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RTOG 76-11

RADIATION THERAPY ONCOLOGY GROUP

PROTOCOL TO STUDY NEUTRON THERAPY IN THE TREATMENT OF MALIGNANT GLIOMAS

RTOG Acting Study Chairman: Lawrence W. Davis, M.D.

RTOG Site Chairman: Simon Kramer, M.D.

RTOG Co-Chairman: Lawrence W. Davis, M.D.

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RTOG Protocol for Neutron Therapy

Malignant Gliomas

STRATIFY

Histology
Grade III
IV

Institution

BIOPSY PROVEN
YES
NO

RANDOMIZE

A. Photons whole brain 5000 rad/5-5½ weeks. Photons coned down boost 1500 rad/ 1½-2 weeks.

B. Photons whole brain 5000 rad/5-5½ weeks. Neutrons coned down boost 1500 rad equivalent/1½-2 weeks.

Photons: 180-200 rad/fraction; 5 fractions/week.

Neutrons: 2, 3, or 4 fractions/week; 900-1000 equivalent rad/week.

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1.0 INTRODUCTION

The malignant gliomas are rarely controlled by any treatment and are almost uniformly fatal. Survival following conventional neurosurgical intervention and radiotherapy can be measured in terms of months with the median survival from the start of treatment being 10 to 13 months and survival frequencies in the range of 55-67% at 6 months, 27-39% at 12 months, and 8-20% at 24 months. Relentless local growth of tumor rather than metastases kills the host.

Considerable effort has been made by investigators in recent years to search for newer avenues of approach, including higher doses of conventional photon radiation, combination of chemotherapy and photon radiation, and high-LET radiations.

The RTOG has a current protocol which tests standard whole brain radiation using photons to a total dose of 6,000 rads against the same radiation dose with a 1,000 rad boost added, or the addition of chemotherapy using BCNU or Methyl CCNU + DTIC. Preliminary analysis of this data show no difference among the four-treatment randomizations. These preliminary findings are consistent with the early reports of the Brain Tumor Study Group investigation of radiation alone versus radiation plus BCNU.

Inasmuch as there are theoretical biological bases for better responses of these tumors to high-LET radiation, a pilot study with fast neutron whole-brain radiotherapy was undertaken and some initial observations are available. As of 4/30/76 a total of 33

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patients with Grade III or IV astrocytomas received fast-neutron teletherapy at the University of Washington. Of the initial 21 patients covering a time span from 9/10/73 through 11/8/74 all but 2 have died. The average survival for the Grade III astrocytoma patients in this group was 9.4 months, and for the Grade IV patients it was 7.6 months. Overall average survival was 8.2 months. Since 11/8/74 an additional 12 patients received fast-neutron teletherapy. The average survival for the Grade III patients in this group was 5.4 months, and for the Grade IV patients was 8.0 months with an average survival of 6.25 months. It must be stated that many of these patients have only recently completed their course of radiation, so that these average survivals should improve. Considering the entire group of 33 patients, the average survival is 7.5 months. These figures could be compared to the photon-radiated patients at the University of Washington with Grade IV astrocytomas who provide historical controls. This group of patients has an average survival of 7.0 months. The 6-month survivals for the fast neutron and the photon-radiated patients are comparable, as are the 12-month survivals.

One would expect the 12-month survival for the Grade IV astrocytoma patients in the total group of 33 fast-neutron treated patients to improve with time, as many of the recently radiated patients are still alive.

Autopsy studies on fast-neutron radiated patients indicate that the tumors are being effectively destroyed with the involved

brain appearing grossly normal on cut section. In only a few instances was there significant mass effect and any degree of edema and/or herniation. Microscopic studies confirm the presence of coagulative necrosis without macrophage response of essentially the entire mass of tumor surrounded by a rim of dense fibroblastic reaction with sparse tumor cells which appear mainly to be bizarre multinucleated cells. Within the involved brain including the diencephalon and brainstem, a diffuse gliosis is observed which is judged by the reviewing neuropathologists to be in excess of that observed to date with equivalent doses of photon radiation. Possible explanations are that the RBE with fast neutrons for normal brain may be greater than anticipated and excessive normal tissue injury may have resulted, or there may be some, as yet unexplained, response of normal brain unique to neutrons and/or other high-LET radiation. Lower neutron doses may still achieve a satisfactory tumor response with improved tolerance by the normal brain. Different fractionation patterns or combinations of photons and neutrons may also achieve a more optimum response. Because of the higher oxygen enhancement ratio with photon radiation, it is postulated that the cells persisting following photon radiation may reflect largely the more resistant hypoxic-anoxic component. If this is true, then fast-neutron boost radiation following photons may be more effective than photons alone.

Dr. Catterall has given preliminary results of treatment of malignant gliomas with the Hammersmith Neutron Beam. Approximately 35 patients were treated with a total neutron dose of 1,620 rads given in 12 fractions over 4 weeks. All these patients expired and autopsy findings reported extensive tumor necrosis with no definite viable tumor present.

Because of these results, a second group of patients were treated with a total dose of 1,320 rads given in 12 fractions over 4 weeks. These patients all died and autopsy findings showed no brain damage from the radiation therapy; however, viable tumor was present in all cases.

Because of these two pilot studies, the current protocol is being undertaken to compare standard whole-brain photon treatment with a photon boost versus a neutron boost. Since the neutrons have been shown to effectively control glioblastoma, it is felt that the combination of photons followed by a neutron boost is the most effective treatment scheme to test.

2.0 OBJECTIVES

Assessment will be made of the primary endpoints.

2.1 Survival rates.

2.2 Interval to symptomatic recurrence.

2.3 Radiation toxicology. To establish the tolerance of the normal brain to a neutron boost versus a photon boost, both following whole-brain irradiation using photons.

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3.0 SELECTION OF PATIENTS

The basis for selection will be a histologically-proven malignant glioma Grades III or IV.

3.1 Conditions for Patient Eligibility:

3.11 Histopathologically confirmed malignant gliomas: Malignant glioma is a group of tumors variably called glioblastoma multiforme, astrocytoma Grade III or IV, spongioblastoma multiforme, malignant astrocytoma, etc. They have common pathologic characteristics which may include cytologic pleomorphism, anaplasia and mitotic figures, necrosis, invasiveness, stromal reaction, hemorrhage and vascular hyperplasia. Clear-cut survival differences between these groups of malignant gliomas have not been well demonstrated.

3.12 Diagnosis can be made by surgical removal which may be grossly complete or incomplete depending on the surgeon's judgement. Surgical decompression will be performed consistent with acceptable limits at tumor bed location and institution.

3.13 Tumor must be supratentorial in location.

3.14 Patient must be 16 years of age or older.

3.15 Patient or family must give informed consent.

3.2 Conditions for Patient Ineligibility:

3.21 Previous treatment with radiation therapy or chemotherapy in the cranium or head-and-neck region.

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3.22 Previous cancer except for small skin cancers outside of the cranial region.

3.23 Major neurologic deficit, major medical illness or psychiatric impairment which, in the principal investigator's opinion, will prevent completion of protocol studies. Reasons for exclusion to be stated in population form.

3.24 Patient who, for any reason, cannot be regularly followed by investigators.

3.25 Patients in whom metastatic disease in spinal cord or distant sites is detected.

3.26 Patient less than 16 years of age.

4.0 RECOMMENDED WORK-UP: In most cases will have been done prior to craniotomy. The patient work-up should include the following:

4.1. Detailed Neurologic Examination.

4.11 Assessment of performance status to permit functional classification using the Karnofsky Performance Scale (see Appendix I).

4.2 Fundoscopic and opthalmological examination as indicated.

4.3 Skull films

4.4 Electroencephalogram (EEG)

4.5 Necessary imaging and/or contrast studies to optimally define the location and extent of the tumor including brain scan, CAT scan, echogram, cerebral arteriography and/or air studies, i.e., ventriculogram, pneumoencephalogram.

4.6 Chest X-ray

4.7 Complete blood count (CBC)

5.0 STRATIFICATION, REGISTRATION, AND RANDOMIZATION

5.1 Stratification: For the purposes of randomization, patients will be stratified (i.e., divided into separate subgroups) depending on:

a. The patient's institution

b. The histologic grade of the tumor.

5.2 Registration: To enter a patient on study, the physician will call the RTOG Operations Headquarters at 215-574-3191 between 9 a.m. and 5 p.m., ET, Monday through Friday, and relate the following information:

a. Name of the protocol

b. Name of the patient

c. Name of the institution

d. Grade of malignancy

The physician, in turn, will receive a treatment assignment which has been randomly chosen. This treatment assignment will later be confirmed by mail.

5.3 Randomization: Randomization will be to one of the following treatments:

a. Photon irradiation - whole brain 5000 rad/5-5½ weeks.
Photon irradiation - coned boost 1500 rad/1½-2 weeks.

b. Photon irradiation - whole brain 5000 rad/5-5½ weeks.
Neutron coned-down boost 1500 rad equivalent/1½-2 weeks.

6.0 RADIATION THERAPY PROGRAM

6.1 Photons Only

Therapy is to be administered as specified in the section on randomization. The standard dose of photons is 5,000 rads to the whole brain given in 180-200 rad daily fractions, 5 fractions per week, 900-1000 rad per week. A coned-down boost of 1500 rads given in 8 to 10 fractions in 1½ to 2 weeks will follow the whole-brain radiation therapy. All photon radiation must be with megavoltage equipment (Cobalt 60 or 2 MeV or greater).

6.2 Photons then Neutrons

Sequential photon and neutron irradiation will be carried out delivering a dose of 5,000 rads in 25-28 fractions over 5 to 5½ weeks with photons. This will be followed by a coned-down boost using neutrons in a dose equivalent to 1500 rads in 3 to 8 fractions given in 1½ to 2 weeks.

6.3 Field Definition

6.31 5,000 rad photons will be delivered to the whole brain.

6.32 The whole brain is defined as the entire intracranial contents which are to be treated through bilateral parallel opposed fields with both fields to be treated daily.

6.33 The coned-down boost field should be determined by defining the volume of the tumor prior to initiation of radiation and allowing for a margin of at least 2 cm, but sparing as much brain as possible. The brain stem should be excluded, if possible. This volume should then be irradiated with AP opposed, bilateral opposed, wedged pairs or whatever other technique that will encompass this volume and be as sparing of uninvolved brain as possible.

6.4 Dosimetry Data

6.41 Fraction size may be varied by plus or minus 10% to correct for missed treatment, errors in dosage calculations, etc., but corrections beyond this degree must be made by giving additional fractions. At least 90% of the planned neutron dose must be given with neutrons.

6.42 Localization films will be obtained at the start of treatment and for the boost fields.

6.43 All patients will require full isodose curves as defined in the treatment planning workbook. Each participating institution must maintain proper quality control for localization and treatment techniques within its network. The Radiologic Physics Center and Neutron Therapy Physics Group will be responsible for maintaining quality control of the physics.

6.44 Neutron doses that are considered approximately equivalent to 1500 rads of photons given in 1½ to 2 weeks at each facility are as follows:

University of Washington	450 rad
MANTA	468 rad
TAMVEC	480 rad
NAL	480 rad

7.0 STUDY PARAMETERS

7.1

Study Parameters	Time of Study				
	Prior to therapy	During therapy	At completion	At 1 month post-treatment	3 months during follow-up
Neurological exam	X	Weekly	X	X	X
Skull films	X				
Chest X-ray	X				
EEG	X				
Ophthamological exam	X				
CBC	X	Every 2 weeks			
CAT scan	X*		X*		X*
Air studies	X*				
Angiography	X*				
Brain scan	X		X		X

*At the discretion of the investigator for definition prior to surgery and for follow-up assessment especially if there is a change in neurological status. Though these studies are not mandatory, they are desirable. Whenever possible serial CAT scanning should be performed, though in lieu of this, conventional brain scanning should be performed.

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7.2 Measurement of Specific Endpoints

7.21 Tumor response cannot be measured directly, although the serial studies suggested may provide some very useful observations. Whenever available, CAT scanning is recommended and once a baseline is obtained, serial interval scans are recommended to help assess tumor response. Optionally, conventional brain scanning should be obtained if CAT scanning is not available.

7.22 Survival will be measured from the time that treatment starts to death.

7.23 Symptomatic palliation will be measured by changes in neurologic function, Karnofsky performance, signs and symptoms. They will be clinically determined when a patient goes on study and then assessed at each follow-up.

7.24 Postmortem examination of the cranial contents should be obtained at death whenever possible.

8.0 GENERAL MANAGEMENT AND ADDITIONAL TREATMENT

8.1 General Medical Care: Note associated medical diseases which will require care, specifically as related to toxicity of therapy.

8.2 If there is evidence of increased intracranial pressure despite the surgical decompression, the use of cortico-steroids such

as Decadron 4 mg q 6 h, or its equivalent, may be used. Corticosteroids should be tapered and discontinued as soon as it is judged possible.

8.3 Infections: Antibiotics used for infection should be noted.

8.4 Pain: Analgesics as required.

8.5 Any radiation therapy added at the time of first recurrence or relapse must be recorded.

9.0 STATISTICAL CONSIDERATIONS AND FORMS

9.1 The calculations described below are predicated on the following assumptions:

a. That in using photon irradiation, the median survival for the patients in question is approximately 7-9 months.

b. That treatment which uses photon-neutron combinations will need to result in approximately a doubling in the median survival now being achieved (i.e. will produce a median survival in the range of 12-18 months).

c. That such a difference be associated with a significance level of $p = 0.05$ using a one-sided test of significance.

d. That there be a reasonable likelihood (i.e. at least say 85%) that such a difference be detected.

e. That treatment comparisons will first be made within each institution, in order to minimize inter-institution differences.

Based upon these assumptions, it is estimated that the treatment comparison can be made if each of 4 institutions can supply a total of approximately 9 patients to each of the 2 treatments being compared. It is anticipated that this can be achieved in 2-3 years.

9.2 Data Reporting

Form:	Due Date:
On-Study Form:	To be submitted within 1 week of entry on study, including copy of pathology request, copy of treatment plans, localization films, and isodose distribution, if done.
Radiotherapy Form:	To be submitted at end of radiotherapy.
Follow-Up Form:	To be submitted at 3-month* intervals and at patient's death.

All reports are to be forwarded to the Operations Office.

*First 3 month follow-up will include assessments during and immediately following treatment.

10.0 CENTRAL PATHOLOGY REVIEW

Central pathological review is necessary and will be required in each instance. It will not be necessary to complete this review prior to randomizing the patient and initiating the treatment. Randomization will be based on the institutional pathology report.

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REFERENCES

1. 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 of the C3H mouse to x-rays and cyclotron neutrons: Effect of mixed neutron-photon fractionation schemes. European J. Cancer 11:891-901, 1975.

2. Parker, R.G., Berry, H.C., Gerdes, A.J., Soronen, M.D. and Shaw, C.M.: Fast-neutron beam radiotherapy of glioblastoma multiforme. Amer. J. Roentgenol. 127(2):331-335, 1976.

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APPENDIX I

R.T.O.G. (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 signs or symptoms of disease.
70	Cares for self; unable to carry on normal activity or to 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.