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Fast neutron radiation therapy for glioblastoma multiforme

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Results of an RTOG study

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BETWEEN JANUARY 1977 AND SEPTEMBER 1980, 166 patients were entered on a RTOG protocol comparing neutron-boost radiotherapy with standard treatment for patients with glioblastomas. Eighty-three patients were randomized to receive a neutron boost and 83 to receive a photon boost after 50 Gy photon, whole-brain irradiation. Of these, six were ineligible and two were cancelled, leaving 158 patients available for analysis. The median survival for the neutron-boost group was 9.8 months, compared to 8.6 months for the photon-boost group. The difference is not statistically significant. Autopsies revealed actively growing persistent tumor in all photon-treated patients compared to no evidence of actively growing tumor in the majority of neutron-treated patients.

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Although uncommon when compared to other human malignancies, approximately 11,000 new cases of primary central nervous system tumors are reported each year.[1] With an incidence of 4.5 cases/100,000 population, 2% of all cancer-related deaths are caused by primary brain tumors. Forty-three percent of these tumors are malignant gliomas.[16]

High grade astrocytomas (glioblastomas and anaplastic astrocytomas) make up approximately 40% of the malignant gliomas, and are among the most lethal of all human malignancies.[2] The median survival for patients with these tumors treated with surgery and supportive care alone is only 14 weeks. Postoperative photon radiation therapy, with or without chemotherapy, was demonstrated in a randomized study conducted by the Brain Tumor Study Group to increase the median survival by 150% to 36 weeks; however, the 2-year survival rate remained less than 10%.[16] This has been confirmed by a recent cooperative study of the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group which demonstrated a median survival of 36–38 weeks for patients treated with postoperative radiation therapy alone.[8] The addition of postoperative adjuvant chemotherapy has been disappointing.[8,10,15–17]

Recently, in an attempt to increase the survival of these patients, hypoxic cell radiosensitizers have been combined with radiation therapy in several clinical trials. These studies are based on the premise that the failure of photon radiation therapy

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to cure high-grade astrocytomas might result from the significant population of radioresistant hypoxic cells known to be present in these tumors. Phase III studies are currently ongoing; however, a pilot study utilizing misonidazole was recently reported by the RTOG to have a median survival of only 39 weeks.[5]

Another approach to the treatment of high-grade gliomas is irradiation with high linear energy transfer (LET) particles such as fast neutrons, pi mesons, and heavy ions. These particles have two significant theoretical advantages over conventional photons: 1) a lower oxygen enhancement ratio (OER), and 2) a predominantly direct effect form of cell damage which is less susceptible to repair by tumor cells. The charged particles also have dose distribution advantages over photons. All of these theoretical advantages are potentially important in the treatment of high-grade astrocytomas.

Pilot studies were conducted with fast neutron beam radiation therapy in the treatment of high grade astrocytomas at the University of Washington and Hammersmith Hospital between 1973 and 1977. Thirty-six patients were treated at the University of Washington and 30 were treated at Hammersmith Hospital. All patients eventually died, and subsequent autopsy data revealed excellent tumor control with a better than 90% tumor sterilization rate. Those patients died from a diffuse gliosis and demyelinization of normal brain tissue resulting from an underestimation of the neutron relative biological effectiveness (RBE) for brain.[9] The median survival rates were not significantly different from those obtained in historical control, photon-treated patients.[6,11]

The high tumor sterilization rates reported in these studies with neutron therapy stand in marked contrast to those reported after conventional photon treatment. The tumor sterilization rates reported with photon radiation therapy are poor regardless of dose.[4,13] Based on this information, the RTOG designed a phase III, prospectively randomized study to test the effects of neutron irradiation given as a boost restricted to the tumor volume after whole brain photon irradiation. This paper reports the results of that study.

Materials and methods

Between January 1977 and September 1980, 166 patients with high-grade gliomas were entered on the RTOG Neutron Boost Glioma study. Patients who had histologically proven, supratentorial malignant glioma, Kernohan grades III or IV, were eligible provided they had given informed consent to participate in the study. Diagnosis was made by surgical removal which was grossly complete or incomplete, depending on the surgeon's judgment. Patients were excluded if they had conditions which would preclude completion of protocol therapy, such as neurologic deficit, concurrent major illness, or psychiatric impairment. Also excluded were patients under 16 years old, those with previous cancer (except limited, noncranial skin cancers), and patients with evidence of metastatic disease.

Eligible patients were randomized by calling a central office. Stratification was based on the histological grade of the tumor and the neutron facility at which treatments were to be administered if the neutron arm was selected. Prior to randomization, all patients had a detailed neurological examination and localizing contrast radiographic studies. Early in the study, cerebral arteriography was used to define the location and extent of the tumor. Later, CT scanning replaced arteriography.

Treatments

The treatments were as follows:

Photon boost (control). 50 Gy whole brain photon irradiation followed by a 15 Gy coned-down photon boost. The whole brain dose was given in 1.8–2 Gy daily fractions, 5 fractions per week, 9–10 Gy per week. The boost dose was administered in 8–10 fractions over 1½ to 2 weeks. Megavoltage equipment was used for all photon therapy.

TABLE 1

Administrative Information

	Treatment		
	Neutron Boost	Photon Boost	Total
Cases randomized	83	83	166
Ineligible	2	4	6
Cancelled	1	1	2
Analyzable Cases	80	78	158

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TABLE 2

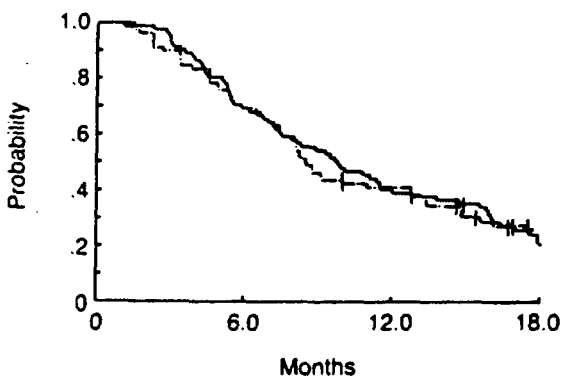
Facility RBE Adjusted Neutron Boost Doses

Facility	Machine	Neutron Reaction	RBE Adjusted Neutron Boost Dose
UW	Cyclotron	22 $MeV_{d\text{-}Be}$	4.5 $Gy_{n\gamma}$
GLANTA	Cyclotron	25 $MeV_{d\text{-}Be}$	4.5 $Gy_{n\gamma}$
MANTA	Cyclotron	35 $MeV_{d\text{-}Be}$	4.68 $Gy_{n\gamma}$
Tamvec	Cyclotron	50 $MeV_{d\text{-}Be}$	4.8 $Gy_{n\gamma}$
Fermi Lab	Cyclotron	66 $MeV_{p\text{-}Be}$	4.8 $Gy_{n\gamma}$

Neutron boost. 50 Gy whole brain photon irradiation followed by a coned-down neutron boost in a dose equivalent to 15 Gy. The whole brain dose was given in 1.8–2 Gy daily fractions, 5 fractions per week, 9–10 Gy per week. The boost dose was given in 6–8 fractions in 1½ to 2 weeks. The equivalent doses were based on the RBE for each facility.

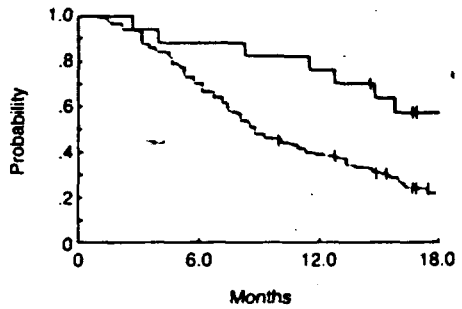
A total of 166 patients entered the study. Of these, six were ineligible and two were cancelled. Of the ineligible cases, five did not have the proper histologic types and one did not provide informed consent. The cases which were cancelled included one patient who expired before the onset of treatment and one who decided not to accept any treatment. There remain 158 analyzable cases representing 95% of the patients accrued to the study (Table 1).

Patients were referred to one of five participating neutron facilities: the University of Washington, GLANTA, MANTA, TAMVEC, and the Fermilab. The methods of neutron production and RBE adjusted dose recommendations for the neutron boost are listed in Table 2.



Treatment	Alive	Dead	Total	Median
—— NEUTRON	12	68	80	9.8
-·-·- PHOTON	16	62	78	8.6

FIGURE 1. Survival by treatment.



Histology	Alive	Dead	Total	Median
—— ANAPLASTIC ASTROCYTOMA	8	9	17	24.6
-·-·- GLIOBLASTOMA	17	102	119	8.8

FIGURE 2. Survival by histology.

Use of corticosteroid therapy was permitted to control increased intracranial pressure. Analgesics as required for pain and antibiotics as needed for infection were also permitted. Use of any of these drugs was noted.

Patients were seen for follow-up visits every 3 months until death. At these visits, laboratory parameters (including results from either a brain scan or CT scan), additional treatments, and neurologic signs and symptoms were recorded. The primary endpoint of the study was survival time.

Data quality was insured by carefully checking forms at the RTOG Statistical Center. The radiotherapy treatment plans were reviewed by a panel of radiotherapists. Histologic diagnosis was made

TABLE 3

Nelson Classification System

Astrocytoma:	Uniform cells closely resembling mature, resting or reactive, nonneoplastic astrocytes; moderate cell density; mitoses absent or very rare.
Anaplastic astrocytoma:	Multifocal or diffuse cellular and/or nuclear pleomorphism; increased cell density; increased mitotic figures; increased vascular prominence; *no tumor necrosis.*
Glioblastoma multiforme:	Features of anaplastic astrocytoma plus one or more foci of coagulation necrosis involving neoplastic astrocytes.

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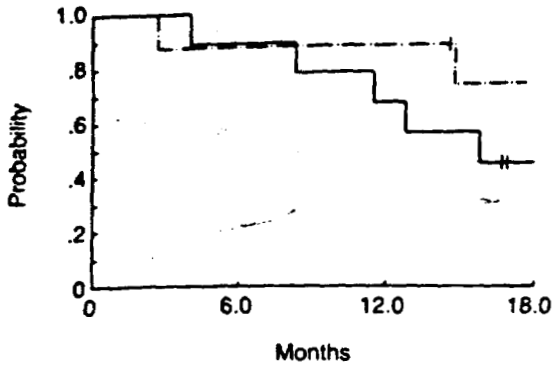
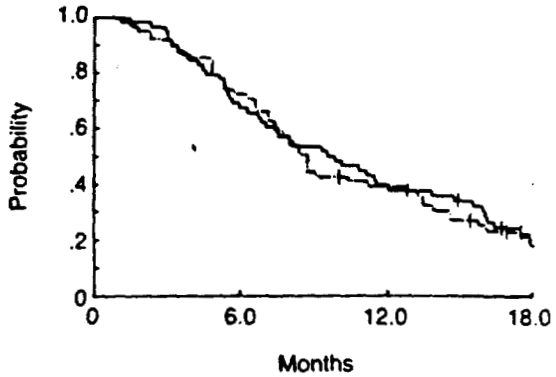


Treatment	Alive	Dead	Total	Median
—— NEUTRON	3	6	9	15.8
-·-·- PHOTON	5	3	8	26.3

FIGURE 3. Survival by treatment: anaplastic astrocytoma only.



Treatment	Alive	Dead	Total	Median
—— NEUTRON	7	51	58	9.6
-·-·- PHOTON	10	51	61	8.5

FIGURE 4. Survival by treatment. glioblastoma multiforme only.

from an operative specimen forwarded to the study neuropathologist. All relevant data for each patient were summarized by the statistical center and verified by a review of the patients' records by the study chairman.

Survival comparisons will be made using the logrank test. Survival curves were calculated using the life table method of Kaplan and Meier. The proportional hazards regression model of Cox is used in a step-up manner to find the variables with the greatest prognostic significance.

Results

Figure 1 plots the survival curves by treatment. The median survival for patients treated with a neutron boost was 9.8 months, compared to 8.6 months for photon-treated patients. A stepwise Cox model was used to determine prognostic variables. In order of importance, the variables were performance status, age, motor deficit, and cranial nerve deficit. There were no significant differences in either the uncorrected analysis or the analyses corrected for prognostic variables.

A central pathology review was required for all surgical specimens by an RTOG neuropathologist. Based on its improved prognostic value, the histologic classification system described by Dr. James Nelson was utilized in place of the Kernohan system (Table 3).[7,12] Although the numbers are relatively small, this study appears to confirm the results of the joint RTOG–ECOG trial with respect to the prognostic difference between histologic diagnosis of anaplastic astrocytoma and glioblastoma multiforme. Figure 2 presents survival curves by diagnosis. Figures 3 and 4 show survival by treatment for anaplastic astrocytoma and glioblastoma multiforme, respectively. The differences are not significant ($p = 0.23$ for anaplastic astrocytoma and $p = 0.92$ for glioblastoma multiforme).

Table 4 summarizes the results of the radiotherapy review. The compliance rates are ap-

TABLE 4

Protocol Compliance

Overall Evaluation	Neutron Boost		Photon Boost		Total	
	Number	Percent	Number	Percent	Number	Percent
Per protocol	54	68	48	62	102	65
Minor variation—acceptable	14	17	19	24	33	21
Major variation—unacceptable	12	15	11	14	23	15

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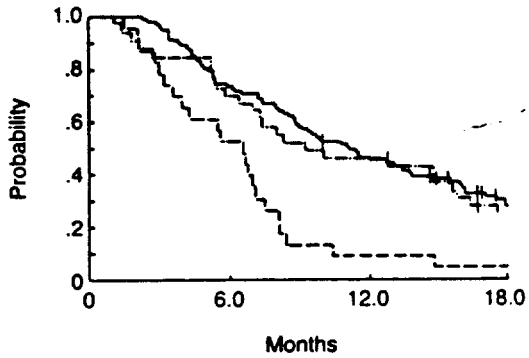
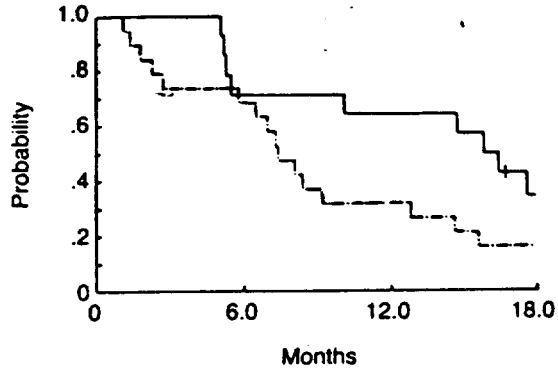


Compliance	Alive	Dead	Total	Median
PER PROTOCOL	21	81	102	11.1
MINOR VARIATION	6	27	33	9.2
MAJOR VARIATION	1	22	23	6.6

FIGURE 5. Survival by protocol compliance.



Treatment	Alive	Dead	Total	Median
NEUTRON	4	10	14	16.1
PHOTON	2	17	19	7.4

FIGURE 6. Survival by treatment: minor treatment variation only.

proximately the same in the two groups ($p = 0.57$). Figure 5 shows the overall survival curves by protocol compliance. The differences seen are significant ($p = 0.001$). It is not possible to ascribe causality to the relationship between major violations and poor survival experience, i.e., one cannot say whether the patients' deterioration resulted from inadequate treatment or if treatments were curtailed as a result of the patients' deterioration.

Figure 6 plots survival curves by treatment for patients with minor treatment variations ($p = 0.07$). Minor variations were caused by deviations in the

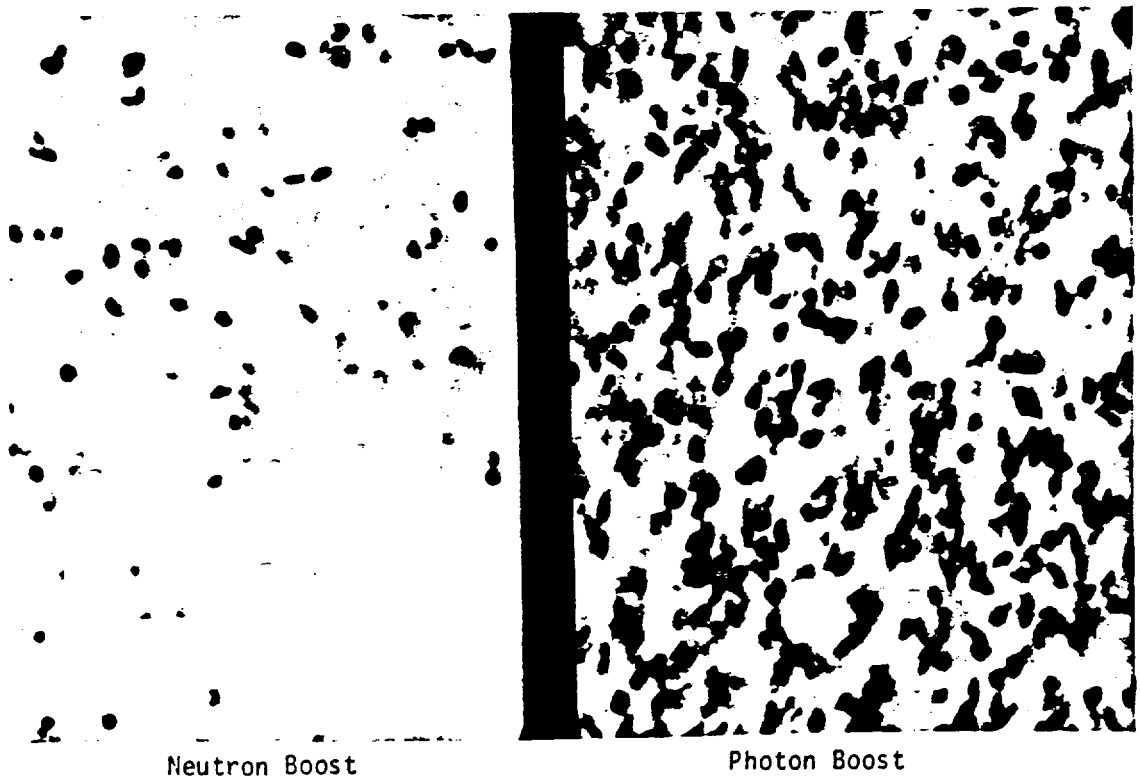


FIGURE 7. Autopsy findings: neutron boost—photon boost.

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treatment time course or dose to the tumor volume of ±10% of that prescribed by the protocol. Although suggestive, extensive analysis using the Cox model with neutron dose as a covariate failed to detect a statistically significant influence of dose.

Autopsies were reported for approximately 20% of the deaths. Twelve autopsies were performed on patients treated with neutrons and 12 were performed on photon-treated patients. In nine out of 12 autopsied cases treated with a neutron boost, significant necrosis of the primary tumor was observed with only sparsely scattered bizarre cells present in the original tumor site. No infiltrative, proliferating tumor masses could be identified. This finding stands in sharp contrast to the photon-treated patients, all of whose autopsy specimens revealed infiltrating, proliferating, viable tumor masses with an actively proliferating vascular component surrounding central necrotic regions (see Fig. 7). Whether the bizarre cells seen in the neutron-treated patients represent reactive astrocytes or perhaps a radioresistant tumor component is not known at this point, but it is clear that there was no expansively growing tumor component resulting in the patients' deaths. Death in these patients is thought to be due to the consequences of neutron effects on normal brain tissues.

Discussion

The rationale for the use of fast neutron radiation therapy in treatment of patients with glioblastomas lies in the potential for neutrons to eradicate the population of photon-radioresistant hypoxic cells known to be present in these tumors. This finding was demonstrated in pilot studies both in the United States and in Europe.[3,6,15] The significant finding of this study is that neutron doses as low as 4.5 $Gy_{n\gamma}$ given after 50 Gy_{γ} whole brain photon irradiation can result in the destruction of these tumors.

While there is evidence that neutron radiation as delivered in this study is capable of eradicating high-grade gliomas, patients are still dying of the biological effects of fast neutrons on normal brain tissue. These effects have been previously described by Shaw and others.[6,11,14] Nevertheless, at the present time, fast neutron radiation therapy is the only known mode of treatment capable of eradicating these tumors consistently. It is hoped that further modifications of dose–time relationships and neutron–photon mixes will lead in the future to prolonged survival and possibly even to cure for patients with this lethal disease.

ACKNOWLEDGMENT

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