

**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 96-10**

**PHASE I/II STUDY OF CONCOMITANT RE-IRRADIATION,  
HYDROXYUREA AND 5-FLUOROURACIL IN PATIENTS WITH  
RECURRENT SQUAMOUS CELL CANCER OF THE HEAD AND NECK**

**Study Chairmen**

Medical Oncology                      Richard H. Wheeler, M.D.  
Mayo Clinic-Scottsdale  
13400 East Shea Boulevard  
Scottsdale, AZ 85259  
(602) 301-5380  
FAX # (602) 301-8572

Radiation Oncology                      Sharon Spencer, M.D.  
(205) 934-5670  
FAX# (205) 975-6161

Activation Date:                      August 16, 1996

**Current Edition:                      September 8, 1998  
Includes Revision 1**

This protocol was designed and developed by the Radiation Therapy Oncology Group (*RTOG*) of the American College of Radiology (*ACR*). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

## INDEX

Schema

Eligibility Check

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluations
- 5.0 Registration Procedures
- 6.0 Radiation Therapy
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Pathology
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Form
- Appendix II - Karnofsky Performance Status
- Appendix III - Staging System
- Appendix IV - Toxicity Criteria
- Appendix V - Adverse Reaction Reporting Guidelines

## RADIATION THERAPY ONCOLOGY GROUP

### RTOG 96-10

#### PHASE I/II STUDY OF CONCOMITANT HYDROXYUREA, 5-FLUOROURACIL AND RE-IRRADIATION IN PATIENTS WITH RECURRENT SQUAMOUS CELL CANCER OF THE HEAD AND NECK

##### SCHEMA

R

E

G

I

Radiation Therapy + Hydroxyurea + 5-Fluorouracil

S

Weeks 1, 3, 5, 7

T

E

R

##### Radiation Therapy

60 Gy total dose, 1.5 Gy/fraction twice daily (6 hours between fractions)/5 days on weeks 1, 3, 5, and 7.  
Treatment must begin on a Monday

##### Chemotherapy

HU 1.5 gm orally 2 hours prior to second daily RT dose.  
5-FU 300 mg/m<sup>2</sup> IV bolus 30 minutes prior to second daily RT dose.

##### Eligibility: (See Section 3.0 for details)

- Recurrent squamous cell cancer from a primary in the head and neck (*excluding the nasopharynx and salivary gland tumors*) or second primary within a previously irradiated field.
- Uni- or bi-dimensionally measurable tumor confined to the head and neck with no distant metastases.
- The patient is not a candidate for complete surgical resection.
- The majority of the tumor volume (75%) must have been previously treated to  $\geq 45$  Gy and  $\leq 75$  Gy that was completed at least 6 months prior to disease recurrence.
- The entire tumor volume can be included in a treatment field without exceeding total spinal cord dose (*previous and planned treatments*) of 50 Gy.
- KPS  $\geq 60$ .
- WBC  $\geq 4000/\text{mm}^3$ , granulocytes  $\geq 2000/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$ , bilirubin,  $\leq 1.5$  mg/dl, creatinine,  $\leq 1.8$  mg/dl.
- Radiation records, including simulation and portal films, from the primary (*previous*) course of treatment must be submitted to RTOG
- Study-specific consent form

**Required Sample Size: 82**

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

RTOG 96-10

**ELIGIBILITY CHECK (9/8/98)**

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

(page 1 of 2)

- \_\_\_\_\_(Y) 1. Does the patient have recurrent or second primary tumor of the upper aerodigestive tract which is in an area that has been previously irradiated?
- \_\_\_\_\_(Y) 2. Has the recurrence been pathologically confirmed and found to be squamous cell carcinoma?
- \_\_\_\_\_(Y) 3. Did the first recurrence occur  $\geq 6$  months following radiotherapy?
- \_\_\_\_\_(N) 4. Is the primary site (*initial or current site*) a nasopharynx or salivary gland tumor?
- \_\_\_\_\_(Y) 5. Is the tumor measurable?
- \_\_\_\_\_(Y) 6. Is the recurrence confined to the head and neck area superior to the clavicles?
- \_\_\_\_\_(N) 7. Any evidence of distant metastases?
- \_\_\_\_\_(N) 8. Is the patient a candidate for complete surgical resection?
- \_\_\_\_\_(Y) 9. Has 75% or more of the current tumor area been previously irradiated to a minimum of 45 Gy and not more than 75 Gy?
- \_\_\_\_\_(Y) 10. Can the entire tumor volume be included in treatment fields that will limit the total spinal cord dose from all courses (*previous and current*) to  $\leq 50$  Gy?
- \_\_\_\_\_(N) 11. Any intercurrent medical condition that will impair patient's tolerance of treatment or limit survival?
- \_\_\_\_\_(N) 12. Has the patient received any chemotherapy for recurrent tumor?
- \_\_\_\_\_(N) 13. Any chemotherapy or radiation therapy within 6 months of the currently planned treatment?
- \_\_\_\_\_( $\geq 18$ ) 14. What is the patient's age?
- \_\_\_\_\_( $\geq 60$ ) 15. What is the patient's Karnofsky Performance Status?
- \_\_\_\_\_( $\geq 4$ ) 16. What is the white blood count(*mm3*) per 1000?
- \_\_\_\_\_( $\geq 2$ ) 17. What is the granulocyte count (*mm3*) per 1000?
- \_\_\_\_\_( $\geq 100$ ) 18. What is the platelet count (*mm3*) per 1000?
- \_\_\_\_\_( $\leq 1.5$ ) 19. What is the serum bilirubin (*mg/dl*)?

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



## **1.0 INTRODUCTION**

### **1.1 Recurrent Head and Neck Cancer**

Local failure after curative intent radiation therapy alone or in combination with surgery and/or chemotherapy is still a significant problem, especially in advanced stage head and neck cancer.<sup>1</sup> Fifty to 60% of patients will die as a direct consequence of locally recurrent disease.<sup>2</sup> Surgical salvage is sometimes successful, but not always feasible due to disease extent or involvement of critical structures.

Chemotherapy is widely used for palliation of patients with recurrent, unresectable head and neck cancers and generally produces a less than 50% response rate and a median survival of 5-6 months.<sup>3</sup> Even best results reported from single institution trials report a complete response rate of 27% and a median survival of eight months.<sup>4</sup> Clearly new approaches need to be evaluated in this poor prognostic patient population.

### **1.2 Re-irradiation in Recurrent Head and Neck Cancer**

Re-irradiation, except for nasopharyngeal carcinoma, has not been used frequently in the past due to previous high radiation dosage and concern for limited tissue tolerance.<sup>5</sup> However, local control rates up to 50% and a five-year survival of 20% are reported with external beam re-irradiation.<sup>6-9</sup> Interstitial implantation also has been used for salvage treatment of recurrences at the primary site or in the neck with 40-60% local control and a 14% five-year survival.<sup>10-13</sup> Hyperthermia has been added to interstitial or external modalities resulting in 40-70% complete responses.<sup>14-16</sup> Unfortunately, the size and location of most recurrences does not allow the optimal use of interstitial therapy or hyperthermia.

Preclinical studies have attempted to evaluate normal tissue tolerance to repeated doses of radiation. It has estimated that the amount of dose which can be given ranges from 0-40% of the initial dose.<sup>7</sup> However, there is also evidence that soft tissue can tolerate a repeat dose as high as approximately 90% of the original dose if the second treatment is applied six weeks to ten months after the first.<sup>17</sup> Other studies suggest that tolerance depends upon whether early or late reactions are being assessed. Tolerance is also dependent upon fraction size. The dose compensation factor for the previous irradiation varied for 6-10% for prediction of acute reactions and from 21-38% to estimate late toxicity.<sup>18,19</sup>

The incidence of tissue necrosis following repeat irradiation varies from 0-40%.<sup>7-10,19-22</sup> The dose used have ranged from 35 Gy to greater than 65 Gy, with the dose per fraction varying from 1.80 Gy to 2.40 Gy. Most authors conclude that doses of greater than 50 Gy are necessary to yield substantial response rates. Langlois demonstrated that a reduction in the size of the re-irradiated volume decreases the probability of complications.<sup>7</sup> Re-irradiation fields greater than 70 cm<sup>2</sup> correlated with increased frequency of complications. Radiation myelitis is a major complication which must be avoided. Recent studies emphasize that fraction size as well as total dose is important in predicting the probability of the development of myelitis. If fraction sizes are kept at 1.8 - 2.0 Gy per fraction, the risk of myelitis should be less than 6%.<sup>23</sup> Total re-irradiation doses of 60 Gy or greater have been given with acceptable late toxicity rates of 25% or less.<sup>10,11</sup>

### **1.3 Chemoradiotherapy for Recurrent Head and Neck Cancer**

In an attempt to improve local control and palliation for patients with recurrent head and neck cancer after previous full dose radiation therapy, an outpatient treatment regimen incorporating 5-fluorouracil (5-FU) and hydroxyurea (HU) with radiation has been used at the University of Alabama at Birmingham. 5-FU has single agent activity against head and neck cancer and is a radiation sensitizer;<sup>24-26</sup> HU also has some single agent activity in head and neck cancer and is also a radiation sensitizer;<sup>27-29</sup> HU may biochemically modulate 5-FU activity by depleting cellular deoxyuridine monophosphate (*dUMP*), thus facilitating the competitive binding of the active 5-FU metabolite, 5-fluorodeoxyuridine monophosphate (*5-FdUMP*), to the target enzyme thymidylate synthase.<sup>30-32</sup> Vokes et al. have employed a similar approach using infusional 5-FU and HU which have shown encouraging results but with substantial local toxicity with a high rate of complete and overall response and a 24% long-term disease-free survival has also been reported with concomitant cisplatin, 5-FU infusion and re-irradiation.<sup>32,33</sup>

To provide optimal radiation-chemotherapy interaction, both modalities should be given concomitantly, usually necessitating a split in the radiation therapy regimen. Although single modality split course radiation therapy is reported to be inferior to continuous course radiation therapy<sup>34,35</sup> due to prolongation

of overall treatment time and accelerated repopulation,<sup>31-36</sup> improved local control and survival has been reported with split course radiation therapy and the addition of concomitant chemotherapy.<sup>32,37-39</sup>

In the UAB series, thirty-five patients with recurrent head and neck cancer, a Karnofsky performance status of a least 50, who had received prior curative intent radiation therapy, including the site of failure, have been treated. The median age was 63 years (*range 42 to 76; 28 were male and seven were female*). The mean performance status at the beginning of treatment was 60 (*range 50 to 90*). The mean prior radiation dose to the site of recurrence was 62.8 Gy. Fourteen patients had previous chemotherapy, seven as part of their primary management, six as treatment for recurrent disease, and one in both settings. Three patients had metastatic disease outside the head and neck area. Median time from previous radiation to retreatment was 24 months (*range 7 to 144 months*).

Three dose variations were examined. In all regimens, treatment was given on weeks 1, 3, 5, and 7 with no therapy on weeks 2, 4 and 6. The initial eleven patients received HU 2 g by mouth 2 hours before, and 5-FU 300 mg/m<sup>2</sup> IV bolus 20 to 30 minutes before, single daily fraction (*2.0 Gy/fraction, 40 Gy total dose*) radiation therapy. The single radiation dose was 2 Gy per treatment. Significant myelosuppression was encountered in these patients, but no dose-limiting in field toxicity. The schedule was then modified for the next nine patients. Radiation therapy was given twice per day at 1.2 Gy per fractions, 6 hours apart to a total dose of 48 Gy. The dose for HU was reduced to 1.5 g. Hematologic tolerance was much improved and again severe radiation toxicity was not deserved. For the last fifteen patients, the radiation dose was increased to 1.5 Gy per fraction bid, 6 hours apart to a total dose of 60 Gy. The HU and 5-FU dose remained as per the second modification. Both 5-FU and HU were timed in respect to the afternoon radiation therapy. Radiation therapy was given based on a treatment planning CT scan with the goal to treat all know disease with a 2 cm margin. The preliminary results of this trial have been published and presented.<sup>40,41</sup> A final summary is in preparation.

Twenty-six patients (69%) completed all four planned courses of combined therapy. One patient completed all courses of radiation but received only one course of chemotherapy. This patient had hepatic insufficiency unrelated to his malignancy or therapy. Three patients did not receive the fourth week of treatment because of persistent neutropenia, and one patient did not complete the fourth week because of persistent diarrhea. Four deaths occurred during treatment. Two patients expired after three courses of treatment, one with neutropenia and secondary sepsis, and a secondary with aspiration pneumonia. The third patient died secondary to carotid artery rupture. The fourth patient expired on the third day of treatment with no evidence of toxicity.

There were three grade 4 and one grade 5 hematologic toxicities all in regimens 1 and 2. The skin and mucosal toxicities were acceptable in all three regimens with no grade 4 or 5 toxicities noted. Seventeen patients lived  $\geq 12$  months, four of whom have developed late complications. One patient developed TIA-like symptoms  $\geq 2$  years post re-treatment. It was not clear if the symptoms were secondary to perturbation of blood flow as a result of radiation fibrosis. Two patients developed esophageal strictures. The stricture in one patient was clearly out of the re-irradiate volume. This patient did, however, develop significant fibrosis of the tongue and required a gastrostomy. He died with widely metastatic lung cancer. The stricture in the second patient was located in the surgically reconstructed cervical esophagus which was within the re-irradiated volume. He, likewise, required feeding tube placement and died with progressive local disease noted at the level of stricture formation. The fourth patient developed trismus one year after re-treatment. He had received a surgical resection of recurrent disease 21 months prior to re-irradiation. The TMJ was within the re-irradiation volume. He is currently gastrostomy-dependent. The acute and late infield toxicities were not different in the three treatment groups.

Fifteen patients had a complete response. Eleven patients had a partial response. Nine patients, including the four who died during treatment are considered non-responders. The overall median survival was 10.5 months. There was no statistical difference in the median survival among the three regimens. The median survival was 12.5, 8 and 9.5 months for regimens 1, 2 and 3, respectively. Patients who had complete responses had a longer median survival compared to those who had partial responses or no response. Patients who received their initial course of radiation 24 months or more prior to the repeat course had a median survival of 15 months versus 6.5 months in patients who were retreated within one year of their initial therapy.

#### **1.4 Rationale for the Proposed Study**

The response rate of 72% (43% CR and 29% PR) and median survival of 10.5 months in patients with recurrent head and neck cancer who were all pretreated appears higher than usually achieved with chemotherapy alone. In addition a re-irradiation approach appears to produce a small (15-25%) but definite long-term progression-free survival rate. The purpose of the proposed RTOG study is to determine whether these results can be duplicated in a multi-institutional setting, and to expand the patient population for evaluation of survival and late toxicity.

Based on the UAB experience and published trials, a total re-irradiation dose of 60 Gy can be delivered without a substantial rate of late complications, and offers the best chance for long-term disease-free survival. This dose with concomitant HU and 5-FU has therefore been selected for this trial.

## **2.0 OBJECTIVES**

- 2.1 To identify and estimate the incidence rate of acute and late toxicities associated with combined chemotherapy and re-irradiation in patients with recurrent squamous cell cancer of the head and neck.
- 2.2 To estimate the long-term (*defined as two year*) disease-free survival rate and overall survival of the treated patients.
- 2.3 To determine the pattern of disease progression in recurrent disease patients treated with chemoradiotherapy.

## **3.0 PATIENT SELECTION**

### **3.1 Conditions for Patient Eligibility**

- 3.1.1 Patients must have pathologically confirmed recurrence (*reappearance of previously cleared*) squamous cell cancer primary in the upper aerodigestive tract or a second squamous cell primary. Patients may have experienced more than one recurrence as long as the first recurrence occurred  $\geq 6$  months following the end of the prior RT.
- 3.1.2 The recurrence or second primary must have defined bi- or uni-dimensional measurements.
- 3.1.3 Recurrence or second primary must be confined to the head and neck above the clavicles (*loco-regional recurrence*).
- 3.1.4 The patient must not be a candidate for complete surgical resection.
- 3.1.5 The majority ( $\geq 75\%$ ) of the tumor volume must have been in areas previously irradiated to  $\geq 45$  Gy. The previous irradiation must not exceed a maximum of  $\leq 75$  Gy.
- 3.1.6 The entire tumor volume must be included in a treatment field that limits the total spinal cord dose to 50 Gy (*prior RT and anticipated RT*).
- 3.1.7 Patients must be at least 6 months from prior chemotherapy and radiation therapy.
- 3.1.8 Patients may have received prior chemotherapy as a component of their primary treatment, but not for recurrent disease.
- 3.1.9 Individuals 18 years or older are eligible.
- 3.1.10 Karnofsky status  $\geq 60$ .
- 3.1.11 WBC  $\geq 4000/\text{mm}^3$ , granulocytes  $\geq 2,000/\text{mm}^3$ , platelets  $\geq 100,000/\text{mm}^3$ , serum bilirubin  $\leq 1.5$  mg/dl, creatinine  $\leq 1.8$  mg/dl within 2 weeks prior to registration.
- 3.1.11.1 If LFT's are  $\geq 2$  x normal, liver ultrasound or CT is required.
- 3.1.12 Must be able to submit previous radiation records, including simulation and portal films, in order to assure that cord tolerance is not exceeded.
- 3.1.13 Patients must sign a study-specific informed consent form.

### **3.2 Conditions for Patient Ineligibility**

- 3.2.1 Distant metastases.
- 3.2.2 Primary in the nasopharynx or of the salivary gland.
- 3.2.3 History of other invasive malignancies within the past five years.
- 3.2.4 Intercurrent medical illnesses which would impair patient tolerance of therapy or limit survival.

## **4.0 PRETREATMENT EVALUATIONS**

- 4.1 Patient must have completed the following within 2 weeks of registration unless noted.
  - 4.1.1 Physical examination to define measurable disease.
  - 4.1.2 Baseline CT or MRI scan of head and neck that includes entire disease extent (*within 1 month of protocol treatment*).
  - 4.1.3 Chest x-ray (*within 1 month of protocol treatment*).
  - 4.1.4 Liver ultrasound or CT scan if the liver chemistries (*SGOT/SGPT, bilirubin*) are  $\geq 2$  times normal values.

- 4.1.5 CBC with differential and platelet count.
- 4.1.6 SMA 12/24 (*must include bilirubin, SGOT or SGPT, creatinine*).
- 4.1.7 Additional studies (*bone scan, barium swallow, etc.*) to exclude distant metastases or second primaries as indicated.
- 4.1.8 Information on prior radiation field(s) and dose(s) to permit assessment of eligibility (*Section 3.1*) and planning of current treatment field(s) (*Section 6.0*).

## **5.0 REGISTRATION PROCEDURES**

- 5.1 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. The following information must be provided:
  - Institution Name & Number
  - Patient's Name & ID Number
  - Verifying Physician's Name
  - Medical Oncologist's Name
  - Eligibility Criteria Information
  - Demographic Data
  - Treatment Start Date

## **6.0 RADIATION THERAPY**

### **6.1 Dose Fractionation (9/8/98)**

RT will be given as two daily fractions (*1.5 Gy per fraction*) separated by at least 6 hours for five consecutive days every other week for four weeks (*weeks 1, 3, 5, and 7*). HU and 5-FU are given prior to the second daily RT treatment. Total dose 60 Gy in 40 fractions. ***The spinal cord must be limited to 50 Gy total (prior plus current)***. Decay factors are not permitted. No treatment is given on weeks 2, 4 and 6. Treatment should begin on Mondays. The exact time and date of each treatment is to be recorded. If the patient misses more than two days, i.e., 4 fractions, make up missed treatments, with chemotherapy, the alternate week, i.e., the week the patient is on break.

### **6.2 Physical Factors**

- 6.2.1 Linear accelerators with appropriate photon and electron energies for supplemental boosting or cobalt machines must be used.
- 6.2.2 Photon beams of  $\geq 1.25$  MeV and/or electron beams from 4-25 MeV are allowed.
- 6.2.3 Treatment distance must be  $\geq 80$  cm SSD or greater, or  $\geq 80$  cm SAD for isocentric techniques.

### **6.3 Localization Requirements**

- 6.3.1 Simulation of all fields is mandatory. Patients must be reproducibly immobilized. Radio-opaque markers should be used whenever possible to delineate the extent of nodal disease, skin involvement, and any gross disease. The use of customized blocks is strongly recommended.

- 6.3.2 Treatment planning CT scans are strongly recommended to facilitate accurate dosimetry. The tumor volume should be clearly marked.

- 6.3.3 Beam localization films (*portal films*) should be obtained for all photon and electron fields.

#### **6.3.4 Target Volume**

A combination of lateral opposing fields, single fields, anterior and lateral wedge pair fields, and oblique fields may be used for the site of recurrent tumor. The treatment fields should encompass the recurrent tumor with adequate margins of at least 2.0 cm, whenever possible. **Margins of less than 2.0cm is an acceptable deviation only in instances of spinal cord encroachment. Partial miss or gross tumor cut through is an unacceptable deviation.** 3-D treatment planning is strongly encouraged.

#### **6.3.5 Dose Calculation**

- 6.3.5.1 Isodose distribution are required summing all fields. If the spinal cord is in close proximity to the treatment volume, off axis isodose distributions should be performed as well. This will enable an accurate computation of the maximum and minimum dose to the spinal cord. The maximum dose to the spinal cord must be carried on the daily treatment record. The specification of the protocol target dose is in terms of a dose to a point at or near the center of the target volume.

- 6.3.5.2 The dose for arrangement of two or more intersecting beams should be at the intersection of the central ray of the beams.

- 6.3.5.3 The dose for two opposed coaxial equally weighted beams should be on the central ray at mid-separation of beams.

- 6.3.5.4 The dose for more complex arrangements should be at the center of the target area.  
 6.3.5.5 The inhomogeneity within the target volume should not exceed  $\pm 10\%$  of the target dose.

#### 6.4 Evaluation Criteria

##### 6.4.1 Dose

<u>Total Dose Variation</u>	<u>Overall Evaluation</u>
$\leq 4\%$	Per Protocol
$> 4\%$ to $\leq 9\%$	Variation Acceptable
$> 9\%$	Deviation Unacceptable

##### 6.4.2 HFX Fractionation

<u>Fractionation</u>	<u>Overall Evaluation</u>
$\leq 2$ Days of non HFX	Per Protocol
3-5 Days of non HFX	Variation Acceptable
$> 5$ Days of non HFX	Deviation Unacceptable

#### 6.5 Dose Modifications

- 6.5.1 Acute local toxicity (*skin and mucosa*) must be  $\leq$  grade 2 at the beginning of each treatment week. If toxicity is  $>$  grade 2, treatment may be held up to two weeks until  $\leq$  grade 2 is attained. Chemotherapy should be held until RT is resumed. Patients who cannot resume treatment within two weeks will be removed from study. These patients must be followed for survival.
- 6.5.2 If a treatment delay for local acute toxicity is required, only the dose of chemotherapy will be modified (*Section 7.3.4*).
- 6.5.3 If treatment delay is required for chemotherapy toxicity, RT will also be held until both can be resumed.
- 6.5.4 Treatment breaks must be clearly indicated in the treatment record.

## 7.0 DRUG THERAPY

**Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.**

### 7.1 Doses

- 7.1.1 Hydroxyurea 1.5 gm will be given orally 2 hours prior to the second daily RT dose.
- 7.1.2 5-fluorouracil 300 mg/m<sup>2</sup> will be given IV bolus within 30 minutes prior to the second daily RT dose.
- 7.1.3 Given in weeks 1,3,5, and 7; no treatment in weeks 2,4 and 6.
- 7.1.4 The times of daily drug administration must be noted in the institutional records. The interval in minutes, from the administration of drug to the start of radiotherapy, will be recorded on the data forms.

### 7.2 Hydroxyurea

#### 7.2.1 Classification

Anti-metabolite

#### 7.2.2 Method of Action

HU has as its primary mechanism of action the inhibition of the enzyme ribonucleoside diphosphate reductase which catalyses the conversion of ribonucleotides to deoxyribo-nucleotides, a rate-limiting step in the synthesis of DNA. The compound is phase specific, and inhibits radiation repair. It is readily absorbed from the GI tract with peak plasma concentrations achieved within 2 hours. Approximately 80% of the drug is recovered in the urine within 12 hours.

#### 7.2.3 Procurement and Storage

Hydroxyurea is commercially available from Bristol-Myers Squibb (*Hydrea*) as 500 mg capsules for oral use. It is stable at room temperature.

#### 7.2.4 Side Effects

The major and dose-limiting toxicity is myelosuppression predominantly leukopenia (*granulocytopenia*). Megaloblastic anemia and thrombocytopenia are less common. Nausea or skin rash occur uncommonly. Mucositis and alopecia are observed rarely.

### 7.3 5-Fluorouracil (5-FU, Adrucil, Efudex)

#### 7.3.1 Classification

Anti-metabolite

#### 7.3.2 Method of Action

5-FU is a pyrimidine anti-metabolite that blocks the methylation reaction of deoxyuridylic acid, interfering with the synthesis of DNA. It is also incorporated into RNA and interferes with its functions. The drug is metabolized by the liver and partially excreted via the kidneys. 5-FU is

active in a number of malignancies including carcinomas of the colon, stomach, ovary, and breast. It has modest activity as a single agent in esophageal cancer.

**7.3.3** Procurement and Storage

5-FU is commercially available from Roche and Adria Laboratories in 500 mg/10 cc ampules. It is stable if protected from light. If a precipitate is present, it is to be gently heated to not greater than 140°F in a water bath. Store at room temperature. Colorless to faint yellow aqueous solution, pH adjusted with sodium hydroxide to 8.6 to 9.0.

**7.3.4** Incompatibilities

1. Possibly incompatible with methotrexate (*Am J Hosp Pharm* 33:1010-1013, 1976).
2. Definite incompatibility with doxorubicin and other anthrocyclines. When giving doxorubicin IV push or through a running IV, flush line before giving 5-FU (*Drug Intell Clin Pharm* 11:690, 1977).

**7.3.5** Side Effects

1. Gastrointestinal: nausea, vomiting, stomatitis, anorexia, diarrhea.
2. Dermatologic: dermatitis, nail changes, hyperpigmentation, hand and foot syndrome.
3. Alopecia.
4. EENT: eye irritation, nasal discharge, watering of eyes, blurred vision.
5. Blood: leukopenia, thrombocytopenia, anemia.
6. Neurologic: cerebellar syndrome (*headache and cerebellar ataxia*).
7. Other: weakness and malaise.

**7.4** Dose Modifications

**7.4.1** This study requires that all treatment be given concurrently. Therefore, if a treatment delay is required for either acute radiation effects (*Section 6.5*) or myelosuppression, treatment with both modalities is delayed until recovery.

**7.4.2** The granulocyte count must be  $\geq 2000/\text{mm}^3$  and the platelet count  $\geq 100,000/\text{mm}^3$  at the beginning of each treatment week. If the values do not meet these limits, all treatment will be held for one week and the hematologic values repeated. One additional week delay is permitted if the counts have not recovered. Chemotherapy will be terminated if treatment interruption exceed two weeks. The patient will be removed from study and followed for survival. If additional treatment is administered it will be reported as non-protocol therapy.

**7.4.3** Chemotherapy dose modification is based on hematologic nadir values (*Section 7.4.4*), the grade of non-hematologic toxicity observed in the previous course (*Section 7.4.5*), and on the recovery values at the time treatment is due (*Section 7.4.2*). Drug dose will not be increased after a dose reduction mandated by toxicity.

**7.4.4** Treatment modification for nadir counts

<u>Nadir from prior course</u>	<u>Doses for Next Course</u>	
	<u>HU</u>	<u>5-FU</u>
Granulocytes $\geq 500/\text{mm}^3$ and platelets $\geq 30,000/\text{mm}^3$ *	No Change	No Change
Granulocytes $< 500/\text{mm}^3$ or platelets $< 30,000/\text{mm}^3$ * ( <i>and no prior dose reduction</i> )	1.0 gm/day	200 mg/m <sup>2</sup> /day
Granulocytes $< 500/\text{mm}^3$ after one dose reduction or sepsis*	0.5 gm/day	150 mg/m <sup>2</sup> /day

\* Note recovery limits in Section 7.4.2

**7.4.5** Dose reduction for non-hematologic toxicity (prior course).

Must be Grade 2 £to resume treatment.

	<u>Doses for Next Course</u>	
	<u>HU</u>	<u>5-FU</u>
$\leq$ Grade 2	No Change	No Change
Grade 3	No Change	200 mg/m <sup>2</sup> /day
Grade 4 and no prior dose reduction <u>or</u> Grade 3 after prior dose reduction	1.0 gm/day	150 mg/m <sup>2</sup> /day
Grade 4 after prior dose reduction	1.0 gm/day	discontinue

**7.4.6** Adherence to Protocol Guidelines (9/8/98)

The protocol requires that a CBC be obtained at the beginning of each treatment week. It is critical that this timing be followed. Studies obtained earlier may not fully reflect the developing hematologic toxicity. Secondly, the dose modification guidelines require that the granulocyte count be  $\geq 2,000/m^3$ . It is also important that this guideline be followed. On review of patients entered to date, the two patients who suffered fatal leukopenia-associated sepsis had violations of these guidelines. Even following these guidelines closely will not eliminate the possibility of grade 4 myelosuppression and patients must be followed with this possibility in mind. Close adherence to the dose modification guidelines should ensure even greater safety in the utilization of this therapy.

**7.5** Adverse Drug Reaction Reporting

**7.5.1** The following guidelines for reporting adverse drug reactions (ADR's) apply to any research protocol which uses commercial anticancer agents. The following ADR's 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 ten working days:

**7.5.1.1** Any ADR which is both serious (*life-threatening, fatal*) and unexpected.

**7.5.1.2** Any increased incidence of a known ADR which has been reported in the package insert of the literature.

**7.5.1.3** Any death on study if clearly related to the commercial agent(s).

**7.5.1.4** Acute myeloid leukemia (AML). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc., and protocol identification.

**7.5.2** The ADR report should be documented on FDA Form 3500 (*Appendix V*) and mailed to the address on the form and to:

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

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

**8.0** SURGERY

**8.1** Patients who initially respond to therapy but recur with a resectable lesion inside or outside the re-treatment field may undergo resection (*overall medical condition permitting*) and no additional treatment. Surgery of the recurrent head and neck primary or regional nodes subsequent to protocol therapy must be reported on the Surgery Form. The surgical report and the resection pathology report must be also submitted to RTOG.

**8.2** The surgical and/or reconstructive procedures employed are at the discretion of the surgeon.

**8.3** Patients who have pathologically proven complete response with a non-healing major defect should be considered for debridement and repair by flap or free tissue transfer. All resected tissue must be submitted for local pathology review.

**8.4** Any surgical procedure(s) and their complications must be noted in the protocol data forms.

**9.0** OTHER THERAPY

Does not apply to this study.

**10.0** PATHOLOGY

Does not apply to this study.

**11.0** PATIENT ASSESSMENTS

**11.1** Study Parameters

Study	Treatment			Follow-up
	Pre Entry	Weekly	Monthly(d)	Q 4 Monthly(d)

Clinical evaluation PE, KPS, weight	X	X	X	X
Toxicity scoring		X	X	
CBC with platelet count	X	X <sup>(b)</sup>		X <sup>(f)</sup>
SMA-12	X	X <sup>(c)</sup>		X <sup>(f)</sup>
Chest x-ray	X			X <sup>(f)</sup>
Head and neck CT or MRI	X		X <sup>(e)</sup>	
Tumor measurements	X		X	
Liver ultrasound or CT bone scan, barium swallow, etc.	X <sup>(a)</sup>			X <sup>(a)</sup>

- a. As needed to assess distant metastases or second primaries.
- b. Repeat weekly times two after last course of treatment.
- c. Repeat every two weeks during treatment.
- d. Follow-up evaluations will be monthly for one year then every two months until progression. Evaluations are required on a more frequent schedule than submissions (See Section 12.1).
- e. Repeat two months after completion of therapy for response assessment, then as needed to document progression.
- f. Repeat every six months after the first year.

## **11.2 Other Information**

- 11.2.1** Prior radiation treatment fields and doses must be documented relative to the recurrence. Previous treatment records and films must be available for submission to RTOG Headquarters. See Section 12.0.
- 11.2.2** After treatment completion, any late toxicity must be documented relative to all treatment fields and doses.
- 11.2.3** All post-treatment surgical procedures and complications must be documented.
- 11.2.4** All recurrences must be documented relative to the re-treatment fields(s).
- 11.2.5** All toxicities will be evaluated according to the grading system in Appendix IV.
- 11.2.6** Survival will be measured from the time treatment starts.
- 11.2.7** All patients will be followed for survival.
- 11.2.8** Intervals between each drug administration and radiotherapy must be recorded in the patient record.

## **11.3 Criteria for Discontinuing Therapy**

- 11.3.1** The development of unacceptable toxicity not amenable to dose reduction.
- 11.3.2** Greater than two weeks delay between treatment courses.
- 11.3.3** Intercurrent illness that precludes further treatment.
- 11.3.4** Patient request.

## **11.4 Methods of Malignant Disease Evaluation**

- 11.4.1** Measurable, bi-dimensional  
Malignant disease measurable (*metric system*) in two dimensions by rulers or calipers with surface area determined by multiplying the longest diameter by the greatest perpendicular diameter (*i.e., metastatic pulmonary nodules, lymph nodes and subcutaneous masses*). Malignant disease with sharply defined borders visualized by ultrasonography or computerized axial tomography is considered measurable. Repeat studies should be performed at the same pre-therapy sites(s) or malignant disease.
- 11.4.2** Measurable, un-dimensional  
Malignant disease measurable (*metric system*) in one dimension by ruler or calipers.
- 11.4.3** Non-measurable, evaluable  
Malignant disease evident on clinical (*physical or radiographic*) examination, but not measurable by ruler or calipers.
- 11.4.3.1** Photographs should be taken prior to and after therapy to document response (*i.e., skin and subcutaneous metastases, intraoral lesions*).
- 11.4.3.2** Bone scans cannot be used to evaluate response.
- 11.4.4** Non-measurable, non-evaluable Malignant disease found to be surgically unresectable, but not clinically detectable.

## **11.5 Objective Criteria of Response**

- 11.5.1** All tumor measurements must be recorded in centimeters and should consist of the two longest perpendicular cross-diameters. Patients will be separately assessed for response by physical exam and

by CT scan prior to and two months following completion of therapy. Both the clinical (*physical exam*) and radiographic (*CT scan*) response will be recorded on the study forms.

- 11.5.2 Complete response** - The disappearance of all known disease determined by two assessments not less than four weeks apart.
- 11.5.3 Partial response** - A 50% or more decrease in total tumor size of bi-dimensionally measured lesions, or in the single dimension of uni-dimensional lesions, which have been measured to determine the effect of therapy determined by two observations not less than four weeks apart. Non-measurable, evaluable lesions must have decreased in size.
- 11.5.4 Stable disease** - A 50% decrease in total tumor measurement cannot be established nor has a 25% increase in the measurement of one or more lesions been demonstrated. In addition, there can be no appearance of new lesions.
- 11.5.5 Progressive disease** - A 25% or more increase in the size of one or more measurable lesions, the appearance of new lesions or 50% increase in evaluable non-measurable lesions.
- 11.5.6 Relapse-**
- 11.5.6.1** The appearance of new lesions in previously responding patients.
- 11.5.6.2** The reappearance of old lesions in patients who have achieved a complete remission.
- 11.5.6.3** For patients in partial remission, an increase of 25% or more in the product of the diameters of any measured bi-dimensional lesion or of the single measurement of a uni-dimensional lesion or a 50% increase in evaluable, non-measurable lesions over that which was obtained at the time of maximum regression.
- 11.6 Completion of an Adequate Trial**
- 11.6.1** An evaluable case must have received at least one cycle of therapy and undergone tumor measurements to evaluate the patient's response status.
- 11.7** Duration of response shall be measured from the achievement of that response to the first sign of relapse.
- 11.8** All patients receiving the therapeutic agent and developing toxicity or surviving four weeks will be considered evaluable for toxicity. An adequate therapeutic trial will be defined as one infusion of therapy and four weeks survival or death from tumor progression within four weeks.

## **12.0 DATA COLLECTION**

**RTOG HQ, 1101 Market Street, Philadelphia, PA 19107**

### **12.1 Summary of Data Submission (9/8/98)**

<u>Item</u>	<u>Due</u>
Demographic Form ( <b>A5</b> )	Within 1 week of study entry.
Initial Evaluation Form ( <b>I1</b> )	Within 2 weeks of study entry.
Primary Site Diagram ( <b>I6</b> )	
Nodal Diagram ( <b>I7</b> ) (to reflect extent of disease at study entry)	
Prior Radiotherapy Materials ( <b>TM</b> ) Prior simulation and portal films, prior RX record including calculation summary, prior isodose distribution	
<u>Preliminary Dosimetry Information:</u> RT Prescription ( <i>Protocol Treatment Form</i> ) ( <b>T2</b> ) Films ( <i>simulation and portal</i> ) ( <b>T3</b> ) Calculations ( <b>T4</b> ) Treatment Planning CT ( <b>C1</b> )	Within 1 week of start of RT.
Chemotherapy Flow Sheets ( <b>M1</b> )	At 4 weeks from start of therapy and 3 weeks after last treatment cycle
<u>Final Dosimetry Information:</u> Radiotherapy Form ( <b>T1</b> ) Daily Treatment Record ( <b>T5</b> ) Isodose Distribution ( <b>T6</b> ) Boost Films ( <i>simulation and portal</i> ) ( <b>T8</b> ) Polaroid/Photo ( <i>electron field</i> ) ( <b>T7</b> )	Within 1 week of RT ending.

Follow-up Form (F1)	Every three months from treatment start for one year; every four months during year 2; every six months during years 3-5; then annually. Also at progression/relapse and at death.
Surgery Form (S1) Report (S2) Surgical Pathology Report (S5)	Following resection as described in Surgical Section 8.1.
Autopsy Report (D3)	As applicable.

**12.2** Radiotherapy records and films of prior treatment to the head and neck must be routinely submitted. All prior material must be recorded on the transmittal form. Credit will not be given until every item has been submitted. If a prior isodose summations was not done, this must be clearly noted on the transmittal form.

**13.0 STATISTICAL CONSIDERATIONS**

**13.1 Study Endpoints**

- 13.1.1** To identify and estimate the incidence rate of acute and late toxicities associated with combined chemotherapy and re-irradiation in patients with recurrent squamous cell cancer of the head and neck.
- 13.1.2** To estimate the long-term (*defined as two year*) disease-free survival rate and overall survival of the treated patients.
- 13.1.3** To determine the pattern of disease progression in recurrent disease patients treated with chemoradiotherapy.

**13.2 Overview**

This is a group-wide, single treatment arm non-randomized treatment study which is based upon an institution pilot study done at the University of Alabama at Birmingham. There were no late (*> 12 month*) RT grade 3, 4, or 5 (*fatal*) related toxicities observed. A rate of 5% for late RT related grade 4 (*not including salivary gland*) or 5 (*fatal*) would be deem acceptable in this population but, if it is  $\geq 20\%$ , it would be clinically unacceptable. The sample size was determined to rule out such a high rate.

**13.3 Sample Size**

Blackwelder’s approach to proving the null hypothesis will be used to test whether the true probability of late grade 4 or 5 RT toxicities is clinically acceptable.<sup>42</sup> The following conditions were set:

$\alpha$  = .05 - chance of incorrectly accepting the salvage treatment program which is too toxic;

$\beta$  = .20 - chance of incorrectly rejecting the salvage treatment program which is, in fact, safe;

$\gamma$  = level of late toxicities for the salvage treatment program;

$\delta$  = acceptable level of 5% for late toxicities

$\epsilon$  = clinical unacceptable increase of 15% for late toxicities

$$H_0: \gamma \geq \delta + \epsilon$$

$$H_1: \gamma < \delta + \epsilon$$

If the patients survived 12 months, then 30 patients would be required under above conditions. Based upon the pilot study, the probability of surviving beyond 12 months is 40%. Using it as a projection, then 75 ( $= 30 / .40$ ) patients would be required. Guarding against a loss up to 10% due to ineligibility and unevaluable data, **the targeted sample size for the study was increased to 82 patients.**

**13.4 Accrual Rate and Study Completion**

A survey of the RTOG institution suggested that 100 patients per year would be available for this study. Assuming an annual accession rate of 40 patients, the patient accrual phase should be completed within two years.

### **13.5 Analysis Plans**

#### **13.5.1 Interim analysis of accrual and toxicity**

Interim reports with statistical analysis are prepared every six months until the initial treatment paper reporting the treatment results has been submitted for publication. In general the interim reports will contain information about:

- 1) patient accrual with a projected completion date;
- 2) timeliness, completeness and accuracy of submitted data;
- 3) treatment compliance;
- 4) frequency and severity of treatment related toxicities.

#### **13.5.2 Analysis of primary study endpoints**

Interim analysis of primary efficacy endpoints (*tumor clearance, response duration, and survival*) will be performed when the accrual target has been achieved and then annually until the treatment report is submitted for publication.

#### **13.5.3 Analysis and reporting of initial treatment results**

This major analysis will be conducted when each patient has been potentially followed for a minimum of eighteen months. The usual components of this analysis are:

- 1) tabulations of all cases entered and any excluded from the analysis with the reasons for such exclusions;
- 2) reporting of institutional accrual;
- 3) distribution of pretreatment characteristics;
- 4) frequency and severity of acute and late toxicities;
- 5) observed results with respect to the primary efficacy endpoints.

## REFERENCES

1. Marcial VA, Pajak TF, Kramer S, Davis LW, Stetz J, Laramore GE, Jacobs JR, Al-Sarraf M, Brady LW: Radiation Therapy Oncology Group (RTOG) studies in head and neck cancer. *Sem Oncol* 15:39-60, 1988.
2. Hong WK, Bromer RH, Amato DA, Shapshay S, Vincent M, Vaughan C, Willett B, Katz A, Welch J, Fofonoff S, Strong MS: Patterns of relapse in locally advanced head and neck cancer patients who achieved complete remission after combined modality treatment. *Cancer* 45:1242-1245, 1985.
3. Hong WK, Bromer R: Chemotherapy in head and neck cancer. *N Engl J Med* 308:75-79, 1983.
4. Kish JA, Weaver A, Jacobs J, Cummings G, Al-Sarraf M: Cisplatin and 5-fluorouracil infusion in patients with recurrent and disseminated epidermoid cancer of the head and neck. *Cancer* 53:1819-1824, 1984.
5. Wang CC: Re-irradiation of recurrent nasopharyngeal carcinoma-treatment techniques and results. *Int J Radiat Oncol Biol Phys* 13:953-956, 1987.
6. Emami B, Bignardi M, Devineni VR, Spector GJ, Hederman MA: Re-irradiation of recurrent head and neck cancers. *Laryngoscope* 97:85-88, 1987.
7. Langlois D, Eschwege F, Kramar A, Richard JM: Re-irradiation of head and neck cancers. *Radiother and Oncol* 3:27-33, 1985.
8. Pomp J, Levendag PC, van Putten WLJ: Re-irradiation of recurrent tumors in the head and neck. *Am J Clin Oncol* 11:543-549, 1988.
9. Skolyszewski J, Korzeniowski S, Reinfuss M: The re-irradiation of recurrences of head and neck cancer. *Br J Radiol* 53:462-465, 1980.
10. Stevens KR, Britsch A, Moss WT: High-dose re-irradiation of head and neck cancer with curative intent. *Int J Radiation Oncol Biol Phys* 29:687-698, 1994.
11. Emami B, Marks JE: Re-treatment of recurrent carcinoma of the head and neck by afterloading interstitial <sup>192</sup>Ir implant. *Laryngoscope* 93:1345-1347, 1983.
12. Mazeron JJ, Langlois D, Glaubiger D, Huart J, Martin M, Raynal M, Calitchi E, Ganem G, Faraldi M, Feuilhade F, Brun B, Marin L, LeBourgeois JP, Baillet F, Pierquin B: Salvage irradiation of oropharyngeal cancers using iridium 192 wire implants: 5-year results of 70 cases. *Int J Radiat Oncol Biol Phys* 13:957-962, 1987.
13. Puthawala AA, Syed AMN: Interstitial re-irradiation for recurrent and/or persistent head and neck cancers. *Int J Radiat Oncol Biol Phys* 13:1113-1114, 1987.
14. Emami B, Marks JE, Perez CA, Nussbaum GH, Leybovich L, Von Gerichten D: Interstitial thermoradiotherapy in the treatment of recurrent/residual malignant tumors. *Am J Clin Oncol* 7:699-704, 1984.
15. Puthawala AA, Syed AMN, Sheikh KMA, Rafie S, McNamara CS: Interstitial hyperthermia for recurrent malignancies. *Endocrine Therapy/Hyperthermia Oncol* 1:125-131, 1985.
16. Tupchong L, Waterman FM, McFarlane JD: Hyperthermia and radiation therapy for advanced regional disease due to recurrent head and neck carcinoma. *Int J Radiat Oncol Biol Phys* 19:1099, 1990. Abstract
17. Hendry JH, Rosenberg I, Greene D, Stewart J: Re-irradiation of rat tails to necrosis at six months after treatment with a tolerancy dose of x-ray or neutrons. *Br J Radiol* 50:567-572, 1977.

18. Brown JM, Probert JC: Early and late radiation changes following a second course of irradiation. *Radiology* 115:711-716, 1975.
19. Denekamp J: Residual radiation damage in mouse skin 5 to 8 months after irradiation. *Radiology* 115:191-195, 1975.
20. Fu KK, Newman H, Phillips TL: Treatment of locally recurrent carcinoma of the nasopharynx. *Radiology* 117:425-431, 1975.
21. Nisar Syed AM, Feder BH, George FW, Noblett D: Iridium-192 afterloaded implant in the re-treatment of head and neck cancer. *Br J Radiol* 51:814-820, 1978.
22. Thompson RW, Scottie Doggett RL, Bagshaw MA: Ten year experience with linear accelerator irradiation of cancer of nasopharynx. *Radiology* 97:149-155, 1970.
23. Jeremic B, Djuric L, Mijatovic L: Incidence of radiation myelitis of the cervical spinal cord at doses of 5500 cG or greater. *Cancer* 68:2138-2141, 1991.
24. Byfield JE, Frankel SS, Sharp TR, Hornbeck CL, Callilpari FB: Phase I and pharmacologic study of 72-hour infused 5-fluorouracil and hyperfractionated cyclical radiation. *Int J Radiat Oncol Biol Phys* 11:791-800, 1985.
25. Lo TCM, Wiley AL, Ansfield FJ, Brandenburg JH, Davis HL, Gollin FF, Johnson RO, Ramirez G, Vermund H: Combined radiation therapy and 5-fluorouracil for advanced squamous cell carcinoma of the oral cavity and oropharynx: A randomized study. *Am J Roentgenol* 126:229-235, 1976.
26. Vokes EE, Weichselbaum RR: Concomitant chemoradiotherapy: Rationale and clinical experience in patients with solid tumors. *J Clin Oncol* 8:911-934, 1990.
27. Richards GJ, Chambers RG: Hydroxyurea: A radiosensitizer in the treatment of neoplasms of the head and neck. *Am J Roentgenol* 105:555-565, 1969.
28. Richards GJ, Chambers RC: Hydroxyurea in the treatment of neoplasms of the head and neck. *Am J Surg* 126:513-518, 1973.
29. Rominger CJ: Hydroxyurea and radiation therapy in advanced neoplasms of the head and neck. *Am J Roentgenol* 111:103-108, 1971.
30. Frankfurt OS: Enhancement of the anti-tumor activity of 5-fluorouracil by drug combinations. *Cancer Res* 33:1043-1047, 1973.
31. Moran RG, Danenberg PV, Heidelberger C: Therapeutic response of leukemic mice treated with fluorinated pyrimidines and inhibitors of deoxyuridylylate synthesis. *Biochem Pharmacol* 18:2929-2935, 1982.
32. Vokes EE, Haral DJ, Mick R, McEvelly JM, Weichselbaum RR: Intensified concomitant chemoradiotherapy with and without filgrastim for poor-prognosis head and neck cancer. *J Clin Oncol* 12:2351-2359, 1994.
33. Hartsell WF, Thomas CR, Murthy AK, Taylor SG, Haslow RE: Pilot study for the evaluation of simultaneous cisplatin/5-fluorouracil infusion and limited radiation therapy in regionally recurrent head and neck cancer (ESTP-C385). *Am J Clin Oncol (CCT)* 17:338-343, 1994.
34. Parson JT, Bova FJ, Million RR: A re-evaluation of split-course technique for squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 6:1645-1652, 1980.
35. Perez CA, Stanley K, Grundy G, Hanson W, Rubin P, Kramer S, Brady LW, Marks JE, Perez-Tamayo R, Brown GS, Concannon JP, Rotman M: Impact of irradiation technique and tumor extent in tumor control and survival of patients with unresectable non-oat cell carcinoma of the lung. *Cancer* 50:1091-1099, 1982.

36. Archambeau JO, Hauser D, Shymko RM: Swine basal cell proliferation during a course of daily irradiation, five days a week for six weeks (6000 rad). *Int J Radiat Oncol Biol Phys* 15:1383-1388, 1988.
37. Adelstein DJ, Sharan VM, Earle AS, Shah AC, Vlastou C, Haria CD, Carter SG, Damm C, Hines JD: Long-term results after chemoradiotherapy for locally confined squamous-cell head and neck cancer. *Am J Clin Oncol* 13:440-447, 1990.
38. Stryker JA, Harvey HA, Houck JR, Manders EK, Bradfield JJ: Advanced head and neck cancer: Low-dose, split-course radiation therapy and simultaneous infusion 5-fluorouracil and cisplatin. *Radiology* 176:567-571, 1990.
39. Taylor SG, Murthy AK, Caldarelli DD, Showel JL, Kiel K, Griem KL, Mittal BB, Kies M, Hutchinson JC, Holinger LD, Campanella R, Witt TR, Hoover S: Combined simultaneous cisplatin/fluorouracil chemotherapy and split course radiation in head and neck cancer. *J Clin Oncol* 7:846-856, 1989.
40. Weppelmann B, Wheeler RH, Peters GE, Kim RY, Spencer SA, Meredith RF, Salter MM: Treatment of recurrent head and neck cancer with 5-fluorouracil, hydroxyurea and re-irradiation. *Int J Rad Oncol Biol Phys* 22:1051-1056, 1992.
41. Spencer S, Wheeler R, Meredith R, Peters G, Robert F, Kim R, Salter M: Simultaneous hydroxyurea, 5-fluorouracil and high-dose BID irradiation in previously irradiated patients with recurrent squamous cell cancer of the head and neck. Third International Conference on Head and Neck Cancer, San Francisco, CA. July 1992.
42. Blackwelder WC: "proving the null hypotheses" in clinical trials. *Controlled Clin Trial* 3: 345-353,1982.

## **APPENDIX I**

### **RTOG 96-10**

#### **Phase I/II Study of Concomitant Hydroxyurea, 5-Fluorouracil and Re-Irradiation in Patients with Recurrent Squamous Cell Cancer of the Head And Neck**

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

#### **RESEARCH STUDY**

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

#### **PURPOSE OF THE STUDY**

It has been explained to me that I have recurrent cancer of the head and neck that has been previously treated with radiation and cannot be surgically removed. My doctors have proposed participation in this study as treatment of this recurrence. The purposes of this study are to determine how often a combination of chemotherapy and further radiation will shrink the tumor and prevent it from returning, and to determine the side effects of this type of treatment.

#### **DESCRIPTION OF PROCEDURES**

This treatment includes chemotherapy with two agents, Hydroxyurea (*HU*) and 5-fluorouracil (*5-FU*), and radiation therapy. All three treatments (*HU*, *5-FU*, and *radiation*) are given Monday through Friday (*five days in a row*), every other week. There will be a total of four weeks of treatment, each alternating with three weeks of no treatment over a seven-week period. Occasionally a treatment week might be delayed to allow recovery from treatment side effects. The overall treatment time would be longer in this case.

The treatment will be given on an outpatient basis. The radiation is given twice a day with at least 6 hours between the treatments. The HU is taken by mouth 2 hours before the second radiation treatment each day. The 5-FU is given as a shot into a vein just before the second radiation treatment. Blood counts will be measured weekly to check for side effects of the treatment.

After all treatment is completed, I will be followed on a regular basis. Examinations, blood work and x-rays will be done to determine how well the cancer has responded to treatment, whether it returns, and whether it has spread to any organs.

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 be dependent on my insurance company.

#### **RISKS AND DISCOMFORTS**

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

Risks from radiation include: temporary skin redness or peeling, difficulty in swallowing, or reduction in blood counts. Late effects may include dryness of the mouth, dental cavities, continued soreness in the mouth and throat, stiffness of the neck, hoarseness, or damage to the jaw bone causing bone destruction that might produce pain or require surgery if severe. Another late effect may be significant fibrosis (*hardening or thickening*) of the treatment area causing swallowing difficulty. If severe enough a feeding tube may be required.

Risks from chemotherapy include: nausea and vomiting and loss of appetite; low blood counts with increased risk of bleeding, bruising, or infection that could be severe, life-threatening or require hospitalization; hair loss or skin rash; mouth sores with difficulty swallowing; diarrhea, skin or nail darkening; excessive tears (*eyes*); or blurring of vision; increased reaction to radiation, headache and rarely, allergic reaction.

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

This study may be harmful to an unborn child. I am advised to avoid the possibility of conception during treatment. There is insufficient medical information to see whether there are significant risks to a fetus carried by a mother who is participating in this study. Therefore, participants who are still menstruating and have not been surgically sterilized must have a negative pregnancy test prior to participating in this study. This requires that blood be drawn by venipuncture within 7 days prior to the study. The results will be made available to the study participant prior to the initiation of this study.

### **CONTACT PERSONS**

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

### **BENEFITS**

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

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

### **ALTERNATIVES**

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

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

### **CONFIDENTIALITY**

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

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

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

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign 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

### American Joint Commission AJC Staging, 4th Edition 1992

#### AJC STAGING-Primary Tumor (T)

##### Oral Cavity

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

TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma *in situ*  
T1 Tumor  $\leq 2$  cm in greatest dimension  
T2 Tumor  $> 2 - \leq 4$  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*).

#### PHARYNX

##### Oropharynx

Faucial arch including soft palate, uvula and anterior tonsillar pillar  
Tonsillar fossa and tonsil  
Base of tongue including glossoepiglottic and pharyngoepiglottic folds  
Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

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

##### Nasopharynx (Ineligible for this study)

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

TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma *in situ*  
T1 Tumor limited to one subsite of nasopharynx  
T2 Tumor invades more than one subsite of nasopharynx  
T3 Tumor invades nasal cavity and/or oropharynx  
T4 Tumor invades skull and/or cranial nerve(s)

## Hypopharynx

Pyramidal sinus  
Postcricoid area  
Posterior hypopharyngeal wall

- TX Tumor that cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma *in situ*  
T1 Tumor limited to one subsite of hypopharynx.  
T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, without fixation of hemilarynx.  
T3 Tumor invades more than one subsite of hypopharynx or an adjacent site, with fixation of hemilarynx.  
T4 Tumor invades adjacent structures (*e.g. cartilage or soft tissues of neck*).

## LARYNX

### Supraglottis

Ventricular bands (*false cords*)  
Arytenoids  
Suprahoid epiglottis (*both lingual and laryngeal aspects*)  
Infrahyoid epiglottis  
Arytenoepiglottic folds (*laryngeal aspect*)

- TX Tumor that cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma *in situ*  
T1 Tumor limited to one subsite of supraglottis with normal mobility.  
T2 Tumor invades more than one subsite of supraglottic or glottis with normal vocal cord morbidity.  
T3 Tumor limited to larynx with vocal cord fixation and/or extension to involve postcricoid area, medial wall of pyriform sinus, or pre-epiglottic tissues.  
T4 Massive tumor extending beyond the larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage.

### Glottis

True vocal cords including anterior and posterior commissures

- TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma *in situ*  
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., oropharynx, or soft tissues of neck*)

### Subglottis

- TX Primary tumor cannot be assessed  
T0 No evidence of primary tumor  
Tis Carcinoma *in situ*  
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. to the oropharynx, or soft tissues of the neck*)

### **Nodal Involvement (N)**

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 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 a multiple ipsilateral nodes, none more than 6 cm in greatest dimension.

N2c Bilateral or contralateral lymph node more than 6 cm in greatest dimension.

N3 Metastases in a lymph node more than 6 cm in greatest dimension.

### **Stage Groupings**

Stage I - T1, N0, M0

Stage II - T2, N0, M0

Stage III - T3, N0, M0  
T1-3, N1, M0

Stage IV - T4, N0-1, M0  
T1-4, N2-3, M0  
Any T, or any N, M1

## APPENDIX V

### ADVERSE REACTION 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 special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). 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.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report 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.
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 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 (<sup>3</sup> *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 (<sup>3</sup> *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 ( <i>grade 4</i> ) 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