

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0244

A PHASE II STUDY OF SUBMANDIBULAR SALIVARY GLAND TRANSFER TO THE SUBMENTAL SPACE PRIOR TO START OF RADIATION TREATMENT FOR PREVENTION OF RADIATION-INDUCED XEROSTOMIA IN HEAD AND NECK CANCER PATIENTS

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SCHEMA

R
E Surgery for the Primary/Neck Nodes and
G Submandibular Salivary Gland Transfer Followed by
I Post-operative Radiation Therapy Within 4-6 weeks of
Surgery
S
T XRT Dose: 54-70 Gy over 5.5 – 7 weeks, 2.0 Gy/fraction
E
R

NOTE: Prophylactic use of amifostine and pilocarpine is not allowed (see Section 9.0)

Eligibility: (See Section 3.0 for details)

- Biopsy-confirmed histological diagnosis of squamous cell carcinoma of oropharynx, hypopharynx, larynx, or patients with unknown primary tumor with unilateral metastases to the neck nodes.
- Radiation volume \geq 80% of major salivary glands (parotids); \geq 50 Gy delivered to that volume.
- Zubrod Status 0-1.
- Patients must be \geq 18 years of age.
- Hemoglobin must be \geq 10 gm/dL.
- No prior radiotherapy to the head and neck or surgery to the head and neck for any reason.
- No prior malignancies unless disease-free for \geq 3 years except basal and squamous cell carcinoma of the skin.
- No prior chemotherapy \leq 3 years.
- No salivary gland malignancy.
- No salivary gland disease, e.g., Sjögren's syndrome.
- No recurrent disease.
- Patients using cholinergic drugs, anti-cholinergic drugs, and tricyclic drugs are ineligible.
- Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus.
- Signed study-specific consent form prior to study entry.

Required Sample Size: 48

RTOG Institution # _____

RTOG 0244

ELIGIBILITY CHECKLIST (8/5/03)

Case # _____

(Page 1 of 2)

- _____(Y) 1. Does the patient have biopsy-confirmed, untreated, squamous cell carcinoma of the head and neck as outlined in Section 3.1.1?
- _____(Y) 2. Will the patient receive radiation therapy in accordance with Section 3.1.2?
- _____(Y) 3. Is the Zubrod Status 0-1?
- _____(Y) 4. Is the patient 18 years of age or older?
- _____(Y) 5. Is the hemoglobin at least 10 gm/dl?
- _____(N) 6. Did the patient have prior radiotherapy or surgery to the head and neck?
- _____(N) 7. Has the patient received chemotherapy within the last three years for any condition?
- _____(Y/N) 8. Does the patient have a history of any malignancy other than basal and/or squamous cell carcinoma of the skin?
_____(Y) If yes, has the patient been disease-free for at least three years?
- _____(N) 9. Does the patient have any salivary gland disease?
- _____(N) 10. Is this recurrent disease?
- _____(N) 11. Is the patient using any cholinergic, anti-cholinergic and/or tricyclic drugs?
- _____(N) 12. Is the patient pregnant (if applicable)?
- _____(Y) 13. Have all pretreatment studies in Section 4.0 been obtained in the time frame indicated ?
- _____(Y) 14. Has the patient signed a study-specific informed consent form?

RTOG Institution # _____

RTOG 0244

Case # _____

ELIGIBILITY CHECKLIST (4/5/04)

(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 Initials (Last, First)
- _____ 6. Verifying Physician
- _____ 7. Patient's ID Number
- _____ 8. Date of Birth
- _____ 9. Race
- _____ 10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- _____ 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. Surgical Oncologist
- _____ 17. Date of Planned Surgery
- _____ (Y/N) 18. Will the patient receive chemotherapy concurrently with post-operative radiation therapy?

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.

Completed by _____

1.0 INTRODUCTION

1.1 Background

Over 40,000 individuals are diagnosed as having head and neck cancer every year in the United States.¹ Radiation is a primary or secondary therapeutic modality in most cases and results in salivary gland dysfunction in most patients.² Humans produce approximately 600 ml of saliva per day, not 1000 -1500 ml as quoted in several textbooks³. Radiation-induced xerostomia is a significant morbidity in head and neck cancer patients receiving radiation treatment and adversely affects a patient's quality of life.^{4,5} Xerostomia is generally accepted as the subjective complaint of a dry mouth, that is poorly correlated with the objective findings of salivary gland dysfunction.⁶ Xerostomia impairs mastication, deglutition, gustation, and alters oral microbial flora leading to the development of caries. The oral mucosa becomes dry, cracked, and painful. The speech and sleep patterns may also be altered. Patients have low tolerance for dental prostheses because of tissue friability and lack of lubrication. They may also have abnormal swallowing patterns, in which movement of a bolus from the mouth to the pharynx is slowed.⁷ Oral symptoms can alter food choices and may lead to nutritional compromise⁸. Sleep disruptions are common because the patient wakes up to moisten the dry mouth or to relieve the polyuria experienced because of polydipsia.⁹ These all have a negative impact on a patient's quality of life.^{4,5}

Several strategies are being explored to address the problem of radiation-induced xerostomia, use of Amifostine,¹⁰⁻¹³ intensity modulated radiation treatment (IMRT) to spare the parotid glands,¹⁴⁻¹⁸ Pilocarpine,¹⁹⁻²⁶ and acupuncture.²⁵ These all have met with varying degrees of success.

Intensity modulated radiation treatment (IMRT) techniques have focused on protecting one parotid salivary gland while submandibular salivary gland transfer strategy has focused on protecting one submandibular gland.^{14-18, 27-28} We feel that the sparing of the submandibular gland is theoretically preferable for the following reasons:

1. The parotid glands normally contribute only about 20% of the total volume of unstimulated saliva, while the submandibular salivary glands contribute 65% and the sublingual salivary glands 7-8%.^{29, 30} At high flow rates, the parotid becomes the dominant gland, contributing about 50% of the whole saliva.²⁹ However, it is the unstimulated saliva (resting state) that is far more important in the subjective feeling of xerostomia. Stimulated saliva is produced during eating, which lasts only for approximately 54 minutes per day.²⁹
2. The metastatic spread of head and neck tumors into cervical lymph nodes follows predictable pathways in the previously untreated neck. The subdigastric group of lymph nodes (Level II) is the most commonly involved group of lymph nodes and lie close to the parotid gland.³¹⁻³⁵ Dawson et al. reported a 21% recurrence rate, with almost all of the recurrences occurring in the high dose volumes.³⁶ Comparatively, a transferred submandibular gland in the submental space, and the sublingual salivary glands, are situated in the area of the level I nodes which are the least commonly involved nodes in head and neck carcinomas with the exception of primaries in the oral cavity.⁴²

We therefore believe that the "transferred submandibular salivary gland" is a safer and a better target for prevention of radiation-induced xerostomia, except when the primaries are in the oral cavity.

1.2 Recent Studies

The Seikaly and Jha method of transfer has been described in detail. Jha, Seikaly, McGaw et al. successfully demonstrated prevention of xerostomia by surgical transfer of the submandibular salivary gland to the submental space prior to starting radiation treatment.²⁷⁻²⁸ Surgery was the prime modality of the management, followed by radiation treatment. The most recent unpublished update of that study has 84 patients on the study, 76 of which are evaluable. Eight patients were not evaluable: in five patients, only the ipsilateral neck was irradiated; one patient had malignant melanoma; one patient did not have a selective neck dissection on the side of the transfer; in one patient, < 50% of the parotid gland was irradiated. There are 59 men and 17 women; the ages ranged from 36 to 79 years. The sites of disease and stages at presentation are shown in Tables 1 and 2. The median follow up is 14 months.

Sixteen patients had surgery and radiation treatment with no salivary gland transfer; seven of these did not have any salivary gland transfer due to proximity of disease found at surgery, nine were entered as control subjects. Sixty patients had surgical transfer of the submandibular salivary gland to the submental space, the sites of disease and stages at presentation are shown in Tables 3 and 4. In eight (see Table 5, row B) of these 60 patients, although the transfer was done, there was disease found in the proximity on the permanent pathology, so no attempt was made to protect the transferred salivary gland. In nine (see Table 5, row C) of these 60 patients, no post-operative XRT was given: four patients did not require post-operative radiation treatment, three patients refused radiation treatment after the surgical transfer, and two patients died before start of radiation treatment.

Of the 60 patients with salivary gland transfers, there were 43 patients (see Table 5, row A) who had surgery for the primary, and post-operative radiation treatment with the protection of the transferred salivary gland. For these 43 patients, results of prevention of xerostomia (“amount of saliva” score as per University of Washington Quality of Life Questionnaire [see Appendix VI]) at various intervals after radiation treatment, are depicted in Figure 1. The lower scores (10 and 20) depict none or minimal loss of saliva (xerostomia) while higher scores (30 – 50) indicate moderate to severe loss of saliva. At the end of radiation treatment, 81% of the patients had none or minimal xerostomia and 19 % developed moderate to severe xerostomia as shown in Figure 1. The salivary flow, unstimulated and stimulated, at various time intervals after radiation treatment are shown in Figure 2.

Of the 60 patients with salivary gland transfers, four patients (6.6%) recurred locally and were within the radiation fields (see Table 6). None had recurred in the submental space, which is the site of relocation of the transferred salivary gland. Six patients (10%) developed distant metastases (Table 6). One of these patients with recurrence showed both local and distant failure. Eight patients (13.3%) have died, four from progressive disease, three from myocardial infarctions months after treatment, and one patient died from pulmonary infarction within 24 hours of surgery.

The surgical transfer was relatively simple and added 45 minutes to the surgical procedure. There were no complications attributed to the submandibular gland transfer procedure itself.

Table 1. Sites of Disease (76 patients)

Oral Cavity (controls)*	2(3%)
Oropharynx	24 (32%)
Hypopharynx	6 (8%)
Larynx	23(30%)
Unknown Primary	16(21%)
Recurrent Disease	3(4%)
Skin (Ear) With Neck Node	2(3%)

Table 2. Stages at Presentation (76 patients)

NODE	Tx	T1	T2	T3	T4
N0	0	1	5	8	12
N1	4	2	3	3	6
N2	11	1	4	6	4
N3	2	1	0	1	0
RECURRENT DISEASE	2 patients (recurrent disease at presentation)				
TOTAL	76 patients				

Table 3. Sites of Disease (60 patients with surgical transfers)

Oral Cavity	0
Oropharynx	17 (28%)
Hypopharynx	5 (8%)
Larynx	21(35%)
Unknown Primary	13(22%)
Recurrent Disease	3(5%)
Skin (Ear) With Neck Node	1(2%)

Table 4. Stages at Presentation (60 patients with surgical transfers)

NODE	Tx	T1	T2	T3	T4
N0	0	1	4	6	11
N1	4	2	3	3	4
N2	9	1	3	2	4
N3	1	0	0	0	0
RECURRENT DISEASE	2 patients (recurrent disease at presentation)				
TOTAL	60 patients				

Table 5

	SUBGROUPS OF PATIENTS	NO. OF PATIENTS
A	Surgery + Transfer + XRT (STX)	43
B	Surgery + Transfer +XRT (Gland not shielded) (STX-ng)	8
C	Surgery + Transfer + No XRT (ST)	9
D	Total number of salivary gland transfers (A +B + C)	60

Table 6. Salivary Gland Transfer (60 patients)

Median Follow-Up	14 Months
Local Recurrence	4 (6.6%)
Distant Metastases	6 (10%)
Dose to Salivary Gland	800 to 1400 cGy
Died of progressive disease	4 (6.6%)

Saliva of Salivary Gland Transfer Patients

Figure 1

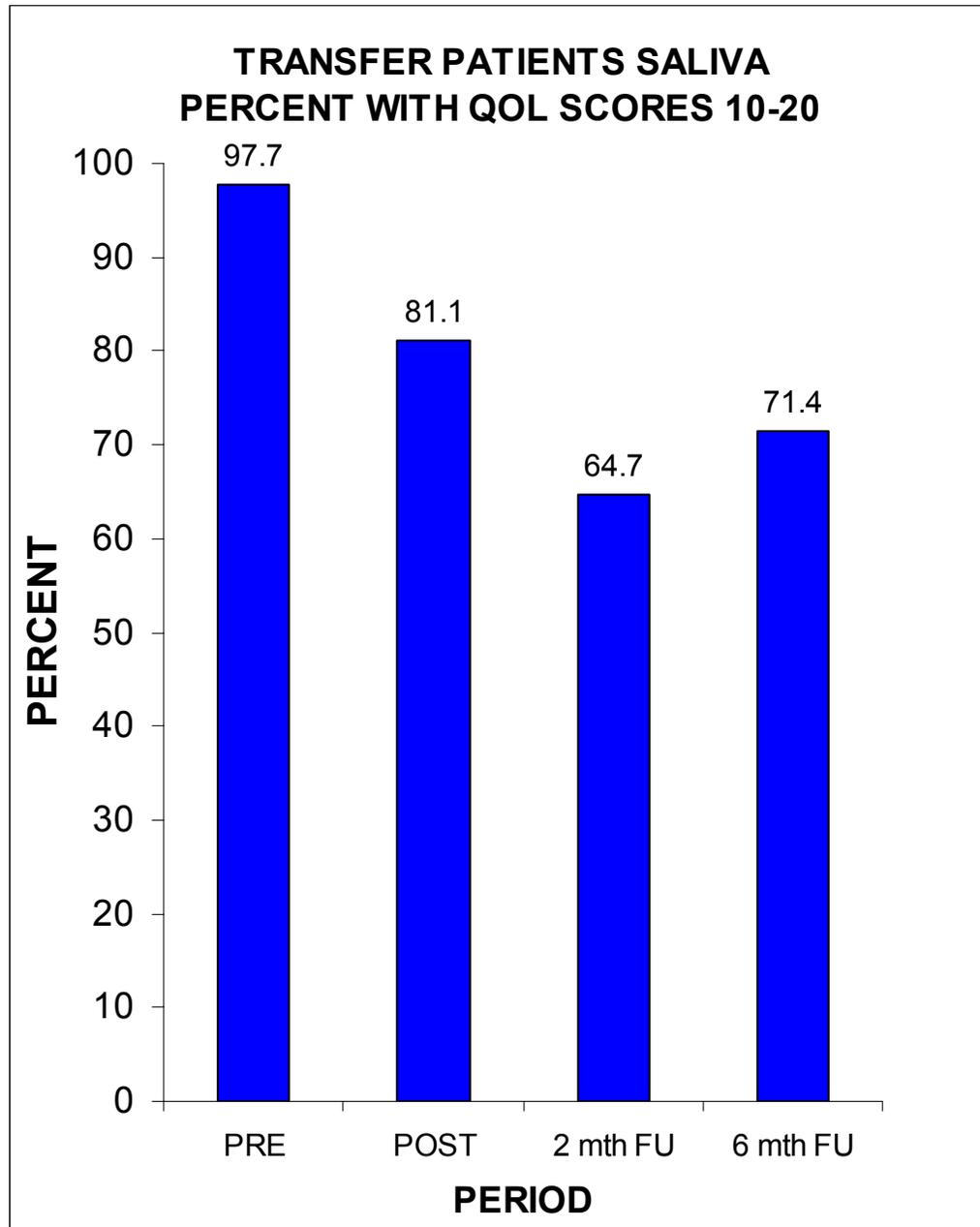
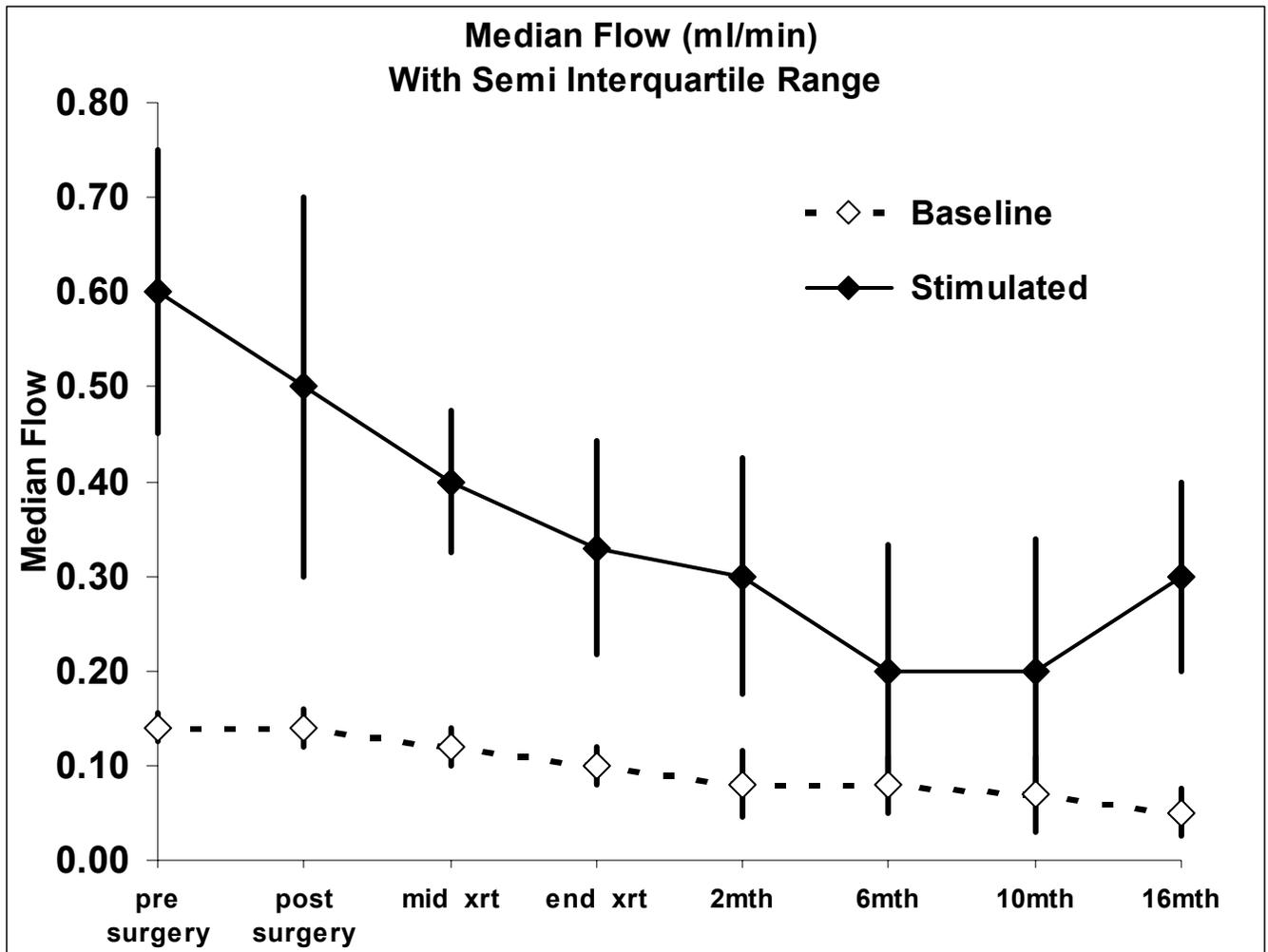


Figure 2



1.3 Quality of Life

Over the past decade, there has been a dramatic increase in the use of Quality of Life measurement in clinical trials. This has evolved from the growing interest and focus on supportive care and comprehensive health outcomes. Improving the quality of patients' lives has become as important as extending the quantity of life. The term, quality of life, refers to "a patient's appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal". Since the dimensions of quality of life are subjective, they are best measured from the patient's perspective.

Recent advances in cancer treatments for locally controlling cancers of the head and neck have prompted clinicians to turn their attention to supporting and preserving their patients' quality of life. Radiation therapy continues to be one of the primary modalities for treating head and neck cancers. Radiation-induced xerostomia remains an acute and commonly chronic complication of irradiation to the head and neck. It can produce pain and discomfort, increased cariogenesis, susceptibility to opportunistic oral infections, difficulty in speaking, chewing, swallowing and sleeping, and lifetime ageusia. These manifestations can lead to further problems of severe oral disease, nutritional deficiencies and an overall decline in homeostasis.

It is assumed that the relief of a symptom is valued because of its benefit to a patient's functioning and well-being. Equally important is evaluating the effectiveness of the intervention in improving the quality of life (e.g., improved appetite, eating, etc.). This study will determine the

effectiveness of submandibular salivary gland transfer for prevention of radiation-induced xerostomia and also determine its impact on the quality of life of these patients.

2.0 OBJECTIVES

- 2.1 To determine the reproducibility of the surgical technique of submandibular salivary gland transfer in a multi-institutional setting.
- 2.2 To estimate the rate and severity of radiation-induced xerostomia following submandibular salivary gland transfer.
- 2.3 To evaluate quality of life outcomes in patients receiving submandibular salivary gland transfer.
- 2.4 To evaluate the pattern of recurrence, disease-free and overall survival.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

- 3.1.1 Previously untreated and biopsy-confirmed histological diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, and larynx, and patients with unknown head and neck primary tumor with unilateral metastases to the neck nodes. Surgery is the prime modality of treatment, to be followed by radiation therapy within 4-6 weeks of surgery.
- 3.1.2 Radiation volume to encompass $\geq 80\%$ of major salivary glands (parotids) and ≥ 50 Gy delivered to that volume via external beam.
- 3.1.3 Zubrod Status 0-1.
- 3.1.4 Patients must be ≥ 18 years of age.
- 3.1.5 Hemoglobin must be ≥ 10 gm/dL.
- 3.1.6 The patient must sign a study-specific informed consent prior to study entry.
- 3.1.7 The participating institution must have the facility and capability of performing salivary scans.

3.2 Conditions for Patient Ineligibility

- 3.2.1 Carcinomas of oral cavity, nasopharynx, N3 disease, bilateral neck node involvement, pre-epiglottic space involvement, involvement of level 1 nodes on either side of the neck and patients with recurrent disease or any prior head and neck malignancy other than basal and squamous cell carcinoma of the skin.
- 3.2.2 Prior malignancies unless disease-free ≥ 3 years.
- 3.2.3 Prior chemotherapy ≤ 3 years.
- 3.2.4 Salivary gland malignancy.
- 3.2.5 Salivary gland disease, e.g., Sjögren's syndrome.
- 3.2.6 Use of cholinergic drugs, anti-cholinergic drugs, and tricyclic drugs.
- 3.2.7 Prior head and neck irradiation or prior surgery to the head and neck for any reason.
- 3.2.8 Recurrent disease.
- 3.2.9 Pregnant women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus; patients with childbearing potential must practice appropriate contraception.

4.0 PRETREATMENT EVALUATIONS (WITHIN FOUR WEEKS PRIOR TO STUDY ENTRY UNLESS OTHERWISE SPECIFIED) [7/21/04]

- 4.1 Complete history and physical examination including mucosal assessment.
- 4.2 Diagram of lesions and nodes.
- 4.3 Quality of Life Questionnaire (copyright: University of Washington).
- 4.4 Laboratory studies **within two weeks prior study entry**: serum pregnancy tests for women of childbearing potential; CBC with platelet count; serum electrolytes; liver function tests (bilirubin, alkaline phosphatase, AST/ALT).
- 4.5 Radiographic studies **within six weeks prior to study entry**:
 - 4.5.1 Chest radiograph, PA and lateral;
 - 4.5.2 CT/MRI scan of the head and neck region with standard slice increments;
 - 4.5.3 Salivary scan using sodium pertechnetate ($\text{Na-}^{99\text{m}}\text{TcO}_4^-$) (see Section 11.3);
- 4.6 Dental Examination within 3-4 weeks prior to start of radiation therapy (see Appendix V). Patients should be advised that good oral hygiene should be well maintained especially during and after radiation therapy.

5.0 REGISTRATION PROCEDURES

- 5.1** Participating surgeons and radiation oncologists must review the surgical video/CD ROM prior to entering any patients onto this protocol. Please call the study chair, Dr. Jha, at 780-432-8755 to request a copy of the surgical video/CD ROM. After viewing the surgical video/CD ROM, complete Appendix VIIA/B and mail/fax to Cancer Trial Support Unit (CTSU):
- CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX # (215) 569-0206
- 5.2** Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met (prior to surgery). 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 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

NOTE: IMRT treatment techniques are not allowed on this protocol.

6.1 Physical Factors

- 6.1.1** Equipment: Linear accelerators with appropriate photon and electron energies for supplemental boosting to the nodes.
- 6.1.2** Selection of appropriate photon energy should be based on optimizing the RT dose distribution within the target volume and minimizing the dose to the normal tissue.
- 6.1.3** Treatment distance must be ≥ 80 cm. SSD (or S.A.D for isocentric techniques).

6.2 Localization Requirements

- 6.2.1** Simulation: Simulation of all fields is mandatory. Patients must be reproducibly immobilized. The use of customized blocks to shape the treatment fields is recommended. Simulation films of each field, initial port films, and the calculation form will be sent to RTOG Headquarters in the first week of therapy, together with the treatment prescription for radiation therapy quality assurance review.
- 6.2.2** Verification: Beam verification (port) films must be obtained for each field. This should be done at least once in the first week of treatment and whenever any field adjustments are made. Port films of each field must be submitted to RTOG Headquarters.

6.3 Target Volume Irradiation Portals

- 6.3.1** Standard three-field techniques using two parallel opposed lateral fields will be used for the primary tumor site at the discretion of the investigator for the case. A single anterior A-P field will be used to treat the neck below the fields for the primary tumor. When there is (are) positive node(s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node (s). All fields must be treated on each treatment day. The lower neck and supraclavicular field should abut the primary field at the skin.

For patients with short necks, right and left superior inferior oblique fields or any other standard techniques may be used.

For oropharynx primaries, a midline block 2 cm wide and at least 2 cm in length on the skin surface will be placed in the anterior lower neck field to shield the larynx and the spinal cord in the junction region. For larynx and hypopharynx primaries, a lower lateral block, 2 cm in height, should be placed in the lateral upper neck fields to shield the areas from potential overlap of diverging beams over the spinal cord. Use of right and left superior – inferior oblique fields technique is also acceptable. Appropriate bolus around the stoma is to be used.

The primary treatment fields should encompass the primary tumors with adequate margins along with sites of known and/or suspected lymph node disease in the upper neck. There should be a minimum 2-3 cm margin around the primary tumor and positive node(s) and should include upper neck nodes to be irradiated electively for the initial target volume. Appropriate field reductions are to be made at the discretion of the treating radiation oncologist. The maximum spinal cord dose should not be more than 45 Gy – 46Gy.

- 6.3.2** Oropharynx:
- 6.3.2.1** The upper border of the field includes the nodes in the upper jugular region and should be placed at the level of the zygomatic arch, to include the parotids in the field.
- 6.3.2.2** The ipsilateral posterior cervical nodes must be irradiated if the primary tumor is T3 or T4.
- 6.3.2.3** Both the ipsilateral and contralateral posterior cervical nodes must be irradiated if there are clinically positive cervical nodes in the anterior chain.
- 6.3.3** Supraglottic larynx:
- 6.3.3.1** The upper border of the field includes the nodes in the upper jugular region and should be placed at the level of the zygomatic arch to include the parotids in the field.
- 6.3.3.2** The lower border of the field encompasses the larynx usually at or below the level of C5.
- 6.3.3.3** The ipsilateral posterior nodes should be treated for T3 and T4 lesions.
- 6.3.3.4** Both ipsilateral and contralateral posterior nodes should be treated if there are clinically positive nodes in the anterior chain.
- 6.3.4** Hypopharynx:
- 6.3.4.1** The superior border is placed at the level of the zygomatic arch, to include the base of skull (above C1) and the retropharyngeal nodes. Nodes in the upper jugular region and posterior triangle are included.
- 6.3.4.2** The lower border of the field encompasses the lower border of the cricoid cartilage.
- 6.3.5** Unknown Primaries:
- 6.3.5.1** All the potential sites of primaries and bilateral neck nodes are to be treated. The typical three field (two laterals and an anterior field arrangement) or right and left superior-inferior oblique field arrangement is acceptable.
- 6.3.6** Lower neck:
- 6.3.6.1** A single anterior lower neck field will be used to treat the neck and the supraclavicular fossa below the fields for the primary tumor. When there is (are) positive node (s) in the lower neck, an additional posterior field may be necessary to deliver a supplemental dose to the positive node (s).
- 6.3.6.2** The lower border of the field will be just below the clavicle or 1 cm below the clavicle when there are positive nodes in the supraclavicular fossa.
- 6.4** **Dose Calculation (4/5/04)**
- 6.4.1** Dose to the supraclavicular field is calculated at 3 cm depth or d Max depending on the clinical situation and at the discretion of the treating Radiation Oncologist. Cumulative isodose distributions at the level of the tumor center, a copy of the treatment record indicating cumulative doses, and boost field simulation and portal films must be submitted at the completion of radiotherapy.
- 6.4.2** Missing tissue equivalent compensators should be used to ensure homogeneity of dose distribution so that variation within the target volume does not exceed 10% of the target dose.
- 6.4.3** Boost doses will be specified at the actual site(s) of gross primary and nodal disease.
- 6.5** **Standard Fractionation**
- 6.5.1** Treatment to the primary tumor and upper neck will be given at 2.0 Gy per fraction, once a day, five days a week to a total dose of 54 Gy - 70 Gy in 27 -35 fractions in five and a half to seven weeks. Fields must be reduced to exclude the spinal cord at 38-44 Gy at the midplane. However, the entire neck must be irradiated to a dose of 54 Gy (even NO stage) as the anatomical levels of lymph node spread, usually 2-4 cm below the skin surface.
- Clinically positive neck nodes should receive a dose of 62 Gy -70 Gy in 31 - 35 fractions in 6 -7 weeks. To supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include additional electron beam (≥ 9 MeV) to the posterior neck.
- The anterior lower neck field will be treated at 2 Gy per fraction at 3 cm depth, once a day, to a total dose of 54 Gy in 22 fractions in 5.5 weeks. The total dose to the primary tumor and clinically positive nodes will be 62-70 Gy in 31-35 fractions in 6-7 weeks.
- 6.5.2** Radiation treatment (XRT) is to be started within 4 – 6 weeks of surgery.
- 6.5.3** Patients may not be irradiated with homolateral electron beam or wedge-pair techniques.
- 6.5.4** Wedge-pair techniques to boost the primary tumor can only be used if it does not interfere with the shielding of the transferred submandibular salivary gland in the submental space.

6.6 Shield for the Transferred Submandibular Salivary Gland in the Submental Space

The transferred salivary gland is identified with the help of the CT scans done in the treatment position. The volume of the transferred salivary gland is drawn on each slice of the CT scan showing the transferred submandibular salivary gland. The shielding is then drawn to cover > than 70% of the transferred submandibular salivary gland, and the major part of the sublingual salivary glands (Figure 1 [explained in the CD-ROM / video]). The posterior border of this shield must always be just in front of the hyoid bone. Careful attention must be paid not to shield the disease or the potential site of spread of the disease.

Sometimes the permanent pathology reveals disease (missed at frozen section) in level 1 lymph nodes or disease on the side chosen for the salivary gland transfer (contralateral to the primary site). In such a situation, although the salivary gland has been transferred to the submental space, no attempt is made to shield the transferred salivary gland in order to remain oncologically sound.

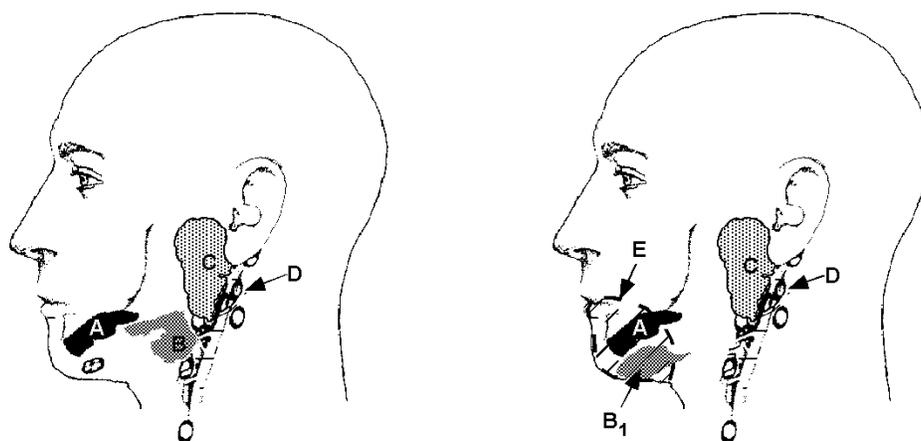


Figure 1: A = Sublingual Gland B = Submandibular Gland B₁ = Transferred Submandibular Gland
C = Parotid Gland D = Subdigastic Nodes E = Shielding

6.7 Radiation Therapy Toxicity Adjustments

6.7.1 Treatment Interruptions

Interruptions in radiation therapy may be necessitated by skin reactions, mucositis, ulceration, edema, or other acute complications. Radiation therapy will be continued without interruption if at all possible. Any interruption of radiation therapy for whatever reason (pain, machine malfunction, intercurrent illness, lack of transportation or social obligation) must be clearly indicated in the treatment record.

6.7.2 CBC is required to be done before radiation therapy or during the first week of radiation therapy.

6.8 Toxicity Reporting Guidelines

6.8.1 For acute radiation effect, through day 90 of treatment, the NCI CTC Version 2.0 will be used.

6.8.2 Late radiation effects will be evaluated and scored per the RTOG/EORTC Late Effects Scale.

6.8.3 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.

6.8.4 Required 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 (7/21/04)

Postoperative chemoradiotherapy is allowed; the choice of chemotherapy is at the discretion of the treating physician. Neoadjuvant chemotherapy is not permitted.

8.0 SURGERY

8.1 Seikaly and Jha Method of Submandibular Salivary Gland Transfer

The choice of the side for submandibular salivary gland transfer is dependent on: 1) the side of the uninvolved neck and 2) the side of primary tumor. As follows:

- Well lateralized primary cancer with unilateral neck involvement: Transfer is performed on the contralateral N0 neck;
- Well lateralized primary cancer with no neck involvement: Transfer is performed on the contralateral N0 neck;
- Midline primary cancer with unilateral neck involvement: Transfer is performed on the contralateral N0 neck;
- Midline primary cancer with no neck involvement: Transfer is performed on either one of the N0 necks.

8.2 Surgical Technique

8.2.1 Incision and flap elevation: A neck incision is performed from the mastoid tip to the mentum approximately 4 cm below the body of the mandible. The incision may also be incorporated with other neck incision as per the preference of the surgeon as long as the surgeon is able to fully visualize the submental/submandibular spaces and perform the selective neck dissection. The neck flaps are elevated in the sub-platysmal plane preserving the greater auricular nerve. The marginal mandibular nerve is identified superiorly, dissected free from the surrounding structures and preserved. Care must be exercised at this point in order not to damage the distal facial vessels.

8.2.2 Neck Dissection: The fascia over the sternocleidomastoid muscle is incised and the muscle is lifted off the underlying structures. The spinal accessory nerve is identified and dissected free up to the posterior belly of the digastric muscle. A level II and III neck dissection is then performed; the inclusion of level 2b is optional. The lymph nodes are removed en bloc preserving the jugular vein, spinal accessory nerve, hypoglossal nerve and the sensory rootlets of the neck. Anteriorly the dissection proceeds along the posterior belly of the digastric and anterior belly of the omohyoid. The facial artery and vein are left intact. Level one is then dissected separately and all the facial and pre glandular nodes are removed piecemeal. The submental space is cleared from the contralateral belly of the digastric to the ipsilateral mylohyoid muscle. The distal facial vessels are identified and preserved during the level I dissection and the submandibular gland is left in place. Any suspicious nodes (enlarged or hard) from level II and III and all level I lymph nodes (submental and submandibular) are sent for frozen section evaluation. If any of these nodes are involved with metastatic cancer, the transfer is abandoned, and the neck is treated appropriately

8.2.2.1 Rational for Neck Dissection On The Side of Transfer (4/5/04)

Neck dissection on the side of the transfer is part of the procedure and provides the information needed to safely shield the transferred submandibular gland post-operatively. In a review of the first 38 patients enrolled in the Cross Cancer Institute phase II trial with two year follow up, Seikaly et al.³⁸ found that the procedure was abandoned in 7 (18%) patients based on frozen section, and disease was found on permanent pathology in the neck dissection on the side of the transfer in 5 (13%) patients. All of the patients with disease found on permanent section did not have the gland shielded post-operatively. There has been no recurrence to date in the submental space. Seikaly et al. concluded that the lack of recurrence was due to the strict criteria used for shielding the gland, based in part on the final pathologic examination of the neck dissection.

8.2.3 Submandibular Salivary Gland Transfer: Once the lymph nodes are cleared, the facial vessels are identified proximally at the posterior and lower aspect of the submandibular triangle and distally as they enter the face. The submandibular gland is released from the surrounding facial structures and mylohyoid muscle but remains pedicled on the facial vessels, submandibular ganglion, and duct. Care must be exercised when dissecting the gland off the deep structures and the mylohyoid muscle not to damage the submandibular ganglion or the duct.

Retrograde or reverse flow is assessed in the facial artery by ligating the proximal end just medial to the posterior belly of the digastric and partially cutting the artery distal to the ligation. If there is no retrograde flow, the transfer is abandoned. If, however, flow is observed, the facial artery and vein are ligated and cut just proximal to their branches supplying and draining the gland. This leaves the gland pedicled on the distal facial vessels and thus supplied and drained via the retrograde flow through these vessels. The gland is then swung anteriorly and the remainder of the fascial attachments are released.

The mylohyoid muscle is bisected. The gland is then repositioned in the submental space anterior and superficial to the anterior belly of the digastric. The bisected mylohyoid muscle allows repositioning of the submandibular duct and submandibular ganglion. The gland is anchored between the anterior bellies of the digastric muscles to the periosteum of the mentum with absorbable sutures. The anterior, posterior and inferior borders of the gland are marked with 25 - gauge wire to help identify the position of the gland postoperatively.

A suction drain is placed in the surgical field. The platysma muscle is approximated with absorbable suture and the skin is closed.

8.2.4 Pearls and pitfalls:

- 8.2.4.1** The contralateral facial artery should be preserved, if possible, when a neck dissection is performed on the side contralateral to the transfer. We have, however, found excellent back flow in the artery on the transfer side even if the contralateral artery is sacrificed.
- 8.2.4.2** The facial artery must be ligated proximal to the first arterial branch to the submandibular gland.
- 8.2.4.3** The retromandibular vein at times joins the facial vein fairly distally. This anatomic configuration does not allow adequate mobilization of the gland anteriorly. The retromandibular vein in such a situation is safely sacrificed to allow mobilization.
- 8.2.4.4** We have identified veins which run with the submandibular duct, submandibular ganglion and within the fascia surrounding the facial artery. These veins do not hinder anterior mobilization and should be preserved. At times these are the only veins draining the gland.
- 8.2.4.5** A small cuff of fascia should be left on the gland as that provides a place to anchor the sutures.
- 8.2.4.6** The deep dissection of the submandibular gland is performed bluntly in order not to damage the underlying structures.
- 8.2.4.7** Extreme care must be exercised when releasing the gland from the deep structures so as not to damage the ganglion. The ganglion usually lies far more anteriorly than expected under the mylohyoid muscle.
- 8.2.4.8** The wire is anchored to the periosteum of the mentum and mid body of the mandible. Care must be taken when anchoring the posterior suture so as not to damage the distal facial vessels. We also anchor the wire inferiorly to the digastric tendon to limit its mobility.
- 8.2.4.9** When a mandibular split is used for the surgical approach, the surgeon must insure that the closure sutures do not violate or encroach on the submandibular duct ostium when closing the floor of mouth.
- 8.2.5** The transfer will be abandoned if: 1) any of the nodes on the side of the transfer are involved with metastatic cancer clinically or on frozen section; 2) there is no retrograde flow in the facial artery. (A CD-ROM / video describing the technique of submandibular salivary gland transfer will be provided to the participating institutions.)
- 8.2.6** The surgical evaluation form must be completed and photographs of the final position of the gland are mandatory at the end of the procedure. Please see Section 12.2.

9.0 OTHER THERAPY (7/21/04)

- 9.1** Postoperative chemoradiotherapy is allowed; the choice of chemotherapy is at the discretion of the treating physician. Neoadjuvant chemotherapy is not permitted.
- 9.2** Prophylactic use of amifostine and pilocarpine is not allowed. These agents and their derivatives are not allowed during radiation or within three months of completion of radiation. Administration of pilocarpine and its derivatives is discouraged before six months post-treatment. However, pilocarpine can be used if there is no salivary flow following the first post-treatment sialometry study. Any use of these agents and their derivatives including start and stop dates must be reported on the case report forms.

10.0 PATHOLOGY

10.1 Pathology reports must document the following:

- 10.1.1 Site of the primary;
- 10.1.2 Extent of disease;
- 10.1.3 Vascular invasion; lymphatic invasion;
- 10.1.4 Perineural invasion;
- 10.1.5 Margins;
- 10.1.6 Neck dissection information (number of nodes removed; number of nodes involved, extracapsular invasion, and involvement of adjacent structures);
- 10.1.7 Frozen section of level 1 from the side of transfer of submandibular salivary gland;
- 10.1.8 Frozen section from other node levels on the side of transfer if performed;
- 10.1.9 Pre-epiglottic space involvement.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (7/21/04)

Assessment	Pre-Surgery	At Surgery	Before RT	During RT	Follow-up ^j
Complete H&P including mucosal assessment	X ^a			X ^G	X ^I
Zubrod PS, Weight	X ^a				X ^I
Biopsy	X				X ^I
Tumor Diagram	X ^a				X ^H
Dental Evaluation			X ^K		
QOL Assessment	X				X ^J
CBC, platelet count	X ^b		X		
Serum electrolytes, bilirubin, Alk Phos, AST/ALT	X ^b				
Serum pregnancy test	X ^b				
Chest X-ray	X ^c				
CT/MRI H&N	X ^c				X ^H
Salivary Scans	X ^c		X ^e		X ^e
Toxicity Evaluation				X ^G	X ^I
Photograph		X			
Surgical Pathology		X ^d			
Surgery Evaluation/ Morbidity			X ^d		

- a. Within four weeks prior to study entry.
- b. Within two weeks prior to study entry.
- c. Within six weeks prior to study entry.
- d. Within one week of starting RT.
- e. **First scan 2-3 weeks post-surgery** and second scan six months from start of RT.
- f. For confirmation of recurrent tumor in the head and neck as applicable.
- g. Weekly during RT.
- h. As clinically indicated.
- i. Every 3 months through year 2, every 6 months for years 3-5.
- j. QOL assessment at 3, 6, and 12 months from start of RT.
- k. Within 3-4 weeks prior to start of RT

11.2 Quality of Life

11.2.1 A patient self-assessed questionnaire has been selected for QOL evaluation. The components of the questionnaire include four domains of QOL and head and neck symptom-specific items. Because of the different focus of this study (intervention vs. disease outcome), the QOL assessments will include a baseline assessment and assessment at three, six, and 12 months from start of radiation treatment.

11.2.2 Hassan and Weymuller of the University of Washington, Seattle, developed the questionnaire.⁴³ This questionnaire was designed specifically to address problems incurred by head and neck cancer patients. The University of Washington QOL questionnaire was tested on 75 head and neck cancer patients. The questionnaire was compared to two established tools, the Karnofsky and the Sickness Impact Profile (SIP), for validity, acceptability, reliability and responsiveness. The overall results demonstrated that the University of Washington Head and Neck Symptom Scale (HNSS) was equivalent to the Karnofsky and SIP for reliability and responsiveness; it was the preferred test format for 97% of the tested patients. The scores on the HNSS correlated well with the KPS and SIP, indicating validity. The test-retest reliability coefficient was 0.95.

11.2.3 The University of Washington QOL tool was selected because of its inclusion of symptom-specific effects that may result from the intervention of salivary gland transfer (i.e., related to saliva, eating, taste, swallowing, pain). The scale consists of ten symptom-specific categories, each of which describes important daily living function/limitations of head and neck cancer patients. Each category has five possible item choices. The highest level or "normal" is scored 10 points while the lowest (or greatest dysfunction) is scored 50 points. The options between are in multiples of 10. The patient is asked to circle the statements which best describe their current status. The scores are totaled and then adjusted to obtain the final range from 0 to 100. The lower the score, the greater the QOL, and conversely, the higher the score, the lower the QOL.

11.3 Evaluation of Salivary Gland Function using Salivary Gland Scintigraphy

Salivary gland scintigraphy is a standard, simple, safe and reproducible procedure, particularly because it is well supported in the literature as a competent marker of salivary gland function after radiotherapy intervention. There are several very good reports in the literature correlating salivary gland scintigraphy with salivary secretion rates, and showing the ability of salivary gland scintigraphy to demonstrate changing, preserved or lost function following radiotherapy.³⁹⁻⁴² Bagesun et al shows direct correlation between salivary gland scintigraphy and whole salivary secretion rates showing that it acts as a very good surrogate.³⁹ Tsujii used salivary gland imaging following radiotherapy and showed it to be a satisfactory marker of preserved function. The temporal changes following radiotherapy are well demonstrated by the paper of Valdes-Olmos et al., who used repeat studies very much in the same setting that we will be doing.⁴¹⁻⁴²

11.3.1 Salivary Scan Information: This procedure is of value in determining salivary gland function which is altered in certain systemic diseases, such as Sjogren's disease or ankylosing spondylitis. A sialogogue (lemon juice) is administered halfway through the study to determine if secretory function is maintained. Views of the head and neck are taken at the end of the study to show salivary gland morphology.

Radiopharmaceutical: Sodium pertechnetate (Na-^{99m}TcO₄⁻)
Dose: Adult: 350 MBq
Settings: ^{99m}Tc photopeak (140KeV)
Collimator: LEHR or LEGAP (Low Energy High Resolution or Low Energy General All Purpose)
Collection Parameters: **Dynamic Sequence:** 30 seconds/frame for 20 minutes
Static Images: Anterior and lateral views for 3 minutes per view
Materials:

- Extension tubing
- 3 ml lemon juice in a syringe (no needle attached)
- Stopwatch

11.3.2 Salivary Scan Procedure: Position the patient supine under the camera, with the salivary glands in the center of field of view. Inject the patient and acquire the "dynamic" phase (begin imaging when activity is seen in the heart and lungs, starting prior to this misses the initial flow to the salivary glands). Start a stopwatch upon injection. With 5-8 minutes remaining in the study, advise the patient not to move and that you will be giving him or her a small drink. Wearing gloves, administer 3 ml of lemon juice orally (per institutional standard procedure) to the patient using a syringe and extension tubing. Note the time of administration. DO NOT warn the patient in advance that he or she will be receiving lemon juice!! After the dynamic phase is complete, acquire 3 minute anterior and lateral views of the head and neck. This investigation is sensitive to artifact induced by movement; care in set up, patient positioning

and patient comfort is required to minimize artifact induction. This is particularly true in patients with head and neck cancers. Tape or Velcro **MUST** be used in all patients to stabilize head position during the scan.

11.3.3 Analysis

11.3.3.1 Qualitative analysis: There is a characteristic shape to the uptake and clearance curve in the patient with normal salivary function. This is illustrated in Figure 3. There is clear evidence of an uptake phase, a clearance phase in response to sialogogue, and an early re-uptake phase. As function deteriorates, all three phases show impairment until the curve is effectively a straight line in patients with no significant salivary function.

It is possible to characterize 4 patterns of abnormality:

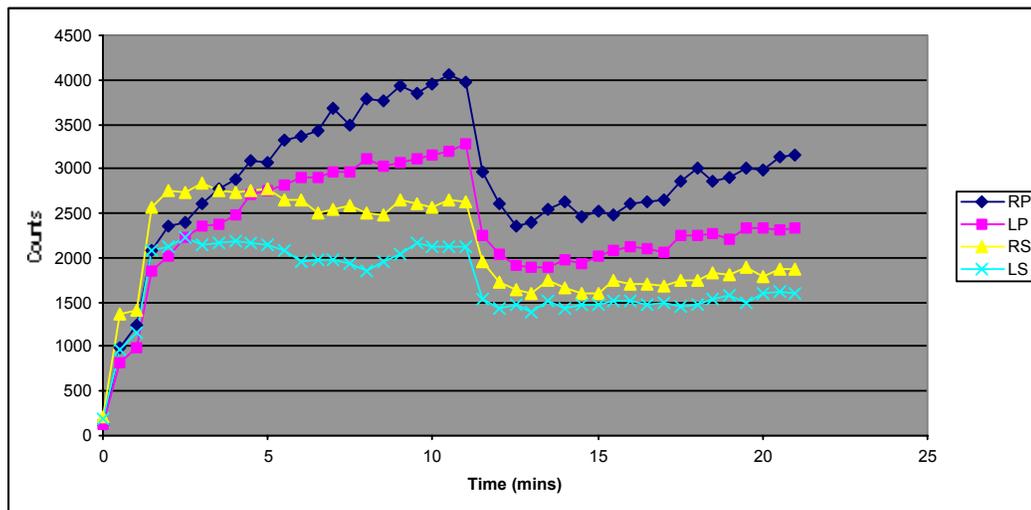
Normal function: → curve as above.

Mild functional impairment → mild impairment of uptake and sialogogue response.

Severe functional impairment → Significant impairment of uptake and almost absent sialogogue response; impaired reuptake.

Absent function → No discrimination to curve shape.

Figure 3



RP: Right Parotid; LP: Left Parotid; RS: Right Submandibular; LS: Left Submandibular

Qualitative analysis can be used to evaluate function in individual patients one month and six months after the end of RT to confirm that function is maintained in the transplanted gland. Quantitative analysis will be used to evaluate the patient population and to provide a numerical comparison of function pre and post intervention.

11.3.3.2 Quantitative Analysis: Region of interest (ROI) analysis is performed for each of the four salivary glands: Right and Left Parotid (RP and LP) and Right and Left Submandibular (RS and LS). A background region is obtained from the skull distribution from above the ear to the mid calvaria. Time activity curves (TAC's) are generated from the ROI's for each of the glands and subsequently corrected for background activity. Two parameters are extracted from each curve and a weighted average from all glands is also calculated to give the following parameters:

$$\text{Response (Percentage)} = 100 \times \frac{y(t_{\max}) - y(t_{\min})}{y(t_{\max})}, \text{ where } t_{\max} \text{ is the time at which the TAC}$$

reaches its first maximum and t_{\min} is the time at which the TAC reaches its first minimum after t_{\max} .

Pre-Stimulus Uptake (counts/minute/MBq) – average slope of TAC from t=0 to t=tmax divided by the injected activity (in MBq). The uptake value is to be calculated using the following formula:

$$\text{Uptake} = \frac{2 \int_0^{t_{\max}} \text{TAC}(t) dt}{t_{\max}^2}$$

A database of normal and abnormal responses has been established and qualitative ratios of surgical and radiation effects developed. For assessment of surgical success, the qualitative analysis provides “yes/no” data on continuing normal gland function. For post-radiation effects, quantitative analysis may provide a more subtle indicator of radiation effects.

- 11.3.3.3 (7/21/04) Salivary Scan Data Transfer:** Data format must be DICOM 3 Part 10 (or non-Part 10). Each patient file must be cleansed of any patient identification information (name, DOB, hospital, study date, etc.) and include only the RTOG study number and case number. Please send the CD's to RTOG Headquarters, 1818 Market Street, Suite 1600, Philadelphia, PA 19103. A central review of the salivary scan data will subsequently be done by Dr. McEwan at the Cross Cancer Institute.

11.4 Criteria for Removal from Protocol Treatment

Note: The following criteria are for removing a patient from protocol treatment, not for removing a patient from the study. Follow-up should continue on patients removed from protocol treatment.

- 11.4.1** Positive surgical margins on final pathology (including carcinoma *in situ*).
- 11.4.2** Progression of disease while on treatment.
- 11.4.3** Sustained severe radiation mucositis resulting in dehydration and poor nutrition unresponsive to tube feeding or any other toxicity that requires more than a 14 day break from therapy. Every effort should be made to sustain the patient so as to avoid such complications.
- 11.4.4** Patients' refusal to continue participation (reasons to be clearly specified on data forms).

12.0 DATA COLLECTION (7/21/04, 8/4/04)

Data should be submitted to:

**RTOG Headquarters
1818 Market Street, Suite 1600, Philadelphia, PA 19103**

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)	
Pathology Report (P1)	
Nodal Site Staging Worksheet (I7)	
QOL Questionnaire (QL)	
Salivary Scan (C6)*	
Salivary Scan Report (C7)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (<i>Protocol Treatment Form</i>) (T2)	
Films (<i>simulation and portal</i>) (T3)	
Calculations (T4)	
Operative Report (S2)	
Surgical Pathology Report (S5)	
Surgical Evaluation/Morbidity Form (S1)	
Post-operative salivary scan (C6)*	
Salivary Scan Report (C7)	
Photographs (see Section 12.2)	

<u>Final Dosimetry Information:</u> Radiotherapy Form (T1) Daily Treatment Record (T5) Isodose Distribution (T6) Boost Films (<i>simulation and portal</i>) (T8)	Within 2 weeks of RT end
Initial Follow-up Form (FS)	Week 13 (<i>Day 90 from the start of radiation therapy</i>)
Follow-up Form (F1)	At six months from the start of RT then every 3 months for 2 years; then q 6 months x 3 years. Also at progression/relapse and at death.
QOL Questionnaire (QL)	Three, six and 12 months from start of RT
Salivary Scan (C6)* Salivary Scan Report (C7)	Six months from start of RT
Autopsy Report (D3)	As applicable

*NOTE: CD must be submitted to RTOG Headquarters; see Section 11.3.3.3 for details.

12.2 Photographs

Photographs (35 mm slides or prints) are mandatory for each transfer. Please label with the patient ID number, institution, and the date of surgery. Submit the anterior view of the submental space after transfer, and lateral view of the submental space after the transfer. Please send photographs to:

Hadi Seikaly, M.D.
University of Alberta
Cross Cancer Institute
11560 University Avenue
Edmonton, Alberta CAN T6G-1Z2

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary

The primary endpoint of this trial is to determine the reproducibility of the surgical technique of submandibular salivary gland transfer in a multi-institutional setting.

Reproducibility is the primary endpoint because whether or not the surgical technique is widely applicable in a multi-institutional setting must be demonstrated prior to undertaking a phase III trial. The criteria used to judge the reproducibility of the surgical technique is described in Sections 13.2 and 13.3. The ability of various clinical sites to perform the surgery successfully will provide a measure of feasibility for this technique. With the rapid turnaround review process as described in Section 13.3.1, a high percentage of “per protocol prescription” surgeries is expected. Since treatments from the study chair’s institution are most likely to be scored “per protocol prescription”, the accrual from this institution will be capped at 15%.

13.1.2 Secondary

13.1.2.1 Rate of acute xerostomia.

13.1.2.2 Salivary scan evaluation: all the salivary scans will be evaluated by a central review process as outlined in Sections 13.2 and 13.3.

13.1.2.3 Quality of life as measured using the University of Washington Head and Neck Symptom Questionnaire.

13.1.2.4 Toxicity associated with protocol surgery.

13.1.2.5 Toxicity associated with protocol radiation therapy.

13.1.2.6 Disease-free survival (failure: persistent or recurrent disease or death without progression).

13.1.2.7 Overall survival (failure: death due to any cause).

13.2 Study Design

The sample size will be determined by the first endpoint in Section 13.1.1, namely, the reproducibility of the surgical technique. The Study Chair and the RTOG Head and Neck Committee Surgical Chair will perform the central review. Surgery will be scored as "per protocol prescription" or "not per protocol prescription", using the criteria in Section 13.3.1. Thus, each surgery will receive two scores; only a surgery determined as "per protocol prescription" by *both* reviewers will be scored as "per protocol prescription". The criteria in the Surgical Evaluation Form – Part A will also be used for evaluation purposes.

If a surgery is scored as "not per protocol prescription", the study chair and the RTOG Head and Neck Committee Surgical Chair will contact the treating surgeon for further discussion of the case.

The optimal two-stage design by Simon⁴⁴ will be used. Let p be the true probability that the final review is "per protocol prescription". A p close to 1 implies that the surgical technique is reproducible in a multi-institutional setting. If p is less than or equal to 60%, the goal is to have at most a 5% probability of concluding that the technique is reproducible. On the other hand, if p is greater than or equal to 80%, the desired level, the goal is to have at most a 20% probability of concluding that the technique is not reproducible. With these specifications, 11 eligible patients will be required in the first stage. It is required that the study chair's institution enters no more than 1 eligible patient for this stage. If 4 or more surgeries in the first 11 patients are scored "not per protocol prescription", then discontinuation will be recommended to the Study Chair, the RTOG Head and Neck Surgery Chair, and the RTOG Head and Neck Chair. Following the review of the data and discussion, a joint recommendation about the study will be made to the RTOG Research Strategy Committee for its approval. Data will be presented about the total number of surgeries scored "not per protocol prescription", and also whether or not the surgery was the first performed by a given surgeon. Otherwise, the trial will continue until a total of 43 eligible patients are accrued. The maximum number of patients that the study chair's institution can enter is 6 eligible patients. If 13 or more of the 43 surgeries are scored "not per protocol prescription", the technique will be considered not reproducible, and a phase III study will not be pursued. Otherwise, this technique will be considered reproducible, and may be considered for phase III study, pending the results with respect to xerostomia, as defined below.

In the U.S. Bioscience phase III Amifostine trial,⁴⁵ the use of Amifostine reduced acute xerostomia (grade ≥ 2) from 78% to 51%. This trial was chosen because approximately 2/3 of the patients were treated in the post-operative setting. Patients who experience grade ≥ 2 xerostomia or start Amifostine or Pilocarpine in the acute period will be considered as having acute xerostomia. A rate of acute xerostomia equal or lower than those observed in the U.S. Bioscience trial (namely 51%) will be considered acceptable. Acute toxicity will be scored using the NCI CTC Version 2.0.

If the surgical technique is reproducible and the xerostomia is acceptable, this study will be considered for a further randomized phase III study testing the addition of submandibular gland transfer to surgery and radiation therapy.

13.3 Analysis Plans (4/5/04)

13.3.1 Criteria for judging the reproducibility of surgical technique:

Evaluable patients must have the Surgical Evaluation Form - Part A completed prior to meeting the following criteria for a surgery to be considered "per protocol prescription". There are three criteria for determining if the surgical transfer has been "per protocol prescription" or not. All three criteria, as follows, have to be satisfied for the surgical transfer to be scored as per protocol description:

- If the transferred salivary gland (2-3 weeks post-op) still shows perfusion to the gland in the translocated position in the submental space, then a criterion is met;
- If the transferred salivary gland responds to stimulation by citric acid, then a criterion is met;
- If a Level 1-3 neck dissection on the side of the transfer has been successfully performed, then a criterion is met.

13.3.2 Statistical Methods

The surgical rates of “per protocol prescription” and “not per protocol prescription” will be estimated along with their 95% confidence intervals. Salivary functions will be evaluated as described in Section 11.3. In addition, the rates of grade 3 and grade 4 xerostomia, as well as the rates of other toxicities will be estimated with 95% confidence intervals. Disease-free and overall survival rates will be estimated by the Kaplan-Meier method.⁴⁶

13.3.3 Interim Reports

Interim reports are prepared every six months until the closure of the study. In general, the interim reports will include: The patient accrual rate and projected completion date; institutional accrual; protocol compliance and quality of submitted data; the frequency and severity of toxicity.

13.3.4 Initial Analyses for Reporting Results of Surgical Technique

The analyses reporting the results about the surgical techniques performed will be carried out after both the Study Chair and the RTOG Head and Neck Surgical Chair have reviewed all surgeries in the first stage (n=11) and the second stage (n=43), respectively.

13.3.5 Initial Analysis for Reporting Efficacy Results

The analysis for reporting the efficacy results will be performed after each patient has been potentially followed for 12 months. Rates of toxicity, disease-free and overall survival will be estimated.

13.4 Patient Accrual

For the maximum sample size of 43 patients and allowing for a 10% ineligible rate, we expect to accrue approximately **48 patients**. Patient accrual will be temporarily suspended after 11 eligible patients have been entered to review the surgical procedures. Patient accrual is projected to be approximately 30 patients per year. Allowing for this accrual suspension and institutional IRB approvals, the study should be completed within 2 years. If accrual is less than 1 patient per month, the study will be reevaluated with respect to feasibility.

13.5 Inclusion of Women and Minorities

In conformance with the National Institutes of Health Revitalization Act of 1993 with regard to inclusion of women and racial/ethnic minorities in clinical research, we have also considered the possible interaction between race and treatments. Based on the accrual statistics from RTOG 9709, we project that 75% of patients enrolled to this study will be men, and 25% women. The study was designed with the assumption that there is no difference in the rate of surgeries determined “per protocol prescription” between the genders or among the races. The following table lists the projected number of patients in each gender and race category.

Planned Gender and Minority Accrual Estimates

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	1	1
Not Hispanic or Latino	12	35	47
Ethnic Category: Total of all subjects	12	36	48
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	0	1	1
Black or African American	2	4	6
Native Hawaiian or other Pacific Islander	0	0	0
White	10	30	40
Racial Category: Total of all subjects	12	36	48

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APPENDIX I

RTOG 0244

SAMPLE CONSENT FOR RESEARCH STUDY

A PHASE II STUDY OF SUBMANDIBULAR SALIVARY GLAND TRANSFER TO THE SUBMENTAL SPACE PRIOR TO START OF RADIATION TREATMENT FOR PREVENTION OF RADIATION-INDUCED XEROSTOMIA IN HEAD AND NECK CANCER PATIENTS

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?

You have been diagnosed with cancer of the head and neck area. Surgery and radiation therapy has been recommended to treat this disease. Radiation therapy is a form of cancer treatment using high energy x-rays. One of the possible side effects of radiation therapy is a significant and permanent lessening of normal mouth moisture. Although there are medications to treat dry mouth after radiation therapy, it might be better to protect the salivary glands during the radiation.

Another side effect from radiation therapy given to the head and neck region is the development of sores in the mouth. This condition (radiation mucositis) can produce significant redness and painful ulcers. These interfere with talking and eating for a period of several weeks during the radiation.

This study will see if moving one salivary gland outside the radiation field, before the start of radiation treatment during your planned surgery, will be able to preserve oral moisture by protecting the salivary glands during the radiation therapy. This study will also collect information about your quality of life, including how the treatment affects your diet, pain, activity, eating, speech, and other side effects that may occur.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 48 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (4/5/04)

At the time of surgery for your cancer, one of your salivary glands (from the side of your neck opposite the site of the cancer) will be surgically moved and placed under the chin region. This salivary gland usually sits near the angle of the jaw and will be moved to underneath the chin region, where it can be shielded from the effects of radiation treatment. This will take one additional hour of surgery time. Then, 4-6 weeks after your surgery, you will receive standard radiation treatment. You will start radiation treatments once a day, five days a week for 5 1/2-7 weeks.

Radio-isotope Studies of Salivary Glands

In order to evaluate the function of the “transferred” salivary gland, you will have a salivary gland scan taken. This involves the injection of a radioactive dye (radio-isotope) into your vein followed by a special camera that takes pictures of the salivary gland region. This will take about 30 minutes. The amount of radiation exposure is equal to that of a chest x-ray.

At about 15 minutes into the procedure, you will be asked to swallow lemon juice in order to stimulate the flow of saliva and more pictures will be taken as described earlier. This procedure is not painful. This study will be done before surgery and at one month and six months after the end of radiation therapy to evaluate function of the “transferred gland”.

University of Washington Quality of Life Questionnaire

This is a list of questions designed to assess the quality of life in head and neck cancer patients receiving treatment. You will be asked on a regular basis to fill out this questionnaire to assess the quality of your life. This takes 20-30 minutes.

After your surgery, most of your treatment will be done as an outpatient at your institution.

The following procedures that are part of regular cancer care and may be done even if you do not join the study:

- Physical Exam
- Blood Tests
- Chest X-ray or CT scan
- CT/MRI scan of tumor
- Endoscopy (examination of the inside of your throat)
- Biopsy
- Tumor Measurements
- Dental Evaluation

Standard procedures being done because you are in this study:

<u>Schedule</u>	<u>Procedure</u>
Before surgery, weekly during radiation treatment, every 3 months through year 2, every 6 months years 3-5	Physical examination
Before surgery	Pregnancy test if appropriate
Weekly during radiation treatment, every 3 months through year 2, every 6 months years 3-5	Evaluation for Side Effects
Before surgery, before or during the first week of radiation therapy, and as needed	Blood Tests
Before surgery, 2-3 weeks following surgery, and six months from the start of radiation.	Salivary scans
Presurgery, and at three, six, and 12 months from the start of radiation. These questionnaires will take between 20-30 minutes to complete.	Quality of Life Questionnaires

HOW LONG WILL I BE IN THE STUDY?

About 4-6 weeks after your surgery, you will receive radiation treatment five days a week for approximately five and a half to seven weeks. After you finish your treatment, you will be seen for follow up every 3 months through year 2, and every six months for years 3-5.

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.

The researcher may decide to take you off this study if your disease gets worse despite the treatment, the side effects of the treatment are very serious, or new information about the treatment 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.

WHAT ARE THE RISKS OF THE STUDY?

The majority of the selected patients will be undergoing some form of surgery or neck dissection as part of their treatment. The risks of surgery, anesthesia, and the postoperative recovery period are not compounded or affected by the gland transfer. Some of the complications that can occur with any surgery are:

Infection, bleeding, swelling of face, shoulder weakness, neck numbness, pain, blood clot in the legs and lungs and in rare cases nerve damage, swelling of brain, blindness and sudden death.

Several problems related to the gland transfer may occur:

- a) The transferred salivary gland may not 'take'; the gland may then decrease in size and form scar tissue. If it remains uninfected, then no additional treatment may be required. If it does get infected, you may have to undergo another surgical procedure to remove the "transferred gland."
- b) There may be a slight "bulge" underneath your chin region because of the transferred gland.
- c) The transferred gland may not remain functional. In such an event, if the gland remains uninfected, no additional procedure may be required.
- d) A possibility that cancer may spread to underneath the chin area.
- e) There may be lower lip and shoulder weakness on the side of the gland transfer.

The above complication "d" has not occurred so far in any of our patients in the pilot study (80 patients).

While on the study, you are also at risk for the side effects listed below. 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 therapy and chemotherapy are stopped, but in some cases side effects can be long-lasting or permanent.

Risks Associated with Radiation Therapy (7/21/04)

Very Likely

Sores in the mouth and throat that are likely to interfere with swallowing

Temporary hair loss (of the face/chin/neck)

Tanning, redness, or blistering or peeling of skin in treatment area

Loss of teeth, or cavities in teeth, if strict dental care is not followed

Hardness and tightness of the skin and muscles of the head and neck

Loss of appetite

Weight loss

Ear pain/pressure

Thick mucus in the mouth

Hoarseness/cough
Fatigue

Less Likely

Dryness of the mouth or altered taste that may be permanent
Permanent hair loss (of the face/chin/neck)

Less Likely, But Serious

Decrease in function of thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
Temporary pain or scarring around nerves in the shoulder, which could cause numbness and/or weakness
Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia
Severe damage to the jawbone and/or voice box which could require major surgery to correct or even to remove the jaw bone and/or voice box
Serious ear infections and/or hearing loss
Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”

This study may be harmful to a nursing infant or an unborn child. Sufficient medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive during this study may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant, you must tell your doctor immediately.

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 cancer of the head and neck region 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) once or twice a day radiation therapy; (2) chemotherapy; (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. These treatments could be given either alone or in combination with each other. There may also be other treatment trials in which you could participate.

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

Another option may be to get the treatment plan for advanced head and neck cancer described in this study at this center or at another center even if you do not take part in the study.

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

WHAT ABOUT CONFIDENTIALITY?

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

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (*FDA*), the National Cancer Institute (*NCI*) or its authorized representatives, qualified representatives of applicable drug manufacturers, 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. You may find a National Cancer Institute Guide: "Clinical Trials and Insurance Coverage – a Resource Guide" helpful in this regard. You may ask your doctor for a copy, or it is available on the world wide web at

<http://www.nci.nih.gov/ClinicalTrials/insurance> (and click on printable version).

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. Medicare should be considered a health insurance provider.

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 you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

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

A group of experts in head and neck cancer from the RTOG Head and Neck Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the 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:
(OHRP) 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 at
<http://cancertrials.nci.nih.gov> or for accurate cancer information including PDQ (Physician Data Query) visit <http://cancernet.nci.nih.gov>.

CancerFax

Includes NCI information about cancer treatment, screening, prevention, and supportive care. To obtain a contents list, dial 301-402-5874 or 800-624-2511 from a fax machine hand set and follow the recorded instructions.

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's Name

Patient's Signature

Date

Name of Person Obtaining Consent

Signature

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>).
5	Death

APPENDIX III

AJCC STAGING SYSTEM HEAD & NECK, 6th Edition

STAGING-PRIMARY TUMOR (T)

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

PHARYNX

Nasopharynx

- 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, orbit, or masticator space.

Oropharynx

- 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
- T4a Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
- T4b Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

Hypopharynx

- 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.
- T4a Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.
- T4b Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.

LARYNX

Supraglottis

- T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility
- T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx.
- T3 Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
- T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
- T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Glottis

- T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
 - T1a Tumor limited to one vocal cord
 - T1b Tumor involves both vocal cords
- T2 Tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility
- T3 Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
- T4a Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus).
- T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

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
- T4a Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus).
- T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

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 in 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.

DISTANT METASTASIS (M)

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

STAGE GROUPING Excluding Nasopharynx

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0
Stage IVA	T4a, N0-2, M0 Any T, N2, M0
Stage IVB	T4b, Any N, M0 Any T, N3, M0
Stage IVC	Any T, Any N, M1

STAGE GROUPING Nasopharynx

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

APPENDIX V

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

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

Pre-irradiation Care and Procedures

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

Group 1

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

Group 2

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

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

Group 3

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

Group 4

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

Extraction of Teeth

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

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is moulded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

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

Failure to Control Decay

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

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

Hypersensitivity of Teeth

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

Infections

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

Bone Necrosis

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

APPENDIX VI

UNIVERSITY OF WASHINGTON QUALITY OF LIFE QUESTIONNAIRE

(This form is not to be used for data collection).

Case No.: _____

Institution: _____ Institution No.: _____

Patient's Name: _____ Patient's ID No.: _____

This sheet represents the first page of the pretreatment Head and Neck Symptom Scale and is completed by the medical staff (nurse, research associate, physician, etc.) each time the patient is scheduled to complete the questionnaires.

- i When sending a Head & Neck Symptom Scale, complete questions 1 and 2 a-e on this sheet and attach to the FRONT of the questionnaire before sending to RTOG Headquarters.**
- ii If a questionnaire is not completed by the patient (no questionnaire items filled out) or a data collection point is missed, complete ONLY the cover sheet (questions 1, 2a & 3) and submit to RTOG Headquarters.**
- iii A separate cover sheet must be completed for each questionnaire, at each data collection point, whether the questionnaire was completed or not.**

1 SCHEDULED DATA POINT

- 1 Pre-treatment assessment:
Date protocol treatment started: ___/___/___
- 2 At 4 weeks ___/___/___
- 3 At follow-up, specify interval or calendar date ___/___/___
- 4 Other, specify _____

QUESTIONNAIRE COMPLIANCE

2a Did the patient complete any items on the questionnaire?

- 1 No (skip to 3)
- 2 Yes (attach completed cover sheet to questionnaire)

Date patient filled out questionnaire ___/___/___

2b Did the patient require any assistance in completing the questionnaire?

- 1 No (skip to e)
- 2 Yes (complete c-e)
- 9 Unknown if assistance given (skip to e)

2c Specify the person who assisted the patient and the extend of the assistance

- 1 Staff member
- 2 Family
- 3 Other, specify _____
- 9 Unknown

2d Extent of assistance given

- 1 Read items to patient
- 2 Interpreted items for patient
- 3 Marked items per patient's response
- 4 Combination of above, specify _____
- 5 Other, specify _____

- 2e 9 Unknown
- Specify method of completion
- 1 At appointment
- 2 By mail
- 3 By telephone
- 9 Unknown

- 3 REASON QUESTIONNAIRE WAS NOT COMPLETED
- 1 Patient refused due to illness
- 2 Patient unable to be contacted
- 3 Questionnaire not completed due to institutional error
- 4 Patient unable to communicate in English
- 5 Patient refused/other reason, specify _____
- 9 Unknown

COMMENTS:

Person completing cover sheet: _____

Case No.: _____ Patient's Name: _____

INSTRUCTIONS:

Page 1 and 2 of this questionnaire is an identification cover sheet completed by the medical staff. Pages 3-5 are completed by you. Please recheck to see that you have not omitted any questions. If you do not wish to complete an item, please initial it so we may know that you did not wish to record an answer. Record the date you filled out the questionnaire. If you needed assistance, note who helped you, e.g., wife, and the reason for the assistance, e.g., poor eyesight, etc.

Date form filled out ___/___/___

I was assisted by: _____

Reason:

Each of the following items lists different numbered statements. Think about what each statement says, then place a circle around the one statement that most closely describes how you have been feeling during the past week, including today. Please circle only one statement for each item.

Example: In the past week and today, if you have not experienced any pain from your cancer or treatment, you would circle sentence 10 for Item I (I have no pain).

I PAIN (General)

A General

- 10 I have no pain.
- 20 There is mild pain not needing medication.
- 30 I have moderate pain - requires regular medication (codeine or non-narcotic).
- 40 I have severe pain controlled only by narcotics.
- 50 I have severe pain not controlled by narcotics.

B Mouth

- 10 I have no pain in my mouth.
- 20 I have mild pain but it is not affecting my eating.
- 30 I have moderate pain that is affecting my eating.
- 40 I have severe pain and need medication in order to eat.
- 50 I have severe pain and cannot eat even with the medication.

C Throat

- 10 I have no pain in my throat.
- 20 I have mild pain but it is not affecting my eating.
- 30 I have moderate pain that is affecting my eating.
- 40 I have severe pain and need medication in order to eat.
- 50 I have severe pain and cannot eat even with the medication.

II DISFIGUREMENT

- 10 There is no change in my appearance.
- 20 The change in my appearance is minor.
- 30 My appearance bothers me but I remain active.
- 40 I feel significantly disfigured and limit my activities due to my appearance.
- 50 I cannot be with people due to my appearance.

Case No.: _____ Patient's Name: _____

III ACTIVITY

- 10 I am as active as I have ever been.
- 20 There are times when I can't keep up with my old pace, but not often.
- 30 I am often tired and I have slowed down my activities although I still get out.
- 40 I don't go out because I don't have the strength.
- 50 I am usually in a bed or chair and don't leave home.

IV RECREATION / ENTERTAINMENT

- 10 There are no limitations to recreation at home and away from home.
- 20 There are a few things I can't do but I still get out and enjoy life.
- 30 There are many times when I wish I could get out more but I'm not up to it.
- 40 There are severe limitations to what I can do, mostly I stay home and watch TV.
- 50 I can't do anything enjoyable.

V EMPLOYMENT

- 10 I work full time.
- 20 I have a part time but permanent job.
- 30 I only have occasional employment.
- 40 I am unemployed.
- 50 I am retired (circle one below):
- 51 not related to cancer treatment
- 52 due to cancer treatment

VI EATING

A Chewing

- 10 I can chew as well as ever.
- 20 I have slight difficulty chewing solid foods.
- 30 I have moderate difficulty chewing solid foods.
- 40 I can only chew soft foods.
- 50 I cannot chew soft foods.

B Swallowing

- 10 I swallow normally.
- 20 I cannot swallow certain solid foods.
- 30 I can only swallow soft foods.
- 40 I can only swallow liquid foods.
- 50 I cannot swallow.

VII SALIVA

A Amount

- 10 I have a normal amount of saliva.
- 20 I have a mild loss of saliva.
- 30 I have a moderate loss of saliva.
- 40 I have a severe loss of saliva.
- 50 I have no saliva.

B Consistency

- 10 My saliva has normal consistency.
- 20 My saliva is slightly thicker.
- 30 My saliva is moderately thicker.
- 40 My saliva is extremely thicker.

50 I have saliva that dries in my mouth and/or on my lips.

Case No.: _____ Patient's Name: _____

VIII Taste

- 10 I can taste food normally.
- 20 I can taste most foods normally.
- 30 I can taste some foods normally.
- 40 I can taste few foods normally.
- 50 I cannot taste any foods normally.

IX SPEECH

- 10 My speech is the same as always.
- 20 I have difficulty with saying some words, but can be understood over the phone.
- 30 I have moderate difficulty saying some words, and cannot use the phone.
- 40 Only my family and/or friends can understand me.
- 50 I cannot be understood.

X MUCUS OR PHLEGM

A AMOUNT

- 10 I have a normal amount of mucus.
- 20 I have a mild amount of mucus.
- 30 I have a moderate amount of mucus.
- 40 I have a severe amount of mucus.
- 50 I have no mucus.

B CONSISTENCY

- 10 My mucus has normal consistency
- 20 My mucus is slightly thicker.
- 30 My mucus is moderately thicker.
- 40 My mucus is extremely thicker.
- 50 I have no mucus.

Comments: _____

—

—

—

—

Patient's Signature: _____

Date: ____/____/____

RTOG 0244

APPENDIX VIIA
Head and Neck Surgeon's Questionnaire

Participating surgeons and radiation oncologists must review the surgical video/CD ROM prior to entering any patients onto this protocol. Please call the study chair, Dr. Jha, at 780-432-8755 to request a copy of the surgical video/CD ROM. After viewing the surgical video/CD ROM, complete Appendix VIIA/Appendix VIIB and mail/fax to Cancer Trial Support Unit (CTSU):

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX # (215) 569-0206

I have viewed the surgical video/CD ROM provided for this protocol, **RTOG 0244**:

Signature of Physician completing this form

Institution Name:

Printed Name of Physician

Institution Number:

Telephone Number of Physician

Physician's Specialty

Date

RTOG 0244

APPENDIX VIIB
Radiation Oncologist's Questionnaire

Participating surgeons and radiation oncologists must review the surgical video/CD ROM prior to entering any patients onto this protocol. Please call the study chair, Dr. Jha, at 780-432-8755 to request a copy of the surgical video/CD ROM. After viewing the surgical video/CD ROM, complete Appendix VIIA/Appendix VIIB and mail/fax to Cancer Trial Support Unit (CTSU):

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX # (215) 569-0206

I have viewed the surgical video/CD ROM provided for this protocol, **RTOG 0244**:

Signature of Physician completing this form

Institution Name:

Printed Name of Physician

Institution Number:

Telephone Number of Physician

Physician's Specialty

Date