93/102

EXERCISE CAPACITY FOLLOWING RADIATION THERAPY IN PATIENTS WITH STAGE II AND III NON-SMALL CELL LUNG CANCER

PRINCIPLE INVESTIGATOR: Timothy R. Murray CPT MC
Fellow, Pulmonary/Critical Care

ASSOCIATE INVESTIGATOR: Bernard J. Roth MAJ MC
Staff, Pulmonary/Critical Care

Rahul N. Dewan LTC MC
Staff, Radiation Oncologist

Steven S. Wilson MAJ MC
Staff, Radiation Oncologist

FACILITY: Madigan Army Medical Center

ANTICIPATED START DATE: August 1993

ANTICIPATED COMPLETION: June 1995

OBJECTIVE: To study the physiologic effects of therapeutic radiation of the lung in patients with stage II or III non-small cell lung cancer and attempt to identify a relationship between volume of lung irradiated and interval change in work capacity (V_{O_2}). A prohibitive work capacity to RT will be sought.

HYPOTHESIS: Work capacity will decrease by at least 10% when measured over time, while pulmonary function testing (FEV_1) will show no significant interval change. Further, a relationship between volume of lung irradiated and change in work capacity will be identified.

CURRENT STATUS: Radiation therapy (RT) is commonly used in the treatment of locally advanced pulmonary malignancy.[1, 2] It is frequently combined with surgery and chemotherapy to decrease recurrence and possibly improve survival.[2 thru 8]

Adverse sequelae to the surrounding lung parenchyma from RT is well documented.[9, 10, 11] Tissue destruction results directly from radiation induced injury and inflammation[12] or indirectly from retractions related to fibrosis. This fibrotic process is associated with a decrease in pulmonary function and may take as long as 8-10 months to manifest following radiation therapy. RT can have significant morbidity and mortality in patients with compromised pulmonary function.[13, 14, 15, 16] Modified dosage and limited fields of

radiation can decrease some of the complications related to RT but local control and curative rates are adversely affected.[1, 3, 8, 17, 18, 19]

To overcome this dilemma, extensive work has been done to predict post RT pulmonary function. This would allow treatments that would maximize the amount of radiation delivered, yet preserve enough pulmonary function to maintain quality of life. Most of this work has been based on FEV_1 as a measure of pulmonary reserve and has incorporated perfusion lung scans and radiation port size to predict post RT residual function.[18, 20, 21, 22] Unfortunately, these techniques have met with partial success and mixed results.[19, 23, 24]

Predicting post RT impairment in patients with respiratory compromise is a complicated problem given the dynamic interaction between lung disease, its natural history, the pathophysiology of radiation injury and concurrent medical problems.[23] Although FEV_1 is a reliable measure of pulmonary function, it is only one of many variables that determines functional status. Some recent data would suggest that FEV_1 is a poor measure of functional status.[25] FEV_1 may actually increase after radiation therapy as a result of airway retraction from fibrotic lung.

Exercise testing can quantify functional reserve because it incorporates nutritional, metabolic and musculoskeletal status as well as cardiopulmonary reserve. It is very reproducible with less than 4% test to test variability in individuals.[25a] Exercise capacity has been used successfully in predicting post-thoracotomy morbidity.[26]

The use of exercise capacity in the post RT setting has been quite limited. Two studies have investigated work capacity following RT. Both of these studies involved mantle irradiation for Hodgkin's disease only. Jones et.al.[27] included patients with normal lung function and noted increased minute ventilation (VE), ventilatory equivalent for O_2 and CO_2 (VE/V_{O_2}, VE/V_{CO_2}) acutely but these abnormalities tended to return towards baseline after six months. Høst and Vale[28] concluded that no significant influence on pulmonary gas exchange occurred following mantle RT. In another study of mantle RT for Hodgkin's disease, Laszlo G. et.al.[29] completed only pre RT exercise studies but noted that those with abnormal studies pretreatment were predisposed to develop pulmonary extension of their lymphoma. Interestingly, all of the asymptomatic patients with abnormal exercise studies developed effort intolerance and decreased VC.

To our knowledge no studies have been completed investigating exercise testing in patients receiving chest RT for pulmonary parenchymal malignancy.

MEDICAL APPLICATION: It is our assertion that exercise testing in patients receiving chest RT for pulmonary malignancies will

show detectable decrements in work capacity (and other measures of pulmonary reserve) when measured over time. These changes may not correlate with changes in FEV_1. Prediction of post RT exercise capacity may be possible using pre-radiation exercise capacity, radiation dosage and lung volumes involved. This may become an important instrument to predict optimal dosing of RT in patients with marginal pulmonary function thereby maximizing therapeutic benefits yet avoiding associated morbidity and mortality.

OVERVIEW OF PROTOCOL

Assessment of potential effects of RT on exercise capacity will be completed in the following manner:

1. All subjects will be evaluated within two weeks of initiation of RT and then 3, 6 and 12 months after initiation of RT.

2. At each visit the subject will receive a brief history and physical examination. Subjects will be asked to complete a questionnaire (See Appendix A) that will subjectively assess their functional status by detailing:

    a) Tobacco use
    b) Weight
    c) Degree of anorexia
    d) Dyspnea score[31]
    e) Karnofsky performance status[32]
    f) Occupation and related activity level
    g) Recreational activities or hobbies

    This data will be assessed at each visit and compared to objective data obtained from the exercise test.

3. A clinical data flow sheet will be completed and updated at each visit (Appendix B). This form will profile pertinent information regarding tumor characteristics, treatment history, response to therapy as well as history and physical exam findings.

4. Radiation treatment history will include total radiation dose and calculation of lung volume irradiated by combining radiation port size (cm^2) and anterior-posterior chest dimensions. These measurements will be done by superimposing the radiation ports onto the CXRs and CT scans, thereby allowing direct assessment of pulmonary parenchyma involved in the treatment and calculation of volumes.

5. Full pulmonary function testing will be completed at each visit. This will include:

    a) Spirometry
    b) Diffusion Capacity (D_LCO)
    c) Lung Volumes by body plethysmography
    d) Maximal Voluntary Ventilation (MVV)
    e) Pulse Oximetry (P_SO_2) at rest

    All studies will be completed on a SensorMedics Autobox D_L 6200, Yorba Linda, CA using Standard Clinic Protocol.

5. Stage I exercise studies will be completed at each visit on a stationary, calibrated, electronically-braked cycle as per clinic protocol. (Appendix C) Subjects will be assessed at rest for 3 minutes pedaling at 0 watts for 3 minutes then at incremental work rates increasing at a fixed rate between 20 and 50 watts per minute. During this period of assessment, inhaled and exhaled gases will be measured in the form of minute ventilation (VE), work capacity (also called oxygen uptake) (V_{O_2}), Carbon Dioxide output (V_{CO_2}) and recorded every 20 seconds. Heart rate, respiratory rate and P_SO_2 are documented every 20 seconds. Blood pressure and 12 lead ECG are recorded every 3 minutes. Subjects will be asked to exercise to their voluntary limits.

SPECIFICS OF PROTOCOL

NUMBER OF PATIENTS: 30

AGE: Greater than 18 years old

GENDER SELECTION: None

SOURCE OF PATIENTS: Those referred for radiation therapy for treatment of stage II and III non-small cell carcinoma of the lung.

INCLUSION CRITERIA:

1. Clinical or surgical stage II or III non-small cell carcinoma
2. Meet criteria for Radiation Therapy
3. Receive conventional dosing and fractionation techniques[5]. Representative therapy would be as follows:

    a) Total dose 5000 - 6500 cGy
    b) Single fractions of 180 - 200 cGy per day, 5 days a week over 5 to 6 1/2 weeks

4. Ability to give consent.

EXCLUSION CRITERIA:

1. Inability to perform exercise study because of physical limitations.
2. New York association Class III/IV Angina.
3. Require supplemental oxygen.
4. Thoracotomy for lobectomy or pneumonectomy occurring during the period of evaluation. Lobectomy or pneumonectomy prior to enrollment would not be exclusionary.
5. Treatment with chemotherapy that is known to have pulmonary toxicity.

CONSENT: Written consent for enrollment into the protocol will be obtained before initiation of RT. Written consent for exercise testing will be obtained individually before each study.

RISK TO PATIENTS: Risk associated with the protocol would arise from the exercise studies. These risks would include low blood pressure, fainting, abnormal heart rhythm, heart attack or death. All of these sequelae are extremely rare. Duration and intensity of exercise is determined by the voluntary limits of the patient.

**Note: The principal investigator confirmed that pregnant patients would be ineligible for radiation treatment. Therefore, pregnancy would not be an issue in this study.

PRECAUTION: A physician will be present for each exercise study and emergency equipment will be immediately available to deal with any unusual situation.

SUBJECT IDENTIFICATION: Name and Social Security Number

MEDICATION: None

FOLLOW UP: No follow up will occur after completion of the protocol.

STATISTICAL ANALYSIS: A sample size of 30 was calculated using a mean V_{O_2} of 2200 ml of O_2 per minute and standard deviation of 430ml of O_2 per minute from Hansen JE et. al.[32] to identify a 10% change in exercise capacity using a Type I error of 0.05 and power of 80%. Data will be examined for interval changes in work capacity and correlated with radiation dose, port size and lung volumes involved. A subset analysis will be attempted on patients receiving chemotherapy.

DISPOSITION: Results of investigation will be submitted for publication in a peer reviewed medical journal and presentation at a national conference.

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IMPACT STATEMENT

BED OCCUPANCY: None

NURSING: None

TECHNICIAN SUPPORT: Pulmonary technician time: 360 hours over 16 months (PFT's - 1.0 hours per study, exercise test- 2.0 hours per study including printing and clean-up).

ADMINISTRATIVE: Clerical support to log in 120 visits over 16 months.

PATHOLOGY: None

RADIOLOGY: None - (all CXRs and CT scans used to calculate lung volumes (see overview of protocol) will have previously been obtained during the patient's pre-radiation diagnostic evaluation or for radiation treatment planning).

			Source
COST:	Technical support	$4860.00	Pulmonary
	Calibration gas for PFT's and exercise machine	$480.00	Pulmonary
	ECG electrodes	$300.00	Pulmonary
	Paper and printer tape	$15.00	Pulmonary
	Reprints of publication	$250.00	DCI
	PAL filters	$625.00	Pulmonary
	Mouth pieces	$10.00	Pulmonary
	Drying cartridges	$600.00	Pulmonary
	Statistical analysis program	$500.00	Pulmonary
	Travel	$1200.00	DCI
	TOTAL ----------	**$8840.00**	

(See appendix D for cost breakdown)

SIGNATURES:

Primary Investigator

(see investigator's statement)
Chief: Dept. of Medicine

W. Hal Guyton MD
Chief: Dept. of Pulmonary Medicine

Mary Moore CRT, CPFT
Senior Pulmonary Technician

APPROVE/~~DISAPPROVE~~

FOR THE COMMANDER:

Dan C Moore

DAN C. MOORE, M.D.
COL, MC
Chief, Department of Clinical Investigation
MEDCEN Approving Official

29 Mar 93

PROTOCOL TITLE: Exercise Capacity Following Radiation Therapy in Patients With Stages II and II Non-small Cell Lung Cancer by CPT Timothy R. Murray, MC

INVESTIGATOR'S STATEMENT

I agree to conduct this study as written and in accordance with the policies set forth in AR 40-38, paragraph 2-10c as listed below:

(1) Prepare a protocol following the policies and procedures in this regulation.
(2) Prepare and maintain adequate records on -
  (a) Receipt, storage, use, and disposition of all investigational drugs issued to the investigator by the pharmacy and investigational devices issued to the investigator by the activity responsible for storing them.
  (b) Case histories that record all observations and other data important to the study.
  (c) Volunteer informed consent documents.
(3) Prepare progress reports, including annual reports (Clinical Investigation Program, RCS MED-300(R1), as determined by the approving authority and regulatory agencies.
(4) Prepare and file an investigator sponsored IND (Investigational New Drug) or IDE (Investigational Device Exemption) as appropriate.
(5) Promptly notify the approving official through the medical monitor and the Human Use Committee of adverse effects caused by the clinical investigation.
(6) Report serious and unexpected adverse experiences involving the use of investigational drugs or devices to the sponsor or the FDA in accordance with AR 40-7.
(7) Ensure that the clinical investigation has been approved by the proper review committee(s) before starting, changing, or extending the investigation
(8) Ensure that all subjects or their representatives, including subjects used as controls, are fully informed of the nature of the investigation to include potential risks to the subject.
(9) Ensure that investigational drugs or devices are administered only to subjects under the investigator's personal supervision or that of a previously approved associate investigator.
(10) Ensure that a new principal investigator (PI) is appointed if the PI cannot complete the clinical investigation for reasons such as permanent change of station or retirement.
(11) Apprise the Human Use Committee of any investigator's noncompliance with the clinical investigation.
(12) Seek Human Use Committee approval for other investigators to participate in the clinical investigation.
(13) Ensure that studies involving attitude or opinion surveys are approved in accordance with AR 600-46.

Timothy R. Murray — 28 Nov 93

Signature of Principal Investigator — Date

I have reviewed this protocol with the investigators for:
a. scientific merit
b. experimental design
c. expenditure of money and manhours
d. risks and safeguards in the use of human subjects

This proposal is forwarded with my full support and approval.

[signature] — 29 Nov 93

Signature of department chief — Date

APPENDIX A

PATIENT QUESTIONNAIRE

NAME: SSN:

DATE:

ARE YOU SMOKING? YES / NO

WHAT IS YOUR WEIGHT?

HOW IS YOUR APPETITE? GOOD FAIR POOR

BREATHLESSNESS SCORE:

(Please circle the number which most closely fits your situation)

0) Not troubled with breathlessness except with strenuous exercise

1) Troubled by shortness of breath when hurrying on the level or walking up a slight hill

2) Walk slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level

3) Stops for breath after walking about 100 yards or after a few minutes on the level

4) Too breathless to leave the house or breathless when dressing or undressing

PERFORMANCE STATUS (KARNOFSKY PERFORMANCE STATUS SCALE)

(Please check the box which most closely fits your situation)

Normal activity without difficulty
Normal activity with some effort
Normal activity with much effort
Moderate activity / 100% self care
Require some assistance
Require frequent assistance

HAVE YOU NOTICED A CHANGE IN YOUR ABILITIES SINCE YOUR LAST ASSESSMENT? YES / NO

WHAT IS YOUR OCCUPATION?

DOES IT REQUIRE LIFTING? YES/NO How Many Pounds? lb

DO YOU HAVE DIFFICULTY WITH YOUR JOB BECAUSE OF SHORTNESS OF BREATH? YES / NO

WHAT ARE YOUR HOBBIES?

APPENDIX B

CLINICAL DATA BASE COVER SHEET

NAME:

SSN:

DIAGNOSIS: PATH:

STAGE:

LOCATION: CENTRAL - PERIPHERAL

TUMOR SIZE: cm

CXR / CT / PATH

TREATMENT HISTORY:

RADIATION ONLY
RADIATION/CHEMO
POSTOP/RADIATION
POSTOP/RADIATION/CHEMO

SURGICAL DATA:

TYPE:
DATE:

COMPLICATIONS:	I	II	III	IV

CHEMO DATA:

AGENTS:
CYCLES:

COMPLICATIONS:	I	II	III	IV

RADIATION DATA:

TOTAL DOSE:
DURATION:
FRACTIONATION:
PORT SIZE (cm2):
PULMONARY WINDOW (cm2):
A-P DIMENSION:
TOTAL LUNG VOLUME:
REGIONS INCLUDED:

COMPLICATIONS:	I	II	III	IV

APPENDIX B

CLINICAL DATA BASE COVER SHEET

NAME:	SSN:

RESPONSE TO THERAPY:

	I	II	III	IV
Complete (Resolution of mass by CXR)				
Partial (>25% Reduction of mass by CXR)				
None (<25% Reduction of mass by CXR)				
Unable to Assess				
Recurrences				

MEDICATIONS:

I	II	III	IV

PHYSICAL EXAM:

I	II	III	IV

APPENDIX B

CLINICAL DATA BASE

NAME:	SSN:

		PRE RT	3 MONTHS	%CHG	6 MONTHS	%CHG	12 MONTHS	%CHG
	DATE:							
FEV1	(predicted)							
	(measured)							
FVC	(predicted)							
	(measured)							
SVC	(predicted)							
	(measured)							
FEV1/FVC	(predicted)							
	(measured)							
TLC	(predicted)							
	(measured)							
RV	(predicted)							
	(measured)							
RV/TLC	(predicted)							
	(measured)							
DLCO	(predicted)							
	(measured)							
DLCO/VA	(predicted)							
	(measured)							
MVV	(predicted)							
	(measured)							
RESTING	PSO2							

APPENDIX B

CLINICAL DATA BASE

NAME:	SSN:

	PRE RT	3 MONTHS	%CHG	6 MONTHS	%CHG	12 MONTHS	%CHG
DATE:							
WORK CAPACITY (VO2%PRED)							
VO2/KG							
METABOLIC REQUIREMENT VO2/WR)							
MINUTE VENTILATION (VE) AT PEAK VO2)							
VENTILATORY EQUIVALENT FOR CO2 (VE/VCO2)]							
VENTILATORY EQUIVALENT FOR O2 (VE/VO2)]							
ANAEROBIC THRESHOLD							
HEART RATE AT PEAK VO2)							
HEART RATE RESERVE 1-(HRMX-HRRST/HRPMX-HRRST)]							
RESPIRATORY RATE AT PEAK VO2)							
BREATHING RESERVE 1-VE/MVV)							
O2 PULSE VO2/HR)							
SO2 REST							
SO2 PEAK							

LINEAR ANALOG SCALE

NO SHORTNESS OF BREATH

SEVERE SHORTNESS OF BREATH

Please place an X on the line which best characterizes your breathing

APPENDIX C

Protocol for Pulmonary Exercise Physiology Testing

1. All patients must be seen by a pulmonary physician prior to performing an exercise study. Patients should be NPO for four (4) hours prior to their test. All patients will sign a form attesting to informed consent prior to testing. Please see sample consent form (Attachment 1 & 2). Physician will also complete the check list which will be kept in the patients pulmonary convenience file (Attachment 3).

2. Contraindications to exercise testing include the following:

a. Uncontrolled hypertension with diastolic pressures greater than 110 mmHg.

b. Ischemic changes on resting EKG.

c. Obvious exacerbation of underlying obstructive lung disease.

d. Orthopedic or neurologic processes that preclude patient from pedalling a bicycle.

3. Exercise study requires one pulmonary technologist and one physician for all symptom limited exercise tests.

4. All patients will perform spirometry and a maximum minute ventilation maneuver (MVV) prior to the exercise test. The MVV will be used as the predicted maximal ventilation except for patients who have known restrictive lung disease, for which the measured FEV_1 X40 will be used as the predicted maximal ventilation.

5. The predicted maximal work rate will be obtained from the exercise computer based on age, sex, and height. This will be used to determine the ramp (or work rate increment per minute) in order to allow the patient to achieve maximal work rate in 8-12 minutes. Ramps should be adjusted down in ill or very unfit patients and should be adjusted up in well conditioned patients.

6. Ventilation, oxygen consumption, carbon dioxide production, and work rate will be measured continuously by the Med Graphics computer. 4-lead EKG and continuous pulse oximetry will also be monitored in all patients. All patients over age 35 will have 12-lead EKG monitoring that consists of a baseline EKG at rest, an EKG every three (3) minutes during the exercise, an EKG immediately post peak exercise, and an EKG three (3) minutes into recovery. This is not necessary in patients with a normal cardiology evaluation within 3 months. Blood pressure will be measured by the physician every three (3) minutes unless an arterial line is placed for continuous measurement.

7. If a non-diagnostic Stage I exercise test results, any patient in which the question of mild underlying lung disease is suspected should have repeat testing with invasive arterial monitoring and arterial blood gases drawn at rest and every two (2) minutes during exercise. Other indications for Stage II exercise include previous suspected desaturation or questionable pulmonary disease. The dead space calculation will be ignored and crossed off the final report unless arterial blood gases are used to determine it. Blood pressure monitoring will be performed with the arterial line if it is being used.

8. The exercise study will be terminated for any of the following reasons:

a. Patient feels they have reached their maximum exercise tolerance. The patients reason for stopping should always be noted (i.e. shortness of breath, leg pain, fatigue, etc.).

b. Chest pain felt to be significant by the patient or physician.

c. Drop in systolic blood pressure of greater than 15mmHg from the previous measurement.

d. Diastolic blood pressure over 120 mmHg.

9. Immediate post exercise, auscultation of the heart and lungs should be performed by the physician.

10. Patients will be monitored for two (2) minutes at rest, three (3) minutes of cycling at zero watts, during exercise to symptom limit, and for three (3) minutes of unloaded cycling post peak exercise. Monitoring will be prolonged at the discretion of the physician, if any cardiovascular problem is suspected.

11. ACLS equipment will be available in case of any emergency.

12. The pulmonary technologist will then be responsible for printing and collecting the following:

a. Summary report

b. Tabular report

c. Nine (9) panel Wassermann plot

d. Enlarged V-slope plot and summary plot

e. ABG summary

f. EKG's

13. The physician will then interpret the study with the following questions:

a. Is exercise capacity decreased (maximum VO_2)?

b. Is metabolic requirement increased (VO_2/WR)?

c. Is exercise limited by impaired oxygen flow (ECG, BP, AT, La, HCO_3, VO_2/WR, VO_2/HR, COHb)?

d. Is exercise limited by ventilatory capacity (BR, Vd/Vt, TV)?

e. Is there pathologic VQ mismatch (A-a gradient, a-ET, Vd/Vt, Ve/VCO_2)?

f. Is there a muscle oxygenation or electron transport chain defect (blood lactate)?

g. Is exercise limited by a behavioral problem (breathing pattern)?

h. Is work output reduced because of poor effort (HHR, BR, peak RER, AT).

14. All exercise protocols done by pulmonary fellows will be reviewed with a staff pulmonologist.

15. After the exercise test is completed the physician will complete the results section of the check list and will submit the form to the clinic nurse for quality assurance tracking.

as submitted (A)

MEDICAL RECORD — REQUEST FOR ADMINISTRATION OF ANESTHESIA AND FOR PERFORMANCE OF OPERATIONS AND OTHER PROCEDURES

A. IDENTIFICATION

1. OPERATION OR PROCEDURE

CardioPulmonary Exercise Test

B. STATEMENT OF REQUEST

1. The nature and purpose of the operation or procedure, possible alternative methods of treatment, the risks involved, and the possibility of complications have been fully explained to me. I acknowledge that no guarantees have been made to me concerning the results of the operation or procedure. I understand the nature of the operation or procedure to be

(Description of operation or procedure in layman's language)

In order to assess the function of your heart and lungs you will ride a stationary bike with increasing work. You will be asked to exercise as long and hard as you can. The risks include low blood pressure, fainting and an abnormal heart rhythm. Very rarely this can lead to a heart attack or death. A physician will be present and emergency equipment is available to deal with any unusual situation which may arise.

which is to be performed by or under the direction of Dr. _____

2. I request the performance of the above-named operation or procedure and of such additional operations or procedures as are found to be necessary or desirable, in the judgment of the professional staff of the below-named medical facility, during the course of the above named operation or procedure.

3. I request the administration of such anesthesia as may be considered necessary or advisable in the judgment of the professional staff of the below-named medical facility. Such procedures may include transfusion of blood and blood components.

4. Exceptions to surgery or anesthesia, if any, are: _____

(If "none", so state)

5. I request the disposal by authorities of the below-named medical facility of any tissues or parts which it may be necessary to remove.

6. I understand that photographs and movies may be taken of this operation, and that they may be viewed by various personnel undergoing training or indoctrination at this or other facilities. I consent to the taking of such pictures and observation of the operation by authorized personnel, subject to the following conditions:

a. The name of the patient and his/her family is not used to identify said pictures.
b. Said pictures be used only for purposes of medical/dental study or research.

(Cross out any parts above which are not appropriate)

C. SIGNATURES (Appropriate items in Parts A and B must be completed before signing)

1. COUNSELING PHYSICIAN/DENTIST: I have counseled this patient as to the nature of the proposed procedure(s), attendant risks involved, and expected results, as described above.

I have also counseled this patient as to the risks and benefits of blood transfusions as well as alternatives, including the risks of not receiving transfusions, if needed, and/or the use of autologous blood.

(Signature of Counseling Physician/Dentist)

2. PATIENT: I understand the nature of the proposed procedure(s), attendant risks involved, and expected results, as described above, and hereby request such procedure(s) be performed.

(Signature of Witness, excluding members of operating team)	(Signature of Patient)	(Date and Time)

3. SPONSOR OR GUARDIAN: (When patient is a minor or unable to give consent) I, _____ sponsor/guardian of _____ understand the nature of the proposed procedure(s), attendant risks involved, and expected results, as described above, and hereby request such procedure(s) be performed.

(Signature of Witness, excluding members of operating team)	(Signature of Sponsor/Legal Guardian)	(Date and Time)

PATIENT'S IDENTIFICATION (For typed or written entries give: Name—last, first, middle; grade; date; hospital or medical facility)

REGISTER NO.	WARD NO.

STANDARD FORM 522 (Rev. 10-76)
General Services Administration &
Interagency Comm. on Medical Records
FIRMR (41 CFR) 201-45.505
522-110

*U.S. Government Printing Office: 1991 — 281-782/20320

SPECIAL CONSENT TO OPERATION, POST OPERATIVE CARE, MEDICAL/DENTAL TREATMENT, ANESTHESIA OR OTHER PROCEDURE

Patient _____

Washington State law guarantees that you have both the right and obligation to make decisions concerning your health care. Your physician/dentist can provide you with the necessary information and advice, but as a member of the health care team, you must enter into the decision making process. This form has been designed to acknowledge your acceptance of treatment recommended by your physician/dentist.

I UNDERSTAND THAT THE EXPECTED RESULTS OF SAID TREATMENT CANNOT BE GUARANTEED. THE PHYSICIANS, SURGEONS OR DENTISTS OF MADIGAN ARMY MEDICAL CENTER HAVE DISCUSSED TO MY SATISFACTION THE FOLLOWING:

A. THE NATURE AND CHARACTER OF THE PROPOSED TREATMENT/ PROCEDURE.

B. THE ANTICIPATED RESULTS OF THE PROPOSED TREATMENT/PROCEDURE.

C. THE RECOGNIZED ALTERNATIVE FORMS OF TREATMENT/PROCEDURE.

D. THE RECOGNIZED SERIOUS POSSIBLE RISKS, AND COMPLICATIONS OF THE TREATMENT/PROCEDURE AND OF THE RECOGNIZED ALTERNATIVE FORMS OF TREATMENT/PROCEDURE, INCLUDING NON-TREATMENT.

E. THE ANTICIPATED DATE AND TIME OF THE PROPOSED TREATMENT/ PROCEDURE.

MY PHYSICIAN/DENTIST HAS OFFERED TO ANSWER ALL INQUIRIES CONCERNING THE PROPOSED TREATMENT/PROCEDURE. I UNDERSTAND THAT I AM FREE TO WITHHOLD OR WITHDRAW CONSENT TO THE PROPOSED TREATMENT/ PROCEDURE AT ANY TIME.

I certify this form has been fully explained to me, that I have read it or have had it read to me, that the blank spaces have been filled in, and that I understand its contents. This form consists of two pages and I have read both pages.

DATE _____ TIME _____ AM PM _____
Patient/Other Legally Responsible Person Sign

_____ _____
Counseling Physician/Dentist Relationship of Legally Responsible Person to Patient

APPENDIX D

BREAK DOWN OF COST

SUPPLIES REQUIRED PER TEST

15 electrodes
1 mouthpiece
1 PAL filter
3 hours of technical support at $13.50/hour
20 sheets of paper
1 drying cartridge
Calibration gas (30 tests/tank)

BULK SUPPLIES

ECG electrodes	$50.00/300 ct box
Mouthpieces	$40.00/500 ct box
PAL filter	$125.00/25 ct box
Calibration gas	$120.00/tank
Drying cartridges	$60.00/12 ct box
Paper	$13.50/2500 ct box
Printer tape	$1.50/ribbon

as approved

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

Authority:	10 USC 3013, 44 USC 3101 and 10 USC 1071-1087
Principle Purpose:	To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.
Routine Uses:	The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law. Information may be furnished to Federal, State and local agencies.
Disclosure:	The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____ SSN _____ having full capacity to consent and having attained my _____ birthday, do hereby volunteer to participate in **Exercise Capacity Following Radiation Therapy in Patients with Stage II and III Non-Small Cell Lung Cancer** under the direction of **Dr. Timothy R. Murray** conducted at **Madigan Army Medical Center.**

The implications of my voluntary participation and consent; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____.

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights on study-related injury I may contact the *Center Judge Advocate* at *Madigan Army Medical Center, (206) 968-3113.*

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required (*military volunteer*) or requested (*civilian volunteer*) to undergo certain examinations if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - EXPLANATION OF WHAT IS TO BE DONE

INTRODUCTION: You have been invited to participate in a clinical research study conducted at Madigan Army Medical Center. It is very important that you read and understand the following general principles that apply to all participants in our studies: (a) your participation is entirely voluntary; (b) you may withdraw from participation in this study or any part of the study at any time by contacting **Dr. Murray** at **(206) 968-1095**; (c) refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled; (d) after you read the explanation, please feel free to ask any questions that will allow you to clearly understand the nature of the study.

Radiation Therapy is frequently used to treat lung cancer, alone, or in combination with surgery and chemotherapy. The maximum dose of radiation therapy is always balanced by the side effects of the radiation on the surrounding tissue. The effects of radiation therapy on lung function may take up to 9 months to become apparent. Predicting before treatment the amount of injury to the lung from radiation would allow physicians to use the optimal amount of radiation therapy to maximize its effect, while preserving enough lung function to maintain quality of life. Unfortunately, it is difficult to accurately predict the loss in lung function from radiation therapy. Exercising on a stationary bicycle while measuring inhaled and exhaled gases is an accurate test of lung function. This has never been used to assess lung function when using radiation therapy for lung cancer.

The purpose of this study is to see if we can use the results of exercise testing to predict lung function and functional status after radiation therapy for lung cancer. Your participation in the study will last approximately one year after the start of radiation therapy. Approximately 30 patients will be enrolled in this study.

PROCEDURES: If you choose to participate the investigation will be conducted in the following manner:

1) Your exercise ability will be assessed 4 times; before starting radiation therapy and at 3, 6, and 12 months after initiation of radiation therapy. You will be asked to exercise on the stationary bicycle to the best of your ability. You will breathe through a mouthpiece which is connected by a tube to a computer which will measure your gas exchange (breathing ability). Your blood pressure and pulse will also be measured.

2) Pulmonary function (ability to move air) will also be assessed by having you breath several different ways through a tube attached to a meter before each exercise test.

3) You will be asked to complete a questionnaire regarding your current level of activity at each visit.

POTENTIAL BENEFITS: You may not directly benefit from this investigation. However, because you are being closely monitored with exercise testing, any potential problems with your lung function could be detected sooner. Also, you will help doctors understand more about radiation's effect on the lung.

RISKS, INCONVENIENCES, AND DISCOMFORTS: Any risk association with this protocol would arise from riding the exercise cycle. These risks would include low blood pressure, fainting, abnormal heart rhythm, heart attack or death. All of these risks are extremely rare. The duration and intensity of the exercise will be determined by you.A physician will be present for each exercise study and emergency equipment will be immediately available to deal with any unusual situation.

ALTERNATIVES TO PARTICIPATION: If you do not participate in this investigation, you will receive the standard medical care for

your lung cancer as determined by your doctor.

CONFIDENTIALITY OF RECORDS: The case records from this study will be available for review by members of the Institutional Review Board at Madigan and by representatives of the Food and Drug Administration. Otherwise, only the physicians conducting this study will have access to the records from this study. The information gained from this study may be used as part of a scientific publication, but you in no way will be personally identified.

OTHER INFORMATION: Significant findings that occur during this study that might affect your decision to participate in the study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained from your physician. Your participation in this study may be terminated without your consent if conditions occur which could make your continued participation detrimental to your health.

If you should require medical care for injuries or disease which result from participation in this study, the medical care to which you will be entitled is the same as that to which you are already entitled as a DoD health care beneficiary. This does not include domiciliary or nursing home care.

You are encouraged to ask any questions, at any time, that will help you to understand how this study will be performed and how it will affect you. **You may contact Dr. Murray at (206) 968-1095.**

IF THERE IS ANY PORTION OF THIS EXPLANATION THAT YOU DO NOT UNDERSTAND, ASK THE INVESTIGATOR BEFORE SIGNING THIS FORM.

I do ☐ do not ☐ (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record.

You will be given a signed copy of this form to keep.

SIGNATURE OF VOLUNTEER	DATE	
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS SIGNATURE OF WITNESS DATE SIGNED	

Exercise capacity following Radiation therapy...
PF = TR Manual

as submitted (B)

CONSENT - PART B

Radiation Therapy (RT) is frequently used to treat lung cancer, alone or in combination with surgery and chemotherapy. The maximum dose of RT given is always balanced by the side effects of the radiation on the surrounding tissue. The effects of RT on lung function may take up to 9 months to manifest. Predicting the amount of injury to the lung from the radiation before treatment would allow optimal dosing of RT to maximize its effect but preserve enough lung function to maintain quality of life. Unfortunately, it is difficult to accurately predict the loss in lung function from RT. Exercising on a stationary bicycle while measuring inhaled and exhaled gases is an accurate test of lung function. This has never been used to assess lung function in the setting of RT for lung cancer. We would like to use exercise testing to see if we can predict lung function and functional status after RT in patients receiving RT by completing serial exercise tests. The investigation would be conducted in the following manner:

PROCEDURE:

1. Your exercise ability will be assessed 4 times; before RT, and 3, 6 and 12 months after starting RT. This will be done on a stationary cycle, where you will be asked to exercise to the best of your ability while your vital signs and gas exchange are measured.

2. Pulmonary function will also be assessed before each exercise test.

3. You will be asked to complete a questionnaire regarding your current level of activity at each visit.

NUMBER OF PATIENTS TO BE STUDIED: 30

RISK TO PATIENTS: Any risk associated with this protocol would arise from riding the exercise cycle. These risks would include low blood pressure, fainting, abnormal heart rhythm, heart attack or death. All of these side effects are extremely rare. Duration and intensity of exercise is determined by your voluntary limits.

PRECAUTION: A physician will be present for each exercise study and emergency equipment will be immediately available to deal with any unusual situation.

BENEFITS: You may not directly benefit from this investigation. However, because you are being closely monitored with exercise testing, any potential problems with your lung function could be detected sooner. Also, you will help doctors' understand more about radiation's effect on the lung.

ALTERNATIVES TO PARTICIPATION: If you do not participate in this investigation, you will receive the usual medical care associated with radiation therapy and lung cancer.

CONFIDENTIALITY OF RECORDS: The case records from this study will be available for review by members of the Institutional Review Board at Madigan and by representatives of the Food and Drug Administration. Otherwise, only the physicians conducting this study will have access to the record from this study. The information gained from this study may by used as part of a scientific publication, but you in no way will be personally identified.

OTHER INFORMATION: Significant findings that occur during this study that might affect your decision to participate in the study will be discussed with you. Any significant findings developed from this study will be available to you and may be obtained by your physician. Your participation in this study may be terminated without your consent if conditions occur which make your continued participation detrimental to your health.

If you should require medical care for injuries or disease which result from participation in this study, the medical care to which you will be entitled is the same that to which you are already entitled as a DoD health care beneficiary. This does not include domiciliary or nursing home care.

Participation in this study is entirely voluntary; you may withdraw from participation in this study or any part of the study at any time. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

Please feel free to ask any question that will allow you to clearly understand the nature of the study. You are encouraged to ask questions at any time. The point of contact will be Dr. Murray who can be reached at (206) 968-1095

HSHJ-CI (AR 40-38) 29 Nov 93

MEMORANDUM FOR: Dr. Timothy Murray

SUBJECT: Exercise Capacity Following Radiation Therapy in Patients With Stages II and II Non-small Cell Lung Cancer by CPT Timothy R. Murray, MC

The subject protocol was approved by the Human Use Committee, 3 Sep 93. The consent form has been revised as stipulated by the Committee. The protocol may now be implemented.

for DAN C. MOORE, M.D.
COL, MC
C, Department of Clinical Investigation

Enclosure: Revised consent form (20 copies)

FY 94 RESEARCH PROJECT STATUS REPORT

Answers on this form may be handwritten, but please write legibly. The summary is an essential part of this report, and the status report request will be returned if this is omitted. If more space is needed for answer, please use the back of this form.

PI & Number: Murray TR 93/162
Department: Med

TITLE: Exercise Capacity Following Radiation Therapy in Patients With Stages II and III Non-small Cell Lung Cancer

1. Status of protocol: On-going X Completed ___ Terminated ___

   Definitions: Completed - all work completed except for writing paper, Terminated - use only if protocol was terminated for technical or other reasons which made completion of the protocol unfeasible or impossible.

   If principal investigator (PI) has left MAMC and the protocol is on-going, a new PI who is assigned to MAMC must be appointed.

   If transferring to new PI, please give name: N/A and furnish a CV.

2. Number of subjects entered 14 of 30 needed

3. Adverse reactions (number, description, and outcome).
   ~~None~~ Tam 2 patients - considered for the protocol were found in Rapid AF Before starting protocol.

4. Publications (FY 94 only) (Please furnish copy if not already forwarded to DCI):
   0

5. Presentations (FY 94 only) (Please furnish abstract if not already forwarded to DCI):
   0

6. Summary of work (testing, procedures, etc.) done on protocol during FY 94 to include any findings or conclusions thus far (200 words or less). Please make this a concise, informative summary of what you have accomplished on the protocol in the last fiscal year and not a summary of the plan or objective.

Difficult to summarize interim results given the duration of study period (each pt followed for one yr) Currently attempting to analyze the pre & 3 month (post) studies for poster presentation.

Timothy R. Murray 25 Oct 94
SIGNATURE DATE