

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0022

**PHASE I/II STUDY OF CONFORMAL AND INTENSITY MODULATED IRRADIATION FOR
OROPHARYNGEAL CANCER**

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SCHEMA

R

E

Treatment Plan:

G

Planning Target volumes (*PTVs*) of the primary tumor, lymph node metastases, lymph nodes at risk of metastatic disease, critical organs and the major salivary glands will be

I

outlined on planning CT scans. Conformal and/or IMRT techniques will be utilized. Gross

S

disease PTV dose will be 66 Gy/30 fractions and subclinical PTV dose 60-54 Gy/30 fractions.

S

The major salivary glands will be spared according to specified criteria (*see Section 6.4*).

T

Saliva output will be measured before and following therapy.

T

E

A boost of 4-6 Gy in 2-3 fractions to the gross tumor PTV is optional.

R

Eligibility: (*See Section 3.0 for details*)

- Confirmed histopathologic diagnosis of oropharyngeal (*tonsil, base of tongue or palate*) squamous cell carcinoma requiring primary irradiation
- Stage T1-T2, N0-N1, M0; both sides of the neck are judged to be at risk of metastatic disease
- Surgery of the primary tumor or lymph nodes is limited to incisional or excisional biopsies
- Zubrod performance status 0-1
- Must undergo pre-treatment evaluation of tumor extent and tumor measurement.
- Nutritional and general physical condition must be considered compatible with the proposed radiotherapeutic treatment
- No prior radiotherapy to the head and neck; no concurrent chemotherapy; no previous chemotherapy ≤ 3 months from start of RT
- No prophylactic use of amifostine or pilocarpine
- No other malignancy except non-melanomatous skin cancer or a carcinoma not of head and neck origin ≤ 5 years
- No evidence of distant metastasis
- No other treatment for head and neck cancer
- No active untreated infection
- No major medical or psychiatric illness
- Signed study-specific informed consent form prior to registration

Required Sample Size: 64

RTOG Institution # _____

RTOG 0022

ELIGIBILITY CHECK

Case # _____

(page 1 of 2)

- _____(Y) 1. Is the primary tumor site arising from the oropharynx?
- _____(Y) 2. Is the confirmed histology squamous cell cancer?
- _____(I-III) 3. What is the biopsy proven stage?
- _____(Y/N) 4. Was there surgery on the primary tumor or lymph nodes?
_____(Y) If yes, was surgery limited to incisional or excisional biopsies?
- _____(0,1) 5. What is the Zubrod Performance status?
- _____(Y) 6. Has the patient undergone pretreatment evaluation of tumor for extent and measurement?
- _____(N) 7. Does the patient have any serious medical or psychiatric illness that would preclude informed consent?
- _____(N) 8. Is the patient on any other therapeutic treatment for head and neck cancer?
- _____(N) 9. Is there evidence of distant metastases?
- _____(N) 10. Did the patient have any previous irradiation for head and neck cancer?
- _____(N) 11. Is the patient receiving concurrent chemotherapy?
- _____(N) 12. Has the patient received chemotherapy within the past 3 months?
- _____(Y/N) 13. Any prior malignancy (*other than non-melanomatous skin cancer*)?
_____(Y) If yes, has the patient been continuously disease-free for 5 years?
- _____(N) 14. Does the patient have an active, untreated infection?
- _____(N) 15. Has the patient taken amifostine or pilocarpine prophylactically?
- _____(Y) 16. Have all pretreatment studies in Section 4.0 been obtained in the time frame indicated?
- _____(Y) 17. Is your institution pre-approved for IMRT studies by the IMRT QA Committee and the physics center (*See Section 5.1*)?

(continued on next page)

RTOG Institution # _____

RTOG 0022

ELIGIBILITY CHECK

Case # _____

(page 2 of 2)

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
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Social Security Number
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code
- _____ 14. Patient's Insurance Status
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Treatment Assignment

Completed by _____

Date _____

1.0 BACKGROUND

The major salivary glands (*parotid, submandibular and sublingual*) produce about 90% of salivary secretions, and the minor salivary glands produce the remainder.¹ The standard radiation for advanced oropharyngeal tumors typically involves administering a high radiation dose to the major salivary glands bilaterally. In most cases this causes a marked reduction in oral saliva output. Xerostomia is the most prevalent late side effect of radiation for head and neck malignancies and is cited by patients as the major cause of decreased quality of life.²⁻⁵ In addition to its effects on subjective well-being, decreased saliva output causes alterations in speech and taste and difficulties with mastication and deglutition that create secondary nutritional deficiencies. Oral mucosal dryness creates a predisposition to fissures and ulcers, and changes in the composition of the oral flora lead to dental caries and infections. The reduction in the salivary flow may also contribute to the risk of osteonecrosis of the mandible⁶ and to esophageal injury by decreasing acid clearance.⁷

The treatment of radiation-induced salivary gland dysfunction and xerostomia has been unsatisfactory. Saliva substitutes are generally ineffective. Patients who have residual salivary function may benefit from stimulation of the glands by pilocarpine but the sequelae from chronic use of this cholinergic agent may limit its usefulness.⁸ The use of the radiation protector WR-2721 (*amifostine*) has been reported in a pilot study to result in some salivary function improvement over time⁹ and early results from a randomized study are encouraging.¹⁰ However, it requires i.v. drug infusions on each day during the radiation course, limiting its utility.

The degree of xerostomia has been reported to depend on the radiation dose and the salivary gland volume irradiated. At doses of 30-50 Gy the hyposalivation may be reversible, while higher doses generally produce irreversible destruction of the salivary glands with permanent dryness.¹¹ Mira et al. have reported that more than 50% of the parotid glands had to be outside the radiation fields to prevent severe dryness; irradiation of the submandibular and sublingual glands only had a minor effect.¹² Examination of the relationships between the three-dimensional dose distributions in parotid salivary glands and their saliva production revealed the existence of dose and volume thresholds: mean parotid gland dose thresholds were 24 Gy and 26 Gy for the unstimulated and stimulated flow rates, respectively, and partial volume thresholds were 67%, 45%, and 24% gland volume receiving more than 15 Gy, 30 Gy and 45 Gy, respectively.¹³ Measurements of whole mouth saliva revealed that significant salivary output was retained if at least 20 cc of the combined volume of both parotid glands received no more than 20 Gy.¹⁴ These studies show that dose-volume-response relationships in the salivary glands exist, and that it may be possible to improve significantly saliva production, post-radiation xerostomia and quality of life, if radiation techniques can be devised that would spare the salivary glands.

In recent years, conformal radiation techniques have evolved which may allow irradiation of targets in the head and neck defined on planning CT scans, while sparing substantial portion of the major salivary glands. These techniques include “standard” conformal radiotherapy using beams-eye-views, static segmental intensity modulation, and dynamic intensity modulation techniques (*IMRT*).¹⁵⁻¹⁸ It has been demonstrated that using these techniques, adequate irradiation of the targets while sparing major salivary glands is feasible in patients with head and neck cancer. Early clinical experience has demonstrated substantial sparing of saliva flows following radiation and suggests an improvement of tumor control^{17,18} and of xerostomia^{17,19}, compared with patients receiving standard radiation techniques.

While the limited institutional experience is encouraging, there are several important issues regarding the use of conformal and IMRT techniques in head and neck cancer that need to be verified. A major issue is the adequacy of the target definitions and outlining on the planning CT. The tight isodoses around the defined target volumes increase the potential of missing areas containing subclinical disease, compared with standard radiation techniques. This may increase the risk of marginal or out-of-field locoregional recurrences. It has been shown that significant variations among physicians exist in the definitions of head and neck nodal volumes.^{20,21} Recent efforts to define accurately the location of lymph nodes in the head and neck for adjuvant radiation, using cadaver CT scans, have been described.²² Such efforts may be used to standardize target definitions.

In addition to accurate clinical and radiologic definitions of the targets, IMRT poses dosimetric and treatment planning issues that are not encountered in standard RT.

IMRT capabilities are now becoming available through commercial vendors and are spreading to both academic centers and community radiation facilities. The optimal way to address many of the issues involved in their use is not yet known.

Accelerated RT schedules have recently been developed in order to shorten treatment duration, to overcome accelerated repopulation of surviving tumor clonogenic cells during the latter phase of therapy. A recent analysis of RTOG 90-03 revealed significantly higher disease control in patients with head and neck cancer receiving an accelerated schedule compared with standard RT.²³ Treatment of patients on this study will, therefore, use an accelerated scheme. It will include of a high fraction dose delivered to the gross tumor, and a standard fraction dose delivered to tissue at risk of subclinical disease. The dose received by the gross tumor will be equivalent biologically to 70 Gy and will be delivered over 6 weeks. It is anticipated that the use of conformal and IMRT techniques will facilitate a higher than standard fraction dose to the gross tumor by limiting the noninvolved tissue receiving these doses, thus limiting acute and late sequela. These considerations will be tested in this study.

The main objectives of this study are to: 1) assess whether adequate radiologic definitions of the targets and adequate target irradiation and major salivary gland sparing can be achieved in a multi-institutional study of patients with oropharyngeal cancer; 2) evaluate xerostomia in patients treated with IMRT techniques.

2.0 OBJECTIVES

- 2.1** To assess the feasibility of adequate target coverage and major salivary gland sparing in patients with oropharyngeal cancer treated with IMRT techniques.
- 2.2** To determine the rate and pattern of locoregional tumor recurrence.
- 2.3** To determine the nature and prevalence of acute and late side effects (*using RTOG scales*) and their relationship to local dose.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1** Biopsy-proven stage I-III (*T1-T2, N0-N1*) squamous cell carcinoma of the oropharynx (*tonsil, base of tongue, or palate*) with primary RT as the treatment plan. The neck staging is based on palpation. Patients who are “upstaged” by imaging to N2 are still eligible. Lymph nodes in both sides of the neck are at risk of metastatic disease, according to clinical judgment, and require irradiation. Where node positive disease is based on presence of nodal disease found only on CT/MRI scans, i.e., not palpable on clinical examinations, the size of the node(s) detected with imaging must be > 1.0 cm in its minimal axial diameter or contain necrotic regions regardless of size.
- 3.1.2** Surgery of the primary tumor or lymph nodes is limited to incisional or excisional biopsies.
- 3.1.3** Zubrod performance status 0-1 (*Appendix II*).
- 3.1.4** All patients must undergo pre-treatment evaluation of tumor extent and tumor measurement. Tumor may be measurable or evaluable.
- 3.1.5** Patient’s nutritional and general physical condition must be considered compatible with the proposed radiotherapeutic treatment.
- 3.1.6** Patient is judged to be mentally reliable to follow instructions and to keep appointments.
- 3.1.7** Patient is on no other treatment for head and neck cancer.
- 3.1.8** Signed study-specific informed consent prior to registration (*see Appendix I*).

3.2 Ineligibility Criteria

- 3.2.1** Evidence of distant metastases.
- 3.2.2** Previous irradiation for head and neck tumor; concurrent chemotherapy; previous chemotherapy \leq 3 months from start of RT.
- 3.2.3** Other malignancy except non-melanomatous skin cancer or a carcinoma not of head and neck origin and controlled at least 5 years.
- 3.2.4** Active untreated infection.
- 3.2.5** Major medical or psychiatric illness, which in the investigators’ opinions would interfere with either completion of therapy and follow-up or with full and complete understanding of the risks and potential complications of the therapy.
- 3.2.6** Prophylactic use of amifostine or pilocarpine is not allowed.

4.0 PRETREATMENT EVALUATIONS (9/30/03)

- 4.1 Each patient must have completed the following studies within 21 days prior to irradiation:
 - 4.1.1 Complete history and physical exam including weight and performance status.
 - 4.1.2 Complete diagrammatic and descriptive documentation of the extent of the primary and regional disease (*if any*) following appropriate endoscopic procedures.
 - 4.1.3 Complete dental and nutritional evaluation. Any required dental repairs must be made and prophylaxis instituted prior to radiotherapy.
 - 4.1.4 Completion of the following laboratory studies: CBC and platelet count; liver function tests including SGOT, bilirubin and alkaline phosphatase; thyroid stimulating hormone (*TSH*).
 - 4.1.5 Completion of the following radiologic studies: Chest X-ray; CT of head and neck with ≤ 3 mm contiguous slices in immobilization system (*with contrast, unless contraindicated*); liver CT (*must be done only in the presence of elevation to more than twice the normal range of alkaline phosphatase, SGOT, or bilirubin or other clinical indicator*); bone scan (*only in the presence of elevation to more than twice the normal range of alkaline phosphatase or other clinical indicator*).
MRI of head and neck with T1 contrast with gadolinium and T2 sequences (*optional*).
 - 4.1.6 Audiogram (*if middle or inner ear is to be irradiated at dose ≥ 40 Gy*).
 - 4.1.7 Measurement of unstimulated and stimulated whole mouth saliva (*see Section 11.2.2*).

5.0 REGISTRATION PROCEDURES (9/30/03)

- 5.1 The institution must be pre-approved for IMRT studies by the IMRT QA committee and the Image-Guided Therapy Center. See Appendix VI. A copy of IMRT approval will be forwarded to RTOG Headquarters from the Image-Guided Therapy Center. RTOG Headquarters will notify the CTSU Regulatory Office upon receipt of an institution's IMRT approval.
- 5.2 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.

6.0 RADIATION THERAPY

6.1 Treatment Planning, Imaging and Localization Requirements

- 6.1.1 The immobilization device should include neck and shoulder immobilization. A thermoplastic face mask alone may not provide sufficient neck immobilization. A description of the immobilization system used by each institution and data regarding the range of positioning errors (*if data exists*) should be provided.
- 6.1.2 Treatment planning CT scans will be required to define tumor, clinical, and planning target volumes. MRI scans are optional. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment.
- 6.1.3 All tissues to be irradiated must be included in the CT scan. CT scan thickness should be 0.3 cm through the region that contains the primary target volumes. The regions above and below the target volume may be scanned with slice thickness 0.5 cm. MRI scans may be included to assist in definition of target volumes, especially when targets extend near the base of skull. If possible, the treatment immobilization device should also be used for the MRI scan. If this is not possible, it may be necessary to employ image correlation methods to correlate the MRI and CT scans.
- 6.1.4 The GTV, CTV and PTV (*see Section 6.4*), and normal tissues must be outlined on all CT slices in which the structures exist.

6.2 Volume and ICRU Reference Point Definitions (10/29/01)

- The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.
- 6.2.1 The Gross Tumor Volume (GTV) is defined as all known gross disease determined from CT, clinical information, endoscopic findings and MRI in the case of tumors treated after biopsy alone.
 - 6.2.2 The Clinical Target Volumes (CTV) is defined as the GTV plus areas considered to contain potential microscopic disease, delineated by the treating physician. The margin between the each GTV and its CTV will be typically 1-2 cm, with a minimum of 5 mm except in those areas where the GTV is immediately adjacent to structures known to be uninvolved. In postoperative cases, The CTV includes the operative bed and margins according to an assessment of the risk of subclinical disease.

6.2.3 The Planning Target Volume (PTV) will provide a margin around each CTV (*i.e. both the primary tumor and the lymph nodes containing clinical or radiographic evidence of metastases*) to compensate for the variabilities of treatment set up and internal organ motion. Studies should be implemented by each institution to define the appropriate magnitude of the uncertainty components of the PTV. Until the results of that study are available, a minimum of 5 mm around the CTV is required in all directions to define each respective PTV. Careful consideration should be made when defining the superior and inferior margins in three dimensions.

6.3 Target and Critical Normal Tissue Definitions (10/29/01)

6.3.1 Targets are defined as primary (*requiring a higher dose*) and secondary (*targets at lower risk requiring a lower dose*). The primary targets are PTV66 of the primary tumor and lymph nodes containing clinical or radiographic evidence of metastases. The secondary target is the PTV54 of lymph node groups or surgical neck levels at risk of subclinical metastases. If an excisional biopsy was performed before RT, the surgical bed will be outlined and defined as CTV, and will be expanded to yield the surgical bed PTV. **Note:** an optional target volume (*PTV60*) may be defined at the discretion of the treating physician. It will contain subclinical disease deemed to be at high risk (*first echelon nodes or dissected neck area containing lymph node metastases and requiring a higher dose than PTV54*).

6.3.2 Lymph node groups at risk include the following:

- a. Submental nodes (*surgical level IA*): In cases where the floor of mouth or level IB are involved.
- b. Submandibular nodes (*surgical level IB*): All cases except primary palate tumors which do not extend to the tonsil or base of tongue. Only the ipsilateral level IB is a target, unless tumor crosses the midline. Level IB is a target in the neck side with upper jugular metastases in all cases.
- c. Upper deep jugular (*junctional, parapharyngeal*) nodes: all cases (*at the neck side ipsilateral to the primary tumor*).
- d. Subdiaphragmatic (*jugulodigastric*) nodes, midjugular, lower neck, and supraclavicular nodes (*levels II through IV*): all cases, bilaterally.
- e. Posterior cervical nodes (*level V*): all cases, at the neck side where there is an evidence of jugular nodal metastases.
- f. Retropharyngeal nodes: all cases.

The lymph node groups at risk will be determined and their volumes (*CTVs*) will be outlined on the treatment planning CT according to image-based nodal classification.²⁴ Alternatively, the surgical neck levels at risk will be determined and will be outlined as CTVs on the planning CT according to Nowak et al.²² A detailed slice-by-slice guide for surgical neck levels outlining according to Nowak et al. is available on-line for study participants.

A list of the lymph node groups or surgical neck levels outlined for treatment, and the doses prescribed, will be submitted to the Quality Assurance Center.

6.3.3 Critical Normal Structures

The normal tissue volume to be contoured will include the skin surface, brainstem, spinal cord, mandible, glottic larynx and parotid and submandibular salivary glands. The spinal cord contours will be defined at least 5 mm larger in the radial dimension than the spinal cord (*i.e. the cord diameter on any given slice will be 10 mm larger than the cord itself*). The normal tissues will be contoured and considered as solid organs. The tissue within the skin surface and outside all other critical normal structures and PTVs is designated as unspecified tissue.

6.4 Planning (10/29/01)

6.4.1 The treatment plan used for each patient will be based on an analysis of the volumetric dose, including DVH analyses of the PTV and critical normal structures. A “forward” iterative planning or “inverse” planning using computerized optimization are allowed. The treatment aim will be the delivery of radiation to the PTVs and the exclusion of noninvolved tissue as feasible.

6.4.2 Dose Specification

6.4.2.1 The prescription dose is the isodose which encompasses at least 95% of the planning target volume (*PTV*).

No more than 20% of any planning target volume (*PTV*) will receive >110% of its prescribed dose.

No more than 1% of any planning target volume (*PTV*) will receive <93% of its prescribed dose.

No more than 1% or 1 cc of the tissue outside the PTVs will receive >110% of the dose prescribed to the primary PTV.

6.4.2.2 Prescription dose to the PTVs shall be according to the following:

The gross tumor and lymph node metastasis including non-palpable lymph nodes suspicious for metastasis according to radiologic criteria (*primary PTVs*) will receive 30 fractions of 2.2 Gy/fraction, total 66 Gy.

Subclinical disease (*PTV54*) will receive 30 fractions of 1.8 Gy/fraction, total 54 Gy. Subclinical PTV60 at high risk (*first echelon nodes or dissected neck area containing lymph node metastases*) may receive 30 fractions of 2.0 Gy/fraction, total 60 Gy. Treatment will be delivered once daily, 5 fractions per week, over 6 weeks. All targets will be treated simultaneously.

A boost of 4-6 Gy in 2-3 fractions to the gross tumor PTV is optional.

Breaks in treatment should be minimized. Break in treatment time of more than 5 days will be considered a major variation.

6.4.2.3 The reported doses for each PTV shall include the prescription dose (*Section 6.4.2*) as well as the maximum point dose, % target volume receiving > 110% and >115% of its prescribed dose and the % target volume receiving \leq 93% of the prescribed dose, and the mean dose to the PTV.

6.4.2.4 The method used for tissue heterogeneity calculations shall be reported. Corrected dose distributions shall be calculated and submitted to the RTOG 3-D QA Center. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

6.4.3 Critical Normal Structures

DVHs must be generated for all critical normal structures and the unspecified tissues. Dose constraints to normal tissues should be as follows:

Glottic Larynx	2/3 below 50 Gy
Brainstem	54 Gy
Spinal cord	45 Gy
Mandible	70 Gy
Unspecified tissue outside the targets:	\leq 110% of the prescribed dose to PTV66

Participants are strongly encouraged to remain within these limits.

6.4.4 Planning Goals: Salivary Glands

Parotid glands:

- 1) Mean dose to either parotid < 26 Gy or
- 2) At least 50% of the either parotid gland will receive < 30 Gy or
- 3) At least 20 cc of the combined volume of both parotid glands will receive < 20Gy.

Submandibular/sublingual glands and oral cavity: Reduce the dose as much as possible.

6.4.5 Planning Priorities

Critical normal structure constraints followed by the prescription goals are the most important planning priorities. The priorities in addressing the protocol aims and constraints will be in the following order:

- 1) Critical Normal Structure Constraints (*Section 6.4.3*),
- 2) Prescription Goals (*Section 6.4.2.1, 6.4.2.2*),
- 3) Planning Goals: salivary glands (*Section 6.4.4*).

6.5 External Beam Equipment and Beam Delivery Methods

Megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator or dynamic intensity modulation (*using a multileaf collimator or tomotherapy*) is required. Other techniques are acceptable as long as dose specifications and constraints are satisfied.

A conventional anterior low-neck field is allowed. Dosimetric details regarding the match between this field and the upper neck therapy should be provided.

6.6 Treatment Verification (10/29/01)

Verification and orthogonal films or images are required. For all forms of IMRT dose delivery, orthogonal films or images that localize the isocenter placement shall be obtained. The length of the treatment field shall be indicated on these films.

6.7 Quality Assurance of Target Volumes and Critical Structure Volumes (9/30/03)

The study chair (*assisted by the Image-guided Therapy Center [ITC], formerly the 3D QA Center*) will review PTV, CTV, GTV and designated critical structures on initial cases submitted by each institution. After an institution has demonstrated compliance with protocol, future cases may be spot -checked.

6.8 Quality Assurance of Field Placement (9/30/03)

6.8.1 Conventional 3DCRT: The Image-guided Therapy Center [ITC] (*formerly the 3DQA Center*) will review initial placement films for the first 5 cases submitted by each institution. At least one port film along with the DRR from the treatment planning program or, alternatively, a simulation verification radiograph

shall be submitted for evaluation except where geometrically impractical. Subsequent cases may be spot checked only.

- 6.8.2** IMRT: The Image-guided Therapy Center [ITC] (*formerly the 3DQA Center*) will review one set of orthogonal (*anterior-posterior and lateral*) prescription images for isocenter (*or IMRT reference point*) localization for each group of concurrently treated beams for the first 5 cases submitted by each institution. The DRR from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation except where geometrically impractical. Subsequent cases may be spot checked only.

6.9 Quality Assurance of Dose Distribution (10/29/01)

- 6.9.1** The accuracy of each planning system needs to be verified by assessing the calculated dose distributions and measured doses in hypothetical phantom cases.
- 6.9.2** The 3-D QA Center will display, and compare with hard copies, isodose distributions (*as outlined in Appendix VI, QA Guidelines*) through the planning target volume to verify correct digital submission and conversion.
- 6.9.3** The 3-D QA center will compare the submitted digital dose-volume histograms (*DVHs*) for the PTVs, the designated critical structures, and unspecified tissues with DVHs calculated by the 3-D QA Center.
- 6.9.4** Each treatment shall be scored with regard to the coverage of each PTV (*i.e. PTV66, PTV60, and PTV54*) and with regard to the level of salivary gland sparing; the scores to be assigned are defined below. **(9/30/03)**
- 6.9.4.1** PTV66 Scoring:
- 1) No variation: the prescription criteria in Sections 6.4.2 are fulfilled.
 - 2) Minor variation: The prescription criteria in Section 6.4.2 are not met, but the ALL of the following dose limits are fulfilled: The 60.0 Gy isodose surface covers no less than 99% of the PTV66, and the 66 Gy isodose surface covers no less than 90% of the PTV66. The 72.6 Gy isodose surface covers no more than 25% of the PTV66.
 - 3) Major deviation: Neither of the dose limits for either No Variation or Minor Variation are met.
- 6.9.4.2** PTV54 and PTV60 Scoring: (1/15/02, 9/30/03)
- 1) No variation: the prescription criteria in Sections 6.4.2 are fulfilled.
 - 2) Minor variation: The prescription criteria in Section 6.4.2 are not met, but all of the following dose limits are fulfilled: The 47.0 Gy isodose surface covers no less than 99% of the PTV54, and the 54 Gy isodose surface covers no less than 90% of the PTV54. The 52.0 Gy isodose surface covers no less than 99% of the PTV60, and the 60 Gy isodose surface covers no less than 90% of the PTV60. The 72.6 Gy isodose surface (*110% of PTV66 prescription dose*) covers no more than 20% of the PTV54 and PTV60 scoring (*excepting coincident PTV66*).
 - 3) Major deviation: Neither of the dose limits for either No Variation or Minor Variation are met.
- 6.9.4.3** Parotid Gland Scoring:
- 1) No variation: any of the three criteria specified in section 6.4.4 are met.
 - 2) Minor variation: no more than 60% of either parotid gland may receive dose in excess of 30 Gy.
 - 3) Major deviation: greater than 60% of each parotid gland receives an excess of 30 Gy.

6.10 Radiation Therapy Toxicity Adjustments

6.10.1 Treatment Interruptions

Interruptions in radiotherapy may be necessitated by skin reaction, mucositis, ulceration, edema, or other acute complication. The reason for and the length of any such interruption must be documented. If the sum total of such interruptions exceeds 5 normally scheduled treatment days, the treatment may be considered in major violation of protocol. Radiation therapy will be continued without interruption if at all possible. Should confluent mucositis, moist desquamation unresponsive to topical dressings, or severe stomatitis resulting in weight loss greater than 15% occur, radiation may be interrupted in order to relieve morbidity. The use of tube feedings in this situation is encouraged; it is anticipated to minimize treatment interruptions.

6.11 Toxicity Reporting Guidelines

- 6.11.1** For acute radiation effect, through day 90 of treatment, the NCI CTC Version 2.0 will be used.
- 6.11.2** Late radiation effects will be evaluated and scored per the RTOG Late Effects scale.
- 6.11.3** All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to ACR Headquarters Data Management and to the Study Chairman within 24 hours of discovery.
- 6.11.4** All life-threatening (*grade 4*) toxicities from protocol treatment must be reported by telephone to the Group Chairman, ACR Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.

6.11.5 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).

7.0 DRUG THERAPY (9/30/03)

Prophylactic use of amifostine and pilocarpine is not permitted (*see Section 3.2.6*). These agents and their derivatives are not allowed during radiation or within three months of completion of radiation. Administration of amifostine, pilocarpine, and their derivatives is discouraged before six months post-treatment. Any use of these agents and their derivatives, including start and stop dates, must be reported on the T1, FS, and F1 case report forms (*see Section 12.1*).

8.0 SURGERY

- 8.1** Neck surgery (*excisional biopsy or neck dissection*) is optional. Surgery in the primary tumor is expected to be incisional biopsy for diagnostic purposes alone. Both the operative report and post surgical CT/ MRI must document gross residual tumor at the primary tumor site.
- 8.2** Surgery following radiation for salvage of residual tumor is allowed in this protocol.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Patient Assessments (10/29/01)

	Prestudy^a	During RT^c	Follow-up^d
History & Physical	X	X	X
Disease Documentation	X		
Dental Evaluation	X		
Nutritional Evaluation	X		
CBC/Platelets	X		
Biochemistry Panel (<i>including SGOT, bilirubin, alk phos</i>)	X		X ^e
Thyroid Function Test (<i>TSH</i>)	X		X ^e
Chest X-ray	X		X ^e
CT of head and neck	X ^b		
MRI of head and neck	X ^f		
Weight	X	X	X
Toxicity Evaluation ^h		X	X
Salivary Flow Measurements	X		X ⁱ
Audiogram ^g	X		X
Endoscopic and/or mirror eval			X

- a. Studies completed 21 days prior to irradiation.
- b. Liver CT must be done in presence of elevated alkaline phosphatase, SGOT, or bilirubin or other clinical indicator; bone scan must be done in presence of elevated alkaline phosphatase or other clinical indicator.
- c. Weekly during radiotherapy
- d. Follow-up will be performed after RT and then every 3 months during the first two years; every 6 months during years 3 to 5; then annually.
- e. These tests will be performed every 6 months during the first 3 years.
- f. At approximately 3, 6, and 12 months following RT.
- g. See Section 11.2.3.
- h. See Section 6.11.
- i. Optional: with T1 contrast with gadolinium and T2 sequences

11.2 Evaluations

11.2.1 Every Follow-up Visit (10/29/01)

All patients will enter a common follow-up program following completion of radiotherapy. For those patients requiring surgery after radiation, follow-up will begin one month after last protocol treatment received. Routine follow-up care: complete head and neck examination, including mirror and/or endoscopic examination, Performance Status and weight, Toxicity Notation.

11.2.2 Sialometry (before initiation of the first radiation fraction, and at approximately 3,6,and 12 months after the completion of radiation):

11.2.1.1 Unstimulated Whole Saliva: Patients should refrain from eating, drinking or dental hygiene for at least 60 minutes before collection. During collections patients should be seated and instructed to minimize orofacial movements and not to attempt to influence salivary flow (*such as by sucking or swallowing*). Just before the collection, the patient should be instructed to swallow. He/she should then be instructed to allow saliva to accumulate in the floor of mouth for 60 seconds without swallowing. The patient should then spit the accumulated saliva into a pre-weighted 50-ml vial. The patient should repeat this procedure 4 more times for a total collection time of 5 minutes. Subjects should be instructed not to swallow during the entire collection procedure.

11.2.2.2 Stimulated Whole Saliva: After the collection of unstimulated saliva, patients will have 2% citrate solution applied with cotton tipped applicators to the lateral tongue bilaterally 5 times over a two minutes period (*0, 30, 60, 90 and 120 seconds*). The mouth should then be emptied of retained citrate solution. Saliva should then be collected for 5 minutes, the same as for unstimulated saliva.

11.2.3 Other Studies

- Chest X-ray: For persistent cough, hemoptysis, chest pain, or loss of vocal cord mobility (*in addition to routine follow-up chest X-ray, see Section 11.1*).
- Biopsy: Any suspicious mucosal lesion in the upper aerodigestive tract; pharyngeal pain referred to the ear; any firm node that persists longer than four weeks; epistaxis; chronic nasal congestion thought not to be due to radiation mucosal changes.
- Audiogram: Pre-RT and yearly if the inner ear and/or middle ear receives ≥ 40 Gy, or if any hearing loss, vertigo or tinnitus occur.

11.3 Objective Response Criteria (10/29/01)

11.3.1 Tumor Response Measurements

All tumor measurements must be recorded in centimeters and should consist of the longest perpendicular diameters. In no case will complete response be reported unless all clinically demonstrable disease has disappeared.

11.3.1.1 Complete Response (CR)

No measurable tumor is present on clinical and radiological examination.

11.3.1.2 Partial Response (PR)

A greater than 50% decrease in the product of the longest diameter multiplied by its perpendicular diameter when compared to the initial 'on-study product, providing there is no increase greater than 25% of any area of known disease or the appearance of any new lesions.

11.3.1.3 Minor Response (MR)

The difference between products is less than 50 percent of the initial product. No new lesions have appeared.

11.3.1.4 Stable Disease (ST)

Tumor size has not changed; no progression, no new lesions.

11.3.1.5 Progression (PG)

The second product shows a greater than 25 percent increase over the initial product, or appearance of new lesions.

11.4 Criteria for Removal from Treatment

11.4.1 Progression of disease while on treatment.

11.4.2 Sustained severe radiation mucositis resulting in dehydration and poor nutrition unresponsive to tube feeding and break from radiation for up to 2 weeks. Every effort should be made to sustain the patient so as to avoid such complications. Should the patient be removed from study, surgical removal followed by radiation post-operatively may be attempted.

11.4.3 Patients' wishes (*reasons to be clearly specified on Data Forms*).

12.0 DATA COLLECTION

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

12.1 Summary of Data Submission (9/30/03)

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) Diagnostic Pathology Report (P1) Sialometric Evaluation Form (L4)	Within 2 weeks of study entry
*Radiotherapy Form (T1) <i>(copy to Image-guided Therapy Center)</i>	Within 1 week of end of RT
*Initial Followup Form (FS)	At 13 weeks
*Follow-up Form (F1)	Every 3 months during the first two years after RT; every 6 months during years 3-5; then annually. Also at progression/relapse and at death.
Sialometric Evaluation Form (L4)	At 3, 6, and 12 months from end of RT.
Long Term Follow-up Form (FF)	Yearly after 5 years in place of the F1 form, as applicable. See FF Form for instructions.
Autopsy Report (D3)	As applicable
* Any use of amifostine, pilocarpine, or similar derivatives must be reported on case report forms <i>(see Section 7.0)</i>	

12.2 Summary of RT QA Requirements (Washington University)

<u>Preliminary Dosimetry Information:</u> Digital patient data <i>(CT scans, critical normal structures, all GTV/CTV/PTV contours, doses for all fraction groups, DVHs for total dose plan)</i>	Within 1 week of start of RT
Simulation and port films as defined in Appendix VI	
Hard copy isodoses for total dose plan as defined in Appendix VI	
Digital Patient Submission Information Form (T2)	
<u>Final Dosimetry Information:</u> Digital patient data for any modified or changed planning data <i>(contours, doses or DVHs)</i>	Within 1 week of end of RT
Hard copy isodoses for total dose plan if any changes made after initial submission.	
Simulation and port films for boost and/or field changes as defined in Appendix VI	
Copy of Daily Treatment Record	

Radiotherapy Form (T1)

12.2.1 For Mail or Federal Express (9/30/03)

James A. Purdy, Ph.D.
Image-guided Therapy Center
Washington University School of Medicine
4511 Forest Park Ave., Suite 200
St. Louis, MO 63108
Tel. 314/747-5415 Fax # 314/747-5423

12.2.2 To send over Internet or Using Magnetic Tape (9/30/03)

Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the ftp account assigned to the submitting institution shall be used and e-mail identifying the data set(s) being submitted shall be sent to:

itc@castor.wustl.edu

For tape submission, please contact the Image-guided Therapy Center (ITC) [formerly the 3D QA Center] about acceptable tape types and formats.

12.2.3 See the Image-guided Therapy Center's (formerly the 3D QA Center) web site at <http://itc.wustl.edu> for additional helpful information, the current Facility Questionnaire document, and the Quality Assurance and Dry Run Guidelines as necessary for acquiring institutional credentials. (9/30/03)

12.3 Timely Data Submission for Toxicity Evaluation

Timely data submission is critical in order to meet the study's objectives for toxicity evaluation and to safely assign treatment levels.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Acute salivary gland toxicity

13.1.2 Locoregional control

13.1.3 Whole mouth saliva output relative to pre-RT measurements

13.1.4 Acute mucositis and other acute and late toxicities

13.2 Sample Size (10/29/01)

The head and neck registry study, RTOG 76-19, included 84 patients with primary disease in all oropharyngeal sites and thus was used to estimate 2-year locoregional control rate. The 2-year locoregional control rate in this group was 80%. More recent RTOG head and neck studies (79-13, 79-15, 85-27, 90-03) included only Stage II base of tongue while excluding all other oropharyngeal sites. However, the head and neck registry study did not use RTOG toxicity criteria, so to estimate acute salivary gland toxicity, data from RTOG 79-13, 79-15, 85-27, and 90-03 were used. Acute salivary gland toxicity (\geq grade 2) was experienced by 84% of the patients in this patient population (see table 13.2.1).

In the U.S. Bioscience Amifostine trial²⁵, acute salivary gland toxicity (\geq grade 2) was reduced from 78% to 51% using Amifostine, for a relative reduction of 35%. A relative reduction of 35% will be considered as the smallest relative reduction for which this therapy will be recommended for further study. From the RTOG head and neck database, we would expect an acute salivary gland toxicity (\geq grade 2) rate of 84%, and if a reduction of 35% is achieved in this study, that rate would be reduced to 55%. To calculate sample size, we hypothesize that 20% of patients will fail locoregionally in the first 2 years. Fleming's One-Stage Multiple Testing Procedure is utilized here.²⁶ A locoregional failure rate of 35% is set as highest acceptable rate. We chose Type I error of 0.10 and Type II error of 0.10. Fifty-seven analyzable patients will be needed.

Assuming we accrue the target goal of 57 evaluable patients, a 55% acute salivary gland toxicity rate equates to 31.35 patients with toxicity. If we have 31 or fewer patients with toxicity, this therapy will be considered for further study. In addition, we must also meet the goals for locoregional control (Section 13.3). Assuming the target goal of 57 patients, locoregional control will be considered acceptable if 15 or fewer patients have locoregional recurrence within the first two years. For this therapy to be recommended for further study, both the toxicity and locoregional control outcomes must be considered acceptable. This equates to 31 or fewer patients with acute salivary gland toxicity, and 15 or fewer patients with locoregional recurrence. If the study accrues more or less than 57 evaluable patients, these numbers will be

adjusted accordingly. With a sample size of 57 patients, we have a $\geq 95\%$ (*two-sided*) confidence interval around a hypothesized 42% acute salivary gland toxicity rate with margin of error $\leq 13\%$. The upper bound of this interval corresponds to a relative reduction of approximately 35% (*84% to 55%*), similar to that of the Amifostine trial. If an additional 10% of the sample is added to guard against ineligible or inevaluable (*no data*) cases, **then the target total accrual for this study will be 64 patients.**

Table 13.2.1
Acute Salivary Gland Toxicity

Toxicity Grade		
0	1	2
10%	7%	84%

13.3 Monitoring for Unacceptable Locoregional Failure Rate

As mentioned above, the locoregional control rate in this patient population is approximately 80%. We wish to ensure that this treatment does not reduce salivary gland toxicity at the expense of locoregional control. If at any time the following boundaries are crossed, all data pertaining to the events will be reviewed by the study chairs and a recommendation will be made to the RTOG Research Strategy Committee for their consideration. The results of this review will determine the future course of action. If accrual has not been completed, it will be suspended. The following table gives the number of locoregional failures that are considered unacceptable as calculated by the method of Fleming. For example, if there are 8 failures reported in the first 14 patients, the study will immediately undergo special review. Note that these are the first 14 patients entered (*and eligible*) consecutively onto the trial. It is not the first 14 patients for whom we have data.

<u>Number of Locoregional Failures</u>	<u>Total Number Evaluable</u>
8	14
10	28
13	42
16	57

13.4 Patient Accrual

It is projected that there will be approximately a 6-month period with very slow accrual at the beginning of this study to allow for institutional IRBs and approval by the QA Center. After this initial period, it is projected that this study will accrue approximately 3 patients per month. At this rate, it will take 27 months to complete accrual. If the average monthly accrual is less than 1.5 patients per month, the study will be reevaluated with respect to feasibility.

13.5 Analysis Plans

13.5.1 *Interim Analyses of Accrual and Toxicity Data*

- Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about:
- accrual rate with projected completion date
- pretreatment characteristics of patients accrued
- quality of submitted data with respect to timeliness, completeness, and accuracy
- compliance rate of treatment delivery with respect to the protocol prescription
- frequency and severity of toxicity.

13.5.2 *Analysis and Reporting of Initial Treatment Results*

The analysis to report the initial results of treatment will be undertaken when each patient has been potentially followed for a minimum of 6 months. The emphasis of this analysis will be on acute toxicity. The usual components of this analysis are:

- patients excluded from the analyses with their reasons for exclusion
- institutional accrual
- distribution of the important baseline prognostic variables
- patient accrual rate
- observed results with respect to the endpoints described in Section 13.1

Further subgroup analysis will not be undertaken because of the relatively small sample sizes. The rates of acute salivary gland toxicity, locoregional control, saliva output, and acute mucositis will be estimated with 95% confidence intervals.

13.5.3 Analysis and Reporting of Final Treatment Results (10/29/01)

The analysis to report the final results of treatment will be undertaken when each patient has been potentially followed for a minimum of 2 years. The emphasis of this analysis will be on locoregional control. The usual components of this analysis are:

- patients excluded from the analyses with their reasons for exclusion
- institutional accrual
- distribution of the important baseline prognostic variables
- patient accrual rate
- observed results with respect to the endpoints described in Section 13.1.

Further subgroup analysis will not be undertaken because of the relatively small sample sizes. The rates of locoregional control at one and two years will be estimated with 95% confidence intervals.

13.5.4 Inclusion of Women and Minorities

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

13.5.4.1 Gender

In the head and neck chemoprevention study, RTOG 91-15, 70% of the patients eligible for this trial were male, and 30% were female. So for planning purposes, we assume 70% of patients entered into this protocol will be male, and 30% female.

13.5.4.2 Race

In RTOG 91-15, 92% of the patients eligible for this trial were white, and 8% were non-white. So for planning purposes, we assume 90% of patients entered into this protocol will be white, and 10% non-white.

13.5.4.3 Salivary Gland Endpoint

For males we have an 89% confidence interval (*two-sided*) with an upper bound of 55% around the hypothesized 42% salivary gland toxicity rate, and a 71% confidence interval for females. Also, for males we have a 95% confidence interval with an upper bound of 57% around the hypothesized 42% salivary gland toxicity rate, and a 95% confidence interval with an upper bound of 65% for females.

For whites we have a 93% confidence interval (*two-sided*) with an upper bound of 55% around the hypothesized 42% salivary gland toxicity rate, and a 47% confidence interval for non-whites. Also, for whites we have a 95% confidence interval with an upper bound of 56% around the hypothesized 42% salivary gland toxicity rate, and a 95% confidence interval with an upper bound of 81% for non-whites. The following table gives the expected number of patients in each race and gender group.

Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian	Black or African American	Hispanic or Latino	Native Hawaiian or Pacific Islander	White	Other or Unknown	Total
Male	0	0	0	4	0	41	0	45
Female	0	0	1	0	0	18	0	19
Total	0	0	1	4	0	59	0	64

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APPENDIX I

RTOG 0022

SAMPLE CONSENT FOR RESEARCH STUDY

PHASE I/II STUDY OF CONFORMAL AND INTENSITY MODULATED IRRADIATION FOR OROPHARYNGEAL CANCER

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

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

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test whether the use of advanced radiation therapy delivery techniques can spare your normal tissue, including salivary glands, from radiation.

This research is being done to try to reduce radiation side effects, especially mouth dryness, which happens with the standard radiation methods.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 64 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (10/29/01)

- All patients will receive the following treatment:

Radiation therapy will be given once a day, five days a week, for six weeks. This will be given as an outpatient.

- Procedures that are part of regular cancer care and may be done even if you do not join the study.

Procedure

Physical Exam

Blood Counts

Chest X-Ray or Chest CT

Thyroid Function Test

Endoscopic and/or Mirror Evaluation

CT Scan of the head and neck

Schedule

Prior to study entry, weekly during treatment, and at follow-up visits

Prior to study entry and at follow-up visits

Prior to study entry and at follow-up

Prior to study and every 6 months for 3 years

At follow-up

Prior to study entry

- Standard procedures being done because you are in this study.

Dental and Nutritional Evaluation

Prior to study entry

Audiogram (if ear is in radiation field)

Prior to study entry and yearly if necessary based on side effects and treatment area.

CT Scan of Liver

Prior to study entry if medically indicated

Bone Scan

Prior to study entry if medically indicated

MRI of the head and neck

Optional; Prior to study entry if indicated

Biopsy

If suspicious lesions or severe nose bleeds occur; if throat pain or nasal congestion persists

- Other procedures that are being tested in this study.

Saliva Measurement

Prior to treatment start , at approximately 3, 6, and 12 months from the end of treatment.

Blood counts, chemistries, and follow-up visits may be more frequent because you are enrolled in a research study.

- Follow-up visits with your physician will be scheduled after radiation therapy, then every three months from the end of treatment for two years, then every six months for three years, and then annually for the rest of your life.

HOW LONG WILL I BE IN THE STUDY?

Your radiation will last for a total of 6 weeks. Follow-up visits will continue for the rest of your life according to the schedule above.

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

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

WHAT ARE THE RISKS OF THE STUDY?

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

Risks Associated with Radiation Therapy

Very Likely

- Redness and irritation of skin within the treatment area
- Difficulty, pain or burning sensation when swallowing
- Dry mouth may remain after treatment
- Mouth sores
- Hair loss at the treatment area
- Nausea and/or vomiting
- Loss of appetite and/or taste
- Skin in treatment area may remain permanently dry
- Decrease in blood counts while undergoing treatment
- Fatigue

Less Likely

- Voice hoarseness may remain after treatment

Less Likely, But Serious

- Injury to the jaw or tissue of the neck
- Thyroid gland dysfunction requiring thyroid hormone pills in the future
- Irritation of the spinal cord

If you receive radiation therapy according to the techniques employed in this study, the chance that your cancer will be eradicated may be different than if you receive standard radiation. There is probably a small risk that your chance of cure may be lower.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with head and neck cancer in the future.

WHAT OTHER OPTIONS ARE THERE?

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

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

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

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

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

WHAT ARE THE COSTS?

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

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

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

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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

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

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at **1-800-4-CANCER (1-800-422-6237)** or **TTY: 1-800-332-8615** Visit the NCI's Web sites for comprehensive clinical trials information **<http://cancertrials.nci.nih.gov>** or for accurate cancer information including PDQ **<http://cancernet.nci.nih.gov>**. **SIGNATURE**

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

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

Patient Signature (*or legal Representative*)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE SCALE

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

APPENDIX III

AJCC STAGING HEAD & NECK, 5th Edition

STAGING-PRIMARY TUMOR (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T_{is} Carcinoma *in situ*

ORAL CAVITY

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

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

PHARYNX

Nasopharynx

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

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

Oropharynx

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

- T1 Tumor 2 cm or less in greatest dimension
- T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
- T3 Tumor more than 4 cm in greatest dimension

- T4 Tumor invades adjacent structures (*e.g. pyteryoid muscle[s], mandible, hard palate, deep muscle of tongue, larynx*)

Hypopharynx

Pyriiform fossae
Postericoid region
Lateral and posterior hypopharyngeal walls

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

LARYNX

Supraglottis

Suprahyoid epiglottis
Infrahyoid epiglottis
Aryepiglottic folds (*laryngeal aspect*)
Ventricular bands (*false cords*)
Arytenoids

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

Glottis

True vocal cords including anterior and posterior commissures

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

Subglottis

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

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

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

REGIONAL LYMPH NODES (N) Nasopharynx Only

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

DISTANT METASTASIS (M)

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

STAGE GROUPING Excluding Nasopharynx STAGE GROUPING Nasopharynx

Stage 0	Tis, N0, M0	Stage 0	Tis, N0, M0
Stage I	T1, N0, M0	Stage I	T1, N0, M0
Stage II	T2, N0, M0	Stage IIA	T2a, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0	Stage IIB	T1-T2a, N1, M0 T2b, N0-1, M0
Stage IVA	T4, N0-1, M0 Any T, N2, M0	Stage III	T1-T2b, N2, M0 T3, N0-2, M0
Stage IVB	Any T, N3, M0	Stage IVA	T4, N0-2, M0
Stage IVC	Any T, Any N, M1	Stage IVB	Any T, N3, M0
		Stage IVC	Any T, Any N, M1

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

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

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

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

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

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

of termination of the agent.

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

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

ii. Phase II, III Studies Utilizing Investigational Agents

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

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

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

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

APPENDIX VI (9/30/03)

**3DCRT and IMRT for Oropharyngeal Cancer
Quality Assurance Guidelines**

The current version of the Quality Assurance Guidelines for **RTOG 0022** must be obtained from the web site of the Image-guided Therapy Center (ITC) [formerly RTOG 3D QA Center]

<http://itc.wustl.edu>

The Quality Assurance Guidelines contain the following informational and directive items:

1. Background information to assist participants in meeting protocol specified radiation therapy treatment planning and delivery requirements.
2. Credentialing requirements to be completed for eligibility to enroll patients in the protocol.
 - a. Facility Questionnaire assistance. Note the Facility Questionnaire form is available only from the ITC's web site identified above. Only acquire this form in close time proximity to when it will be completed as it may be updated depending on protocol developments and modifications.
 - b. Dry Run test requirements.
3. Patient digital data and hard copy data submission requirements.
4. Evaluation criteria and scoring system applied to submitted radiation therapy patient data.
 - a. Scoring system for critical structures and tumor/target volumes.
 - b. Scoring system for port and isocenter localization films.
 - c. Scoring system for dose delivery analysis.
 - d. Methods of obtaining scores assigned.

Corvus Data Transmission to ITC

Procedures for Sending both CTV and PTV Structures, based upon the TJU approach.

The user must independently define on two separate plans, one containing user defined the CTV and the other containing the user defined PTV, as the ITC is not able to read the Corvus defined PTV's. The first plan will be a standard plan and will be the plan used to insure that the protocol requirements are met. This plan will be used by the ITC to read the CTV's. The second plan will contain the PTV's and will be a phantom plan using the same patient CT data set.

The following procedures assume that the contours have been defined external to Corvus, e.g. on AcQsim or some other virtual simulation platform. If the contours are being defined on Corvus, it will be necessary for the oncologist to define the appropriate structures on both the standard plan, which contains the user defined CTVs, and the phantom plan, which contains the user defined PTV's.

Each Corvus institution is asked to define an 0022 structure set, which contains the following structure names:

Standard Name	Description
Brainstem	Brain stem
Larynx	Larynx
Mandible	Mandible
Mandible_Lt	Left Mandible
Mandible_Rt	Right Mandible
Parotid_Lt	Left parotid
Parotid_Rt	Right Parotid
Skin	External patient contour
Spinal_cord	Spinal cord
PTV66_1	Planning target volume 66 Gy
PTV66_2	Planning target volume 66 Gy (assuming a second 66 Gy PTV)

PTV60_1	Planning target volume 60 Gy
PTV60_2	Planning target volume 60 Gy (assuming a second 60 Gy PTV)
PTV54_1	Planning target volume 54 Gy
PTV54_2	Planning target volume 54 Gy (assuming a second 54 Gy Gy PTV)
GTV	Gross Tumor Volume
GTV_PTV	Gross Tumor Volume grown to PTV

1. Generate a treatment plan, beginning with the patient info mode. Enter all appropriate information. Enter "Patient" as the treatment plan type. In the Image Registration mode, identify and process the pertinent items. Set the ROI such that it encompasses the entire CT data set, i.e. 512 x 512. (In Version 5 and above, the data sets are automatically made square.)
2. After image registration, enter the Anatomy Mode and edit tissue (skin). Exit the plan and copy the plan. The purpose of this is to generate two data sets with identical external contours. For the second data set, enter "Phantom" as the treatment plan type and modify the name to include PTV.
3. Return to the patient plan type (the first data set). In the Anatomy mode, use the DICOM-RT structure association tool to associate the GTV and all CTVs. Remember to associate in order of small organs to large organs and higher dose to lower dose volumes. The parotids should be associated before the nodal chains. The cord, mandible, and brainstem should be associated before the skin. Do not associate any user defined PTV's.
4. After the associations have been made, enter the Prescription mode. Set the localization uncertainty to 5 mm or greater. As Corvus' users know, this will define the Corvus PTV's. Define all prescription parameters such that the 0022 protocol requirements are met.
5. Review the final plan to insure that all 0022 specifications are met. (When this plan is sent to the ITC, they will read the all CTVs, the parotids, the mandible, and the brainstem.)
6. Now exit and enter the second phantom plan. (Remember that you must first run a simple plan in order for any phantom plan to be included on the list of phantoms.) This second phantom plan will have the same external contour as the first plan.
7. Enter the anatomy mode and use the DICOM-RT structure tool to associate the GTV with the GTV-PTV. Use the Grow Filled Structure Operator to grow the GTV_PTV by 5 to 10 mm, depending upon clinical judgment. Do this for all slices that contain the GTV_PTV. For the most superior and inferior slices, the growth the GTV_PTV is left to the judgment of the user. The user can copy the previous contour to the superior or inferior slice and then shrink it by 3 mm.
8. Use the DICOM-RT structure tool to associate the CTV66 with the PTV66_1. Grow this by 5 mm. Please remember to start with the highest dose smallest volumes. Do the association and then the growth one volume at a time.
9. After all of the volumes have been associated, calculate a simple plan so that this phantom will appear on the list of phantoms. Wait for this simple plan to be calculated.
10. Exit from the second phantom plan and go to the Select Plan Screen. Highlight the first plan and go to the Create hybrid Phantom Plan from Study. Select the second plan as the phantom plan. Enter the coordinates of the selected study's calculation point and the coordinates of the phantom document's measurement point. (These two sets of coordinates should be the same.) Perform the calculation on the phantom plan.

After review, send both plans to the ITC. As noted above, the ITC will extract the CTV contours from the patient plan and the contours from the phantom plan