

RADIATION THERAPY ONCOLOGY GROUP  
RTOG 80-04

PHASE I/II PROTOCOL TO STUDY FAST NEUTRON RADIATION THERAPY  
IN THE TREATMENT OF METASTATIC MALIGNANT MELANOMA

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*Closed*

REPOSITORY Fermi Lab  
Neutron Therapy Facility  
COLLECTION Neutron Therapy Experiments  
Protocols  
BOX No. Binder on Shelf Rm X6W 413  
RTOG Protocol Copies  
FOLDER Closed 7/26/84 at Fermilab  
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## INDEX

### Schema

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluation
- 5.0 Registration
- 6.0 Radiation Therapy
- \*7.0 Drug Therapy
- \*8.0 Surgery
- \*9.0 Other Therapy
- \*10.0 Pathology
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations
- 14.0 Additional Treatment

### References

- Appendix I - Modified Karnofsky Scale
- Appendix II - Acute Skin Reactions
- Appendix III - Late Radiation Morbidity Scoring Scheme
- Appendix IV - Sample Consent Form

\* Does not apply to this study.

0016020

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SCHEMA

R  
E  
C  
O  
R  
D

Tumor Size  
-0 - 3 cm  
> 3 < 6 cm  
> 6 cm (size of  
lesion)

D  
O  
S  
E  
  
S  
C  
H  
E  
M  
E  
  
D  
U  
L  
E  
S

Neutrons: 1400 rad<sub>ny</sub> (Seattle)  
in 7 fractions over 4  
weeks

Neutrons: 1600 rad<sub>ny</sub> (Seattle)  
in 8 fractions over 4  
weeks

Neutrons: 1800 rad<sub>ny</sub> (Seattle)  
in 9 fractions over 5  
weeks

## 1.0 INTRODUCTION

### 1.1 Rationale

Malignant melanoma is a tumor thought to be "radioresistant" by most radiation oncologists.<sup>1</sup> In a recent prospective study "Radiotherapy of Malignant Melanoma," Hebermalz and Fischer (1976) have shown that skin metastases do not respond to fractionation schemes with individual doses smaller than 500 rad regardless of the size of the total dose.<sup>2</sup> Cell survival curves obtained in vitro from melanoma cells derived from three human malignant melanomas (Barranco et al., 1971) and rat melanoma (Dewey, 1971) all showed a large shoulder before becoming exponential. These curves indicate that the cells had a large capacity to accumulate and repair sublethal radiation damage, and might explain the reputed radioresistance of some melanomas to fractionated regimes of radiation therapy (Hornsey, 1972).<sup>1,3,4</sup> There are other examples of malignant melanoma cells grown in vitro which do not show such large shoulders on their survival curves after photon irradiation (Malaise et al., 1975).<sup>5</sup> Such variation between malignant melanoma cell lines may be a factor contributing to the variation in radiation response seen in the human disease. Combined data from clinical trials from Yale, the Melbourne Clinic, and the United Kingdom showed that the response to fraction sizes of 400-800 rad was significantly better (p about 0.01) than to fraction sizes of 200-299 rad.<sup>6</sup> These results are consistent with the view that the radioresistance frequently observed in the clinical situation may be due to the large capacity of melanoma cells to accumulate and repair radiation damage.

### 1.2 General Outline

This protocol study is confined to metastatic or locally recurrent malignant melanoma in skin, subcutaneous tissues, or peripheral lymphatics. Patients who are undergoing

0016022

concomitant chemotherapy or immunotherapy are not eligible for this study; however, patients who after completing the course of planned radiation, subsequently receive chemotherapy for progressing disease will continue to be followed.

The three treatment regimes are designed to deliver increasing doses of radiation. Ten patients will be entered on treatment #1 and response recorded. If no adverse normal tissue effects are seen the dose will be increased to treatment #2. If no adverse normal tissue effects are seen after ten patients have been treated on treatment #2, the dose will be escalated to treatment #3.

## 2.0 OBJECTIVES

The objective of this study is to evaluate the dose response rates of fast neutron beam teletherapy for metastatic malignant melanoma by evaluating the following:

- 2.1 Degree and rate of tumor regression.
- 2.2 Time to onset of local tumor regrowth (if any) and rate of regrowth.
- 2.3 Time of onset and evaluation of severity of radiation injury to surrounding normal tissue.

## 3.0 PATIENT SELECTION

### 3.1 Eligibility Criteria

- 3.1.1 Patients with histologic evidence of malignant melanoma metastatic or recurrent in the skin, subcutaneous tissues, or peripheral lymphatics.
- 3.1.2 Patients without any previous radiation therapy to the area to be treated.
- 3.1.3 Patients with measurable disease.
- 3.1.4 Patients must sign an informed consent form indicating they are aware of the investigational nature of the study (See Appendix IV).

0016023

### 3.2 Ineligibility Criteria

- 3.2.1 Patients with Karnofsky status < 50 (See Appendix I).
- 3.2.2 Age > 75 years.
- 3.2.3 Patients for whom the required visits to the neutron facility would be logistically impossible.
- 3.2.4 Patients for whom follow-up is unlikely.

### 4.0 PRETREATMENT EVALUATION

- 4.1 History and physical examination.
  - 4.1.1 General condition assessment using Karnofsky scale (Appendix I).
  - 4.1.2 Accurate measurement in maximum dimension and at right angles to this of the lesion to be treated. If there are multiple lesions within the anticipated treatment field, the size of the the reference lesion must be measured and reported at each assessment time.
- 4.2 General evaluation.
  - 4.2.1 CBC
  - 4.2.2 SMA12
  - 4.2.3 Chest X-ray
- 4.3 Optional studies (highly desirable).
  - 4.3.1 Biopsy of lesion to be treated.
  - 4.3.2 Liver scan if abnormal liver function.
  - 4.3.3 Lymphangiography where appropriate.
  - 4.3.4 CT scan if needed to evaluate tumor extent.

### 5.0 REGISTRATION

- 5.1 Patients are to be registered for this study by calling RTOG Headquarters (215) 574-3191 between 9:00 a.m. and 5:00 p.m. (Eastern Time) exclusive of weekends or holidays. The caller will give the following information:

- Protocol Name
- Institution Referring Patient
- Neutron Facility

0016024

Physician's Name

Patient's Name

Size of Tumor to be Irradiated ( $-0 \leq 3$  cm,  $> 3 \leq 6$  cm,  
or  $> 6$  cm)

A project case number and the current dose level will be assigned and confirmed by mail.

## 5.2 Treatment Assignment

The three treatment arms of this study are designed to study various doses of fast neutron radiation therapy.<sup>6</sup> Patients with multiple lesions will have the largest lesion treated.

### 5.2.1 Treatment Arms

- 1) Fast neutron irradiation (1400 rad<sub>n+γ</sub> in 7 fractions over 4 weeks);
- 2) Fast neutron irradiation (1600 rad<sub>n+γ</sub> in 8 fractions over 4 weeks);
- 3) Fast neutron irradiation (1800 rad<sub>n+γ</sub> in 9 fractions over 5 weeks).

## 6.0 RADIATION THERAPY

6.1 In most patients a single field will be used to treat the lesions. However, radiation therapy technique will vary depending on the area to be treated. In selected cases, multiple portals may be used to deliver the required dose. Dose variation in the target volume must be less than 10%.

80-04

## 7.0 DRUG THERAPY

Does not apply to this study.

## 8.0 SURGERY

Does not apply to this study.

## 9.0 OTHER THERAPY

Does not apply to this study.

## 10.0 PATHOLOGY

Central pathology review will not be required.

0016025

## 11.0 STUDY PARAMETERS

<u>Parameter</u>	<u>Pretreatment</u>	<u>Weekly</u>	
		<u>During Treatment</u>	<u>Each Follow-up<sup>c</sup></u>
Performance status	x	x	x
Measurement lesion <sup>b</sup>	x	x	x
Chest x-ray	x <sup>a</sup>		
Biopsy of lesion	x <sup>a</sup>		
Liver scan	x <sup>a</sup>		
Lymphangiogram	x <sup>a</sup>		
Tissue Reaction Grade		x	x(See Appendix II & I)

- a. As indicated.
- b. Tumor size; measure maximum dimension and dimension at right angles.
- c. Monthly for 6 months, then every two months for 18 months, then every 3 months through year 5.

### 11.1 Endpoints of Study

- 11.1.1 Objective tumor response. At each evaluation time, the lesion should be measured in the maximum dimension and dimensions at right angles to it.  
Response will be scored as follows:
  - 1+ (25%) regression in area
  - 2+ (50%) regression in area
  - 3+ (75%) regression in area
  - 4+ (100%) regression in area
- 11.1.2 Duration of response will be determined from the day of registration to the date of local regrowth (increase from previous assessment) of tumor.
- 11.1.3 Acute and late normal tissue reactions should be recorded on the scale outlined in Appendix II & III.
- 11.1.4 Measurement of tumor size will be made weekly during treatment and at each follow-up according to section 11.0.

0016026

## 12.0 DATA COLLECTION

### 12.1 Forms

On-study / Initial Evaluation Diagram of lesion	Within 1 week of registration.
Treatment Form	Upon completion of treatment.
Follow-up Form	Six weeks following commencement of treatment and monthly for the first 6 months, then every 2 months through the second year, then every 3 months through the fifth year.
Death Form	Upon death of patient.

## 13.0 STATISTICAL CONSIDERATIONS

The primary purpose of this study is to investigate the response and complication rates at the various treatment dose levels under study. With standard therapy, the proportion of patients who experience a complete response is no more than 10%. Further neutron studies are anticipated if in any of the treatment groups two or more of the ten patients have a complete response and providing no severe complications are observed.

These criteria provide a 91% chance of accepting neutrons for further study if the response rate at any one dose level is 35% and a 26% chance of further testing of a particular dose level if the response rate is no better than conventional therapy. Further, we have a 65% chance of seeing any complication which occurs one time out of ten. If any two of the dose levels can be combined, the power of the experiment will be increased.

## 14.0 ADDITIONAL TREATMENT

Therapy is administered as detailed in Section 6.0. Subsequent therapy shall proceed at the discretion of the patient's referring physician. Indications for subsequent therapy and the therapy performed should be documented in the patient's follow-up records.

0016027

## REFERENCES

1. Barranco, S. C., Ronsdahi, M. M., and Humphrey, R. M.: The radiation response of human malignant melanoma cells grown in vitro. Cancer Res 31:830-833, 1971.
2. Hebermalz, H. J., and Fischer, J. J.: Radiation therapy of malignant melanoma; experience with high individual treatment doses. Cancer 38:2258-2262, 1976.
3. Dewey, D. L.: The radiosensitivity of melanoma cells in culture. Br J Radiology 44:816-817, 1971.
4. Hornsey, S.: The radiation response of human malignant melanoma cells in vitro and in vivo. Cancer Res 32:650-651, 1972.
5. Malaise, E. P., Weiringer, J., Joly, A. M., and Guichard, M.: Measurements in vitro with three cell lines derived from melanoma. In Cell Survival After Low Doses of Radiation: Theoretical and Clinical Implications. pp. 223-225. Ed. T. Alper. Pub. Institute of Physics and John Wiley, London.
6. Thomson, L. F., Smith, A. R., and Humphrey, R. M.: The response of the human malignant melanoma cell line to high LET radiation. Radiology 117:155-158, 1975.

APPENDIX I

KARNOFSKY PERFORMANCE SCALE

- 100 Normal; no complaints; no evidence of disease.
- 90 Able to carry on normal activity; minor signs or symptoms of disease.
- 80 Normal activity with effort; some sign or symptoms of disease.
- 70 Cares for self, unable to carry on normal activity or do active work.
- 60 Requires occasional assistance, but is able to care for most personal needs.
- 50 Requires considerable assistance and frequent medical care.
- 40 Disabled; requires special care and assistance.
- 30 Severely disabled; hospitalization is indicated, although death not imminent.
- 20 Very sick; hospitalization necessary; active support treatment is necessary.
- 10 Moribund; fatal process progressing rapidly.
- 0 Dead.

0016029

APPENDIX II

SKIN REACTIONS

EARLY

<u>Erythema</u>	<u>Dry Desquamation</u>	<u>Moist Desquamation</u>	<u>Pigmentation</u>
0	No Visible Reaction		
1 Follicular	Focal	Focal	Follicular
2 Faint	Confluent one-third	Confluent one-third	Peripheral
3 Dull	Confluent up to half	Confluent up to half	Light
4 Bright	Confluent more than half	Confluent more than half	Moderate
5 Dusky	Whole field	Whole field	Dark

0016030

Appendix III

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 > 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	

0016031

## APPENDIX IV

### Sample Consent Form\*

#### Purpose and Benefits

A new form of radiation (neutron beam) has been developed which theoretically should be more effective than conventional (photon) irradiation for certain types of tumors. The purpose of this study is to determine the effectiveness of irradiating metastatic malignant melanoma with the neutron beam. It is not known at this time if the neutron beam treatment will be more effective than conventional photon irradiation. We are joining with other physicians in the country to study this problem. Patients who decide not to participate in this study will be treated with conventional photon irradiation.

#### Procedures

If you decide to participate in the study, you will be assigned to one of the following three treatments. The treatment you are assigned will depend on how many patients have been entered on this protocol before your assignment.

- A. Seven treatments of experimental neutron irradiation, twice a week, over four weeks.
- B. Eight treatments of experimental neutron irradiation, twice a week, over four weeks.
- C. Nine treatments of experimental neutron irradiation, twice a week, over five weeks.

Routine follow-up, at intervals determined by your physician, will be scheduled at the completion of therapy to follow the results of your treatment. Protocol assessments will be made every month for 6 months, every 2 months for 18 months, and every 3 months thereafter. Follow-up sessions will consist of measurement of tumor size and an assessment of skin reactions and any other symptoms. Photographs may be taken of the treated area to document skin reactions. The patient's medical records will be used in this study; a copy of the radiotherapy record will be submitted to study headquarters.

#### Risks

The side effects of radiation therapy may include skin reactions in the treated area such as redness, dryness and/or peeling. Neutron beam irradiation is experimental so not all possible side effects are known. However, neutrons interact more strongly with non-tumor tissues than do photons and side effects may include scarring of fatty tissue and neurologic damage. The side effects from the neutron beam irradiation may be more severe than those from conventional photon irradiation.

\*Sample consent form submitted by Study Chairman

Other Information

The identity of participants will remain confidential with the following exception: The Radiation Therapy Oncology Group National Headquarters will receive the names of subjects and has the right to review study data which may contain identifying information. Controls over access to this information have been approved by the National Cancer Institute. You are free to withdraw from the study at any time without jeopardizing your relationship with your doctor or your current or future medical care. Costs for normal workup, treatment, and follow-up are billed to the patient; neutron beam treatments will not be charged to you. If you are assigned to receive the new neutron beam treatment, arrangements may be made to provide partial support for housing during the treatment if you live outside the area. Photographs of the treatment fields will be submitted to the study headquarters. There is a possibility that you could be identified from these photographs. You may review and destroy any photographs that you find objectionable.

In the event of complications, the patient will be assessed in Radiation Oncology. The patient's care will be managed by his/her radiation oncologist, or if appropriate, the patient will be referred to another physician specialist. The patient will be responsible for these costs with the following exception: The neutron study grant contains some funds for reimbursing the patient for medical expenses arising from direct complication of neutron irradiation. We will cover such expenses to the extent provided by the grant. However, these moneys are limited and we cannot guarantee that any given patient will receive a reimbursement.

Information obtained in this study will be used to evaluate neutron beam irradiation to determine the value, morbidity, and complication rates. Study data will be retained by the investigators indefinitely.

\_\_\_\_\_  
Investigator's Signature

\_\_\_\_\_  
Date

Subject's Statement

I voluntarily consent to participate in this study. I have been given a copy of this consent form and have had the opportunity to ask questions.

\_\_\_\_\_  
Signature of Subject

\_\_\_\_\_  
Signature of Subject Advocate

\_\_\_\_\_  
Date

\_\_\_\_\_  
Date

\_\_\_\_\_  
Relationship (Relative, Close  
Friend, or someone who knows subject well)

0016033