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RADIATION THERAPY ONCOLOGY GROUP

RTOG 79-07

PHASE III RANDOMIZED
PROTOCOL TO STUDY FAST NEUTRON AND MIXED BEAM (NEUTRON/PHOTON) RADIATION THERAPY IN THE TREATMENT OF LOCALIZED, INOPERABLE NON-OAT CELL CANCER OF THE LUNG (SQUAMOUS CELL, ADENOCARCINOMA AND LARGE CELL UNDIFFERENTIATED TYPE)

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SCHEMA

STRATIFY

1. Histology
   - squamous
   - adenocarcinoma or adenosquamous large cell undifferentiated
2. Primary Size
   - 0-3 cm
   - 3-6 cm (size of primary)
   - > 6 cm
3. Neutron Facility

RANDOMIZE

A. Photons: 6000 rad in 30 fractions over 6-7 weeks

B. Neutrons alone: 1800 rad (Seattle) in 24 fractions over 6-7 weeks (1950 FERM, 12 Fxs)

C. Mixed beam (neutron/photon): (neutron 720 rad in 12 fractions/ photon 3600 rad in 18 fractions) over 6-7 weeks

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1.0 INTRODUCTION

1.1 Disease Background.

According to the most recent statistics for the United States (1), lung cancer is the most common malignancy in the male and the fourth most common malignancy in the female (excluding non-melanoma skin cancer). It is the most common cause of malignancy-related death in the male and the third most common cause of malignancy-related death in the female. In spite of evidence linking the development of lung cancer to cigarette abuse (2), it appears that this disease will remain a serious problem in the foreseeable future (1). In many cases, the lesion appears to be localized to the lung and mediastinum at the time of presentation yet is inoperable by virtue of extent of disease and/or location. Local radiation therapy is the main modality used in treating these patients but the preliminary results of a recent RTOG protocol study with conventional photon irradiation are somewhat disappointing. For localized, unresectable non-oat cell carcinomas, the one-year disease-free survival is 50% and the two-year disease-free survival is 25-30% (3). The most favorable arm of this study (56% one-year disease-free survival) consisted of 6000 rad over 6-7 weeks which is the control arm of the present protocol. Although undetected subclinical distant metastases at the time of presentation remains a concern, it is clear that the problem of local control is an important one, both in terms of absolute survival and in terms of quality of survival(4). Furthermore, patients showing complete response in the RTOG study had improved survival compared to partial and non-responders (75 vs 40 week median survival).

1.2 Rationale for Neutron Radiotherapy.

A characteristic of large, rapidly growing tumors is that they tend to outgrow their blood supply resulting in necrotic areas surrounded by populations of hypoxic cells which tend to be resistant to conventional low-linear-energy-transfer (low-LET)

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megavoltage photon irradiation (5). This may account in part for the difficulty in achieving local control in inoperable lung carcinomas. A characteristic of high-LET radiation is a low oxygen enhancement ratio (OER) which makes this type of radiation of interest for treating such tumor systems. Preliminary clinical studies on hypoxic cell systems such as malignant gliomas (6) and on advanced cervical adenopathy from head and neck primaries (7) show a higher rate of local control for fast neutrons than for conventional megavoltage photon therapy. In addition, there are some laboratory studies by Rasey et al (8,9) which show that combining fast neutrons with conventional photon irradiation as part of a "mixed beam" regime leads to an enhanced therapeutic ratio compared with fast neutrons alone. The results of several clinical pilot studies tentatively support these laboratory findings by yielding either an equal (6) or higher (7,10) rate of local control for the mixed beam mode compared with neutrons alone. The mixed beam mode also appears to cause less morbidity (7,10) than neutrons alone. The purpose of this study is to compare the results of fast neutron radiotherapy alone and as part of a mixed beam regimen with the best currently available treatment scheme utilizing conventional photon irradiation. The use of neutrons alone is to be compared with the mixed beam regimen since, if the mixed beam regimen is equivalent or superior to neutrons alone, this mode of treatment would most effectively utilize the net limited treatment time on the relatively small number of clinically-based neutron units projected for the United States in the foreseeable future.

1.3 General Outline.

This protocol study is confined to limited but non-resectable or inoperable non-oat cell carcinomas of the lung and bronchi. Patients who have received chemotherapy, are undergoing concomitant chemotherapy, or for whom chemotherapy is being planned, are not eligible for this study. While the use of

chemotherapy for these tumor systems is a subject of current investigational interest, its effectiveness has not been proved and including such patients would introduce an additional element of uncertainty into the study. However, patients who, after completing the course of planned radiation, subsequently receive chemotherapy for either progressing local disease and/or distant metastases will continue to be followed.

The three treatment arms are designed to deliver the same weekly equivalent and total radiation dose after correction is made for the increased radiobiological effectiveness ($RBE_{n/\gamma}$) of the neutron beam. The exact value used for $RBC_{n/\gamma}$ will depend upon the energy spectrum of the neutron beam and will vary among neutron facilities. Patients will be treated five times a week on the photon arm, four times a week on the neutron-only arm, and on the mixed beam arm will receive neutrons twice a week and photons three times a week.

2.0 OBJECTIVES

The objectives of this study are to compare fast neutron teletherapy, both neutrons alone and as part of a mixed beam (neutron/photon), with the best available conventional photon therapy for inoperable non-oat cell lung cancer by evaluating the following:

2.1 Degree and rate of regression of tumor volume.

2.2 Time to onset of tumor regrowth (if any) and rate of regrowth.

2.3 Disease-free survival.

2.4 Absolute survival.

2.5 Time of onset, evaluation and severity of any radiation injury to surrounding normal lung tissue and adjacent critical structures such as heart, esophagus and spinal cord.

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3.0 PATIENT SELECTION

3.1 Eligibility Criteria.

3.1.1 Patients with histological evidence (biopsy or Class V cytology) of a malignant tumor of the lung or bronchi.

3.1.2 Squamous cell or epidermoid carcinomas, adenocarcinomas, adenosquamous, and undifferentiated large cell carcinomas are acceptable.

3.1.3 Patients without previous radiation therapy for the lung neoplasm and who have not had previous radiation therapy to the tissue volume to be irradiated in this study.

3.1.4 Tumor must be measurable in at least two dimensions on chest x-ray (both PA and Lateral views).

3.1.5 No evidence of cerebral, hepatic or osseous metastases or of other distant metastases (patients with positive supraclavicular nodes are acceptable).

3.1.6 No major resection of the primary or involved nodes.

3.1.7 Patients must have a Karnofsky status $\geq$ 50 (see Appendix II).

3.1.8 Patients must be < 80 years of age.

3.1.9 Patients must sign an informed consent form (see Appendix III).

3.2 Ineligibility Criteria.

3.2.1 Karnofsky status < 50 (see Appendix II).

3.2.2 Evidence of severe incapacitating lung disease such as chronic bronchitis, emphysema, or severe incapacitating cardiac disease who are judged not capable of tolerating the expected diminution of lung function following irradiation.

3.2.3 Patient for whom the required visits to the neutron facility would be logistically impossible.

3.2.4 Histology of small cell undifferentiated carcinoma or any of its histologic sub-types (e.g., oat cell).

3.2.5 A prior or concurrent malignancy (except non-melanoma skin cancer).

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3.2.6 Pleural effusion (regardless of cytology).

3.2.7 Patients $\geq$ 80 years old.

3.2.8 Prior surgical resection of primary or nodes.

3.2.9 Distant metastases with the exception of positive supraclavicular nodes.

3.3.0 Prior radiation to the anticipated treatment volume.

3.3.1 Prior, concurrent or anticipated subsequent chemotherapy.

4.0 PRETREATMENT EVALUATION

4.1 History and physical.

4.2 Mandatory Laboratory Procedures.

4.2.1 CBC including WBC, differential and platelets.

4.2.2 Blood chemistry studies including routine liver function tests (SGOT, LDH, bilirubin, alkaline phosphatase).

4.3 Mandatory Imaging Procedures.

4.3.1 Chest x-ray (PA and lateral).

4.3.2 Liver scan.

4.3.3 Bone scan.

4.3.4 Brain scan (if there is clinical evidence of CNS metastases).

5.0 ADMISSION TO STUDY AND RANDOMIZATION

5.1 Randomization Procedure.

To randomize a patient on this study call the RTOG Headquarters (215) 574-3191 between 9:00 a.m. and 5:00 p.m., EST, Monday through Friday, and give the following information:

Protocol name
Institution referring patient
Neutron facility
Physician's name
Patient's name

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Histology (adenocarcinoma, adenosquamous carcinoma, squamous cell carcinoma or large cell undifferentiated carcinoma).

Size of primary (0-3 cm, 3-6 cm, or > 6 cm).

A project case number and treatment will be assigned which will be confirmed by mail.

5.2 Treatment Arms.

5.2.1 Treatment A. Megavoltage photon irradiation (600 rad in 30 fractions over 6-7 weeks).

5.2.2 Treatment B. Fast neutrons alone: 1800 rad (1950 FERMILAB) (Seattle) in 24 (12 fractions FERMILAB) fractions over 6-7 weeks delivering four fractions per week.

5.2.3 Treatment C. Mixed beam (neutron/photon): 720 rad neutron/3600 rad photon over 6-7 weeks. Neutrons will be given twice a week (60 rad per fraction) and conventional megavoltage photon irradiation (200 rad per fraction) three times a week. Hence, of the net photon rad equivalent dose, 40% will be given via the neutron beam and 60% via conventional photon irradiation.

6.0 TREATMENT

6.1 Radiation Therapy.

Radiation therapy will be initiated within three weeks of establishing the histological diagnosis.

6.2 General Considerations.

6.2.1 The tumor doses will be calculated at mid-depth along the central axis with no corrections being made for tissue inhomogeneity factors.

6.2.2 If a cyclotron is used to generate the neutron beam, the energy distribution of the neutrons must be at least of the quality obtained from the reaction of 21.5 MeV deuterons on a beryllium target. The output from a deuterium-tritium neutron generator tube is also acceptable.

6.2.3 Megavoltage equipment is required for the photon phase of irradiation. The effective photon energy must be greater than 1 MeV (^{60}Co, 4 MeV or greater linear accelerators). High energy electrons are not allowed.

6.2.4 Each port should be treated daily.

6.2.5 The spinal cord dose shall be limited to 4500 photon rad equivalent in the photon-only and mixed beam treatment arms. Because of the apparent larger value of the RBE($_{n/\gamma}$) for late damage to neural tissue (10,6), the spinal cord dose shall be limited to 1300 rad$_n$ in the neutron-only treatment arm.

6.2.6 If the supraclavicular regions are clinically negative, they may be treated with photons alone regardless of which treatment arm is drawn. In such cases, it is recommended that they receive 4500 rad$_\gamma$ at a depth of 3 cm and that a midline spinal cord block be used provided that it does not protect regions of known disease.

6.3 Target Volume and Dose Fractionation.

6.3.1 The specific design of the irradiation portals will be left to the discretion of the participating radiotherapist although the following anatomical sites must be treated:

(a) Target volume of primary must include the complete extent of the visible primary tumor with a margin of 2 cm minimum around its radiographic boundaries. For extensive lesions complicated by atelectasis or pneumonitis, the entire lung may be treated.

(b) The target volume of the lymph node must include:

(i) Superior mediastinum (above carina).

(ii) Ipsilateral hilum.

(iii) Subcarina to at least 5 cm below the carina.

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(iv) Inferior mediastinum to the level of diaphragm for lower lobe lesions only

(v) Supraclavicular region for upper lobe lesions or with positive superior mediastinal nodes.

6.3.2 The irradiated volume will be defined by individually shaped ports utilizing primary collimation, secondary lead blocks, or tailor made blocks.

6.3.3 Compensating filters may be used as necessary.

6.3.4 The doses will be specified at mid-depth along the central axis of the fields. The dose across the target volume must not vary more than ± 10%.

6.3.5 The daily fractionation should be 200 ± 10% rad photon or 60 rad neutrons (Seattle).

6.3.6 Isodose distribution calculations should assume that the central axis is in the midplane of the tumor.

6.3.7 Localization films taken on simulators or treatment machines and photographs of the treatment portals will be made and submitted to RTOG Headquarters within one week of randomization.

7.0 PATHOLOGY

Does not apply to this study.

8.0 PATIENT ASSESSMENT

In the table below, the specific studies prior to, during and after completion of treatment are listed:

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8.1 Study Parameters.

Parameter	Pre-treatment	During Treatment	Upon Completion of Treatment	Follow Up
History and physical	x		x	x
Karnofsky status	x		x	x
Chest radiograph (PA, lateral)	x		x	x
Bronchoscopy	x			x[a]
CBC, differential	x	q 1-2 wks	x	x[a]
Chemistries	x			x[b]
Pulmonary functions	x[a]			x[a]
Liver scan	x	x[a]	x[a]	x[a]
Bone scan	x	x[a]	x[a]	x[a]
Brain scan	x[a]	x[a]	x[a]	x[a]

a - As clinically indicated b - Every four months at follow-up

8.2 Completion and Follow-up Studies and Parameters.

8.2.1 Follow-up visits as follows: every two months following the start of treatment to ten months, then every four months for the second year, every six months for the third year and annually thereafter.

8.2.2 Chest films at completion and each follow-up.

8.2.3 CBC, WBC and differential at completion.

8.2.4 Performance status and assessment of symptoms.

8.2.5 Blood chemistry every four months.

8.2.6 Pulmonary function tests are optional. If done, it is recommended that they be performed two months after treatment, every four months for the remainder of the first year, and every six months thereafter.

8.2.7 Bronchoscopy if indicated to establish recurrence.

8.2.8 Late normal tissue reactions should be recorded at the time of each follow-up according to the scale in Appendix IV.

8.2.9 Biopsy of suspicious nodes or nodules, if accessible.

8.3 Endpoints of Study.

8.3.1 Symptomatic relief interval: this is measured from the time of onset of treatment to the time of disappearance of symptoms.

8.3.2 Frequency of symptom response is recorded as none, partial and complete.

8.3.3 Symptom-free interval: this is measured from the time of relief of symptoms to their reappearance at the same site or another.

8.3.4 Relapse-free interval: this is measured from the time of objective disappearance of original lesion(s) to the appearance of new objective disease as recurrence or metastases.

8.3.5 Objective Regression of Measurable Lesions.

8.3.5.1 Complete Response - Complete disappearance of all radiographically detectable tumor(s).

8.3.5.2 Partial response - All of the following criteria must be met:

8.3.5.2.1 A reduction by at least 50% of the product of the longest perpendicular diameter of the most clearly measurable mass lesion.

8.3.5.2.2 No increase of 50% or more of any other indicator lesion and no new areas of malignant disease may appear.

8.3.5.2.3 No significant deterioration in weight ($\leq$ 10%), symptoms, or performance status (20 points).

8.3.6 Objective Regression of Evaluable Non-Measurable Lesions.

A definite decrease in size of disease areas amounting to an estimated 80% regression ("close to complete regression") or better. This should be confirmed by at least two investigators evaluating independently and x-rays should be submitted to the study chairman for confirmation.

8.3.7 No Change - All of the Following Criteria:

8.3.7.1 Insufficient regression of primary indicator lesion to meet criteria above.

8.3.7.2 Less than 50% increase in any measurable lesion.

8.3.7.3 No new areas of malignant disease.

8.3.7.4 No significant deterioration in weight, symptoms or performance status.

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8.3.8 Objective Progression - Any of the Following Criteria:

8.3.8.1 Increase in any measurable lesion by greater than 50% on two successive bi-weekly visits.

8.3.8.2 Appearance of new areas of malignant disease.

8.3.8.3 Significant deterioration in symptoms, decerase in weight (> 10%) or decrease in performance status (> 20 points).

8.4 Survival after Treatment (from day of randomization until death):

8.4.1 Tumor sterilization at primary site and lymph nodes when histological sections are available.

8.4.2 Sites of metastatic dissemination after initial therapy.

8.4.3 Quality of survival as measured by the code for Performance Status.

8.4.4 It is highly desirable that changes in pulmonary function be determined and serially recorded for improvement or decline during and after therapy.

8.4.5 Complications of treatment.

8.5 Post-Mortem Studies to Include:

8.5.1 Status of tumor at primary site.

8.5.2 Status of lymph nodes in hilar area and mediastinum with careful mapping of removed and examined nodes.

8.5.3 Status of irradiated lung.

8.5.4 Detailed mapping and recording of metastatic spread.

8.5.5 Irradiated organs should be carefully examined for radiation effects whenever possible (surgical specimens or at post-mortem examination).

9.0 DATA COLLECTION

Records to be kept and reporting schedule:

9.1 The investigator must submit the appropriate RTOG lung forms to RTOG Headquarters according to the following schedule:

Form	Due
On study forms. Localization films Treatment prescription	Within one week of randomization Within one week of start of treatment
Radiation therapy form Radiation therapy record Reduced field films and isodose summation, if done	Within 1 month of completion of treatment
Follow-up forms	At 2 months following the start of treatment, then every 2 months to 10 months, then every 4 months for the 2nd year, every 6 months for the 3rd year and annually thereafter.
Death form	Upon death of patient

9.2 Pulmonary Function Reports.

Pulmonary function reports, although optional, will be submitted separately as pretherapy evaluation, at 2 months after completion, every 4 months for the remainder of the first year and every 6 months thereafter (for participating institutions).

10.0 STATISTICAL CONSIDERATIONS

If eighty patients are entered on each arm of this study, it should be possible with approximately 85% certainty to detect an increase in the 2-year disease free survival from 25% to 45% (using a one-sided test of significance with a type I error of 5%).

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11.0 ADDITIONAL TREATMENT

11.1 The best supportive care is to be given to every patient. Additional radiotherapy may be given for relief of pain or vital indications (i.e. visceral involvement, bony metastases, superior vena cava syndrome). This will be at the discretion of the radiation therapist.

11.2 Antineoplastic agents are not to be administered in conjunction with protocol therapy. Corticosteroids are permissible for short-term control of hypercalcemia, superior vena caval syndrome or symptomatic cerebral metastases.

11.3 Senior investigators may remove a patient from the scheduled treatment if it clearly is in the patient's best interest to do so. Such deviations should be documented in detail.

REFERENCES

1. American Cancer Society: 1978 Cancer Facts and Figures.

2. U.S. Surgeon General Advisory Committee on Smoking and Health: Smoking and Health; Report of Advisory Committee to Surgeon General of the Public Health, U.S. Dept. of Health and Welfare, Washington, D.C., 1964.

3. Perez, C.A., Stanley, K., Mietlowski, W., Simpson, J., Rubin, P., Kramer, S., Brady, L., Perez-Tamayo, R., Brown, S., Concannon, J., Seydel, H.G. and Rotman, M.: Randomized studies of several dose and fractionation schedules in non-oat cell carcinomas of the lung. In Proc Am Soc Ther Radiol 1978.

4. Rubin, P., Ciccio, S., and Setisarn, B.: The controlversial status of radiation therapy in lung cancer. In Proc Sixth Nat Can Conf 855-865, 1970.

5. Withers, H.R.: Biological basis for high LET radiotherapy beam. Med Phys 4:379-386, 1977.

6. Laramore, G.E., Griffin, T.W., Gerdes, A.J. and Parker, R.G.: Fast neutron and mixed (neutron/photon) beam teletherapy for Grades III and IV astrocytomas. Cancer 42:96-103, 1978.

7. Griffin, T.W., Laramore, G.E., Parker, R.G., Gerdes, A.J., Hebard, D.W., Blasko, J.C. and Groudine, M.: An evaluation of fast neutron beam teletherapy of metastatic cervical adenopathy from squamous cell carcinomas of the head and neck region. Cancer (in press).

8. Nelson, J.S.R., Carpenter, R.E. and Parker, R.G.: Response of mouse skin and the C3HBA mammary carcinoma of the C3H mouse to x-rays and cyclotron neutrons: effect of mixed neutron-photon fractionation schemes. Europ J Can 11:891-901, 1975.

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9. Rasey, J.S., Carpenter, R.E., Nelson, N.J. and Parker, R.G.: Cure of EMT-6 tumors by x-rays or neutrons: effect of mixed and fractionation schemes. Radiology 123:207-212, 1977.

10. Laramore, G.E., Blasko, J.C., Griffin, T.W., Groudine, M.T. and Parker, R.G.: Fast neutron teletherapy for advanced carcinomas of the oropharynx. In Proc Am Soc Ther Radiol 1978.

APPENDIX I

Anatomical Staging for Lung Cancer

(RTOG Modification of American Joint Committee Staging)

1. Anatomical Staging:

Each case must be assigned the T, N and M category that most accurately describes the extent of disease. The anatomical staging will be described as clinical or radiological when only a bronchoscopic biopsy, cytology or percutaneous needle biopsy is available to confirm the tumor type.

Where node biopsies including scalene node biopsy, mediastinoscopy or mediastinotomy have been performed, the staging is classified as "pathological."

In patients who have undergone exploratory thoracotomy or resection, use will be made of the pathological and operative findings obtained by the surgeon and the staging will as "surgical."

Biopsies which are negative for malignancy, but which fall into the above mentioned categories will make the patient eligible for surgical or pathological staging.

2. TNM Categories: (Note Modifications*)

T-Primary Tumor

T-0 No evidence of primary tumor.

T-X Tumor proven by the presence of malignant cells in secretions, but not by roentgenograph or bronchoscopy.

T-1 Intrapulmonary, localized; a solitary tumor 3.0 cm or less in greatest diameter, surrounded by lung or visceral pleura and without evidence of invasion proximal to a lobar bronchus at bronchoscopy.

T-2 Intrapulmonary, extensive; a tumor more than 3.0 cm in greatest diameter or a tumor any size which, with its associated atelectasis or obstructive pneumonitis, extends to the hilar region. At bronchoscopy, the proximal extent of demonstrable tumor must be at least 2.0 cm distal to the carina. Any associated atelectasis or obstructive pneumonitis must involve less than an entire lung; there must be no pleural effusion.

*T-3 Extrapulmonary, intrathoracic localized; this includes T lesions which invade through the visceral pleura into the pleural space or adhere to the parietal pleura; bronchogenic cancers within 2 cm of the carina; no visceral, vascular, neurologic, osseous or cardiac (including pericardial) invasion.

*T-3.1 T lesions meeting such criteria, limited to one lobe, including associated atelectasis and infiltration.

*T-3.2 T lesion as stated, limited to two lobes.

*T-3.3A T lesion as stated, limited to one main bronchus, without atelectasis.

*T-3.3B T lesion with pleural effusion, negative cytology.

NB: It is important to recognize that T3 lesins may require thoracic exploration for classification. T3.1, T3.2 and T3.3 represent T, T2 lesions both clinically and radiographically assessed, but are beyond resection based on their location or evidence of extrapulmonary invasion at the time of surgery.

*T-4 Extrapulmonary, intrathoracic extensive: a very extensive T lesion, invading nerves, major vessels, heart, vertebrae and chest wall sites. It is beyond parietal pleura and is into the chest wall, viscera and/or deep mediastinal structures. This does not include patients wtih extrathoracic visceral metastasis.

*T-4.1 Pleural effusion with positive cytology.

*T-4.2 Superior vena cava obstruction associated with any T lesion.

N-Regional Lymph Nodes

N-0 No demonstrable spread to lymph nodes.

N-1 Spread to lymph nodes in the ipsilateral hilar region.

*N-2.1 Subcarinal and lower mediastinal.

*N-2.2 High mediastinal.

*N-2.3 Contralateral hilar nodes.

*N-2.4 Posterior mediastinal nodes, diaphragmatic and pericardial.

*N-3 Supraclavicular or biopsied scalene nodes.

*M-Distant Metastasis

M-1 Solitary, isolated metastasis confined to one organ or anatomic site. This also applies to cervical, axillary or abdominal coeliac nodes.

M-2 Multiple metastatic foci confined to one organ system or one anatomic site, i.e., lungs, skeleton, liver, etc.

M-3 Multiple organs metastatic involvement.

3. Staging Grouping of Carcinoma of the Lung

Stage 0:	T-X, N-0, M-0, an occult carcinoma based upon positive cytology.	
*Stage I:	T-1, N-0, M-0, a tumor that can be classified T-1 without any spread to nodes or distant metastases.	
*Stage II:	T-1, N-1, M-0 T-2, N-0, M-0 T-2, N-1, M-0	A pulmonary intrathoracic tumor classified as T-2, or spread to the lymph nodes in the ipsilateral hilar region only (N-1), or both T-2 and N-1.
*Stage III:	T-3, N-0, N-1 N-2 with T-1 T-2, T-3, M-0	Any extrapulmonary extrathoracic tumor spread to the lymph nodes in the mediastinum.
*Stage IV:	T-4 with any N, N-3 with any T, M of any category	Extensive extrapulmonary invasion into viscera and bone with extrathroacic but regional spread, metastases may also be present.

APPENDIX II

KARNOFSKY PERFORMANCE STATUS

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 process progressing rapidly.
0	Dead.

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Think over what you have just read. If you have any questions, please ask them. We will try to answer any questions that you might have about the study. If you would like to take more time to answer, and feel that you can't sign a consent now, please take the time to think it over more carefully. If you do decide to participate in the study, and at any future date change your mind, you are perfectly free to withdraw your consent, and this will in no way jeopardize your relationship with your doctor or the care which you will receive. Likewise, if you decide not to participate in the study from the beginning, you will still receive the best available care from your doctor.

_____	_____
Signature of Witness	Signature of Patient
_____	_____
Date	Date

I have fully explained the study and the treatment plan to the above patient.

(P 149 #2)

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APPENDIX III

Sample Consent Form
for Participation in the RTOG Protocol for
the Treatment of Lung Tumors

You have been diagnosed as having a tumor of the lung which cannot be completely removed by surgery. This tumor may be treated by conventional radiation therapy or by a new type radiation called neutrons. A significant number of tumors continue to be locally incurable at doses within the tolerance of the surrounding normal structures. Neutrons have been proposed as a means of improving the control of tumors while keeping complications to a minimum. Whether conventional radiation or neutrons is a more effective means of treatment is not certain. In order to find an answer, concerned physicians have agreed to treat patients with tumors such as yours either with conventional radiation or neutron radiation or a combination of treatments. If you agree to participate in this study, the type treatment used will be determined by randomization.

The side effects of either type of radiation include redness of the skin of the chest, scarring of the irradiated lung, cough and temporary soreness with swallowing. Later, additional side effects may occur, but this is unlikely. These late problems include cough, shortness of breath, or paralysis.

Alternate treatment includes conventional radiation, chemotherapy or a combination.

The hospital and institution where I am being treated does not provide compensation for any treatment for disability incurred as a result of participating in this research.

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RTOG/EORTC Late Radiation Morbidity Scoring Scheme

Organ/Tissue	0	1 Mild	2 Moderate	3 Severe	4 Life Threatening	5*
SKIN	None	Slight atrophy Pigmentation change Some hair loss	Patchy atrophy Moderate telangiectasia Total hair loss	Marked atrophy Gross telangiectasia	Ulceration	
SUBCUTANEOUS TISSUE	None	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture (< 10% linear reduction)	Severe induration and loss of subcutaneous tissue Field contracture > 10% linear measurement	Necrosis	
MUCOUS MEMBRANES	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucus	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness Poor response on stimulation	Complete dryness No response on stimulation	Necrosis	
SPINAL CORD	None	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono or para quadriplegia	
BRAIN	None	Mild headache Slight lethargy	Moderate headache Great lethargy	Severe headache Severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or Paralysis Coma	
EYE	None	Asymptomatic cataract Minor corneal ulceration or keratitis	Symptomatic cataract Moderate corneal ulceration Minor retinopathy or glaucoma	Severe keratitis Severe retinopathy or detachment Severe glaucoma	Panophthalmitis Blindness	
LARYNX	None	Hoarseness Slight arytenoid edema	Moderate arytenoid edema Chondritis	Severe edema Severe chondritis	Necrosis	
LUNG	None	Asymptomatic or mild symptoms (dry cough) Slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough) Low grade fever. Patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis Dense radiographic changes	Severe respiratory insufficiency Continuous oxygen Assisted ventilation	
HEART	None	Asymptomatic or mild symptoms Transient T wave inversion and ST changes Sinus tachycardia > 110 (at rest)	Moderate angina of effort Mild pericarditis Normal heart size Persistent abnormality T wave and ST changes Low QRS	Severe angina Pericardial effusion Constrictive pericarditis Moderate heart failure Cardiac enlargement EKG abnormalities	Tamponade Severe heart failure Severe constrictive pericarditis	
ESOPHAGUS	None	Mild fibrosis Slight difficulty in swallowing solids No pain on swallowing	Unable to take solid food normally Swallowing semi-solid food Dilatation may be indicated	Severe fibrosis Able to swallow only liquids May have pain on swallowing Dilatation required	Necrosis Perforation, Fistula	
SMALL/LARGE INTESTINE	None	Mild diarrhea Mild cramping. Bowel movement < 5 times daily. Slight rectal discharge or bleeding	Moderate diarrhea and colic Bowel movement > 5 times daily. Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis Perforation, Fistula	
LIVER	None	Mild lassitude, nausea dyspepsia Slightly abnormal liver function	Moderate symptoms Some abnormal liver function tests Serum albumin normal	Disabling hepatitic insufficiency Liver function tests grossly abnormal Low albumin Edema or ascites	Necrosis Hepatic coma or Encephalopathy	
KIDNEY	None	Transient albuminuria No hypertension Mild impairment renal function Urea 25-35 mg% Creatinine 1.5-2.0 mg% Creatinine Clearance > 75%	Persistent moderate albuminuria (2+) Mild hypertension. No related anemia. Moderate impairment renal function Urea > 36-60 mg% Creatinine 2.5-4.0 mg% Creatinine Clearance (50-74%)	Severe albuminuria Severe hypertension Persistent anemia (< 10g%) Severe renal failure Urea > 60 mg% Creatinine > 4.0 mg% Creatinine Clearance < 50%	Malignant hypertension Uremic coma Urea > 100 mg%	
BLADDER	None	Slight epithelial atrophy Minor telangiectasia (microscopic hematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic hematuria	Severe frequency & dysuria Severe generalized telangiectasia (often with petechiae). Frequent hematuria. Reduction in bladder capacity (< 150 cc)	Necrosis Contracted Bladder (capacity < 100 cc) Severe hemorrhagic cystitis	
BONE	None	Asymptomatic No growth retardation Reduced bone density	Moderate pain or tenderness Retardation of growth Irregular bone sclerosis	Severe pain or tenderness Complete arrest bone growth Dense bone sclerosis	Necrosis Spontaneous fracture	
JOINT	None	Mild joint stiffness Slight limitation of movement	Moderate stiffness Intermittent or moderate joint pain Moderate limitation of movement	Severe joint stiffness Pain with severe limitation of movement	Necrosis Complete fixation	

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Grade 5: Death directly related to radiation late effect

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Revisions/Clarifications

RTOG 79-07: Neutron Lung February 20, 1981

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Section 6.3.1 b: Treatment of the contralateral hilum is optional but <u>is</u> recommended if it would not involve irradiating an unacceptable large amount of lung tissue.

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