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RADIATION THERAPY ONCOLOGY GROUP

**RTOG 91-11
ECOG R 9111
SWOG 9201**

**Phase III Trial to Preserve the Larynx: Induction Chemotherapy
and Radiation Therapy versus Concomitant Chemotherapy and
Radiation Therapy versus Radiation Therapy**

SCHEMA

S	Location:	R	CDDP/5-Fu	
T	1. Glottic	A	CR,PR x 1 Cycle,	RT*
R	2. Supraglottic	N		
A	T Stage:	D	CDDP/5-Fu	
T	1. T2	0	Arm 1: x 2 Cycles	
I	2. T3, fixed cord	M		
F	3. T3, no cord fixation	I	N R Surgery	RT****
T	4. T4**	Z		
Y		E	Arm 2: Radiation Therapy* + CDDP	
	N Stage		Arm 3: Radiation Therapy*	
	1. N0, N1			
	2. N2, N3			

** Limited questionable cartilage destruction only, without tumor penetration outside the larynx (based on imaging).
Limited involvement of base of tongue not to exceed 1 cm.

Chemotherapy

Arm 1: Cisplatin 100 mg/m² over 20-30 minutes followed by 5-FU 1 gm/m²/24 hours by continuous infusion over 120 hours. Administered x 3, three weeks apart.

Arm 2: Cisplatin 100 mg/m² over 20-30 minutes administered on days 1, 22, and 43 of RT.

***Radiation Therapy**

Arms 1,2 and 3: 70 Gy Total dose, 2.0 Gy/5 days a week for seven weeks.

Treatment for Arm 1 will begin 3 weeks after the start of the third chemo cycle or 2-3 weeks after surgery as applicable.

*** Post-surgical RT: 50-70 Gy total dose, 2.0 Gy x 5 days a week for 5-7 weeks.

Eligibility (See Section 3.0 for details)

- Stages III and IV (excluding T1) squamous cell cancer of the glottic and supraglottic larynx as assessed by CT scan and clinical evaluation.
- Resectable disease
- No prior surgery, chemotherapy, or radiotherapy
- KPS ≥ 60
- WBC ≥ 3500, platelets ≥ 100,000, creatinine clearance ≥ 50 ml/ min
- No distant metastases
- No synchronous primary

Required Sample Size: 546

**12/23/94
6/3/96**

RTOG Institution # _____
RTOG 91-11
(ECOG R9111, SWOG 9201)
RTOG Case # _____
Other Group Seq.# _____

ELIGIBILITY CHECK (9/8/98)
(Page 1 of 2)

- _____(Y) 1. Has a diagnosis of squamous cell carcinoma been histologically confirmed?
_____ 2. What is the site of origin of the primary tumor? (supraglottis or glottis)
_____(N0-N3) 3. What is the clinical N-Classification (1988 AJC criteria)? (cannot be "N0" if Q4 = T2)
_____(T2-T4) 4. What is the T-Classification (1988 AJC criteria)? (T2 or T3, skip to Q9)
_____ 5. If T4, specify basis for T4 classification (1) thyroid cartilage invasion or 2) invasion of tongue base
(If tongue base, skip to Q8)
_____(N) 6. If basis is cartilage invasion, does cartilage extend beyond the larynx?
_____(Y) 7. Is the cartilage invasion limited to radiographic detection only? (skip to Q9)
_____(Y) 8. If basis for T4 stage is invasion of tongue base, is the extent of invasion
≤ 1 cm, clinically and radiographically?
_____(Y) 9. Is the tumor judged to be technically resectable?
_____(Y) 10. Is the tumor considered potentially curable with conventional surgery and radiotherapy?
_____(N) 11. Any evidence of distant metastasis?
_____(N) 12. Any medical contraindications to surgery, radiotherapy or chemotherapy?
_____(Y) 13. Is the patient's pulmonary, cardiac, and nutritional status judged to be adequate to tolerate
the proposed therapy?
_____(N) 14. Any prior irradiation of the head or neck area?
_____(N) 15. Any evidence of a synchronous primary tumor within the head or neck area or elsewhere?
_____(Y/N) 16. Except for non-melanoma skin cancer, has the patient had a prior second invasive primary tumor?
_____(Y) If yes, has the patient been disease free for ≥ 3 years?
_____(Y) Has the second malignancy histology been discussed and has the patient's
entry been approved by Dr. Goepfert?
_____ Date of Dr. Goepfert's approval.
_____ Site of prior malignancy.
_____ Date of tumor eradication.
_____(Y) 17. Within the past 4 weeks has the patient undergone endoscopic evaluation of the primary tumor? (chest
CT and barium esophagram may be done in place of panendoscopy)
_____(Y) 18. Using the protocol definition, is the primary tumor measurable?
_____(≥ 3.5) 19. Report the most recent (done within 2 weeks of today) WBC (per 1000)?
_____(≥ 100) 20. Report the most recent (done within 2 weeks of today) platelet count (per 1000)?
_____(Y) 21. Has a serum calcium been done within the past 2 weeks with results within normal range?
_____(Y) 22. Has a creatinine clearance (by 24 hour urine collection or nomogram calculation) been done within the
past 2 weeks with results ≥ 50 ml/min?

RTOG Institution # _____
RTOG 91-11

ELIGIBILITY CHECK
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(ECOG R9111, SWOG 9201)

RTOG Case # _____

Other Group Seq.# _____

- _____(Y/N) 23. Is the patient female? (If no, skip to Q24)
_____ (Y/N) If yes, does the patient have child-bearing potential?
_____ (Y) If yes, does the patient had a negative test for pregnancy within the last two weeks?
_____ (Y) Does the patient use effective birth control?
- _____(Y) 24. Have all other pretreatment evaluations specified in protocol Section 4.0 been completed as indicated with regard to results and time frame?
- _____(≥ 60) 25. What is the patient's Karnofsky Performance Status? (KPS)
- _____(Y) 26. In the opinion of the investigator is the patient considered mentally reliable in following instructions and keeping appointments?
- _____(Y) 27. Has the patient signed a study-specific consent form?
- _____(Y) 28. Will protocol treatment begin within 72 hours (3 working days) of randomization?

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)
_____ Tumor Location (glottic vs. supraglottic)
_____ T Stage (T2 vs. T3 fixed cord vs. T3 no cord fixation vs. T4)
_____ Nodal Stage (N0, N1 vs. N2, N3)
_____ Name of Responsible Medical Oncologist
_____ Patient's Birthdate
_____ Sex
_____ Race
_____ Social Security Number
_____ Zip Code (9 digit if available)
_____ Method of Payment
_____ Will any component of the patient's care be at VA or military facility?
_____ Treatment Start Date
_____ Treatment Assignment

Completed By _____

Telephone # _____

1.0 INTRODUCTION

1.1 There are approximately 12,400 new cases of laryngeal cancer reported each year in the United States and some evidence that the disease is increasing in incidence in industrial areas worldwide.^{1,2}

Early stage disease of the glottis and supraglottic, T1 N0 and T2 N0, is nearly always treated with a single modality, local radiation therapy or excision. The 5-year survival rates range from 75%-90% for stage I disease and 60-80% for stage II disease.³⁻⁵ Advanced disease, defined as T3 N0, T4 N0 or any T stage with nodal metastases has been variously treated with surgery only, primary radiation with surgical salvage or surgery combined with pre or post-operative RT.⁶⁻¹⁰ Although some improvement in local-regional control is reported with initial combined treatment,^{11,12} five year survival rates remain poor because of a high incidence of local-regional recurrence, distant metastases, and second primaries.^{13,14}

1.2 Laryngeal Preservation

In 1985 the VA Cooperative Studies Program mounted a prospective randomized trial to determine survival and laryngeal preservation rates in patients treated with induction chemotherapy followed by radiation therapy compared to a standard treatment of laryngectomy and post-operative radiation therapy.¹⁵ The induction chemotherapy was cisplatin and 5-fluorouracil which has been tested in multiple trials resulting in overall response rates of 80-90% with 30-40% complete responses.^{16, 17}

Laryngeal cancer was selected as an important site for organ preservation because of debilitating functional and psychosocial effects of the loss of natural speech^{18,19}. In addition, many patients are reluctant to undergo laryngectomy and choose radiation alone with surgical salvage.^{7,8,20,21}

VACSP #268 completed accrual in March 1989 with a total of 332 patients randomized to induction chemotherapy or standard surgery and post-op RT. Patients randomized to induction chemotherapy underwent response assessment after two cycles of cisplatin/5-FU. Those achieving at least a partial response received a third cycle followed by definitive RT, 66-76 Gy, reserving surgery for later salvage for persistent or recurrent disease. Non-responders to induction chemotherapy underwent immediate surgery followed by RT.

At a median follow-up of 33 months, the 2 year survival was 68% for both treatment groups ($p = .9846$) and the larynx was preserved in 64% of patients. The response rate to induction chemotherapy was 85% after two cycles and 98% after three cycles with a histologically confirmed complete response rate of 64%. Chemotherapy associated toxicity was acceptable and did not interfere with subsequent RT or surgery.²² There was no significant difference in survival based on site within the larynx (glottic or subglottic), stage (III or IV), and chemotherapy response. However, the pattern of recurrence differed between the two groups. There was a significantly higher rate of recurrence at the primary site in the induction chemotherapy group but no difference in regional node recurrence rates. The incidence of both distant metastases and the second primary malignancies was significantly higher in the surgery treated group.²³

An analysis of subsets of patients showed that achieving less than a complete response to chemotherapy in patients with N2 or N3 neck disease was significantly associated with a need for later salvage surgery ($p=.0007$). Seventy five percent of those patients died. The majority of deaths were due to local regional disease with 43% unresectable in the neck at the time of salvage surgery.²⁴ Thus although this randomized controlled trial of induction chemotherapy demonstrated that laryngeal preservation is possible without jeopardizing survival, alternative strategies to preserve organ function that will improve local-regional control and survival need to be investigated.

1.3 Concomitant Chemotherapy and Radiation Therapy

One approach tested by the RTOG in unresectable head and neck cancer is concomitant cisplatin with RT. RTOG 81-17 accrued 124 patients with stage III and IV unresectable squamous carcinoma of the head and neck. Treatment consisted of standard irradiation and cisplatin 100 mg/m² every three weeks for three doses as previously piloted by Wayne State University investigators. A complete response rate was observed in 69% of all patients, 68% of non-nasopharynx patients and 87% of a small number of laryngeal cancer patients. At four

years after treatment, local-regional control and survival of non-nasopharynx patients was 38% and 26%, respectively. A retrospective survival comparison with RTOG database patient suggested improvement in survival with concomitant cisplatin/RT for both nasopharynx and non-nasopharynx patients^{25,26}. Other investigators have tested concomitant cisplatin alone or combined with other cytotoxics and radiotherapy with improvements in survival and local-regional control suggested by comparison to historic controls^{27, 28, 29}.

Cisplatin has been shown to potentiate radiation damage in laboratory studies although the exact mechanism is not clearly understood. There is hypoxic cell sensitization when cisplatin is given immediately following radiation. This may be due to an inhibition of sublethal radiation damage repair^{30,31}. Clinically, the radiosensitizing effects of cisplatin are supported by investigators of Ensley and colleagues from Wayne State University. In 1984, they reported that only 5.5% of the patients achieving less than a partial response to induction chemotherapy responded to subsequent radiation therapy³². Similar results were also reported by the RTOG³³. However, in a recent trial, 50% of the non - responders to induction chemotherapy who were subsequently treated with concomitant cisplatin and RT achieved a complete response³⁴. Further, the results of 2 randomized trials indicate that concomitant chemotherapy is superior to sequential combined modality treatment approaches. Adelstein randomized Stage II - IV patients to concomitant cisplatin-based chemotherapy and RT or induction chemotherapy. A significant difference in complete response rate (67% vs. 32%, p=0.02) and disease-free survival (60% vs. 39%, p=0.03) was observed favoring concomitant treatment³⁵. In locally advanced, unresectable patients, Vannetzel and Taylor and colleagues observed a difference in time to treatment failure, 9.8 months for the induction chemotherapy group compared to greater than 16 months for concomitant chemotherapy and RT, p=0.07. The tendency for improved results was most apparent for regionally advanced disease³⁶.

Thus, based on the RTOG experience using concomitant cisplatin and RT and data from other investigators exploring this approach, we hypothesize that the percent of responding patients and local-regional control may be superior with concomitant compared to sequential (induction) chemotherapy and radiation or radiation alone as definitive treatment with surgical salvage.

1.4 Radiation Therapy with Surgical Salvage

The contribution of chemotherapy in the preservation of laryngeal function in patients treated with definitive radiation with surgical salvage has not been determined. For T₃ N₀ disease, in particular, treated with radical radiation, the results from the RTOG data base, and published series³⁷⁻⁴⁰ indicate 5-year overall survivals of approximately 50% and laryngeal preservation in 65-73% of surviving patients.

Table 1
**Results with Radiation Therapy
with Surgical Salvage**

<u>Author</u>	<u>Stage & Site</u>	<u>Patients</u>	<u>Survival</u>
RTOG database	T ₃ N ₀ , Glottic + Supraglottic	47	49.5% at 2-yrs
<u>Author</u>	<u>Stage & Site</u>	<u>Patients</u>	<u>Survival</u>
Harwood ³⁷	T ₃ N ₀	89	49% at 5 yrs Intact larynx in: 65% of survivors 45% of all patients
Harwood ³⁸	T ₃ , T ₄ N ₀ Supraglottic	128	51% at 5-yrs Intact larynx in:

			64% of survivors
Croll ³⁹	T ₃ N ₀₋₃ , T ₄ N ₀₋₂ glottic Supraglottic	58 (76%N0)	52% at 5-yrs Intact larynx in: 73% of survivors 65% of all patients
Meredith ⁴⁰	T ₃ , T ₄ N ₀ glottic & Supraglottic	109	53% at 5-yrs

Because the patients in this laryngeal preservation trial will have an elective neck dissection for disease ≥ 3 cm or multiple nodes at initial staging, the results reported by other investigators in patients with initial N0 disease may prove comparable. Only through a randomized trial design can the potential benefit by adding chemotherapy to radiation therapy (sequentially or simultaneously timed) be determined.

1.5 The control of neck disease in patients receiving organ preservation treatment remains a significant problem as shown by the results of the VA cooperative studies laryngeal preservation trial. Induration and fibrosis occurring in the neck after combined chemotherapy and RT can make the early detection of persistent or recurrent disease difficult and delay salvage surgery. The results of radiation therapy alone with surgical salvage in T3 and T4 patients indicate that the presence or absence of neck node metastases has a major impact on regional control and survival³⁸⁻⁴⁰. The major goal of the proposed trial is preservation of function at the primary site. Therefore, to address the problem of regional control, an elective neck dissection will be performed 6-8 weeks after the completion of RT for all patients with ≥ 3 cm nodal disease or multiple nodes at the time of randomization.

1.6 In summary, this study aims to identify the optimal treatment for laryngeal carcinoma that results in preservation of laryngeal function while not compromising survival. The primary outcome of interest will be survival at two years with preserved laryngeal function.

1.7 Quality of Life

According to Cella and Cherin, "Quality of Life refers to a patients' appraisal of and satisfaction with current level of functioning as compared to what they perceive to be possible or ideal".⁴³ The objectives for measuring QOL outcomes in clinical trials are twofold: 1) to obtain information useful to improving treatment procedures, and 2) the collection of information to evaluate which of several treatments gives better results for the majority of patients.⁴⁴ It is generally agreed that QOL assessment should be multi-dimensional and at the very least, address physical functions, psycho/social, emotional and spiritual well-being.⁴³⁻⁴⁵ Minimally, measurements of these domains should occur pretreatment, during treatment and post treatment.^{43,45}

The recent publication of the Laryngeal Preservation Study (VA268) brings the need to assess QOL in the advanced laryngeal cancer population to the forefront. The current standard treatment is total laryngectomy alone or in conjunction with post-operative radiation therapy. This study reports that, without compromising survival, chemotherapy combined with radiation therapy is at least as effective as the present standard treatment. Sixty four percent of all patients who received the experimental treatment (induction CT and XRT) retained their larynx.⁴⁶

A recent review of literature reveals only a few studies addressing some aspect of quality of life in head and neck cancer patients.^{47-50,53} Current QOL studies deal with the evaluation of assessment tools used for measuring QOL in this group of patients.^{43,47-49} However, researchers involved in these studies concur that there is a need to account for the impact of therapy on quality of life. This is best accomplished by a patient-based assessment tool.

Based on well documented problems of dysfunction, disfigurement and maladaptation reported by Summers⁵¹ and David⁵², one might assume that patients who have undergone laryngectomy experience a lower QOL than patients who have retained their larynx. A retrospective study performed by Burns⁵⁰ found that 56% of the patients having had laryngectomy would accept the same treatment, 29% would not and 15% were unsure. In

contrast a study by Harwood⁴⁸ discovered that the QOL outcome for advanced laryngeal cancer treated successfully with radiation was superior to surgically treated patients in all parameters except dryness of the throat. Morton⁴⁹, in his retrospective study, reported that there was no significant difference for depression, pain, psychological well being or life satisfaction when comparing laryngectomy patients to patients treated successfully with RT. It is our charge to begin to unravel this morass.

In this study, the proposed treatment modalities (chemotherapy, RT) have both short and long-term effects. The short-term side effects of RT include: sore mouth, difficulty swallowing, weight-loss, and skin reactions. The long term effects include: increased hoarseness, change in food taste and permanent dry mouth. Similarly, the chemotherapy (5FU, Cisplatin) although primarily drug and dose-related, has side effects which can affect many body systems. Thus, separately or combined, these treatments, at the very least, will impact the patients social and physical functioning. The first hypothesis of the QOL portion of this study is that patients who preserve their larynx will have a greater QOL than patients who receive a salvage laryngectomy. The second hypothesis asserts that the QOL outcomes will not be significantly different among patient receiving the adjuvant therapies outlined in RTOG 91-11.

2.0 OBJECTIVES

The primary endpoint is survival with preservation of laryngeal function. In achieving this overall goal the following outcomes will be assessed:

- 2.1 length of disease-free survival with a preserved larynx
- 2.2 length of overall survival
- 2.3 evaluation of tumor response at the completion of chemotherapy prior to RT for induction chemotherapy (*Arm 1*) and at the completion of RT for concomitant treatment (*Arm 2*).
- 2.4 patterns of relapse: local and regional recurrence and distant metastasis. The incidence of second primary tumors
- 2.5 incidence of adverse effects: acute and late
- 2.6 concomitant morbidity of neck dissection and/or laryngeal salvage surgery.
- 2.7 QOL for patients with laryngeal preservation versus patients requiring salvage laryngectomies.
- 2.8 to evaluate QOL outcomes between patients receiving radiation therapy alone and those receiving adjuvant therapy.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility (3/15/93, 8/16/93, 12/23/94)

- 3.1.1 Biopsy-proven, previously untreated, squamous cell carcinoma of the glottic and supraglottic larynx.
- 3.1.2 Stages III and IV (excluding T1) (Appendix III). T4 tumors must meet the following criteria:
 - a) questionable cartilage invasion by CT scan only (clinically T3) without penetration beyond larynx, or
 - b) supraglottic primary with invasion of the base of tongue up to 1 cm both clinically and on imaging studies.
- 3.1.3 Patients must have tumors which are potentially curable with conventional surgery and radiation therapy.
- 3.1.4 Karnofsky Performance Status ≥ 60 .
- 3.1.5 Within two weeks of study entry: WBC ≥ 3500 , Platelets $\geq 100,000$, normal serum calcium, creatinine clearance ≥ 50 ml/min by 24 hr urine collection or nomogram calculation:
$$\text{CrCL Male} = \frac{(140 - \text{age}) \times (\text{wt in kg})}{(\text{SCr}) \times (72)}$$
$$\text{CrCl Female} = 0.8.5 \times (\text{CrCl male})$$
Useful only if creatinine clearance is not changing rapidly.
- 3.1.6 Pretreatment endoscopic tumor staging and measurable tumor. Must be done within four weeks prior to randomization.
 - 3.1.6.1 A chest CT scan and a barium esophagram may be performed in lieu of panendoscopy.
- 3.1.7 Nutritional, pulmonary and cardiac status must be considered adequate to tolerate the proposed chemotherapy, radiation therapy and surgical salvage treatment.
- 3.1.8 Patients must be judged mentally reliable to follow instructions and to keep appointments.
- 3.1.9 Patients must give study-specific informed consent.
- 3.1.10 Women of child-bearing potential should have a negative pregnancy test and use effective birth control.

3.2 Conditions for Patient Ineligibility (12/23/94)

- 3.2.1 Prior radiotherapy to the head and neck region

- 3.2.2 Other invasive malignancy except non-melanoma skin cancer; patients with prior cancers who have been disease free ≥ 3 years may be entered with the approval of Dr. Goepfert.
- 3.2.3 Distant metastases.
- 3.2.4 Primary subglottic tumors
- 3.2.5 Synchronous primaries
- 3.2.6 Unresectable disease
- 3.2.7 T4 primaries which are more extensive than allowed in Section 3.1.2

4.0 PRETREATMENT EVALUATIONS (8/16/93, 12/23/94)

- 4.1 Satisfactory biopsy of the primary tumor.
- 4.2 Each patient must have completed the following studies within 4 weeks prior to randomization:
 - 4.2.1 Complete history and physical examination including height, weight, performance status and nutritional status.
 - 4.2.2 Complete diagrammatic and descriptive documentation, including measurements, of the extent of primary and regional disease.
 - 4.2.3 Dental evaluation (optional for edentulous patients).
 - 4.2.4 High resolution computerized tomography of the primary site and the neck and chest x-ray.
 - 4.2.4.1 Where N+ disease is based on presence of nodal disease found only on CT or MRI scans, i.e, not palpable on clinical examinations, the size of the node(s) detected with imaging must be ≥ 1.0 cm in its minimal axial diameter or contain necrotic regions regardless of size.
 - 4.2.5 Bone scan if elevated alkaline phosphatase.
 - 4.2.6 Liver scan (CT or radionuclide) if elevated bilirubin, alkaline phosphatase or SGOT.
- 4.3 The following studies must be completed within 2 weeks prior to randomization:
 - 4.3.1 CBC, platelets and granulocyte count.
 - 4.3.2 BUN, creatinine, creatinine clearance, uric acid, serum calcium, magnesium, phosphorus, total protein, albumin, serum electrolytes (sodium potassium, chloride, CO₂) and TSH (thyroid-stimulating hormone).
 - 4.3.3 Baseline QOL Assessment (prior to the start of protocol treatment)
 - 4.3.4 Pregnancy test for women of child-bearing potential.

5.0 REGISTRATION PROCEDURES

Protocol treatment should begin within 72 hours (3 working days) after randomization.

5.1 RTOG Institutions (6/21/93)

Patients can be randomized only after pretreatment evaluation is completed and eligibility criteria are met. Patients are randomized 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 following information must be provided:

- Patient's Name & ID Number
- Institution Name & Number
- Physician's Name
- Eligibility Criteria Information
- Stratification Information
- Medical Oncologist's Name
- Patient's Demographics
- Treatment Start Date

5.2 ECOG Institutions (6/21/93, 12/23/94)

- 5.2.1 Note: A signed HHS 310 Form for this protocol must be on file at the ECOG Operations Office before any ECOG institution may enter a patient.
- 5.2.2 To register a patient, the investigator will telephone the Central Randomization Desk at the ECOG Statistical Center Data Management Office (617) 632-2022 from 8:30 a.m. to 5:00 p.m. ET Monday-Friday. The following information will be requested:
 - Protocol Number
 - Investigator Identification
 - Institution name and/or affiliate
 - Investigator's name
 - Patient Identification
 - Patient's name or initials and chart number
 - Patient's Social Security number
 - Patient Demographics: sex, birthdate(MM/YY), race, nine digit zip code, method of payment

- Treatment Start Date
- 5.2.3 Patients must meet all of the eligibility requirements listed in the protocol document. The randomization specialist will verify eligibility by asking questions from the checklist. Upon confirming eligibility, the ECOG Statistical Center will place a call to RTOG Headquarters to receive an RTOG case number and treatment assignment which will be relayed to the ECOG member.
- 5.2.4 RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group will forward a copy of the calendar to the participating institution.
- 5.2.5 Additional Intergroup information is in Appendix VIII.
- 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 Registration. In addition, the Statistical Center will request the date informed consent was obtained and the date of IRB approval for 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 institution.
- 5.3.2 Patients must be registered prior to the initiation of treatment (no more than three working days prior to the planned start of treatment). The information listed on the RTOG Eligibility Check must be provided at the time of registration. The caller must also be prepared to provide the date of Institutional Review Board approval for this study. Patients will not be registered if the IRB date is not provided or is > 1 year prior to the registration date.

6.0 RADIATION THERAPY PARAMETERS

6.1 Radiation Dose (6/3/96)

6.1.1 Arms 1,2 and 3 (except after surgery after no response to chemotherapy)

Treatment to the primary tumor and upper neck will be given at 2.0 Gy per fraction, once a day, five days a week to a total dose of 70 Gy in 35 fractions in seven weeks. Fields must be reduced to exclude the spinal cord at 44 Gy at the midplane. However the entire neck must be irradiated to a dose of at least 50 Gy (even in N0 stage) at anatomical levels of lymph nodes usually 2-4 cm below the skin surface. Clinically positive neck nodes should receive a minimum dose of 70 Gy in 35 fractions in 7 weeks. To supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include additional electron beam to the posterior neck, wedge pair or oblique fields.

The anterior lower neck field will be treated at 2 Gy per fraction once a day to a total dose of at least 50 Gy in 25 fractions in 5 weeks. The total dose to the primary tumor and clinically positive nodes will be 70 Gy in 35 fractions in 7 weeks.

Maximum dose (direct beam, not scatter) to spinal cord is 44 Gy/22 fx in 4.5 weeks. Treatment for Arm 1 will begin 2-3 weeks after the completion of the third chemo cycle provided the patient has recovered from any chemo reaction or 2-3 weeks after surgery as applicable. Treatment beginning > 6 weeks after chemo or surgery will be scored as a protocol deviation. The reason for such delay should be clearly documented.

- 6.1.2 If surgery is required in Arm 1 for progression or no response, post operative RT doses will be a minimum of 50 Gy to a maximum of 70 Gy, at 2 Gy a day x 5 times a week for 5-7 weeks, depending on margins and residual tumor.

6.2 Physical Factors (12/23/94)

- 6.2.1 **Equipment:** linear accelerators with appropriate photon and electron energies for supplemental boosting to the nodes or Cobalt⁶⁰ machines must be used.

- 6.2.2 Photon energies of 1.25 to 6 MV and/or electron energies from 8-17 MeV are allowed.

- 6.2.3 Minimum treatment distance must be ≥ 80 cm SSD (or SAD for isocentric techniques).

6.3 Localization Requirements

- 6.3.1 **Simulation:** Simulation of all fields is mandatory. Patients must be reproducibly immobilized.

Radio-opaque markers should be used to delineate the extent of nodal disease and whenever possible, the primary tumor. The use of customized blocks to shape the treatment fields is recommended. Simulation films of each field, initial port films, and the calculation form will be sent to RTOG Headquarters in the first week of therapy, together with the treatment prescription for radiation therapy quality assurance review.

- 6.3.2** Verification: Beam verification (port) films must be obtained for each field. This should be repeated whenever any field adjustments are made. Port films of each field must be submitted to RTOG Headquarters.
- 6.3.3** Electron fields utilized for supplemental nodal boosting must be verified by either portal verification, simulation or polaroid films. Copies of the method selected shall be submitted to RTOG Headquarters.

6.4 Target Volume Irradiation Portals

6.4.1 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 for the case. A single anterior A-P field will be used to treat the neck below the fields of the primary tumor. When there is (are) positive node(s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node(s). All fields must be treated on each treatment session. The lower neck and supraclavicular field should abut the primary field at the skin. A lower lateral block, 1-2 cm in height could be placed in the lateral upper neck fields to shield the areas of potential overlap of diverging beams over the spinal cord, if a midline block in the anterior supraclavicular field is not suitable to prevent spinal cord overlap.

The primary treatment fields should encompass the primary tumor with adequate margins (minimum 1.5 cm) along with sites of known and/or suspected lymph node disease in the upper neck. The primary treatment fields by tumor site and the lower neck field are as follows:

6.4.2 Primary (12/23/94)

6.4.2.1 The upper border of the field includes the nodes in the upper jugular region. One cm of the posterior horizontal mandible is to be included to obtain adequate coverage.

6.4.2.2 If there is involvement of the pyriform sinus and/or lateral hypopharyngeal wall, the superior border is placed at the base of the skull (above C1) to include the retropharyngeal nodes.

6.4.2.3 The lower border of the field encompasses the larynx usually at the inferior border of the cricoid cartilage.

6.4.2.4 The ipsilateral posterior nodes should be treated for T3 N0 lesions.

6.4.2.5 Both ipsilateral and contralateral posterior nodes should be treated if there are clinically positive nodes in the anterior chain.

6.4.3 Lower neck

6.4.3.1 A single anterior lower neck field will be used to treat the neck and supraclavicular fossa below the fields for the primary tumor. When there is (are) positive node (s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node (s). (See Section 6.4.1)

6.4.3.2 The lower border of the field will be just below the clavicle or 1 cm below the clavicle when there are positive nodes in the supraclavicular fossa.

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

6.4.4 Photon beam portal arrangements

The following portal arrangements require dose specifications as follows:

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

6.4.4.2 For arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

6.4.4.3 Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas)

6.4.5 Electron beam dose specifications (12/23/94)

6.4.5.1 The energy and field size shall be chosen so that the target volume is encompassed within 90% or higher of the maximum dose.

6.5 Dose Calculations

6.5.1 Doses are specified as mid-depth at central axis when parallel opposed techniques are used or at the intersection of the central axis for other techniques. Complete isodose curves are required. Lithium fluoride dosimetry is recommended as a further check on tumor dose.

6.5.2 Variation within the target volume are not to exceed $\pm 5\%$ of the target dose. (12/23/94)

6.5.3 Fields must encompass the primary tumor and its suspected projections with a minimum 1.5 cm margin in all directions. This tumor (target) volume should receive 90% or greater of the central axis mid-depth dose. Fields must be reduced to exclude the spinal cord at a dose of 44 Gy at the mid sagittal plane. To supplement the dose to gross adenopathy in the neck, boost techniques may include electrons, wedge pairs, or oblique fields.

6.6 Time and Dose Modifications

6.6.1 Treatment interruptions are strongly discouraged. Treatment interruptions, and the reason for these must clearly be indicated in the treatment record. If treatment interruptions other than weekends occur, the case may be considered a protocol "variation" of acceptable or unacceptable degree.

6.7 Expected Side Effects and Toxicities

- 6.7.1** Reversible mucositis, epilation, and various degrees of skin reactions in the treatment area are expected. Side effects within 90 days of the treatment start should be graded according to the Acute Radiation Morbidity Scoring Scale in Appendix IV. Radiation effects persisting beyond or appearing after the first 90 days are measured on the Late Effects Scale.
- 6.7.2** Other expected acute reactions include xerostomia, hypogeusia, and dysphagia. Unusual severity of either of these should be noted, especially if supplemental feeding (tube) is required.
- 6.7.3** Late effects may include xerostomia and occasionally persistent dysphagia. Mandibular osteoradionecrosis will rarely if ever occur in these patients but can be reduced by thorough dental evaluation which is recommended before irradiation. Pretherapy extraction of badly diseased teeth should be carried out with conservation of restorable teeth where possible. If an extraction site in the mandible has to be included in the field, 10 to 14 days should be allowed for healing before the start of irradiation.
- 6.7.4** Radiation-induced myelopathy can occur in less than 1% of patients providing cervical spinal cord dose remains below 44 Gy. Transient radiation effects, manifested by L'hermites sign, may be more frequent and should be fully documented.

6.8 Surgical Salvage (12/23/94)

Surgical removal of the primary tumor should be performed only when biopsy proof of persistent cancer at least eight weeks after completion of radiotherapy confirms failure in a clinically abnormal site. Arbitrary biopsies in clinically negative site are contraindicated.

7.0 DRUG THERAPY

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

7.1 ARM 1: Cisplatin and 5-FU will be administered every 3 weeks for 3 courses prior to radiation. If a patient does not achieve at least partial response at the primary following 2 cycles of therapy, the third cycle is not allowed and the patient will receive surgery and post-operative RT. Patients who show clinical regression of the primary tumor and have neck nodes that have regressed or are stable will receive a third cycle of chemotherapy. If a patient has progressive disease at anytime, chemotherapy will be discontinued and surgery performed at the earliest possible date. **(3/15/93, 12/23/94).**

7.1.1 Chemotherapy Course: One course of chemotherapy will consist of cisplatin (100 mg/m²) given over 20-30 minutes with prehydration and diuretics followed by 5-FU (1 gm/m²/24 hours) by continuous infusion over 120 hours. **(11/30/92)**

7.1.2 If cycle 2 is delayed for more than 14 days because of low granulocytes or platelets, this will constitute an unacceptable toxicity and the patient should be taken off study and receive immediate surgery and post-op radiotherapy. If cycle 3 is delayed for more than 14 days, and the patient has achieved at least a partial response, then the patient should proceed directly to full-course radiotherapy and will not receive a third cycle of chemotherapy. **(12/23/94)**

7.2 ARM 2: Patients receiving definitive radiation therapy will also receive cisplatin (100 mg/m²) every three weeks during radiation for a total of 3 courses (days 1, 22, 43). Cisplatin must be given on days radiotherapy is administered.

Chemotherapy will be delayed appropriately if radiotherapy is delayed (i.e. second and third courses are administered on the 22nd and 43rd day of radiation therapy). If the second and third doses are delayed more than 14 days because of hematologic or renal toxicity, that dose will be omitted. If radiation is completed before cycle 3 is due for any reason, cycle 3 should still given up to 2 weeks after completion of RT. **(12/23/94, 10/15/96)**

7.3 Cisplatin

7.3.1 Pharmacologic Data: Cisplatin is a heavy metal complex which functions as an alkylating agent providing inter- and intrastrand DNA cross-links. It is extensively bound to plasma proteins and tissue sites and slowly excreted via the renal route. It can cause significant renal tubular damage unless administered with fluids and with mannitol induced diuresis.

7.3.2 Pharmaceutical Data: The drug is marketed commercially in 10 mg and 50 mg vials. It is diluted in sterile water to a concentration of 1 mg/ml and infused over 20-30 minutes.

7.3.3 Dose: Cisplatin dose = 100 mg/m² given on days 1, 22 and 43. All patients receiving Cisplatin must have a creatinine clearance ≥ 50 cc/min before starting each dose.

7.3.4 Administration Guidelines:

- Patients will be prehydrated with two liters of 5% D/1/2 NS and 40 mEq. KC1/1. This is to be followed by 12.5 gm mannitol immediately before administration of cisplatin.
- Cisplatin is given over 20-30 minutes followed by 1L of 5% D/1/2 NS and 40 mEq. KC1 and 25 gm Mannitol over four hours, followed by 1L 5% D/1/2 NS and 40 mEq. KC1 and 8 mEq. MgSO4 over eight hours.
- Patients should receive at least 3L of fluids over the ensuing 24 hours, either parenterally or orally.
- The anti-emetic regimen for this combination is to be determined by the local investigator.

7.4 5-Fluorouracil

7.4.1 Pharmacologic Data: 5-FU is an anti-metabolite that is metabolized to fluoridine monophosphate (F-UMP) and incorporated into RNA to produce a fraudulent RNA. The F-UMP may also be converted to F-dUMP, an irreversible inhibitor of thymidylate synthetase, an enzyme needed in the synthesis of DNA. There is substantial evidence to suggest that there is synergy between platinum derivatives and 5-FU. The drug is metabolized by the liver and in extra-hepatic sites. Dosage modifications are not needed for hepatic or renal impairment.

7.4.2 Pharmaceutical Data: The drug is marketed commercially in 500 mg. ampules.

7.4.3 Dose: 5-FU dose = 1 gm/m²/24 hr by continuous infusion for 120 hours to start on days 1, 22 and 43 after the second mannitol infusion is completed.

7.4.4 Administration Guidelines: The total daily dose is administered by continuous infusion over 24 hours daily for 5 days.

7.5 Dose Modifications

7.5.1 Hematologic Toxicity: ~~(8/16/93, 12/23/94, 6/3/96)~~

1) On the day of scheduled treatment patients must have the following counts (cells/ul): granulocytes ≥ 1000, platelets ≥ 100,000 (no dose modifications). If counts are inadequate, treatment will be delayed with counts repeated weekly and doses modified based on the nadir count of the preceding cycle:

<u>Nadir</u>		<u>Dose</u>	
<u>Platelets</u>	<u>Granulocytes</u>	<u>Cisplatin</u>	<u>5-FU</u>
≥ 50,000	and ≥ 1000	100%	100%
< 50,000	or < 1000	80%	* 80%

* Infusion to be shortened to 1 gm/m²/day x 96 hours.

7.5.2 Gastro-intestinal Toxicity: Hold treatment until recovery. Resume with dose modification indicated.

<u>Stomatitis/diarrhea</u>	<u>Cisplatin</u>	<u>5-FU</u>
Grade 1-2	100%	100%
Grade 3-4	100%	* 80%

* Infusion to be shortened to 1gm/m²/day x 96 hours

7.5.3 Dermatitis Secondary to 5-FU:

For generalized symptomatic macular, papular, or vesicular eruption (grade 3), hold 5-FU until recovery. Resume at 80% of the previous dose.

7.5.4 Nephrotoxicity secondary to cisplatin:

Dose will be modified based on the serum creatinine and/or creatinine clearance immediately prior to each cisplatin dose. If the serum creatinine is ≤ 1.5, creatinine clearance is not necessary for treatment with full dose, 100 mg/m². If the serum creatinine is > 1.5, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly) and the dose modified as indicated.

<u>Serum Creatinine</u>		<u>Creatinine Clearance</u>	<u>Cisplatin Dose</u>
≤ 1/5	or	> 50 cc/min	100 mg/m ²
> 1.5	and	40-50 cc/min	60 mg/m ²
> 1.5	and	< 40 cc/min	0

7.6 Adverse Drug Reaction Reporting/RTOG Members (12/23/94)

7.6.1 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:

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

- 7.6.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.6.1.3 Any death on study if clearly related to the commercial agent(s).
- 7.6.1.4 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.
- 7.6.2 The ADR report should be documented on FDA Form 3500 (Appendix V) and mailed to the address on the form and to:

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

- 7.6.3 Death from any cause while the patient is receiving protocol treatment, or up to 30 days after the last protocol treatment, must be reported to RTOG Headquarters within 10 days of discovery.

7.7 Adverse Drug Reaction Reporting/ECOG Members

The following adverse reactions must be reported to ECOG and NCI in the manner described. In addition, your local IRB should be notified.

7.7.1 Deaths

Any death from any cause while a patient is receiving treatment on this protocol or up to 30 days after the last dose of protocol treatment, or any death which occurs more than 30 days after protocol treatment has ended but which is felt to be treatment related must be reported as follows:

Commercial Agents - An Adverse Drug Reaction (ADR) Form for Investigational Drugs (#391R) must be sent to the ECOG Statistical Center Data Management Office (ATTN: ADR) within 10 working days of the event. Upon receipt, the ECOG Statistical Center will fax the ADR form to RTOG Headquarters. This form must be signed by the treating investigator.

Mailing address for ECOG ADR reporting is:

**ECOG Statistical Center
Data Management Office
303 Boylston Street
Brookline, MA 02146-7215
ATT: ADR**

7.7.2 Unexpected Toxicities

Commercial Agents - For any unexpected toxicity (not reported in the literature or the package insert) an Adverse Drug Reaction (ADR) Form for Investigational Drugs (#391R) must be submitted to the NCI and to the ECOG Statistical Center Data Management Office (ATTN: ADR) within 10 working days of the event. Upon receipt, the ECOG Statistical Center will fax the ADR form to RTOG Headquarters. This form must be signed by the treating investigator.

7.7.3 Expected Toxicities

Commercial Agents - Expected grade ≤ 4 toxicities need not be reported.

7.7.4 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 Flow Sheets submitted to the ECOG Statistical Center Data Management Office (ATTN: DATA) to be forwarded to RTOG Headquarters according to the protocol.

7.8 Adverse Drug Reaction Reporting/SWOG Members

- 7.8.1 All Southwest Oncology Group (SWOG) investigators are responsible for reporting of adverse drug reactions according to the NCI and Southwest Oncology Group Guidelines. SWOG investigators must:

Call the SWOG Operations Office 210/677-8808 within 24 hours of any suspected adverse event deemed either drug-related, or possibly drug-related.

Instructions will be given as to the 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 Headquarters Data Management Staff as listed in the RTOG reporting guidelines.

- 7.8.2 **Within 10 days the investigator must send the completed (original) DCT form** (for regimens using investigational agents) or the FDA 3500 form (for regimens using only commercial agents) **(11/30/94)** to the NCI:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824**

- 7.8.3 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 (11/30/92):

ADR Program
SWOG Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3218

8.0 SURGERY (3/15/93,8/16/93,12/23/94)

8.1 Pretreatment Evaluation

- 8.1.1** The head and neck surgeon will perform a complete head and neck examination. The extent of the primary tumor and the presence of cervical metastasis will be described in detail on the data collection forms.
- 8.1.2** An AJC stage (Appendix III) will be assigned to each patient.
- 8.1.3** A direct laryngoscopy and a biopsy will be performed on each patient for histologic confirmation and assessment of tumor extent.
- 8.1.4** Complete dental and nutritional evaluation will be obtained on each patient.
- 8.1.5** A CT scan will be obtained and, along with the head and neck examination, will be used to determine stage.

8.2 Treatment Evaluation

- 8.2.1** Patients in Arm 1 will undergo an indirect laryngoscopy and CT scan after the second cycle of chemotherapy.

8.3 Management of Cervical Metastasis

- 8.3.1** Patients with clinically positive lymph node metastasis ≥ 3 cm in greatest diameter or multiple lymph nodes will undergo a neck dissection at 8 weeks post completion of therapy. At the time of neck dissection, a direct laryngoscopy will be performed to assess the status of the primary tumor; however, a biopsy will be taken only when mucosal abnormality is present. If persistent tumor is documented at the primary (see Section 6.8), a salvage laryngectomy will be performed along with the neck dissection.
- 8.3.1.1** If frozen exam is used to evaluate primary site disease status, the surgeon may elect to wait for results based on permanent section thereby performing the primary site surgery at a subsequent date.
- 8.3.2** The type of neck dissection performed will be at the discretion of the attending surgeon. This may range from a regional to classical radical neck dissection. In every case the lymph node group (s) involved prior to treatment will be removed. The regions dissected, lymph node groups removed and anatomic structures sacrificed and surgical morbidity will be detailed on the data collection forms which will include 1) type of neck dissection, 2) operative findings, 3) operative defect, 4) post operative morbidity and complications, 5) status of nodes and surgical margins.

8.4 Post-Treatment Evaluation

- 8.4.1** The patients in each arm of study will be seen in follow-up at 8 weeks post-therapy. If a mucosal abnormality is present or if persistent disease is suspected, examinations under anesthesia and direct laryngoscopy will be performed. Biopsies will be obtained if persistent disease is suspected (See Section 6.8). In most situations, biopsy should not be performed before the 8 week period.
- 8.4.2** After the 8 week post-treatment examination, the patients will be followed at 3 month intervals for the first year then semiannually.

8.5 Salvage Laryngectomy

- 8.5.1** Two groups of patients will undergo salvage laryngectomy:
- 1) Patients with histologically proven recurrent or persistent squamous cell carcinoma of the larynx following all treatment; and
 - 2) Patients in Arm 1 who achieve less than a partial response at the primary site or unequivocal progression of nodal disease after 2 cycles of induction chemotherapy. Surgery should be performed within seven working days from the time of tumor assessment. A neck dissection unilateral or bilateral will be performed as dictated by the presence of lymph node metastasis or at the discretion of the surgeon.
- 8.5.2** Every attempt will be made to obtain a clear margin of resection. A minimum margin of resection will be 1 to 2 cm for the gross tumor and the absence of tumor at the resection margin will be determined by frozen section examination.
- 8.5.3** The type of pharyngeal closure will be left to the discretion of the attending surgeon. Primary closure will be attempted whenever possible. Reconstruction with flaps or grafts, when required, may be used. Prophylactic antibiotics are mandatory in all patients and they will be administered just prior to surgery and continued for 24 to 48 hours postoperatively.

8.5.4 The operative report must accurately and completely describe the location and the extent of the primary tumor, clinical metastasis at the time of salvage surgery, and margin of resection of gross tumor in cm. The results of intraoperative frozen section should be included. A copy of the operative report, the Surgical Form and surgical morbidity must be submitted on each patient.

9.0 OTHER THERAPY

Does not apply to this study.

10.0 PATHOLOGY (4/14/95, 11/15/95, 9/8/98)

10.1 Fixed Tumor Repository Study

- 10.1.1** Patients entered on this study are also eligible for the RTOG Tissue Bank.
- 10.1.2** To receive an additional RTOG case credit. The following must be provided to RTOG:
 - 10.1.2.1** One paraffin block of tumor or 15 unstained slides. Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.
 - 10.1.2.2** Pathology report documenting that submitted block or slides contain tumor.
- 10.1.3** A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the RTOG Tissue Bank.
- 10.1.4** To encourage compliance, your Pathology Department could be reimbursed for obtaining blocks or cutting slides. Contact RTOG Administrator.
- 10.1.5** 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*).
- 10.1.6** The specified materials are sent to:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
8th Ave & C Street
Salt Lake City, UT 84143**

10.1.7 ECOG institutions should only submit 15 unstained slides, a copy of the pathology report, and the RTOG Pathology Submission Form. Do NOT send paraffin blocks. If paraffin blocks are submitted, they will be returned to the contributing institution and slides will be requested. ECOG members should send pathology materials to: ECOG Pathology Coordinating Office, Evanston Hospital Room B634, 2650 Ridge Avenue, Evanston, IL 60201-1797. The materials will be logged into the ECOG pathology database and the slides will be forwarded to RTOG Headquarters.

11.0 PATIENT ASSESSMENTS

11.1 Required Studies (8/16/93, 12/23/94, 9/8/98)

Physical Tests	Pre Study	During TX	During FollowUp
History and Physical Exam	X	X ^a	X
Weight & KPS	X	X ^a	X
Panendoscopy/Biopsy ⁿ	X		X ^b
Indirect laryngoscopy		X ^c	X ^d
Direct laryngoscopy	X		X ^m
Tumor measurement	X	X ^e	X ^d
Toxicity notation		X ^g	X
Dental Exam ^o , Nutritional Status	X		
QOL Questionnaire	X		X
ASA Status		X ^l	X ^l
Laboratory			
CBC/diff/platelets	X	X ^g	x ^f
Creatinine, CrCl, BUN	X	X ⁱ	x ^f

Alk phos/SGOT/Bilirubin	X		
Urinalysis	X		
Thyroid Stim. Hormone	X		x ^j
Serum electrolytes	X	X ⁱ	x ^f
Serum calcium, Uric Acid, Total Protein, Albumin	X		
Magnesium, Phosphorus	X	X ⁱ	
X-rays and Scans			
Chest X-ray	X		X ^j
CT of primary & neck	X	X (arm 1, after chemo #2)	X ^h
Liver Scan & Bone scan	X ^k		X ^k

- a. days 22 and 43
- b. biopsy if mucosal abnormality is present or recurrence is suspected
- c. arm 1: days 36
- d. arms 1, 2 and 3: at 8 weeks following RT completed, then q followup
- e. arm 1: day 36
arm 2 and 3: none required
- f. 4 weeks after completion of RT
- g. weekly
- h. arms 1,2, 3: 8 weeks after completion of RT
- i. arms 1 and 2: days 22 and 43, repeat CrCl only if SCr > 1.5
- j. every 6 months
- k. if alkaline phosphatase, SGOT, or bilirubin are elevated
- l. before surgery
- m. at time of node dissection, as applicable.
- n. Chest CT and barium esophagram may be substituted.
- o. Dental evaluation not required for edentulous patients

11.2 Patient Follow-Up (3/15/93,12/23/94)

- 11.2.1** All patients will enter a follow-up program commencing one month after the last protocol treatment.
- 11.2.2** At 8 weeks after completing RT those patients initially staged with regional nodal disease ≥ 3 cm or with multiple nodes will undergo neck dissection.
- 11.2.3** Follow-up year 1:
- 11.2.3.1** Each visit will consist of routine follow-up care with complete head and neck examination, performance status, weight, and evaluation for late toxicity effects.
- 11.2.3.2** Repeat laboratory and scans as indicated on study calendar.
- 11.2.3.3** All patients in Arms 1, 2 and 3 will have a followup CT scan of the head and neck at eight weeks post treatment.
- 11.2.4** Follow-up year 2 & 3:
- 11.2.4.1** Routine follow-up care to consist of a complete head and neck examination, performance status, weight and evaluation for late toxicity.
- 11.2.4.2** TSH and chest x-ray will be obtained every 6 months. Repeat CT scan of the primary and neck will be obtained if clinically indicated.
- 11.2.5** QOL questionnaires will be collected prior to treatment (onstudy), at eight weeks after the completion of protocol treatment (not to include node dissection), then every 3 months during the first year, then semiannually..

11.3 Criteria for Evaluation and Endpoint Definitions

- 11.3.1** **Measurable Disease:** Bidimensionally measurable, with clearly defined margins on photograph, x-ray or scan. At least one diameter must be $> .5$ cm. Bone lesions are not included.
- 11.3.2** **Evaluable Disease:** Undimensionally measurable lesions, masses with margins not clearly defined, palpable nodal disease, lesions with both diameters $< .5$ cm, bone disease. Markers which have been shown to be highly correlated with extent of disease are also considered evaluable.

11.3.3 Objective Status to be Recorded at Each Evaluation: If an organ has too many measurable lesions to measure at each evaluation, choose three to be followed before the patient is entered on study. The remaining measurable lesions in that organ will be considered evaluable for the purpose of objective status determination. Unless progression is observed, objective status can only be determined when ALL measurable and evaluable sites and lesions are assessed.

11.3.3.1 Complete Response (CR): Complete disappearance of all measurable and evaluable disease. No new lesions. All measurable, evaluable and non-evaluable lesions and sites must be assessed.

11.3.3.2 Partial Response (PR): Applies to patients with at least one measurable lesion: Greater than or equal to 50% decrease under baseline in the sum of the products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. All measurable and evaluable lesions and sites must be assessed.

11.3.3.3 Stable: Does not qualify for complete response, partial response or progression. All measurable and evaluable sites and lesions must be assessed.

11.3.3.4 Progression: 50% increase in the sum of products of measurable lesions over smallest sum observed (over baseline if no decrease), OR reappearance of any lesion which had disappeared, OR clear worsening of any evaluable disease, OR appearance of any new lesion/site, OR failure to return for evaluation due to deteriorating condition (unless deterioration is clearly unrelated to this cancer).

11.4 Definitions and Outcome Measures (3/15/93,12/23/94)

11.4.1 Survival Time: Time from randomization to death.

11.4.2 Time to Treatment Failure: Time from randomization to either time of disease progression, further treatment or death for patients who do not achieve a CR to protocol treatment or time of disease recurrence or death for patients achieving a CR.

11.4.3 Objective Tumor Response with Induction Chemotherapy (Arm 1): For patients randomized to induction chemotherapy, primary and nodal status will be assessed two weeks following the second cycle of chemotherapy by indirect laryngoscopy and clinical examination. **Patients who show no clinical tumor response or show progression will undergo surgery within one week of tumor assessment.** For patients who show clinical regression of the primary tumor and have neck nodes that have regressed or are stable will receive a third cycle of chemotherapy. Response will be defined as complete, partial, stable or progression. Patients who receive radiation therapy following completion of chemotherapy will have a final tumor assessment, indirect laryngoscopy and CT scan 8 weeks after completion of RT. Response will be categorized as complete or persistent residual disease documented by biopsy.

11.4.4 Objective Tumor Response with Concomitant Chemotherapy and Radiation Therapy (Arm 2) and Radiation Therapy Alone (Arm 3): Response will be determined by indirect laryngoscopy and CT scan 8 weeks after completion of radiation therapy. Patients will be categorized as having complete response, or persistent residual disease which must be documented by biopsy.

11.4.5 Tumor Recurrence: Tumor recurrence will be classified according to the site of recurrence and by the interval between randomization and time of first recurrence. Time of recurrence is defined as the date of clinical examination at which recurrence is confirmed, either by biopsy or other indicators. The site of recurrence will be categorized as:

11.4.5.1 Local: at or immediately adjacent to the site of the original primary;

11.4.5.2 Regional: Within the neck, either as a nodal or extra nodal focus located according to the regional classification listed in the section of pathologic evaluation; or

11.4.5.3 Combined: Local and regional recurrence.

11.4.5.4 Distant: Any other site classified according to the organ involved;

11.4.5.5 Second primary cancer.

11.5 Quality of Life Assessments

11.5.1 Two tested and validated patient administered questionnaires have been selected. Between the two questionnaires, four domains of QOL and ten symptom-specific items will be measured and evaluated.

11.5.1.1 The first questionnaire developed by Cella et al. is the Functional Assessment of Cancer Therapy for Head and Neck (FACT - H&N). The F.A.C.T. - H&N (Version 2) is a 43 item inventory. Of the 43 items, 28 are summarized into five subtest scores representing the different domains of QOL being measured (physical, social, emotional well-being, contentment and relationship with doctor). In addition, five of the

43 items ask patients to rate the importance of each subtest with respect to their QOL. The remaining nine items under the sixth subtest (Additional Concerns) are site specific for head and neck cancer patients (eg., swallowing, dry mouth, etc.). The inventory produces five scores, one for each domain (subtest) and one total score incorporating the site specific items.

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

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

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

12.0 DATA COLLECTION

12.1 Summary of Data Submission (11/30/92, 12/23/94, 4/14/95, 9/8/98)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 1 week of randomization
Initial Evaluation Form (I1)	Within 2 weeks of randomization
Tumor Diagrams: Primary (I6) Nodes (I7)	
Diagnostic Pathology Report (P1)	
Blocks/Slides (P2)	
PreRx Symptom Scale (PQ)	
FACT - H&N Form (FA)	
CT Report (<i>Neck</i>) if T4 (C3)	
<u>Preliminary Dosimetry Information:</u>	Within 1 wk of start of RT
RT Prescription (Protocol Treatment Form) (T2)	
Films (simulation and portal) (T3)	
Calculations (T4)	

Chemotherapy Flowsheets (M1) (Arms 1&2)	At 4 and 8 weeks from chemo start, upon onset of \geq grade 4 toxicity, and within one week of last dose if terminated early.
Interim Report (F9) (Arm 1)	2 weeks following completion of the second cycle of chemotherapy.
<u>Radiotherapy Form (T1)</u> Final Dosimetry Information: Treatment Record (T5) Isodose Distribution (T6) Boost Film (simulation and portal) (T8)	Within 1 week of RT end
Surgery Form (S1) Surgical Report (S2) Operative Path Report (S5) Surgical Checklist (S7)	When applicable (within two weeks of surgery)
Follow-up Form (F1)	At 8 weeks after completion of protocol treatment, q 3 months for one year; then q 6 months in years 2 and 3; then annually; at progression/relapse, toxicity \geq grade 4, and at death
Symptom Scale-Followup (QL) FACT - H & N Form (QF)	With every followup.
Notification Form (O2)	At 2 years after randomization; at laryngectomy; at death if < 2 years
Autopsy Report (D3)	As applicable

12.2 ECOG AND SWOG DATA SUBMISSION (9/8/98)

- 12.2.1** ECOG: The required forms must be submitted to the ECOG Statistical Center Data Management Office, 303 Boylston Street, Brookline, MA 02146-7215 (ATTN: DATA). They will be forwarded to RTOG by the ECOG Statistical Center.
- 12.2.2** SWOG: The original data forms as listed in this section should be submitted at the required intervals to the Southwest Oncology Group Statistical Center, Fred Hutchinson Cancer Research Center, 100 Fairview Avenue North, MP-557, P.O. Box 19024, Seattle, WA 98109-1024. Include the RTOG Protocol number and patient case number as well as the Southwest Oncology Group study number and patient number. It is not necessary to submit extra copies.
- 12.2.3** Rapid Review Items: Time critical data which requires rapid submission must be sent directly to RTOG:

- T2 - Protocol Treatment Form
- T3 - Photon Localization film (for all fields treated initially)
- T4 - Photon dose calculations (for all fields treated initially)

Send to:

**Radiation Therapy Oncology Group (RTOG)
ATT: Dosimetry
1101 Market Street
Philadelphia, PA 19107**

12.2.4 Both the ECOG or SWOG and RTOG assigned case and study numbers must be recorded on all items submitted. Unidentified data will be returned

12.2.5 Request for Study Information and Forms Request:

Requests for additional information or clarification of data will be routed through ECOG/SWOG for distribution to the individual institution. The RTOG memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response. Periodically (generally three times per year) computer generated lists identifying delinquent material are prepared and are routed by RTOG through ECOG/SWOG for distribution.

13.0 STATISTICAL CONSIDERATIONS

This study aims at identifying the optimal treatment for laryngeal carcinoma which results in preservation of laryngeal function while not compromising survival. One of the three treatments involving induction chemotherapy followed by radiation therapy, recently examined by the VA, suggested a two-year survival rate of 65% with successful laryngeal preservation in a patient group comparable to that being targeted in this trial. The comparison arm in the VA trial involved laryngectomy, yet showed a similar rate of two-year survival. This study aims at replicating the results of the induction chemotherapy + RT arm of the VA study and compare clinical outcomes from this treatment arm to those from two other treatment procedures (RT only and concurrent chemo-RT treatment) used in previous RTOG trials. It is believed that the RT only treatment will yield organ preservation and survival outcomes similar (or at least not substantially worse) than those experienced in the VA treatment regimen while not subjecting patients to toxicity and treatment complications associated with chemotherapy. The other treatment arm, involving concurrent chemotherapy and radiotherapy, hopes to demonstrate improved organ preservation and survival outcomes as compared to the VA arm. The primary outcome of interest will be laryngectomy-free survival at two years from date of randomization.

13.1 Study Endpoints

Each treatment will be evaluated with respect to the primary endpoint of **laryngectomy-free survival at two years from the date of randomization**. Using this endpoint a patient will be considered to exhibit a treatment "failure" at the time of death or the time laryngectomy is performed. In addition, several secondary endpoints will also be examined for the purpose of devising future clinical investigation:

- disease-free survival;
- absolute survival;
- local-regional control at end of chemotherapy (in VA arm) and at end of RT;
- patterns of disease relapse, development of metastatic disease;
- development of second primary tumors;
- incidence of acute and late adverse reactions associated with treatment; and,
- patterns of laryngeal function/speech quality (a quality of life endpoint).

13.2 Sample Size

This trial will aim at detecting, with 80% power and a Type-I error rate of 5%, a 15% difference from a baseline two-year survival rate of 65%, expected in the induction chemotherapy + RT treatment arm (VA arm). In order to accomplish this, and adjusting for the multiple comparisons between the two comparison arms and the VA treatment arm, we will require 163 eligible patients to be entered on each of the three treatment arms.⁴¹ Allowing for 10% of the patients initially considered eligible to be found ineligible upon chairman review of on-study information, **a total of 546 patients will be entered onto this study (182 per treatment arm)**.

With 546 patients, we are likely, with 80% probability ($1-b=0.80$), to detect a significant difference between the RT only treatment arm and the VA arm, and/or between the concurrent chemo + RT treatment arm and the VA arm, if either or both of the true two-year laryngectomy free survival rates in the two comparison arms differ from a 65% rate assumed in the VA arm by at least 15%, i.e., as low as 50% (or lower), or as high as 80% (or higher). We will have a 5% chance of erroneously concluding a significant difference between these arms when no difference truly exists (two-sided $\alpha = 0.05$).

13.2.1 Sample Size Adjustment in Response to Treatment Noncompliance

All analyses will be conducted based on the assigned treatment of patients entered onto this trial, regardless of the actual treatment received. Although it is accepted that this approach will yield the most valid estimates of treatment efficacy, such estimates can be severely affected by high rates of treatment noncompliance. To adjust for the effect of such noncompliance, the required sample size can be modified once we have fairly reliable estimates of the noncompliance rate in each of the treatment arms and can provide estimates of the rate of response that is to be expected in those patients failing to complete the planned therapy. This

adjustment is based on the computation of the "observable" response rate (p_i^*) in a particular treatment group (i) as follows:

$$P_i^* = l_i P_i (1 - l_i) P_i'$$

where l_i is the rate of compliance in treatment arm (i), p_i is the assumed rate of response in patients that receive that treatment per protocol and p_i' is the rate of response that is expected in those patients that did not receive therapy as prescribed in the protocol. Having computed these values for each of the treatment arms, we can recompute the required sample size needed to detect a difference between the treatment arms, using these modified rates.

From past experience it is expected that the two treatment arms that involve chemotherapy are most likely to experience the highest degree of treatment noncompliance. The treatment compliance experience in RTOG 81-17, which forms the basis for the treatment to be administered to patients assigned to Arm 2 of this trial, suggests that 84% of the patients will receive at least two courses of chemotherapy, and 86% will receive an acceptable level of planned RT. Experience in the VA trial suggested very high compliance to what will be our Arm 1. However, the VA study had a very particular patient population and treatment setting. The third arm of the this trial involves RT only and thus it is expected compliance in this arm will be quite high.

The one critical component missing in our providing estimates of the effects of noncompliance on required sample size is our lack of knowledge concerning the expected response rates in patients not completing protocol therapy in each group. It is logical that we can assume patients not receiving full chemotherapy will respond similar to those patients on the RT only arm, however estimating the response rate for patients on the RT only arm is precisely one of the goals of this study and is obviously not known *a priori*. Thus, in this trial we must wait until a reliable estimate of this rate is established before any sample size adjustment is considered. It is our intention, therefore, to obtain estimates of treatment response for the subgroups of patients receiving/not receiving therapy per protocol and of the treatment-specific compliance rates at the time of the first planned interim analysis (see below, Section 13.6). After we have this information, we can consider modifying the required sample size to allow adequate power for observing a clinically relevant treatment difference with consideration for the effect of these patients on our observable response rates. This adjustment will be performed prior to reaching the initially targeted sample size and thus prior to termination of the accrual phase of the study.

13.3 Patient Accrual

A recent survey of RTOG institutions suggested that between 275 and 319 patients per year would meet the eligibility requirements of this study. It was further estimated that of these patients, 168-196 patients per year would consent to be randomized. These estimates suggest the accrual phase of the study may be completed in about three years (allowing two months for IRB review), or can possibly require just over three years (41 months with two month delay for IRB). These estimates considered only accrual from RTOG participating institutions. Intergroup participation in this trial would significantly reduce the duration of the accrual phase.

13.4 Randomization Scheme (12/23/94)

The treatment allocation will be done using a randomized permuted block design within strata to balance for patient factors other than institution. There will be a check on the balance of treatment assignments within each full member institution.

Based on analyses of the RTOG head neck database, three factors were identified as influencing the treatment outcomes of interest, and will thus be treated as stratification variables in the randomization process. These variables (with stratification levels indicated in parentheses) are: Site of Primary (glottic vs supraglottic), N-Stage (N_{0-1} vs N_{2-3}), and T-Stage with consideration of involvement of relevant physical structures (T_2 vs T_3 with fixed cord involvement vs T_3 with no cord fixation). The protocol was revised to include patients with T4 lesions. Instead of adding another subdivision to existing T stage variable, patients with T4 lesions will be randomized among three treatment options without further stratifying for site or N stage.

13.5 Analysis Plans (12/23/94)

13.5.1 Background for revision

The original study monitoring committee for this study has been replaced by the external RTOG Data Monitoring Committee (DMC) which consists of a radiation therapist, surgeon, medical oncologist, statistician, and ethicists. These individuals are from institutions that do not otherwise participate in RTOG studies. The description of the analyses plans has been revised to clearly delineate the DMC's role and to add further details about the analyses.

13.5.2 Interim Analyses to monitor the study progress:

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 distributions of important prognostic baseline variables and the frequencies and severity of the toxicities by treatment arm. If these analyses suggest the occurrence of unexpected toxicities or unacceptable protocol compliance in one or more treatment arms, corrective action will be considered. This may result in modifications of treatment regimen(s), modification of sample size requirements, or termination of one or more treatment arms (due to toxicity outcomes). The interim report will not contain the results from the treatment comparisons with respect to the efficacy endpoints. (Laryngectomy-free survival, *disease free survival*, *absolute survival*)

13.5.3 Significance testing for early termination

In order to ensure that patients entered on this protocol are not being randomized to an inferior treatment or being denied an obviously superior treatment, significance testing of all treatment outcomes will be conducted at the earliest point in the study that meaningful differences can be ascertained. The primary endpoint for this study is laryngectomy-free survival at two years from date of randomization. This endpoint will be tested twice for early termination of the trial. First significance test will be performed when the first 137 patients (25% of the total sample size of 546) have two-year follow-up data available. If it yields a statistically significant difference laryngectomy-free survival between the VA arm and either of the two comparison arms, at a $\alpha = 0.0025$ ($0.005/2$, taking into consideration the two comparisons with the control group), then a recommendation would be made to the RTOG DMC that subsequent patient entry to the less favorable arm(s) of the protocol be terminated. The result from the tests will be then reported to the RTOG Data Monitoring Committee(DMC) for their consideration. If no significant difference is found, the study will continue as planned and a second significance test will be conducted when 410 patients (75% of 546 patients) have two year follow-up information available. A response difference will be considered statistically significant in this analysis at a nominal alpha level of 0.014. The result from the tests will be then reported to the RTOG Data Monitoring Committee for their consideration.

The significance levels were selected using the approach per O'Brian and Fleming⁴² but were adjusted to allow less conservative early stopping at the first significance test (see Lan and DeMets⁵⁷).

13.5.4 Analysis for Reporting the Initial Treatment Results:

This major analysis will occur after each patient has been potentially followed for a minimum of 24 months unless the study is stopped earlier. It will include tabulation of all cases entered, and those excluded from the analyses with the reasons, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints mentioned in Section 13.1. The primary hypothesis for the study is whether the control and the experimental arms have different effects on two-year laryngectomy-free survival rate. All eligible patients randomized will be included in the comparison. All eligible patients randomized will be grouped by assigned treatment arm in the analysis. Then, a treatment difference will be considered statistically significant at a nominal alpha level of 0.045 to preserve an overall Type I error rate of 0.05 because of the two earlier tests.

The primary hypothesis of treatment benefit will be tested using the Cox proportional hazard model with the stratification factor of location or primary, T-stage, and N-stage included as covariates. Additional analyses of treatment effect will include modifying factors such as age, sex, race, and other patient characteristics. These analyses will also use the Cox proportional hazard model. The treatment comparison on disease free survival, local control rate, and absolute survival will be analyzed in a similar fashion.

Quality of life will be assessed at fixed time points post therapy to and evaluate the differences between modalities and/or subpopulation using factor analysis and categorical techniques.⁵⁴ Longitudinal changes in quality of life will be assessed using a modification of the TWiST methodology.^{55,56} This utilizes the changes in aspects of QOL as measured by the FACT-H & N and QOL questionnaire to incorporate this via weights to adjust survival. Correlations between the two quality of life assessment instruments will be made, as well as associations with late toxicities and Karnofsky performance status. Evaluation of quality of life data will be undertaken after the accrual phase has been completed.

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APPENDIX I

**RTOG 91-11
ECOG R9111
SWOG 9201**

Phase III Trial to Reserve the Larynx: Induction Chemotherapy and Radiation Therapy versus Concomitant Chemotherapy and Radiation Therapy versus Radiation Therapy

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so 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 cancer of the throat and that treatment with surgery will require removal of my voice box (larynx). Removal of my voice box would result in loss of natural speech. My doctors feel that participation in this study may help me save my voice box. The purpose of this study is to try to preserve my voice box (larynx) by using a non-surgical treatment. Three treatments will be compared: 1) chemotherapy followed by radiation, or 2) chemotherapy given at the same time as radiation, or 3) radiation alone.

DESCRIPTION OF PROCEDURES (4/14/95)

This study involves assigning patients with larynx cancers to receive either radiation or radiation plus chemotherapy.

It is not clear at the present time which of the three procedures is better. For this reason, the procedure 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 one of the procedures to me and that the chance of my receiving any one of the three offered options are approximately equal. The treatments are:

- Treatment 1: Cisplatin and 5-FU will be given twice three weeks apart then I will be evaluated. If my throat cancer shows signs of shrinkage or has disappeared altogether, I will get another dose of chemotherapy followed by radiation once a day, five days a week for seven weeks. Or, if after the first two doses of chemotherapy, my cancer has not gotten appreciably smaller, I will have surgery to remove the remaining disease and then radiation for approximately 5 weeks.
- Treatment 2: Cisplatin will be given once every 21 days (for three doses on Days 1, 22, and 43) during radiation which will be given once a day, five days a week for seven weeks.
- Treatment 3: Radiation without chemotherapy will be given once a day, five days a week for seven weeks.

Radiation can be given on an outpatient basis. Cisplatin is given into the vein over 20-30 minutes. 5-FU is given into the vein by continuous infusion over 120 hours following cisplatin administration in Treatment 1. Since cancer treatments may affect a fetus, I am advised to avoid the possibility of conception during chemotherapy.

After all treatment is completed I will be re-examined. If cancer cells are still present, surgery will be recommended to me. If the cancer involved the lymph nodes in my neck at the time I was first examined, I may be required to have surgery to my neck only which my doctors believe may lessen the risk of tumor recurring in the neck.

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.

In addition, in order to evaluate how the treatment I am undergoing is affecting the quality of my lifestyle, I will be asked to complete two questionnaires at several time points. Although some questions may be of a personal nature, I can complete only as many as I feel comfortable answering.

RISKS AND DISCOMFORTS (11/30/94)

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

Risks from radiation include: Temporary skin redness or peeling, difficulty swallowing, or reduction in blood counts. Late effects may include dryness of the mouth, dental cavities, continued soreness in the mouth and throat, stiffness of the neck, hoarseness, or damage to the jaw bone causing bone destruction that might produce pain or require surgery if severe.

Risks from chemotherapy include: Cisplatin - nausea or vomiting, hearing dysfunction, kidney malfunction, hair loss, lowered blood counts possibly leading to increased risks of infection or bleeding, and rarely, the risk of an allergic reaction or acute leukemia. 5-Fluorouracil nausea, vomiting, mouth soreness, diarrhea, lowered blood counts, darkening of the skin, excessive tearing (eyes). Hair loss is uncommon but has been seen.

Risks from surgery: bleeding, infection, formation of fistulous tracts (opening between organs) and the possible complications of anesthesia.

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

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 or receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator in charge, at _____ . In addition, I may contact _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the 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 radiation therapy alone twice a day, chemotherapy, surgery, or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future. I will be provided with a written list of procedures related solely to research which would not otherwise be necessary. These will be explained to me by my physician. Some of these procedures may result in added costs but may be covered by insurance.

VOLUNTARY PARTICIPATION

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

CONFIDENTIALITY

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

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

Patient Signature (or legal Representative)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

APPENDIX III

AJC Staging - 3rd Edition, 1988

Primary Tumor (T)Larynx

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

Supraglottis

- T1 Tumor limited to one subsite of supraglottic with normal vocal cord mobility
- T2 Tumor invades more than one subsite of supraglottic or glottis, with normal vocal cord mobility
- T3 Tumor limited to larynx with vocal cord fixation and/or invades postcricoid area, medial wall of pyriform sinus, or pre-epiglottic tissues
- T4 Tumor invades through thyroid cartilage, and/or extends to other tissues beyond the larynx (e.g., to oropharynx, soft tissues of neck)

Glottis

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

Subglottis

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

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
- N2 Metastasis in a single ipsilateral lymph node,

- more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N2a Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
- N2b Metastasis in multiple ipsilateral lymph nodes, none, more than 6 cm in greatest dimension
- N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
- N3 Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

- MX Presence of distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T4	N0, N1	M0
	Any T	N2, N3	M0
	Any T	Any N	M1

APPENDIX V

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).
2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.
3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.
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), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.
7. See the specific protocol for criteria utilized to grade the severity of the reaction.
8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.
9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.
10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (grade 5) or life threatening (grade 4) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq grade 2) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. Form 1639 is to be used in reporting details (see attached). All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq grade 3) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting and 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 only a reasonable suspicion.

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

i. Phase I Studies Utilizing Investigational Agents

- | | |
|--|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |
| - All life threatening (grade 4) events which may be due to agent. | As above |
| - First occurrence of any toxicity (regardless of grade). | Report by phone within 24 hours to IDB <u>drug</u> monitor and RTOG Headquarters.
**A written report <u>may</u> 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 NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

Physical Status Classification American Society of Anesthesiologists (ASA)*

<u>Status</u>	<u>Disease State</u>
ASA Class 1	No organic, physiologic, biochemical or psychiatric disturbance
ASA Class 2	Mild to moderate systemic disturbance that may or may not be related to the reason for surgery Examples: Heart disease that only slightly limits physical activity, essential hypertension, diabetes mellitus, anemia, extremes of age, morbid obesity, chronic bronchitis
ASA Class 3	Severe systemic disturbance that may or may not be related to the reason for surgery Examples: Heart disease that limits activity, poorly controlled essential hypertension, diabetes mellitus with vascular complications, chronic pulmonary disease that limits activity, angina pectoris, history of prior myocardial infarction
ASA Class 4	Severe systemic disturbance that is life-threatening with or without surgery Examples: Congestive heart failure, persistent angina pectoris, advanced pulmonary, renal, or hepatic dysfunction
ASA Class 5	Moribund patient who has little chance of survival but is submitted to surgery as a last resort (resuscitative effort) Examples: Uncontrolled hemorrhage as from a ruptured abdominal aneurysm, cerebral trauma, pulmonary embolus
Emergency Operation (E)	Any patient in whom an emergency operation is required. Example: An otherwise healthy 30-year-old female who requires a dilatation and curettage for moderate but persistent hemorrhage (ASA Class 1 E)

* From information in American Society of Anesthesiologists, New classification of physical status, Anesthesiology: 24: 111, 1963.

APPENDIX VII

Treatment Sequence
Arm 1

- a. If a mucosal abnormality is present on indirect laryngoscopy, obtain CT scan of the head and neck at 12 weeks post-treatment. **(3/15/93)**
- b. A neck dissection will be performed if nodal disease ≥ 3 cm or multiple nodes were present at the time of randomization regardless of response to treatment.
- c. A direct laryngoscopy will be performed at the time of neck dissection. Biopsy will be performed only if a mucosal abnormality is present.

APPENDIX VII
Treatment Sequence

Arm 2

- a. If a mucosal abnormality is present on indirect laryngoscopy, direct laryngoscopy and biopsy will be performed. Obtain CT scan of the head and neck. **(3/15/93)**
- b. A neck dissection will be performed if nodal disease ≥ 3 cm or multiple nodes were present at the time of randomization regardless of response to treatment.
- c. A direct laryngoscopy will be performed at the time of neck dissection. Biopsy will be performed only if a mucosal abnormality is present.

APPENDIX VII **Treatment Sequence** **Arm 3**

- a. If a mucosal abnormality is present on indirect laryngoscopy, direct laryngoscopy and biopsy will be performed. Obtain CT scan at 12 weeks. **(3/15/93)**
- b. A neck dissection will be performed if nodal disease ≥ 3 cm or multiple nodes were present at the time of randomization regardless of response to treatment.
- c. A direct laryngoscopy will be performed at the time of neck dissection. Biopsy will be performed only if a mucosal abnormality is present.

APPENDIX VIII

INTERGROUP PARTICIPATION IN RTOG STUDIES

GENERAL GUIDELINES

- I. REGISTRATION:** RTOG will be responsible for all registration/ randomizations. The procedure is:
- Each institution affiliated with a Cooperative Group will phone their group and supply the eligibility check information.
 - The participating Cooperative Group will then telephone RTOG 215/574-3191 between 8:30 a.m. and 5:00 p.m. ET and supply the necessary eligibility and stratification information. RTOG will then assign a case number and treatment assignment. The participating Cooperative Group will then inform its member institution.
 - RTOG will send a Confirmation of Registration and a Forms Due Calendar to the participating Cooperative Group for each case registered. The participating Group forward a copy of the calendar to the participating institution.
- II. PROTOCOL DISTRIBUTION:** Each participating cooperative group is responsible for distribution of the protocol to its members. All protocol amendments will be sent by RTOG to each participating Group office for distribution to member institutions. All communication with NCI regarding this protocol will be routed through the RTOG.
- III. INSTITUTIONAL PARTICIPATION:** It is the responsibility of each participating Cooperative Group to decide which of its member institutions may participate in this protocol. Each participating Cooperative Group must ensure that IRB approval was obtained prior to accession of cases.
- IV. CONFIRMATION/CALENDARS:** A Confirmation of Registration notice and a Data Collection Calendar is produced for each case registered and/or randomized. These will be distributed by RTOG to the appropriate cooperative group office for distribution to their members, if appropriate.

The form identification code which appears on the Calendars in the "key" columns is found on the form in the lower right corner.

You are expected to respond to each of the items listed either by submitting the item, by notifying us in writing that the item is not available or that the assessment was not done. The calendar may also list items which are not forms (CAT Scan reports, pathology reports) but are specific source documents. These items will be noted in the data collection section of the protocol but will not be listed on the Forms Package Index.

Additional items/forms may be required depending on events that occur e.g. if surgery was done a surgical report may be required. See the protocol for conditional requirements.

Unless specified otherwise, all patients are followed until death or termination of the study.

- V. FORMS:** Forms packages may be obtained from the participating Cooperative Group office. Attached is a list (Forms Package Index) of all data collection forms used in the study, the toxicity criteria for this study, if applicable and a sample of the data collection forms.

The RTOG assigned case and study number must be recorded on all data items submitted. Except for material which requires rapid review (see below), data should be routed according to the mechanism set up by the participating Group. Generally the participating group will require forms to be routed through their office and they will send the forms to

American College of Radiology
Radiation Therapy Oncology Group - 14th Floor
1101 Market Street
Philadelphia, PA 19107

VI. LABELS: Preprinted labels are available for source document data items (radiographic reports, etc.) Supplied white labels are to be used for film identification.

The blank labels will be supplied to the participating Group for distribution to the individual institutions as patients are registered at RTOG.

When completing the labels, be specific when describing films, e.g.: "Pre op CT Brain Scan, "Large Photon Localization Film", "Follow-up Bone Scan", etc.

Data managers are advised to consult technical staff for assistance when labeling radiotherapy films. Correct film identification is the responsibility of the institutions and is essential to maintain efficient data flow.

VII. CANCELLATION/INELIGIBILITY: Patients who are found to be ineligible subsequent to registration are to be followed according to plan unless you receive written instructions to the contrary.

Patients who receive no treatment whatsoever may be cancelled, however, written notification and an explanation must be received at RTOG Headquarters as soon as this has been determined. We must receive this notification not later than two weeks after registration. We will notify you of the determination made regarding the status of the case and instructions regarding subsequent data submission.

VI. RAPID REVIEW ITEMS: Time critical data which requires rapid submission must be sent directly to RTOG (See Section V). These items are:

M2 - Medical Oncology Treatment Planning Form (if required by the Protocol)

T2 - Protocol Treatment Form

T3 - Photon Localization film (for all fields treated initially)

T4 - Photon dose calculations (for all fields treated initially)

IX. REQUEST FOR STUDY INFORMATION

AND FORMS REQUEST: Requests for additional information or clarification of data will be routed through the participating Cooperative Group office for distribution to the individual institution.

The memo requesting the additional information must be returned with the response. Responses should be returned according to the procedure used to submit data forms. You may receive reminders prompting response.

Periodically (generally three times per year) computer generated lists identifying delinquent material are prepared. These are routed by RTOG through the participating group for distribution.

X. QUESTIONS REGARDING:

Randomization/Registration Registration Secretary (215) 574-3191

Pathology Pathology Coordinator (215) 574-3161

**Data/Eligibility/Treatment/
Adverse Reactions** Data Manager (215)574-3214

Data Management Procedures Data Manager (215)574-3214

Protocols/Amendments Protocol Administrator (215) 574-3195

**Radiotherapy data items (films, Dosimetry Clerk (215) 574-3219
radiographs, isodose summations,
treatment records, scans,
reports and calculations)**

If you are unable to reach the person noted, and your call is urgent, ask to speak to any data manager.

XI. ADVERSE REACTIONS/AND TOXICITY

From Radiotherapy: Unusual toxicities, and all grade 4-5 toxicities are to be reported by telephone to RTOG Headquarters, the Group Chairman Dr. James Cox and to the Study Chairman. If the Chairman is unavailable, ask to speak to the Data Manager for this study.

From Investigational Agents: Are to be reported according to NCI guidelines. In addition, RTOG Headquarters and the Study Chairman are to receive notification as outlined by the NCI procedures, i.e. if telephone notification is necessary, RTOG and the Study Chairman must also be called.

Copies of all toxicity reports and forms submitted to NCI must be sent to RTOG Headquarters also.

From Commercial Drugs: Are to be reported according to NCI/FDA guidelines. A copy of the reports and forms submitted to FDA must be sent to RTOG.