

RADIATION THERAPY ONCOLOGY GROUP

RTOG 78-07

PROTOCOL TO STUDY NEUTRON THERAPY
IN THE TREATMENT OF LOCALIZED, NON-RESECTABLE,
NON-OAT CELL CANCER OF THE LUNG

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closed

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INDEX

- Schema
- 1.0 Introduction
 - 2.0 Objectives
 - 3.0 Selection of Patients
 - 4.0 Staging and Work-up
 - 5.0 Randomization
 - 6.0 Radiation Therapy
 - 7.0 Chemotherapy
 - 8.0 Study Parameters
 - 9.0 Statistical Considerations
 - 10.0 Forms Submission
 - Appendix I - TNM Staging of Lung Cancer
 - Appendix II - Treatment Fields
 - Appendix III - Patient Consent Form
 - Appendix IV - Late Radiation Morbidity Scoring Scheme

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RTOG 78-07

RTOG PROTOCOL FOR NEUTRON THERAPY OF LOCALIZED,
NON-RESECTABLE, NON-OAT CELL LUNG CANCER

Record

1. Primary size:
2. Histology:
 - Adeno or adenosquamous
 - Squamous or undifferentiated
3. Post-radiotherapy chemotherapy:
 - Planned
 - Non-planned

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Neutrons

1200 rads in
6 fractions over
3 weeks.

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1.0 INTRODUCTION

1.0 Preamble

Carcinoma of the lung is one of the most common and least effectively treated human solid tumors. Little in the way of effective therapy has been developed over the past 20 years. Surgical resection and local high dose radiation therapy continue to have disappointing overall cure rates. Failure to control small primary tumors appears to be due to subclinical metastatic disease which becomes evident later. Large unresectable primary tumors are difficult to eradicate despite high doses of conventional irradiation. Various combinations of radiation and chemotherapy have also been described but usually with disappointing results.

One major reason for failure to control lung cancer by available modalities is the presence of unsuspected metastases at the time of diagnosis. Patients with non-oat cell tumors also show a high incidence of persistent local disease (approximately 50% in RTOG studies investigating various radiation doses). Consequently, any treatment plan designed to improve survival in carcinoma of the lung must take into account the necessity of achieving both effective methods of local control and also of clinically occult microscopic disease.

Experience over the past two and half years in more than 50 patients in the use of combination of radiation therapy at the doses specified in this study and chemotherapy in the treatment of lung cancer at Michael Reese Hospital indicates that survival may be prolonged when compared to historical controls treated with radiation therapy alone. An analysis of failures in this group, which had received conventional radiation to the primary tumor followed by radical systemic chemotherapy, showed that metastases appear to be well controlled in all cases where a good response had been achieved in the primary tumor. The major cause of failure,

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therefore, was persistence or early recurrence of the primary tumor rather than metastases. For this reason it was felt that any procedure leading to better local control should substantially improve the results of the combined therapy. Neutron irradiation of the primary tumor and regional nodes in continuity could achieve this end. The object of the study is to determine whether neutron irradiation will result in a greater probability of local control of the primary tumor, and thereby improve overall results with respect to survival and if these patients can subsequently be treated with systemic chemotherapy without unexpected toxicity.

1.2 General Outline

This protocol is confined to non-resectable carcinomas of the lung and bronchi. The prospects of 5-year survival by conventional methods range from 5% to 25% depending on stage. Because of the relative radioresistance of these tumors and the serious or even lethal consequence of radiation injury to the surrounding normal lung, the prospect of palliation, long-term control, or possible cure justifies adopting combinations of radiation and chemotherapy for clinical trial. The possibility that an adequate tumor response with preservation of normal tissue function might be obtained with combinations of chemotherapy and irradiation using conventional low-LET photon beam therapy is being explored in several institutions in the Chicago area. Initial results have been promising and the possibility of improving the therapeutic ratio by use of high-LET neutron beams for sterilization of radioresistant components in the tumor cell population, seems to be worthwhile.

2.0 OBJECTIVES

The objectives of the study are to study the relative merits of high-LET (neutron) schedules by evaluation of:

- 2.1 The degree of palliative relief attained;
- 2.2 The degree and rate of regression in tumor volume;
- 2.3 The duration of symptomatic and objective remission;

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- 2.4 The time of onset and rate of regrowth of recurrent tumor if any;
- 2.5 The time of onset, evolution and severity of radiation injury in surrounding normal lung;
- 2.6 The tumor-free and total survival rates;
- 2.7 Determination of dose-time parameters and isoeffect functions for irradiated human lung;
- 2.8 Determination of dose-time parameters and isoeffect functions for local control of epidermoid, adeno, adenosquamous, and anaplastic carcinomas in the lung.
- 2.9 The toxicity associated with subsequent treatment with systemic chemotherapy.

3.0 SELECTION OF PATIENTS

3.1 Eligibility Criteria

- 3.1.1 Only patients who have a biopsy proven malignant tumor of the lung or bronchi are acceptable.
- 3.1.2 Squamous cell or epidermoid carcinomas, adenocarcinomas, adenosquamous carcinomas and anaplastic carcinomas are acceptable for inclusion in this protocol.
- 3.1.3 There must be no previous specific radiotherapeutic or chemotherapeutic treatment for the current neoplasm.
- 3.1.4 There must be no evidence of cerebral, hepatic or osseous metastases (exclusion by scans) or other distant metastases; however, patients with metastatic disease limited to supraclavicular nodes are eligible.
- 3.1.5 The contralateral lung must be entirely free of neoplastic disease.
- 3.1.6 Patients must be ambulatory and capable of outpatient visits to the neutron therapy facility (Karnofsky status > 50).

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3.2 Ineligibility Criteria

- 3.2.1 Any patient with evidence of severe incapacitating lung disease (chronic bronchitis, emphysema, old unresolved or fibrotic pulmonary inflammatory lesions) or severe incapacitating cardiac insufficiency must be excluded from this study since these patients are unlikely to tolerate significant diminution of lung function following irradiation.
- 3.2.2 Any patient logistically unable to be treated as an outpatient at the neutron facility.
- 3.2.3 Patients with small (oat) cell carcinoma.
- 3.2.4 Patients with distant metastases, except supraclavicular nodes.
- 3.2.5 Age \geq 80 years.

4.0 STAGING AND WORK-UP

4.1 Required Studies

- 4.1.1 Chest X-rays. The lesion must be visualized on antero-posterior and lateral chest films so that its extent can be defined for the purpose of determining field-sizes and estimating tumor-volumes. Transverse axial tomograms or conventional tomography defining the depth and extent of the lesion are acceptable.
- 4.1.2 Pathology. An unequivocal positive biopsy must be obtained, or if this is not possible, a cytological diagnosis based on a Class V cytology report could be accepted.
- 4.1.3 Regional nodes. Should be evaluated by mediastinoscopy or CT scan.
- 4.1.4 Thoracotomy with inspection, evaluation of operability, and (if inoperable) biopsy, is required if other means do not furnish an unequivocal diagnosis;
- 4.1.5 Isotopic scans. A bone scan and CT scan should be done to exclude metastases. If the CT scan is not available, then a radionuclide scan may be used. If liver function tests are abnormal, a liver scan should be done.

4.2 Optional Studies

- 4.2.1 A lung scan.
- 4.2.2 Pulmonary function tests.
- 4.2.3 Dynamic nuclear study of pulmonary function.

5.0 REGISTRATION

When the required work-up has been completed and the patient has been found to be eligible, the patient may be placed on study by phoning RTOG Headquarters (215) 574-3191 between 9:00 a.m. and 5:00 p.m., ET, and giving the following information:

Protocol name

Institution referring patient

Neutron facility

Physician

Patient's name

Size of primary

Histology

Post-radiotherapy chemotherapy: Planned vs. non-planned.

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

6.0 RADIATION THERAPY

- 6.1 Radiation therapy will be initiated within 2 weeks of diagnosis.
- 6.2 Patients will be treated by means of an anterior and posterior oblique field to include the primary lesion with a 2 cm margin and the entire mediastinum. The weighting will be 3:1 for the anterior and posterior oblique fields respectively.
- 6.3 The spinal cord will be excluded from the posterior oblique field so that the total dose to the cord will not exceed 75% of the prescribed tumor dose.
- 6.4 An additional anterior field to the supraclavicular nodes will be treated to the same dose calculated at a depth of 4 cm. A mid-line shield should be used to protect the spinal cord and larynx.

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6.5 More extensive tumors will be treated with wide fields encompassing the whole affected area or entire hemithorax if necessary. Minimal shielding of obviously normal lung will be included and the posterior oblique field will be angled so as to avoid the spinal cord.

6.6 Dosage

6.6.1 Neutron beam therapy (dosimetry should not correct for tissue inhomogeneity): midplane dose of 1200 rad (Fermilab) in 6 fractions over 3 weeks.

7.0 CHEMOTHERAPY

7.1 While the decision regarding the choice of a specific chemotherapy regimen will be left to each participating institution, the CAMP regimen is recommended. Details of all chemotherapy must be submitted on RTOG medical oncology flow sheets.

8.0 STUDY PARAMETERS

8.1 Studies

	<u>Pre Treatment</u>	<u>During Radiotherapy</u>	<u>At Follow-up</u>	<u>Every 6 Months</u>
History & Physical	x	x		
CBC (Including platelets & differential) ^a	x	x	x	
SMA-12	x			
Chest x-ray	x	x	x	
Brain Scan	x			
Liver Scan	x			x
Bone Scan	x			x

a. A minimum of every cycle if receiving chemotherapy

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

8.3 Schedule

Follow-up information will be submitted every two months the first year, and every four months thereafter.

9.0 STATISTICAL CONSIDERATIONS

The major objective of this Phase I/II study is to detect an unacceptable complication rate from neutron therapy alone or when subsequent chemotherapy is added. The following table shows the probability of detecting a 5% or 10% complication rate.

<u>Sample Size</u>	<u>Complication Rate</u>	
	<u>10%</u>	<u>5%</u>
25	.79	.54
20	.88	.64
25	.93	.72
30	.96	.79

In addition on the basis of the results of RTOG Study 73-01 with patients with comparable disease but slightly poorer performance status than patients in this study, one might expect a historical one year control rate of 45%. With 22 patients, there would be a 90% probability of detecting an improvement of response to 65%.

Therefore, approximately 30 evaluable patients will be entered into this Phase I/II study.

10.0 FORMS SUBMISSION

Forms will be submitted to RTOG Headquarters according to the following schedule:

On-Study form	Within one week of
Treatment prescription	randomization.
Localization films	
Radiotherapy form	At completion of
Copy of treatment record	radiotherapy.
Follow-up forms	First year, every 2 months.
Flow sheets (if receiving	Every 4 months thereafter.
chemotherapy)	
Death form	At death.

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APPENDIX I

AMERICAN JOINT COMMITTEE FOR CANCER STAGING AND END RESULTS REPORTING

TNM STAGING OF LUNG CANCER

STAGE I

T1 NO MO

T1 N1 MO

T2 NO MO

STAGE II

T2 N1 MO

STAGE III-M0

T3 Any N MO

Any T N2 MO

STAGE III-M1

Any T Any N M1

TNM DEFINITIONS

T1 Less than 3.0 cm. No invasion proximal to a lobal bronchus.

T2 Greater than 3.0 cm or any size extending to hilum, at bronchoscopy. Carina negative.

T3 Any tumor involving carina, chest wall or mediastinum or complete obstruction of entire lung or malignant effusion.

NO No nodes involved.

N1 Peribronchial or ipsilateral hilar nodes involved including direct extention.

N2 Mediastinal nodes involved.

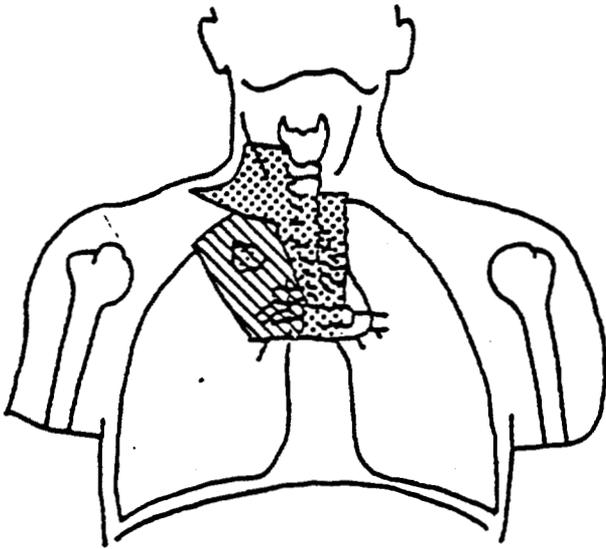
MO* Mediastinal nodes involved.

M1* Metastases present.

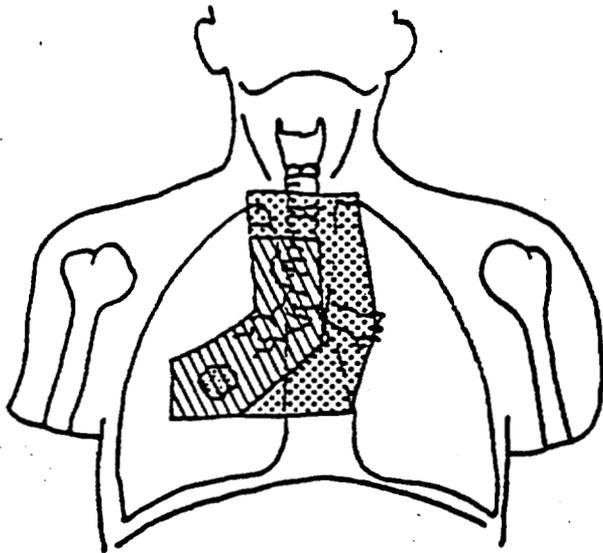
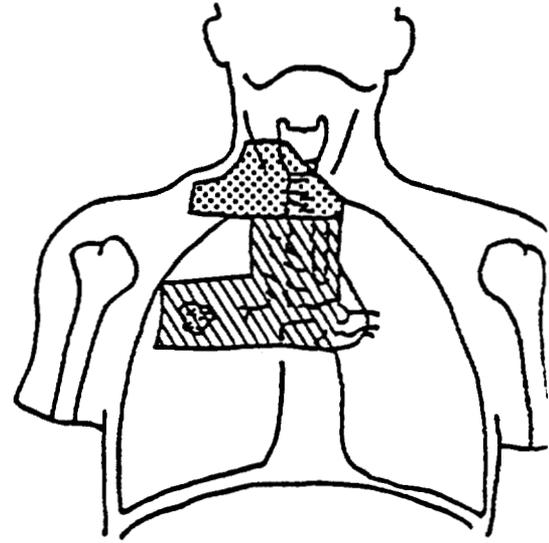
*For the purposes of this study MO refers to no metastases beyond the supraclavicular nodes; M1 disease includes all other forms of distant metastatic disease.

Non-Oat Cell Ca Lung

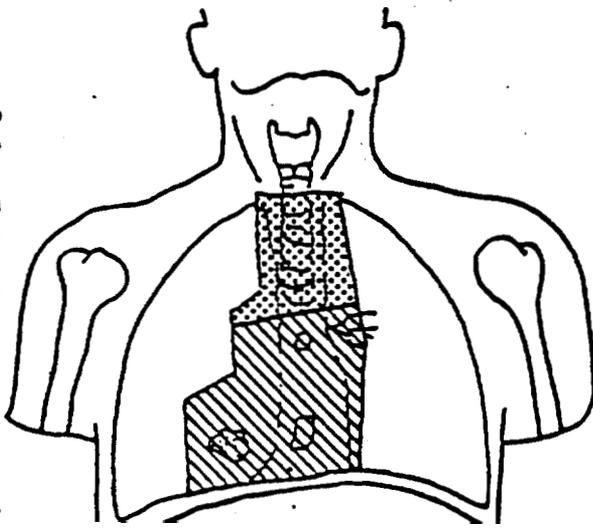
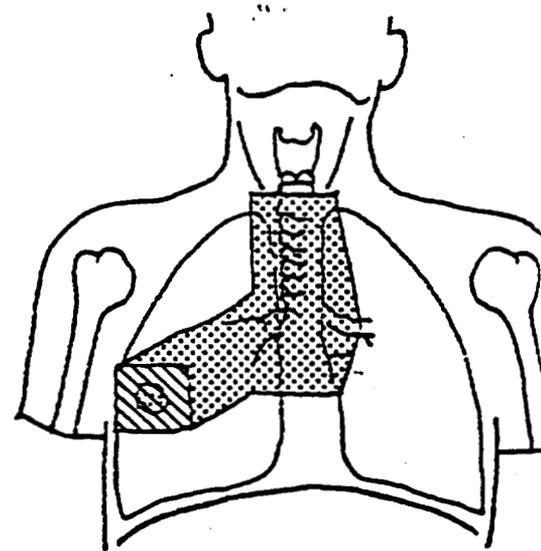
AP Portals



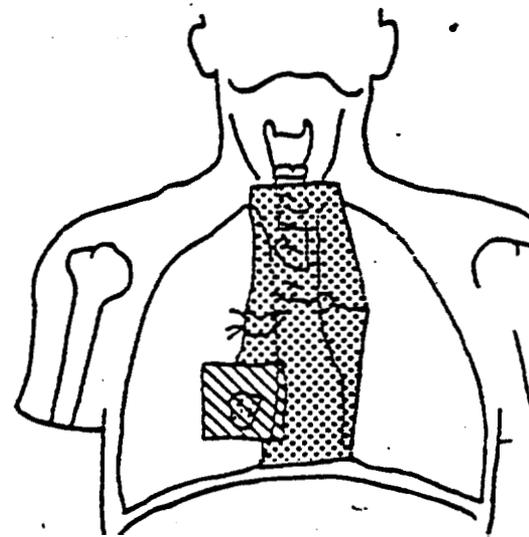
Upper Lobes



Middle Lobes
or Lingula



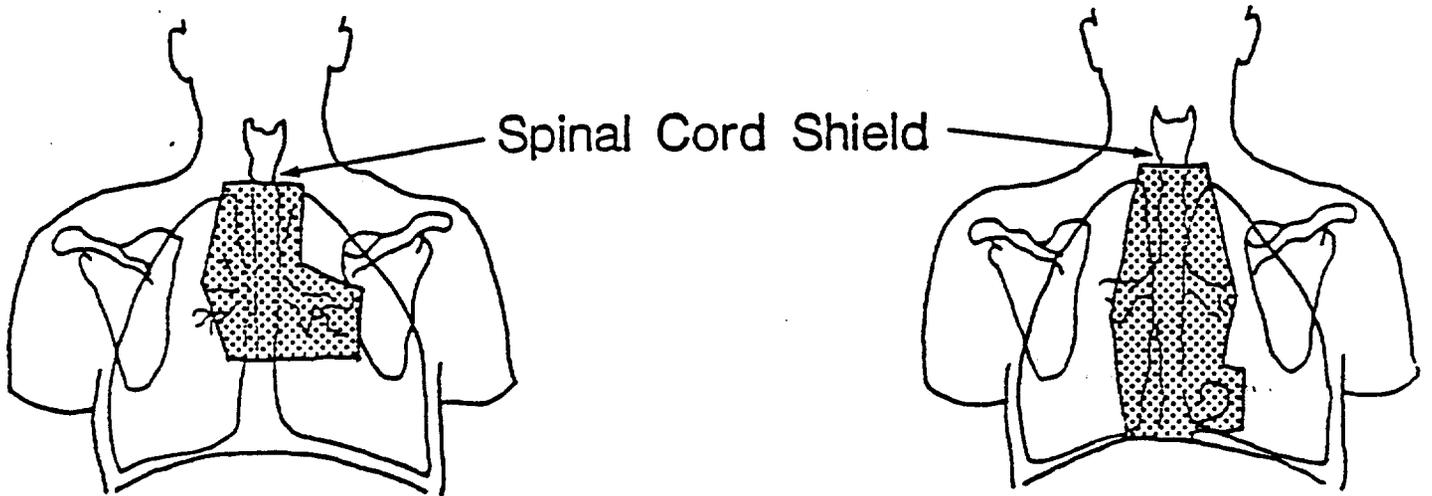
Lower Lobes



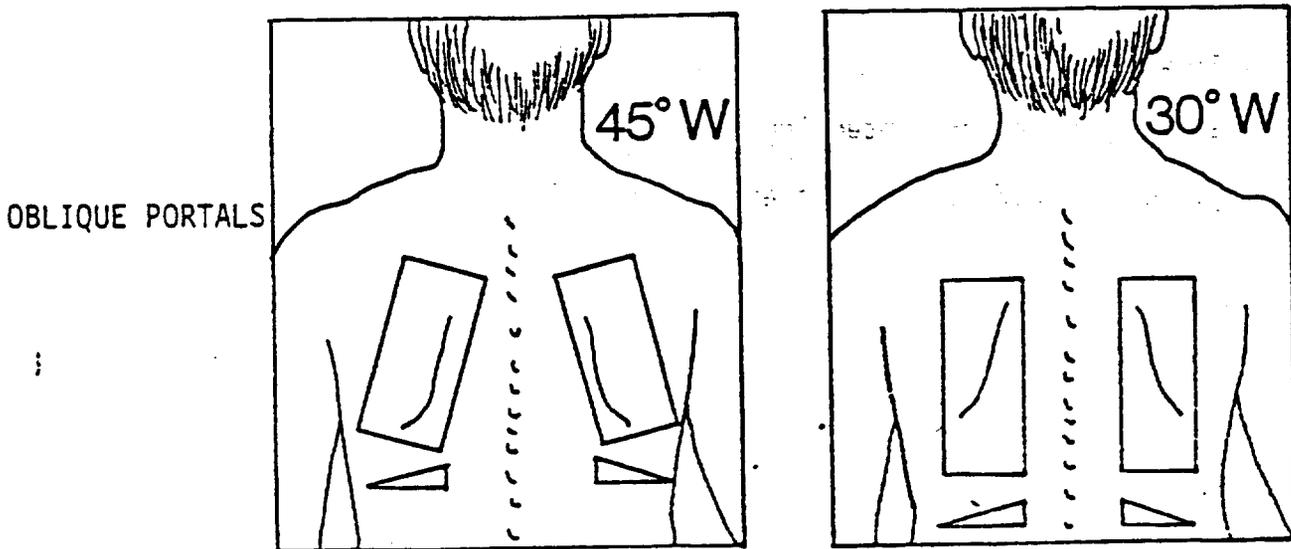
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Non-Oat Cell Ca of Lung

PA Portals



PA Portals Diagram



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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. If you agree to participate in this study, neutrons will be used to treat your tumor.

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

Alternate treatment includes conventional radiation chemotherapy or a combination.

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

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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 this 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.

Appendix IV

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 hepatic 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 > 50 mg% Creatinine > 4.0 mg% Creatinine Clearance < 50%	Malignant hypertension Severe 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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