Combined Modality Therapy of Operated Astrocytomas Grade III and IV. Confirmation of the Value of Postoperative Irradiation and Lack of Potentiation of Bleomycin on Survival Time:

A Prospective Multicenter Trial of the Scandinavian Glioblastoma Study Group*

K. KRISTIANSEN, MD,* S. HAGEN, MD,* T. KOLLEVOLD, MD,* A. TORVIK, MD,* I. HOLME, M STAT,* R. NESBAKKEN, MD,† R. HATLEVOLL, MD,† M. LINDGREN, MD,‡ A. BRUN, MD,‡ S. LINDGREN, MD,§ G. NOTTER, MD,§ A. P. ANDERSEN, MD, AND K. ELGEN, M PHARM¶

In a controlled, prospective, randomized investigation, started in 1974, 118 patients with supratentorial astrocytoma Grade III–IV were divided into three groups. Groups 1 and 2 received 45 Gy postoperatively to the whole supratentorial brain. Bleomycin in 15-mg doses and a total dose of 180 mg or placebo was given intravenously three times a week, one hour prior to radiotherapy, during weeks 1, 2, 4 and 5. Group 3 received conventional care but no radiotherapy or chemotherapy. Median survival rates of patients were 10.8 months in Groups 1 and 2, and 5.2 months in Group 3, a statistically significant difference. With regard to performance, the patients in Group 3 deteriorated faster than patients in Groups 1 and 2. Bleomycin had no positive or negative influence on survival.

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SINCE 1974, A CONTROLLED STUDY of combined neurosurgical, radiologic, and chemotherapeutic treatment with bleomycin of astrocytomas Grade III-IV has been carried out in the Scandinavian countries. The total population of Denmark, Finland, Norway, and Sweden is 22 million people, with a relatively uniform ethnic origin suitable for epidemiologic studies. The investigation has as its main purpose the evaluation of the results of postoperative radiation therapy and of combined postoperative radiation-chemotherapeutic treatment. The first stage of the study was completed in the fall of 1978.

Material and Methods

One-hundred-eighteen patients of both sexes between 20 and 69 years of age with a malignant glioma in the cerebral hemispheres received standardized preoperative examinations. The decision as to whether a patient should be included in the trial was made after the neuropathologic examination of the resected tumor. The histologic description of the tumors included in the investigation was "astrocytic gliomas with marked cellular anaplasia, pleomorphism, endothelial proliferation, and necrosis." Smaller areas with oligodendroglioma or ependymoma appearance were accepted.

Classification of the tumor material was done by one Norwegian and one Swedish neuropathologist independently. Another condition for inclusion in the trial was that it had been possible to do a large tumor resection giving a satisfactory internal decompression.

After postoperative randomization, the patients were referred to one of three groups:

(1) Whole brain irradiation and intravenous injections of bleomycin.

(2) Whole brain irradiation and intravenous injections of placebo.

(3) No postoperative irradiation or chemotherapy.

The number of patients in each group was 45, 35, and 38, respectively.

* Ullevål Hospital, Oslo, Norway.
† National Hospital (Rikshospitalet), Oslo, Norway.
‡ University Hospital, Lund, Sweden.
§ Sahlgrenska Hospital, Gothenburg, Sweden.
¶ Municipal Hospital, Århus, Denmark.
¶ H. Lundbeck & Co., Copenhagen, Denmark.
Address for reprints: Steinar Hagen, Head Department of Radiation Therapy, Ullevål Hospital, Oslo 1, Norway.
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TABLE 1. Distribution of Material According to Sex, Age, Preoperative Functional Status, and Postoperative Treatment

	Group 1	Group 2	Group 3
Postoperative treatment	Yes	Yes	No
Number of patients	45	35	38
Men	23	23	25
Women	22	12	13
Age	56	53	55
Postoperative functional status	3.7	3.7	3.8

The postoperative treatment for two thirds of the patients was started on Monday in the second, third, or—at the latest—fourth week after the craniotomy. A double-blind technique with a placebo was applied for groups 1 and 2.

The whole supratentorial brain was irradiated with megavolt equipment five days a week for five weeks. The field size was 10–11 cm by 12–14 cm, and the base of the field corresponded to the base of the skull. Two opposing lateral fields were treated in each sitting. The midline dose was 1.80 Gy, and the total absorbed dose 45 Gy.

Bleomycin was chosen as the chemotherapeutic agent because of its inhibitory effect on the restitution of cells damaged by sublethal radiation doses.[2-4] Fifteen mg of bleomycin or placebo in a 20-ml solution was given intravenously during 3–5 minutes one hour before irradiation on the first, third, and fifth day of the first, second, fourth and, fifth week of the irradiation treatment. The total dose was 180 mg.

If serious side effects necessitated interruption of treatment for more than 14 days, the patient was excluded from the trial, but the registration would be continued.

Steroids were given as dexamethasone according to the patient's needs.

When signs of tumor growth occurred after the completion of the primary treatment, a reoperation could be performed or any other kind of palliative treatment applied if considered desirable by the neurosurgeon and oncologist in charge.

The postoperative registrations of the patient's somatic and mental status were performed according to detailed schemes after three days, two weeks, two months, and three months, and, later, every three months.

TABLE 2. Distribution of Intracranial Tumor Location

	Group 1	Group 2	Group 3	Total
Postoperative treatment	Yes	Yes	No	
Frontal	7	6	8	21
Temporal	9	8	14	31
Parietal/parieto-occipital	14	10	6	30
Others	15	11	10	36
TOTAL	45	35	38	118

Results

The main questions to be answered were whether the procedure had influenced the length of the survival period, the frequency of recurrences, and the functional capacity of the patients. The material includes 118 patients, with a fairly equal distribution among the three groups, a mean age of 55 years, and a male predominance (Table 1).

The performance status was graded as follows:

(1) Full capacity for work.

(2) Partially incapacitated for work.

(3) Unable to work, but able to take care of him/herself.

(4) Needs assistance, but not confined to bed.

(5) Bedridden.

The mean preoperative functional capacity score was equal in the three groups with a status corresponding to a person who is almost able to take care of him/herself.

With regard to the tumor site, the distribution showed a certain preponderance of temporal lobe tumors in Group 3 and a correspondingly smaller number of parietal and parieto-occipital tumors (Table 2).

In September 1978 a statistically significant difference was obtained between the 2 groups of patients with postoperative irradiation on one hand and the third group, without postoperative therapy, on the other hand.

The median survival time was 10.8 months in the two postoperatively treated groups, as against 5.2 months among the patients with operative treatment only (Figure 1 and Table 3). Similar results with regard to survival rate in operated patients with and without postoperative irradiation have been obtained by Andersen.[1] Already in May 1978 the statistical evidence was so strong that it was decided to continue the trial with only "two arms": postoperative irradiation to all patients, with or without bleomycin, without breaking the code, until the study group agreed upon the details of the next step of the investigation.

The two groups of postoperatively treated patients showed practically identical results with regard to the number of patients surviving more than 6 months (Figure 2). Bleomycin in this dosage scheme had evidently not had any positive or negative effect as complement to radiotherapy with regard to survival time.

It is necessary to consider whether the longer period of survival in patients with postoperative irradiation represents a "useful survival." As a rule, the first few weeks or months after a resection of a malignant

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glioma are most likely to be of benefit for the patient and the family. Five of these weeks are required for the postoperative treatment, which for many patients will prolong the stay in hospital and perhaps entail some uncomfortable side effects.

Full or partial working capacity (performance status 1 and 2) was achieved after 6 months in Group 1 by more than 25%, in Group 2 about 35% and in group 3 less than 10%. After 12 months, 23 of 80 patients in Groups 1 and 2 still had the same working capacity; in Group 3, however, none did.

Between two-thirds and three-quarters of all patients were able to take care of themselves for shorter or longer periods of their postoperative life, the percentage among irradiated patients being slightly higher than among patients treated surgically only (Figure 3).

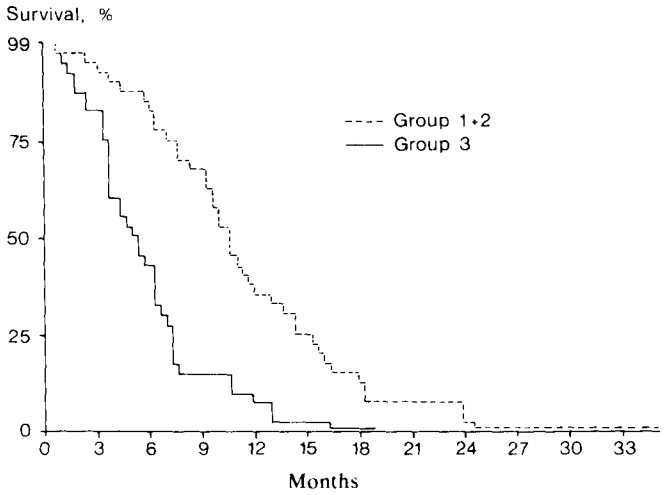


FIG. 1. Survival of the three groups in the trial.
Group 1: Surgery + radiotherapy + bleomycin;
Group 2: Surgery + radiotherapy + placebo;
Group 3: Surgery alone.

Discussion

The value of postoperative radiotherapy with or without chemotherapeutic agents in patients with malignant gliomas has been a matter of dispute. Until 1973, no controlled trials had been published. Information was not available on whether the economic and personnel resources spent on this group of patients had any effect on the length of survival after surgical intervention or on the quality of life during this period. Since 1973, several investigations have been initiated with the purpose of providing statistical data on these issues. At the National Cancer Conference in Philadelphia Walker[8] presented the work of the Brain Tumor Study Group, which showed a significant increase in the survival period for patients treated with radiotherapy and bischloronitrosourea (BCNU).

Walker *et al.*[9] have recently analyzed the results of this randomized study comprising 222 patients who complied with the protocol criteria. Postoperative radiotherapy proved a significant increase in median survival. There was no significant difference between patients receiving BCNU in addition to radiotherapy versus those who were treated with radiotherapy alone. BCNU alone had only a marginal effect on survival compared with patients without postoperative treatment. Other investigations have been started, for instance by the European Organization for Research on Treatment of Cancer (EORTC). Paoletti *et al.*[6] reported the results of a controlled clinical trial with combined therapy in 1978, and Buge *et al.*[3] and Heiss[5] have examined the effects on chemotherapy, particularly with chlorethyl-cyclohexyl nitrosourea (CCNU). A comparison of results in these papers is difficult because of inconsistent tumor classification.

The main purpose of this initial phase of the investigation has been to provide statistical proof of a benefit of postoperative irradiation in patients with malignant astrocytomas Grade III–IV. Our results have confirmed earlier investigations showing that postoperative radiation therapy increases survival time and working ability in patients suffering from these types of gliomas. The addition of bleomycin has had no influence on the length of survival.

No serious complications were observed during the trial. Irradiation and bleomycin were well tolerated. With regard to experiences with bleomycin in brain tumor therapy, readers may be referred to Takeuchi.[7]

To collect an adequate number of patients, a longer period of observation has been necessary than anticipated in 1974. The main reason has been that many centers have been unable to join because of lack of personnel and hospital beds.

As a result of the first stage of the multicenter study a platform has been established on which further evidence may be built. A detailed protocol for the next stage has been worked out, including two modalities of radiation treatment, with and without a radiosensitizer, and subsequently a randomized study of the additional effect of CCNU.

TABLE 3. Number of Deaths and Months of Survival*

	Group 1	Group 2	Group 3
Postoperative treatment	Yes	Yes	No
Number of patients	45	35	38
Number of dead	36 (80%)	28 (80%)	37 (97%)
Survival months			
Total	371	293	227
Mean	10.3	10.5	6.1
Median	10.8		5.2

* The difference between Groups 1 and 2, and Group 3 is statistically significant.

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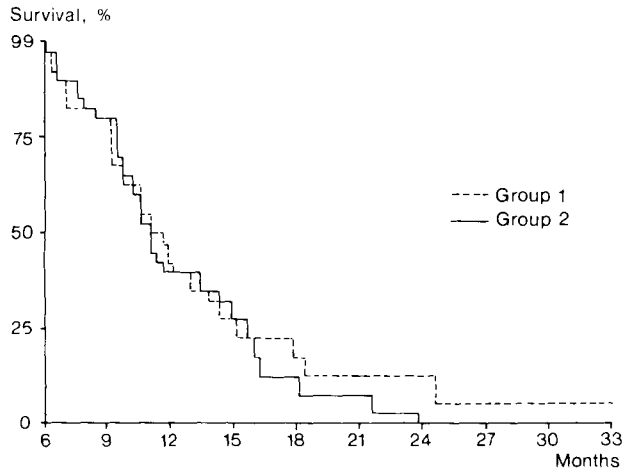


FIG. 2. Patients surviving more than six months in Groups 1 and 2: surgery and radiotherapy ± bleomycin.

Summary

A controlled, prospective, randomized study evaluated the use of radiotherapy with concomitant bleomycin or placebo in the treatment of patients who had been subjected to an adequate tumor resection and had histologic confirmation of astrocytoma Grade III–IV. A total of 118 patients with supratentorial tumors met the protocol criteria. The patients were divided into 3 randomized groups. Groups 1 and 2 received 45 Gy postoperatively to the whole supratentorial brain through bilateral opposing fields during five weeks, five treatments per week. Bleomycin in 15-mg doses or placebo was given intravenously 3 times a week, one hour prior to radiotherapy, during weeks 1, 2, 4, and 5. Group 3 received conventional care but no radiotherapy or chemotherapy except steroids, which were given to all patients according to need. Radiotherapy and bleomycin were well tolerated. Median survival of patients was equal in Groups 1 and 2: 10.8 months, compared with 5.2 months in Group 3, a statistically significant difference. The performance status was equal before surgical intervention in the 3 groups. After an initial postoperative improvement in all groups, the patients in Group 3 deteriorated faster than patients in Groups 1 and 2. Bleomycin in the doses administered had no positive or negative influence on survival.

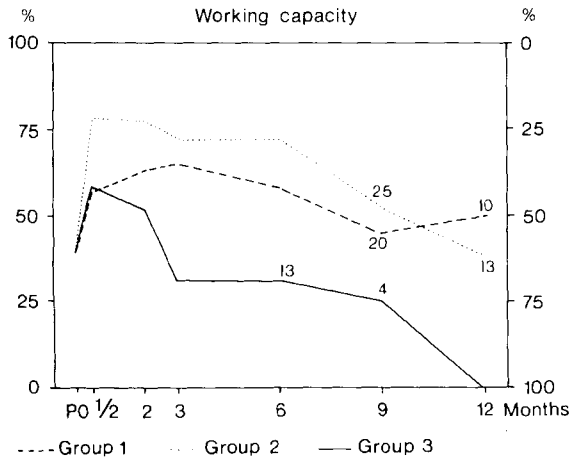


FIG. 3. Working capacity of patients. Performance status 1, 2, and 3 (*left-hand scale*) below the curves, performance status 4 and 5 (*right-hand scale*) above the curves.

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