

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 97-09**

**A PHASE III STUDY TO TEST THE EFFICACY OF THE PROPHYLACTIC USE  
OF ORAL PILOCARPINE TO REDUCE HYPOSALIVATION AND MUCOSITIS  
ASSOCIATED WITH CURATIVE RADIATION THERAPY  
IN HEAD AND NECK CANCER PATIENTS**

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**SCHEMA**

S T R A T I F Y	<p><b><u>RT Fractionation</u></b></p> <p>1. Standard (<i>once daily</i>)</p> <p>2. Hyperfractionated</p>	R A N D O M I Z E	<p><b><u>Double-Blinded Randomization</u></b></p> <p>Pilocarpine Tablets, 5mg vs. Placebo Tablets</p> <p>Both arms begin 3 days prior to irradiation, one tablet four times a day for three months.* See Section 7.2.</p> <p>Irradiation will be given at 1.8 to 2 Gy once a day <u>or</u> 1.2 Gy b.i.d &gt; 6 hours apart. Total Minimum Dose: 60 Gy over 6-7 weeks.</p> <p>* After three months, all patients will receive non blinded pilocarpine for an additional three months.</p>
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**Eligibility:** (See Section 3.0 for details)

- Confirmed histopathologic diagnosis of oral or oropharyngeal squamous cell carcinoma; metastases to the neck from unknown primary provided the dose to  $\geq 50\%$  of the salivary gland is  $\geq 50$  Gy.
- Karnofsky Performance Score  $\geq 60$
- Age  $\geq 18$
- No prior radiotherapy to the head and neck
- Primary tumor in oral cavity or oropharynx
- No uncontrolled asthma, acute iritis, or narrow angle glaucoma
- Signed study-specific consent form

**Required Sample Size: 244**

**9/8/98  
1/8/99  
4/1/99**

Institution # \_\_\_\_\_  
RTOG 97-09 \_\_\_\_\_  
Case # \_\_\_\_\_

**ELIGIBILITY CHECK (4/1/99)**  
(page 1 of 2)

- \_\_\_\_\_(Y) 1. Histologically confirmed diagnosis of oral cavity and/or oropharyngeal carcinoma or other site as specified in Section 3.1.1?
- \_\_\_\_\_(N) 2. History or presence of salivary gland disease or salivary gland malignancy?
- \_\_\_\_\_(N) 3. Prior irradiation to head or neck area?
- \_\_\_\_\_(Y) 4. Will the planned radiation therapy volume encompass  $\geq 50\%$  of the parotid glands and include an external beam dose of  $\geq 50$  Gy?
- \_\_\_\_\_(N) 5. Any allergy to pilocarpine?
- \_\_\_\_\_(N) 6. Any use of cholinergic drugs, anti-cholinergic drugs and tricyclic drugs?
- \_\_\_\_\_(N/NA) 7. Is the patient pregnant or lactating?
- \_\_\_\_\_(Y/NA) 8. If there is childbearing potential, has the patient agreed to use an effective method of contraception?
- \_\_\_\_\_( $\geq 18$ ) 9. What's the patient's age?
- \_\_\_\_\_( $\geq 60$ ) 10. What is the Karnofsky Performance Score?
- \_\_\_\_\_(N) 11. Does the patient have uncontrolled asthma, acute iritis, or narrow angle glaucoma?

**The following questions will be asked at Randomization:**

- \_\_\_\_\_(Y) 1. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_(Y) 2. Is the patient eligible?
- \_\_\_\_\_ 3. Date the study-specific Consent Form was signed? (*must be prior to randomization*)
- \_\_\_\_\_ Patient's Name
- \_\_\_\_\_ Verifying Physician
- \_\_\_\_\_ Patient ID #
- \_\_\_\_\_ Referring Institution # (*if different*)
- \_\_\_\_\_ Type of RT Fractionation (*standard vs. hyperfractionated*)

(continued on next page)

Institution # \_\_\_\_\_

**RTOG 97-09**

**Case #** \_\_\_\_\_

**ELIGIBILITY CHECK** (4/1/99)

(page 2 of 2)

\_\_\_\_\_ Birthdate  
\_\_\_\_\_ Sex  
\_\_\_\_\_ Race  
\_\_\_\_\_ Social Security Number  
\_\_\_\_\_ Zip Code (*9 digit if available*)  
\_\_\_\_\_ Method of Payment  
\_\_\_\_\_ Will any component of the patient's care be given at a VA or military facility?  
\_\_\_\_\_ Treatment Start Date  
\_\_\_\_\_ Treatment Assignment

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background**

An oral formulation of pilocarpine hydrochloride, a parasympathomimetic drug, has been shown in prospective randomized placebo-controlled clinical trials to increase salivary output and demonstrate significant subjective improvement in oral moisture and oral comfort in head and neck cancer patients following radiation therapy.<sup>1-3</sup> Pilocarpine is a muscarinic agonist that has long been recognized as an effective sialogogue.<sup>4</sup> It has also been shown that preemptive use of oral pilocarpine hydrochloride prior to and concurrent with therapeutic irradiation in head and neck cancer patients may have a positive effect upon retention of a beneficial level of post irradiation salivary function. A preliminary report by workers at the National Institutes of Health demonstrated decreases in salivary hypofunction and symptoms of xerostomia in five patients who were administered oral pilocarpine simultaneously with irradiation for treating head and neck neoplasms.<sup>5</sup> It was postulated that functional stimulation of the salivary glands decreased radiation-induced damage to the glands by decreasing toxic products associated with cell death. The supposition is that partial elimination of oxygen free-radicals, lipid peroxidation and other oxidative debris would, by action of secretagogue-stimulated salivary lavage, decrease exposure of these toxic complexes to the salivary glands and thus afford a level of protection to them. Others have related possible radioprotection to prevention or moderation of radiation-induced apoptotic programming as measured by interactive regulation and expression of genes p53 and bcl-2.<sup>6-10</sup> Based upon the work of ven den Brenk and his co-investigators, one might also infer that prevention of indolent hyperamylasaemia via moderation of amylase degranulation in acinar cells lends partial explanation to the mechanism(s) of salivary gland sheltering and, by means of apoptotic events, a way of verifying these events during irradiation.<sup>11,12</sup> However, at this juncture, there are no broadly identified explanations of exactly what dynamics occur at the cellular level of salivary glands when pilocarpine coerces salivary flow when these glands are in propinquity to a tumor mass designated for curative radiation therapy.

### **1.2 Recent Studies**

LeVeque et al.<sup>13</sup> conducted a phase I pilot study using prophylactic oral pilocarpine tablets (*5 mg/qid*) in 12 head and neck cancer patients about to be treated with curative radiation therapy. To insure reasonable homogeneity among the study group, all patients had to have >50% of their parotid glands within the irradiation field and have >50 Gy delivered to that volume. Data from 10 evaluable patients completing the study (*December 1994-July 1995*) appear to indicate that: 1) The average retention of post-irradiation resting (*unstimulated*) whole saliva was 30% at 30 days and 28% at 45 days while the retention of stimulated whole saliva was 43% and 35%, respectively. 2) Post-irradiation subjective measurements of oral dryness recorded in this study group showed significant improvement over pre-irradiation baseline scores of the patient group enrolled in the pivotal therapeutic trials wherein a minimum of 4 months had to have elapsed from the completion of radiation therapy.<sup>9,10</sup> 3) Although not a study endpoint, oral mucosal changes were assessed during the course of the radiation therapy and it was discovered that there was notably less objective oral/oropharyngeal mucositis and significantly less mucositis-associated pain. 4) Investigators' study notes reported that all of the patients demonstrated an early return to mucosal integrity and moisture, as compared to other matched patients. Later, Zimmerman et al.<sup>14</sup> published a retrospective study comparing head and neck cancer patients who were given pilocarpine concurrently with radiation therapy to patients who were not. The comparisons were made by subjective assessments including oral dryness, oral comfort, ability to have uninterrupted sleep, ability to speak, and in eating. The pilocarpine group attained statistical superiority in all assessment comparisons individually and with the average of the combined assessments ( $p < 0.01$ ).

### **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.<sup>15,16</sup> 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".<sup>17</sup> Since the dimensions of quality of life are subjective, they are best measured from the patient's perspective.<sup>16,18-20</sup>

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 translating into improvement in the quality of life (*e.g., improved appetite, eating, etc.*). In this study the focus will be two-fold: 1) to determine the impact of xerostomia on quality of life for patients receiving irradiation to the head and neck and, 2) the impact of symptom relief with pilocarpine as relates to quality of life.

## **2.0 OBJECTIVES**

- 2.1 To determine if prophylactic use of pilocarpine can shelter unstimulated and stimulated whole salivary flow by objective measurement (*sialometry*).
- 2.2 To determine if prophylactic use of pilocarpine can moderate xerostomia as measured by subjective means.
- 2.3 To determine whether prophylactic use of pilocarpine can reduce the grade and duration of radiation-induced mucositis in the same patient group.
- 2.4 To evaluate quality of life outcomes between patients receiving pilocarpine to patients receiving placebo.
- 2.5 To evaluate the impact of xerostomia on patients receiving irradiation to the head and neck.

## **3.0 PATIENT SELECTION**

### **3.1 Eligibility Criteria (4/1/99)**

- 3.1.1 Confirmed histologically diagnosis of oral cavity and/or oropharyngeal carcinoma. Patients with unknown primary tumor metastatic to the neck, who are treated per Section 6.0 (*treatment field to include  $\geq 50\%$  of salivary gland to a minimum of 50 Gy*) are eligible.
- 3.1.2 Radiation volume to encompass  $\geq 50\%$  of parotid glands and have  $\geq 50$  Gy delivered to that volume via external beam.
- 3.1.3 Karnofsky Performance Score  $\geq 60$  (*Appendix II*).
- 3.1.4 Minimum age for entry, 18 years.
- 3.1.5 The patient must sign a study-specific informed consent prior to study entry (*see Appendix I*).

### **3.2 Ineligibility Criteria (9/8/98, 1/8/99, 4/1/99)**

- 3.2.1 Salivary gland malignancy
- 3.2.2 Salivary gland disease, e.g, Sjögren's syndrome.
- 3.2.3 Use of cholinergic drugs, anti-cholinergic drugs and tricyclic drugs.
- 3.2.4 Pregnant or lactating females are not eligible. Patients of childbearing potential should agree to use an effective method of contraception.
- 3.2.5 Prior head and neck irradiation.
- 3.2.6 Allergy to pilocarpine.
- 3.2.7 Patients with uncontrolled asthma, acute iritis, or narrow angle glaucoma.

## **4.0 PRETREATMENT EVALUATION (4/1/99)**

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

- 4.1.1 Complete history and physical examination
- 4.1.2 Chest radiograph, PA and lateral
- 4.1.3 Diagram of lesion & nodes
- 4.1.4 CT scan of oral cavity/oropharynx with standard slice increments

### **4.2 Mandatory Evaluations (within 4 weeks prior to study entry)**

- 4.2.1 Sialometry measuring unstimulated whole saliva
- 4.2.2 Sialometry measuring stimulated whole saliva
- 4.2.3 Objective, site-specific mucosal assessment
- 4.2.4 Objective mucosal assessment (*RTOG Scale*)
- 4.2.5 Subjective assessment of oral moisture
- 4.2.6 Subjective assessment of oral/oropharyngeal mucosal pain

### **4.3 Other Evaluations (prior to any radiation therapy)**

- 4.3.1 Dental examination (*Appendix VI*). Patients should be advised that good oral hygiene should be well maintained especially during and after radiation therapy.
- 4.3.2 Complete QOL Head and Neck Symptom Questionnaire

## **5.0 REGISTRATION PROCEDURES**

- 5.1 Each institution must submit a Study Agent Shipment Form (*Appendix VIII*) to RTOG Headquarters prior to the randomization of its first case. Allow adequate processing *time (7-10 days)* before calling to register your first case.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. *Online registration by the institution may not be used for this study.* The following information must be provided:
- Institution Name & Number
  - Patient's Name & ID Number
  - Verifying Physician's Name
  - Eligibility Criteria Information
  - Stratification Information
  - Demographic Data
  - Treatment Start Date

## **6.0 RADIATION THERAPY (9/8/98, 4/1/99)**

- 6.1 *Field:* Treatment portals must include > 50% of the oral cavity, oropharynx, or both. This will ensure inclusion of significant portions of the parotid glands so that  $\geq 50\%$  of the parotid glands receive  $\geq 50$  Gy. (*See Appendix VII*)
- 6.2 *Technique:* Salivary glands should be included as part of the treatment field and must be irradiated with opposed photon portals. Wedge-pair techniques that spare mucosa on one side will be excluded except when used to boost the primary tumor.
- 6.2.1 Patients may not be irradiated with homolateral electron beam or wedge-pair techniques.
- 6.3 *Dose:* The dose to  $\geq 50\%$  of the salivary gland should be  $\geq 50$  Gy given over 5 to 5 ½ weeks at 1.8-2 Gy once daily or 1.2 Gy b.i.d. > 6 hours apart, 5 days a week.
- 6.4 *Equipment:* Cobalt-60, 4 to 6 MV x-rays or any combination of these megavoltage beams is acceptable.
- 6.5 *Blocks:* Portal margins may be collimated or shaped using cerrobend blocks.
- 6.6 *Compensating or wedge filters:* Compensating or wedge filters should be used to assure dose homogeneity throughout the irradiated volume that is  $\pm 5\%$  of the central axis dose.
- 6.7 *Dose distribution:* A central axis distribution of radiation dose should be submitted for review.
- 6.8 *Timing with Study Drug:* See Section 7.2.

## **7.0 DRUG THERAPY (DOUBLE-BLINDED)**

### **7.1 Pilocarpine (IND 55,084)**

- Pilocarpine hydrochloride (*proprietary name: Salagen Tablets®*) is a secretagogue that is FDA approved for treating post irradiation xerostomia in head and neck cancer patients. *Salagen Tablets®* that will be used in this study are round small white 5 mg tablets that are stored at room temperature (59-86 °F).
- 7.1.1 *Pharmacokinetics and Metabolism*  
Pilocarpine hydrochloride tablets when ingested have an elimination half-life of 0.76 hours. Metabolism and elimination are thought to occur at neuronal synapses and probably in plasma. Pilocarpine and its degradation products are excreted in the urine.
- 7.1.2 *Pharmacodynamics*  
Pilocarpine is a cholinergic parasympathomimetic agent that can exert a broad spectrum of action with predominant muscarinic action. Pilocarpine causes increased secretion by the exocrine glands including sweat, salivary, lachrymal, gastric, pancreatic, intestinal and mucous cells of the respiratory and other mucosal tracts. Dose related smooth muscle stimulation can also occur. This can affect the intestinal, respiratory and urinary tracts. Ocular increase in parotid flow occurs within twenty minutes of dosing, peaks at one hour, and lasts approximately 3-5 hours. Pilocarpine hydrochloride tablets are contraindicated in patients with uncontrolled asthma and in patients with known sensitivity to pilocarpine.
- 7.1.3 *Reported Side Effects*  
Previous studies<sup>1-3</sup> have shown the more common effects of oral pilocarpine to be: sweating, urinary frequency, rhinitis, flushing, muscle tremors, nausea and vomiting, increased lacrimation and asthenia. No serious adverse experiences have been associated with the use pilocarpine. Pilocarpine should be administered with caution in patients, and under dose medical supervision, with significant cardiovascular disease, controlled asthma, chronic bronchitis, or chronic obstructive pulmonary disease requiring

pharmacotherapy. In addition, the pharmacokinetics of pilocarpine in patients with renal and hepatic disease is unknown.

#### **7.1.4** *Effect of Pilocarpine upon the Cytotoxicity of $\gamma$ -Radiation*<sup>21</sup>

A recent study was performed to determine whether pilocarpine affects the survival of squamous carcinoma cells (*line SCC-25*) following  $\gamma$ -radiation treatment. The survival of SCC-25 cells, after the exposure of cells to pilocarpine at concentration of 0-100 ng/ml given 0-1 hour prior to radiation at dose 0-20 Gy was determined by an *in vitro* colony formation assay. The survival fractions of SCC-25 cells were identical for the control and pilocarpine treated samples at all tested conditions. Calculated  $D_0$  and  $D_q$  values did not depend on the presence of pilocarpine and were not affected by the time of incubation prior to irradiation. The results indicate that pilocarpine at clinically relevant concentrations, given to the SCC-25 cells 1 hour prior or at the time of irradiation did not affect survival of SCC-25 cells *in vitro*. It has been concluded that pilocarpine does not sensitize or protect these tumor cells from the effects of  $\gamma$ -radiation, suggesting that this agent should not compromise the tumoricidal effects of radiotherapy.

#### **7.1.5** *Formulation and Packaging and Storage*

Pilocarpine will be supplied as 5 mg white tablets. Subjects randomized to placebo will receive matched placebo tablets. Pilocarpine and placebo will be provided in bottles of 100 tablets. All packages of pilocarpine and placebo should be stored securely in a dry place at room temperature.

### **7.2** **Doses and Dose Modifications**

**7.2.1** *Dosing Prior to Initiation of First Fraction:* Beginning three days prior to irradiation, patients will be instructed to take one study tablet (*double-blinded active drug or placebo*) by mouth 4 times daily: at meals and before retiring. A study tablet must be taken by the patient 45-60 minutes prior to the start of RT; there should be 3-4 hours between study tablets.

**7.2.2** *Dosing During Course of Irradiation:* In order to effect amylase degranulation at the optimal time, one study tablet should be given 45-60 minutes prior to each fraction during the course of irradiation. In the case of single fractions, the three additional scheduled tablets should be planned from the time of the prefraction dose. For instance, if the prefraction tablet is given at 14:00, the other tablets would likely be given at 10:00, 18:00, and 22:00 hours. In the case of b.i.d. fractions, a tablet should be given 45-60 minutes prior to each fraction, with the remaining two tablets each given approximately 3.5 to 4 hours from the prefraction tablets.

**7.2.3** *Dosing After Completion of Radiation Therapy:* Upon completion of irradiation, patients should return to the original q.i.d. dosing schedule, i.e., at meals and before retiring.

**7.2.4** *Dosing Break at Three Months Post irradiation:* At about 3 months from the start of radiation therapy, patients will stop taking the tablets for 3-4 days. This will allow for multiple half-life passages (*mean elimination half-life for 5 mg pilocarpine = 0.76 hrs.*). After the 3-4 day break, sialometric measurements will be repeated and subjective information will be collected as it was during the active phase of the study.

#### **7.2.5** *Dosing, 3 -6 Months*

After completion of the initial three month period, pilocarpine should be reinstated by physician prescription. Dosing schedules will be defined for each patient individually, based upon need for secretagogue therapy. Pilocarpine administration must be reported on the followup forms as "non-protocol treatment" with start and stop dates as applicable.

#### **7.2.6** *Patient Compliance*

Patients must not miss more than three consecutive days of study drug, nor miss more than 15% of all scheduled doses during the course of irradiation. The pre-fraction pills (*the ones taken 45-60 minutes prior to each fraction*) must not be missed more than three (3) times in conventional fractionation, nor more than six (6) times in b.i.d. fractionation.

#### **7.2.7** *Dose Modification*

During treatment, the daily dose may be reduced from q.i.d. to t.i.d. in order to lessen side effects (*usually sweating*) should that occur. No increase above four tablets per day will be allowed.

#### **7.2.8** *Salagen Information Helpline*

MGI provides an information Helpline for irradiated head and neck patients suffering with dry mouth and their Healthcare providers. Call (800) 644-4811 9:00 a.m. to 8 p.m. ET Monday through Friday. All calls are answered by a registered pharmacist and remain confidential.

### **7.3** **Supplier and Distribution**

**7.3.1** Pilocarpine and placebo for the first three months of this trial will be provided by MGI Pharm, Inc. and distributed by McKesson BioServices. The non blinded administration of pilocarpine for the next three months will be by prescription (*not supplied by MGI or McKesson*).

- 7.3.2** Each institution must submit a Study Agent Shipment Form (*Appendix VIII*) to RTOG Headquarters prior to the randomization of its first case. Allow adequate processing *time (7-10 days)* before calling to register your first case.
- 7.3.3** After randomization, RTOG will provide the double-blinded treatment assignment to McKesson BioServices who will ship four bottles (*100 tablets/bottle*) of Salagen/Placebo to the randomizing institution by second day Federal Express or equivalent service. Study product for randomizations done after 2 p.m. will be shipped the following business day. For example, supplies for a 3 p.m. Friday randomization will be shipped on Monday (*Tuesday, if Monday is a holiday*).
- 7.3.4** Bottles will be numbered with the patient-specific double-blinded number assigned at randomization. The label will include the drug identification number, the RTOG case number, and the daily amount of drug to be taken. A complete protocol treatment course is three months.
- 7.3.5** Each bottle will also include the protocol number, packaging lot number, storage requirements and all necessary information required by Federal Regulations.
- 7.3.6** Study Agent Accountability (4/1/99)  
Patients will be issued diaries to record daily doses. The reporting of drug administration will be based upon pill count. The number of pills dispensed, the number that the patient should have taken during the time period, and the number taken based on the pill count, will be recorded. The remaining pills will be returned to the patient after the pill count is recorded. At the completion of the three month period, all remaining study drug (*and empty bottles*) must be returned for a final count. Diary-indicated pill use and the number of pills the patient should have taken will be compared with the actual remaining pill count. Patients will be asked to bring in their diaries and unused pills. The number of pills dispensed minus the number of pills returned will indicate the number of pills taken. This number should correspond with the diary; however, any discrepancy should be investigated and reviewed with the patient and ultimately with the principal investigator. There will be no combining of study drug used in the first three months with prescribed pilocarpine (*Salagen*) taken after three months. **All unused product must be returned to McKesson BioServices.**

**Att: Product Return/RTOG 97-09**  
**McKesson BioServices Pharmaceutical Services Division**  
**14665 Rothgeb Drive**  
**Rockville, MD 20850**  
**(301) 762-0069**

**7.4 Adverse Drug Reaction Reporting**

- 7.4.1** The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol which uses commercial agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:
- 7.4.1.1** Any ADR which is both serious (*life threatening, fatal*) and unexpected.
- 7.4.1.2** Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.4.1.3** Any death on study if clearly related to the commercial agent(s).
- 7.4.2** The ADR report should be documented on Form FDA 3500 (*Appendix V*) and mailed to the address on the form, to RTOG Headquarters and to:

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

**8.0 SURGERY**

Not applicable to this study.

**9.0 OTHER THERAPY**

Not applicable to this study.

**10.0 PATHOLOGY**

Not applicable to this study.

**11.0 PATIENT ASSESSMENTS**

**11.1 Patient Evaluation (1/8/99)**

<b>Assessment</b>	<b>Pre Rx</b>	<b>During Rx</b>	<b>At Followup See Section 12.1</b>
Complete history, P&E	X		X
KPS and weight	X	X <sup>c</sup>	X
Biopsy	X		X <sup>a</sup>
CT oral cavity/oropharynx	X		
Dental Evaluation	X		
Tumor Diagram	X <sup>b</sup>		
Toxicity Evaluation		X <sup>c</sup>	X
QOL Assessment	X	X <sup>d</sup>	X <sup>e</sup>
Mucosal Assessment	X	X	X
Sialometry	X	X	X
Chest X-ray	X		

- a. for confirmation of recurrent tumor in the head and neck as applicable
- b. as applicable
- c. weekly
- d. week 4 of RT
- e. at 3 and 6 months from start of RT

**11.2 Mucosal Reaction**

**11.2.1** *Objective Scoring:* Visual signs of radiation mucositis will be independently assessed three times a week by the radiation oncologist using the RTOG and the protocol-specific scoring system. Separate assessments of those areas being irradiated, the pharyngeal wall, palate, buccal mucosa and lateral margin of the tongue will be made.

Acute Effects of Radiation

Grade	Signs
0	No reaction
1	injection ( <i>erythema</i> ), mild pain, no analgesics
2	patchy mucositis, moderate pain, ± analgesics
3	confluent mucositis, severe pain, ± narcotics
4	ulceration, hemorrhage, necrosis

**11.3 Objective Assessments, Sialometry**

**11.3.1** *Unstimulated Whole Saliva*

During all collections, patients should be seated with eyes open and head tilted slightly forward and should be instructed to minimize orofacial movements and not to attempt to influence salivary flow (*such as by sucking or swallowing*). Just before the collection, the patient should be instructed to swallow. He/she should then be instructed to allow saliva to accumulate in the floor of the mouth for 60 seconds without swallowing. The patient should then spit the accumulated saliva into a pre-weighed 50 mL vial. The patient should repeat this procedure 4 more times for a total collection time of 5 minutes. Subjects should be instructed not to swallow during the entire collection procedure. These assessments will be made before initiation of the first radiation fraction, at the end of radiation therapy (< 10 days) and at approximately 3 and 6 months from start of irradiation.

**11.3.2** *Stimulated Whole Saliva (9/8/98)*

To effect stimulation of salivary flow, two distinct methods are commonly used. One method uses an inert gum base to facilitate mechanical stimulation by the act of chewing at a measured pace over a set period of time. The other method relies upon gustatory stimulation. Both methods have been validated, however, the gustatory method will be used for this study as mechanical stimulation would not be comparable in dentate vs. recently edentulous patients. The technique used for gustatory stimulation relies upon use of a 2% citrate solution applied to the dorso-lateral borders of the tongue in the following manner: Patients

will first empty their mouths of any saliva or mucous. It may be necessary to use a 4x4 sponge to aid in the removal of viscous material. Patients will then have 2% citrate solution applied, with cotton tipped applicators, to the lateral tongue bilaterally 5 times over a two minute period (0, 30, 60, 90 and 120 seconds). The mouth should then be emptied of retained citrate solution. Saliva should then be collected for 5 minutes. These assessments will be the same as for unstimulated saliva.

#### **11.4 Objective Assessments, Mucosa**

The oral/oropharyngeal mucosa will be assessed prior to the first radiation fraction. The baseline examination of the mucosa can be performed anytime from 10 days prior to the first day of radiation therapy. The mucosal examination will follow the RTOG format and a wholly objective site-specific grid. However, at baseline, any mucosal aberrations should be noted. These would include residual processes of healing from ablative surgery, areas of erythema, aphthous ulcerations, etc.

The grading of mucosal changes (*mucositis*) occurring during the course of irradiation will be performed thrice weekly (*Monday, Wednesday and Friday*). RTOG and oral mucosal site-specific tools will be used. It is imperative that some degree of consistency be maintained in the use of these tools. Although it is not always possible to have the same examiner throughout the course of radiation therapy, it would be optimal to have personnel at each site calibrated to the intended specifics of the RTOG and site-specific gradations of mucositis.

#### **11.5 Quality of Life**

**11.5.1** A patient self-assessed questionnaire has been selected. 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, week 4 during RT and at 3 and 6 months from start of RT.

**11.5.2.1** The questionnaire was developed by Hassan and Weymuller of the University of Washington, Seattle.<sup>22</sup> 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 the U of W HNSS tool to be equivalent to the Karnofsky and SIP for reliability, responsiveness, and was preferred test format for 97% of the tested patients. The scores on the HNSS correlated well with KPS and SIP indicating validity. The test-retest reliability coefficient was 0.95.

**11.5.2.2** The selection of the U of W QOL tool is for its reference to specific symptom related effects (*saliva, eating, taste, swallowing, pain*) of the intervention of oral pilocarpine. The scale consists of ten symptom-specific categories each describes important daily living dysfunctions/limitations of head and neck cancer and the treatment outlined for this study. 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 then adjusted to obtain the final range from 0 to 100. The higher the score, the greater the QOL, and conversely, the lower the score, the lower the QOL.

## **12.0 DATA COLLECTION**

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

### **12.1 Summary of Data Submission**

<u>Item</u>	<u>Due</u>
Demographic Forms (A5)	Within 2 wks of study entry
Initial Evaluation Form (I1)	
Diagnostic Pathology Report (P1)	
Primary Site Staging Worksheet (I6)	
Nodal Site Staging Worksheet (I7)	
Pretreatment Symptom Scale Questionnaire (QL)	
<u>Preliminary Dosimetry Information</u>	Within 1 wk of start of RT
Protocol Treatment Form ( <i>RT Prescription</i> ) (T2)	
Films ( <i>simulation and portal</i> ) (T3)	
Calculations (T4)	
Radiotherapy Form (T1)	Within 1 wk after end of RT
<u>Final Dosimetry Information</u>	

Daily Treatment record (T5)  
 Isodose Distribution (T6)  
 Boost Films (*simulation and portal*) (T8)

Sialometric Data Form (L4)  
 Diary (DP)  
 Tissue Reaction Form (F2)  
 (*must include pretreatment baseline assessments*)  
 Study Specific Flowsheet (SF)

Within 2 wks after completion or termination Patient  
 of RT, and at 13 and 26 wks

Followup Symptom Scale Questionnaire (SS)

At 4, 13 and 26 wks from start of RT

Follow-up Form (F1)

At 13 and 26 wks from start of RT

### **13.0 STATISTICAL CONSIDERATIONS**

#### **13.1 Study Endpoints**

- 13.1.1 The primary endpoint of this trial is the acute salivary gland toxicity.
- 13.1.2 This study will examine the acute mucositis in the pharynx, palate, tongue, or buccal.
- 13.1.3 Quality of life as measured using the University of Washington Head and Neck Symptom questionnaire.
- 13.1.4 This study will determine effects of continuing pilocarpine out to six months from start of treatment.

#### **13.2 Sample Size**

##### **13.2.1 Mucositis Endpoint**

The primary endpoint of this trial is the incidence of acute radiation salivary gland toxicity. RTOG 85-27 was a randomized phase III head and neck study where patients on the standard arm were treated with radiation therapy alone. The incidence of acute radiation salivary gland toxicity was:

Grade of Salivary Gland Toxicity			
0	1	2	3-4
19%	35%	46%	<1%

Toxicity data is ordered categorical, and Whitehead's sample size formula for this type of data was employed.<sup>23</sup> Assuming that the application of pilocarpine during and post radiotherapy reduces the incidence of grade 2 or worse salivary gland toxicity by 40%, we can estimate all probabilities as follows:

Estimated Incidence on the Pilocarpine Arm Grade of Salivary Gland Toxicity		
0	1	2
34%	38%	28%

Setting the significance level at 95% and statistical power at 90% the estimated sample size is 233 patients. In order to ensure the required sample size is analyzable an additional five percent will be required to adjust for ineligible and unanalyzable (*patients with no data submitted*) cases. Therefore, 122 cases per arm will be required or **a total of 244 randomized patients**. This sample size will ensure an 90% ( $\alpha = 0.10$ , *type II error*) probability of detecting a 40% decrease in acute salivary gland toxicity while rejecting the null hypothesis at the 95% level ( $\alpha = 0.05$ , *two-sided type I error*).

##### **13.2.2 Mucositis Endpoint**

The secondary endpoint of this trial is the incidence of acute radiation mucositis. In RTOG 85-27 the incidence of acute radiation mucositis was:

Grade of Mucositis				
0	1	2	3	4
14%	22%	45%	18%	1%

This is the worst severity observed in either the pharynx, palate, tongue, or buccal within 90 days from the start of radiotherapy. Assuming that the application of pilocarpine during and post radiotherapy reduces the incidence of grade 3 and 4 mucositis by 40%, we can estimate all probabilities as follows:

Estimated Incidence on the Pilocarpine Arm				
Grade of Mucositis				
0	1	2	3	4
31%	21%	37%	11%	0%

Setting the significance level at 95% and statistical power at 80% the estimated sample size is 200 patients. This is within the sample size required for the primary endpoint.

**13.2.3** Quality of Life Endpoint

The possible benefit of pilocarpine is the reduction of salivary gland, and possibly mucositis toxicity; however, what value is this to the patient? Another endpoint of this trial is assessing the difference in quality of life between patients randomized to the two treatments. The University of Washington Head and Neck Symptom questionnaire summary score (*HNSS*) will be the primary variables of interest in assessing quality of life. With 233 evaluable patients there will be greater than 90% power to detect a difference of 10 in the average quality of life at the end of radiotherapy between the two treatments adjusted for their baseline value.

**13.2.4** Patient Accrual

The following table displays the length of time necessary to accrue 244 patients given different average monthly accruals.

Average Monthly Accrual Time to Accrue 244 Patients

12.0	1.7 years
11.0	1.8 years
10.0	2.1 years
9.0	2.3 years

The average monthly accrual is expected to be 10 patients per month, thus it will take 2.1 years to complete the accrual phase of this study. However, if the monthly accrual is less than 5 patients per month the feasibility will be re-evaluated.

**13.2.5** Randomization Scheme

The treatment allocation will be done using a randomized permuted block within strata to balance patient factors other than institution. There will be a check on the balance of treatment assignments within each institution. Patients will be assigned with equal probability to each treatment by the RTOG.

**13.2.6** Inclusion of Women and Minorities

In conformance with the National Institute of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research, we make the following observations. The recursive partitioning analysis of the RTOG database for patients entered into operable head and neck trials failed to show any treatment interaction with gender.<sup>24</sup> Analysis of the operable Intergroup study 0034 and RTOG 88-24 also failed to show a treatment interaction with gender.<sup>25</sup> No information about race was collected in the RTOG Registry study and treatment studies prior to 1990. The SEER data suggest a difference in outcome by for patients treated for laryngeal cancer at a single institution was reported.<sup>26</sup> The RTOG Special Population Committee is unaware of any other published data on patients with clinically localized head and neck cancer. Since there are no publications found to support a possible interaction between different radiation therapy schedules and either gender or race, the sample size will remain the same. The participation rates of minority participation are estimated below.

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total

Female	0	1	7	2	38	0	48
Male	0	2	40	13	140	1	196
Unknown							
Total	0	3	47	15	178	1	244

### 13.3 Analysis Plans

#### 13.3.1 Interim Analyses of Accrual and Toxicity Data

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with projected completion date for the accrual phase;
- b) the distribution of patients with respect to pretreatment characteristics;
- c) compliance rate of treatment delivery with respect to the protocol prescription;
- d) the frequency and severity of the toxicities not separated by treatment arm.

#### 13.3.2 Interim Analyses of Primary Study Points

There will be three interim analyses of acute radiation salivary gland and mucositis toxicity. The interim analyses will proceed according to the table below after all patients have been followed for three months. All endpoints will be tested independently at these significance levels.

<u>Total Accrual</u>	<u>Significance Level</u>
25%	0.003
50%	0.004
75%	0.0049
100%	0.046 ( <i>final analysis</i> )

If any of the interim analyses exceed the listed significance level, which were calculated to ensure an overall significance level of 0.05, then accrual will be terminated. The results of these interim analyses will be reported in a blinded fashion, only to the RTOG data monitoring committee as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the data monitoring committee, not results, will be reported to the head and neck committee, which responsible for this study and, if necessary, the CCOP and RTOG executive committees, so that corrective action can be taken.

#### 13.3.3 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken when every patient has been potentially followed for a minimum of six months. The usual components of this analysis are:

- a) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
- b) reporting institutional accrual;
- c) distribution of the important prognostic factors by assigned treatment;
- d) observed results with respect to the study endpoints.

The two-sided p-value of 0.046 will be used for comparing treatment arms, thus correcting for previous interim tests.

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## APPENDIX I

### RTOG 97-09

#### **A PHASE III STUDY TO TEST THE EFFICACY OF THE PROPHYLACTIC USE OF ORAL PILOCARPINE TO REDUCE HYPOSALIVATION AND MUCOSITIS ASSOCIATED WITH CURATIVE RADIATION THERAPY IN HEAD AND NECK CANCER PATIENTS**

##### **Sample Patient Consent Form**

### RESEARCH STUDY

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

### PURPOSE OF THE STUDY

I have been diagnosed with cancer of the head and neck area. Radiation therapy has been recommended to treat this disease. Radiation therapy is a form of cancer treatment using high energy x-rays. The method of giving the radiation therapy has been discussed with me by my radiation oncologist.

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 (*caused by irradiated salivary gland*) after radiation therapy, it might be better to protect the salivary glands during the radiation. Another side effect of radiation therapy given to the head and neck region is 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. Previous, but as yet unproved, studies have shown that both dry mouth and radiation mucositis may be lessened by taking pilocarpine hydrochloride pills just before and during the radiation therapy. So far, pilocarpine hydrochloride (*Salagen*) is an approved drug for treating dry mouth after radiation therapy to the head and neck. This study will see whether oral pilocarpine for three months, including during radiation, will be able to: 1) reduce the expected radiation mucositis and, 2) preserve oral moisture by protecting the salivary glands during the radiation therapy. In addition, this study will attempt to see how I see the quality of my life before treatment, during treatment, at the end of treatment and at intervals after completion of my treatment.

### DESCRIPTION OF PROCEDURES

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

- If I am assigned to this group, I will receive pilocarpine tablets 4 times a day beginning three days before radiation therapy and continuing regularly for three months. Three days after I start the pills, I will start radiation treatments once or twice a day, five days a week for 6-7 weeks. My physician will decide on whether I get the once a day or twice a day schedule before I begin radiation treatments. At the three month time point, I will be asked to continue with pilocarpine for an additional three months. The pharmaceutical company will provide the pills for the first three months at no cost to me. The second three months will be by prescription at either my expense or my insurance company's expense.
- If I am assigned to this group, I will receive a placebo (*a non-active tablet*) 4 times a day beginning three days before radiation therapy, and continuing regularly for three months. Three days after I start the pills, I will start radiation treatments once or twice a day, five days a week for 6-7 weeks. My physician will decide on whether I get the once a day or twice a day schedule before I begin radiation treatments. At the three month time point, I

will be asked to start taking pilocarpine (*not more placebo*) for an additional three months. The pharmaceutical company will provide the pills for the first three months at no cost to me. The second three months will be by prescription at either my or my insurance company's expense.

### Study Evaluations

#### Salivary Flow

I will have my salivary flow measured before the first radiation therapy treatment, and within 10 days after completion of radiation therapy. It will also be measured at three and six months from the start of treatment. Salivary flow will be measured in two ways, unstimulated and stimulated. Unstimulated salivary flow samples are collected by emptying my mouth of saliva into a tube over a 5 minute period. Stimulated salivary flow samples are taken after a citrate solution on a cotton swab is rubbed on my tongue.

#### Oral Moisture

I will check my normal mouth moisture a few days before the first radiation treatment and during the radiation therapy. During the radiation, I will check for oral moisture three times a week using a diary that I will keep throughout the treatment. I will return the diary to the research staff at the end of my radiation. At approximately 3 and 6 months, I'll check my oral moisture again.

#### Mucositis Grading

The lining of my mouth, lips, cheeks, tongue, palate, gum and denture-bearing areas will be examined by my physician or one of his/her research staff. They will check me before the first radiation treatment and then three times a week throughout the radiation therapy. After completion of the therapy, I will be examined again by the research staff with a bright penlight. Changes noted will be marked on a scoring sheet.

#### Mucositis Pain

Just as I checked my mouth moisture, I will also measure mouth pain when at rest and while speaking or eating. This will be done before, during and after radiation therapy also by use of a diary.

### **RISKS AND DISCOMFORTS**

Drugs often have side effects. The drug used in this study, pilocarpine hydrochloride tablets, is a Food and Drug Administration (*FDA*)-approved agent for treating dry mouth caused with radiation therapy. It has been used after radiation treatments to the head and neck cancer are finished. It is marketed as *Salagen*. Not all of the side effects of this drug are known. Previous studies have shown the more common side effects to be sweating, watery eyes, urinary frequency, increased heart rate, muscle shaking, blurred vision, runny nose, dizziness, flushing, chills and tiredness. My physician will be checking me closely to see if any of these side effects are occurring. My physician will also be checking me closely if I have significant cardiovascular or lung disease treated with medication. The effect of *Salagen* in patients with liver or kidney disease is not known. Patients who have taken *Salagen* for long periods have tolerated its use well. This institution is not financially responsible for treatments of side effects caused by the study treatment.

There may be laboratory testing and procedures required by this study for research purposes. These additional tests may increase my medical bills although the impact will depend on my insurance company.

### **CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be paid for medical care other than what my insurance carrier may provide. I will not receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. \_\_\_\_\_ the investigator in charge at \_\_\_\_\_.

\_\_\_\_\_. In addition, I may contact \_\_\_\_\_ at \_\_\_\_\_.

for information regarding patients' rights in research studies.

**BENEFITS**

The treatment I am being offered has been established as safe and effective for stimulating salivary flow after radiation treatment for head and neck cancer. I may benefit by having some of my salivary gland tissue protected during radiation therapy. This may reduce my need for medication after radiation. I might also benefit by having less mucositis pain with radiation. This would allow me to continue the radiation more comfortably and without delays.

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

**ALTERNATIVES**

There are no other proven treatments for protecting salivary function and/or preventing or lessening the mucositis associated with irradiation to the head and neck region. The pain of mucositis can be somewhat controlled by use of pain control medications. On occasion, if the mucositis becomes unbearable, my physician may stop the radiation for a few to several days to allow some mucosal healing.

I have been told that I should feel free to discuss my disease and my outcome with the doctor. The physician involved in my care will be available to answer any questions I have. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

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

**VOLUNTARY PARTICIPATION**

Participation in this study is voluntary. No compensation for participation other than free tablets for three months will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time. Refusal to participate will involve no penalty or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

**CONFIDENTIALITY**

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

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

\_\_\_\_\_  
Patient Signature (or Legal Representative)

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

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

## APPENDIX III

### AJCC STAGING HEAD & NECK, 1997

#### STAGING-PRIMARY TUMOR (T)

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

#### ORAL CAVITY

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

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

#### PHARYNX

##### **Nasopharynx**

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

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

##### **Oropharynx**

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

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

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

### **Hypopharynx**

Pyramidal fossae  
Postcricoid region  
Lateral and posterior hypopharyngeal walls

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

## **LARYNX**

### **Supraglottis**

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

- T1 Tumor limited to one subsite of supraglottis with normal vocal cord mobility  
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (*e.g., mucosa of base of tongue, vallecula, medial wall of 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.  
T4 Tumor extends through the thyroid cartilage, and/or extends into soft tissues of the neck, thyroid and/or esophagus.

### **Glottis**

True vocal cords including anterior and posterior commissures

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

### **Subglottis**

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

**REGIONAL LYMPH NODES (N) Excluding Nasopharynx**

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

**REGIONAL LYMPH NODES (N) Nasopharynx Only**

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

**DISTANT METASTASIS (M)**

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

**STAGE GROUPING Excluding Nasopharynx**

Stage 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	T4, N0-1, M0 Any T, N2, M0
Stage IVB	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

### ADVERSE EVENT REPORTING GUIDELINES

#### A. GENERAL GUIDELINES

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

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

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

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

#### B. RADIATION TOXICITY GUIDELINES

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

## C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

### Commercial and Non-Investigational Agents

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

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

### Investigational Agents

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

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

#### i. Phase I Studies Utilizing Investigational Agents

- |  |  |
|--|--|
| - All deaths during therapy with the agent.              | Report <b>by phone</b> within 24 hours to IDB and RTOG Headquarters.<br>**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above   |

- All life threatening (*grade 4*) events which may be due to agent. As above
  - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **\*\*A written report may be required.**
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours **\*\*A written report must be sent to RTOG within working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)**
  - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **\*\*A written report to follow within 10 working days.**
  - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. **\*\*Report in writing** to RTOG Headquarters and IDB within 10 working days.

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

## **APPENDIX VI**

### **Dental Evaluations**

#### **Dental Care for Irradiated Patients**

Goals for a dental care program include:

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

#### **Preirradiation Care and Procedures**

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

##### **Group 1**

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

##### **Group 2**

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

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

##### **Group 3**

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

##### **Group 4**

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

#### **Extraction of Teeth**

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

#### **Causative Factors**

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

### **Preventive Program**

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of fluoride carriers, custom-made mouth guards which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded 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 VII**

**SAMPLE PORTAL DIAGRAMS**

**APPENDIX VIII (4/1/99)**

**RTOG 97-09**

**SALAGEN® (pilocarpine)/PLACEBO SHIPMENT FORM**

Double-blinded pilocarpine/placebo will be shipped only to institutions who have identified a single individual associated with the investigational drug unit of the institution. This form must be completed and returned to RTOG Headquarters prior to registering any patients on study. Allow adequate processing time (*7-10 days*) before calling to randomize your first patient.

**SHIP TO:**

Name: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone: \_\_\_\_\_

Fax#: \_\_\_\_\_

RTOG Institution#: \_\_\_\_\_

Institution Name: \_\_\_\_\_

IRB Approval Date: \_\_\_\_\_

Investigator (*PI*) Signature \_\_\_\_\_ Date: \_\_\_\_\_

Investigator Name (*Print*) \_\_\_\_\_

Investigator NCI # \_\_\_\_\_

*Send Completed Form to:*

*RTOG Headquarters  
1101 Market Street  
Philadelphia, PA 19107*

**ATTN: ELAINE PAKURIS  
FAX# 215/574-0300**

RTOG Headquarters Approval \_\_\_\_\_ Date: \_\_\_\_\_