RADIATION THERAPY ONCOLOGY GROUP

RTOG 93-04

PHASE III CONVENTIONAL THERAPY WITH OR WITHOUT RECOMBINANT b-INTERFERON FOR PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER

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SCHEMA

STATIFY

Weight Loss
(in last 3 months)
1. < 5%
2. ≥ 5%

Stage
1. IIIA
2. IIIB

RANDOMIZE

Arm 1 Radiation therapy to the chest 2 Gy once a day, five days a week for a total of six weeks. Total dose 60 Gy.

plus

16×10^6 IU β-interferon given by i.v. bolus on the first three *consecutive* days of treatment in conjunction with radiation therapy: *(Mon-Wed, Tue-Thurs, or Wed-Fri)* on weeks one, three and five

Arm 2 Radiation therapy to the chest 2 Gy once a day five days a week for a total of six weeks. Total dose 60 Gy.

Arm 1: On the *first three consecutive days of treatment with radiation therapy*, β-interferonwill be given 30 minutes before radiation therapy. This may be done on Monday through Wednesday, Tuesday through Thursday, or Wednesday through Friday. Weeks three and five will be identical to this for a total of nine doses of β-interferon. The other two days of the week, radiation only is given. The same three days should be used throughout the treatment for β-interferon administration. *(e.g., if the patient begins treatment on Tuesday the first week, the other weeks of b-interferon administration will also begin on Tuesday).* During weeks two, four and six, radiation therapy is given alone.

Arm 2: Radiation therapy without interferon. Treatment will be five days a week, Monday through Friday for a total of six weeks.

Eligibility: *(See Section 3.0 for details)*

- Histologically confirmed non-small cell lung cancer
- Loco-regionally advanced tumor without evidence of hematogenous metastases *(Stages IIIa or IIIb)*, who are considered inoperable or are found to be unresectable at surgery
- Primary tumor measurable or evaluable radiographically
- Age ≥ 18
- Karnofsky performance status ≥ 50 but ≤ 70. Patients with KPS > 70 will be eligible only if they have weight loss of more than 5% in the past three months
- No prior non-cutaneous malignancies unless disease-free ≥ 5 years
- No unexplained liver function test abnormalities
- Serum creatinine ≤ 1.5, BUN ≤ 25
- Serum Hgb ≥ 8.0 gm/dl, WBC count ≥ 4,000 and platelet count ≥ 100,000
- Satisfactory pulmonary function as defined by FEV_1 of 800 ml or more
- Signed study-specific informed consent form

Required Sample Size: 166
Case credit : TWO, effective 6/3/96

2/14/95
6/3/96

Institution # _____
RTOG 93-04
Case # _____

ELIGIBILITY CHECK (2/14/95, 6/3/96)
(page 1 of 1)

_____(Y) 1. Is the malignancy a loco-regionally advanced non-small cell cancer without evidence of hematogenous metastases?

_____(IIIa/b) 2. What is the stage?

_____(N) 3. Is the patient operable?

_____(Y) 4. Is the primary measurable or evaluable radiographically?

_____(≥ 18) 5. Patient's age?

_____(≥ 50) 6. Patient's KPS?

_____(Y) If KPS is > 70, has the patient had a weight loss of > 5% in the three months prior to diagnosis?

_____(Y/N) 7. Has the patient had a prior malignancy other than skin within the past last 5 years?

_____(Y) If yes, has patient been disease free ≥ 5 yrs?

_____(N) 8. Is there evidence of distant mets?

_____(Y/N) 9. Does the patient have any abnormal liver function tests?

_____(Y) If yes, are the abnormalities due to nonmalignant conditions?

_____(≤ 1.5) 10. State the serum creatinine.

_____(≤ 25) 11. State the BUN.

_____(≥ 8) 12. What is the hemoglobin?

_____(≥ 4) 13. What is the WBC *(per 1000)*?

_____(≥ 100) 14. What is the platelet count *(per 1000)*?

_____(Y) 15. Does the patient have satisfactory pulmonary function as defined by FEV_1 of ≥ 800 ml?

_____(N) 16. Has the patient received any prior radiation or chemotherapy?

_____(N) 17. Has the patient had a myocardial infarction within 6 months of diagnosis of lung cancer?

_____(N) 18. Does the patient have symptomatic heart disease *(angina, congestive heart disease, uncontrolled arrythmia)*?

_____(N) 19. Was patient operated upon for cure, and may now have intrathoracic recurrence?

_____(N/NA) 20. Is the patient pregnant or lactating?

_____(Y/NA) 21. Has the patient been advised regarding contraception and avoiding pregnancy during treatment?

Institution # _____
RTOG 93-04
Case # _____

ELIGIBILITY CHECK (2/14/95, 6/3/96)
(page 2 of 2)

_____(Y) 22. Did the patient sign a study-specific informed consent form?

_____(Y/N) 23. Is there evidence of pleural effusion?

_____(Y/N) If yes, did it appear only after a thoracotomy or mediastinotomy was attempted.

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID#

_____ Referring Institution

_____ Weight loss *(< 5% vs ³ 5%)*

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code *(9-digit if available)*

_____ Method of Payment

_____ Treatment Start Date

_____ Treatment Assignment

Completed _____ Date _____

1.0 INTRODUCTION

1.1 Background *(refers to studies reported in old IU's)*

In 1992, 168,000 new cases of lung cancer will be diagnosed and it will be the cause of death in 146,000 men and women.[1] Worldwide, lung cancer results in one death every minute year round and it is estimated that by the year 2000 the annual incidence will be two million. The majority of patients present with advanced, unresectable disease for which radiation therapy is the standard form of treatment. Unfortunately the prognosis remains poor, regardless of therapy administered, with 5 year survival rates in the range of 5-7%.[2-4] New strategies are desperately needed and any improvement in the therapeutic ratio would benefit a significant number of patients.

Besides the established antitumor effects of interferon alone, there is evidence that interferon increases radiation cytotoxicity in vitro *(Table 1)*.

TABLE 1

PRECLINICAL STUDIES UTILIZING COMBINED INTERFERON AND RADIATION

System	Interferon Type	Results/Conclusions	References
Murine Swiss 3T3 cells	Mouse L cell	Potential of radiation: reduction of the shoulder of the radiation survival	5
Human glioma cells *(U-118, U-251)*	Human alpha	Additive effect on growth delay	6
HeLa cells	Human beta	Synergistic cytotoxic effect: reduction of the shoulder of the radiation survival curve	7
Human bronchogenic carcinoma cells	Human alpha and beta	Sensitization of radiation killing by interferon beta, but not by interferon alpha: reduction of the shoulder of the radiation survival curve	8
Lewis lung carcinoma in C57 B1 mice	Interferon inducer, poly *(ICLC)*	Improved tumor response and survival in vivo following combined interferon inducer and irradiation	9
Human hypernephroma tumor cells	Human alpha beta, gamma	Potentiation of radiation killing, associated with increased blockage at the G2-M phase of the cell cycle	10

Clinical studies are necessary to evaluate increased antitumor effects of combined interferon and radiation. Alpha-interferon combined with radiation in the treatment of localized small cell lung cancer resulted in the development of radiation pneumonitis in six of 14 patients, three of whom died shortly after completing radiation with no evidence of tumor at autopsy.[11] Beta-interferon (IFN-β) appears to be less toxic[12] and better tolerated than a-interferon and has demonstrated radiosensitization of human bronchogenic carcinoma cells.[8]

Betaseron[R] *(recombinant human interferon beta$_{ser}$, rHuIFN-β$_{ser}$, Berlex Laboratories, Richmond, CA [formerly Triton Biologics, purchased by Shering AG]* [21,22,23] is less toxic and better tolerated than either HuIFNa *(Le)* or rHuIFN-a2[12] and has approximately the same potentiation effect on radiation cytotoxicity of ACHN cells as rHuIGN-aD. In a study with A549 human lung adenocarcinoma cells, Gould[8] showed that HuIFN-b, but not HuIFN-a, potentiated the cytolethal effects of radiation.

Tolerance to Betaseron[R] therapy has been evaluated in a total of 3,000 subjects in phase I, II, and III clinical trials. Sixty-four percent of these subjects were treated in studies involving intravenous, subcutaneous, intramuscular, or intracerebral therapy; 34% were enrolled in studies evaluating intranasal treatment, and the remaining 2% participated in topical or intravesical studies. Overall, therapy has been

well-tolerated by all routes of administration and at a variety of doses and schedules. Eight phase I studies have evaluated tolerance to Betaseron[R] in subjects with advanced cancer. Treatment was given intravenously, intramuscularly, or subcutaneously; both escalating and fixed-dose regimens were investigated. In one study which compared Betaseron[R] and natural β-interferon, no differences were seen in safety and tolerance between the two treatment groups. Maximum tolerated single doses *(MTD)* defined in these studies were 60 to 300 million *(10.67 - 17.78 MIU, new IU units)* intramuscular and 10 to 400 million IU *(1.78 - 71.1 MIU new units)* intravenous.[12,13]

A phase I/II study, based on in vitro evidence of radiosensitization by Betaseron[R][10] was undertaken at the University of Rochester Cancer Center(URCC).[24] The objectives were to determine the safety, and tolerance of escalating doses of Betaseron[R] given in combination with radiation therapy and to evaluate the efficacy of this combined treatment. Eligible patients had histologically proven non-small cell lung cancer which was considered to be inoperable. Patients with recurrent disease post surgery or with metastatic disease, except brain or liver metastases, were eligible. Patients who had prior radiation or chemotherapy were ineligible.

Treatment was given in the following manner *(Fig. 1)*: Radiation to the chest, including the primary tumor with a 2 cm margin and the regional lymph nodes, was given in 1.8 Gy fractions, 5 fractions/week for six weeks, for a total dose of 54 Gy. Betaseron[R] was administered as an i.v. bolus 30 minutes prior to radiation on days 1, 2, and 3 of treatment and again on days 11, 12, 13 and 21, 22, 23 for a total of nine administrations. The dose of Betaseron[R] per administration was escalated after acceptable toxicity was established in at least six patients at each dose level. This escalation began at 10 million units and advanced to 30 to 60 to 90 million units. After acceptable toxicity was established for the highest interferon dose, the radiation dose was increased to 59.4 to bring the radiation therapy dose into line with current standard treatment.

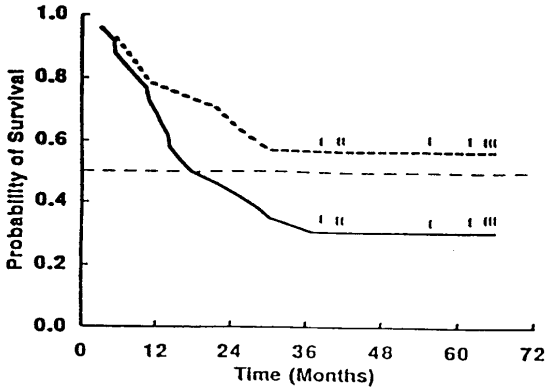
Figure 1: Treatment Schema

Thirty-nine patients were accrued to this study. The numbers of patients at Betaseron[R] dose levels 10, 30, 60, 90 x 10^6 *(and 54 Gy)* were 6, 6, 8, 6 respectively. An additional 13 patients were treated at 90 x 10^6 units IFN-β with increased radiation dose at 59.4 Gy. Seven patients were excluded from analysis due to histology, non-completion of treatment or becoming lost to follow-up. Therefore 32 patients were evaluated. There were 18 male and 14 female patients. Their median age was 61.9 years. Fifty percent had adenocarcinoma, 34% squamous cell carcinoma and the rest large cell and adenosquamous carcinoma. Twenty-six patients *(66%)* had stage III disease and 11 patients *(34%)* had metastatic disease or recurrent disease post surgical resection. Thirteen patients *(41%)* had poor performance criteria as defined by a Karnofsky Performance Status *(KPS)* of 70 and/or more than 5% decrease of body weight in three months prior to diagnosis. The median tumor size was 6.9 cm. Response to therapy was measured using CT scans of the chest, which were performed every three months post treatment for at least two

years. Partial response was defined as 50% or more reduction in tumor size. Complete response *(CR)* was defined as complete disappearance of tumor with a scar density remaining on the CT. Local control was defined as stabilization of scar density for at least six months after a CR had been achieved. Response of interferon treated patients was compared to a control group of 45 patients with stage III disease treated with radiation only at the University of Rochester. Response to therapy is shown in Figure 2.

Figure 2: Response to stage III and IV patients treated with Betaseron^R is compared to response of stage III patients treated with radiation therapy only. Complete response is represented by the open bars and partial response by the shaded bars.

Local control was achieved in 14 of the 32 patients *(44%)* treated with Betaseron^R and radiation and partial response was achieved in 12 patients *(38%)*. The Kaplan-Meier survival curve for the 14 patients, both stage III and IV, achieving local control is shown in Figure 3; of these more than 50% have survived 3 to 5 years. For the stage III patients in Figure 3 *(solid line)* the actuarial 3 and 5 year survival is 31% and plateaus after 3 years. The Kaplan-Meier survival for the Betaseron^R treated patients is compared with the survival of 45 stage III patients treated with radiation therapy alone in Figure 4. The Betaseron^R treated patients achieved a median survival of 19.7 months versus 12.5 months for the historical control group. This represents a substantial gain in survival compared to the best arm of RTOG 73-01 in which 3 and 5 year survival was 15% and 4.6% respectively. The median follow up is 60 months, with a minimum of 30 months. There are eight survivors in the interferon treated patients all of whom had stage III disease; all the patients with metastatic or recurrent disease have died. Of the survivors, five had adenocarcinoma, and all had tumors in the upper lobes, with the exception of one who had a right middle lobe tumor. All eight received 30 million units or higher of Betaseron^R. Toxicity was minimal; side effects of Betaseron^R are summarized in Table 2. There were no treatment related deaths nor any event of life threatening toxicity. Of the eight patients surviving 3 to 5 years, KPS indices of 90 to 100 have been maintained, respiratory symptoms are minimal and no long term toxicity has been observed. Fibrosis, measured by radiographic criteria, appeared to occur less than in the matched control group. Of particular interest was the fact that volume loss, as a measure of late radiation lung damage, was seen much less in the Betaseron^R treated patients than the radiation only control group.



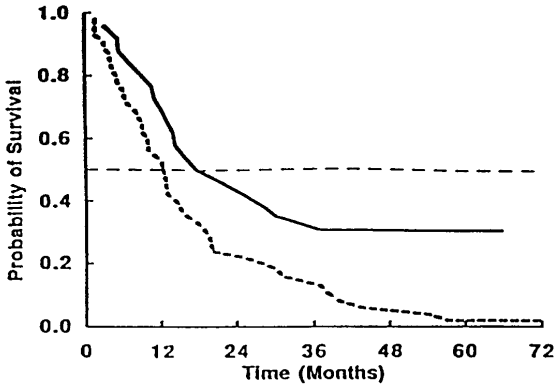


Figure 3: K-M Survival for all stage III patients treated with Betaseron[R] and radiation therapy *(n=26) (solid line)* is compared to those who achieved complete response *(n=14) (dotted line)*

Figure 4: K-M Survival for stage III patients treated with Betaseron[R] and radiation therapy *(solid line)* is compared to survival of 45 stage III patients treated with radiation therapy only *(dotted line).*

TABLE 2: OCCURENCE OF TOXICITIES IN URCC β-IFN/RT STUDY

IFN Grade 3 or 4 Toxicity		
Fever	13%	
Headache	9%	
Nausea/Vomiting	9%	
RT Effects	IFN Trial	U of R Controls
Pneumonitis	13%	13%
Fibrosis	41%	53%
Volume Loss	3%	24%

2.0 OBJECTIVES

2.1 To determine if the addition of β-IFN to conventional radiation therapy can improve the local control rate for patients with locally advanced NSC lung cancer without unacceptable morbidity.

2.2 To determine if the addition of β-IFN to conventional radiation therapy can improve the survival rate for patients with locally advanced NSC lung cancer with unfavorable performance status.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (6/3/96)

3.1.1 Histologically confirmed non-small cell lung cancer patients with loco-regionally advanced tumors without evidence of hematogenous metastases *(Stages IIIa or IIIb, see Appendix III)* who are considered inoperable or are found to be unresectable at surgery provided they meet all eligibility requirements in this section.

3.1.2 The primary tumor must be measurable or evaluable radiographically.

3.1.3 Age ≥ 18.

3.1.4 Karnofsky performance status ≥ 50 but ≤ 70. *(See Appendix II.)* Patients with KPS >70 will be eligible only if they have weight loss of more than 5% in the past three months.

3.1.5 No prior non-cutaneous malignancies unless disease-free ≥ 5 years.

3.1.6 No pleural effusion *(negative or positive)* or unexplained liver function test abnormalities. Elevation of liver functions must be non-cancer related.

3.1.6.1 Pleural effusion appearing only after thoracotomy or other invasive thoracic procedure was

attempted is eligible. **(2/14/95)**

3.1.7 Serum creatinine ≤ 1.5 mg/dl. BUN ≤ 25 mg/dl.

3.1.8 Serum Hgb ≥ 8 gm/dl *(transfuse as needed to achieve and maintain this level during radiation)*, WBC count ≥ 4000/mm^3, and platelet count ≥ 100,000/mm^3.

3.1.9 Satisfactory pulmonary function as defined by FEV_1 of 800 ml or more.

3.1.10 Patients must sign a study-specific informed consent form.

3.1.11 Patients must not be eligible for RTOG 93-09. **(2/1/96)**

3.2 Ineligibility Criteria (6/3/96)

3.2.1 Undifferentiated small cell *(oat cell)* carcinoma, any stage.

3.2.2 Stage I, II, or IV non-small cell lung carcinoma.

3.2.3 Patients with complete tumor resection.

3.2.4 Patients operated upon for cure who have intrathoracic recurrence.

3.2.5 Karnofsky performance status < 50 or > 70 *(KPS > 70 is eligible only if weight loss is greater than 5%).*

3.2.6 Patient age < 18.

3.2.7 Patients with a concurrent malignancy. Prior malignancy *(except for non-melanomatous skin cancer)* is ineligible unless disease free for ≥ 5 years.

3.2.8 Patients who have received prior radiotherapy or chemotherapy.

3.2.9 Patients refusing to sign the informed consent form.

3.2.10 Serum creatinine > 1.5, BUN > 25, WBC < 4000 /mm^3, platelets < 100,000/mm^3, hemoglobin < 8.0 gm/dl.

3.2.11 Unexplained or cancer-related liver function test abnormalities, any pleural effusion, or distant metastases.

3.2.12 Patients with a myocardial infarction within six months or symptomatic heart disease including angina, congestive heart failure, uncontrolled arrhythmia are ineligible.

3.2.13 Concomitant chemotherapeutic agents or other investigational agents while on study.

3.2.14 Pregnancy or lactation. Women capable of childbearing must take adequate precautions to prevent pregnancy during treatment.

3.2.15 Significant CNS dysfunction *(with seizure activity)* within the past year.

4.0 PRETREATMENT EVALUATIONS (6/3/96)

4.1 History & physical to include neurologic exam.

4.2 Chest X-Ray; chest and abdominal CT scan within one month of registration.

4.3 Surgical staging optional

4.4 Complete staging workup including brain CT and bone scan within six weeks prior to randomization.

4.5 CBC; platelets, calcium, bilirubin, urinalysis, EKG; blood for cytokine studies *(see Appendix VII).*

4.6 SAP, SGOT, creatinine.

4.7 VC, FEV_1, DLCO *(pulmonary function tests).*

4.8 Weight and KPS.

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
- Physician's Name
- Eligibility Criteria Information
- Stratification Information
- Demographic Data
- Treatment Start Date

6.0 RADIATION THERAPY

6.1 Treatment Regimen

The total dose to involved areas will be 60 Gy. This will be administered at 2 Gy daily 5 times weekly to deliver 50 Gy target dose in 5 weeks to the large field. An additional 10 Gy to be delivered to initial tumor with reduced fields at 2 Gy daily in five days for a total dose of 60 Gy.

6.2 Treatment Techniques

6.2.1 *Doses*: All doses are to be prescribed and calculated assuming a homogeneous patient, that is there will be no heterogeneity corrections used in the definitions in these doses. The doses shall be prescribed and calculated according to the following RTOG guidelines for external treatments using photons and electrons *(Section 6.2.1.7)*:

6.2.1.1 At the center of the target area on the central ray for a single beam.

6.2.1.2 At mid-separation on the central ray for two opposed coaxial equally weighted beams.

6.2.1.3 At the center of the area on the central ray for two opposed coaxial unequally weighted beams.

6.2.1.4 At the point of intersection of the central rays for two or more intersecting beams which are not coaxial.

6.2.1.5 At the center of the rotation in the plane of rotation containing the central axis for rotation or arc therapy.

6.2.1.6 At the center of the target area for complex treatment arrangements which are not covered above.

6.2.1.7 At the depth of maximum build-up, for single electron beams. Select an electron beam energy which provides at least 90% dose at 3 cm depth

Two different target volumes shall be considered, the initial large field target volume consisting of primary and mediastinum and the boost target volume consisting of the primary and involved nodal area only.

In treating the initial fields, various sets of fields may be used, which may be coplanar but not coaxial or may not even be coplanar. No part of the field lesion and hilar and mediastinal lymph nodes *(within a 2 cm margin)* will receive a dose less than 48 Gy from the initial large fields. In cases where the central rays of the large fields do not intercept the center of the boost target volume, it will be necessary to calculate the contribution from the initial sets of fields to the center of the boost target volume. The maximum dose in any part of either target volume should not exceed the prescribed dose by more than 15%.

Irregular field type of calculations may be required to determine the doses to the center of the target volume and the various nodal groups from the initial fields.

The final dose to the center of the boost target volume is 60 Gy. Since there may be a difference between the dose delivered per fraction from the initial boost fields, which is 50 Gy, and the dose received to the center of the boost target volume, it may be necessary to adjust the dose delivered per fraction in the boost portion of the treatment regimen or to change the number of fractions of the boost fields. Deviations of the daily dose of up to 5% are allowed. In patients where the difference in dose between the initial large field target volume and boost target volume is such that a 5% change in the boost dose would not result in the proper final dose being delivered by the prescribed number of fractions, additional fraction(s) can be added to reach the dose of 60 Gy.

As an example of the above, assume that a patient who is being treated according to the protocol receives 48 Gy to the center of the boost target volume after 50 Gy has been delivered along the central rays of the initial fields at the point of mid-separation of the beams. The center of the target volume has received 2 Gy less than prescribed. This patient could then receive on extra fraction of 2 Gy to the boost field.

6.2.2 *Irradiation Portals*: The irradiated target volume must be defined by the individual shaped ports with secondary lead blocking or tailor-made blocks.

6.2.2.1 Target volume of primary tumor

a) Includes complete extent of visible primary tumor as defined radiographically with a minimum of 2 cm and a maximum of 2.5 cm around the mass.
b) Entire lung may be included for extensive lesions if complicated by atelectasis or pneumonitis.

6.2.2.2 Target volume of lymph nodes. The following nodes must be included: **(2/14/95)**

a) Supraclavicular lymph nodes - if primary is in upper lobes and main stem bronchus lesions. It is acceptable to treat the ipsilateral supraclavicular nodes only.
b) Ipsilateral hilar lymph nodes - always *(2 cm margin)*
c) Superior mediastinal lymph nodes *(above carina)* - always *(ipsilateral 2 cm margin).*
d) Subcarinal lymph nodes *(contralateral 1 cm margin to 5 cm below carina)* - always.
e) Inferior mediastinal to diaphragm with lower lobe lesions only, *(margin as above)*

6.2.3 *Technical Factors*

6.2.3.1 Beam Energy. Megavoltage equipment is required with effective photon energies higher than 1 MeV. Electrons with at least 90% dose at the depth of maximum build up may be used to boost supraclavicular lymph nodes. Provide verification of electron fields by simulation and portal films and/or polaroids.

6.2.3.2 Treatment Distance. Minimal treatment distance to skin should be 80 cm for SSD technique and minimum isocenter distance should be 80 cm for SAD techniques.

6.2.3.3 Blocking

a) In the case of x-ray beams, the primary collimation may be used, and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be irradiated.

b) However, with Cobalt 60, beam trimmers or secondary blocking must be used all the way around the ports.

6.2.3.4 Compensating Filters or Wedges

In the case of a large sloping contour, such as is usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may also be used as a two dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation to critical structures.

6.2.3.5 Fractionation

a) Each field to be treated every day.

b) Adherence to the fractionation schemes is required although slight deviation in the daily dose fraction is allowed *(+5%).*

6.2.3.6 Therapy Interruptions

a) If interruption of therapy up to two weeks becomes necessary, irradiation should be completed to the prescribed doses. **Total number of fractions and elapsed days should be carefully reported and documented in the treatment record.**

b) Betaseron will be discontinued during any interruption of radiation therapy. When radiation therapy is resumed the patient will be considered to be in the same point in the schedule where he/she was at the time of the interruption. For example, if treatment is interrupted at the end of week 3, when it is resumed it will be considered the beginning of week 4 and no drug will be given until the following week the "new" week 5.

c) If more than a two week interruption is required, resumption of the treatment is at the discretion of the radiation oncologist. The patient will be considered a major protocol deviation although follow-up will be continued.

6.2.3.7 Treatment Planning

a) Treatment planning should be performed in accordance with the prescribing doses to each target volume, together with restrictions in dose to normal tissues as given in Section 6.2.4.

b) An isodose distribution at the mid-transverse plane of the boost target volume should be submitted. Provide a composite if the capability exists at your institution.

c) In addition to the isodose distribution, the following specific points of dose calculation should be included:

1) Spinal Cord Dose. If compensating filters are not used the point at which the spinal cord dose is to be calculated is 2 cm below the superior margin of the posterior field. If compensating filters or wedges are used then the point of maximum dose to the spinal cord must be determined. **Maximal spinal cord dose should not exceed 45 Gy at any level**. **Daily cord dose must be recorded in treatment chart.**

2) Subcarinal Nodes. Assumed to be at mid-plane.

3) Ipsilateral Normal Lung Dose. This is to be calculated at the level of the central rays of the boost fields at the point of maximum dose in the lung which lies at least 2 cm outside the projected borders of the initial treatment fields in the ipsilateral lung.

4) Contralateral Normal Lung Dose. This is to be calculated at the level of the central rays of the boost field at the point of maximum dose in the lung which lies at least 2 cm outside of the projected border of the initial treatment fields in the contralateral lung.

5) Maximum Normal Tissue Dose. This is to be calculated at level of the central rays of boost fields as the maximum total dose at least 2 cm outside of the target volume.

6.2.3.8 Localization Films

Localization films taken on simulators and/or on the treatment machine will be necessary in all cases. Film copies of all fields treated should be submitted to Headquarters.

6.2.3.9 Dosimetry Monitoring

The American Association of Physicists in Medicine *(Radiological Physics Center, Houston, Texas)*

may conduct a field survey of equipment in the participating institutions.

6.2.3.10 Rapid Turnaround Review and Final Dosimetry Review

All initial dosimetry and final dosimetry material specified in Section 12.0 must be submitted directly to RTOG Headquarters, 1101 Market St., 14th Floor, Philadelphia PA 19107 accompanied by a dosimetry transmittal sheet.

6.2.4 *Anticipated Side Effects or Toxicities*

6.2.4.1 Suggested maximum uncorrected doses to critically sensitive normal structures:

Organ	Maximum Doses
Normal Lung	
Ipsilateral	25 Gy
Contralateral *(only if necessary)*	20 Gy
Spinal Cord *(maximum Dose)*	45 Gy
Heart	
Entire Organ	45 Gy
Less than 50%	50 Gy
Esophagus	60 Gy

6.2.4.2 The uncorrected dose to the spinal cord must be limited to 45 Gy.

A posterior spinal cord shield will not be an acceptable technique. Oblique or lateral field arrangements should be considered. Utilization of a posterior spinal cord shield will result in a variation at final review.

6.2.4.3 Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy, while radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiation pneumonitis occurs in about 15% of patients while the subsequent fibrosis of the lung will occur in 100% of patients receiving 40 Gy to the lung, usually within the first six months after initiation of treatment so it is essential to spare all the normal lung possible.

6.2.4.4 Radiation therapy may be interrupted for periods of up to 10 treatment days for significant *(³ grade 3)* esophagus toxicity: i.e. inability to tolerate liquids, and/or supplemental feedings are necessary. Patients experiencing grades 3-4 toxicities will be followed weekly until the resolution of toxicity to ≤ grade 2.

6.2.4.5 Post-treatment pneumonitis thought due to radiation should be treated with prednisone after excluding microbial causes.

7.0 DRUG THERAPY

7.1 Drug Information b-Interferon (NSC#660166)

In July 1993, Berlex informed the NCI that the standard for potency of the international units of IFN Beta was changed. The new labels identify the vial contents as 9.6 x 10^6 international units *(IU's)* per vial. Previously, the labels expressed the contents of 54 x 10^6 IU/vial. **The vial content *(0.3 mg)* has not changed.** However, studies older than July 1993 may refer to doses of Interferon Beta which are expressed in the old potency units.

7.1.1 Betaseron^R is a genetically altered, recombinant human interferon in which serine has been substituted for the cysteine residue normally found at position 17 of the β-IFN molecule. The resulting molecule exhibits a specific activity similar to that of active β-IFN and in vitro studies have shown that the biological properties of the two molecules are remarkably similar.

7.1.2 *Animal Tumor Data* *(refers to studies reported in old IU's)*

The pharmacokinetics of Betaseron^R have been studied in African green monkeys. The first study evaluated twice daily dosing by the intravenous, intramuscular, and subcutaneous routes at several dose levels.[19] The intravenous dose was 1 million IU/kg; doses of 1 and 10 million IU/kg were evaluated for the intramuscular and subcutaneous routes. For the 1 million IU/kg dose groups, serum interferon concentrations in samples taken just prior to either subcutaneous or intramuscular administration on day 10 ranged from 50 to 200 IU/ml. At the 10 million IU/kg level, serum interferon values were in the 300 to 2,000 IU/ml range. These values indicate that on the repeated dosing regimen used, interferon may be accumulating in the serum. At the 1 million IU/kg dose level, bioavailability after a single subcutaneous dose was calculated to be 31%. Comparison of area under the curve *(AUC)* for the 1 million IU/kg and 10 million IU/kg doses did not result in a ratio of 1:10. These results may indicate that the pharmacokinetic parameters for Betaseron^R are not linearly related to dose in this model.

7.1.3 *Supply*: B-Interferon is manufactured by Chiron Corporation for Berlex Laboratories which then distributes vials to NCI's Cancer Therapy Evaluation Program for use in NCI-sponsored studies. Investigators will order β-Interferon from NCI using the NIH-986 Drug Order Form.

7.1.4 *Formulation/Reconstitution*: Interferon Beta *(Berlex)*, is provided as a sterile lyophilized powder. Each 5cc vial, labeled 9.6 x 10^6 IU/vial, contains 0.3 mg of Interferon Beta, albumin human USP, and dextrose for solubilitiy and stability. Each Interferon Beta vial is shipped with a vial containing 2 ml of sterile 0.54% Sodium Chloride in water for use as a diluent. Each vial of Interferon Beta should be aseptically reconstituted with 1.2 ml of diluent, then gently swirled to dissolve the lyophilized cake. Diluent should be directed against the side of the vial to avoid excess foaming. The resultant solution contains 0.25 mg/ml of Interferon Beta *(8x 10^6 IU/ml)*. Two vials of Interferon Beta should be prepared for each administration. Before use, the solution should be inspected visually for particulate matter and discoloration. **(6/3/96)**

7.1.5 *Storage*: Intact vials are stored in the refrigerator (2-8° C/36-48° F) with protection from light. Each vial of interferon bears an expiration date. Since vials of drug and dilutent contain no preservative, **reconstituted solution should be used within three hours**.

7.2 Dosage of Betaseron^R (6/3/96)

Betaseron^R will be given i.v. bolus on the first three consecutive days of treatment in conjunction with radiation therapy *(Monday through Wednesday, Tuesday through Thursday, or Wednesday through Friday)* in weeks one, three and five of radiation therapy, for a total of nine doses. The administration of ß-IFN must continue on the same three days of weeks one, three and five, i.e., if the first dose is given on Monday of week one, then it will begin on Monday of weeks three and five. If it begins on Tuesday on week one, then it will begin on Tuesday of weeks three and five, etc. Betaseron® dose will be 16 x 10^6 IU *(2 ML)*. **One ml of reconstituted Interferon Beta should be extracted from each vial.** Sterile technique should be used when administering Betaseron®. Patients may be premedicated with acetaminophen *(650 mg)* at the discretion of the physician in an effort to reduce the potential for fever.

7.3 Timing of b-IFN Administration and Radiation Treatment (6/3/96)

On weeks one, three and five of treatment, on the three days that β-interferon is given, radiation treatment will follow the administration of β-IFN by 30 minutes. The time of the drug administration and the time of the commencement of radiotherapy must be recorded in the patient's radiotherapy chart. A drug administration worksheet indicating the military time of radiation therapy and Betaseron^R injection must be a part of the institution's source documentation.

7.4. Drug Dose Modification

If a drug-related grade 3 or 4 toxicity occurs, Betaseron^R will be held until toxicity returns to grade 2 or less, at which time Betaseron^R will be restarted at 50% reduction in dose *(8 x 10^6 IU - 1 ml from vial)*. The dose of Betaseron^R will remain at this 50% level for the remainder of the study. If the grade 3 or 4 toxicity recurs, Betaseron^R administration for that patient will be discontinued.

7.5 Drug Toxicity

7.5.1 Toxicity must be rated according the the Cooperative Group Common Toxicity Criteria *(Appendix IV)* and recorded on the flow sheets. These criteria, however, do not score some symptoms commonly seen with IFN-beta such as chills, rigors, fatigue, malaise, myalgias, arthralgias, etc. Refer to Appendix VI for a supplemental toxicity grading scale which includes side effects frequently seen with IFN-beta. The time in relation to drug administration of the onset of these toxicities must be recorded. Radiation reactions are to be reported on the radiotherapy and follow-up forms. Other known adverse effects of Betaseron^R include fever, headache, anorexia, nausea, vomiting, diarrhea, paresthesias, and diaphoresis.

7.5.2 Pain, redness, ulceration, cellulitis, and necrosis at the injection site, transient visual disturbances, dizziness, mental confusion, dementia, and seizures have been reported. Laboratory abnormalities reported in parenterally treated subjects include leukopenia, anemia, thrombocytopenia, neutropenia, granulocytopenia, proteinuria, elevation of liver enzymes, hypertriglyceridemia, and rarely, nonfasting hyperglycemia, usually in subjects with known underlying risk factors.

7.5.3 Use of Betaseron^R is contraindicated in subjects who have had clinical manifestations of sensitivity to the drug or any of its components, either those present in the formulation or those used during manufacture *(e.g., albumin human USP, dextrose injection USP)*.

7.5.4 Betaseron^R should be administered with caution to subjects who are severely debilitated or who suffer from serious cardiac disorders, such as recent myocardial infarction or uncontrolled congestive heart disease. Reported cardiovascular adverse experiences include ectopic beats, tachycardia and hypotension. Cardiomyopathy, arrhythmias, myocardial infarction, and congestive heart failure have been reported.

7.5.5 Betaseron^R should also be used cautiously in subjects with uncontrolled seizure disorders, severe

depression, or other organic brain abnormalities. Seizures and suicides have been reported rarely; dementia has been reported in subjects with brain tumors. The safety of Betaseron[R] use with other agents has not been established.

7.5.6 No studies have been conducted to evaluate carcinogenicity, effects on fertility or reproduction, or teratogenic effects of Betaseron[R] therapy. While taking the agent, contraception must be used. Betaseron[R] should not be taken during pregnancy, and nursing should be discontinued during therapy.

7.6 Adverse Reactions Reporting

7.6.1 Grades 4 and 5 unknown reactions. Phone report to RTOG Study Chairman, and IDB within 24 hours. A written report to follow within 10 working days.

7.6.2 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.

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

7.6.4 Address for submitting ADR reports:

Investigational Drug Branch
Box 30012
Bethesda, MD 20824

7.6.5 Further information for reporting Adverse Drug Reactions is detailed in Appendix V.

7.6.6 All adverse events will be reported to RTOG by calling 215/574-3214.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Patients should receive additional supportive care as needed. In particular, dosing with acetaminophen *(650 mg)* is recommended before each Betaseron[R] injection and may be repeated 2 or 3 times a 4-hour intervals as necessary to control fever and chills.

10.0 PATHOLOGY (6/3/96)

10.1 Fixed Tumor Repository Study *(Optional)*

10.1.1 Patients entered on this study are also eligible for the Fixed Tumor Repository.

10.1.2 To receive an additional RTOG case credit, the following must be provided to RTOG:

10.1.2.1 One additional paraffin block of tumor or 15 unstained slides *(maximum thickness of 5 microns each).* Block/slides must be clearly labeled with the pathology identification number that agrees with the Pathology Report.

10.1.2.2 Pathology report documenting that submitted block or slides contain tumor.

10.1.2.3 A Pathology Submission Form must be included and must clearly identify the enclosed materials as being for the Fixed Tumor Repository.

10.1.3 To encourage compliance, your Pathology Department could be reimbursed for obtaining blocks or cutting slides.

10.1.4 Patient consent form should give the Pathology Department authority and responsibility to comply with this request *(pathology blocks belong to the patient from whom tissue has been removed).*

10.1.5 Materials will be sent to:

Pathology Coordinator
RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107

10.2 Fresh Tissue Repository *(Optional)*

10.2.1 Fresh specimens are eligible for RTOG 93-08, the fresh/frozen tumor repository study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (6/3/96)

	DEFINITIVE THERAPY							POST TREATMENT		
Procedure	At On-Study	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Month 3	Month 6	At Follow-up
History & PE Karnofsky & Wt. Neurologic Assess.	X	X	X	X	X	X	X	X	X	X

Chest X-ray	X						X	X	X	X
Chest CT	X							X	X	X[b]
Abdominal CT	X									
Head CT	X									
Bone Scan	X									
EKG	X									
PFT's	X									
Bronchoscopy & Biopsy *(optional)*	X									X *(6 mos.)*
Urinalysis	X									
CBC, platelets	X	X	X	X	X	X	X	X	X	X
SMA 6 & 12	X		X		X		X	X	X	X
Toxicity		X	X	X	X	X	X[a]	X	X	X
Cytokine Studies	X	X	X	X	X	X	X[c]	X	X	X

a. To continue weekly until grade ≤ 2
b. CT scans will be done at 3,6,9, and 12 months post treatment, then every 4 months in year 2, every 6 months in year 3, and annually thereafter.
c. Blood for cytokine levels will be drawn pre treatment; then before XRT once a week on the same day of the week as the start of treatment; then once each week on weeks 2,4,8,&12 after treatment is completed; then every three months through month 18 *(See Appendix VII).*

11.2 Evaluations

Patients on both arms of the study will be evaluated weekly during treatment with a complete physical examination that includes performance status, weight, vital signs, laboratory testing, and tumor measurement. Bronchoscopy and biopsy will be done optionally at six months post treatment to confirm radiological tests. After completion of therapy, patients will be seen for two follow-up visits at 6-week intervals and then per Section 12.0. All patients with toxicity ≥ 3 will be seen weekly until the resolution of all treatment-related toxicity to grade ≤ 2.

11.3 Clinical Syndromes

The clinical syndromes of pneumonitis and fibrosis are associated with radiation therapy. The pneumonitic phase is enhanced with β-interferon and radiation therapy and the fibrotic phase is inhibited.[25] Therefore we will be monitoring these patient toxicities or lack thereof. The clinical descriptions are briefly outlined below.

11.3.1 *Pneumonitis*: Pneumonopathy might be a better term than pneumonitis, since this is not an infective process. The clinical syndrome usually occurs one to three months after the completion of radiation or drug therapy, but occasionally an accelerated phase of the syndrome develops within a period of days after an offending drug is administered. Five to fifteen percent of irradiated patients develop acute radiation injury which is more likely to be evident radiologically, particularly on computed tomography *(CT)* studies, than symptomatically or on pulmonary function studies. During the period when clinical pneumonitis would occur, some radiologic abnormalities can be found in about 50% of all irradiated patients. The severity of symptoms of the acute pneumonitis syndrome is dependent on the degree of pulmonary involvement. There may be low grade fever, non-specific respiratory symptoms such as congestion, cough and fullness in the chest. In more severe cases, dyspnea, pleuritic chest pain and non-productive cough may be present.

Physical signs in the chest are usually absent, but evidence of consolidation is sometimes found in the region corresponding to pneumonitis. Pleural friction rub or pleural fluid may be detected. When tolerance doses are exceeded pneumonitis can be very severe and produce acute respiratory distress with the patient experiencing spiking temperatures and acute cor pulmonale that can lead to death. Patients who survive this phase experience a protracted period of pneumonitis, possibly several months, that does not persist indefinitely. This is the stage at which the mortality and most of the morbidity occurs. No gross abnormalities in lung function occur before 48 weeks after completion of a course of radiotherapy.

In late responding normal tissue such as lung, the latent time for expression of injury is dose-dependent, occurring sooner after higher doses. Generally the pneumonitis phase with the acute symptoms is relatively short in duration and may be easily managed by a dose of 30 -60 mg of prednisone per day for 2-3 weeks, with taper. After the acute phase there is the intermediate phase during which histologic

changes described continue, but in which symptoms would not be as marked. This progresses to the eventual fibrotic phase.

11.3.2 *Fibrosis*: In contrast to the acute reaction, chronic effects of cytotoxic therapy are observed from months to years following treatment, even though histologic/biochemical changes are evident sooner. Pulmonary fibrosis develops insidiously in the previously irradiated field, and stabilizes after one or two years. The clinical symptomatology related to radiographic changes is proportional to the extent of the lung parenchyma involved and the patients' pre-existing pulmonary reserves. Most patients with radiation fibrosis are asymptomatic. In a few patients, particularly those with severe pneumonitis, chronic respiratory failure may be present: dyspnea on effort, reduced exercise tolerance, orthopnea, cyanosis, sometimes chronic cor pulmonale and finger clubbing. Symptoms are minimal if fibrosis is limited to less than 50% of one lung: if the volume increases above this limit, dyspnea may manifest clinically and progressive chronic cor pulmonale leading to right heart failure may occur. A mild deterioration in pulmonary function may occur as fibrosis develops.

Radiologic changes consistent with fibrosis are seen in most patients who have received lung irradiation even if they did not develop acute pneumonitis. Late effects have been described that were not preceded by acute effects.

The late lung injury is characterized by progressive fibrosis of alveolar septa thickened by bundles of elastic fibers. The alveoli collapse and are obliterated by connective tissue. These changes can lead to the radiographic appearance of lung scarring on chest radiography, which corresponds to the shape of the radiation portal. Eventually, the previously irradiated lung can develop dense fibrotic nodules, especially in the area of previous tumor. CT is currently favored to image regions subjected to radiation therapy.[20]

11.4 Response

Patients will be evaluated for tumor response based on physical examination, radiographic studies and laboratory parameters that best define extent of disease. It is unusual for the CT scan of the chest to return to normal after a patient with lung cancer has been irradiated. Some density is usually visible due to radiation reaction *(pneumonitis/fibrosis)*. This should stabilize between 3 and 6 months. Response criteria will be defined as follows:

11.4.1 *Complete Response* ***(CR)*** - disappearance of all clinical evidence of active tumor and stable density on chest CT for at least 6 months. Patients must be free of any symptoms related to cancer. Patients would be evaluable for CR at 9 months to one year by these criteria.

11.4.2 *Partial Response* ***(PR)*** - 50% or greater decrease in the sum of the products of all diameters of the measured lesions *(for measurable lesion)*, or a definite decrease in tumor size agreed upon by two investigators *(for non-measurable but evaluable lesions)* of at least 4 weeks duration, with no new lesions or progression *(thus smaller primary but larger regional adenopathy would not qualify)*.

11.4.3 *Stable Disease* **(SD)** - steady state or response not qualifying for either partial remission or progression. There may be no appearance of new lesions and no worsening of symptoms.

11.4.4 *Local Control Rate* **(LCR)** Local control is defined at one year based on stabilization of CT density post-irradiation for at least six months prior to that time.

11.4.5 *Progressive Disease* **(P)** - increase of at least 25% in the size of any measurable or evaluable lesion, appearance of new lesion. This includes those who had SD or PR.

11.4.6 *Relapse* **(R)** - appearance of new lesions or regrowth of initial ones after a CR.

11.5 Withdrawal Criteria

The patient may be withdrawn from treatment if any of the following occurs:

11.5.1 Radiation pneumonitis. Study therapy will be terminated if pneumonitis develops but the patient will be followed for response and survival.

11.5.2 Disease progression.

11.5.3 Need for anticancer therapy other than Betaseron^{R} and radiation.

11.5.4 Interruption of therapy resulting in delay of scheduled dosing for greater than two weeks, except when a result of resolution of toxicity.

11.5.5 Second recurrence of grade 3 or 4 toxicity, or persistence of grade 3 or 4 toxicity at next scheduled time of Betaseron^{R} administration.

11.5.6 Intolerable adverse effects.

11.5.7 Deterioration of Karnofsky performance status to below 30 or weight loss greater than 10% of baseline weight if caused by disease or study treatment.

11.5.8 Patient refusal to continue treatment for any reason.

11.6 Followup for Cancelled and Ineligible Cases

11.6.1 Eligible patients who refuse all treatment will continue to be followed for survival.

11.6.2 Ineligible cases receiving at least 50% of the protocol therapy will be followed for survival and morbidity data.

11.6.3 Ineligible cases who do not receive <u>any</u> protocol therapy will not be followed.

12.0 DATA COLLECTION

12.1 Summary of Data Submission

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Chest X-rays **(C4)** and CT Scans **(C1)** and Reports **(C3)**	Within 2 weeks of study entry
<u>For Fixed Tumor Repository</u> *(see Section 10.1)* Pathology Report **(P6)** Pathology Blocks/Slides **(P7)**	Within 4 weeks of randomization
<u>Preliminary Dosimetry Information:</u> RT Prescription *(Protocol Treatment Form)* **(T2)** Films *(simulation and portal)* **(T3)** Calculations **(T4)**	Within 1 week of start of RT
Radiotherapy Form **(T1)** <u>Final Dosimetry Information:</u> Daily Treatment Record **(T5)** Isodose Distribution **(T6)** Boost Films *(simulation and portal)* **(T8)** Chest X-ray **(C4)** and Report **(C3)**	Within 1 week of RT end
Specimen Transmittal Form **(ST)** *original sent with specimens to Dr.Williams)*	At 8 weeks and 18 months *(copy to RTOG,*
Study Specific Flowsheet **(SF)** ***(Arm 1 only)***	At 2,4, and 6 weeks from treatment start.
Follow-up Form **(F1)** then q 3 months x 3; q 4 months x 1 year, q 6 months x 3 years, then annually. Also at progression/relapse and at death	At 12 and 18 weeks from treatment start;
Chest X-rays **(C4)** and CT scans **(C2)** Reports **(C3)** every 4 months in year 2, every 6 months in year 3, and annually thereafter.	At 3, 6, 9, and 12 months post treatment, then and
Autopsy Report **(D3)**	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is overall survival.

13.1.2 The frequency of severe *(³ grade 3)* toxicities will be examined, with emphasis on esophageal toxicity.

13.2 Sample Size

Assuming a local control rate *(LCR, as defined in Section 11.4)* of 20% on the RT arm[27], and an ineligibility/inevaluability*(no data)* rate of 15% then **166 patients will be needed** *(82 per arm)* to ensure an 90% *(b=0.10, type II error)* probability of detecting a 25% overall improvement in LCR, while rejecting the null hypothesis at the 95% level *(a=0.05, two-sided type I error).*

The data from McDonald et al.[24] was utilized to estimate the one-year survival for the study population treated with b-interferon plus standard radiotherapy *(b-I RT)*. An analysis of 512 potentially eligible, poor prognosis patients from the RTOG database were used to estimate the one-year survival for patients treated with RT alone. It is estimated the one-year survival for patients on the RT arm will be 30%, compared to 60% on the b-I RT arm. Freedman's[26] sample size formula which assumes constant proportionality of the hazards and survival comparisons with the logrank statistic was utilized to calculate the sample size. This sample size will ensure an 97% *(b=0.03, type II error)* probability of detecting a 30% overall improvement in one-year survival, while rejecting the null hypothesis at the 95% level *(a=0.05, two-sided type I error)*.

The question is which regimen has the lowest *(best)* toxicity rate. The occurrence of severe or worse *(> grade 3)* toxicities will be assessed for each treatment, and their rates will be ordered from highest to lowest. Using an approach by Gibbons, et al.[28], this study will have sufficient numbers to detect an overall toxicity rate of at least 12% better *(less)* than the next lowest rate. This trial will have a probability of choosing the best arm of 90%.

The noncompliance rate to β-I *(patients receiving less than 2/3 of the prescribed dose)* will have an impact upon the detectable difference for LCR and overall survival; therefore, this rate will be monitored and modifications to the sample size may be necessary if this rate is larger than 5%.

13.3 Patient Accrual

The patient accrual is projected to be 5 patients per month, based upon the accrual of this patient group to RTOG 83-11. This trial should complete the accrual phase in 2.8 years. If the monthly accrual is less than 3 cases per month, the study will be re-evaluated with respect to feasibility.

13.4 Randomization Scheme

The treatment allocation will be one using a randomized a permuted block within strata to balance for patient factors other than institution. The stratifying variables are Stage IIIa versus Stage IIIb and weight loss *(within 3 months prior to entering the trial)* less than 5% versus greater than or equal to 5%.

13.5 Analyses Plans

13.5.1 *Interim analyses of accrual and toxicity data*

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

a) the patient accrual rate with projected completion date for the accrual phase;
b) the distribution of patients with respect to pretreatment characteristics;
c) compliance rate of treatment delivery with respect to the protocol prescription;
d) the frequency and severity of the toxicities.

13.5.2 *Interim analyses of study endpoints*

There will be two interim analyses of the primary study endpoint *(local control rate, survival)*. The interim analyses will proceed according to the following table[29].

Total Accrual	Significance Level
50%	0.00250
100%	0.00296

If any of the interim analyses exceeds the listed significance level, which were calculated to ensure an overall significance level of 0.05, the accrual will be suspended. The results of these interim analyses will only be reported, in a blinded fashion, the RTOG Data Monitoring Committee *(DMC)* as privileged communications. A report with recommendations will be given to the study chairman. Any problems or recommendations identified by the DMC, not results, will be reported to the Lung Committee, which responsible for this study and, if necessary, the RTOG Executive Committee, so that corrective action can be taken.

13.5.3 Analysis and reporting of initial treatment results

This major analysis will be undertaken when each patient has been potentially followed for a minimum of 12 months. The usual components of this analysis are:

1) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
2) reporting institutional accrual;
3) distribution of the important prognostic factors by assigned treatment;
4) observed results with respect to the study endpoints.

Further subgroup analyses may be conducted *(depending upon the sizes within the subgroups)* for the purpose of identifying patterns of treatment responses. The p-value of 0.04831 will be used,

thus correcting for previous interim tests.

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APPENDIX I

RTOG 93-04

PHASE III CONVENTIONAL THERAPY WITH OR WITHOUT RECOMBINANT b-INTERFERON FOR PATIENTS WITH LOCALLY ADVANCED NON-SMALL CELL LUNG 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

I have been told that I have a tumor in my lung which cannot be surgically removed. Standard therapy for this would be treatment with radiation. Radiation is the treatment of tumors with X-rays. A research study is being conducted by the Radiation Therapy Oncology Group *(RTOG)* in which patients with my kind of lung cancer will be treated with radiation and Recombinant Beta Interferon. Interferons are proteins produced by cells as part of the body's normal response to viral infection. They are named because of their ability to "interfere" with these infections. The interferon that is produced in the laboratory is called "Recombinant" Beta Interferon. There has been some preclinical evidence that interferon may enhance the effects of radiation on some tumors. The purpose of this study is to determine if radiation therapy with beta interferon is more effective in treating lung cancer than radiation therapy alone.

DESCRIPTION OF PROCEDURES (6/3/96)

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

Treatment plan 1: In the three days of my radiation treatment *(three days in a row),* I will receive Interferon intravenously *(through a vein in my arm)* 30 minutes before the radiation therapy. The next 10 days, I receive only radiation. Weeks three and five will be identical to this. During weeks two, four, and six, I receive only radiation five days a week.

Treatment plan 2: I will receive radiation treatment to my chest without interferon administration. Treatment will be five days a week, Monday through Friday for a total of six weeks.

The Division of Cancer Treatment, National Cancer Institute, will provide me with the investigational IFN-beta free of charge for this study. Should this agent become commercially available during the course of the study, however, I may be asked to purchase subsequent doses of the drug.

Before treatment begins, I will have several tests and evaluations. These include a bone scan, CT scans of the head, chest, and abdomen, pulmonary function tests to evaluate my lung capacity, chest X-ray, EKG, and blood tests. Physical examinations and blood tests will be done each week while I am receiving treatment, and at follow-up visits. Approximately three tablespoons of blood will be drawn for the blood tests. This may cause some soreness and/or black and blue marks at the site but this is only temporary. I will be seen for follow-up evaluations after treatment is completed, and at specific intervals thereafter. A chest X-ray, chest CT scan, and blood tests will be done at some of these follow-up visits.

Also, at the time of my diagnosis by biopsy, all or some of my tumor was removed. As is usually done, this tissue went to the hospital's pathology department for routine testing and diagnosis. After that process was complete, remaining tumor

samples were stored in the pathology department. I am being asked for permission to use the remainder of the tumor for additional tests. Since this tissue was removed at the time of surgery or biopsy, the permission to use my tissue will not involve any additional procedure or expense to me. The tumor tissue's cells will be examined to see if any special "markers", tests which predict how a patient with tumors like mine responds to treatment, can be identified.

RISKS AND DISCOMFORTS

Cancer treatments often have side effects. 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.

One side effect common to both is a reduction in my blood counts *(white blood cells, red blood cells, and platelets)* which can lead to increased risk of infection, weakness, fatigue, and may cause easy bruising, easy bleeding, and slow wound healing. If a severe reduction in these blood counts occurs, I might be given a transfusion of blood products. Although rare, transfusion of blood products includes the risk of developing hepatitis. Since pregnant women may not be treated according to the methods in this study, I have been told that if pregnancy is a possibility, I must use adequate contraception.

Radiation to the chest may cause redness, dryness or itching of my skin and hair loss within the treated area. It may cause pain or a burning sensation with swallowing, loss of taste or appetite, fatigue, and weight loss. Rarely, it may cause tissue injury *("necrosis")* in the area treated. Late developing effects may include some irritation of my lung, called pneumonitis *(a pneumonia-like condition)* which could lead to fibrosis *(scarring)* of my lung, This could occur weeks to months after treatment and result in chronic shortness of breath and a cough. I may also have some fibrosis of my esophagus, which could cause it to become narrower and could result in difficulty swallowing. Radiation to the chest can cause damages to my heart or spinal cord; however, this is rare since these organs will be shielded during the radiation therapy to reduce this risk.

Interferon may cause low blood pressure, fatigue, and loss of appetite, which may become more noticeable over time, but will often return to normal when treatment is discontinued. Chemical abnormalities in the blood and urine which reflect any damage to the liver and kidneys may develop. An increase of non-fasting blood sugar and blood triglycerides may occur. Some patients have experienced neurologic symptoms such as decreased vision, blurred vision, altered perception or decreased perception to light. Others have noted slowness in their thinking, impairment of intellectual function, confusion and dizziness. Rarely, mild numbness and tingling in hands and fingers is noted. There is also the possible risk of an allergic reaction or seizure. Among severely depressed patients, rare instances of suicide have been reported. Some patients have had cardiac problems such as myocardial infarction, congestive heart failure, cardiomyopathy, and arrhythmias. Fever shaking chills, sweating, joint and muscle aches, headaches, nausea and vomiting, diarrhea and malaise are flu-like symptoms which will almost certainly occur. Lastly, pain, redness, inflammation, peeling, and rarely, ulceration at the injection site can occur.

I may experience none, some, or all of these side effects and they may be mild, moderate, or severe. Many of the side effects disappear after treatment is stopped. In addition, there is always the risk of some very rare or previously unknown side effect occurring. The side effects may be increased by using the combination of interferon and radiation therapy. Ongoing clinical studies show that some patients may develop antibodies to interferon as a result of treatment with interferon, The significance of this is unknown. Interferon is a relatively new drug and its effects on the fetus or unborn child are not known. My doctors will be checking closely with blood tests and physical examination for the occurrence of side effects any may prescribe medication to ease the discomfort I may have if any of these effects occur. They will also caution me about medications I may not take during this treatment. In addition, if any severe reaction to interferon or radiation therapy occurs, my doctors may interrupt or discontinue the treatment.

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 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 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. 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 alone, chemotherapy, a combination of other drugs and radiation 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. 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 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 III

ANATOMICAL STAGING FOR LUNG CANCER
(IUCC-AJCC, 1988)

TNM CATEGORIES (Note Definitions)

T-Primary Tumor

TX Tumor proven by the presence of malignant cells in broncho-pulmonary secretions but no visualized roentgenographically or bronchoscopically, or any tumor that cannot be assessed as in a retreatment staging.

T0 No evidence of primary tumor. TIS Carcinoma in situ.

T1 A tumor that is 3.0 cm or less in greatest dimension, surrounded by lung or visceral pleura, and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.

T2 A tumor more than 3.0 cm in greatest dimension, or a tumor of any size that either invades the visceral pleura or has associated atelectasis or obstructive pneumonitis extending to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be within a lobar bronchus or at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung.

T3 A tumor of any size with direct extension into the chest wall (including superior sulcus tumors). diaphragm. or the mediastinal pleura or pericardium without involving the heart, great vessels, trachea, esophagus or vertebral body, or a tumor in the main bronchus within 2 cm of the carina without involving the carina.

T4 A tumor of any size with invasion of the mediastinum or involving heart, great vessels, trachea, esophagus, vertebral body or carina or presence of malignant pleural effusions.

Definitions

T1 The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall which may extend proximal to the main bronchus is classified as T1.

T4 Most pleural effusions associated with lung cancer are due to tumor. There are, however, some few patients in whom cytopathological examination of pleural fluid (on more than one specimen) is negative for tumor, the fluid is non-bloody and is not an exudate. In such cases where these elements and clinical judgment dictate that the effusion is not related to the tumor, the patients should be staged T1, T2 or T3 excluding effusion as a staging element.

N-NODAL INVOLVEMENT

N0 No demonstrable metastasis to regional lymph nodes.

N1 Metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region, or both, including direct extension.

N2 Metastasis to ipsilateral mediastinal lymph nodes and subcarinal lymph nodes.

N3 Metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene or supraclavicular lymph nodes.

Distant Metastasis

MO No (known) distant metastasis

M1 Distant metastasis present - Specify Site(s)

STAGE GROUPING OF CARCINOMA OF THE LUNG

Occult Carcinoma		TX	N0		M0
Stage 0		TIS	Carcinoma in situ		
Stage I		T1	N0		M0
		T2	N0		M0
Stage II		T1	N1		M0
		T2	N1		M0
Stage IIIa	T3	N0		M0	
		T3	N1		M0
		T1-3	N2		M0
Stage IIIb	Any T	N3		M0	
		T4	Any N		M0
Stage IV	Any T	Any N		M1	

APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures 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 and to the Headquarters Data Management Staff *(215/574-3214)* within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.

a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.

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

3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol *(FAX #215/928-0153).*

4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.

5. For those incidents requiring telephone reporting to the National Cancer Institute *(NCI)*, Investigational Drug Branch *(IDB)* or Food and Drug Administration *(FDA)*, the Principal Investigator should first call RTOG *(as outlined above)* unless this will unduly delay the notification process required by the federal agencies.

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

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.

7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.

8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities *(grade 5)* resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

2. All life-threatening *(grade 4)* toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.

3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

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

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

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

Commercial and Non-Investigational Agents

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

ii. Unknown adverse reactions *(³ 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 *(³ grade 3)* from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.

iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

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

Investigational Agents

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

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

i. *Phase I Studies Utilizing Investigational Agents*

- All deaths during therapy with the agent.	Report **by phone** within 24 hours to IDB and RTOG Headquarters. **A written report to follow within 10 working days.

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

ii. *Phase II, III Studies Utilizing Investigational Agents*

- All fatal *(grade 5)* and life threatening *(grade 4)* known adverse reactions due to investigational agent.	Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours **A written report must be sent to RTOG within working days with a copy to IDB. *(Grade 4 myelosuppression not reported to IDB)*
- All fatal (grade 5) and life threatening (grade 4) unknown adverse reactions resulting from or suspected to be related to investigational agent.	Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. **A written report to follow within 10 working days.
- All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent.	**Report **in writing** to RTOG Headquarters and IDB within 10 working days.

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

APPENDIX VI

SIDE EFFECTS COMMONLY SEEN WITH IFN-beta

TOXICITY - FLU-LIKE SYMPTOMS	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Fever in absence of infection	none	37.1-38.0°C 98.7 - 100.4°F	38.1 -40°C 100.5 -104.°F	> 40°C > 104°F for less than 24 hrs.	> 40°C (104.0°F) for more than 24 hrs. or fever accompanied by hypotension
Chills	none	mild or brief	pronounced or prolonged	--	--
Mylagia/Arthragia	normal	mild	decrease in ability to move	disabled	--
Sweats	normal	mild and occasional	frequent or drenching	--	--
Malaise/Fatigue	none	mild, able to continue normal activities	impairment of normal daily activity or bed rest < 50% of waking hours	in bed or in chair > 50% of waking hours	bed ridden or unable to care for self
Other Flu-Like Symptoms-(specify)	--	mild	moderate	severe	life-threatening

APPENDIX VII

CYTOKINE STUDIES

Samples should be collected in green top tubes *(4-8 cc per test)* and placed on ice until they can be spun. Centrifugation and separation should be done as soon as possible. *(Centrifuge at 12,000 x g for 20 minutes. A refrigerated centrifuge is not required).* The plasma should be separated and transferred to plastic tubes and carefully sealed. Samples must be labeled and frozen at -4 $^{\circ}$C *(regular freezer).* Labels are available from RTOG and to provide the following information:

CYTOKINE STUDIES

Protocol # RTOG 93-04 Case # _____

Patient Name _____ Date of Sample ____/____/____

Specimen Sequence # _____ Dose Level _____ Gy

Institution # _____ PI _____

The label should be completed with non-water soluble pen and sealed with non-water soluble tape. Samples should be collected and kept frozen during the period from pre-treatment to the end of treatment. At that time all samples may be packaged in dry ice and sent via an overnight delivery service. Regulations for packaging require that all samples must be placed in a plastic bag with absorbent material in case of spillage. The package should be clearly marked "FROZEN MATERIAL." A specimen transmittal form must be included in the package and a duplicate kept in the patient's file. The name of the person sending the samples, along with phone number and complete address should be included.

The remaining samples collected during follow up may be stored in the institution's freezer until collection is complete *(either through 18 months of follow up or death of the patient whichever comes first)* and then forwarded to the address below.

To assure that samples will be attended to promptly upon arrival, do NOT ship on Thursday, Friday or Saturdays nor prior to any holiday.

Ship samples to:

Jacqueline Williams, Ph.D.
University of Rochester Medical Center
Room G-6608
601 Elmwood Avenue
Rochester, NY 14642
(716) 275-1687