

RADIATION THERAPY ONCOLOGY GROUP

RTOG 95-12

**A RANDOMIZED STUDY OF HYPERFRACTIONATION
VERSUS CONVENTIONAL FRACTIONATION IN T₂ SQUAMOUS CELL
CARCINOMA OF THE VOCAL CORD**

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RTOG 95-12
EORTC 22992

A RANDOMIZED STUDY OF HYPERFRACTIONATION
VERSUS CONVENTIONAL FRACTIONATION IN T₂ SQUAMOUS CELL
CARCINOMA OF THE VOCAL CORD

SCHEMA

S		R	
T		A	Arm 1: 70 Gy/2 Gy once per day/7 Weeks (35 Fractions)
R		N	
A	<u>Stage</u> 1. T _{2a} 2. T _{2b}	D	Arm 2: 79.2 Gy/1.2 b.i.d/6.5 weeks (66 Fractions)
T		O	
I		M	
F		I	
Y		Z	
		E	

Eligibility: (See Section 3.0 for details)

- Histopathologically-proven squamous cell glottic larynx (*verrucal and adenocarcinoma are excluded*)
- Age \geq 18
- Modified AJCC Stage II (*T_{2a}, T_{2b}, N₀*)
- Karnofsky \geq 60
- No prior radiotherapy, chemotherapy or surgery other than biopsy
- No prior (\leq 5 years) or concurrent malignancy
- Signed study-specific consent form prior to randomization

Required Sample Size: 240

4/30/01

RTOG Institution # _____

RTOG 95-12

RTOG Case # _____

EORTC 22992, Case # _____

ELIGIBILITY CHECK (4/30/01)

(page 1 of 2)

(must be completed prior to study randomization)

- _____(Y) 1. Is the primary tumor site arising from the true vocal cord?
- _____(Y) 2. Is the confirmed histology squamous cell cancer?
- _____(T2a-b) 3. What is the T-classification and subclassification (*as defined by the protocol*)?
- _____(Y) 4. Is the bulk of the tumor on the vocal cord?
- _____(Y/N) 5. Is mobility of the vocal cord impaired?
- _____ _____(Y) If yes, has the impaired mobility been confirmed on examination by at least two physicians?
- _____(N) 6. Any evidence of cord fixation, cartilage, pyriform sinus or pre-epiglottic space invasion?
- _____(N) 7. Any evidence of N-positive disease (*see Section 3.2.3*)?
- _____(N) 8. Any evidence or suspicion of distant metastases?
- _____(N) 9. Other than biopsy, was any treatment given to the neck or larynx including stripping or laser excision of primary or prior radiotherapy to the neck?
- _____(Y/N) 10. Any prior malignancy (*other than non-melanoma skin cancer*)?
- _____ _____(Y) If yes, has the patient been continuously disease free for ≥ 5 years?
- _____(Y/N) 11. Does the patient have child-bearing potential? (*If no, skip to Q. 13*)
- _____ _____(Y) If yes, has the patient agreed to use effective contraception?
- _____(≥ 60) 12. What is the patient's KPS?
- _____(Y) 13. Has the patient agreed to follow-up by the registering physician?

(cont'd on next page)

RTOG Institution # _____

RTOG 95-12

ELIGIBILITY CHECK (4/30/01)

RTOG Case # _____

(page 2 of 2)

EORTC 22992, Case # _____

(must be completed prior to study randomization)

The following questions will be asked at Study Registration:

- _____ 1. Name of institutional person registering this case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name or initials (*last, first*)
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number (*U.S. patients*)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip or Postal Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility (*U.S. patients*)?
- _____ 16. Treatment Start Date
- _____ 17. T stage (*T2a or T2b*)
- _____ 18. Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

According to the American Cancer Society (ACS 1994), larynx cancer will be diagnosed in 12,800 patients in the United States in 1994. Ten thousand of these will be males, 2,600 females; approximately 3,800 patients will die from larynx cancer. The overall five-year survival is 67% for whites and 53% for blacks. Approximately 75% of tumors are located in the glottis.⁷

In general, the treatment policy in the United States for early glottic cancer consists of definitive radiotherapy with surgery reserved for salvage. While some patients with T2 disease are selected for surgery, many patients are offered radiotherapy alone as the initial step in management.

Early T1 and T2 regions of the vocal cord are usually treated with small fields (4-6 cm) encompassing the primary site only. Total doses have varied from 56.25 Gy to 78 Gy depending on the extent of tumor and fractionation.^{6,13,14} Within this dose range, a variety of fractionation schedules have been used. In once-a-day programs, fraction size has varied from 1.8 Gy to 3.4 Gy.^{3,9,11} Conventional treatment is considered to be 1.8-2.0 Gy per fraction to a total dose of 60-70 Gy. Several tumor related, patient related and treatment related factors have been found to influence the chance of local control: stage, impaired cord mobility, gender, anterior commissure involvement, subglottic extent, obesity, fraction size, field size, overall time and total dose. While more than 3,000 patients have been reported in the literature, nearly all of these come from single institution retrospective studies. Prospective trials focusing on laryngeal carcinoma and evaluating stage, fractionation or other factors have not been performed to our knowledge.

1.1 Altered Fractionation in Head and Neck Cancer

For T2 vocal cord carcinoma, fractionation schedules can be grouped into three categories: hypofractionation (2.5-3.4 Gy per fraction, once a day), conventional fractionation (1.8-2.25 Gy per fraction, once a day), and hyperfractionation (1.1-1.2 Gy per fraction, twice a day). Slevin et al. have recently reviewed the influence of tumor dose versus dose per fraction on local control and the occurrence of late normal tissue complications using hypofractionation versus conventional fractionation.¹⁰ Interestingly, local control was essentially equivalent (70-75%) regardless of fraction size or dose. However, patients receiving 3.3 to 3.4 Gy per fraction experienced a higher incidence of late complications including necrosis, severe edema or stenosis resulting in laryngectomy in approximately 4% of patients.

Hyperfractionation has been used in small retrospective studies for laryngeal carcinoma. The University of Florida has reported improved results in 35 patients treated with hyperfractionation in comparison to historical controls in T2 lesions.^{3,8} Fein et al. have shown that local control at five years appears to increase from 81% to 91% when comparing 2.25 Gy once a day (*total dose 67.5 Gy*) to 1.2 Gy twice a day (*total dose 74.4-76.8 Gy*). A similar retrospective comparison was performed at M.D. Anderson Cancer Center.²⁵ Forty one patients with T2 and T3 supraglottic cancers showed improved two-year control (87% vs. 76%, $p = 0.4$) using hyperfractionation compared to conventional treatment.

Hyperfractionation in head and neck cancer using doses of 1.1-1.2 Gy per fraction twice daily has been tested in several prospective studies including a completed RTOG (79-13) randomized phase III trial, and EORTC trial, an Indian trial, and an RTOG (83-13) randomized phase I/II trial.^{1,2,4,5} In the EORTC trial,⁴ patients with oropharyngeal carcinoma, Stage T2-T3, N0-N1 (< 3 cm) were randomized to receive conventional radiotherapy with 70 Gy in 35 fractions in seven weeks or hyperfractionated radiotherapy with 80.5 Gy in 70 fractions (1.15 Gy per fraction) in seven weeks. Results show a significantly improved local-regional control (59% vs. 40% at 5 years) rate for patients with T2-3N0-N1 disease when treated with hyperfractionated radiotherapy compared to conventional treatment ($p=0.001$). A borderline significant advantage in five year survival for all patients enrolled was seen in the hyperfractionation arm ($p=0.08$). In the Indian trial, 212 patients with T2-T3, N0-N1 head and neck cancers were randomized to receive once-a-day radiotherapy with 2 Gy per fraction to 66 Gy in 33 fractions over 6.5 weeks or twice a day radiotherapy with 1.2 Gy per fraction to 79.2 Gy in 66 fractions over 6.5 weeks. Of the 176 evaluable patients, those treated with the BID regimen had a significantly better two-year disease free survival rate (63% vs. 33%, $p < 0.01$) and actuarial survival (71% vs. 45%, $p < 0.005$).² However, the total dose (66 Gy) for the standard fractionation arm is lower than that which is commonly used in the United States for these patients.

The RTOG has conducted a dose searching randomized phase I/II trial of hyperfractionation in advanced head and neck cancer (*RTOG 83-13*) suggesting an increase in local-regional control with an increase in dose from 67.2 Gy to 81.6 Gy with no increase in late toxicities.^{1,26} In a previous randomized trial (*RTOG 79-13*), patients treated with hyperfractionated radiotherapy with an interval of more than 4.5 hours between the two daily fractions had less acute and late toxicity than those treated with shorter interfraction intervals.

The biological basis and the rationale for hyperfractionation has been reviewed by Withers et al.^{12,15,16} The objective of hyperfractionation is to increase the therapeutic differential between tumor response and late normal tissue injury through an increased opportunity for tumor cell redistribution and reoxygenation, greater sparing of late reacting normal tissues and a possibility of a lower enhancement ratio (*OER*) at low doses. Hyperfractionation, using 1.2 Gy twice a day, also includes some component of acceleration which results in a more rapid rate of dose delivery and an effective shortening of overall time per dose delivered. Dose escalation is also a major feature since late effects appear to be equal to conventional fractionation despite a 10-15% higher total dose.

In addition to its treatment studies, the RTOG has also directed its attention to the identification of tumor and treatment related factors which potentially influence the patient outcome. In 1977, the RTOG opened a Registry Study for patients with head and neck cancer to establish a large data base for evaluating the disease outcome following radiation treatment with and without other treatment modalities. All patients with head and neck tumors treated by participating RTOG institutions between February 1977 and February 1980 were entered except for those patients who were entered on other RTOG clinical trials. The following data points on each patient were prospectively collected: location of the primary site, AJC T-stage and N-stage, age, sex, Karnofsky performance Score (*KPS*), tumor histology, tumor differentiation as scored at the participating institution, extent of disease, details of treatment delivery and outcome. The 1976 TNM staging system, according to the American Joint Committee (*AJC*) for Cancer Staging and End Results Reporting, was used. The findings from the registry study in previously untreated patients with T-2 glottic carcinoma whose initial treatment plan was radiation therapy alone will be used as the baseline data to generate a sample size for this study. Of the 2066 cases entered into the Registry, 74 T-2 glottic patients met this criteria and had adequate study and follow-up information for analysis. Sixty-seven (91%) were male, 59 (80%) had pretreatment *KPS* of 90 or 100, and their median age was 65.5 years old (*range*: 41-86). Information was available about cord mobility in 72 patients of whom it is impaired in 31 (43%). The median maximum and minimum doses to the primary were 67.2 and 66.0 Gy respectively. Twenty-two patients experienced a local failure for an estimated rate of 31% at five years. All but one of the local failures occurred in the first four years from the start of RT. The risk of failing locally decreases with time (18.1% - year 1; 9.2% - year 2; 4.4% - year 3; 2.6% - year 4). Forty three have died for an estimated overall survival rate of 64% at 5 years. The cause of death information was available for 37 patients. For only six (16%) cases, the investigator gave the cause of death as primary disease.

The RTOG is currently testing hyperfractionation as part of a large randomized four-arm study in advanced head and neck carcinoma (*RTOG 90-03*). This study is limited to stage III and IV disease and compares standard fractionation to hyperfractionation, accelerated fractionation with a split and accelerated fractionation with a concomitant boost. This trial stratifies patients by site (*oral cavity vs. oropharynx vs. hypopharynx vs. larynx*), stage (*N0 vs. N+*) and Karnofsky performance status (*90-100 vs. 60-80*). Despite the large number of patients being enrolled in the trial, there will be insufficient numbers to evaluate fractionation by T stage in each site category. It is therefore important to evaluate each site of disease and stage of disease within that site to fully appreciate the impact of altered fractionation on outcome. Most patients with moderate stage to advanced laryngeal carcinoma will be enrolled in RTOG 91-11 testing chemoradiotherapy versus conventional radiotherapy.

Hyperfractionation is now increasingly used in the management of head and neck cancer and is probably the most popular altered fractionation schedule used off protocol in the United States today. While it promises to increase the rate of local control and organ preservation, it is associated with increased inconvenience and up to a 60% increase in cost. Therefore, we believe it is important to test hyperfractionation in earlier stage disease in a phase III randomized trial. Laryngeal carcinoma represents 40% of all head and neck cancer, 75% of these originate in the glottis with most of these being early stage. This site and stage represents a relatively homogeneous clinical model (*histology, bulk of disease, performance status*) for testing the value of hyperfractionation in early stage disease. In a recent review of the RTOG head and

neck registry, the ratio of T1 to T2 vocal cord carcinomas was found to be 3 to 1. A survey of the RTOG membership indicates approximately 250 patients per year with stage T2 disease may potentially be accrued to this phase III randomized trial.

1.2 Research Strategy

While on the surface this study may seem to be "just another fractionation study", it represents an important component of the research strategy of RTOG head and neck trials.

Outcome analysis in head and cancer has always been complicated by competing causes of failure and death including local-regional failure, distant metastases, and second malignancies. These factors have made it difficult to demonstrate improvements in survival in randomized trials where treatment innovations are aimed at only one or two components. The RTOG Research strategy aims to improve overall survival using a "multipronged approach". Enhancements in local regional control and organ preservation (*RTOG 90-03, 91-11*) can be combined with agents that reduce the risk of second malignancy (*RTOG 91-15*). The addition of effective systemic therapy will hopefully allow improvements in local-regional control to translate into improved survival (*RTOG 91-11*).

Many of the fractionation trials to date have been conducted in advanced, often unresectable disease where modest improvements in the effectiveness of a local modality can be overwhelmed by the biology of near end-stage disease. A notable exception, EORTC 22791 targeted middle stage carcinomas of the oropharynx (*T2-T3, N0-N1*) and showed a significant (*19 point*) improvement in local-regional control. Patient loss to second malignancy and comorbid disease constrained this advance to only a trend for improved survival ($p = .08$). By targeting early vocal cord carcinoma with an intermediate risk of local failure (*30%*) but a negligible risk of nodal and distant disease we may be able to uncover the full potential of altered fractionation to improve organ preservation. Furthermore, it is well recognized that subsites within the head and mucosa may have differential responses to radiotherapy, arguing for rigorous testing in each subsite. To our knowledge, this will be the first randomized trial to test hyperfractionation in early stage disease with relatively homogeneous tumor volume and biology.

Lastly, we have chosen hyperfractionation from among the various altered fractionation schedules since it has the best published experience in laryngeal carcinoma. The combination of dose escalation along with modest acceleration appears best suited to the well to moderately differentiated tumors most often seen in this site.

1.3 Tumor Kinetics and the p105 Assay

Tumor proliferative activity may be an important prognostic indicator in head and neck cancer.^{28,29,30} p105 is a proliferation associated nuclear antigen which identifies proliferating but not resting cells. The p105 assay utilizes a mouse monoclonal antibody against p105 enabling the immunohistochemical detection of cycling cells from a paraffin block by flow cytometry without any specific exposure of fresh tissue before immunostaining. Among the currently available proliferative assays, the p105 assay appears to be the simplest and most practical to adapt to cooperative clinical trials.

To evaluate the potential of p105 labeling indices as a predictive assay, the RTOG has retrospectively analyzed the pre-treatment tumor biopsies of 146 patients with advanced squamous cell carcinoma of the head and neck treated with radiotherapy alone in RTOG trials 79-13, 79-15 and 83-13²⁸ p105 labeling indices and DNA analyses were correlated with local-regional control and survival in 143 patients evaluable. Oropharynx was the most common site (*65 patients*). Eighteen patients with supraglottic tumors were evaluated and there were no patients with glottic tumors in the study. The disease was stage T₃ or T₄ in 80% and N₂ or N₃ in 50% of the patients. A multivariate analysis showed that T stage ($p = .001$) and p105 antigen density ($p = .0044$) were significant for local-regional control, and T stage ($p = .0080$), N stage ($p = .0021$), primary site ($p = .0110$) and p105 antigen density ($p = .0326$) were significant prognostic factors for survival.²⁸

Based on these encouraging results more studies of p105 as a predictive assay in head and neck cancer are needed. In particular, there are no studies to date that have focused on early stage disease and no studies of

large numbers of patients with disease from a single subsite. Therefore, we propose to incorporate the p105 assay into this prospective trial of radiotherapy for early glottic carcinoma.

2.0 OBJECTIVES

- 2.1 To test whether hyperfractionation improves the local control rate for early stage (*T2N0*) squamous cell carcinoma of the true vocal cord (*compared to conventional fractionation*).
- 2.2 To determine the acute and late radiotherapy toxicity associated with each of the fractionation schedules.
- 2.3 To examine overall and disease-free survival patterns associated with each of the fractionation schemes.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients with histologically proven invasive squamous cell carcinoma arising from the true vocal cord.
- 3.1.2 Disease limited to stage T2N0 (*See modified AJCC staging, Appendix III*). The bulk of the tumor must be present on the vocal cord (*i.e. the "epicenter"*) with extension to adjacent areas.
- 3.1.3 For lesions causing impaired mobility (*T2b*) at least two physicians must be in agreement that the vocal cord is impaired (*preferably a radiation oncologist and a surgeon*).
- 3.1.4 The minimum age for entry is 18 years.
- 3.1.5 Karnofsky performance status ≥ 60 (*Appendix II*).
- 3.1.6 The patient must sign a study-specific informed consent form.

3.2 Ineligibility Criteria (10/1/96)

- 3.2.1 Patients with verrucal carcinoma or adenocarcinoma are excluded.
- 3.2.2 Patients with tumors extending to pre-epiglottic space, pyriform sinus, a fixed cord or cartilage invasion are not eligible (*T3-T4*).
- 3.2.3 Clinical or radiographic evidence of adenopathy in the neck. A radiographic-positive node must be greater than 1 cm in size or contain a low density center consistent with necrosis. Clinically positive nodes must be greater than 1 cm in size and firm in consistency on palpation to be considered positive. Subcentimeter nodes either radiographically or clinically are considered negative.
- 3.2.4 Evidence or suspicion of distant metastases.
- 3.2.5 Patients with a prior or concurrent malignancy (*other than non-melanoma skin cancer*) are ineligible, unless previous cancer was treated 5 years or more prior to the current tumor and the patient has remained continually disease free.
- 3.2.6 Karnofsky status < 60 .
- 3.2.7 Patients with complete stripping or laser excision of all gross disease.
- 3.2.8 Prior radiotherapy to the mid-neck or larynx.
- 3.2.9 Patients with recurrence or persistent tumor following any treatment.
- 3.2.10 Patients for whom follow-up by the registering physician is not feasible.
- 3.2.11 Patients of childbearing potential should agree to use an effective method of contraception.

4.0 PRETREATMENT EVALUATION

4.1 Mandatory Evaluations (within 6 weeks prior to study entry)

- 4.1.1 Complete history and physical exam.
- 4.1.2 Biopsy of primary tumor.
- 4.1.3 Chest x-ray, PA and lateral.
- 4.1.4 Detailed diagram of lesion.
- 4.1.5 CT scan of neck/larynx with thin (*2-3 mm*) slices through larynx.

4.2 Optional Studies (encouraged)

- 4.2.1 Videostroboscopy for documentation of stage.

5.0 REGISTRATION PROCEDURES (4/30/01)

5.1 RTOG Members

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

5.2 EORTC Members

See Appendix VII, Section 2.

6.0 RADIATION THERAPY

6.1 Dose Fractionation

6.1.1 Standard Fractionation (Arm 1)

Treatment to the primary site will be given at 2 Gy per fraction, once a day, five days a week to a total dose of 70 Gy in 35 fractions in seven weeks. Boost fields will begin at 50 Gy so that the target volume (*primary site plus at least 1.0 cm dosimetric margin*) will receive at least 90% of maximum dose (*Appendix VI, Fig. 2B*).

6.1.2 Hyperfractionation (Arm 2)

Treatment to the primary site will be given at 1.2 Gy per fraction, twice a day with a minimum of a 6 hour interval, five days a week to a total dose of 79.2 Gy in 66 Fractions in 6-1/2 weeks. The exact date and time of each treatment should be clearly documented on the treatment record. Boost fields will begin at 60 Gy so that the target volume (*primary site plus at least 1.0 cm dosimetric margin*) will receive at least 90% of maximum protocol dose (*Appendix VI, Fig. 2B*).

6.1.3 Time and Dose Modifications

6.1.3.1 Standard Fractionation Treatment breaks must be clearly indicated in the treatment record. Treatment breaks, if necessary, should not exceed five treatment days at a time and 10 treatment days total and should be allowed only for healing of severe normal tissue reactions. If the total interruptions exceed five days, the case will be considered a protocol minor deviation; exceeding 10 treatment days will be a major deviation.

6.1.3.2 Hyperfractionation Treatment breaks must be clearly indicated in the treatment record. Treatment breaks, if necessary, should not exceed five treatment days at a time and 10 treatment days total and should be allowed only for healing of severe normal tissue reactions. If the total interruptions exceed five days, the case will be considered a protocol minor deviation; exceeding 10 treatment days will be a major deviation.

6.1.4 Interfraction Interval

Documentation of interfraction interval must be provided on the daily treatment record. A minimum 6 hour interfraction interval is required.

6.2 Physical Factors

6.2.1 Equipment: Linear accelerators with photon energies 4-6 MV or Cobalt machines must be used. Institutions using 6 MV photons should consider using thin (*2-5mm*) bolus over the anterior half of the larynx in patients with lesions involving the anterior larynx or patients with minimal soft tissue anterior to the thyroid cartilage.

6.2.2 Treatment distance must be > 80 cm S.S.D. (*or S.A.D. for isocentric techniques*).

6.3 Localization Requirements

6.3.1 Simulation: Simulation of all fields is mandatory. Patients must be reproducibly immobilized. Simulation films of each field, initial portal 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 (*final composite isodose plan will be submitted at the end of therapy*).

6.3.2 Verification: Beam verification (*port*) films must be obtained for each field on a weekly basis. Additional films should be obtained whenever any field adjustments are made. Port films of each field (*and any reductions*) must be submitted to the RTOG Headquarters. A treatment planning CT of the larynx obtained in the treatment position is strongly encouraged to facilitate accurate dosimetry. The tumor volume must be clearly marked.

6.4 Target Volume Irradiation Portals

6.4.1 Lateral opposing fields with at least a 2.0 cm margin in all directions around the tumor volume will be used for the first 50 Gy (*Arm 1*) and 60 Gy (*Arm 2*). Minimum field borders are illustrated in Appendix VI, Fig 1: a 6x6 cm field is centered over the mid thyroid cartilage with upper border 0.5-1.0 cm above the thyroid notch, posterior border 1 cm behind the thyroid cartilage, inferior border at the bottom of the cricoid cartilage and at least 1 cm fall off anteriorly. Larger field sizes may be needed to fully cover some tumor volumes with a 2 cm margin in all directions. There will be no direct intention to include regional lymph nodes in the portal, but it is recognized that portions of the neck lymphatic chain will be inadvertently treated. Tissue compensators (*wedges*) are encouraged to enhance homogeneity. After the first 50 to 60 Gy, weighted lateral fields, oblique fields or an AP field may be used to boost the primary site at the discretion of the treating radiation oncologist. Boost field borders must encompass the initial tumor volume with at least a 1.0 cm margin. In the absence of gross disease involving the posterior one

third of the cord, the posterior border of a lateral boost field may be reduced after 50 Gy (*Arm 1*) and 60 Gy (*Arm 2*) to put the arytenoids into the field penumbra. All fields must be treated on each treatment day. Thin bolus (2-5 mm) over the anterior larynx should be used in anterior tumors treated with 6 MV photons (see Section 6.2.1).

6.5 Dose Calculation

6.5.1 Protocol dose to the large lateral fields is prescribed at mid-depth along central axis for the first 50 Gy (*Arm 1*) and 60 Gy (*Arm 2*). Target volume for large fields will be defined as tumor volume plus at least 1.0 cm margin. Optimally, the target volume should receive at least 95% of the prescribed dose and should never receive less than 90% of prescribed dose (*Appendix VI, Fig. 2A*). Boost doses may be delivered through non-lateral or weighted fields calculated to a target volume encompassing the tumor volume plus a 1 cm dosimetric margin with homogeneity of dose distribution so that variation within the target volume does not exceed 10% of prescribed dose (*Appendix VI, Fig. 2B*). Submission of isodose plan for all fields is required.

6.5.1.1 For two opposed coaxial equally weighted beams, dose is specified on the central ray at mid-separation of beams.

6.5.1.2 For arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

6.5.1.3 For other treatment arrangements at the center of the target area.

6.5.2 Tissue equivalent compensators (*wedges*) should be used to ensure homogeneity of dose distribution so that variation within the target volume does not exceed 10% of the protocol dose.

6.6 Anticipated Side Effects and Toxicities

6.6.1 Reversible radioepithelitis of laryngeal mucosa is expected and its timing with dose and severity should be noted and graded according to the RTOG Acute Radiation Morbidity criteria for mucous membrane.

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

6.6.3 Other possible acute reactions include mild dry throat, mild loss of taste, hoarseness, and dysphagia. Unusual severity of any of these symptoms should be noted, especially if supplemental feeding tube is required. See RTOG Toxicity Criteria for Acute and Late Effect grading (*Appendix IV*).

6.6.4 Late effects include thyroid dysfunction, permanent dry throat or larynx, laryngeal necrosis (*soft tissue or cartilage*) arytenoid edema, chronic hoarseness.

6.6.5 Chronic mild to moderate edema is expected in up to one-third of all patients and should be managed conservatively (*i.e., observation or steroids if severe*). See Section 8.2 regarding indications for biopsy.

6.7 RTOG Adverse Reaction Reporting (4/30/01)

6.7.1 All deaths within 30 days of completion or termination of protocol treatment regardless of cause.

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

6.7.3 All life-threatening (*grade 4*) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

6.7.4 Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report (*FAX# 215/928-0153*).

6.7.5 A MedWatch Form (*Appendix V*) must be submitted on all fatal (*grade 5*) toxicities resulting from protocol therapy and submitted to RTOG Headquarters within 10 working days of the telephone report.

6.8 EORTC Adverse Reaction Reporting (4/30/01)

See Appendix VII, Section 4.

7.0 DRUG THERAPY

Not applicable to this study.

8.0 SURGERY

8.1 Initial (Pretreatment) Biopsy

Routine forceps biopsy is suggested. There should be no attempt at complete removal, debulking or laser excision of the primary.

8.2 Post Treatment Biopsies

Routine post treatment biopsies must be avoided unless there are signs or symptoms of recurrence (*e.g., persistent mass, new onset of pain and edema with ulcer, new onset decreased mobility*). Chronic mild to

moderate laryngeal edema without pain or suspicious mass should be managed conservatively, since biopsies may precipitate necrosis. Post treatment biopsy will be reported on the data collection forms.

8.3 Surgical Removal (Salvage) of the Primary Tumor

Surgical removal (*salvage*) of the primary tumor should be performed only when biopsy proven persistent cancer confirms failure in a clinically abnormal site at least six weeks after completion of radiotherapy. Patients with severe chronic laryngeal edema, pain or apparent necrosis may harbor persistent cancer. The decision for salvage surgery lies in the judgement of the attending ENT surgeon to perform a partial or a total laryngectomy. The primary lesion must be widely excised with negative margins. Frozen sections should be taken from the patient and not the surgical specimen. Marking the surgical margin in ink at the site corresponding to where the frozen section was obtained for the patient is recommended to determine if there was a sampling error in obtaining clear margins. If grossly viable or palpable tumor remains unresectable at a margin that is histologically positive or when gross tumor removal is not performed, the patient will be considered to have gross residual disease after surgery. Details of all surgical treatment must be reported.

8.4 Neck Dissection

The decision for ipsilateral (*or bilateral*) neck dissection at the time of salvage surgery lies in the judgement of the attending surgeon based on the perceived risk of occult disease in the neck. Patients with local recurrence that does not involve a substantial portion of laryngeal mucosa generally are not at high risk for neck failure. Patients with extensive recurrence may benefit from ipsilateral or bilateral neck sampling and/or neck dissections. Postoperative radiotherapy may be indicated to the primary site or neck(s) depending on pathologic risk factors. A suggested technique for re-irradiation has been published.²⁷

8.5 Primary Closure

Primary closure of the surgical defect is to be accomplished whenever possible. Reconstruction or closure with grafts, local or regional skin flaps when required is allowed at the discretion of the responsible surgeon. Close suction drainage will be routinely employed.

8.6 Operative Report

The operative report must accurately describe the location and the extent of the primary lesion and cervical lymph node metastasis. Assessment of the completeness of the resection and results of intra-operative frozen section should be included. Any type of closure utilized should be specified as to the primary, pedicle flap or dermak graft.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY (3/17/98, 4/30/01)

10.1 Institutional Preparation of Tumor Sections

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

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

10.1.3 Pathology slides, blocks, and reports must be accompanied by an RTOG Pathology Submission form and sent to:

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

10.1.4 EORTC Members will submit (*optional*) materials directly to LDS Hospital, not to RTOG Headquarters.

10.2 Preparation of Nuclear Suspensions

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

- 10.2.2** The tissue is deparaffinized in xylene and rehydrated with sequential graded ethanols: 100%, 100%, 95%, 75%, and 50% for 10 minutes each and washed with distilled water.
- 10.2.3** For tissue dissociation, the tissue is incubated in 1 ml of 0.5% pepsin in saline, at a pH of 1.5 adjusted with 2N hydrochloric acid for 30 minutes at 30°C with brief vortexing. The reaction is terminated by placing the tubes on ice and treating with 0.5 ml of 0.5 mg/ml of pepstatin.
- 10.2.4** The nuclei are then filtered through a 37-mm nylon filter and washed twice with 8 ml of BME:HEPES buffer separated by 3-minute centrifugations at 250 g.
- 10.2.5** The nuclei are re-suspended in 8 ml of BME:HEPES and maintained at 4°C for approximately 18 hours prior to staining.

10.3 p105 Antibody and DNA Staining

- 10.3.1** The nuclei are resuspended at 2.0×10^6 in 1 ml of 3% Triton X100 in phosphate buffered saline for 3 minutes.
- 10.3.2** Following centrifugation, the supernatant is decanted and the nuclei are resuspended in 1 ml of appropriately diluted mouse monoclonal antibody (780-3) against p105 antigen for one hour.
- 10.3.3** Following centrifugation, the nuclei are washed with 3% Triton X 100 and re-suspended in 0.33 ml of 1:20 goat antimouse-IgM-fluorescence isothiocyanate for 30 minutes.
- 10.3.4** For DNA staining the nuclei are re-suspended in 1 ml of RNAase (200 U/ml) for 20 minutes at 30°C, centrifuged and re-suspended in 1 ml of propidium iodide (50 mg/ml) and incubated at 4°C for 1 hour in the dark.

10.4 Flow Cytometry

- 10.4.1** Data are acquired in listmode on an EPICS 7920 flow cytometer (Coulter) with use of the 488 nm line of an argon ion laser at 350m W power. Typically, listmode files of 20,000 events containing data on forward-angle light scatter (size), right-angle light scatter (*granularity*), green fluorescence (*FITC stained anti-p105*), red fluorescence (*propidium iodide stained DNA*), and a computer generated time signal are obtained.
- 10.4.2** For standardization of propidium iodide staining, peripheral blood lymphocytes are stained with propidium iodide and the peak is recorded at approximately channel 200 on a 1024-channel histogram.
- 10.4.3** Instrument alignment and standardization of green fluorescence is performed using 10 um of Fullbright Fluorosphere beads seta at green channel 56 on a 64-channel log-linear histogram. A total of 2×10^4 nuclei are run for each case with a flow rate of approximately 10^2 nuclei per second.
- 10.4.4** Quality Control of Flow-cytometry
Standard calibration of instruments will be performed daily. Monthly comparisons of histograms generated in the two major flow laboratories in Salt Lake City, Utah showed that the variation in results over the past two years has been negligible. Controls to be run with each batch of tumor samples include: 1) Positive control: a paraffin embedded seminoma of testes with a high mitotic rate and diploid and aneuploid peaks of known indices, S-phase fractions and p105 antigen densities and 2) Negative control: paraffin block of reactive lymph node without obvious mitosis. Positive and negative controls will be treated exactly like the test samples with propidium iodine and p105 prior to assay.

10.5 Data Analysis

- 10.5.1** Fluorescences results are analyzed on a microcomputer using Coulter Profile software. This program assumes a Gaussian distribution of G0G1 and G2M peaks and applies the quick estimate (*peak reflect*) method to calculate the cell cycle phases. Graphic representation of the data will be prepared with the use of software.
- 10.5.2** The DNA index is determined as the ratio of the aneuploid mean channel divided by the diploid G0G1 mean channel number. The Coefficient of Variation of the diploid DNA peak must be less than 5% or the sample will be discarded and a new one obtained.
- 10.5.3** Immunofluorescence for p105 is determined by the mean channel number on the log scale and recorded as arbitrary fluorescence units for each cell cycle phase: G0, G1, S, and G2M. These phases of the cycle are determined from the DNA histogram. Numbers of cells in each phase which label with antibody to p105 will be recorded.
- 10.5.4** A labeling index (*LI-C*) for p105 will be calculated as follows:

$$\text{LI-C} = \frac{\text{number of cells p105 positive G1, S and G2M phases}}{\text{Total number of cells counted}}$$
 This LI will be calculated independently for the diploid as well as aneuploid DNA (*if present*) in each sample.
- 10.5.5** A labelling index (*LI-S*) analogous to that obtained with BUdR labelling can be calculated as follows:

number of p105 positive cells in S phase

LI-S = Total number of cells counted

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

10.5.7 Data to be collected and sent for correlation with clinical parameters will include:

1. LI-S p105
2. LI-C p105
3. AD p105
4. % DNA diploid
5. % DNA aneuploid
6. DNA Index of aneuploid peak.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Assessments	Prior to XRT (≤ 6 wks)	Weekly During RT	1 mo after XRT	In Followup (Sec. 12)
H&P	X		X	X
Tumor Biopsy	X			
Chest X-ray	X			
Diagram of Lesion	X			
CT of Neck/Larynx	X			X ^a
Videostroboscopy ^b	X			
Toxicity Evaluation		X	X	X

- a. As indicated
- b. Optional but encouraged

11.2 Tumor Clearance

Response of tumor should be documented by visual inspection, routine mirror exam and/or endoscopy and should be made before therapy, weekly during therapy, and subsequently at each follow-up. Failure of clearance (*persistence*) will thus be documented. If suspicious findings are noted in the clinic or clinic exam is insufficient to determine response or disease control, then examination under anesthesia with or without biopsy will be performed. Time of apparent beginning regrowth will be noted.

11.3 Acute Effects

At least weekly during radiotherapy and postradiotherapy until clearance. Note concomitant use of alcohol, tobacco, or other irritants. Use the Acute Radiation Morbidity Scale (*Appendix IV*) < 90 days of RT start.

11.4 Late Effects

At each follow-up visit, note condition of tissues (*larynx, mucosa, skin/subcutaneous, Appendix IV*).

11.5 Survival

Record survival from start of radiation with or without local, regional or metastatic disease.

11.6 Tumor Assessment (*per Section 11.2*)

At the end of treatment.

4 weeks post radiotherapy.

Every three months through year 1.

Every four months through year 2.

Every 6 months for three years, then annually thereafter. Also at progression, relapse, and at death. See Section 12.0 for frequency of data submission.

12.0 DATA COLLECTION (3/17/98, 4/30/01)

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

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Staging Diagram (I6)	
Pathology Report (P1)	

Pathology Blocks (P2)

Preliminary Dosimetry Information: Within 1 wk of start of RT
 RT Prescription (*Protocol Treatment Form*) (T2)
 Films (*simulation and portal*) (T3)
 Calculations (T4)
 Treatment Planning CT (C1)

Final Dosimetry Information: Within 1 week of RT end
 Radiotherapy Form (T1)
 Daily Treatment Record (T5)
 Isodose Distribution (T6)
 Boost Films (*simulation and portal*) (T8)

Follow-up Form (F1) At 4 weeks post RT, every 3 months through year 1; q 4 months through year 2, q 6 months x 3 years, then annually thereafter. Also at progression/relapse, at ≥ grade 4 toxicity, and at death.

Surgery Form (S1) As applicable
 Surgical Report of Operation (S2)
 Surgical Pathology Report (S5)

Autopsy Report (D3) As applicable

12.2 EORTC Data Collection

The Demographic Form (A5) and Dosimetry (T3, C1, T8) films are not required for EORTC members.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 To test whether hyperfractionated radiation therapy improves local control for T-2 glottic patients as compared to standard once-a-day fractionation radiotherapy. (*Failure: persistent or recurrent disease in the primary. Note: new disease in the regional nodes or distantly is not considered a failure here*).

13.1.2 To determine the acute and late radiotherapy toxicity associated with each of the fractionation schedules.

13.1.3 To examine overall and disease-free survival patterns associated with each of the fractionation schemes.

13.2 Sample Size

13.2.1 The baseline information used to generate the sample size came from RTOG head and neck registry study 76-19. There were 74 patients with T-2 glottic lesions initially treated with radiation therapy and 22 had local failure for an estimated 5 year local failure rate of 31%. As seen from the table below all but one of the all the local failures occurred in the first four years. The risk of local failure decreases with time. This pattern of local failure has been observed in many other head and neck studies.

Study year	Probability of local failure during year	Probability of dying without a local failure during year
1	.181	.030
2	.092	.038
3	.044	.044
4	.026	.075
5	.000	.028
6	.000	.118
7	.000	.138
8	.043	.043

An assumption widely used in sample size calculations is that the failures follow an exponential distribution, namely, the patients have a constant failure rate over time. Clearly that is not the case here as seen in the table. The other assumption with the exponential distribution is that all patients will fail locally if followed long enough; hence no cures. Some T-2 patients in the Registry have been followed over ten years without any disease recurrence. One more factor that must be considered is the frequency of patients dying without a reported local failure. The rates of dying without a local recurrence by study year are shown in the above table and are appreciable enough that they must be accounted for when the sample size is calculated. With local failure, the associated yearly hazard rates for the first four years were separately estimated from the RTOG Registry study except that the probability of failing during the first year was lowered to .172. That was done so that the five year estimated local rate becomes .30. Beginning with the fifth year on, the local failure rate was arbitrarily set at .001 per year. For death without a local failure, the associated yearly hazard rates first two years were estimated by combining them. The yearly hazard rates for years three and four were estimated from combining them and so on. The two year intervals were used because it was felt that the estimates of the yearly hazard rates were more conservative and thus led to a slightly larger sample size.

The method and computer program of Lakatos¹⁷ was utilized to derive the sample size because it allows for the different yearly failure rates during the study. It also takes into account non administrative censoring (*death without a local failure*). It is hypothesized that hyperfractionated radiation will reduce the yearly hazard rates for local failure by 55%. This hypothesized improvement would result in a 5 year local failure rate of 14.8% for hyperfractionated RT. The other conditions set for these sample size calculations were $\alpha = .05$, $1 - \beta$ (statistical power) = .80, a two-tailed statistic, and patient accrual in four years with two years of further follow-up. Under these conditions, the study will need to accrue 110 eligible and analyzable patients to each treatment arm. In order to insure that the required total sample size is available for analysis, an additional 10% patient accrual beyond that will be entered. This was done to guard against an ineligibility of up to 10%. **Thus, the projected patient accrual goal is 240.**

13.3 Inclusion of Women and Minorities (3/17/98)

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. In both the RTOG Registry study and the Wang's patient series,²⁴ there approximately 90% males and 10% females among the T2 glottic patients. Wang did report an improved local control rate in females in his series. No information about race was collected in the RTOG Registry study. Wang did not comment about race in his series. Since there are no other publications to support a possible interaction between different radiation therapy schedules and either gender or race, the sample size will remain the same. The projected accruals are estimated below:

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	1	1	2	2	43	1	50
Male	1	1	7	7	173	1	190
Total	2	2	9	9	216	2	240

13.4 Patient Accrual

The study is projected to accrue 75 patients a year. If the average monthly accrual rate is less than 4 cases per month, the study will be re-evaluated for feasibility.

13.5 Randomization Scheme

Patients will be randomized to one of two treatment schedules in order to avoid any patient selection biases. Based on literature review, substage (*T2a vs T2b*) will be used as the only stratifying variable before randomization. The treatment allocation scheme described by Zelen¹⁸ will be used because it balances for patient factors other than institution.

13.6 Analyses Plans

13.6.1 Methods for Estimation and Testing

Gelman et al.¹⁹ and Gaynor et al.²⁰ pointed out in their respective papers that the Kaplan Meier methods tend to overestimate the local failure rates. So the cumulative incidence approach will be used to estimate it as a function of time because this approach specifically accounts for competing risks such as dying

without a local recurrence.²¹ Disease free survival and overall survival will be estimated by the usual Kaplan-Meier method. The distributions of the local failures in time between the two arms will be compared, a method especially developed for the task by Gray.²²

13.6.2 Interim Analysis:

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

The first significance test comparing the local failure rates between the two treatment arms will be performed for the first RTOG semi-annual meeting after 50% of the required sample size is available and the result will be then reported to DMC. If there is highly significant difference in local failure rates between the two arms (*Gray's test with $p < .001$*), the study statistician will recommend to the DMC that the randomization be discontinued and study be immediately written up for publication.

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

13.6.3 Analysis for Reporting the Initial Treatment Results

Otherwise, a major analysis will be undertaken when each patient has been potentially followed for a minimum of 24 months. This analysis will include tabulation of all cases entered, and any cases excluded from the analyses, the distribution of the important prognostic baseline variables, and observed results with respect to the endpoints described in Section 13.1. The significance level of .048 will be used in the final analysis to preserve an overall significance level of .05. The primary hypothesis of local control improvement with hyperfractionated radiation therapy will be tested using the proportional hazards model with fixed covariate, disease substage.²³ The same model will be used to test for treatment improvement in disease free and overall survival.

In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, the treatment comparisons will be done for local control and overall survival within each gender and race group.

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APPENDIX I

RTOG 95-12

A RANDOMIZED STUDY OF HYPERFRACTIONATION VERSUS CONVENTIONAL FRACTIONATION IN T₂ SQUAMOUS CELL CARCINOMA OF THE VOCAL CORD

Sample Patient Consent Form

RESEARCH STUDY

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

PURPOSE OF THE STUDY

I understand that my diagnosis is a malignant squamous cell tumor of my voice box and that further treatment is recommended. Radiotherapy is the treatment of tumors by means of x-rays. I understand that in the past radiation therapy has been usually given in daily doses 5 days per week for 6-8 weeks. Previous studies have shown that alternate ways of giving radiation therapy may produce greater tumor control, however this has not been proven. The experimental aspect of this study is the use of two treatments of irradiation daily. The total dose of irradiation administered is also being investigated in the current study.

It is expected that there will be about 240 persons taking part in this study.

DESCRIPTION OF PROCEDURES

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

Treatment 1

If I receive the standard fractionation treatment as an outpatient. Each radiation treatment will be administered once a day, five days a week to a total dose of 70 Gy in 35 treatments in seven weeks.

Treatment 2

If I receive the hyperfractionation treatment as an outpatient. Two radiation treatments will be administered each day at least six hours apart. Treatment will be administered five days a week to total dose of 79.2 Gy in 66 treatments in almost seven weeks.

Also, at the time of my diagnosis by biopsy, 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.

RISKS AND DISCOMFORTS

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

Risks of Radiation

I have been informed of the discomforts and risks which I may reasonably expect as part of this study. The irradiation may cause temporary skin redness or tanning, loss of hair in the treatment area, tiredness or fatigue, sore throat, loss of appetite, difficulty swallowing and reduction in blood counts which may lead to infection.

Late effects may include continued soreness in the throat, hoarseness, thickening or toughing of tissues in the treatment area, thyroid problems, or damage to the voicebox causing pain or requiring surgery if severe. In rare circumstances, damage has resulted in loss of the voice box organ. I understand that there may be some unknown or unanticipated discomforts or risks in addition to those specified above. My physician will be checking me closely to see if any side effects are occurring and prescribe medication to keep side effects under control. Side effects usually disappear after the treatment is stopped. I understand that the use of medication to help control side effects and could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment. These additional tests may increase my medical bills although the impact will be dependent on my insurance company.

A separate informed consent document will be provided for surgical procedures.

CONTACT PERSONS

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

BENEFITS

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

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

ALTERNATIVES

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

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

VOLUNTARY PARTICIPATION

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

CONFIDENTIALITY

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

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

Patient Signature (*or Legal Representative*)

Date

APPENDIX II

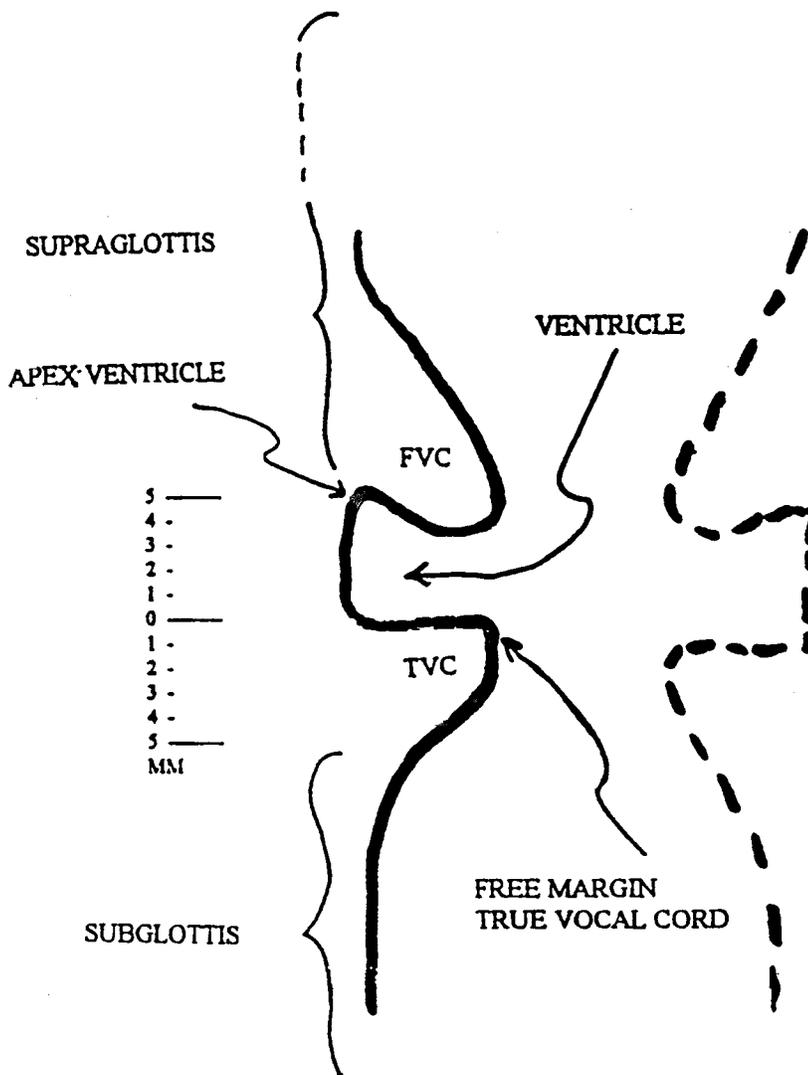
KARNOFSKY PERFORMANCE SCALE

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 of 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

Modified AJCC Staging

- T2a Tumor extends to the supraglottic and/or subglottic structures without impaired mobility.
The supraglottis is defined as beginning superiorly at the apex of the ventricle (or 5 mm above the free margin of the vocal cord). The subglottis is defined as beginning inferiorly 5mm below the free margin of the vocal cord (see below).
- T2b Tumor causes impaired mobility, with or without extension to supraglottic or subglottic structures. (Note: At least two physicians must agree that mobility is impaired).



CORONAL VIEW OF LARYNX MICROANATOMY

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\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. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\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. A special written report may be required.

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

Investigational Agents

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

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

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent.

Report **by phone** within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days.

- All deaths within 30 days of termination of the agent. As above
- All life threatening (*grade 4*) events which may be due to agent. As above
- First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters.
**A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within working days with a copy to IDB.
(*Grade 4 myelosuppression not reported to IDB*)
- All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**.
**A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **Report **in writing** to RTOG Headquarters and IDB within 10 working days.

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

APPENDIX VI
DIAGRAMS

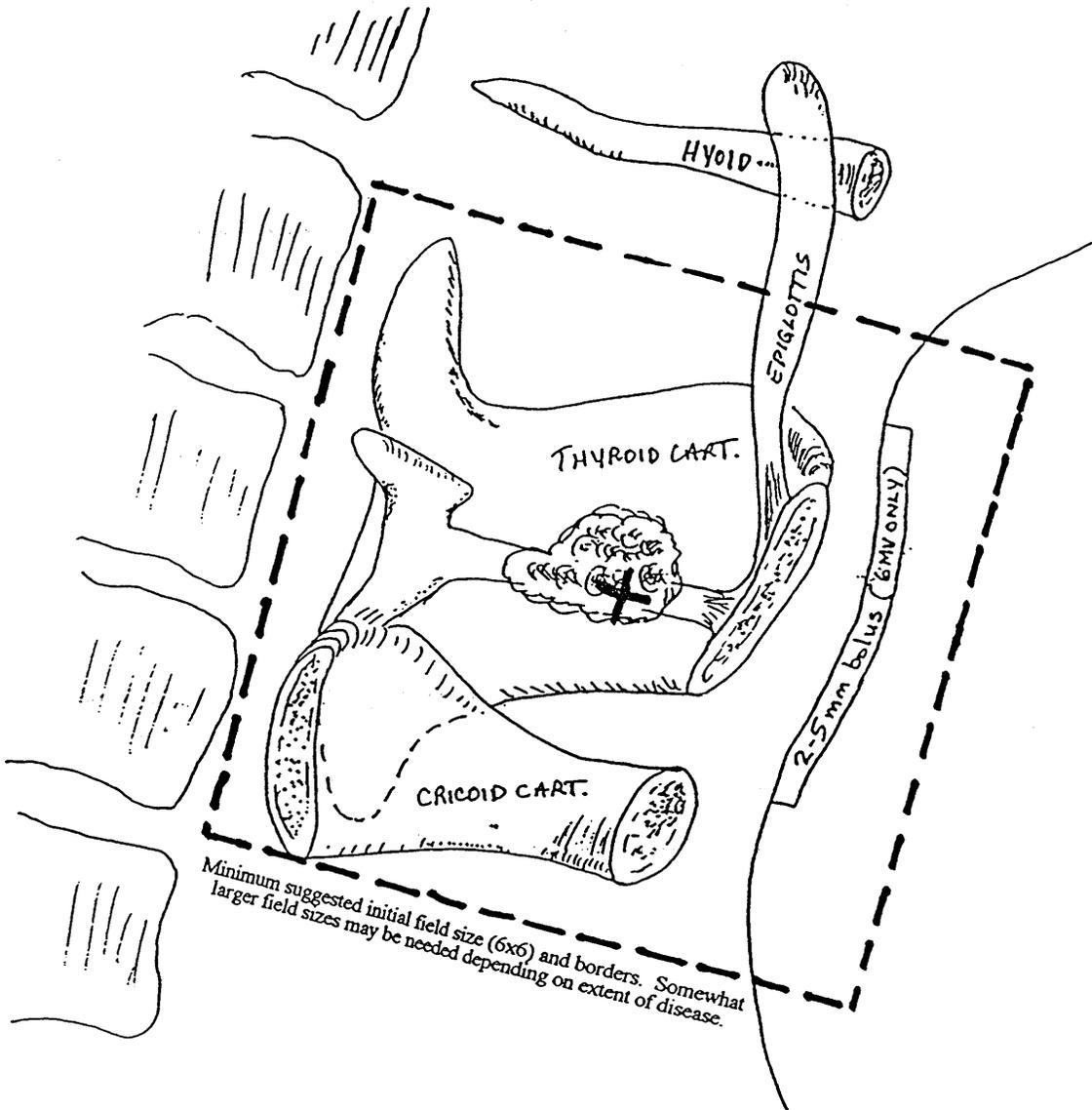


Figure 1

Lateral opposing fields with at least a 2.0 cm margin in all directions around the tumor volume will be used for the first 50 Gy (*Arm 1*) and 60 Gy (*Arm 2*). Minimum field borders are illustrated above: a 6x6 cm field is centered over the mid thyroid cartilage with upper border 0.5-1.0 cm above the thyroid notch, posterior border 1 cm behind the thyroid cartilage, inferior border at the bottom of the cricoid cartilage and at least 1 cm fall off anteriorly. Larger field sizes may be needed to fully cover some tumor volumes with a 2 cm margin in all directions. There will be no direct intention to include regional lymph nodes in the portal, but it is recognized that portions of the neck lymphatic chain will be inadvertently treated. Tissue compensators (wedges) are encouraged to enhance homogeneity. After the first 50 to 60 Gy, weighted lateral fields, oblique fields or an AP field may be used to boost the primary at the discretion of the treating radiation oncologist. Boost field borders must encompass the initial tumor volume with at least a 1.0 cm margin. In the absence of gross disease involving the posterior one third of the cord, the posterior border of a lateral boost field may be reduced after 50 Gy (*Arm 1*) and 60 Gy (*Arm 2*) to put the arytenoids into the field penumbra. All fields must be treated on each treatment day. Thin bolus (2-5 mm) over the anterior larynx should be used in anterior tumors treated with 6 MV photons (*see Section 6.2.1*).

APPENDIX VI

DIAGRAMS

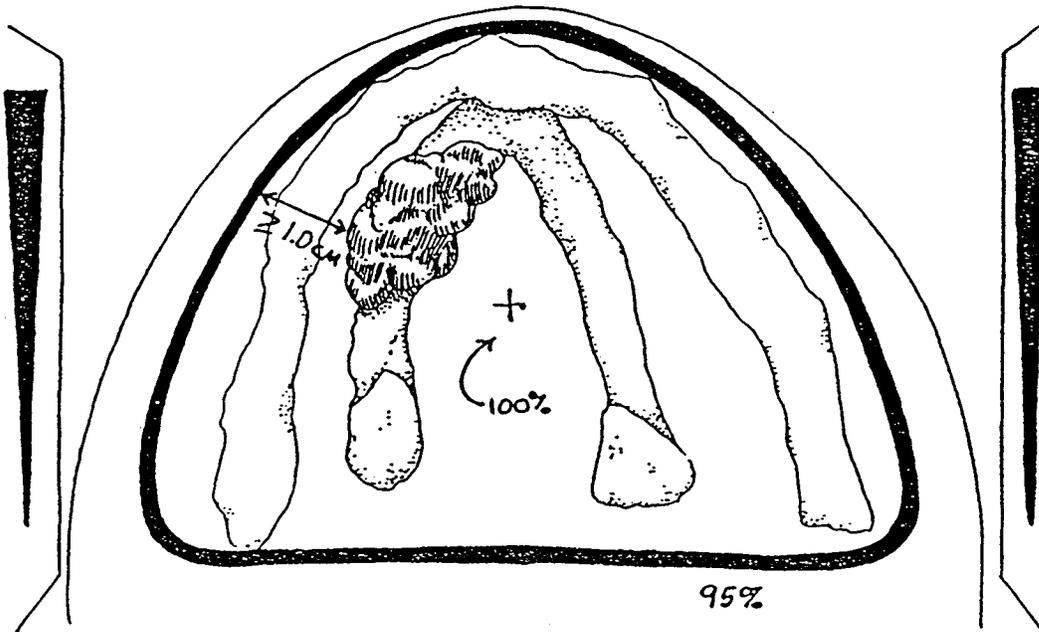


Figure 2A

Suggested target volume for initial 50-50.4 Gy

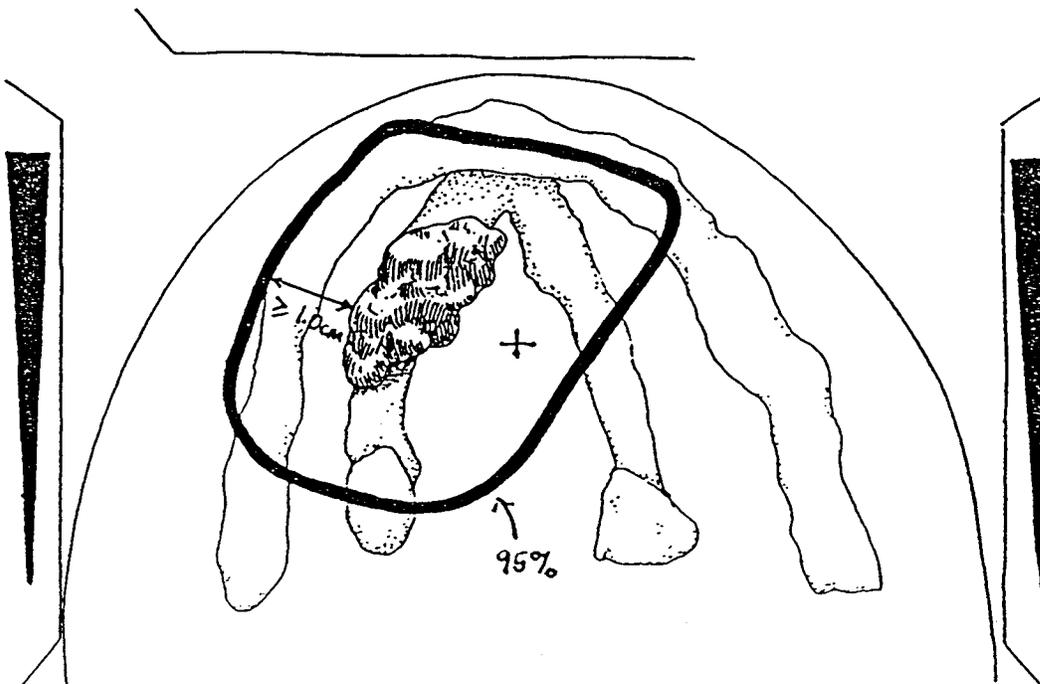


Figure 2B

Suggested minimal target volume for boost fields.

**A randomized study of hyperfractionation
versus conventional fractionation in
T2 squamous cell carcinoma of the vocal cord**

**RTOG protocol 95-12
EORTC protocol 22992**

**Administrative appendix
for EORTC investigators**

EORTC Data Center

April 2001

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1. INTRODUCTION

The present trial has been designed and activated by the Radiation Therapy Oncology Group (*RTOG*) in April, 1996. The EORTC Radiotherapy Cooperative Group has decided to join this trial after it was activated in the RTOG. This trial has become an Intergroup study between the RTOG and the EORTC Radiotherapy Group, and the EORTC study number will be 22992.

The trial is jointly conducted according to the "Guidelines for the Conduct of Intergroup Studies", prepared by Eleanor McFadden (*last revised in February 1994*), to which the EORTC has adhered in May 1997. At that time, a special procedure for ECOG/EORTC collaboration was added. The RTOG/EORTC collaboration in the present protocol will follow the same guidelines.

- The Coordinating Group is the RTOG. The Intergroup Study Chairman is Dr. Andy Trotti.
- The RTOG Statistical center is responsible for all statistical center functions.
- The EORTC Study Coordinator is Dr. Patrick Bontemps.
- The protocol developed by the RTOG will be used by the EORTC, with the present administrative appendix, that will overrule correspondent sections of the protocol. The present appendix is only applicable only to EORTC participants.
- The date forms developed by the RTOG will be used by the EORTC.
- Because of the time zone difference, EORTC patients will be randomized at the EORTC Data Center in Brussels, and the registration/randomization records immediately transferred to the RTOG statistical center.
- Case report forms will be returned by EORTC investigators to the EORTC Data Center, who will transfer them to the RTOG. Data queries will be managed through the EORTC Data Center in Brussels.
- Dosimetry material as needed for this study will be directly submitted to RTOG Headquarters.
- **Submission of pathology material will be optional for EORTC Centers; however, RTOG should be notified if pathology material will not be submitted.**

2. PATIENT RANDOMIZATION PROCEDURE

Patient randomization will only be accepted from authorized investigators.

A patient can be randomized after verification of eligibility directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network.

Alternatively randomization can be done by telephone to the EORTC Data Center from 9.00 am to 5.00 pm (*Belgian local time*) Monday through Friday.

This must be done before the start of the protocol treatment.

- Tel: +32 2 77416 00
- Internet: <http://www.eortc.be/random>

An exhaustive list of questions to be answered during the randomization procedure is included in the Eligibility Checklist, which is part of the protocol. This checklist should be completed by the responsible investigator before the patient is randomized.

- institution number ?
- protocol number ?
- step number (*generally 1, except for multistep studies*) ?
- name of the responsible investigator ?
- patient's initials (*maximum 4 letters*) ?
- patient's chart number (*if available*) ?
- patient's birth date (*day/month/year*) ?
- eligibility criteria ?
- all eligibility criteria will be checked; actual values of the eligibility parameters will be requested when applicable

- stratification factors ?

At the end of the procedure, the treatment will be randomly allocated to the patients, as well as a patient sequential identification number. This number and the allocated treatment have to be recorded on the randomization checklist, along with the date of randomization. The completed checklist must be signed by the responsible investigator and returned to the data center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the randomization procedure identifies the patient and must be reported on all case report forms.

3. FORMS AND PROCEDURES FOR COLLECTING DATA

3.1 Case report forms and schedule for completion

The forms developed by the RTOG will be used for this study.

The identification frame of those forms must be completed as follows:

RTOG study	9512	Case #	<i>case number allocated by the RTOG</i>
Intergroup Study	EORTC 22992	Case #	<i>EORTC sequential identification number, allocated at registration</i>
Institution	<i>Institution name and city</i>	Inst. #	<i>EORTC institution number</i>
Patient name	<i>Patient initials</i>	I.D.	<i>local medical record (if available) date of birth (otherwise)</i>

If a form has several pages, the RTOG case number should be completed on all pages. Patient-specific labels and forms calendars will be provided after each randomization.

The name of the responsible investigator and the date of completion must be indicated at the bottom of each form (*if the form is signed by someone else than the responsible investigator, the name of the responsible investigator must also appear in this section*).

All forms must be send to:

Marianne Pierart
EORTC Data Center
avenue Emmanuel Mounier, 83, bte 11
B - 1200 BRUSSELS

The EORTC Data Manager will check the patient identification, and forward all forms to the RTOG.

Case report forms must be completed according to the following schedule:

A. Before the treatment starts:

- the patient must be registered/randomized at the Data Center by INTERNET or by phone
- the following set of forms has to be returned to the Data Center:
- the Eligibility Checklist
- the demographic data form (*form A5*) (*optional for EORTC members*)
- the initial evaluation form (*form II, pages 1 to 6*)
- the staging diagrams (*form I6, both side or 2 pages*)
- the pathology reports (*form P1*) (*optional*)
- the pathology blocks (*form P2*) (*optional*)

The optimal way to work is to complete the Eligibility Checklist and, if possible, the above set of forms first, and to register the patient through Internet using ORTA system as soon as data are complete. The date of registration and patient sequential identification number are then completed on the checklist, and the whole set can be sent to the Data Center.

Pathology reports and blocks (*optional*) should be sent directly to LDS Hospital. See Section 10.1.3 of the protocol. Also mandatory dosimetry material should be sent directly at RTOG Headquarters, 1101 Market Street, Philadelphia, PA 19107

B. Within 1 week of start of radiotherapy

- the radiotherapy prescription (*form T2*)
- the calculations (*form T4*)

C. Within 1 week of completion of radiotherapy

- the radiotherapy form (*form T1, 4 pages*)
- the daily treatment record (*form T5*). The time of irradiation must be reported for patients in the b.i.d. arm
- the isodose distribution (*form T6*)

D. At each follow-up interval

- a follow-up form (*form F1, 3 pages*)
- 4 weeks post radiotherapy; q 3 months through year 1; q 4 months through year 2; q 6 months through years 3-5; annually thereafter and upon progression / relapse / death / grade ≥ 4 toxicity

E. Upon surgery

- the surgery form (*form S1*)
- the surgery report of operation (*form S2*) (*mandatory for laryngectomy, optional for other surgical intervention, can be replaced by a short summary in English done by the Principal Investigator*)
- the surgery pathology report (*form S5*) (*optional, but in all cases send a brief summary in English done by the Principal Investigator*)

F. Upon death

- a follow-up form (*form F1, 3 pages*)
- the autopsy report (*D3*) (*optional*)

G. Upon occurrence of a Serious Adverse Event

- All serious adverse events occurring during the treatment period and within 90 days after the end of the last radiotherapy treatment must be reported to the EORTC Safety Desk.
- All serious adverse events must be reported by fax to the EORTC Safety Desk **within 24 hours**.
- A serious adverse event form (*form 90*) must be completed and returned to the Data Center within 10 calendar days of the initial observation of the event.

**ALL FORMS MUST BE DATED AND SIGNED
BY THE RESPONSIBLE INVESTIGATOR OR
ONE OF HIS/HER AUTHORIZED STAFF MEMBERS**

3.2 Data flow

The case report forms must be completed and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available, according to the above described schedule.

The list of staff members authorized to sign case report forms (*with a sample of their signature*) must be sent to the Data Center by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the Data Center and that they are completely and correctly filled out.

The original copy must be immediately returned to the EORTC Data Center and a copy must be kept by the investigator.

All forms will be forwarded to the RTOG Statistical Center.

The RTOG Statistical Center will perform consistency checks on the CRFs and issue Query Forms in case of inconsistent data. Those forms will be distributed to the responsible investigators via the EORTC Data Center.

Those Query Forms must be immediately answered and signed by the investigator (*or an authorized staff member*). The original must be returned to the EORTC Data Center and a copy must be appended to the investigator's copy of the CRFs. The EORTC Data Center will forward those forms to the RTOG Statistical Center.

If an investigator (*or an authorized staff member*) needs to modify a CRF after the original copy has been returned to the EORTC Data Center, he/she should notify the Data Center in writing (*and sign and date the notification*) and append a copy of the notification to his own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (*or a written and signed notification*) and the Query Form (*or notification*) reference is indicated on the CRF.

4. REPORTING OF ADVERSE EVENTS

4.1 Definitions

Adverse Events (AE) are any untoward medical occurrences or experiences in a patient which occur following the administration of the trial treatments regardless of the causal relationship. This can include any unfavorable and unintended signs, or symptoms, an abnormal laboratory finding (*including blood tests, x-rays or scans*) or a disease temporarily associated with the trial treatments.

Serious Adverse Events (SAE) are defined as any undesirable experiences occurring to a patient, whether or not considered related to the study treatments. Adverse events which are considered as serious are those which result in:

- death
- a life-threatening event (*i.e. the patient was at immediate risk of death at the time the reaction was observed*).
- hospitalization or prolongation of existing hospitalization
- persistent or significant disability/incapacity or
- a congenital anomaly/birth defect
- any other medically important condition (*i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above*).

4.1.1 Reporting Procedures

4.1.1.1 Non-serious Adverse Events

All Adverse Events (AE) occurring during the treatment period and until 90 days after the last study treatment will be recorded on the treatment and the follow-up forms. The investigator will decide if those events are related to the study treatment (*i.e. unrelated, unlikely, possible, probable, definitely and not assessable*).

The assessment of causality is made by the investigator using the following :

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (<i>e.g. the event did not occur within a reasonable time after administration of the trial medication</i>). There is another reasonable explanation for the event (<i>e.g. the patients clinical condition, other concomitant treatments</i>).
POSSIBLE	There is some evidence to suggest a causal relationship (<i>e.g. because the event occurs within a reasonable time after administration of the trial medication</i>). However, the influence of other factors may have contributed to the event (<i>e.g. the patients clinical condition, other concomitant treatments</i>).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

4.1.1.2 **Serious Adverse Events**

All Serious Adverse Events (SAE) occurring during the treatment period and within 90 days after the last study treatment must be reported to the EORTC Safety Desk. Any late SAE (*occurring after this 90-day period*) at least possibly related to the study treatment should follow the same reporting procedure. This must be done by fax within 24 hours of the initial observation of the event. Details should be documented on the specified Serious Adverse Event Form.

**PLEASE FAX FORM 90 TO:
EORTC SAFETY DESK:
FAX. 32 2 772 8027**

The Safety Desk will forward all reports within 24 hours of receipt to the data manager and the EORTC trial coordinator and the RTOG Headquarters Data Management (*Fax #215-928 0153*).

All unexpected SADR and all expected SADR that are life threatening or caused death, will additionally be forwarded the ICPA committee within 24 hours of receipt.

In order that the EORTC Safety Desk is able to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. When the completed form is not received within this deadline, the Safety Desk will make a written request to the investigator.

**PLEASE SEND THE ORIGINAL FORM 90 TO:
EORTC SAFETY DESK,
AVENUE E. MOUNIER, 83, BTE 11
B- 1200 BRUSSELS, BELGIUM**

It should be recognized that Serious Adverse Events (SAE) which have not been previously documented, or which occur in a more severe form than anticipated (*i.e. they are 'unexpected'*), are subject to rapid reporting to Regulatory Authorities by the sponsor/promoter. This also applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, independent of design or purpose. The source of the report (*investigation, spontaneous, other*) should always be specified.

Any question concerning the SAE reporting can be asked to the Safety Desk by phone: +32 2 774 1676 or e-mail: safetydesk@eortc.be

**ALL FORMS MUST BE DATED AND SIGNED
BY THE RESPONSIBLE INVESTIGATOR OR
ONE OF HIS/HER AUTHORIZED STAFF MEMBERS**

5. INDEPENDENT DATA MONITORING COMMITTEE

This study will be monitored by the RTOG Independent Data Monitoring Committee.

6. QUALITY ASSURANCE

6.1 Control of Data Consistency

Internal data consistency will be checked by the RTOG statistical center. Queries will be issued in case of inconsistencies, and circulated to the investigators via the EORTC Data Center.

6.2 On-site Quality Control

No on-site quality control will be performed for this study, but all EORTC participating centers will be audited and certified according to ICPA requirements (see 6.6).

6.3 Dosimetry

Dosimetry material should be submitted directly to the RTOG Headquarters, 1101 Market Street, Philadelphia, PA 19107, with a copy of appropriate accompanying form.

6.4 Pathology

Pathology material can be optionally submitted to LDS Hospital. The preparation of tumor sections and the submission of material should follow the procedures described in Section 10.1 of the protocol.

6.5 International Cooperative Project Assurance

This protocol will be carried out under the International Cooperative Project Assurance (*ICPA*) in conjunction with the US Office for Human Research Protections (*OHRP*) and the Cooperative Protocol Research Program (*CPRP*). The ICPA allows the EORTC to participate in the CPRP and covers all NCI funded Co-operative Group protocols as well as protocols using NCI-sponsored IND agents.

The ICPA Committee is an EORTC Central Ethics Committee constituted of medical/scientific professionals and non-medical/non-scientific members. Their responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in Co-operative Protocol Research Program trials. The Committee is guided by the ethical principles regarding research involving human subjects set forth in the Belmont Report and the Declaration of Helsinki. These ethical principles guide the institution in the conduct of all its human subjects' research. The Committee is focusing on the ethical aspects of intergroup trials, taking into account the existing social cultural differences between countries and addressing safety issues there with safeguarding the integrity of subjects participating to studies. The ICPA also has to provide public assurance of that protection by, approving the suitability of the investigators, facilities and the methods and materials to be used in obtaining and documenting informed consent of the trial subjects.

Each protocol must include a template for patient information and informed consent form that adheres to the ICH-GCP guidelines (*CPMP/ICH/135/95; September 1997; chapter 4.8.10*) and to the ethical principles that have their origin in the Declaration of Helsinki.

The ICPA Committee has the dedicated task of expressing their opinion on problems in the current procedures and in the patient information sheet and/or informed consent template. The ICPA Committee can impose changes to the patient information and/or informed consent if necessary.

The expedited review committee has the task of determining if a protocol amendment implements changes in the patient information sheet and/or informed consent template.

Each EORTC institute participating in the ICPA trial should translate the original patient information and informed consent template (*see Appendix*) approved by the ICPA Committee, into the local language. Each responsible investigator is required to certify that the translations of the PIS/IC is conform to the original

template. Any change in the PIS/IC translation must be reported and justified to the ICPA Committee. This will be done through the EORTC Data manager.

All participating institutes will be part of the EORTC audit program to verify the quality of the Institution/Department with regards to facilities and quality of data. These audits will be performed at least once every three years.

7. ETHICAL CONSIDERATIONS

7.1 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (*Tokyo, Venice, Hong Kong and Somerset West amendments*) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice.

The protocol will be approved by the Local, Regional or National Ethics Committees.

7.2 Subject Identification

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient's initials (*maximum of 4 letters*), date of birth and local chart number (*if available*) will also be reported on the case report forms.

7.3 Informed Consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This must be done in accordance with the national and local regulatory requirements.

For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

8. INVESTIGATOR AUTHORIZATION PROCEDURE

Only institutions approved by the EORTC and listed in the International Cooperative Project Assurance (ICPA) agreement signed between the EORTC and the US Office for Human Research Protections from (OHRP) can participate in the present trial.

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Data Center:

- a commitment statement/study acknowledgment form, indicating that they will fully comply with the protocol, and that they will participate under the conditions of the ICPA (*see Appendix 2*). This form will include an estimate of their yearly accrual and if any conflict of interest may arrive due to their participation in the trial,
- a copy of the letter of acceptance of the protocol and patient information sheet / informed consent by their local or national (*whichever is applicable*) ethics committee,
- a copy of the accepted PIS/IC sheet together with the completed and signed PIS/IC certificate documenting if any change occurred in content or structure of the PIS/IC compared with the protocol template PIS/IC (*see Appendix 1*). If yes, type of change(s) and reason(s) of change(s) must also be documented on the certificate.

- a signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared by the commitment form.
- and, if the following documents are not yet available at the Data Center:
- their updated Curriculum Vitae,
- the list of the normal ranges, in their own institution, of all laboratory data required by the protocol,
- the list of their staff members authorized to sign case report forms, with a sample of each authorized signature.

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

- all the above mentioned documents are available at the Data Center
- all applicable national health authorities requirements are fulfilled

Patients registration/randomization from centers not (*yet*) included on the authorization list will not be accepted.

9. ADMINISTRATIVE RESPONSIBILITIES

This is an Intergroup study, coordinated by the RTOG.

The Intergroup Study Chair is Dr. Andy Trotti (*see protocol*)

The RTOG Statistical Center is responsible for all statistical center functions (*see protocol*)

The EORTC Study Coordinator has been designated by the EORTC Radiotherapy Group. He will work with the Study Chair in the coordinating group.

EORTC Study Coordinator

Dr. P. BONTEMPS
 CHR DE BESANCON - HOPITAL JEAN MINJOZ
 Radiotherapie & Oncologie
 Boulevard Jean Fleming
 F-25030 BESANCON CEDEX
 France
 Tel +33 381668240
 Fax +33 381668551
 E-mail: xrtbesanco@aol.com

The EORTC Data Center will be responsible for patient randomization, data collection and transfer to the RTOG Statistical Center, and management of the queries issued by the RTOG Statistical Center.

EORTC DATA CENTER

83, avenue Emmanuel Mounier, Bte 11
 B - 1200 BRUSSELS, BELGIUM
 Fax: 32-2-772.35.45

Registration of Patients

Patients will be registered either by electronic network (*Internet*), 24 hours a day, 7 days a week, or by phone to the EORTC Data Center from 9.00 am to 5.00 pm:

Tel.: 32-2-774.16.00
 Internet: <http://www.eortc.be/random>

Data Manager

Marianne Pierart
 Tel.: 32-2-774.16.03

Internet: mpi@eortc.be

All questions concerning membership in the cooperative group should be addressed to the chairman and/or secretary of the group.

Safety Desk:

Phone: + 32 2 774 1676

Fax: + 32 2 772 8027

e-mail: safetydesk@eortc.be

The EORTC Data Center Safety Desk will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons: Dr. P. BONTEMPS (*Fax +33 381668551*) and the RTOG Headquarters Data Management (*Fax: +215/928-0153*)

10. TRIAL SPONSORSHIP/FINANCING

For patients entered on behalf of the EORTC Radiotherapy Group, the sponsor of the study is the EORTC. The Director General of the EORTC is:

Professor Françoise Meunier
EORTC Central Office
Avenue Mounier 83, Bte 11
B 1200 - Brussels (Belgium)
Tel: + 32 2 - 774 16 41
Fax: + 32 2 - 771 20 04

11. TRIAL INSURANCE

The EORTC insurance program covers all patients entered on behalf of EORTC in EORTC studies except patients from USA and Canada. This program will cover all patients entered by members of the EORTC Radiotherapy Group in the present trial.

11.1 Insurance Within the European Union:

When specific requirements are stated in the national laws of the E.U. countries, the insurance program will take these requirements into account.

For countries where there are no specific requirements, the EORTC provides an insurance coverage which is valid for two years after a patient has completed the treatment strategy being studied by the research protocol. This insurance program covers the EORTC as the sponsor, the investigators and all local hospital staff.

11.2 Insurance Outside the European Union:

The EORTC insurance program only covers claims against the EORTC as the sponsor in its role of coordinator of the research and not the investigators and local hospital staff.

12. PUBLICATION POLICY

The results of this trial will be published according to the RTOG publication guidelines for Intergroup Studies that RTOG coordinates.

According to this policy, EORTC will be entitled to one or two authors in all publications, if it contributes respectively for at least 5% and 7% of the total accrual.

All publications, abstracts or presentations including data from the present trial will be submitted for review to the EORTC Data Center, to the EORTC Study Coordinator and to the Steering Committee of the Radiotherapy Group prior to submission.

All manuscripts will include an appropriate acknowledgment section, mentioning EORTC and all investigators who have contributed to the trial, as well as other supporting bodies (*NCI, cancer leagues, sponsors...*).

Appendix 1: Informed consent and Certificate of Patient Information Sheet/Informed Consent Form

Appendix 2: Commitment Statement/Study Acknowledgement Form



EORTC

European Organization for Research
and Treatment of Cancer

EORTC Data Center
Av. E. Mounier 83/11
1200 Brussels, Belgium
Direct phone: + 32 2 774 16 11
Fax: + 32 2 772 35 45

**This is a clinical trial.
Clinical trials include only patients who choose to take part.
Please take your time to make your decision.**

**EORTC 22992, (RTOG 95-12)
A RANDOMIZED STUDY OF HYPERFRACTIONATION
VERSUS CONVENTIONAL FRACTIONATION IN T2 SQUAMOUS CELL
CARCINOMA OF THE VOCAL CORD**

1. Invitation to Participate in the Study

"The EORTC Radiotherapy Cooperative Group is joining an international research study on patients that have a disease similar to yours. The study will be conducted at International level under the supervision of physicians recognized as experts in this field of medicine. Today, you will be invited to take part to this research project after you are given full information about the study"

2. Introduction

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

I understand that my diagnosis is a malignant squamous cell tumor of my voice box and that further treatment is recommended. Radiotherapy is the treatment of tumors by means of x-rays. I understand that in the past radiation therapy has been usually given in daily doses 5 days per week for 6-8 weeks. Previous studies have shown that alternate ways of giving radiation therapy may produce greater tumor control, however this has not been proven. The experimental aspect of this study is the use of two treatments of irradiation daily. The total dose of irradiation administered is also being investigated in the current study.

3. Description of Procedures

This study involves at random (*by chance*) assignment to one of two treatment arms. It is not clear at the present time which of the two regimens is better. For this reason the therapy which is to be offered to me will be based upon the method of selection called randomization. Randomization means that my physician will call a statistical office, which will assign me one of the two regimens by computer. The chance of my receiving either therapy is approximately equal. I understand that my physician has no influence in the allocation process and I will be prepared to accept either form of treatment.

I will be assigned to one of two treatments:

Treatment 1

If I receive the standard fractionation treatment as an outpatient. Each radiation treatment will be administered once a day, five days a week to a total dose of 70 Gy in 35 treatments in seven weeks.

Treatment 2

If I receive the hyperfractionation treatment as an outpatient. Two radiation treatments will be administered each day at least six hours apart. Treatment will be administered five days a week to total dose of 79.2 Gy in 66 treatments in almost seven weeks.

After treatment completion, the physicians will ask me to undergo appropriate clinical and diagnostic examinations regularly. The initial frequency of every three months during the first year after therapy will gradually decrease with time, to reduce to a single annual visit after 3 years from treatment completion.

Also, at the time of my diagnosis by biopsy, 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.

It is expected that there will be about 240 persons taking part in this study.

4. Description of Foreseeable Risks and Discomforts

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

Risks of Radiation

I have been informed of the discomforts and risks, which I may reasonably expect as part of this study. The irradiation may cause temporary skin redness or tanning, loss of hair in the treatment area, tiredness or fatigue, sore throat, loss of appetite, difficulty swallowing and reduction in blood counts which may lead to infection.

Late effects may include continued soreness in the throat, hoarseness, thickening or toughening of tissues in the treatment area, thyroid problems, or damage to the voice box causing pain or requiring surgery if severe. In rare circumstances, damage has resulted in loss of the voice box organ. I understand that there may be some unknown or unanticipated discomforts or risks in addition to those specified above. My physician will be checking me closely to see if any side effects are occurring and prescribe medication to keep side effects under control. Side effects usually disappear after the treatment is stopped.

5. Expected Benefits

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

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

6. Description of Alternative and Conditions for Withdrawal

Alternatives which could be considered in my case include surgery or chemotherapy plus radiation therapy 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.

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.

7. 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 American research organization that initiated the study (*Radiation Therapy Oncology Group, RTOG*). The confidentiality of the central computer record is carefully guarded. During their required reviews, Duly authorized persons (*EORTC staff, national and/or foreign health authority representatives*) 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.

8. Contact Persons

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.

9. Additional Information

Insurance has been taken by the EORTC according to the current legislation. Everything has been done and will continue to be done to prevent additional health problems occurring as a result of participation in this trial.

This research protocol has been submitted to an ethics committee whose mission is to verify all conditions for your safety and respect of your rights are respected. Approval to this research has been given by the Ethics Committee of _____
on _____."

Please take your time to consider this information and do not hesitate to ask further questions of your doctor if anything is not clear. You are entitled to keep a copy of this document after you and your doctor have signed it.

Acceptance of Participation

- I have been properly informed of the clinical research that is being proposed to me*
- I have received a copy of the patient information sheet*
- All my rights have been clearly explained*
- I have received a copy of the informed consent document*
- "I accept to participate in the research entitled "A randomized study of hyperfractionation versus conventional fractionation in T2 squamous cell carcinoma of the vocal cord" and registered under EORTC study number 22992. My participation is completely voluntary and I have the possibility to withdraw my consent at anytime without explanation. This will not affect my relationship with my treating physician. The data collected on my behalf will be strictly confidential and treated according to the "Directive on Human Protection " and the local applicable laws.*

My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law".

Investigator's Signature: _____ Patient's Signature: _____

Date: _____ Date: _____

Person designated by the investigator to participate in the informed consent process

Title/Position: _____

Signature: _____ Date: _____

This document has been prepared taking into account:

- ◆ International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
- ◆ World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland June 1964. Revised 1975, 1983, 1989 and 1996.
- ◆ ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997



EORTC

European Organization for Research and Treatment of Cancer
International Association under Belgian Law

EORTC ICPA Committee
Av. E. Mounier 83/11
1200 Brussels, Belgium
Phone: +32 2 7741674
Fax: +32 2 7723545
E-mail: cdu@eortc.be

Certificate of Patient Information Sheet/Informed Consent Form

Please complete and return this certificate to the responsible EORTC Data Manager together with a copy of the Patient Information Sheet/Informed Consent (PIS/IC) Form currently in use at your institution.

Name of Investigator: _____

Name and Number of Institution: _____

EORTC Trial Title and Number: _____

- I am making the following declaration (**Please tick one**):
 - I confirm that the current PIS and IC Form in use at my institution is the protocol template without changes in content or structure.
 - I confirm that the current PIS and IC Form in use at my institution is a translation, which conforms to the protocol template both in terms of content and structure.
 - I confirm that the current PIS and IC Form in use at my institution is a modification of the protocol template. The changes/modifications requested by the Institutional Review Board and/or the Health Authorities are listed below.

Please specify all changes and indicate the reasons for change:

Current version of PIS/IC: _____

Date: _____

Signature of Principal Investigator: _____

Date: _____

Signature of IRB Chairman: _____

Date: _____

Commitment Statement/Study Acknowledgment

“Study number” and “Study title”

I, the undersigned declare that I will participate in the above-mentioned study. **I expect to recruit _____ patients per year.**

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol and any subsequent amendments as outlined therein and will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all relevant information I receive to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study and treatment. I understand that the EORTC may terminate the study or suspend enrollment at any time if it becomes necessary to protect the best interests of the study subjects.

I accept the following terms and conditions:

1. As the meetings, correspondence or discussions referred to above may involve matters for which I will be taken into confidence, I will regard as secret and confidential any such information which I may thereby acquire in respect of the manufacturing or commercial interests of the industrial partner, if any and its research. Accordingly I will not disclose such information to a third party.
2. All the trial related minutes of meetings, correspondence or records of discussion together with all other trial documents obtained from the EORTC, other Collaborative groups and/or the industrial partners (*if any*) are confidential and remain the property of the respective partner. This information will be returned to them if requested.

- **I am responsible for Ethics Committee submission.**
- **The following person is in charge of submission:** _____
- **I have no potential conflict of interest**, such as a professional interest, a proprietary interest or any other conflict of interest.
- **YES, I have a potential conflict of interest** (*If you have a potential conflict of interest, please indicate this and we will send you the standard of conduct for conflict of interest/confidentiality policy and a conflict of interest/confidentiality disclosure form requesting further clarification*).
- **YES, I certify that I am authorized by my institution to commit in this intergroup collaboration involving US investigators and I agree to work according to the EORTC International Cooperative Project Assurance (ICPA) policies. I understand that in the event of my noncompliance with the ICPA and with the EORTC Human Research Subjects Protection Policy, the EORTC may withdraw my site from EORTC registration.**

NAME Principal Investigator: _____ EORTC Inst. Nb.: _____ Date _____

Signature: _____

Please complete and return this form, **as soon as possible**, to the responsible data manager at the EORTC Data Center: