O Arm 2
I M RT - 60 Gy in 6 weeks (2 Gy once a day, 5 x a week)
Fplus
Y Z Cisplatin-100 mg/m² i.v. on days 1, 22 and 43 with RT.

E

* If both are present, stratify as "positive margins"

Eligibility (See Section 3.0 for details)

- Histologically-proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx
- ≥ 2 histologically involved regional lymph nodes and/or extranodal disease and/or mucosal margins of resection that contain disease.
- Karnofsky ≥ 60
- Age ≥ 18
- No distant metastases
- No prior chemotherapy or radiation therapy
- WBC ≥ 3500, platelets ≥ 100,000, and creatinine clearance > 50
- Protocol treatment must begin within 8 weeks of first definitive tumor-related surgery
- Study-specific consent form

Required Sample Size: 438
RTOG Inst. # ____________ ELIGIBILITY CHECK (9/8/98)
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RTOG Case # ____________
Other Seq. # ____________

_____ (Y) 1. Has a diagnosis of squamous cell cancer of the oral cavity, oropharynx, hypopharynx or larynx been histologically confirmed?

_____ (N) 2. Is there gross visible or palpable disease left post-operatively?

_____ (Y/N) 3. Is there histologic extracapsular nodal extension? (If yes, skip to Q6)

_____ (Y/N) 4. Is there histologic involvement of ≥ 2 regional lymph nodes? (If yes, skip to Q6)

_____ (Y) 5. Is there microscopic invasion at mucosal margin of resection?

_____ (N) 6. Will protocol treatment begin > 8 weeks (> 56 calendar days) after the first surgical resection?

_____ (Y) 7. Is the surgery in compliance with Section 8.0 of the protocol?

_____ (N) 8. Was prior chemo or RT administered to the head and neck region?

_____ (N) 9. Is there evidence of a synchronous or concurrent head or neck primary tumor?

_____ (N/Y) 10. Except non-melanomatous skin cancer has the patient had another invasive primary tumor? _____ (Y) If yes, has the patient been disease-free for ≥ 5 years?

_____ (N) 11. Is there evidence of distant mets?

_____ (Y) 12. Is the patient medically stable enough to tolerate the proposed treatment?

_____ (≥ 60) 13. What is the patient's KPS?

_____ (≥ 18) 14. What is the patient's age?

_____ (Y/N) 15. Is the patient female? _____ (N) If yes, is the patient pregnant or lactating?

_____ (≥ 100) 16. Report patient's platelet count (per 1000).

_____ (≥ 3.5) 17. Report patient's WBC value (per 1000).

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RTOG Case #  
Other Seq. #  

(Y) 19. Have all required pre-treatment studies been completed within the time specifications outlined in Section 4.0?

(Y) 20. Was the study-specific informed consent signed? Date? 

The following questions will be asked at randomization:

(Y) Was the Eligibility Checklist (above) completed?

(Y) Is the patient eligible for this study?

________________________  Patient's Name
________________________  Verifying Physician
________________________  Patient ID #
________________________  Referring Institution # (if different)
________________________  Patient’s age
________________________  Risk Category  (positive margins vs. other high risk condition [see Schema])
________________________  Medical Oncologist
________________________  Birthdate
________________________  Sex
________________________  Race
________________________  Social Security Number
________________________  Zip Code (9 digit if available)
________________________  Method of Payment
________________________  Will any care be given at a VA or military facility?
________________________  Treatment Start Date  (must be after registration)
________________________  Treatment Assignment

Completed by ____________________________  Date _________________
1.0 INTRODUCTION

1.1 Head and neck carcinomas constitute 5% of all new cancers diagnosed annually in the United States; approximately 31,000 new cases occurred in 1992. These lesions tend to metastasize first to regional lymph nodes and locoregional control traditionally has been the greatest obstacle to the cure of these tumors. Despite aggressive surgical and radiotherapeutic management one in four patients who have advanced, but operable disease will experience locoregional recurrence of disease within one year of treatment and only one in three patients will survive for 5 years. Furthermore, a greater appreciation of the risk of distant metastases recently has become apparent; one in four patients who experience recurrence of disease has distant metastasis as at least a component of the problem.

1.2 Multimodality therapy is now a well-established strategy for control of tumors. A recent trial, RTOG 85-01, clearly demonstrated enhancement of local control and improvement in survival for patients treated with concurrent chemoradiotherapy for carcinoma of the esophagus, another tumor of the upper aerodigestive tract.1 Other RTOG trials have suggested an increase in local control for patients treated by concurrent chemoradiotherapy as compared to radiotherapy alone.2

1.3 Cis-platinum appears to be the drug most suitable for simultaneous chemoradiotherapy of head and neck cancers. It is an active agent in squamous cell cancers of the region; it does not produce stomatitis and appears not to interfere with the delivery of radiotherapy to head and neck structures. It appears to act as a radiosensitizer both in vitro and in vivo.3-10 The cytotoxic activity of cisplatinum appears independent of cell age; whereas, radiation enhancement is both dose and cell cycle dependent.11

1.4 RTOG 81-17 used concurrent chemoradiotherapy (cisplatin based) to treat 134 patients who had unresectable carcinomas of the head and neck.2 The response and survival rates obtained formed the basis of the current intergroup trial testing this regimen in patients who have carcinoma of the nasopharynx (RTOG 88-17).

1.5 Until recently, in the United States, surgery followed by postoperative irradiation for resectable advanced stage carcinoma of the head and neck has been considered to provide superior treatment to radiotherapy alone. Although recent trials that have integrated chemotherapy and radiotherapy in innovative ways brought this belief into question12, there remain a substantial number of patients who, for a variety of reasons, undergo surgical treatment for advanced head and neck carcinomas and require postoperative irradiation.

1.6 Intergroup 0034 (RTOG 85-03)14, a phase III trial to determine the effect of sequential chemotherapy as an adjuvant to surgery and postoperative radiotherapy showed essentially no improvement in outcome when chemotherapy was added to the standard sequence of surgery and postoperative radiation. On the other hand, in the subset of patients who had high risk characteristics, there was a tendency towards decreased loco/regional failure and improved survival in the group receiving chemotherapy and radiotherapy, as compared to radiotherapy alone.

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>% Relapse</th>
<th># at risk</th>
<th>% Relapse</th>
<th># at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>130</td>
<td>0</td>
<td>140</td>
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<tr>
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<td>41</td>
</tr>
<tr>
<td>48</td>
<td>34</td>
<td>15</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>Relapse/total</td>
<td>38/130</td>
<td></td>
<td>31/140</td>
<td></td>
</tr>
</tbody>
</table>

p = 0.07

1.7 Thus, available data suggests that, at least in some subgroups, the addition of chemotherapy to radiotherapy enhances loco/regional control and survival as compared to radiotherapy alone (Intergroup 0034) and that the concurrent use of chemotherapy and radiotherapy is more potent than their sequential administration (RTOG 81-17, RTOG 88-24, and RTOG 85-03). Therefore, the strategy of concurrent chemotherapy currently is being tested in Intergroup 0099 (RTOG 88-17) in patients who have not undergone surgery, and will be tested in this protocol in patients who have required surgery, in a rigorous prospective phase III manner.
Reanalysis of Intergroup 0034 using the criteria suggested by Peters et al. similarly demonstrates that patients who have high-risk features have both a very high locoregional recurrence rate and a decreased survival rate as compared to patients enrolled in the same trial who do not have these high-risk features.

Table 2

<table>
<thead>
<tr>
<th>Years</th>
<th>no risk features, - margins</th>
<th>risk features - margins</th>
<th>any features + margins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% alive</td>
<td>% recurrence</td>
<td>% alive</td>
</tr>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>1</td>
<td>88</td>
<td>11</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
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<td>3</td>
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<td>18</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>62</td>
<td>10</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>10</td>
<td>34</td>
</tr>
</tbody>
</table>

Bachaud et al. prospectively tested the value of cis-platinum, 50 mg i.v. weekly in conjunction with standard postoperative radiation. The preliminary results suggest improvement, particularly in locoregional control for patients receiving both chemotherapy and radiotherapy. Moreover, the chemotherapy regimen used by Bachaud et al. was more similar to the regimen used in RTOG 84-06 (which showed very little value for chemotherapy in patients who had inoperable disease) than it is to the currently planned regimen based on RTOG 81-17 (which suggests a more valuable role for chemotherapy given on a once every three week basis).

Because the potential benefit of postoperative chemoradiotherapy has been suggested most strongly in high risk patients, this trial will be limited to those patients who have the highest risk of locoregional recurrence of disease.

The recently reported study by Peters et al. has placed the assignment of low risk and high risk on more secure scientific footing than was available previously. Current information suggests that the presence of two or more pathologically involved nodes or extracapsular extension of disease renders a patient at high risk for loco/regional recurrence.

Review of Intergroup 0034 has revealed that two subgroups should be considered “high risk” patients. The group having two or more involved nodes or extracapsular extension was just described. The other high risk group had involvement of the mucosal margins of resection. Both groups will be eligible for this trial.

By including only those patients who are considered to be at the highest risk of locoregional recurrence in this trial, this trial will have the greatest chance of detecting a beneficial effect of the experimental therapy.

Tumor proliferative activity appears to be a promising prognostic tool in head and neck cancer. The p105 assay, a flow cytometric method to detect cycling cells has been shown to correlate with local-regional control. This trial will prospectively measure p105 assay to see whether high risk patients can be further stratified.

OBJECTIVES

To determine the efficacy of concurrent cisplatinum and radiotherapy following surgical resection in patients who have advanced squamous cell carcinoma of the head and neck region.

To test whether the use of concurrent chemoradiotherapy following surgery increases locoregional control rates.

To determine if the patterns of first failure are changed by the use of concurrent chemoradiotherapy.

To determine whether the use of concurrent chemoradiotherapy prolongs disease-free survival and or overall survival.

To compare the toxicity of concurrent chemoradiotherapy vs. radiation alone in the postoperative setting.

PATIENT SELECTION

Eligibility Criteria

Biopsy-proven squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx.
3.1.2 One or more of the following must be present: histologic extracapsular nodal extension, histologic involvement of ≥ 2 regional lymph nodes, mucosal margin of resection with invasive cancer (limited to microscopic detection only).

3.1.3 Age ≥ 18.

3.1.4 Karnofsky performance status of ≥ 60.

3.1.5 WBC ≥ 3500, platelets ≥ 100,000, creatinine clearance > 50, and evaluations specified as required in Section 4.0.

3.1.6 Signed study-specific informed consent form.

3.1.7 Protocol treatment must begin within 8 weeks of first tumor-related surgery (not reconstructive surgery).

3.1.8 Pregnant and lactating females are excluded.

3.2 Ineligibility Criteria

3.2.1 Gross (visible or palpable) disease left after surgery.

3.2.2 Complete resection with negative margins and absence of extracapsular nodal extension or < 2 histologically positive regional nodes.

3.2.3 Prior chemotherapy or radiation therapy to the head and neck region.

3.2.4 Evidence of distant metastasis.

3.2.5 Protocol treatment beginning > 8 weeks (56 calendar days) after the first surgical resection.

3.2.6 Presence of synchronous or concurrent head and neck primary tumors.

3.2.7 Prior malignancy within the previous 5 years.

3.2.8 Primary site of the lip, nasopharynx or sinuses.

3.2.9 Surgery not in compliance with Section 8; specifically Sections 8.1, 8.3, 8.6, 8.7.

3.2.10 Patients who because of their medical status are not candidates for the proposed treatment or the prehydration regimen.

3.2.11 KPS < 60.

4.0 PRETREATMENT EVALUATIONS

4.1 Complete history and physical exam with an assessment of the patient's performance and dental status. Presurgical diagrams of the primary and any nodal metastases are required and must be submitted.

4.2 Laboratory Studies (within 2 weeks pre-registration)

4.2.1 Hemoglobin or hematocrit, WBC, differential and platelets.

4.2.2 Urinalysis

4.2.3 SMA 12 or 18 (required BUN, creatinine clearance and creatinine)

4.2.4 Creatinine clearance may be determined by nomogram as long as the creatinine is not changing rapidly; otherwise determine 24 hour urine collection. Nomogram to calculate creatinine clearance is:

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

\[
\text{CrCL Female} = 0.85 \times \left(\frac{\text{CrCL male}}{\text{SCr}}\right)
\]

4.3 Required Imaging Studies (within 4 weeks of surgery and within 12 weeks of registration) (6/3/96)

4.3.1 Thoracic CT or chest x-ray within 12 weeks prior to study entry.

4.3.2 CT of liver only if liver enzymes are elevated > 1.5 times normal.

5.0 REGISTRATION PROCEDURES

5.1 RTOG Institutions

5.1.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:

- Institution Name & Number
- Patient's Name & ID Number
- Verifying Physician's Name
- Medical Oncologist's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date (within 8 weeks of tumor-related surgery)

5.2 ECOG Institutions
5.2.1 A signed HHS 310 Form, a copy of the institution's IRB-approved informed consent document, and written justification of any changes made to the informed consent for this protocol must be on file at the ECOG Coordinating Center before an ECOG institution may enter patients. These will be submitted to: ECOG Coordinating Center, Frontier Science, Attn: IRB 303 Boylston Street, Brookline MA, 02146-7648. Patients must not start protocol treatment prior to registration.

5.2.2 To register eligible patients on study, the investigator will telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022 Monday-Friday between the hours of 8:00 am and 4:30 pm EST, to allow time to call the Radiation Therapy Oncology Group that same day. ECOG members should not call the Radiation Therapy Oncology Group directly. The following information will be requested: Protocol Number, Investigator Identification (including institution name and/or affiliate and investigator's name); Patient identification (including patient's name or initials and chart number; patient's social security number; patient demographics [sex, birth date, race, nine-digit zip code and method of payment]); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 3.0. The randomization specialist will verify eligibility by asking questions from the Checklist. In addition, the Randomization Desk will verify IRB approval. If a patient does not receive any protocol therapy, the patient may be canceled. Reason for cancellation should be noted on the data forms and submitted to the ECOG Coordinating Center (ATTN: DATA) as soon as possible. The On-study form and Eligibility Checklist should be submitted. Written notification and an explanation must be received at RTOG as soon as this has been determined. RTOG will notify ECOG if the patient may be canceled. Once a patient has been given protocol treatment, all forms must be submitted.

5.2.3 ECOG will then phone RTOG Headquarters, Monday-Friday between 8:30 am and 5:00 pm ET and RTOG will assign the treatment option and RTOG case number. After receiving the case number and treatment assignment, ECOG will phone their registering institution and relay this information. The case number and treatment option will be confirmed by mail. RTOG will send a Confirmation of Registration and Forms Due Calendar to ECOG for each case. ECOG will then forward a copy of the calendar and the confirmation to the participating institution.

5.3 SWOG Institutions

5.3.1 Investigators will call the Southwest Oncology Group Statistical Center at 206/667-4623 between the hours of 6:30 a.m. and 1:30 P.m. (PT) Monday through Friday, excluding holidays. This must be done in order for the Southwest Oncology Group Statistical Center to complete the registration with RTOG prior to the close of business. The Statistical Center will obtain and confirm all eligibility criteria and information as per Section 5.1, RTOG Institutions. In addition, the Statistical Center will request the date informed consent was obtained and the date of IRB approval of each entry. The Statistical Center will then contact RTOG to randomize the patient after which the Statistical Center will contact the institution to confirm registration and relay the treatment assignment and case number for that patient. RTOG will forward a confirmation of treatment assignment to the Statistical Center for routing to the participating SWOG institution.

6.0 RADIATION THERAPY

6.1 Treatment Schedule (6/3/96)

6.1.1 Total dose will be 60 Gy in 30 fractions: 2 Gy once a day, five days a week for six weeks. All high risk sites must receive 60 Gy and all sites may receive 60 Gy. A minimum of 54 Gy must be delivered to low risk sites (e.g. areas requiring radiation that are distant from the region that rendered patient high risk as defined in Section 3.1.3). A conedown boost of up to 6 Gy delivered in 3 fractions over 3 days may be administered at the discretion of the investigator to the high risk site(s) only.

6.1.2 Radiotherapy should begin as soon as adequate healing after surgery has been established. Normally, this will be within 2-4 weeks of the surgical procedure but RT must be started no later than 8 weeks (56 calendar days) following surgery. For Arm 2, radiation and chemotherapy must begin on the same day.

6.1.3 A continuous course should be maintained if at all possible. If the radiation reaction requires an interruption of therapy, this should be kept to a minimum and reported. Daily dose reduction to 1.8 Gy is allowed only if a treatment break has become necessary.

6.2 Doses (6/3/96)

6.2.1 The protocol doses will be specified at the center of the target volumes (at central axis in the midplane for parallel opposed beams or at the intersection of the central axes of multiple beams). The protocol dose to the high risk target volume will be 60 Gy in 6 weeks. To the low risk target volume, it shall be at least 54 Gy, at 2 Gy per day, but may receive 60 Gy. For a patient who has a T1 tumor of the oral tongue that is resected without any tumor at the margins, and also has at least two involved nodes in the
mid to low anterior cervical region, it is permissible to treat lateral fields which encompass the oral tongue region to 54 Gy and to treat the dissected hemi-neck to 60 Gy. Alternatively, a patient who has a T3 floor of mouth lesion that is resected, but has microscopic involvement of the margins of resection, and who also has only a single ipsilateral high cervical node containing tumor, needs to have the lateral fields directed to the primary tumor treated to 60 Gy, but could have the neck field treated to only 54 Gy. Dose non-uniformity within the target volume should be kept to within ± 5 % of the protocol dose. If larger differences are anticipated due to contour changes of the neck, then this should be reduced by the use of tissue compensators or appropriate fields reductions. The dose to clinically uninvolved "electively treated" areas of the undissected lower neck will be 44 Gy at a depth of 3 cm.

6.2.2 The dose to the structures anterior to the spinal cord (mid-vertebral body) are to be calculated at the central axis midplane. Posterior to the spinal cord, the dose is calculated at a point 1 cm below the skin surface.

6.2.3 The maximum dose to the spinal cord and the length of spinal cord irradiated must be recorded for each field. The direct beam dose to the spinal cord must not exceed 45 Gy. The maximum dose to spinal cord is likely to occur at the junction of upper and lower field. Details of dose calculation at the junction must be provided.

6.3 Treatment Planning

6.3.1 Localizing films of each field will be taken and the copies sent to RTOG Headquarters in the first week of therapy together with a copy of the treatment prescription and initial calculations for radiation therapy quality assurance.

6.3.2 Localization films and machine portal films will be made on all fields and repeated at the time of any field change and must be submitted. Institutions that cannot provide electron beams portal films may substitute a polaroid picture of the electron beam portal.

6.3.3 Cumulative isodose distributions 1 cm from top of the lateral fields, 1 cm from the bottom of the lateral fields, and at the center, and a copy of the treatment record indicating cumulative doses must be submitted at the completion of radiotherapy.

6.4 Portals

6.4.1 The entire operative bed must be included in the treatment portals. A combination of lateral opposing fields, anterior and lateral wedged fields, or several beam-directed fields will be used for the primary tumor site at the discretion of the investigator. A single anterior A-P field with a mid-line block approximately 2 cm wide, will be used to treat the neck below the fields for the primary tumor. This lower neck field should abut the primary field at the skin. A midline bar should not be used in patients with pyriform sinus, glottic and supraglottic carcinomas; instead the lower edge of the lateral fields should be blocked or angled along the divergence of the upper edge of the lower anterior field or vice versa. With carcinomas in these locations, the tracheostoma must be treated for specific indications as outlined in Section 6.5.6.3. See Appendix VII for sample treatment portals.

6.5 Primary Treatment Fields by Tumor Site

6.5.1 Hypopharynx

6.5.1.1 The superior border is placed at the base of the skull to include the retropharyngeal nodes. Nodes in the upper jugular region and posterior triangle are included. At least one cm of the angle of the mandible is to be included to obtain adequate coverage.

6.5.2 Larynx

6.5.2.1 The upper border of the field includes the nodes in the upper jugular region. At least one cm of the angle of the mandible is to be included to obtain adequate coverage.

6.5.2.2 If there is involvement of the pyriform sinus and/or lateral hypopharynx wall, the superior border is placed at the base of the skull to include the retropharyngeal nodes.

6.5.2.3 Both ipsilateral and contralateral posterior nodes should be treated if there are histologically involved nodes in the anterior chain.

6.5.3 Oral Tongue and Floor of the Mouth

6.5.3.1 The posterior border of the lateral fields should normally lie anterior to the spinal cord. Due to the low incidence of nodal involvement, irradiation of the posterior chain is not required unless there are histologically involved ipsilateral cervical nodes.

6.5.4 Anterior Tonsillar Pillar - Retromolar Trigone

6.5.4.1 Both ipsilateral and contralateral posterior cervical nodes must be irradiated if there are histologically involved nodes in the anterior chain.

6.5.5 Oropharynx

6.5.5.1 The ipsilateral posterior cervical nodes must be irradiated if the primary tumor is T3.
Both the ipsilateral and contralateral posterior cervical nodes must be irradiated if there are histopathologically involved cervical nodes in the anterior chain.

### Lower Neck Field

#### 6.5.6.1 An undissected clinically uninvolved neck must receive at least 45 Gy at 3 cm depth.

#### 6.5.6.2 The lower border of the field will include the supraclavicular nodes and must be below the clavicles.

#### 6.5.6.3 The tracheostoma, if present, must be irradiated in patients with pyriform sinus lesions and in patients with laryngeal primaries whose tumors are T3 or T4, or have subglottic extension, cartilage or pre-epiglottic involvement, tracheostomy prior to time of definitive surgery or tumor microscopically found at the lower extent of resection.

#### 6.5.6.4 For patients with histologically involved nodes in the supraclavicular region, a mediastinal "T" field may be used. This consists of the supraclavicular field described above plus a central portion extending approximately 5 cm more inferiorly to include the upper mediastinal contents. The field is treated only anteriorly to a depth of 1/3 the antero-postero dimension measured from the anterior chest wall. 50 Gy is to be delivered in 5-5 1/2 weeks with the spinal cord dose being kept below 45 Gy. In certain patients this may require "blocking back" the upper portion of the field partway through treatment or using compensating filters. This field may also be used in selected patients who have histologically positive low cervical nodes or who have other factors making the upper mediastinum at risk for metastatic disease.

### Technical Factors

#### 6.6.1 Irradiation will be given with cobalt teletherapy, supervoltage energy equipment (1-6 MV), or electron beams.

#### 6.6.2 The treatment distance will be 80 cm or more to the isocenter. All fields are to be treated each day.

#### 6.6.3 The beam should be shaped with blocks to avoid unnecessary irradiation of normal structures.

### Treatment Interruptions

#### 6.7.1 Interruptions in treatment may be necessitated by skin reaction, mucositis, ulceration, edema or other acute radiotherapy complications. The reason for and the length of an interruption must be documented.

### DRUG THERAPY

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

#### 7.1 Treatment Plan - Arm 2

All patients will receive three courses of cisplatin three weeks apart on days 1, 22 and 43 concurrent with radiotherapy.

One course of chemotherapy will consist of cisplatin (100 mg/m²) given as an i.v. infusion over 1-2 hours with prehydration and diuretics.

Chemotherapy will be repeated every three weeks on days 1, 22, and 43 with RT (provided there is recovery from toxicity) for a total of three courses. If radiation therapy is completed prior to administration of final chemotherapy, the last course should be given unless the interval between the completion of RT and the start of chemotherapy is > 3 weeks.

#### 7.2 Cisplatin

**Formulation:** Cisplatin (Bristol-Myers Oncology) is available in the following formulations:

- 10 mg lyophilized vial, containing Mannitol 100 mg and sodium chloride, 90 mg;
- 50 mg lyophilized vial, containing Mannitol 500 mg and sodium chloride 450 mg;
- 1 mg/ml solution of cisplatin in normal saline, 50 or 100 ml vials.

**Storage:** Room temperature.

**Preparation:** Cisplatin powder for injection is reconstituted by adding 10 or 50 mL of sterile water for injection to a vial labeled as containing 10 or 50 mg of the drug, respectively, to provide solutions containing 1 mg/ml.

**Administration:** Drug should be given as an intravenous infusion over 1-2 hours.

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

**7.2.6 Toxicity**: Toxicity 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 erythrosuppression, is expected. The nadir white cell and platelet counts occur at about two weeks with recovery generally at about three weeks after initiation of therapy. Peripheral neuropathy and acute myeloid leukemia have been reported in a few cases where long-term cisplatin was used in combination with other forms of therapy.

**7.2.7 Supplier**: Commercially available

**7.3 Administration Guidelines (9/8/98)**

**7.3.1** In addition to the hydration described in Section 7.3.2, patients should be hydrated with two liters of fluids i.v. or p.o. both in the 24 hours prior to and post cisplatin.

**7.3.2** At the time of hospital admission correct any pre-existing dehydration. Immediately prior to mannitol and cisplatin, hydrate with 1000 ml D5 1/2 NS over two hours. Mannitol 12.5 gm i.v. bolus just prior to cisplatin, and another 25 gm in 1,000 ml D5 1/2 N.S. plus 30 mEq KCL to run over 4 hours immediately after cisplatin administration.

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

**7.4 Dose Modifications**

**7.4.1 Neutropenia** may occur. If on the day of scheduled treatment with cisplatin *(day 22 and 43)*, the absolute neutrophil count *(ANC)* is < 1000, hold treatment until ANC > 1000 then treat at 100% dose.

**7.4.2 Thrombocytopenia** may occur. If on the day of scheduled treatment with cisplatin *(day 22 and 43)*, the platelet count is < 75,000 hold treatment until platelets are ≥ 75,000 then treat at 100% dose.

**7.4.3 Neurotoxicity**: If any signs of paralysis, moderate myopathy, moderate weakness, seizure or peripheral neuropathy occur, reduce dosage by 40% and contact Dr. Forastiere.

**7.4.4 Renal Toxicity**: Cisplatin should be administered on the scheduled day of treatment using the following guidelines.

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>Creatinine Clearance</th>
<th>Cisplatin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.2</td>
<td>&gt; 50 ml/min.</td>
<td>100 mg/m²</td>
</tr>
<tr>
<td>&gt; 1.2</td>
<td>40-50 ml/min.</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>&gt; 1.2</td>
<td>&lt; 40 ml/min.</td>
<td>Discontinue and notify Dr. Forastiere</td>
</tr>
</tbody>
</table>

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

**7.5 RTOG Adverse Reaction Reporting**

**7.5.1** The following guidelines for reporting adverse drug reactions *(ADRs)* apply to any research protocol which uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

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

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

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

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

**7.5.2** The ADR report should be documented on Form FDA 3500 *(Appendix V)* and mailed to the address on the form, to RTOG Headquarters and to:

Investigational Drug Branch  
P.O. Box 30012
7.5.3 Any death, regardless of cause, while the patient is receiving protocol treatment or occurring within 30 days of completion of treatment must be reported to RTOG Headquarters by telephone.

7.6 ECOG Adverse Reaction Reporting

7.6.1 ADR reporting will be based on the Radiation Therapy Oncology Group Common Toxicity Criteria (Appendix IV). Written Adverse Drug Reaction reports are to be submitted on the Adverse Reaction (ADR) Form for Investigational Drugs (Form 391F), or the FDA form 3500 (Medwatch). The form must be signed by the treating investigator. All ADR Reports are to be accompanied by copies of all available and updated study data (on-study forms, flow sheets, follow-up forms, etc) as well as evidence of notification to the institutional IRB. This protocol does not contain IND agents; toxicities occurring on treatment arms are to be considered commercial. Guidelines for reporting of toxicities occurring with commercially available agents:

- Any ADR which is BOTH serious (life-threatening, Grade 4) or fatal (Grade 5) AND unexpected,
- Any Grade 5 event while on treatment if CLEARLY related to the commercial agent(s).
- Any increased incidence of a known ADR

Submit original written ADR form to the IDB and a copy to the ECOG Coordinating Center within 5 working days of the event.

7.6.2 The ECOG Coordinating Center will call the Radiation Therapy Oncology Group Operations Office to report the telephone ADR calls. The ADR forms will be forwarded to the Radiation Therapy Oncology Group Operations Office by the ECOG Coordinating Center.

**Reporting of All Second Primary Cancers**

<table>
<thead>
<tr>
<th>NCI/CTEP Secondary AML/MDS Report Form¹</th>
<th>ECOG Second Primary Form (Form #630)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AML/MDS</th>
<th>All other secondary cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

¹ To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and to the NCI, accompanied by copies of the pathology report and when available, a copy of cytogenetic report. Call the ECOG Coordinating Center for details of submission of pathology material.

² To be submitted to ECOG within 30 days of diagnosis of a new primary cancer during or after protocol treatment, regardless of relationship to protocol treatment. Not for use for reporting recurrence or metastatic disease. A copy of pathology report should be sent, if available.

NCI Telephone Number: (301) 230-2330  
NCI Mailing Address:  
Investigational Drug Branch  
P.O. Box 30012  
Bethesda, MD 20824  
ECOG Telephone Number: (617) 632-3610  
ECOG Address: Frontier Science  
Attn: ADR  
303 Boylston Street  
Boston, MA 02146-7648

7.6.3 Non-Treatment Related Toxicities: If a toxicity is felt to be outside the definitions listed above and unrelated to the protocol treatment, this must be clearly documented on the data forms which are submitted to the ECOG Coordinating Center according to the Data Submission schedule in Section 12.0. This does not in any way obviate the need for reporting the toxicities described above.

7.7 SWOG Adverse Drug Reaction Reporting
7.7.1 All Southwest Oncology Group (SWOG) investigators are responsible for reporting adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines. SWOG investigators must:
• Call the SWOG Operations Office at 210/677-8808 within 24 hours of any suspected adverse event deemed either drug-related, or possibly drug-related.
   Instructions will be given as necessary steps to take depending on whether the reaction was previously reported, the grade (severity) of the reaction, study phase, and whether the reaction was caused by investigational and/or commercial agent(s). The SWOG Operations Office will immediately notify the RTOG Statistical Center Data Management Office.
• Within 10 days the investigator must send the completed (original) Adverse Reaction Form (ADR) for Investigational Drugs (#391RF) or FDA 3500 Form (for regimens using only commercial agents) to the NCI:

   Investigational Drug Branch
   P.O. Box 30012
   Bethesda, MD 20824

   • In addition, within 10 days, the investigator must send:
     - a copy of the above report,
     - all data records for the period covering prestudy through the adverse event, and
     - documentation of IRB notification, to the following address:

   ADR Program
   SWOG Operations Office
   14980 Omicron Drive
   San Antonio, TX 78245-3217

   • At the SWOG Operations Office, a multilayered review will be performed and findings will be forwarded to RTOG, NCI, the study coordinator, and to the SWOG Statistical Center along with any supporting documentation.

8.0 SURGERY

8.1 Resection of the Primary Tumor
The primary lesion must be widely excised utilizing accepted criteria for adequate excision depending on the region involved. If any questions of the adequacy of margins exists, frozen section examination of the margins should be done.
Frozen sections are to be taken from the patient not the surgical specimen. The operative note or documentation of discussion with the surgeon should define whether grossly visible or palpable tumor remains after resection and whether microscopic margins are still positive on final frozen sections. If grossly visible or palpable tumor remains unresected the patient is not eligible for this study.

8.2 Closure
The primary reconstruction of the surgical defect is to be accomplished whenever possible. Reconstruction or closure with grafts, or local, regional, or free flaps when required, is allowed at the discretion of the responsible surgeon. Closed suction drainage will be employed routinely.

8.3 Neck Dissection
All patients will undergo ipsilateral neck dissections with the exception of patients with T4N0, truly midline supraglottic tumors in whom neck dissections will need not be performed. In patients undergoing elective neck dissection, if previously unsuspected but clinically histologically positive lymph nodes are discovered at the time of surgery, a modified neck dissection can be performed if the 11th nerve can be saved without jeopardizing the resection. Patients with bilateral clinically positive neck nodes, bilateral neck dissections will be performed, one side of which may have preservation of the internal jugular vein at the discretion of the surgeon. Bilateral resections may be performed simultaneously or staged. The 8 week eligibility window is dated from the time of first definitive surgery, not the time of staged second resection. Preservation of the accessory nerve, sternocleidomastoid muscle, and internal jugular vein will be at the discretion of the surgeon.

8.4 Carotid Artery Protection
Carotid artery protection can be used at the discretion of the responsible surgeon.

8.5 Antibiotics
Prophylactic antibiotics are suggested for all patients. Aminoglycosides are contraindicated. Antibiotic coverage should begin immediately prior to surgery and continue intraoperatively and for a minimum of 48 hours postoperatively.

8.6 Operative Report

The dictated operative report must accurately and completely describe the precise location and extent of the primary lesion and clinical metastases. An assessment of the completeness of the resection and the results of intraoperative frozen sections should be included. A copy of the operative report must be submitted with the post-operative form.

8.7 Specific Guidelines

8.7.1 Glottic Larynx

Small glottic primaries (T3 or less) in which the tumor is confined to the true vocal cord or the immediate vicinity may be treated by a partial laryngectomy or total laryngectomy at the discretion of the responsible surgeon. All T4 glottic primaries will be treated by total laryngectomy. Ipsilateral neck dissections will be performed in all patients with clinically positive nodes or T4 primary tumors.

8.7.2 Hypopharynx

In most instances, patients will undergo laryngopharyngectomy. Patients with T1N+ or T2 pyriform sinus primaries may undergo an extended supraglottic laryngectomy provided the apex of the pyriform sinus is clearly free of tumor involvement. Alternatively, these patients could have a laryngopharyngectomy. All T3 and T4 lesions will be treated by laryngopharyngectomy. Neck dissections will be performed on all patients.

8.7.3 Oral Cavity and Oropharynx

Every attempt should be made to preserve the continuity of the uninvolved mandible without compromise of adequate surgical resection margins. Marginal partial mandibulectomy is indicated in patients whom the tumor approaches but does not grossly invade the adjacent bone. Gross bone invasion demands segmental resection, the extent of which depends on the degree of clinical involvement at the time of surgery. Mandibular reconstruction is left to the discretion of the surgeon. Free flap reconstruction is allowed. Neck dissection will be employed in all patients with T3N0 tumors of the oropharynx or retromolar trigone.

8.7.4 Supraglottic Larynx

In most instances, patients will undergo total laryngectomy. Patients with supraglottic primaries whose tumors can be adequately resected with horizontal partial laryngectomy can have that procedure performed. All patients with clinically positive neck nodes will have neck dissection performed.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY (9/8/98)

10.1 Institutional Preparation of Tumor Sections

10.1.1 Paraffin blocks of tumor must be submitted. An H and E stained section will be prepared of the block face. The section will be examined to select an area of tumor that is free of necrosis, inflammation and most benign elements. This area will be marked on the side and outlined on the block face prior to sectioning. Only this region will be subjected to analysis. If unacceptable results are obtained (such as a high coefficient of variation or lack of sufficient cell numbers for analysis), another area will be selected. Sections 10.2 to 10.5 describe Dr. Hammond's analysis.

10.1.2 Institutions not able to submit paraffin blocks of pretreatment biopsies may submit 10-15 unstained slides instead.

10.1.3 Slides/blocks must be labeled with the pathology identification number that agrees with the submitted pathology report.

10.1.4 Pathology slides, blocks, and reports must be accompanied by a completed RTOG Pathology Submission form and sent to:

LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143
10.1.4.1 To encourage compliance, your Pathology Department will be reimbursed for obtaining blocks or cutting slides. Contact the RTOG Administrator.

10.1.4.2 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).*

10.1.5 **ECOG Institutions**

10.1.5.1 ECOG Institutions will submit 10-15 unstained slides, all required reports, and the RTOG Pathology Submission Form to the following address:

**ECOG Pathology Office**
Evanston Hospital
Room B624
2650 Ridge Avenue
Evanston, IL  60201-1797

10.1.5.2 ECOG institutions should not submit pathology materials directly to LDS Hospital and should not use the ECOG pathology submission form (#50), but rather the RTOG Pathology Submission Form. The materials will be logged in the Eastern Cooperative Oncology Group records then forwarded to LDS Hospital.

10.1.6 **SWOG Institutions**

10.1.6.1 SWOG investigators must send the required pathology materials to the following address for forwarding to LDS Hospital:

**Southwest Oncology Group Pathology Office**
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North  P.O. Box 19024  MP557
P.O. Box 19024
Seattle, WA  98109-1024

10.2 **Preparation of Nuclear Suspensions**

10.2.1 Two 50-micron-thick sections from the scored area of the paraffin block are placed in a 10-ml glass centrifuge tube.

10.2.2 For tissue dissociation, the tissue is incubated in 1 ml of 0.5% pepsin in saline, a pH of 1.5 adjusted with 2N hydrochloric acid for 30 minutes at 30 °C with brief vortexing. The reaction is terminated by placing the tubes on ice and treating with 0.5 ml of 0.5 mg/ml of pepstatin.

10.3 **p105 Antibody and DNA Staining**

10.3.1 The nuclei are resuspended at 2.0 x 10⁶ in 1 ml of 3% Triton x 100 in phosphate buffered saline for 3 minutes.

10.4 **Flow Cytometry**

10.4.1 Data are acquired in listmode on an EPICS 7920 flow cytometer *(Coulter)* with use of the 488 nm line of an argon ion laser at 350m W power. Typically, listmode files of 20,000 events containing data on forward-angle light scatter *(size)*, right-angle light scatter *(granularity)*, green fluorescence *(FITC stained anti-p105)*, red fluorescence *(propidium iodine stained DNA)*, and a computer generated time signal are obtained.

10.4.2 For standardization of propidium iodine staining, peripheral blood lymphocytes are stained with propidium iodine and the peak is recorded at approximately channel 200 on a 1024 channel histogram.

10.4.3 Instrument alignment and standardization of green fluorescence is performed using 10 um of Fullbright Fluosphere beads seta at green channel 56 on a 64-channel log-linear histogram. A total of 2 x 10⁴ nuclei are run for each case with a flow rate of approximately 10² nuclei per second.

10.4.4 **Quality Control for Flow-cytometry**

Standard calibration of instruments will be performed daily. Monthly comparisons of histograms generated in the two major flow laboratories in Salt Lake City, Utah showed that the variation in results over the past two years has been negligible. Controls to be run with each batch of tumor samples include:

1) **Positive control:** a paraffin embedded seminoma of testes with a high mitotic rate, diploid and aneuploid peaks of known indices, S-phase fractions and p105 antigen densities and

2) **Negative control:** paraffin block of reactive lymph node without obvious mitosis.
Positive and negative controls will be treated exactly like the test samples with propidium iodine and p105 prior to assay.

10.5 Data Analysis

10.5.1 Fluorescences results are analyzed on a microcomputer using Coulter Profile software. This program assumes a Gaussian distribution of G0G1 and G2M peaks and applies the quick estimate (peak reflect) method to calculate the cell cycle phases. Graphic representative of the data will be prepared with the use of software.

10.5.2 Antigen density (AD) of p105 positive cells will be calculated as the mean amount of fluorescence per cell and is directly proportional to the fluorescence measurements of whole nuclei.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (9/8/98)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Pre Study</th>
<th>at 3 weeks (mid RT)</th>
<th>at 6 weeks (end of RT)</th>
<th>at 9 weeks</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical Exam</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight and KPS</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tumor Assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Evaluation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC and differential, Platelets</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUN, Creatininea</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT, SGPT, Alkaline Phos, Bilirubin, LDH</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR or CT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. And creatinine clearance
b. CT of liver if elevated > 1.5 x normal.
c. Chest X-rays will be performed q 6 months the first year, then q 12 months.
d. Days 15, 22, 36, 43, 57 (Arm 2 only).
e. First followup following RT

11.2 Follow-up assessments are to be reported at 9 weeks, then every three months during the first year following treatment, then every 6 months for the next two years, and annually after the third year. Confirmation by radiographs or biopsy is preferable and agreement by two physicians of different specialties is advisable. The following will be evaluated:

11.2.1 Primary tumor
11.2.2 Regional disease (excluding primary site) and regional nodes
11.2.3 Metastatic spread
11.2.4 Second malignancy
11.2.5 Treatment complications
11.3 Additional treatment must be reported. Details of management are at the discretion of physicians managing the case.

12.0 DATA COLLECTION

12.1 Summary of Data Submission (9/8/98)

<table>
<thead>
<tr>
<th>Item Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
</tr>
<tr>
<td>Diagnostic Pathology Report (P1)</td>
</tr>
<tr>
<td>Pathology Slides/Blocks (P2)</td>
</tr>
<tr>
<td>Surgery Form (S1)</td>
</tr>
<tr>
<td>Surgical Operative Report (S2)</td>
</tr>
<tr>
<td>Surgical Pathology Report (S5)</td>
</tr>
</tbody>
</table>
Preliminary Dosimetry Information:
RT Prescription (Protocol Treatment Form) (T2)
Films (simulation and portal) (T3)
Calculations (T4)

Chemotherapy Flowsheets (M1) (Arm 2) Within 1 week of each chemotherapy cycle

Radiotherapy Form (T1) Within 1 week of RT end

Final Dosimetry Information:
Daily Treatment Record (T5)
Isodose Distribution (T6)
Boost Films (simulation and portal) (T8)
Photo/Polaroids (Electron beam) (T7)

Follow-up Form (F1) At 9 weeks, then every 3 months through year 1; then q 6 mos through year
3; yearly thereafter, and at progression/relapse and at death

Autopsy Report (D3) As applicable

12.2 ECOG Institutions
12.2.1 Forms Submission - The original data forms as listed in Section 12.1 should be submitted at the required intervals to the ECOG Coordinating Center, 303 Boylston Street, Brookline, MA 02146-7648. Include both the RTOG and ECOG study numbers and patient numbers. The ECOG Coordinating Center will forward the forms to the Radiation Therapy Oncology Group Office.

12.2.2 All preliminary and final dosimetry material must be sent directly to RTOG Headquarters, 1101 Market Street, 14th Floor, Philadelphia, PA 19104. All dosimetry material must be identified with labels available from RTOG. Do not send any dosimetry materials to the ECOG Coordinating Center.

12.2.3 All data items must be identified with both RTOG and ECOG study case numbers. Unidentified data/films will be returned.

12.3 SWOG Institutions
12.3.1 Forms Submission - Two copies of the original data forms as listed in Section 12.1 should be submitted at the required intervals to:
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1124 Columbia Street, MP-557
Seattle, WA 98104-2092

12.3.2 Include the RTOG protocol number and patient sequence number as well as the Southwest Oncology Group study number and patient number. The Southwest Oncology Group Statistical Center will forward the forms to RTOG.

12.3.3 All preliminary and final dosimetry material must be sent directly to RTOG Headquarters, 1101 Market Street, 14th Floor, Philadelphia, PA 19104. All dosimetry material must be identified with labels available from RTOG. Do not send any dosimetry materials to the SWOG Coordinating Center.

13.0 STATISTICAL CONSIDERATIONS
13.1 Overview
The primary objective of this study is to evaluate the effectiveness of concurrent radiochemotherapy given post-operatively in reducing loco-regional failure rate. The treatment schedule from RTOG 88-24, a completed phase II study, will be the experimental arm for this phase III trial and will be compared with standard postoperative radiation therapy alone.
A "historical" comparison was made between the RTOG 88-24 patients and all the patients from Intergroup resectable study INT #0034 who received only radiation therapy. Its purpose is to estimate the magnitude of the possible treatment effect when chemotherapy was added during radiation therapy. The comparison was limited to patients with positive margins and patients with two or more histologically positive lymph nodes or with extracapsular spread. These three subgroups were chosen because of their very poor prognosis and because they account for 82% (42/51) of RTOG 88-24 patients. The multivariate Cox proportional hazard model was used to estimate differences while "controlling" for the effects of other important variables on the outcome of interest.

From the INT 0034 study, there were 70 evaluable patients with positive margins and 123 evaluable high risk patients (two or more histologically positive lymph nodes or with extracapsular spread). The Kaplan Meier method was used to estimate the local regional failure (LRF) and the survival rates. At two years, the estimated LRF rate for patients with positive margins was 44% and the LRF rate for the high risk patients was 28%. At two years, estimated survival rate for patients with positive margins was 42% and the estimated rate for the high risk patients was 54%. In RTOG 88-24, 16 patients were identified as high risk and 26 (61%) patients had positive margins. Because of the small sample sizes, the two subgroups were combined. At two years, the LRF and the survival rate was estimated to 20% and 52% respectively. The difference favoring the RTOG 88-24 treated patients is quite striking with respect to local regional control. The only covariate used in Cox proportional hazard model besides treatment was disease category (positive margin vs. high risk). The relative risk associated with study was .457 which approximately translates to 55% reduction in the local regional failure rate. However, there was no dramatic difference favoring the RTOG 8824 treated patients with respect to overall survival. In the Cox model, two covariates used besides treatment effect were disease category and age (< 70 vs. ≥ 70 years). The relative risk associated with study was 0.750 which translates to 25% reduction in the death rate.

For planning purposes, we will assume that all local regional failures will occur in the first two years in this protocol because the percentage of failures post two years is exceedingly low. For sample size estimation a binomial distribution will be used where failure is defined as local or regional recurrence. In addition, the treatments will be also compared with respect to NED survival and overall survival. These two endpoints, however, are considered as secondary endpoints.

### 13.2 Measures of Treatment Effect

13.2.1 Loco-regional control rates Failure: disease progression/recurrent or new disease above the clavicle but not distant metastases only or death from any cause

13.2.2 Overall survival (Failure: death from any cause)

13.2.3 NED survival (Failure: disease progression/recurrent, new disease, second primary, and death from any cause)

13.2.4 Patterns of first failure.

13.2.5 Incidence and severity of various toxicities.

### 13.3 Required Sample Size

The baseline data used to generate the sample size calculations came from two studies (INT #0034 and RTOG 88-24) which have been previously described in the overview. Because of significant differences in outcome between the patients with positive margins and "high risk" patients, the sample sizes were generated for three hypothesized distributions of patients between them. The distributions considered are given in a table below.

<table>
<thead>
<tr>
<th>%patients with + margins</th>
<th>%high risk patients</th>
<th>Weighted LRF rate</th>
<th>Target sample after adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>%60</td>
<td>%40</td>
<td>.376</td>
<td>438</td>
</tr>
<tr>
<td>%50</td>
<td>%50</td>
<td>.360</td>
<td>424</td>
</tr>
<tr>
<td>%40</td>
<td>%60</td>
<td>.376</td>
<td>410</td>
</tr>
</tbody>
</table>

From the analyses with the Cox model, an absolute 15% increase seems to be a reasonable difference to hypothesize between the two arms. The other conditions set for these sample size calculations were \( a = .05, 1 - \beta \) (statistical power) = .80, and a two-tailed statistic. Some patients will die before two years without failing locally and they must be factored into the sample size calculations. Otherwise the statistical power may be reduced. Using the cumulative incidence method, it was estimated that 25% of patients with positive margins from INT #0034 will die without LRF in the first two years and 22% of
high risk patients without it. The sample sizes, which were initially derived with binomial distribution, were then increased by 25%. In order to insure that the required total sample size is available for analysis, an additional 10% patient accrual beyond that will be entered. This was done to guard against an ineligibility of up to 10%. Thus, the projected patient accrual goal for the three scenarios are 410, 424, and 438. The largest number, 438, will be used as an accrual target for the study.

13.4 Patient Accrual

The annual patient accrual rate is projected at 85 patients based on the previous Intergroup study #0034. On the basis of this projected accrual rate, it will require approximately 5 years to enter the estimated number of patients. The patient accrual will be carefully assessed prior to each semi-annual meeting. If the accrual drops below 50 per year, the feasibility of continuing will be carefully reviewed.

13.5 Inclusion of Women and Minorities (6/3/96)

13.5.1 In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into inoperable head and neck trials failed to show any treatment interaction with gender. Analysis of the operable intergroup study 0034 and RTOG 88-24 also failed to show a treatment interaction with gender. No information about race was collected in the RTOG Registry study and treatment studies prior to 1990. The SEER data suggest a difference in outcome by race! In a retrospective analysis, no difference in outcome by for patients treated for laryngeal cancer at a single institution was reported. The RTOG Special Population Committee is unaware of any other published data on patients with clinically localized head and neck cancer. Since there are no publications found to support a possible interaction between different radiation therapy schedules and either gender or race, the sample size will remain the same.

13.5.2 A sensitivity analysis was done with the targeted sample size by gender in testing for treatment differences. Combining the operable intergroup study 0034 and RTOG 88-24, there were 85% males and 15% females. Besides this distribution, a ratio of three men to one female was also used. If 85% and 75% of the patients recruited in this study are males, the statistical power to detect a reduction of an absolute 15% in the 2-year local rate are 0.73 and 0.67 respectively. If 15% and 25% of the patients recruited in this study are women the statistical power to detect a reduction of an absolute 15% in the 2-year local rate are 0.73 and 0.67 respectively. If 15% and 25% of the patients recruited in this study are white/other, the statistical power to detect a reduction of an absolute 15% in the 2-year local rate is 0.74. If 12% of the patients recruited in this study are African-Americans, the statistical power to detect a reduction of an absolute 15% in the 2-year local rate is 0.09. The analysis for reporting the initial treatment results will include treatment comparisons within each gender and race for local control and for overall survival.

13.6 Randomization

Patients will be stratified before randomization with respect to two variables: disease category at entry (positive margins vs. high risk) and age (<70 vs. ≥ 70). Patients will be considered at high risk if there are two or more positive nodes or if extranodal capsule spread is found. The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.

13.7 Analyses Plans

13.7.1 Methods for estimation and testing

Gelman et al. and Gaynor et al. pointed out in their respective papers that the Kaplan Meier methods would tend to overestimate the local regional failure rates. So the cumulative incidence approach will be used to estimate it as a function of time because this approach specifically accounts for competing risks such as dying without a local-regional recurrence. NED survival and overall survival will be estimated by the usual Kaplan-Meier method. The distributions of the local regional failures between the two arms will be compared a method especially developed for the task by Gray.

13.7.2 Interim analysis:

Interim reports with statistical analyses will be prepared twice a year until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about the patient accrual rate with a projected completion date for the accrual phase, data quality, compliance rate of treatment delivery with the protocol distributions of important prognostic baseline variables and the frequencies and severity of the toxicities. Measures of treatment efficacy, such as survival, will be reported in a blinded fashion only to the RTOG Data Monitoring Committee (DMC) until all the required patients have been entered on-study and completed their assigned treatment.

The first significance test comparing the local-regional failure rates between the two treatment arms will be performed for the first RTOG semi-annual meeting after 50% of the required sample size is available and the result will be then reported to DMC. If there is a highly significant difference in local-regional
failure rates between the two arms \((\text{Gray's test with } p < .001)\), the study statistician will recommend to the DMC that the randomization be discontinued and study be immediately written up for publication. Survival comparison will also be provided to the DMC, to be used along with local regional failure, in their deliberations about study termination.

The second significance test comparing the local-regional failure rates between the two treatment arms will be performed for the first RTOG semi-annual meeting after 100% of the required sample size is available and the result will be then reported to DMC. If there is highly significant difference in local-regional failure rates between the two arms \((\text{Gray's test with } p < .001)\), the study statistician will recommend to the DMC that the study be immediately written up for publication. Survival comparison will also be provided to the DMC, to be used along with local regional failure, in their deliberations about study termination.

13.7.3 \textit{Analysis for Reporting the Initial Treatment Results}:

Otherwise, a major analysis will be undertaken when each patient has been potentially followed for a minimum of 24 months. This analysis will include tabulation of all cases entered, and any cases excluded from the analyses, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints described in Section 13.1. The significance level of .048 will be used in the final analysis to preserve an overall significance level of .05. The primary hypothesis of local regional control benefit with the addition of chemotherapy during radiation therapy will be tested using the proportional hazards model with two fixed covariates, disease category and age. The same model will be used to test for a treatment benefit in NED and overall survival. Additional analysis of treatment effect will include the possible confounding effects of gender, race, age, Karnofsky Performance status, and other patient characteristics.

\textit{Note}:

At the time of this analysis, it is projected that there will be .85 statistical power to detect a 33% reduction in mortality rate and .60 power to detect a 25% reduction. These projections were based upon the following preset conditions:

1) survival times are exponentially distributed for each disease condition at entry;
2) the estimated five year survival rate for patients with positive margins was 25% and the five year rate for high risk patients was .33%;
3) two sided test with \(a = .05\);
4) method of Berstein and Lagakos for sample size and power determination for stratified clinical trials was utilized.26
REFERENCES


5. Richmond RC, Zimbrick RC, and Logan ME. Therapeutic Potentiation in a Mouse Mammary Tumor and an Intracerebral Rat Brain Tumor by Combined Treatment with Cis-dichlorodiammineplatinum (II) in Transplantable and Primary Murine Bladder Cancer. Int J Radiat Oncol Biol Phys. 5:1355, 1979

6. Double EB, Richmond RC, and Logan ME. Therapeutic Potentiation in a Mouse Mammary Tumor and an Intracerebral Rat Brain Tumor by Combined Treatment with Cis-Dichlorodiammineplatinum (II) and Radiation. J Clin Hematol Oncol. 7: 585, 1977.


28. Personal communication


* 6/3/96
RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have advanced cancer of the head and neck region. One or more of the following conditions apply to my cancer:

1) there may be cancer cells, too tiny to see at surgery, remaining at the surgical area,
2) there may be cancer cells in the nodes (glands) in my neck,
3) tumor may have spread through the node covering.

My doctor feels that my participation in this study may be helpful. This study includes the use of chemotherapy and radiation therapy. The study will test two different schedules of treatment. The purpose of this study is to see if the combination of these two therapies will control the growth of my tumor and if one schedule has less side effects than the other.

DESCRIPTION OF PROCEDURES

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

_Treatment 1_ will be radiation treatments (no chemotherapy) alone, once a day, five days a week (Monday-Friday) for six weeks.

_Treatment 2_ will consist of the intravenous (into my vein) administration of the drug cisplatin which will be given over a period of 1-2 hours, which is preceded and followed by intravenous salt solutions (given to reduce possible side effects of cisplatin), on day 1, 22 and 43. While I am receiving cisplatin, I will also receive radiation treatments once a day (like Treatment 1) for five days a week (Monday-Friday) for about six weeks.

Also, at the time of my diagnosis by biopsy, all or some of my 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, remaining tumor samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not
involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds to treatment, can be identified. Upon completion of my treatment my disease will be evaluated for response to the therapy. If I have developed local or distant disease or recurrence following therapy, I will be treated by means considered appropriate by my physician.

RISKS AND DISCOMFORTS

Cancer therapies often have side effects. Not all possible side effects of this combination therapy are known but previous studies have shown the more common side effects to be:

**Cisplatin**: May cause a temporary inability of my body to produce blood cells. This may result in an increased chance of developing bleeding, bruising, infection and/or anemia and changes in liver function tests and electrolytes. It may also cause weakness, hair loss, shortness of breath and fatigue. Blood transfusions may be required. Other side effects include nausea and vomiting, which may be severe, loss of appetite and kidney damage. Acute leukemia has been reported rarely in patients treated with cisplatin when used with other anticancer drugs. This drug can sometime cause a loss of muscle or nerve function causing weakness and/or numbness and tingling of the arms and legs. Mild hearing loss, ringing in the ears and rarely, a loss of taste, and allergic reactions may also occur. It is unknown what effects this medication may have on an unborn child. For this reason, I will be asked to practice an effective method of birth control while participating in this study.

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

In order to identify and treat these side effects and the status of my tumor, my doctor will do routine blood tests, x-rays and physical exams.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. the investigator in charge, at . In addition, I may contact for information regarding patients' rights in research studies.

BENEFITS

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

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

ALTERNATIVES

Alternatives which could be considered in my case include surgery or radiation therapy alone *(in a different schedule)*, and/or other chemotherapy in other combination schedules. I may receive treatment to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which may result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various
treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

**VOLUNTARY PARTICIPATION**

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

**CONFIDENTIALITY**

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

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

______________________________
Patient Signature (or Legal Representative)

______________________________
Date
# APPENDIX II

## KARNOFSKY PERFORMANCE SCALE

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


AJC STAGING-Primary Tumor (T)

Oral Cavity

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

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor ≤ 2 cm in greatest dimension
T2 Tumor > 2 - ≤ 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 Tumor invades adjacent structures (e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin).

PHARYNX

Oropharynx

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

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 Tumor invades adjacent structures (e.g. through cortical bone, into deep [extrinsic] muscle of tongue)

Nasopharynx (Ineligible for this study)

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

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

- Pyriform sinus
- Postcricoid area
- Posterior hypopharyngeal wall

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

LARYNX

Supraglottis

- Ventricular bands (false cords)
- Arytenoids
- Suprahypopharyngeal epiglottis (both lingual and laryngeal aspects)
- Infrahypopharyngeal epiglottis
- Arytenoepiglottic folds (laryngeal aspect)

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

Glottis

- True vocal cords including anterior and posterior commissures

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

Subglottis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
</tbody>
</table>
T0  No evidence of primary tumor
Tis  Carcinoma in situ
T1  Tumor limited to the subglottis
T2  Tumor extends to vocal cord(s) with normal or impaired mobility
T3  Tumor limited to larynx with vocal cord fixation
T4  Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g. to the oropharynx, or soft tissues of the neck)

Nodal Involvement (N)

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

Stage Groupings

Stage I    -  T1, N0, M0
Stage II   -  T2, N0, M0
Stage III  -  T3, N0, M0
           -  T1-3, N1, M0
Stage IV   -  T4, N0-1, M0
           -  T1-4, N2-3, M0
           -  Any T, or any N, M1
APPENDIX V

ADVERSE REACTION 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 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. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). 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.

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

3. A written report 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.

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 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

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### Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent. Report by phone within 24 hours to IDB and RTOG Headquarters.

**A written report to follow within 10 working days.**
- All deaths within 30 days of termination of the agent.
  As above

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

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

ii. *Phase II, III Studies Utilizing Investigational Agents*

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

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

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

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form
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 vacutrol 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 treatments 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.
APPENDIX VII

Sample Portal Diagrams