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GLIOBLASTOMA MULTIFORME

AN ANALYSIS OF THE RESULTS OF POSTOPERATIVE RADIOTHERAPY ALONE *VERSUS* RADIOTHERAPY AND CONCOMITANT 5-FLUOROURACIL*

(A Prospective Randomized Study of 32 Cases)

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OVER the past decade several clinical and basic research articles have appeared in the literature concerning the possible additive or potentiating effects of 5-fluorouracil (5-FU) on radiation therapy of certain neoplasms, although most of the studies are not prospectively randomized and there is little conclusive evidence concerning the ultimate effects on survival.[1,2,4,8,9,14,22] In addition, while there have been numerous articles concerning the effects of combined therapy of head and neck, lung and bladder neoplasms,[6,11,12,18] there is little information concerning the effects of combined chemotherapy and radiotherapy upon primary malignant brain tumors. In an attempt to evaluate these parameters, especially with reference to intracranial neoplasms, a prospectively randomized study of the effects of 5-FU and concomitant radiotherapy on the postoperative survival of patients with documented glioblastoma multiforme was undertaken at the University of Wisconsin Medical Center during the period January 1962 through December 1966. This was a cooperative study among the Divisions of Neurological Surgery, Radiotherapy and Clinical Oncology.

MATERIAL AND TREATMENT POLICIES

During the indicated period 32 patients were prospectively randomized and entered into this series. Seventeen patients received radical supervoltage radiotherapy and 15 were treated with radical supervoltage radiotherapy and concomitant 5-FU therapy. This study was not specifically designed to prospectively attempt to evaluate the merits of routine postoperative radiotherapy so that a surgery only group was not added to the randomization. No patients were admitted to this study who were 77 years of age or older or gave a prior documented history of a malignant neoplasm, other than skin cancer.

The tumor grades, classified by our Department of Surgical Pathology according to Kernohan into astrocytoma Grade 3 and Grade 4 (glioblastoma multiforme), were fairly comparable in both groups (Table 1), although the over-all incidence of Grade 3 tumors is higher than reported in most series.[20] The tumor location was supratentorial in all cases in this series as one might expect (Table II). All cases were surgically verified, and an attempt at gross complete removal was made in all but 2 patients in the radiotherapy group and 3 patients in the combined therapy group. These 5 patients, however, were biopsied. All patients originally entered into this randomized study have been included for analysis and no patient has been lost to detailed follow-up evaluation. Seven females were treated by radiotherapy alone and 4 female patients received combined 5-FU and radiation therapy. The 2:1 incidence of males to females conforms to the usual sex distribution reported in most series. The average patient age in the radiotherapy only group was 49 years (30–63), and 50

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TABLE I

DISTRIBUTION OF PATIENTS BY TUMOR GRADE IN BOTH TREATMENT GROUPS

Treatment Group	Grade	
	3	4
Radiotherapy	6	11
Combined Therapy	8	7
Total	14	18

TABLE II

LOCATION OF TUMOR (PRIMARY)

Site	Radiotherapy	Combined Therapy
Frontal	2	4
Frontotemporal	1	1
Frontoparietal	4	2
Parietal	2	0
Temporoparietal	2	1
Parietooccipital	1	1
Temporal	3	6
Occipital	2	0

years (19–66) in the group receiving combined therapy.

RADIOTHERAPY TECHNIQUE

The vast majority of patients were treated on our cobalt 60 teletherapy unit, half value layer (HVL) 12 mm. Pb at a source skin distance (SSD) of 95 cm. Three patients in each treatment group were treated on our 1 mev. resonance transformer unit, HVL 3.4 mm. Pb, at target skin distance of 70 cm. In order to vary as few parameters as possible, the radiotherapy techniques were kept relatively simple and uniform. Parallel opposing coplanar portals usually measuring 12×18 cm. were employed to bring the total supratentorial brain dose to a minimum of 5,000 rads in most cases, over 6 to 7 weeks.

Sixteen patients in the irradiation only group completed the full course of radiotherapy. Except for 1 patient who developed a severe wound infection after receiving a tumor dose of only 1,700 rads, the remaining patients received an average tumor dose of 4,940 rads minimum (4,000–5,170) over an average of 42 days (34–58). Fourteen patients receiving radiotherapy and 5-FU completed the full course of combined therapy. One patient in this group died of postresectional complications after a tumor dose of only 460 rads had been delivered. The remaining combined therapy patients received an average tumor dose of 4,930 rads minimum (4,340–5,090) over an average of 45 days (34–52). It is interesting to note that the concomitant administration of 5-FU did not result in a requirement for increased radiotherapy protraction or a significant reduction in total dosage.

CHEMOTHERAPY TECHNIQUE

The 5-fluorouracil (5-FU) was administered intravenously by the rapid "push-injection technique" to the 15 patients randomized to receive the drug. A single "course" was given, the initial "full dose" of 10 mg./kg. being injected on the first day of radiotherapy and for 2 subsequent days with a "half dose" of 5 mg./kg. on the fourth day to provide a full "loading dose." The 5-FU in concentrated form (50 mg./cc.) was always injected before the radiotherapeutic treatment (usually 30–60 minutes prior to exposure) in order to standardize the technique and eliminate any possible variance due to timing of administration of the drug and the exposure to ionizing radiation, although there is as yet no direct evidence to indicate that this is necessary for this agent since it does not appear to be a true "radiosensitizer." At that time it was our feeling that the fluorinated pyrimidines had to be given to the point of toxicity in order to be clinically effective. Also there is considerable clinical and basic evidence that there is more degradation of 5-FU when given as a continuous slow drip than as a single dose.[16,17]

Subsequently, subject to manifestations of toxicity such as oral mucosal ulceration, diarrhea, and leukopenia below 3,000,

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"half-doses" (5 mg./kg.) were administered 3 times weekly as tolerated during the course of concomitant supervoltage radiotherapy. The range of doses tolerated, considering 2 "half-doses" as 1 "full dose," ranged between 4 and 15 "full doses" (average 9 doses) before significant toxicity supervened. No prolonged complications outside the field of irradiation or apparently directly related acute deaths were encountered with this chemotherapeutic technique.

Acute toxicity from the combined therapy program as employed in our series was not overly severe, but was encountered to a degree in all but 4 patients, since the administration of 5-FU in general was pushed to toxicity. Leukopenia (less than 3,000) was noted in only 1 case. Due to the radiotherapy, significant alopecia, of course, was noted to a degree in all cases completing therapy, confined to the treatment portals. Eight patients developed diarrhea, varying in severity from mild symptoms in the majority to a moderately severe diarrhea in 2 cases. This was the most common clinical factor resulting in temporary or permanent cessation of 5-FU therapy, although it was usually responsive to symptomatic measures. Significant persistent stomatitis was the cause for discontinuing chemotherapy in 1 case.

RESULTS

Since the evaluation of quality of postoperative radiotherapy effects is quite subjective, the results of this investigation have been gauged primarily on survival. The duration of symptoms before craniotomy was relatively short in both treatment groups varying from 1–8 months (average 3.0) in the radiotherapy only group to 1–6 months (average 2.6) in the group receiving combined therapy. This is consistent with most series presented in the literature. Frankel and German[10] report an average duration of symptoms of <6 months in 70 per cent of their patients with glioblastoma multiforme. The interval from surgery to institution of radiotherapy, although relatively short in the majority of cases (1–2 weeks), varied somewhat throughout the study, so that survival time has been measured from the day of surgical exploration (diagnosis). Initially the survival figures appear somewhat more impressive in the radiotherapy only group, with a crossover noted in the absolute cumulative survivals at 12 months (Fig. 1). There is a relative survival plateau for the patients receiving combined therapy through 21 months and then both survival curves are maintained by our 2 living patients at 27 (combined therapy) and 37 (radiation only) months post surgery. The average survival for the entire group was 11.6 months and no statistically significant difference in survival can be detected for the 2 postoperative therapy regimens under investigation. The initial apparent more rapid demise of patients completing a course of combined 5-FU and radiotherapy has been noted in results obtained from combined therapy in other sites, but, other than increased over-all toxicity, no specific factor or factors responsible for this phenomenon have been elicited.

Despite its grossly subjective nature, an evaluation of caliber of survival or "useful life" was attempted (Table III). A post therapy course classified as "excellent" or "good" was noted in 18 patients. Significant improvement was noted in 13 patients classified as showing "good" results, and 5 patients returned to gainful employment or normal former occupations for periods varying from 4 to 35 months and were classified as achieving an "excellent" result. Minimal improvement classified as a "fair" result was noted in 7 patients, and 7 patients who exhibited no improvement clinically or symptomatically were classified as "poor" results. Seventeen patients manifested evidence of neurologic defects following surgery, and 10 patients still exhibited paresis or paralysis after radiotherapy (Table IV). Postirradiation convulsions were noted in 2 patients who received combined therapy, and 4 patients demonstrated persistent visual defects following therapy.

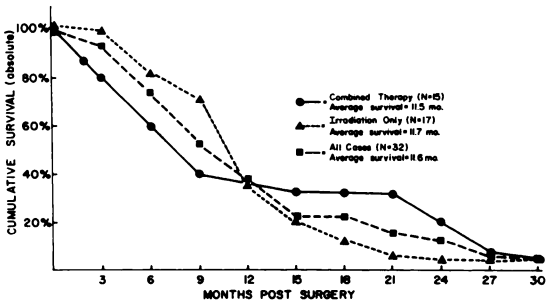


FIG. 1. Composite survival curves for both treatment groups comprising this study.

TABLE III

EVALUATION OF CALIBER OF SURVIVAL

Treatment Group	Excellent*	Good	Fair	Poor†
Radiotherapy Only	3	7	4	3
Combined Therapy	2	6	3	4
Total	5	13	7	7

* Returned to normal occupation.
† Little or no response.

The caliber of survival and incidence of post therapy residuals were not significantly different in the 2 post surgical treatment groups under evaluation. Autopsies were obtained in 6 cases (3 in each treatment group) and all revealed residual tumor. No evidence of spread outside the central nervous system was encountered in any of our patients.

DISCUSSION

The use of chemotherapeutic agents in the treatment of malignant neoplasms of the central nervous system has been evaluated by several workers. Davis and Shumway[5] employed Thio-TEPA for metastatic brain tumors with only fair palliation. Llewellyn and Creech[15] have studied the effects of perfusion of glioblastoma multiforme with various agents (TEM, Thio-TEPA, vinleukoblastin) in 24 patients. It was their opinion that tumors are not eradicated by perfusion with the chemotherapeutic agents presently available and that life was not prolonged. Woodhall *et al.*[21] stated that perfusion of a glioblastoma multiforme by nitrogen mustard in a dose of 1.5 mg./kg. probably would ablate the tumor, but would also destroy the hemisphere and ultimately cause the death of the patient. Most chemotherapeutic approaches to the treatment of primary or secondary brain tumors have been via direct infusion or perfusion routes.[19] While Brennan and Vaitkevicius[3] reported no improvement in 2 patients with glioblastoma multiforme treated with systemic 5-FU (15 mg./kg.) alone, it was our plan to randomly and prospectively evaluate the effect of concomitant systemic chemotherapy upon the postoperative radiotherapeutic management of patients with glioblastoma multiforme.

During the period that this clinical study was in progress, Mukherjee *et al.*[16,17] reported basic work on the metabolism and distribution of 5-FU-2C_{14} within the central nervous system. This information was based upon *in vivo* human studies which included biopsy as well as postmortem specimens. The slow appearance and gradual increase of radioactivity in the cerebral spinal fluid (CSF) of these human patients indicates that either the drug or its meta-

TABLE IV

POST THERAPY RESIDUAL

Treatment Group	Postsurgical Neurologic Defects	Postirradiation Paralysis or Paresis	Postirradiation Convulsions	Persistent Visual Defect
Radiation Only	9	6	0	2
Combined Therapy	8	4	2	2
Total	17	10	2	4

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bolic products are entering the CSF. The levels, however, in the plasma were maintained at a much higher level than in the CSF and it appears that there is no free diffusion of the drug across the blood-brain barrier after intravenous administration. In that study, although the specific activity in some astrocytomas was high, the ability of this type of tumor to convert the drug into "active" or "lethal" nucleotides was poor and the conversion was not greater in central nervous system tumors than in the normal surrounding tissues. Increasing specific activity did, however, appear to be related to the cellularity and anaplasticity of the tumor. Our present randomized clinical series supports the isotopically labeled studies in that 5-FU is ineffective either alone or in conjunction with ionizing radiation in the management of highly malignant astrocytomas.

Despite the lack of improvement in longevity or caliber of survival in patients with proven glioblastoma multiforme who received 5-FU and postoperative radiotherapy over postoperative radiotherapy alone, there is an apparent improvement in longevity for the entire group of patients reported in the literature. Taveras *et al.*[20] report a survival of 7–14 months from first symptom to death in patients receiving no definitive treatment. Elvidge, Penfield and Cone[7] report an average survival of 8.5 months with surgery alone and our over-all average survival was 11.6 months. The total cumulative survival from diagnosis for all patients in this randomized series is indicated in Table v. It must be pointed out, however, that this is a selected series in which only 1 patient entered died during the early phase of postsurgical radiotherapy. Also since surgery alone was not entered into the randomization, any addition of postsurgical radiotherapy to prolongation of life cannot be verified from this series. While we would agree with Taveras *et al.*[20] that at the present time probably nothing better than surgery and irradiation can be offered as specific therapy, a study involving the prospective randomization of patients with proven glioblastoma multiforme into groups receiving only incomplete but as extensive removal as feasible, and those receiving incomplete resection and high dose supervoltage radiotherapy has been undertaken in an attempt to further answer this question.

TABLE V

COMPOSITE SURVIVAL STATISTICS*

Interval (mo.)	Surviving Fraction	Percentage
6	24/32	75
12	12/32	37.5
18	7/32	22
24†	4/32	12.5

* Surgical diagnosis to death.
† 2 patients alive >2 years (26 mo., 37 mo.).

SUMMARY AND CONCLUSIONS

Between January 1962 and December 1966, 32 patients with a histologically confirmed diagnosis of astrocytoma Grade 3 or 4 (glioblastoma multiforme) were entered into a cooperative, prospectively randomized study to compare the effects of postoperative, high dose, supervoltage radiotherapy alone (17 cases) *versus* a similar course of postoperative radiotherapy and concomitant systemic 5-fluorouracil chemotherapy (15 cases).

The average survival from diagnosis (incomplete removal) was 11.7 months in the radiotherapy only group and 11.5 months in the combined therapy group.

Two patients are still alive, 1 at 37 months treated by irradiation alone and 1 at 26 months who received combined therapy.

We conclude that combined therapy with 5-fluorouracil offers no advantage, from the standpoint of duration or caliber of survival, over high dose postoperative radiotherapy alone in the management of patients with glioblastoma multiforme.

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