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● *Special Feature*

RADIATION THERAPY ONCOLOGY GROUP (RTOG) SURVIVAL DATA ON ANAPLASTIC ASTROCYTOMAS OF THE BRAIN: DOES A MORE AGGRESSIVE FORM OF TREATMENT ADVERSELY IMPACT SURVIVAL?

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The RTOG has sponsored several studies for malignant gliomas of the brain that have included tumors classified as either glioblastoma multiforme (GBM) or anaplastic-atypical astrocytoma (AAF) under the Nelson schema. Glioblastoma multiforme, the more aggressive histology, has done poorly under all forms of treatment having a typical median survival of 8–11 months. The less common and less aggressive anaplastic-atypical astrocytoma seems to show a survival that worsens with treatment more aggressive than standard radiotherapy. All patients in this report have had their tumors centrally reviewed by a RTOG neuropathologist and have had the diagnosis of anaplastic-atypical astrocytoma confirmed. We compare three patient groups: standard photon radiotherapy from the 60 and 70 Gy arms of RTOG 74-01/ECOG 1374 and from the 65 Gy control arm of RTOG 76-11; radiation therapy and chemotherapy from RTOG 74-01/ECOG 1374 (60 Gy + BCNU and 60 Gy + MeCCNU + DTIC) and from RTOG 79-18 (60 Gy + BCNU); and photon irradiation plus a neutron boost from RTOG 76-11 and RTOG 80-07. There are 47 analyzable cases treated with photons alone, 78 analyzable cases treated with photons + chemotherapy, and 38 analyzable cases treated with photons + neutron boost. Median survival for the three groups of patients is, respectively, 3.0 years, 2.3 years, and 1.7 years. Actuarial survival curves are presented for each subgroup of patients and then for the patient subgroups further broken down by major prognostic variables—age and Karnofsky performance status. In each "better prognostic category," the median survival decreased as the "aggressiveness" of the treatment increased. The implications of these findings for future clinical trials is discussed.

Neutron Radiotherapy, Anaplastic Astrocytoma, Glioma.

INTRODUCTION

In the United States alone there were approximately 10,200 deaths in 1987 attributed to central nervous system malignancies (13). The majority of these were due to malignant gliomas of the brain. These tumors present a particular challenge to the radiation oncologist since local tumor persistence and/or recurrence followed by inexorable growth tends to be the primary failure mode and cause of death.

In attempts to improve local control, efforts over the years have focused on increasing the dose of conventional radiotherapy delivered to the tumor, adding chemotherapeutic agents which cross the blood-brain barrier to standard radiotherapy, utilizing hypoxic cell sensitizers, or using high linear energy transfer (LET) radiation such as fast neutrons. In general, these efforts have met with little or no success in terms of increased patient survival. One consistent finding in these studies is the important prognostic significance of tumor histology. Initially, the Kernohan schema (6) was used to segregate astrocytomas of the brain into four categories, but then the Nelson schema (10) was shown to be of greater prognostic significance. In the latter approach, malignant gliomas of the brain are divided into three categories: well-differentiated astrocytomas, anaplastic-atypical astrocytomas (AAF), and glioblastoma multiforme (GBM). The last two categories comprise the more aggressive lesions and clinical trials testing various experimental therapies are generally restricted to them. The difference between AAF and GBM relates to the presence of necrosis which occurs in the latter but not in the former (10). In most series, patients with AAF tend to account for about 15–20% of entered cases and in comparing various treatment arms,

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it is important to make sure that they are balanced in regards to this histological distinction. Moreover, this subgroup of patients provides a unique test of the long-term morbidity of various treatment approaches.

In this paper we will analyze the long-term survival data of patients with tumors confirmed on central pathology review as being AAF who were treated on Radiation Therapy Oncology Group (RTOG) protocols designed to test different approaches to the treatment of malignant gliomas: (a) photon radiation alone, (b) photon radiation + chemotherapy, (c) photon radiation + chemotherapy + misonidazole, and (d) photon radiation + neutron radiation. In some sense as one goes from approach (a) to approach (d), the treatment becomes "more aggressive" and we will see that this, unfortunately, *correlates with decreased survival* in patients with AAF. In this context we will use "more aggressive" to refer to a more complicated and/or more comprehensive form of treatment with greater inherent risks to the patient. This seems to hold particularly in the favorable subgroups of "younger" patients and "better" Karnofsky performance status patients. It was also unfortunate that none of these approaches made any significant difference for the subgroup of patients with the more virulent, GBM tumors.

METHODS AND MATERIALS

Patients discussed herein were entered on one of four RTOG protocols. Final reports presenting the detailed results as far as the primary study endpoints were concerned have been previously published and so this information will not be repeated here (1, 4, 7, 9). To be eligible for one of these studies, patients had to have a supratentorial, malignant glioma. The pathology for all the patients was centrally reviewed by one of us (J.S.N.) and classified as to either GMB or AAF (10). Only those patients with the latter histology will be considered in this paper. The design of the four studies and further patient eligibility criteria are outlined below.

RTOG 74-01/ECOG 1374

This was a study done in conjunction with the Eastern Cooperative Oncology Group (ECOG). It was a four-armed study with patients being randomized to either (1) 60 Gy whole brain radiation, (2) 60 Gy whole brain radiation + 10 Gy tumor boost, (3) 60 Gy whole brain radiation + carmustine (BCNU) at 80 mg/m^2 on days 1–3 and subsequently at 240 mg/m^2 every 6–8 weeks (after 3/76, toxicity led to a dose modification to 80 mg/m^2 days 1–3 every 8 weeks), or (4) 60 Gy whole brain radiation + semustine (MeCCNU) + dacarbazine (DTIC) (before 6/75 the DTIC was given at 175 mg/m^2 for 5 days at 4-week intervals and MeCCNU was given at 150 mg/m^2 orally every 8 weeks beginning on the 5*th* day of alternating courses of DTIC; because of toxicity, the DTIC dose was later reduced to 150 mg/m^2 and the MeCCNU to 125 mg/m^2). The chemotherapy was to be given for 2 years following radiotherapy. The radiation was given at the rate of 1.7–2.0 Gy per fraction on a 5 day-a-week basis. Patients had to be in the age range of 18–70 years and have a Karnofsky performance status (KPS) of ≥40. Further study details are found in the original report (1).

RTOG 79-18

This was a two-armed study that randomized patients to either (1) 60 Gy whole brain radiation + carmustine (BCNU) at 80 mg/m^2 IV on days 3, 4, and 5 and then every 8 weeks for 2 years or (2) 60 Gy whole brain radiation + BCNU + misonidazole with the radiation schedule being tailored to the misonidazole delivery. An oral dose of 2.5 gm/m^2 of misonidazole was given on Mondays with 4 Gy being given 4 hr later and then 1.5 Gy was given on Tuesdays, Thursdays, and Fridays. This was repeated for 6 weeks resulting in a total dose of misonidazole of 15 gm/m^2 and 51 Gy to the brain. Following this, five additional treatments of 1.8 Gy were given to bring the total dose to 60 Gy. On arm (1) the radiation was given conventionally at 1.7–2.0 Gy per fraction 5-days-a-week. Patients also had to have a KPS of at least 40, be between 18–70 years old and have normal hematologic status, liver and renal function. Only patients randomized to arm (1) are included in the present analysis. Additional details are noted in Reference 9.

RTOG 76-11

This was a radiation-only study that compared the effects of a neutron boost versus a photon boost. Patients received 50 Gy whole brain photon irradiation in 1.8–2.0 Gy fractions on a 5 day-a-week basis followed by either (1) 15 Gy photon boost or (2) an RBE-adjusted neutron boost to a dose thought to be equivalent to 15 Gy photon irradiation. The photon boost was given in 8–10 fractions over 1.5–2 weeks and the neutron boost was given in 6–8 fractions over 1.5–2 weeks. Further details of the study are given in Reference 4.

RTOG 80-07

This was a randomized study that searched for a safe neutron boost dose that would also give a reasonable probability of irradicating the tumor. This study was based on the observation that in the neutron boost subgroup of RTOG 76-11, there was a high percentage of patients who died of radiation side effects without any evidence of tumor progression. In RTOG 80-07, patients received the neutron irradiation throughout the entire course of radiotherapy using a "field-within-a-field" technique. Patients received 45 Gy whole brain photon irradiation at 1.5 Gy/fraction, 5-days-a-week and on 2 non-successive days received neutron boost irradiation prior to and within 3 hr of the photon irradiation. The randomization schema was complex but eventually six different dose levels were tested 3.6 $Gy_{n\gamma}$, 4.2 $Gy_{n\gamma}$, 4.8 $Gy_{n\gamma}$, 5.2 $Gy_{n\gamma}$, 5.6 $Gy_{n\gamma}$,

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Table 1. Administrative data of the respective studies

	RTOG 7401/ECOG 1374		RTOG 7611		RTOG 7918	RTOG 8007
	Photons only	Photon + chemo	Photon only	Photon + neutron	Photon + chemo	Photon + neutron
Total entered	288	351	83	83	160	203
Ineligible/cancelled/ inevaluable	23	32	5	3	13	13
No onstudy data	5	4	0	0	0	0
Properly entered	260	315	78	80	147	190
No follow-up	0	1	0	0	0	0
No pathology/wrong pathology	22	32	8	11	2	6
GBM cases	199	230	62	60	119	155
Analyzable AAF cases	39	52	8	9	26	29

and 6.0 Gy_{nT}. The neutron boost was given in 12 fractions over the 6 weeks that the whole brain photon irradiation was given. Patients had to be greater than 16 years old and have a neurological function class between I–III. Further details of the study and the rationale for its design are given in the original report (6).

For the purpose of this study, we will combine the patients into three groups:

a. Photons alone—these patients come from arms (1) and (2) of RTOG 74-01/ECOG 1374 and the photon boost arm of RTOG 76-11;
b. Photons + chemotherapy—these patients come from arms (3) and (4) of RTOG 74-01/ECOG 1374 and arm (1) of RTOG 79-18; and,
c. Photons + neutron boost—these patients come from the neutron boost arm of RTOG 76-11 and all six arms of the dose-searching study RTOG 80-07.

The administrative data for these protocols is summarized in Table 1. The bottom line of the table gives the number of analyzable cases that each study contributes to the present report. It was necessary to "pool" the patients because the number of AAF patients was limited in any given study. The pretreatment characteristics of the combined patient groups are listed in Table 2. Note that combining patients from different protocols in this way can lead to an imbalance among prognostic factors such as age and KPS because the patients were not randomly assigned into the three groups we are analyzing. We will attempt to account for this in part by subset analysis according to the relevant variables.

The survival curves in the next section were calculated using the Kaplan-Meier method (5) and differences between curves analyzed using the chi-square (log rank) test with two-sided differences (8, 11). Follow-up times are measured from the initiation of therapy. A Cox stepwise analysis (2) was used to determine prognostic variables relating to survival and linear trend testing was used to compare the changes among the three pooled subgroups (12).

RESULTS

The major endpoint considered in this paper is overall survival. Figure 1 shows patient survival as a function of years from entry into the study. The median survival is 3.0 years for the patients treated with photons alone, 2.3 years for the patients treated with photons and chemotherapy, and 1.7 years for the patients treated with photons

Table 2. Pretreatment characteristics of the three patient subgroups

	Photons only (N = 47)		Photons + chemo (N = 78)		Photons + neutrons (N = 38)	
	No.	%	No.	%	No.	%
Age						
16–39	26	55	29	37	19	50
40–59	17	36	39	50	12	32
60+	4	9	10	13	7	18
Prior surgery						
Biopsy only	18	38	17	22	15	39
Partial resection	25	54	42	54	20	53
Total resection	3	6	15	19	2	5
Other	1	2	2	2.5	1	3
Unknown	0	0	2	2.5	1	3
KPS						
<70	19	40	27	35	11	29
80–100	28	60	51	65	27	71
Neurologic function						
Work	25	53	31	40	16	42
Home	15	32	38	49	20	53
Hospital	6	13	9	11	2	5
Coma	1	2	0	0	0	0

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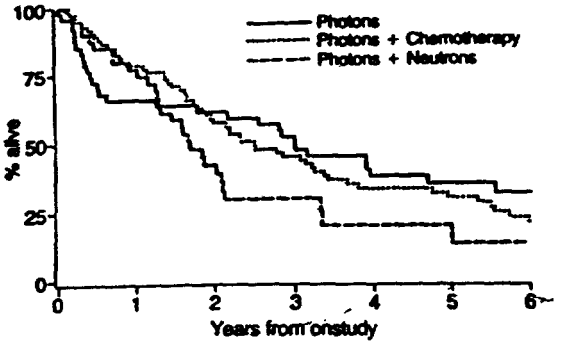

Fig. 1. Patient survival as a function of time from entry onto the respective study. The group treated with photons alone is shown as the solid curve, the group treated with photons and chemotherapy is shown as the dotted curve, and the group treated with photons and a neutron boost is shown as the dashed curve. All evaluable patients with the diagnosis of anaplastic astrocytoma are included in these plots.

and neutrons. Assuming equivalent patient populations, these curves are not statistically different ($p = 0.21$) (8, 11). Survival data is also shown in a tabular form in Table 3 to facilitate numerical comparison at various time intervals. The number of patients at risk for each time interval is also indicated in the table.

All of the studies (1, 4, 7, 9) individually used a Cox step-wise analysis (2) to identify the major prognostic factors relating to survival. Age and Karnofsky performance status were found to be important in all studies. A Cox analysis on the combined data set confirmed age and Karnofsky status as prognostic factors and also identified neurological function class as significant in relation to survival. Although the individual studies were stratified (and balanced) according to the major prognostic factors, once treatment arms from the various studies are combined, this is not necessarily the case. Review of Table 2 shows some obvious differences. To reduce possible biasing from this, we next consider separately the most favorable patient subsets in each treatment category.

Table 3. Tabular display of patient survival for the three patient subgroups

	Photons (N = 47)		Photons + chemo (N = 78)		Photons + neutrons (N = 38)	
Time (years)	No.	%	No.	%	No.	%
0	47	100	78	100	38	100
1	29	65	59	78	29	76
2	26	61	42	56	14	41
3	22	51	31	44	9*	29
4	16	37	25	36	4*	19
5	13	35	17	29	3*	19
6	9*	31	11	20	2*	13
Dead/total	36/47		59/78		29/38	
Median survival	3.0 years		2.3 years		1.7 years	

* Estimates may be unreliable because of small patient numbers.

Figure 2 shows patient survival for the subset of patients under 40 years of age. There were 26 patients in this category treated with photons alone, 29 patients treated with photons and chemotherapy, and 19 patients treated with photons and a neutron boost. Respective median survivals are 5.1 years, 3.2 years, and 2.1 years. The curves themselves are not statistically different ($p = 0.15$), but there is a linear trend ($p = 0.06$) of decreasing survival going from photons alone to photons + chemotherapy to photons + neutrons. Comparing only the photon curve versus the photons + neutrons curve, the p-value is 0.07; comparing photons alone to photons + chemotherapy the p-value is 0.23. Note that the differences between the median survivals in this "more favorable" subgroup are larger than in the overall series. There were no clear trends in the other age groups. Patients in the middle age group (40–59 years) had respective median survivals of 0.5 years, 2.2 years, and 1.7 years ($p = 0.11$). Comparing photons to photons + neutrons was not suggestive of any differences; comparing photons to photons + chemotherapy, the p-value was 0.06 in favor of the addition of chemotherapy. There were too few patients in the oldest group (≥60 years) to generate reliable median survivals as a function of treatment method.

Figure 3 shows patient survival for the subset of patients having a favorable KPS ≥ 80. There were 28 patients in this category treated with photons alone, 51 patients treated with photons + chemotherapy, and 27 patients treated with photons and a neutron boost. Respective median survivals are 3.9 years, 3.1 years, and 2.1 years. These curves are not statistically different (linearized $p = 0.09$). Comparing only the photon curve and the photon

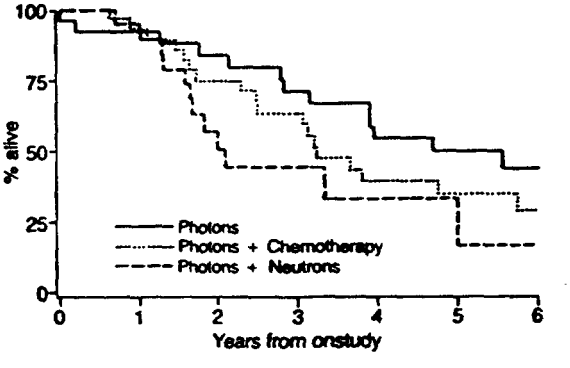

Fig. 2. Patient survival as a function of time from entry onto the respective study for patients in the most favorable age subgroup (less than 40 years old). The group treated with photons alone is shown as the solid curve, the group treated with photons and chemotherapy is shown as the dotted curve, and the group treated with photons and a neutron boost is shown as the dashed curve.

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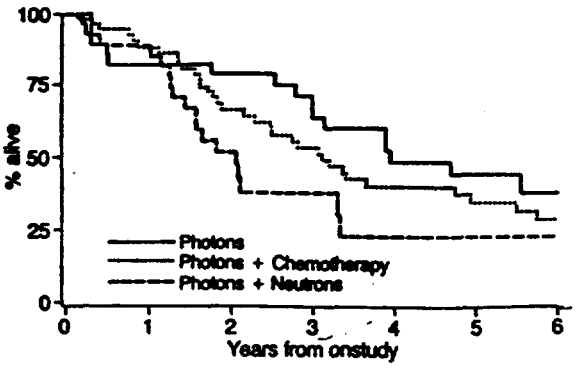

Fig. 3. Patient survival as a function of time from entry onto the respective study for patients in the most favorable KPS subgroup (greater than or equal to 80). The group treated with photons alone is shown as the solid curve, the group treated with photons and chemotherapy is shown as the dotted curve, and the group treated with photons and a neutron boost is shown as the dashed curve.

+ neutron curve, the p-value is 0.08; comparing the photon curve to the photon + chemotherapy curve gives a p-value of 0.61. There were no clear trends in the subgroup with KPS $\leq$ 70 which showed respective median survivals of 0.4 years, 1.6 years, and 0.9 years.

DISCUSSION

In this paper, we have reviewed the survival data on patients with the confirmed histological diagnosis of AAF (10) of the brain who were treated on various RTOG protocols for malignant gliomas. The intent of these protocols was to move towards a more aggressive form of treatment in an attempt to improve survival. The protocols were open to both AAF and the more malignant GBM (10). Review of the protocol reports shows *no difference* in the survival of patients with the confirmed diagnosis of GBM which ranged from 7.7–8.9 months on RTOG 74-01/ECOG 1374 (1), from 10.3–10.7 months on RTOG 79-18 (9), from 8.5–9.6 months on RTOG 76-11 (4), and was 9.9 months on RTOG 80-07 (7). The patients with the diagnosis of AAF, however, seemed to show a trend towards reduced survival on experimental arms when compared with either historical data or a photon control arm (if present in the protocol). The problem is that this trend did not achieve statistical significance because of the relatively small number of patients with this diagnosis. To further investigate this trend, we have combined patients from these protocols by categorizing their treatment as either photon irradiation alone, photons + chemotherapy, or photons + neutron boost. The trend was definitely towards a decreased survival as one moved away from the "standard" treatment of photon irradiation alone but again, because of small patient numbers, statistical significance was not achieved. This "lumping" approach may smear the prognostic stratification variables resulting in an imbalance in the lumped groups. To test this effect, we looked separately at the better prognostic categories of patients who were younger than 40 years and who had the best Karnofsky performance status. In each instance, the linear trend of a more aggressive form of treatment resulting in decreased survival was evident.

Further information is present if one considers the published results of the experimental arm of RTOG 79-18 (9) wherein the addition of misonidazole to photon irradiation + BCNU chemotherapy resulted in a decrease in the median survival of the anaplastic astrocytoma subgroup from 30.3 months to 13.2 months. Note that the time-dose schedule of the radiation therapy was altered on the misonidazole arm and so part of the deleterious effect might be due to this. This data is compared with the median survival results of our present analysis in Table 4. A more complete analysis of the effect of misonidazole in this patient population is in progress (3).

While the measured differences are not statistically significant due to the number of patients at risk (even in the pooled data), we believe the trend pointed out in this paper is real. Hence, we are led to the conclusion that attempts to improve patient survival for high grade gliomas of the brain have not changed survival at all for the more virulent histology of glioblastoma multiforme and have adversely impacted survival for patients with the less virulent histology of anaplastic-atypical astrocytoma with the favorable prognostic factors of age < 40 years and KPS of 80–100. There is an indication in the study reports (1, 4, 7, 9) that some patients treated with a neutron boost had histopathological evidence of tumor sterilization while patients treated with photons ± chemotherapy tended to die of progressive tumor. A detailed analysis of the autopsy information is currently in progress.

These results must be considered in future protocol design. One avenue might be to restrict patient entry to glioblastoma multiforme alone, but this might totally obscure any deleterious late effects of treatment in a patient population having a longer life expectancy. On the other hand, one might decide to include patients with anaplastic-atypical astrocytomas in future studies, but then "informed consent" should clearly point out the increased risk of side effects. The implications for future protocols studying even less aggressive histologies such as well-differentiated astrocytomas or oligodendrogliomas are even more profound.

Table 4. Summary of median survival date (years) from various patient subgroups

Photons	Photons + chemotherapy	Photons + chemotherapy + misonidazole	Photons + neutrons
3.0	2.3	1.2	1.7

Note: The data for photons + chemotherapy + misonidazole is from Reference (9). All patients with the diagnosis of anaplastic astrocytomas are included.

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