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RADIATION THERAPY ONCOLOGY GROUP

RTOG 80-07

PHASE II DOSE-SEARCHING RANDOMIZED STUDY OF MIXED BEAM (NEUTRON/PHOTON) RADIATION THERAPY FOR ANAPLASTIC ASTROCYTOMAS AND GLIOBLASTOMAS

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*not applicable to this study.

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SCHEMA

STRATIFY

Histology
Anaplastic Astrocytoma
Glioblastoma

Neutron Facility

RANDOMIZE

Photons:
4500 rad_{γ} whole brain irradiation in 30 fractions over 6 weeks.

Neutrons:
Two treatments per week (preferably separated by two or more days) given prior to and within 3 hours of the photon irradiation for that day to a boost field geometry localized to the primary tumor volume.

360 $rad_{n\gamma}$* in 12 fractions over 6 weeks.

420 $rad_{n\gamma}$* in 12 fractions over 6 weeks.

480 $rad_{n\gamma}$* in 12 fractions over 6 weeks.

*For the Seattle, Washington Neutron facility. Doses for the other facilities are to be scaled according to the relative RBE's of the respective neutron beams.

Patients may be randomized by calling RTOG Headquarters (215) 574-3191, between 9 a.m. and 5 p.m., EST.

CASE CREDITS: 2 credits per case

1.0 INTRODUCTION

1.1 Disease Background.

Although uncommon compared to other malignancies, recent statistics indicate that there are about 11,000 new cases of primary brain and central nervous system tumors occurring each year.[1] Approximately 2% of all cancer-related deaths are caused by primary brain tumors, and anaplastic astrocytomas and glioblastomas are the most malignant of the intracranial neoplasms. These lesions tend to be highly infiltrating in character and generally cannot be completely removed surgically due to the close proximity of vital brain areas. Following diagnosis and generally a surgical debulking procedure, radiation therapy is routinely given. Nevertheless, local tumor persistence or recurrence rather than metastatic spread constitutes the primary failure mode. At the present time, there is considerable interest in exploring new therapeutic options such as high dose conventional photon radiation, photon radiation in combination with chemotherapy and/or radiation sensitizers, and high linear energy transfer (LET) radiation such as neutrons or pi-mesons.

The issues of high dose conventional photon irradiation and the combination of conventional photon irradiation with chemotherapy are being addressed by a joint RTOG-ECOG protocol (RTOG 74-01, ECOG EST 1374) which randomizes patients among four treatment arms: (A) 6000 rad_γ whole brain irradiation, (B) 6000 rad_γ whole brain irradiation followed by a 1000 rad_γ boost to the primary tumor volume, (C) 6000 rad_γ whole brain irradiation combined with BCNU chemotherapy, and (D) 6000 rad_γ whole brain irradiation combined with MeCCNU and DTIC chemotherapy. As of January 1980, 552 evaluable patients had been placed on the study with median survival among the treatment arms as indicated below.

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Median Survival in Months -- RTOG 74-01, ECOG EST 1374

Treatment Arm	Anaplastic Astrocytoma	Glioblastoma
A	17	8.1
B	30	7.7
C	25	8.5
D	22.8	9.5

The most dramatic result of this study is the prognostic difference between the histological classifications of "anaplastic astrocytomas" and "glioblastomas." In the case of the anaplastic astrocytomas, the addition of high dose boost-field radiation therapy has the most impact on survival. However, for the glioblastomas the addition of MeCCNU and DTIC has the most effect. Nevertheless, in all four treatment arms, local failure is still the predominant failure mode.

The issue of conventional photon irradiation combined with currently available hypoxic cell radiosensitizers has been addressed by RTOG Protocol 78-01 which was a single-armed pilot study utilizing misonidazole with a tailored dose fractionation scheme of conventional photon irradiation. Forty-nine evaluable patients were entered on the study with their median survival being 52 weeks as measured from the onset of radiotherapy. Although important things were learned regarding the toxicity of misonidazole, local tumor persistence or recurrence was still the primary cause of death. This study is now closed.

There is currently an ongoing study (RTOG 79-18) which tests the effect of adding misonidazole to standard photon irradiation plus BCNU chemotherapy. This is a Phase III randomized study which has recently been activated and as yet, no results are available. While this is an important study which may well yield improved patient survival, it must

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be noted that it involves a combination of modalities which, taken separately, thus far have not led to increased local tumor control.

1.2 High LET Radiotherapy.

High LET radiation theoretically has two main advantages over conventional photon irradiation in eradicating certain types of tumors: (1) A lower oxygen enhancement ratio (OER), and (2) A predominantly "multi-site" form of cell damage which is less susceptible to repair by the tumor cells. Malignant gliomas generally have multiple regions of necrosis and presumably these necrotic foci are surrounded by hypoxic cells which would be resistant to conventional photon irradiation. Thus, the lower OER of high LET radiation could be of benefit in tumor control. Even well-oxygenated glioma cells are expected to be fairly radioresistant and there may not be much of a difference in radiosensitivity when compared with normal brain cells. Little is known about the relative abilities of glioma and normal brain tissue to repair radiation damage but it is known that nutritionally-deprived tumor cells can repair potentially lethal damage from low LET radiation and that this type of repair does not occur for tissue cells in their normal growth pattern.[7] Repair of potentially lethal damage apparently does not take place for high LET radiation damage[3,7] and this may be of potential benefit in treating malignant gliomas. In addition, the cell cycle variation in radiosensitivity is less for high LET radiation[4] but it is not clear the extent to which this phenomenon contributes to a therapeutic gain.

At the present time, the only extensive studies involving the use of high LET radiation for malignant gliomas are for fast neutron radiotherapy beams. Catterall, et al.[2] have reported preliminary results from Hammersmith indicating that fast neutron radiotherapy has the potential for eradicating this type of tumor. Initially, 18 patients were treated to a whole brain total neutron dose of 1560 $rad_{n\gamma}$ in 12 fractions

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over 4 weeks. A second group of patients received 1320 $rad_{n\gamma}$ whole brain irradiation in 12 fractions over 4 weeks. All of these patients have since died and in 16 patients there has been a post-treatment assessment of disease status either at a "second-look" craniotomy or at autopsy. In 69% of the cases (11/16) either no tumor was found or only microscopic foci of abnormal cells were noted. Moderate to gross tumor recurrence was noted in the other 31% of cases (5/16). In a "control" group of patients treated with 5000-5500 rad_{γ} photon irradiation moderate to gross disease was noted in 86% (6/7) of the patients who went to autopsy. This indicates a difference in the local control rates for the two forms of radiation. These findings were confirmed by the Phase I pilot study undertaken at the University of Washington in Seattle.[11] Thirty-six patients received whole brain irradiation either using fast neutrons alone or in combination with megavoltage photons as part of a "mixed beam" regime. The latter treatment modality involved treating with neutrons twice a week and with photons three times a week and was based upon laboratory studies by Rasey et al.[13,14] which showed an enhanced therapeutic gain when compared with fast neutron radiotherapy alone. Several clinical pilot studies confirmed this for advanced squamous cell carcinomas of the head and neck region[5,6,10,12] and also indicated less treatment morbidity for the mixed beam mode. In the case of the malignant gliomas, 26 patients were treated with neutrons alone, and in general, received between 1550 $rad_{n\gamma}$ and 1850 $rad_{n\gamma}$ whole brain irradiation over 5-6 weeks. Ten patients were treated with the mixed beam regime and received whole brain irradiation consisting of between 600-660 $rad_{n\gamma}$ and 2800-3200 rad_{γ} over 5 weeks followed by a boost to the primary tumor volume of between 120-180 $rad_{n\gamma}$ and 500-1000 rad_{γ}. There were no discernible differences between the results of these two treatment arms. The mean survival after completing therapy was 10.8 months for the patients with Grade III lesions and 7.5 months for patients

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with Grade IV lesions. These survival figures were less than those for an historical group of patients receiving conventional photon irradiation at the University of Washington -- Grade III lesions mean survival = 26.0 months, Grade IV lesions mean survival = 9.9 months. Autopsies were performed on 15 patients and the tumor was apparently eradicated in 14 instances. The patients' brains exhibited a coagulation necrosis replacing the gross tumor volume with some sparsely-scattered abnormal cells (probably reactive astrocytes) intermixed with the coagulation regions. A diffuse gliosis and a white matter demyelination were found in regions far from the tumor volume and this presumably was related to the ultimate cause of death. Thus, it appeared that fast neutron irradiation could effectively destroy the tumor mass but that the concomitant side effects to the normal brain tissue were too severe.

Based upon the above information, an RTOG protocol (76-11) was designed which restricted the neutron irradiation to the primary tumor volume. CT scanning has made such a program feasible. In this study, all patients first received 5000 rad_{γ} whole brain irradiation in 200 rad_{γ} fractions over 5 weeks and then were randomized to either a 1500 rad_{γ} boost or a 1500 rad equivalent boost (based upon the radiobiological effectiveness [RBE] of the neutron beams at the various participating institutions). At the University of Washington, the neutron boost patients received 450-500 $rad_{n\gamma}$ in 8 fractions over two weeks. As of January 1980, 109 evaluable patients had been placed upon the study with 58 patients receiving the photon boost and 51 patients receiving the neutron boost. A <u>preliminary</u> analysis (January 1980) of the raw data indicates a 7.8-month median survival for the photon boost group and a 9.0-month median survival for the neutron boost group. Ten patients have thus far survived more than one year after completing therapy and of these, 3 come from the photon boost group and 7 come from the neutron

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boost group. This may indicate a significant difference between the tails of the respective survival curves. As of January 1980, 32 patients in the photon boost group and 26 patients in the neutron boost group have died. The cause of death was reported as "primary brain tumor" in 43/44 cases with only one patient (neutron boost group) dying of non-tumor-related causes. In the remainder of the cases, the cause of death was unreported. Thus far, only the autopsied cases from the Seattle neutron facility have been reviewed in detail, but this seems to indicate that simply reporting the cause of death as "primary brain tumor" obscures the treatment results as far as local tumor control is concerned. The neuropathology section of the autopsy reports of 6 patients receiving the neutron boost were reviewed and in 5 cases showed no evidence of persistent tumor. There was significant necrosis of the primary tumor volume with sparsely scattered bizarre cells throughout the region. Whether these are reactive astrocytes or perhaps a radioresistant tumor component is not known at this point but it is certain that there was no expansively growing tumor component that caused the patients' deaths. This was true even for one patient with a Grade IV lesion who survived 32 months after completing treatment. In one case, the autopsy indicated viable tumor present in the treatment volume. This case was somewhat of an anomaly in that fibrosarcomatous-like elements were also present. However, the findings for two patients who received the photon boost are in marked contrast to this. In both cases, a region of infiltrating, proliferating tumor mass with an actively proliferating vascular component was found surrounding a central necrotic region. These two patients died of progressing tumor. The other patients in the Seattle experience have either not been autopsied or the neuropathological component of the study is still pending. Clinically, the courses of the patients in the two sub-groups were identical -- a period of either stability or improvement of neurological function followed by

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a progressive deterioration leading eventually to a bedridden state and eventual death (usually via an infectious pulmonary process).

Hence, there is evidence that the neutron radiation as currently delivered is capable of eradicating high grade gliomas but that the patients are dying of ill-defined, treatment-related causes. Nevertheless, the survival curves indicate some potential benefit for the neutron treatment and so it is certainly worth exploring the use of this modality further. As things stand now, it is the only known mode of therapy capable of eradicating the tumors, but there is no evidence that there is a "therapeutic window" between tumor and normal tissue radiosensitivity. It is the purpose of this protocol to define a new method of delivering the neutron radiation and to explore a range of neutron-photon doses within the context of this method.

1.3 General Outline of Study.

This protocol study is confined to patients with malignant gliomas who may or may not have undergone a surgical debulking procedure. Patients who have received chemotherapy, are undergoing concomitant chemotherapy, or for whom chemotherapy is being planned are not eligible for the study. While the use of chemotherapy for malignant gliomas is a topic of current investigational interest, its possible synergistic effect with neutron radiation with regard to either tumor or normal brain tissue damage would introduce an undesirable element of uncertainty into the study. However, patients who, after completing the planned course of radiation therapy, subsequently receive chemotherapy for progressing disease will continue to be followed.

In the previous protocol (RTOG 76-11), the neutron boost was delivered following the whole brain photon irradiation under the assumption that the radioresistant hypoxic component of the tumor would predominate at that time. However, this also

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subjected the surrounding normal brain tissue to a neutron dose concentrated in time. Furthermore, removing a portion of the hypoxic cell population throughout the treatment course might allow for a partial re-oxygenation of the remaining cells and make them more susceptible to the photon component of the planned dose. In this study, the neutron radiation will be delivered throughout the planned 6 weeks of treatment, but as in RTOG 76-11, it will be delivered only to the primary tumor volume. The patient will receive 4500 rad_{γ} in 150 rad_{γ} daily fractions to the whole brain delivered on a 5-day-a-week basis and on two days of the week will receive neutron "boost-field" irradiation. To take advantage of the presumed limited ability of the tumor cells to repair potentially lethal damage inflicted by the neutron radiation, on the days of the neutron radiation, [redacted] and then the photon treatment given within 3 hours. There will thus be 12 fractions of neutron radiation throughout the planned 6 weeks of treatment and the dose per fraction will vary according to the total neutron dose component. Neutron doses will be specified for the Seattle facility and will be scaled for the other participating institutions according to the relative RBE's of their neutron beams. Forty-five patients will be needed for the study. Patients will be randomized to receive 360 $rad_{n\gamma}$, 420 $rad_{n\gamma}$ or 480 $rad_{n\gamma}$ to the boost region. Based upon probable RBE's for neural tissue in the range of 4-5, the projected rad-equivalent doses are in the range normally used for photon therapy. The whole brain photon component has been reduced from 5000 rad_{γ} to 4500 rad_{γ} because it is felt that with CT scanning, geographic misses will be less of a problem than in the past.[9,15] The proposed searching grid for the total neutron dose is fairly tight since the RBE for normal neural tissue damage is somewhat uncertain and animal studies indicate a fairly sharp threshold for spinal cord damage for fast neutrons.[8] It is felt that 15 patients in each subgroup will allow for reasonable sampling and yet will

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allow the study to be completed within 2 years. Hence, the generated data could be used for protocol design for the new clinically-designed neutron treatment units.

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 normal benign tissue to mixed beam (neutron/photon) irradiation and to hopefully establish a neutron RBE for brain tissue.

3.0 PATIENT SELECTION

3.1 Patient Eligibility.

3.1.1. Histopathologically confirmed malignant gliomas: malignant glioma is a group of tumors variable called anaplastic astrocytoma, 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. The pathologic specimens will ultimately be reviewed by RTOG neuropathologists and be classified as to either anaplastic astrocytoma or glioblastoma in view of the prognostic significance demonstrated between these two categories.

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

3.1.3 Tumor must be supratentorial in location.

3.1.4 $\geq$ 16 years of age.

3.1.5 Patient or family must give informed consent. (Appendix I)

3.2 Patient Ineligibility.

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

3.2.2 Previous cancer except for non-melanoma skin cancers outside of the cranial region.

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

3.2.4 No histopathological confirmation of disease.

3.2.5 Patients who, for any reason, cannot be regularly followed by investigators.

3.2.6 Patients in whom metastatic disease in spinal cord or distant sites is detected or site of primary tumor is infratintoreal.

3.2.7 Patient < 16 years of age.

3.2.8 Patients who will undergo planned chemotherapy for other than progression of disease.

4.0 PRETREATMENT EVALUATION

In most cases this will have been prior to craniotomy. The patient workup should include the following:

4.1 Detailed neurologic examination including assessment of performance status to permit functional classification using the Karnofsky Performance Scale (see Appendix II).

4.2 Funduscopic and ophthalmological examination as indicated.

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4.3 Skull films.

4.4 Necessary imaging and/or contrast studies to optimally define the location and extent of the tumor including brain scan, CAT scan with contrast, echogram, cerebral arteriography and/or air studies, i.e., ventriculogram, pneumoencephalogram. An initial CT scan with contrast is required.

4.5 Chest X-ray.

4.6 Complete blood count (CBC).

5.0 RANDOMIZATION

5.1 To randomize a patient, the physician will call RTOG Operations Headquarters at (215) 574-3191 between 9 a.m. and 5 p.m., EST, Monday through Friday, and relate the following information:

- Protocol name.
- Institution referring patient.
- Neutron facility.
- Physician.
- Patient's name.
- Histologic grade of tumor (anaplastic astrocytoma or glioblastoma).

The physician, in turn, will receive a treatment assignment and project case number which will later be confirmed by mail.

6.0 RADIATION THERAPY

6.1 General Outline.

The patients on this study shall receive concomitant neutron and photon irradiation over an approximate 6-week period. The photon irradiation shall be delivered to the whole brain on a 5-day-a-week basis. The neutron irradiation shall be delivered using coned-down boost fields restricted to the primary tumor volume and shall be delivered on a 2-day-a-week basis.

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6.2 Photon Irradiation.

6.2.1 4500 rad_{γ} photon irradiation shall be delivered to the whole brain in 150 rad_{γ} fractions/6 weeks. The dose shall be calculated to midplane, and right and left lateral fields shall be used. Both fields are to be treated daily. The effective photon energy must be greater than 1 MeV but less than 10 MeV, ^{60}Co units with less than 80 cm SSD/SAD are not allowed. Electrons are not allowed.

6.2.2 Localization films will be obtained for the whole brain fields.

6.2.3 The whole brain is defined as the entire intracranial contents.

6.3 Neutron Irradiation.

6.3.1 Depending upon the randomization, either 360 $rad_{n\gamma}$, 420 $rad_{n\gamma}$ or 480 $rad_{n\gamma}$ shall be delivered in 12 fractions/6 weeks to the primary tumor volume. These doses are for the Seattle, Washington neutron facility and are to be scaled for other participating institutions as follows:

Seattle	GLANTA	FERMILAB	TAMVEC
360 $rad_{n\gamma}$	405 $rad_{n\gamma}$	446 $rad_{n\gamma}$	416 $rad_{n\gamma}$
420 $rad_{n\gamma}$	473 $rad_{n\gamma}$	520 $rad_{n\gamma}$	485 $rad_{n\gamma}$
480 $rad_{n\gamma}$	540 $rad_{n\gamma}$	595 $rad_{n\gamma}$	554 $rad_{n\gamma}$

The doses for the clinical cyclotron soon to be operational at M.D. Anderson Hospital can be scaled according to the RBE relative to the TAMVEC facility.

6.3.2 CT scan shall be used to determine boost volume and localization films of treatment fields.

6.3.3 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 1.5 cm but sparing as much brain as possible. The

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brain stem should be excluded if possible. This volume should then be irradiated with AP opposed, bilateral opposed, wedged pairs or whatever other technique will encompass this volume and be as sparing of uninvolved brain as possible.

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

6.3.5 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.

6.3.6 The boost dose as outlined in 6.3.1 shall be delivered to the target volume and whenever possible a dose variation of ± 10% within the target volume should be achieved. Fraction size may be varied by ± 10% to correct for missed treatments, 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.

7.0 DRUG THERAPY

Does not apply to this study.

8.0 SURGERY

Does not apply to this study.

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9.0 OTHER THERAPIES

Does not apply to this study.

10.0 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 entering the patient and initiating the treatment. Eligibility will be based on the institutional pathology report and the stratification performed after the central pathological review. The pathology slides will be submitted to RTOG Headquarters. Headquarters will remove all identifying marks and replace them with an identifying code number before submitting them to the study pathologist. This will ensure that the pathologist has no knowledge of treatment or survival. The pathologist will determine the histology from initial slides. It is this determination that will be used in the analysis done by the statistical center. The pathologist will review the autopsy slides to determine whether or not there was viable tumor or demyelination.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters.

	Time of Study				
Parameter	Prior to Therapy	During Therapy	At Completion	1 Month Post-treatment	3 Months During Follow-up
Neurological exam	x	Weekly	x	x	x
Skull films	x				
Chest X-ray	x				
Ophthalmological exam	x				
CBC	x	Every two weeks			
CAT scan	x[a]		x*	x	x
Air studies	x*				
Angiography	x*				
Brain scan	x*				x

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[a]Mandatory

*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.

11.2 Measurement of Specific Endpoints.

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

11.2.2 Survival will be measured from the time that treatment starts until death.

11.2.3 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.

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

11.2.5 Late radiation morbidity for brain will be scored at each follow-up assessment using the RTOG scale. (Appendix IV)

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12.0 DATA SUBMISSION

The following items are to be submitted to the RTOG Headquarters:

Data	Submitted
On study/initial evaluation form Treatment plan including central axis calculations Localization films (whole brain and boost)	Within 1 week of study entrance.
Radiotherapy form Copy of daily treatment record and calculations. Isodose distribution, if done (required for boost) Pathology report Diagnostic pathology slide(s)	Upon completion of treatment.
Follow-up form	Upon completion of treatment, at 3 month intervals thereafter and at death.
Autopsy Report for boost) Pathology slide from autopsy	If done.

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample Size.

This study is designed to search for a dose which results in the destruction of viable tumor without exceeding tolerable limits for normal tissue damage. Thus we would like to estimate the proportion of patients with complete response (i.e. tumor destruction) and the proportion with demyelination. A sample of size 15 in each group gives adequate precision to our estimates of these proportions as seen by the following table of approximate 90% confidence intervals for selected values of p.

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P = proportion of population with a given characteristic	90% confidence interval based on sample size of 15
.10	(.00, .20)
.30	(.13, .47)
.50	(.33, .67)
.70	(.53, .87)
.90	(.80, 1.00)

In addition, 15 patients provide a 79% chance of seeing any other complications which occur 10% of the time.

13.2 Randomization.

This study was originally designed to treat the first group of 15 patients with the 350 $rad_{n\gamma}$ dose, the next group with 420 $rad_{n\gamma}$ and the final group with 480 $rad_{n\gamma}$. The intent was to be able to abort the study in its early stages should the treatment effects of the lower doses become too morbid. However, it became apparent that accrual of patients would have been completed for the last group before such an assessment (based on autopsy findings) could have been concluded for the first group. It was decided, instead, to randomize patients to the three dose schedules. Based on our experience in 76-11 (in which a neutron boost of 480 $rad_{n\gamma}$ was given upon completion of whole brain photon irradiation) we do not feel that the proposed doses incur an excessive risk. Randomization protects against trends (over time) in patient characteristics and allows for comparison among the three dose schedules.

13.3 Feasibility/Accrual.

During the first half of 1980, Protocol RTOG 76-11 was accruing approximately 4 patients per month. If all institutions participate in this study, accrual objectives can be met within a year. If will take slightly longer if some facilities opt not to participate.

14.0 ADDITIONAL TREATMENT

14.1 General medical care. Note associated medical diseases which will require care, specifically as related to toxicity of therapy.

14.2 If there is evidence of increased intracranial pressure despite surgical decompression, the use of corticosteroids 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.

14.3 Infections: Antibiotics used for infection should be noted.

14.4 Pain: Analgesics as required.

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

14.6 All chemotherapy added at the time of first recurrence or relapse must be recorded.

14.7 Steroids may be given if clinically indicated.

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APPENDIX I

SAMPLE CONSENT FORM*

Purpose and Benefits

A new form of irradiation (neutron beam) has been developed which theoretically should be more effective than conventional X-ray irradiation (photons) for certain types of tumors. The purpose of this study is to determine the effectiveness of irradiating malignant tumors of the brain with photons and neutrons. 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 this study, you will receive photon whole brain irradiation 5 days per week for 6 weeks with 12 neutron treatments given to a reduced field 2 days per week concomitantly with the photon radiation therapy.

Routine follow-up, at intervals determined by your physician, will be scheduled at completion of therapy. Protocol assessment will be made every month for three months, and every three months thereafter. Follow-up sessions will consist of routine physical exam, and an assessment of any symptoms. Other procedures (brain scan, computed tomography scan) will be performed if indicated. The patient's medical records will be used in this study; copies of the radiotherapy record, pathology report, and pathology slides will be submitted to the study headquarters.

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*Sample consent form submitted by the Study Chairman.

Risks

The side effects of radiation may include nausea, vomiting, headache, blurred vision, convulsions, weakness, or a worsening of the symptoms you already have. Loss of hair from the scalp will always occur. Neutron beam irradiation is experimental, so not all possible side effects may be known. However, neutrons interact more strongly with non-tumor tissues than do photons and side effects may include scarring of fatty tissues and neurologic damage. The side effects from neutron beam irradiation may be more severe than those from conventional irradiation.

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 of normal workup, treatment, and follow-up are billed to the patient; neutron beam treatments will not be charged to you.

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 complications 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.

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

_____

Signature of Investigator 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 Date

_____

Signature of parent/legal guardian/
patient advocate

_____

Relationship (relative, close friend,
or someone who knows the subject well)

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APPENDIX II

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.

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APPENDIX III

FUNCTIONAL CLASSIFICATION

Class I	Able to work or to perform normal activities.
Class II	Able to carry out normal activities with minimal difficulty. Neurologic impairment does not require nursing care or hospitalization.
Class III	Seriously limited in performing normal activities. Requiring nursing care of hospitalization. Patient confiend to bed or wheelchair, or has significant intellectual impairment.
Class IV	Unable to perform even minimal normal activities, requires constant nursing care and feeding. Patient unable to communicate or in coma.

RTOG/EORTC Late Radiation Morbidity Scoring Scheme

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

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Grade 5: Death directly related to radiation late effect