RADIATION THERAPY ONCOLOGY GROUP

RTOG 91-03

PULMONARY FUNCTION OF PATIENTS WITH RADIATION THERAPY FOR NON-SMALL LUNG CANCER

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 91-03

PULMONARY FUNCTION OF PATIENTS TREATED WITH RADIATION THERAPY FOR NON-SMALL CELL LUNG CANCER

SCHEMA

STRATIFY

Patient on another RTOG <u>Lung Study</u>

1. No
2. Yes

RAND

› **PULMONARY FUNCTION TESTS** (PFT): PRE-RT, POST-RT, q 3 months for one year, then yearly

Serum Markers (surfactant apoprotein and procollagen type III) will be measured pre RT and at 10, 20, 30, 40, 50, and 60 Gy.

<u>ELIGIBLE</u> (See Section 3.0 for details)

- Patients entered who will receive standard radiation therapy as outlined in Section 6.0 of this protocol and patients on a currently active RTOG lung protocol provided treatment has not started prior to registration to this study.
- Patients with histologically proven advanced unresectable non-small cell lung cancer.
- Disease must be measurable in at least two dimensions on CXR.
- AJC Stage II or III without distant metastases or pleural effusion.
- KPS ≥ 50, age ≥ 18.
- WBC ≥ 3,500, platelets ≥ 100,000, bilirubin ≤ 1.5, BUN < 30, creatinine ≤ 2.5.
- No prior radiation therapy.
- Disease must be measurable in at least two dimensions radiographically.
- No biological response modifiers other than on an RTOG study
- Concurrent chemotherapy (i.e. RTOG 94-10) is allowed if limited to cisplatin etoposide, taxol, or vinblastine
- Signed study-specific consent form.

Required Sample Size: 187

revised 4/5/93, 2/1/96

Institution # _____ **ELIGIBILITY CHECK**
RTOG 91-03
Case # _____

_____(Y) 1. Does the patient have a histologically or cytologically confirmed diagnosis of lung cancer?

_____(II-III) 2. What is the stage group (AJC)?

_____(Y) 3. Has a histology of undiffentiated small cell (oat cell) type been ruled out?

_____(Y) 4. Is the pathologic diagnosis consistent with one of the histologic types specified in the protocol?

_____(Y) 5. Can all detectable tumor be encompassed by the radiation fields?

_____(N) 6. Has the patient undergone a complete surgical resection or is the patient's tumor considered recurrent following prior resection?

_____(N) 7. Is surgery a part of the current treatment plan?

_____(N) 8. Has the patient received any prior chemotherapy, radiation therapy or has the current treatment with XRT started?

_____(N) 9. Any evidence of pleural effusion or distant metastases?

_____(N) 10. Will the patient receive any biologic response modifiers in a program other than in an RTOG study?

_____(Y/N) 11. Will the patient receive any chemotherapy in a program other than an RTOG study?

_____(Y) If yes, will the chemotherapy be given as described in RTOG 94-10?

_____(N) If no, will the chemotherapy include any cytotoxic drugs other than Cisplatin, Etoposide, Taxol, or Vinblastine?

_____(Y) 12. Is the tumor measurable in at least two dimensions radiographically?

_____(Y/N) 13. Except for non-melanoma skin cancer is there a history of a prior or concurrent malignancy?

_____(Y) If yes, has the patient been disease free for ≥ 5 years?

_____(N) 14. Any history of myocardial infarction within the past 6 months?

_____(N) 15. Any symptomatic angina not controlled by medication, congestive heart failure or uncontrolled arrhythmia?

_____(Y) 16. Will the patient have undergone all mandatory pretreatment evaluations (specified in Section 4.2 and 4.3 of the protocol) before treatment starts?

_____(≥ 18) 17. What is the patient's age?

Institution # _____ **ELIGIBILITY CHECK**
RTOG 91-03
Case # _____

_____(≥ 50) 18 What is the Karnofsky?

_____(≥ 3.5) 19. Report the pre study WBC results (per 1000)?

_____(≥ 100) 20. Report the pre-study platelet count. (per 1000)

_____(≤ 1.5) 21. What is the bilirubin (mg %)?

_____(< 30) 22. What is the pre-study BUN?

_____(≤ 2.5) 23. What is the pre-study serum creatinine (mg%)?

_____(Y) 24. Has a study-specific consent form been signed?

_____(Y/N) 25. Has the patient been registered to an RTOG protocol (must be done before registration to this study)?

_____(Y) If no, will the patient be treated with XRT as specified in Section 6 of this study?

_____(N) If yes, has the patient been assigned to a surgical treatment option?

_____ 26. If on a RTOG lung study, specify the study number followed by the case number.

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # *(if different)*

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code (9 digit if available)

_____ Method of Payment

_____ Treatment Start Date

_____ Study Arm

Completed by _____ Date _____

revised 4/5/93
8/16/93
5/9/94
2/1/96

1.0 INTRODUCTION

1.1 The morphologic and physiologic effects of irradiation on the lungs have been well described.[1] Most animal studies, however, describe the effects of whole lung irradiation and/or irradiation with single doses or a small number of doses.[2-4] These are not comparable to nor are they representative of the effects of protracted, fractionated programs of radiation usually used clinically. Most studies in humans report thoracic irradiation for non pulmonary tumors.[5-8] Studies of the effect of radiation therapy on lung function have shown variable results: some report a decrement[5,9-11] in function, some no change,[12-14] and some, improvement.[11] In most studies performed prospectively, there tends to be a loss of lung volume and a reduction in diffusing capacity apparent about four months after the completion of radiation therapy[1,5,9] From that point, function continues to decline in some patients[5] and improved in others.[1,9] The most sensitive pulmonary function test for radiation-induced lung injury appears to be the carbon monoxide diffusing capacity.[9] Abnormalities in pulmonary function tests do not necessarily correlate with radiographic abnormalities.[9] Factors that affect the incidence and degree of pulmonary injury include the total dose of radiation, the volume of lung treated, concomitant chemotherapy, pre-existing lung disease, the extent of large airway occlusion by tumor and individual variability in response to radiation. There are equations that allow prediction of post treatment lung function.[11] These equations use only initial lung function parameters and perfusion lung scans. The predicted function losses tend to be larger than those actually seen. Current equations do not include other factors that are likely to be good predictors such as radiation dose, lung volume exposed, and clinical parameters. Choi, et al,[15] presented their findings in a study of 100 patients whose pulmonary functions were measured before and 10 to 12 months after post resection radiation therapy. They found that the loss of pulmonary function as a result of radiation therapy is closely related to the degree of impairment of pulmonary function before radiation therapy, the anatomical region of the treatment volume and the presence of significant obstruction of major bronchi and /or pulmonary vessels by centrally located primary tumors or involved lymph nodes. Contrary to expectations, patients with poor pulmonary function reserve showed an improvement of pulmonary function in 52% of the patients, while another 37% showed a small decrease of pulmonary function by less than 10% of the initial value. The combination of two factors contributed to excellent tolerance to radiation therapy, namely irradiation of upper lobe tumors and poor pulmonary function reserve [FEV^1 (Forced Expiratory Volume in 1 second) less than 50% of that predicted]. Brooks, et al[16] studied pulmonary toxicity in small cell lung cancer and found more impairment of pulmonary function when radiation therapy and chemotherapy were combined than when either was used alone. They concluded that improved local control and disease-free survival, however compensated for the increased pulmonary morbidity and mortality associated with the combined modality treatment.

Large numbers of patients with non-oat cell lung carcinoma are treated definitively with radiation therapy, but there is relatively little data about the effects of such irradiation on pulmonary function across the broad spectrum of patients so treated. In depth study of a large number of patients treated in a standardized manner would be of value to determine the net effects of possible deleterious effects of irradiation on pulmonary function versus the potential benefit from relief of airway and vascular obstruction by tumor. Assessment of pulmonary function in these patients before and after irradiation could provide important information in evaluating the net benefit, or detriment, of such treatment.

1.2 Early biochemical markers of normal tissue damage which would predict for late effects can be very useful in aiding early determination if treatment is exceeding normal tissue tolerance. If biochemical markers of tissue damage could be detected in the subclinical phase, prior to the accumulation of significant injury, one could terminate therapy or institute treatment to prevent or attenuate later lesions. An ideal marker should be a simple, reproducible, positive/negative biochemical test. Early release of surfactant during the first week following irradiation is quantifiable in bronchoalveolar lavage, correlates with later radiation pneumonitis and is the first consistent early biochemical marker for later lethal radiation events in 3 murine strains and a rabbit model.[17-19] The protein components of surfactant, called "apoproteins", have a high degree of specificity and can be detected in blood by sensitive immunoassays. The presence of surfactant apoprotein in blood would indicate damage to the capillaryalveolar membrane and leakage into serum. Procollagen type III is synthesized in fibroblasts as a biosynthetic precursor of collagen type III and then released. The propeptides are split off in the extracellular space during the conversion into collagen. The release of peptides of type III procollagen may reflect the degree of biosynthesis of type III collagen, and increased peptide level in serum may suggest inflammation or the beginning of fibrosis. Okazaki et al suggests that an assay for serum type III procollagen peptides may be useful in the early detection of pulmonary fibrosis as a complication in cancer therapy.[20] The ability to predict for potential severe late effects early after fractionated treatment or toward the end of a course of irradiation would allow for intervention.

1.3 The Radiation Therapy Oncology Group treats approximately 400 patients with unresectable lung cancer each year on protocols which specify precise and uniform treatment parameters. We propose to take advantage of this large number of lung cancer patients enrolled by the Radiation Therapy Oncology Group and the amount of data now recorded on those patients by adding serial assessment of simple lung function tests to their evaluation and follow-up regimens. We believe that simple tests should be used because they are widely available, relatively non-invasive and their cost is less than more sophisticated tests. The tests proposed are spirometry, lung volumes, single breath carbon monoxide diffusing capacity, arterial blood gasses and serum apoprotein and procollagen III. The addition of pre and post-radiation therapy pulmonary function assessment to

the extensive data base collected on these patients as part of their protocol treatment will provide unique and invaluable information. In addition, patients who are not entered into RTOG treatment protocols but who have similar histologic types of lung cancer, similar extent of disease and are irradiated with identical techniques can be included.

These studies will yield an extensive body of data on conventionally fractionated irradiation and permit these data to be compared with similar data on patients receiving hyperfractionated radiation or chemotherapy in combination with irradiation. In depth analyses of these physiologic data in conjunction with roentgenographic changes and other variables identified as important from previous RTOG studies will address the question of how the addition of clinical, functional, and treatment parameters can allow an accurate prediction of the rate and magnitude of loss of lung function. Variables to be considered would include, but not be limited to, initial pulmonary function test values, (initial $PaC0_2$, and alveolar-arterial gradient for $P0_2$), dyspnea score[21] (Appendix V), cough, sputum volume, pack years of smoking, systemic symptoms (fever, etc), performance status, percent of body weight loss, chest pain, age, sex, race, other therapy, tumor mass and extent, radiation dose, the volume of lung irradiated, and the presence or absence of complications that involve the lung such as superior vena caval compression syndrome. The approach to this analysis would be to perform a pair wise correlation of the individual variables against the amount of lung function lost. Variables would be analyzed using a step-wise regression analysis to find the cluster of variables that are the best predictors. One could also perform this analysis by using current information about the normal rates of loss of lung function in smokers and nonsmokers to calculate of the loss that might reasonably be attributed to the irradiation.

1.4 Once predictors are identified, one could ask: Are such predictions good enough to provide clinically relevant information that can be used in planning treatment? For example, is the length of survival affected by the initial functional state, and, if so, to what extent? Are the patients' survival and functional outcomes predicted, in part, by initial functional and clinical assessment? If present, is the effect on survival or functional state independent of other clinical factors?

Additional questions that might be addressed include: Do functional changes correlate with radiographic abnormalities? Is there a phase lag between the two? Are functional changes affected by concomitant therapy such as chemotherapy?

2.0 OBJECTIVES

2.1 To estimate the serial changes of pulmonary function before and after definitive thoracic irradiation (radiation alone given with standard fractionation or hyperfractionation, or in combination with chemotherapy) for patients with locally advanced unresectable non-oat cell lung cancer.

2.2 To identify the nature and frequency of radiation related alteration of each of multiple parameters of pulmonary physiology.

2.3 To identify factors which are predictive of satisfactory acute and long-term pulmonary tolerance of definitive irradiation and, conversely, factors which are predictive of excessive impairment of pulmonary function.

2.4 To estimate the frequency of surfactant apoproteins and procollagen III in patients after irradiation to the lung.

2.5 To determine if there is any correlation between early elevation of biochemical markers obtained in blood of irradiated patients and subsequent pulmonary abnormalities as detected by pulmonary function tests and/or radiographic findings of pneumonitis/fibrosis.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria (4/5/93, 8/16/93, 2/1/96)

3.1.1 Patients with histologically-proven, by biopsy or cytology, advanced unresectable lung cancer of the following histologic types:
- Squamous cell carcinoma
- Adenocarcinoma
- Undifferentiated large cell carcinoma
- Unknown (diagnosis on cytology alone)

3.1.2 Patients with AJC Stage II or III (Appendix III) if all detectable tumor can be encompassed by radiation therapy fields, including both the primary tumor and regional lymph nodes. Patients with supraclavicular lymph nodes are eligible provided they meet the above criteria.

3.1.3 Age ≥ 18.

3.1.4 Karnofsky performance status ≥ 50. (See Appendix II).

3.1.5 Patients must have adequate bone marrow, renal and hepatic function, with WBC ≥ 3,500, platelets ≥ 100,000, bilirubin ≤ 1.5, BUN < 30, creatinine ≤ 2.5 milligrams percent.

3.1.6 Tumor must be measurable in at least two dimensions radiographically.

3.1.7 Patients must sign a study-specific informed consent form. (See Appendix I).

3.1.8 Patients to be treated on currently active (non-surgical arm) RTOG lung studies are eligible provided treatment has not started prior to registration to this study. **If not on an RTOG study, treatment shall be specified in Section 6.0 of this study.**

3.1.9 Patients receiving chemotherapy will be eligible for this study as long as the therapy is limited to one or more of the following drugs: Cisplatin, Etoposide, Taxol, or Vinblastine.

3.2 Ineligibility Criteria

3.2.1 Undifferentiated small cell (oat cell) carcinoma, any stage.
3.2.2 Stage I or IV.
3.2.3 Patients with complete tumor resection.
3.2.4 Patients with post-surgical microscopic residual disease or disease which is not measurable radiographically. **(4/5/93)**
3.2.5 Patients operated upon for cure who have intrathoracic recurrence.
3.2.6 Performance status < 50 Karnofsky scale.
3.2.7 Patients < 18.
3.2.8 Patients with a prior or concurrent malignancy except non-melanomatous skin cancer unless disease-free for five years or more.
3.2.9 Patients who have received prior radiotherapy or chemotherapy.
3.2.10 Patients refusing to sign an informed consent form.
3.2.11 Patients with pleural effusion or distant metastases.
3.2.12 Occult cancer (Tx).
3.2.13 Patients with a myocardial infarction within 6 months, symptomatic angina not controlled by medication, congestive heart failure, or uncontrolled arrhythmia. **(5/9/94)**
3.2.14 Patients receiving biological response modifiers which are not part of an RTOG study. **(2/1/96)**
3.2.15 Patients who have not had the pre-treatment evaluations in Section 4.2 and 4.3.
3.2.16 Patients who begin RT before registration to this study.

4.0 PRETREATMENT EVALUATIONS

4.1 History and physical, dyspnea score, and metastatic evaluation.

4.2 Mandatory imaging studies.

4.2.1 Standard PA and lateral chest x-rays.
4.2.2 CT of the chest and upper abdomen.

4.3 Mandatory studies (8/16/93)

4.3.1 CBC
4.3.2 Serum bilirubin
4.3.3 Serum BUN
4.3.4 Serum creatinine
4.3.5 Other laboratory and imaging studies as dictated by the relevant associated treatment protocols.
4.3.6 Serum markers: surfactant apoprotein and procollagen type III. See Appendix VIII for instructions. To be done pre-RT (and at 10, 20, 30, 40, 50 and 60 Gy).

4.4 Spirometry to measure flow volumes.
4.5 Single breath carbon monoxide diffusing capacity.
4.6 Pulse oximetry at rest, breathing room air.

5.0 REGISTRATION PROCEDURES

5.1 Patients who meet the eligibility criteria in section 3.0, sign the consent form, and pass the pretreatment evaluations, may be entered into the study by phoning RTOG Headquarters, (215) 574-3191 Monday-Friday, from 8:30 a.m. to 5:00 p.m. ET prior to any protocol therapy. The following information will be required:

- Patient's Name & ID Number
- Institution Name & Number
- Physician's Name
- Eligibility Criteria Information
- Date of Treatment Start
- Patient's Birthdate, Race, Sex, Social Security Number and Zip Code.
- Study and case numbers of RTOG treatment protocol if applicable.

The case number will be assigned and confirmed by mail.

6.0 RADIATION THERAPY

For patients registered to be treated on current RTOG lung studies, refer to Section 6.0 of the applicable study for radiation therapy parameters.

6.1 Treatment Regimen (for patients not on an RTOG treatment protocol)

6.1.1 RTOG 91-03: For patients treated with conventional, once daily fractionation, total dose to the involved areas will be 60-66 Gy. This will be administered at 2 Gy daily 5 times weekly to deliver 50 Gy target dose in five weeks to the large field. Additional 10-16 Gy to be delivered to initial tumor with reduced fields at 2 Gy daily.

No chemotherapy or biological modifiers are to be administered during or after RT unless there is disease progression. **(2/14/95)**

6.2 Physical Factors

6.2.1 Beam energy - Megavoltage equipment is required, with effective photon energies higher than 1 MeV. Photon beams are required to be used in all treatment areas except the supraclavicular region. Electron beams may be used to treat supraclavicular lymph nodes. The electron beam energy must be such that the minimum target dose specified at depth maximum. Generally, supraclavicular lymph nodes are estimated to be at 2 or 3 cm. depth.

6.2.2 Treatment distance - Minimum treatment distance to skin should be 80 cm. for SSD technique and minimum isocentric distance should be 80 cm. for SAD technique.

6.3 Localization Films

6.3.1 Localization films taken on simulators and portal verification films taken on the treatment machine will be necessary in all cases.

6.4 Irradiated Portals

6.4.1 Target volume of primary tumor (large field and boost)

(a) Includes complete extent of visible primary tumor as defined roetgenographically with a minimum of 2.0 cm and a maximum of 2.5 cm. around the mass on radiograph.

6.4.2 Target volume of lymph nodes. The following nodes must be included in the large field:

(a) Supraclavicular lymph nodes - if primary in upper lobes. It is acceptable to treat the ipsilateral supraclavicular nodes in the upper lobe lesions.
(b) Ipsilateral hilar nodes - Always (2 cm. margin)
(c) Contralateral hilar nodes - Always (1 cm. margin)
(d) Superior mediastinal lymph nodes (above carina) - Always (ipsilateral 2 cm. margin).
(e) Subcarinal lymph nodes - 5 cm. below carina - Always.
(f) Inferior mediastinal to diaphragm. With lower lobe lesions only or if shown to be involved by diagnostic studies or surgery.

Only involved nodes are included in the boost volume. Typical lesions and appropriate portal arrangements to demonstrate desirable volume to be irradiation are shown in Appendix IV.

6.5 Treatment Planning

6.5.1 Isodose Distribution - at the mid-transverse plane of the tumor must be submitted. In addition to this distribution, two specific points of calculation are requested:

6.5.1.1 The spinal cord dose 2 cm. below the superior margin of the posterior field, and

6.5.1.2 Supraclavicular node area at 3 cm. anterior depth (when applicable).

6.5.2 Blocking

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

6.5.2.2 With cobalt 60, beam trimmers or secondary blocking must be used all the way around the ports.

6.5.2.3 A posterior spinal cord shield will not be an acceptable technique to limit the spinal cord dose and the patient must be treated with oblique or lateral fields.

6.5.3 Compensating Filters

6.5.3.1 In case of sloping surface such as the thoracic inlet, compensating filters are recommended.

6.5.3.2 If compensating filters are not available, appropriate reductions in field size must be done at prescribed dose levels to avoid excessive irradiation to critical structures.

6.5.4 Dosimetry Monitoring - The American Association of Physicists in Medicine (Radiological Physics Center, Houston, Texas) will conduct a field survey of equipment. Copies of the daily radiation therapy treatment records and one localization film of each port will be sent to RTOG Headquarters with appropriate radiation therapy forms according to the schedule in Section 12.0.

6.6 Doses

6.6.1 Target Dose - The target dose is in terms of a dose to a point at or near the center of the target volume. The maximum target volume dose should not exceed this by more than 15%. The dose must be expressed in Gy and without correction for increased lung transmission.The following portal arrangements are specified:

6.6.1.1 For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

6.6.1.2 For an arrangement of 2 or more intersecting beams: at the intersection of the central ray of the beams.

6.6.1.3 Other complex treatment arrangements: at the center of the target area.

6.6.2 Fractionation

6.6.2.1 Each field should be treated every day.

6.6.2.2 Adherence to the fractionation schemes is required although slight deviations in the daily dose fractions are allowed (± 10% daily dose).

6.6.3 Therapy Interruptions

6.6.3.1 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.

6.6.3.2 If more than two weeks interruption is required, resumption of treatment is at the discretion of the radiation therapist. Patient will be considered a major protocol deviation although follow-up will be continued.

6.7 Anticipated Side Effects or Toxicities

6.7.1 Patients are not expected to experience any side effects or toxicities from the studies to be done as part of this protocol. However, because of the associated radiation therapy, the following comments are included:

6.7.2 Suggested Maximum Dose to Critically Sensitive Normal Structures. The following maximum doses to normal structures are suggested:

ORGAN	DOSE
Contralateral Normal Lung (excluding margin around tumor)	20 Gy
Heart	
Entire Organ	36 Gy
Less than 50%	45 Gy
Esophagus	50 Gy
Spinal Cord (maximum)	45 Gy

6.7.3 A posterior spinal cord shield will not be an acceptable technique to limit the spinal cord dose and the patient must be treated with oblique or lateral fields.

6.7.4 Reversible alopecia, skin pigmentation and esophagitis are expected side effects of radiation therapy. Radiation induced peri- and myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiation pneumonitis and subsequent fibrosis of the lung will occur to some degree in all patients receiving 30 Gy to the lung, usually within two to six months after initiation of treatment. Bone marrow toxicity may be induced. Radiation should be continued in the presence of moderately induced hematological toxicity, but discontinued at WBC < 2000/mm^3 and/or platelets < 100,000/mm^3, until hematologic recovery above these levels takes place.

6.7.5 Treatment breaks must not be scheduled unless severe reactions or logistic problems arise.

6.8 Lung Volume Measurements

The proportion of lung volume included within the radiation therapy portal is to be estimated by quantitative perfusion lung scanning.[22-26] After injection of Tc 99m macroaggregated albumin, (approximately 4 mCi IV) counts of lung radioactivity are obtained with a gamma camera and stored on the camera's computer. The radiation therapy field is superimposed as a region of interest on the computer generated posterior image of lung perfusion radioactivity. Areas of lung under the blocks are considered as unirradiated. The number of counts within the radiation therapy portal is compared to the total number of lung counts, yielding the fraction of total lung perfusion included in the radiation therapy portal. This fraction corresponds to a conservative estimate of the fraction of pulmonary function (as represented by FEV_1) at risk following radiation therapy. Guides that may be helpful for transferring the radiation therapy field to the nuclear medicine computer image include relationships of the field margins to 1) the faintly visible borders of the heart and aortic arch or perfusion scan, 2) visible perfusion defects on perfusion lung scan due to pulmonary or hilar masses, and 3) midline of the chest and superior, inferior, and lateral margins of the lung on scan. As the posterior radiation therapy fields usually account for two-thirds or more of the radiation dose, utilizing the data from the anterior and posterior radionuclide scans give a reliable approximation of the pulmonary volume at risk for radiation damage.

7.0 DRUG THERAPY

Does not apply to this study.

8.0 SURGERY

Does not apply to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

A central pathology review is not planned for this study.

11.0 PATIENT ASSESSMENTS

11.1 Required Measurements

Parameter	Prior to RX	AT RX end	Post Completion					
			3 mos	6 mos	9 mos	12 mos	18 mos	Yearly
Questionnaire	X	X	X	X	X	X	X	X
Dyspnea Score	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X
Chest X-Ray	X	X	X	X	X	X	X	X
Pulmonary Function Tests:								
Spirometry	X	X	X			X	X	X
Carbon Monoxide Diffusing Capacity	X	X	X			X	X	X
Pulse Oximetry at rest	X	X	X	X	X	X	X	
Perfusion Lung Scan	X							
Serum Markers, surfactant apoprotein and procollagen type III	X*							

* and at 10, 20, 30, 40, 50 and 60 Gy

11.2 Chest x-ray and will be repeated at completion of radiation therapy, then every three months for one year, at 18 months, then yearly. Size of primary tumor and associated atelectasis will be measured.

11.3 Current, usual and commonly available clinical information will allow collection of most of the necessary clinical data. To that data base is added a dyspnea score (Appendix V) and information to quantify cough, sputum volume, and functional state. Physical examination includes a brief description of edema, the pulmonic component of the second heart sound, chest wall and abdominal movement, air movement, and crackles.
Measure spirometry before and after bronchodilator, lung volumes by perfusion lung scanning, single breath carbon monoxide diffusing capacity, pulse oximetry and serum levels of surfactant apoprotein and procollagen type III. Follow-up assessment would occur at 3, 6, 9, 12 and 18 months and yearly thereafter. Each follow-up would include completion of a patient questionnaire, a dyspnea score, a physical examination, and chest x-ray, and pulse oximetry. The serum markers are aimed at early detection, and thus also need to be determined at specific dose points during treatments. (See Appendix VIII for serum submission).

11.3.1 The Baseline and Transitional Dyspnea Indices (Appendix V) were developed to improve the clinical measurements of dyspnea. They have been validated and correlated with other measures of lung function.[22] The Baseline Dyspnea Index rates the severity of dyspnea at the time of initial evaluation and start of treatment. The Transitional Dyspnea Index denotes change from the baseline condition. The ratings in each of the three categories (Functional Impairment, Magnitude of Task, and Magnitude of Effort) are added to form a baseline focal score, ranging from 0 to 12. The lower the total score, the worse the severity of dyspnea. When information is unavailable or insufficient, or when the patient is impaired by other factors (a W, X, Y, or Z response) the grading of dyspnea is not possible.

Baseline Index = Sum of Scores for Functional Impairment + Magnitude of Task + Magnitude of Effort.

Transitional Index = Sum of Scores for Changes in Functional Impairment + Change in Magnitude of Task + Change in Magnitude of Effort.

11.4 Testing Schedule

11.4.1 Prior to starting and at end of treatment, and at 3, 6, 9, 12 and 18 months after completing treatment then yearly:
- Questionnaire
- Dyspnea Score (Appendix V)
- Physical Examination
- Chest x-ray
- Carbon Monoxide Diffusing Capacity (but not at 6 and 9 months)
- Pulse oximetry breathing room air and at rest.
- Lung Volumes by quantitative radionuclide perfusion lung scanning (pretreatment only)

11.4.2 Prior to starting and at end of treatment, and at 3, 12, and 18 months after completing treatment then yearly:
- Spirometry

11.4.3 Serum marker determinations (Surfactant Apoprotein and Procollagen Type III) will be done at the following total dose levels: pretreatment, and at 10, 20, 30, 40, 50, and 60 Gy. These will be sent to Dr. Jacob Finkelstein at the University of Rochester. See Appendix VIII.

12.0 DATA COLLECTION

All data will be submitted to RTOG Headquarters according to the following schedule.

Item	Due
Demographic Form (A5)*	Within 1 week of registration
Initial Evaluation Form (I1)* **Pulmonary Assessment Form (I8)**	Within 2 wks of registration
Preliminary Dosimetry Information: **Chest X-Ray (C4)** RT Prescription (Protocol Treatment Form) (T2)* Films (simulation and portal) (T3)* Calculations (T4)* **Pre-RT Perfusion Lung Scan (PS) and Report (PR)**	Within 1 wk of start of RT
Radiotherapy Form (T1)* **Specimen Transmittal Form (ST)** (original sent with specimens; copy to HQ) Final Dosimetry Information: Treatment Record (T5)* Isodose Distribution (T6)* Boost Film (simulation and portal) (T8)*	Within 1 week of RT end
Follow-up Form (F1)* 18 months, then yearly at ≥ grade 3 toxicity	At completion of treatment, at 3, 6, 9, 12, and progression, and at death.
Follow-up Pulmonary Assessment Form (PA)	At completion of treatment, at 3, 6, 9, 12, and 18 months then yearly until progression.
Autopsy Report (D3)	As applicable

*Does not apply to patients entered on RTOG treatment studies. This information is submitted for the applicable protocol. **The I8, C4, PS, PR, ST, and PA are submitted for all patients.**

13.0 STATISTICAL CONSIDERATIONS

13.1 Endpoints

13.1.1 Primary Endpoints: the serial changes for three pulmonary function tests (FEV1, VC, and DLCO) between the pretreatment determination and post irradiation determination at various designated time points.

13.1.2 Secondary Endpoint: the serial changes in serum markers.

13.2 Sample Size

13.2.1 Of particular interest is the percent of changes in the pulmonary functions tests for patients who survive at least one year. For the purpose of estimating a sample size for the study, the ability to detect a 20% change between the means for the pre-RT and the 12 month post RT pulmonary function test respectively was sought. Since results with serial FEV1 pulmonary tests have appeared in several RT related publications, it was used for the sample size calculations. The following conditions were arbitrarily set:

1) the FEV1 evaluation done before RT and at 12 months post RT are normally distributed with the same standard deviation;
2) two sided test with alpha = .05 and beta = .20 (statistical power of .80);
3) there is no correlation between the pre RT and 12 month RT values in a given patient (This assumption does actually lead the most conservative estimate of the sample size).

In series of 190 patients treated at the Fox Chase Cancer Center, the mean and the standard deviation for the pre-treatment FEV1 test were 1.72 and 0.6 respectively[23] Using the above assumptions and data, a sample size of 50 evaluable patients was derived to detect 20% change in the means between the pre and the 12 month post RT evaluation. In Table 1, the statistical power associated with the various means and standard deviations is presented.

Table 1
Statistical Power With 50 Evaluable Patients to Detect a 20% Change

Initial Mean	Standard Deviation 0.5	0.6	0.7
2.0	.98	.91	.82
1.9	.97	.89	.77
1.8	.95	.84	.73
1.7	.93	.81	.68
1.6	.89	.76	.62

Since the analysis will be performed with a paired test, the statistical power will, in fact, be higher because of the anticipated correlation.

Since not every patient will survive beyond 12 months, the number of patients to be initially entered into the study has to be adjusted upward from the 50 evaluable patients. The estimated probability of surviving beyond 12 months from past RTOG lung studies is 40% in the patients who would be eligible for this study. Ideally, the protocol required pulmonary tests at 12 months will be done in all patients who survive beyond that time but it is anticipated that there will not be perfect compliance. For planning purpose, a rather conservative estimate of compliance was set at .67 (2 out of 3).

Thus the total number of patients to be entered is 187.

13.2.2 In addition, the study will test if there is any correlation between an elevation of biochemical markers after various total doses and subsequent pulmonary abnormalities at six months and one year. Specifically, the null hypothesis is that the correlation "r" between them is zero versus the alternative that the correlation "r" is greater than zero. With an estimated 50 evaluable patients at one year, there will be a greater than 97% chance of detecting "r" $\geq$ .50 at a = 0.5. If only 30 patients were evaluable at one year, there would still be an 83% chance of detection such an "r"[27]

13.3 Study Duration

It is anticipated that the study will accrue the projected sample size of 187 patients between two and three years. If the average monthly accrual falls below 5.0 cases per month, the feasibility of continuing the study will be discussed at a semi-annual RTOG meeting.

13.4 Analyses Plans

13.4.1 Interim Reporting During Patient Accrual Phase

The study will be monitored every six months. A written report which will specifically look at patient accrual and the compliance with performing the prescribed pulmonary function tests and submitting the serum markers will be published in the RTOG Pre-Meeting Book.

13.4.2 Final Reporting After Patient Accrual Phase

Approximately, 18 months after the accrual phase is completed, the analysis looking at serial changes in pulmonary tests and at the correlation between serum marker elevations and pulmonary functions will be performed. Regression models will also be used to describe the relationship between changes at six months and one year, radiation dose, and volume. Serum marker values will be added as covariates in the model to determine whether serum markers improve its predictive accuracy.

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APPENDIX I

RTOG 91-03

Pulmonary Function of Patients Treated with Radiation Therapy for 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

It has been explained to me that I have cancer of the lung. My doctor believes that my participation in this study may be helpful. This study involves measuring how well my lungs are working before and after radiation treatment for my cancer. The purpose of this study is to determine the effects of radiation treatment on lung and breathing function; to help detect and treat possible interference with the breathing action of my lungs as early as possible; to better help select patients who will benefit from radiation treatment; and to identify patients who may not do well with such treatment. Chances of this benefit cannot be accurately predicted.

DESCRIPTION OF PROCEDURES

This study involves measuring how deep and fast I breathe. If I take part in this study, the tests will include spirometry testing of lung volumes and diffusion capacity by breathing through a mouth piece and a short length of attached plastic tubing into a tank of air. The oxygen content in my blood before and after treatment will be measured by placing a clip gently on one of my finger tips. Small amounts of blood will be taken periodically by puncturing the skin in my forearm with a needle and withdrawing 1-2 teaspoonfuls of blood. This blood will be used to measure the amount of surfactant apoprotein and procollagen III in my blood.

Surfactant is a substance which coats the mucus membranes of the small air sacs in my lung, helps keep them suitably moist and aids the exchange of oxygen and other gases between the bloodstream and these air spaces. Procollagen III is a component of scar tissue and other connective tissue. Both of these substances may be present in the blood in abnormal levels when the lung is injured or scarred. Because these may be very early indicators of such lung injury and scarring, they will be measured weekly during treatment and at less frequent intervals afterwards. I will not be asked to do activities which will cause me great discomfort.

These tests are not investigational and should be covered by my insurance carrier.

POTENTIAL 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.

POTENTIAL RISKS

It is not expected that the testing procedures to be done for this study will result in any harmful effects. The risks involved are those associated with radiation therapy to the lung. Cancer treatments often have side effects. The radiation treatment used in this program may cause all, some, or none of the side effects listed.

Risks from radiation are redness and or tanning of the skin, hair loss, irritation or inflammation of my throat any esophagus, weakness and fatigue due to lowering of my blood counts. These effects are usually temporary and usually clear after treatment is completed. Pericarditis (inflammation of the sac surrounding the heart) transverse myelitis (inflammation of the spinal cord) or scarring of the lung causing shortness of breath may occur. Lung injury usually appears two to six months after treatment. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. Side effects usually disappear after the treatment is stopped. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs.

ALTERNATIVES

Alternatives which could be considered in my case include standard clinical examination and observation without these special tests. 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.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment for injury will be available. I understand, however, I will not be provided with reimbursement for medical care aside from what my insurance carrier may provide 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.

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 _____ and also in a computer file at headquarters of the Radiation Therapy Oncology Group. 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) 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 an executed 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

NEW INTERNATIONAL STAGING SYSTEM FOR LUNG CANCER

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 IV

Non-Oat Cell Ca Lung

AP Portals

Upper Lobes

Middle Lobes
or Lingula

Lower Lobes

APPENDIX IV

PA Portals

Oblique Portals

APPENDIX VII

ADVERSE REACTION REPORTING GUIDELINES

A. General Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates.

1. The Principal Investigator will report to the RTOG Group Chairman, the details of any unusual, significant, fatal or life-threatening protocol treatment reactions. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3150). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the specific protocol for criteria to grade the severity of the reaction.

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.
(FAX #215/928-0153)

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

5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process.

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

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

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

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

B. Modality Toxicity Guidelines

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

2. All life-threatening or grade 4 toxicities from altered fractionation protocol therapy or particle radiotherapy must be reported by telephone to the Group Chairman and to RTOG Headquarters' Data Management Staff and to the 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 reported incident.

APPENDIX VIII

SURFACTANT APOPROTEIN AND PROCOLLAGEN TYPE III TESTING

Samples should be collected in green top tubes (4-8 cc per test) and spun. (Centrifuge at 400 x g for 10 minutes. Refrigerated centrifuge not required.) The plasma will be separated and transferred to plastic tubes and carefully sealed. Samples must be labeled and frozen at -4°C (regular freezer). Labels are available from RTOG and will include the following information:

SURFACTANT APOPROTEIN & PROCOLLAGEN III

Protocol #__91-03_____ 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 will be collected and kept frozen during the period from pre-treatment to 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 absorbant material in case of spillage. The package should be clearly marked “Frozen Material.” A submission 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.

To assure that samples will be attended to promptly upon arrival, do NOT ship on Thursday, Fridays or Saturdays or prior to any holiday.

Samples will be sent to:

Jacob Finkelstein, Ph.D.
Annex B-237
University of Rochester Medical Center
601 Elmwood Avenue
Rochester, NY 14642
716/275-5948