RADIATION THERAPY ONCOLOGY GROUP

RTOG 92-11

CORRELATION OF CLINICAL OUTCOME AND THE TUMOR POTENTIAL DOUBLING TIME IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK COMPANION STUDY FOR RTOG 90-03, HEAD AND NECK CANCER

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SCHEMA

R E G I S T E R

200 mg IdUrd i.v. followed
by tumor biopsy 4-9 hours later.

Eligibility: (See Section 3.0 for details)

- Patients must be eligible for and registered on RTOG 90-03.
- Cannot have started treatment on RTOG 90-03.
- Signed study-specific consent form.

Required Sample Size: 334

Institution # _____

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ELIGIBILITY CHECK

Case # _____

_____(Y/N) 1. Has the patient been entered on Study 9003?

_____(N) 2. Has radiotherapy started or is it planned to commence before IdUrd procedure?

_____(N) 3. Any contraindication (medical or technical) to the procedure or IdUrd administration?

_____(Y) 4. Has the patient signed a study-specific informed consent form?

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution

_____ What is the RTOG 90-03 case number for this patient?

_____ Date of registration to this study

Revised: 3/15/93

1.0 INTRODUCTION

Failure to achieve local and regional tumor control with radiation therapy remains a significant problem for a number of anatomic sites and can have a significant negative impact upon survival.[16] There is emerging clinical and laboratory evidence that proliferation of tumor clonogenic cells during treatment may impair such local control.[5-10, 12, 18, 19, 25]

The bromodeoxyuridine/delayed-biopsy technique [2] can be employed to estimate pretreatment tumor potential doubling times (T_{pot}). Recent studies [1, 24] indicate a striking similarity between mean T_{pot}'s determined in this fashion and the effective doubling times of surviving tumor cells during radiotherapy, as estimated from clinical tumor control data.[7, 25] These clinical and laboratory data both indicate that many human tumors have the potential to double their cell number in as short a time as five days or less. Thus, cells that survive initial treatments might rapidly repopulate a tumor during therapy, ultimately leading to local-regional treatment failure.

A possible strategy for overcoming rapid proliferation is a shortening of overall radiation therapy treatment time, a so-called accelerated fractionation that is generally combined with hyperfractionation to maintain late radiation effects at an acceptable level.[4, 12, 20] Indeed, preliminary evidence suggests that accelerated treatment leads to better control of "fast", but not of "slow", head and neck tumors, and that the potential doubling time has prognostic significance even independently of the fractionation employed.[1] In similar fashion, preliminary data indicate that, in patients with advanced primary and recurrent rectal adenocarcinomas, pre-treatment tumor kinetics predicts treatment response to pre-operative chemo/radiotherapy.[14] These intriguing results will need to be substantiated by longer followup and additional clinical trials.

While accelerated radiotherapy may help overcome rapid proliferation, it has morbidity, is inconvenient, and it may not be optimal treatment for slowly proliferating tumors. With slower proliferation, hyperfractionation without acceleration [3, 11] is likely to be superior in that it permits a higher total dose to be delivered while maintaining acceptable late toxicity. Selecting those patients most likely to benefit from one form of fractionation or another will require reliable tumor cell kinetics information.

This study will utilize modifications [17, 23] of the bromodeoxyuridine/delayed-biopsy technique [2] to determine pretreatment proliferation rates in human tumors of the head and neck. The population studied will be that of RTOG protocol 90-03, a randomized trial comparing two accelerated, one conventional and one hyperfractionated radiotherapy schedule. Possible correlations between pretreatment kinetics and local-regional control and survival will be investigated.

2.0 OBJECTIVES

2.1 To measure pre-treatment tumor kinetics in human head and neck tumors in conjunction with RTOG 90-03. The delayed biopsy technique for determination of tumor potential doubling times will be employed. Cell kinetics parameters will include labelling index (the proportion of tumor cells that is synthesizing DNA at a given time), potential doubling time (T_{pot}) (the theoretical time for a tumor to double if there were no cell loss) and DNA index (the ratio of the tumor G0/G1 DNA content to that for normal cells).

2.2 The goals are to investigate the relationship among tumor proliferative potential and local-regional control and survival in patients with Stage III or IV (Stage II base of tongue and hypopharynx) squamous cell carcinoma of the head and neck treated on RTOG 90-03. The prognostic potential of T_{pot} will be evaluated both overall and with respect to fractionation schedule.

3.0 PATIENT SELECTION (3/15/93)

3.1 Conditions for Patient Eligibility

3.1.1 Patients must be eligible for RTOG 90-03.

3.1.2 May not have started treatment on RTOG 90-03.

3.1.3 Study-specific consent form

3.2 Conditions for Patient Ineligibility

3.2.1 Patients registered on RTOG 90-03 prior to the companion study activation date.

3.2.2 Patients registered to this study and not randomized to RTOG 90-03. **RTOG Headquarters must be notified when a patient entered to this study is not subsequently randomized to RTOG 90-03.**

4.0 PRETREATMENT EVALUATION

As per RTOG 90-03 with the additional requirement that patients must be judged able to undergo tumor rebiopsy prior to initiation of radiation therapy.

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:

- Patient's Name & ID Number
- Institution Name & Number
- Eligibility Criteria Information
- Case number on RTOG 90-03
- Patient's Birthdate, Race, Sex, Social Security Number, and Zip Code.

The case number will be assigned and confirmed by mail.

6.0 RADIATION THERAPY

Not applicable to this study.

7.0 DRUG THERAPY

7.1 Iododeoxyuridine (NSC #039661)

7.1.1 Description: Iododeoxyuridine (IdUrd) is an iodinated thymidine analogue that is incorporated into the DNA of cycling cells.

7.1.2 Preparation and Storage: IdUrd is packaged as a white, lyophylized powder in vials containing 200 mg. Intact vials may be stored at room temperature. The contents must be reconstituted with sterile saline for use. After reconstitution, the vials should be discarded within eight hours since the vials do not contain a preservative.

7.1.3 Drug Dosages and Administration: Two hundred (200) mg of IdUrd is reconstituted in 20 ml of sterile, normal saline, The entire 20 ml volume is delivered by i.v. push over 5 minutes. IdUrd is administered 4-9 hours prior to the planned biopsy.

7.1.4 Mechanism of Action

7.1.4.1 The DNA of S phase tumor cells is labeled by a brief administration of i.v. IdUrd to the patient. An interval Δ t, typically 4-9 hours is allowed to pass, during which time the cohort of IdUrd-labelled cases moves through and partially out of S phase.

7.1.4.2 A tumor biopsy is obtained, fixed in ethanol, and mailed to the central laboratory.

7.1.4.3 A suspension of nuclei is prepared from this biopsy.

7.1.4.4 IdUrd incorporated into the DNA of cells in S phase is detected with a monoclonal antibody linked with a green fluorescent compound. The DNA content per cell is indicated by the intensity of red, propidium iodide fluorescence, with G2 cells having twice the intensity of G1 cells.

7.1.4.5 Flow cytometry is performed to generate a bivariate plot. (Figure 1) of IdUrd content versus DNA content per nucleus.

7.1.4.6 With increasing incubation times, the cohort of IdUrd-labeled cells progressed into G2 phase and around into G1 phase after division. The labeled cells completely clear S phase after an interval of time equal to T_S; 8) the fractions of labeled, undivided, f_{lu}, and labeled divided f_{ld}, cells are determined using the flow cytometer software. These, together with the known time interval between labeling and biopsy are used as described in the text to determine the labeling index, the length of S phase, T_S, and the potential doubling time, T_{pot}.

7.1.5 Toxicities: Potential risks are those associated with halogenated pyrimidine administration, with placement of a temporary i.v. line, and with the tumor biopsy. Studies in several different institutions have utilized i.v. BrdUrd or IdUrd in similar or somewhat larger doses for the purpose of cell kinetics studies [1,13,17,24], all without any evidence of ill effect. Many-times larger doses of BrdUrd or IdUrd, when used for chemotherapeutic purposes, have demonstrated hematologic toxicity, but such an effect has not been reported with the dose levels employed in this study. There is a low risk of infection resulting from placement of an i.v. line. The risks of biopsy are primary bleeding and infection.

7.1.6 Availability: IdUrd will be available through the NCI.

7.3 Adverse Reactions Reporting

7.3.1 Grades 4 and 5 unknown reactions and Grades 2 and 3 unknown reactions. Written report to IDB within 24 hours. A written report to follow within 10 working days.

7.3.2 Grades 4 and 5 known reactions and Grades 2 and 3 unknown reactions. Written report to IDB within 10 working days. Copies to Study chairman and RTOG.

7.3.3 Phone report to Investigational Drug Branch (IDB) within 24 hours (301/230-2330), available 24 hours, recorded after hours.

7.3.4 Address for submitting ADR reports:

Investigational Drug Branch
Box 30012
Bethesda, MD 20824

7.3.5 Further information for reporting Adverse Drug Reactions is detailed in Appendix IV.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

10.1 Biopsy Specimens

10.1.1 Specimens are obtained 4-9 hours after IdUrd labeling by using a True Cut™, punch or forcep biopsy technique as appropriate. If tumor size permits, two separate areas should be biopsied to ensure adequate sampling. The specimen(s) is then dropped into a cooled 70% ethanol/30% saline solution for fixation. The specimen container is wrapped in aluminum foil. Patient information, including labeling and biopsy times, is recorded on the tumor kinetics data sheet.

10.1.2 Specimens are stored at 4° C until sent by regular mail to Dr. Ritter (Section 12.2).

10.1.3 Include the data sheet that indicates when the IdUrd was administered and the biopsy was taken, and an RTOG pathology submission form. (Do not include the pathology report).

10.1.4 Specimen vials and preaddressed mailers are available from Dr. Ritter. See Section 12.5.

10.2 Description of Method

10.2.1 Two hundred (200) mg. of IdUrd is administered in 20 ml saline as a single i.v. push [24], followed 4-9 hours later by a True Cut™, punch or forcep biopsy as appropriate. A minimum of about 0.05 g of tissue is required per assay. The tissue is dropped into a 70% ethanol, 30% saline solution in a labeled specimen jar, covered with aluminum foil, and stored at 4° C until it is shipped via regular mail to the processing laboratory. Upon receipt, the specimen is divided into adjacent specimens for flow cytometry and histology purposes. The sample for histology is paraffin embedded, sectioned, and H & E stained in conventional fashion.

10.2.2 Sample preparation for flow cytometry is largely as has been described.[2, 17, 24] The fixed specimen is incubated with 0.04% pepsin in 0.1N HCl for 60 min at 37°C in a shaker water bath.[15] Next, the tissue suspension is aspirated two times through an 18g needle and filtered through a 35µm nylon mesh. Resulting suspensions of nuclei are centrifuged (1400 rpm, 5 min, 23° C), washed with PBS-TB (PBS with 0.5% Tween-20 and 0.1% BSA), and then counted to aliquot about 2 x 10^6 nuclei per assay. A partial DNA denaturation step is then carried out using 2 N HCl for 30 minutes at 37° C. Neutralization is then achieved using 0.01 M sodium borate and the nuclei are resuspended in a PBS buffer with 0.5% Tween-20 and 0.5% BSA.

10.2.3 Specimens are then incubated with 20 µl of Becton Dickinson non-conjugated, monoclonal antibody that recognizes iododeoxyuridine-substituted DNA. After centrifugation and resuspension in 200µl of PBS-TG (PBS-T with 0.1% goat serum), 200 µl of goat anti-Mouse IgG fluorescence isothiocyanate (FITC) is added at a 1:50 dilution and is incubated for 45 min at room temperature in the dark. The preparation is then resuspended in propidium iodide (PI) at a concentration of 10 µg/ml. Five µg/ml of RNase is added 20 min before carrying out flow cytometry.

10.2.4 Flow Cytometry: Flow cytometric analysis is performed on a FACSCAN (Becton Dickinson) flow cytometer using the 488nm line of the argon ion laser. Data are collected in list mode and bivariate displays of IdUd (FITC - green) versus DNA content (PI - red) are created. Any debris and cell doublets or triplets are excluded from the analysis by gating on DNA pulse width versus pulse area displays. A minimum of 30,000 events are analyzed per sample.

10.2.5 Data Analysis: The duration of S phase, T_S, and the potential doubling time, T_{pot}, are determined using White et al's [17, 21, 23] modifications of the relative movement method.[2] Using LYSIS II™ software (Becton Dickinson), windows are placed around labeled divided (ld) and labeled undivided (lu) nuclei (see Figure 1) and the mean red channel number is determined. In addition, the mean red channel number of GO/G1 and G2/M nuclei are determined from DNA cytograms (# nuclei versus DNA content) using the software, MODFIT™. The mean red fluorescences, F_{lu}, F_{G1}, and $F_{G2/M}$, and the fractions of labeled undivided nuclei, f_{lu}, and labeled divided nuclei, f_{ld}, are thereby obtained. The relative movement (RM), a parameter measuring the degree of shift of labeled cells through S phase, is determined from:

$$RM(t) = (F_{lu}(t) - F_{G1})/(F_{G2/M} - F_{G1}) \quad (1)$$

Next, the value of ν, a parameter related to the labeling index [22] is calculated from:

$$\nu = \ln((1 + f_{lu})/(1 - f_{ld}/2)) \quad (2)$$

First order approximations to White et al's [21] equations 4 or 8 for relative movement as a function of time are used, yielding:

$$RM_S(t) \approx RM_S(0) + t/Ts \qquad (\text{for } t < T_{G2/M}) \quad (3)$$

$$RM_L(t) \approx RM_L(0) + t/2Ts \qquad (\text{for } t > T_{G2/M}) \quad (4)$$

where $RM_S(0)$ and $RM_L(0)$ are the zero time RM intercepts of these linear approximations for times less than or greater than $T_{G2/M}$, respectively. These may be calculated from [23]:

$$RM_S(0) = (1 - e^{-\nu}(1 + \nu)) / (\nu(1 - e^{-\nu})) \quad (5)$$

(for $t < T_{G2/M}$) and

$$RM_L(0) = (1 - e^{-\nu} - \nu e^{-1.3\nu}) / (\nu(1 - e^{-1.3\nu}) \quad (6)$$

(for $t > T_{G2/M}$)

Thus, from Equations 3 and 4:

$$T_S \approx t/(RM(t) - RM_S(0)) \quad (\text{for } t < T_{G2/M}) \quad (7)$$

and

$$T_S \approx t/(2 \times (RM(t) - RM_L(0)) \quad (\text{for } t > T_{G2/M}) \quad (8)$$

Finally, the potential doubling time is determined by [23]:

$$T_{pot} = \ln 2 \times T_s / \nu \quad (9)$$

10.2.6 DNA Index

The DNA index is determined as the ratio of the aneuploid mean red channel divided by the diploid G0/G1 mean red channel number. Mean red channel numbers are determined from the DNA cytograms (# nuclei versus DNA content) by using the software, MODFIT™.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

Biopsy specimens will be analyzed as described above, providing estimates of tumor DNA index, labeling index, length of S phase and, from these two, potential doubling time. Parallel histologic examinations will be performed in order to confirm the presence of tumor. Local-regional control and disease-free and overall survival will be followed in RTOG 90-03.

11.2 Toxicity Monitoring

Monthly evaluation is required for any patient in whom an adverse event (related to drug or procedure) is observed or suspected. Reports are submitted monthly until clearance of toxicity.

12.0 DATA COLLECTION

12.1 Data Submission

Item	Due
Tissue sample Ritter (Section 12.2).	Within one week of biopsy, directly to Dr.
Transmittal Form (ST)	Within one week of biopsy procedure.
Pathology Submission Form RTOG Headquarters.	Originals accompany the biopsy; copies to
Toxicity Summary Form (TS) toxicity occurs, submit monthly to RTOG HQ	Within one week of drug administration. If until clearance (Section 11.2)

12.2 The biopsy along with the transmittal form indicating the time IdUrd was administered and the time the specimen(s) was taken should be sent to:

Mark A. Ritter, M.D., Ph.D.
Department of Human Oncology
UW Comprehensive Cancer Center (K4/542)
600 Highland Avenue
Madison, WI 53792

12.3 The pathology submission form provided by RTOG headquarters (no pathology report) must also be included when sending the biopsy. Copies of the pathology submission form and the transmittal form must be sent to Headquarters.

12.4 **No tumor specimens will be sent to RTOG Headquarters.**

12.5 Specimen vials with fixativeand preaddressed mailers are available from Dr. Ritter for those institutions who have IRB approval to participate in this study. Requests should be made in writing and mailed directly to Dr. Ritter (See Section 12.2) or faxed to his attention (FAX # 608-263-9167).

12.6 Required forms are attached (Appendix V); please copy as needed. **Forms packets will not be be mailed**

"per case" for this study because of the short interval between study entry and specimen submission.

13.0 Statistical Considerations

This study aims at identifying associations between clinical outcome of head and neck cancer and tumor potential doubling time (T_{pot}). Although measures of the magnitude of the effect of T_{pot} on clinical outcome have varied, previous studies have suggested that patients with faster cell doubling times, (lower T_{pot} values) have worse clinical outcome than those with slower cell doubling times (higher T_{pot} values).

It should be realized that this study is predominantly investigative. Trends in investigations of smaller series of patients justify the initiation of a study of this type which will serve to more definitely corroborate or refute these observed trends. If this study demonstrates a sufficiently strong association between disease outcome and T_{pot} this would support consideration of inclusion of this factor as a stratification variable or in determining optimal patient treatment in future trials.

13.1 Sample Size

13.1.1 The total sample size of the related treatment study, RTOG 90-03 is 648 patients. Although all patients entered on the parent study would be eligible to participate in this study by consenting to have the pre-treatment biopsy performed, it is anticipated that not all investigators will present patients with this option. Although this may result in some form of patient selection there is no reason to believe that such selection would result in a bias for recruitment of patients with any particular tumor activity profile.

13.1.2 The primary disease endpoint that will be considered is two-year local-regional control (lrc), as defined in the parent treatment study. Only limited information is available from previous cell proliferation trials on the two-year lrc rates for fast versus slow proliferating tumors. A previous trial[1] quoted overall CR rates for patients followed at least one year as 33% for patients with fast proliferation and 73% for patients with slow proliferation, when treated with conventional RT. Assuming an exponential rate of loss we estimate two-year lrc rates of 11% and 53%, respectively. This suggests an overall two-year lrc rate of 30% in these trials. RTOG trials have seen an overall 25% rate for patients treated with conventional RT. This being the case, we assume the 25% rate is composed of a group of patients with fast proliferating tumors that have a two-year lrc rate of 10%, and a group with slow tumors having a 40% rate. Given that there is this degree of difference in response for these two patient subgroups, a difference would be observable (with 80% power, two-sided alpha=0.05) if we note the disease outcome for 38 patients in each of the two cell proliferation groups treated on the conventional RT arm of the parent study. Allowing for an 85% rate of successful biopsy that allows determination of cell kinetics we will plan to enter a total of 90 patients from the conventional RT arm of the parent treatment study. This constitutes only 56% of the total number of patients (162) planned for treatment on this arm.

13.1.3 The effect of cell doubling time on disease outcome for patients treated by other than the conventional RT regimen, i.e., hyperfractionated or accelerated fractionation schedules, is not well defined. Results from the trial referenced earlier[1] specify a local-regional control rate at one year of 56% for patients with fast cell proliferation and 75% for patients with slow cell proliferation treated with accelerated fractionation. Again, assuming an exponential rate of loss, we calculate the corresponding two-year local-regional control rates to be 31% and 56%, respectively. In the parent study, we assume the overall two-year lrc rate to be 40% for patients treated on the altered fractionation arms. Being somewhat more conservative than the reference study[1], we will assume the overall 40% rate is composed of patients with fast cell cycle times having a 30% two-year lrc rate, and patients with slow cell proliferation having a 50% two-year lrc rate. This being the case, we would observe a difference in response outcome between these two patient subgroups (with 80% power and two-sided alpha=0.05) if we note disease outcome for 103 patients in each of the two cell proliferation subgroups. Allowing for a loss of 15% of all biopsies performed, due to insufficient tumor material, we will require a total of 244 patients from all three of the altered fractionation treatment arms (approximately 82 patients from each treatment arm). This constitutes only 50% of the total number of patients (486) planned for treatment on the three altered fractionation arms.

13.1.4 In total, **334 patients will be entered onto this study**. This will require approximately half of all patients entered onto the parent treatment trial, RTOG 90-03, to consent to participate in this study.

13.2 Analysis Plans

13.2.1 Descriptive statistics on the T_{pot} values resulting from the patient assays will be compiled when approximately half of the assays are performed, and again when assay information is available for all patients entered onto this study.

13.2.2 Examination of the relationship between cell doubling time and disease outcome will be conducted using various specifications of the logistic model, where the binary outcome of local-regional control at two years is modeled by numerous concomitant variables, including a binary measure of cell doubling time ("slow" or "fast") as well as the continuous T_{pot} measure. Stepwise analysis procedures will be invoked to determine if the predictive value of the T_{pot} measure significantly contributes to the information obtained from other concomitant variables known to be related to disease outcome (e.g., age, KPS, T-Stage, N-Stage, site of primary), as well as assigned treatment. If it is found that the term in the model associated with the T_{pot} measure drops out of the model in the presence of other known prognostic variables, then we will conclude the additional information provided by the T_{pot} assay is of

limited value. The retention of this term in the model would demonstrate meaningful contribution of the results of the T_{pot} assay in the predication of disease outcome. Appropriate interaction effects will also be examined to investigate whether the information provided by the T_{pot} assay is of greater relevance for specific patient subgroups or when a specific treatment is administered.

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APPENDIX I

RTOG 92-11

CORRELATION OF CLINICAL OUTCOME AND THE TUMOR POTENTIAL DOUBLING TIME IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK COMPANION STUDY FOR RTOG 90-03, HEAD AND NECK CANCER

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 as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply 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 a malignant tumor in my head and neck. The purpose of this study is to participate in a research project investigating the rate of tumor cell growth. This may be helpful in allowing us to understand how rapidly tumor cells divide and how this rate of division might affect cancer therapy. The study involves giving me a type of drug that is incorporated into growing tumor cells, allowing us to track how rapidly these cells are dividing . It is hoped that information obtained might eventually help in determining the best method of treatment.

My participation is entirely voluntary and not part of my routine care. If I choose not to participate, it in no way will effect the quality of care available to me.

DESCRIPTION OF PROCEDURES

The study will involve a small biopsy of my tumor prior to my first radiation treatment on RTOG 90-03. Four to nine hours before the biopsy, I will be given an intravenous (i.v.) infusion of the drug, IdUrd, over a five minute period. This will "tag" the tumor and allow a determination of how rapidly it is dividing. The drug will be provided to me without charge to me by the National Cancer Institute. Other possible associated biopsy changes will be explained by my doctor.

RISKS AND DISCOMFORTS

The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.
Risks: The possible risks of this study are those associated with administration of the drug IdUrd, and with the biopsy. IdUrd is an experimental drug that is incorporated into genes in place of a normal component of genes. Because the dose of this drug to be used in my case is so small, side effects are not anticipated. Ill effects have not been reported in patients receiving similar doses of IdUrd. However, many-times larger doses of IdUrd than will be used in this study can cause temporarily decreased numbers of white blood cells and platelets, skin rash, or sensitivity to light.

The risks of a biopsy are primarily bleeding and infection. Every effort will be made to take the proper precautions to avoid these problems and my doctors will check me to be sure that such problems are not developing.

All patients participating in this study will require the brief placement of an intravenous line for administration of the drug. The placement of such a line causes temporary discomfort, and there is also a small risk of infection. Again, I will be carefully monitored to assure that no side effects are occurring.

My physician will be checking me closely to see if any of these side effects are occurring. 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.

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 or 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.

The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand I am free to ask my physician any questions concerning this program that I may wish in the future.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others.

ALTERNATIVES

An alternative is to not participate in this study. 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.

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 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 drug manufacturer, the National Cancer Institute (NCI) 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 slides, may be sent to a central office for review. 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 IV

ADVERSE DRUG REACTION REPORTING GUIDELINES

General Toxicity Reporting 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.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reaction. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150).

2. The Principal Investigator will also report to the Study Chairman by telephone the details of the significant reaction.

3. When directed, a written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to RTOG Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol.

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), when feasible, 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 (Adverse Reaction Reports or Drug Experience Reports) submitted to NCI, IDB, FDA, or to another Cooperative Group (in the case of RTOG sponsored intergroup studies) must also be submitted to RTOG Headquarters when written documentation is required.

6. When telephone reporting is required, the Principal Investigator should have all relevant material available. See attached reporting form for the information that may be requested.

7. See the specific protocol for criteria utilized to grade the severity of the reaction.

8. The Principal Investigator when participating in RTOG sponsored intergroup studies is obligated to comply with all additional reporting specifications required by the individual study.

9. Institutions must also meet their individual Institutional Review Board (IRB) policy with regard to their toxicity reporting procedure.

10. Failure to comply with reporting requirements in a timely manner may result in suspension of participation, of application for investigational drugs or both.

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.

An unknown adverse reaction is a toxicity thought to have resulted from the agent but had 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 (≥ 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. Form 1639 is to be used in reporting details (see attached). All relevant data forms must accompany the RTOG copy of Form 1639.

iii. All neurotoxicities (≥ 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 and 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 only a reasonable suspicion.

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

i. Phase I Studies Utilizing Investigational Agents

- All deaths during therapy with the agent.	Report by phone within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.
- All deaths within 30 days of termination of the agent.	As above
- All life threatening (grade 4) events which may be due to agent.	As above
- First occurrence of any toxicity (regardless of grade).	Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. **A written report may be required.

ii. Phase II, III Studies Utilizing Investigational Agents

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

- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.	Report by **phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.	**Report **in writing** to RTOG Headquarters and IDB within 10 working days.

** See attached NCI Adverse Drug Reaction Reporting Form