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POSTOPERATIVE IRRADIATION OF GLIOBLASTOMAS

Results in a randomized series

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Glioblastoma multiforme is the most common form of tumour in the cerebral hemispheres and represents about 40 per cent of the total number of cerebral gliomas.

Differences of opinion exist regarding the efficacy of irradiation. Many authors, at least in the past, thought irradiation useless, while others were of the opinion that the treatment of choice was primary surgical decompression and removal of malignant tissue, followed by adequate irradiation (LINDGREN 1969).

In the series of BOUCHARD (1966) treated with a combination of operation and irradiation, 44 per cent survived one year. This result was compared with a series of FRAENKEL & GERMAN (1958) treated by surgery alone in which only 7 per cent survived one year. Drawing upon these results, BOUCHARD recommended postoperative irradiation. Also TAVERAS et coll. (1962) found a prolonged survival in a series of glioblastomas when the operation was combined with postoperative irradiation.

SHELINE (1977) has collected data concerning the effect of postoperative irradiation in glioblastoma multiforme (malignant glioma, grade IV) from four American clinics: Mayo Clinic (UIHLEIN et coll. 1966), University of California, Los Angeles (STAGE & STEIN 1974), Jefferson University (KRAMER 1973) and University of California, San Francisco (SHELINE 1975).

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Table 1

Distribution according to year of treatment during trial period 1-1, 1963–30-4, 1967

Year	No. of cases
1963	30
1964	20
1965	25
1966	22
1967	11
Total	108

The survival rates at one year were 24 per cent in irradiated series compared with 8 per cent in non-irradiated. At three years, 6 per cent of the irradiated patients were living but all of the non-irradiated were dead.

All these reports are impaired by absence of randomization. In the literature no randomized series from the same clinic and in the same period has been found to evaluate the effect of postoperative irradiation in glioblastomas.

Therefore in these departments a randomized investigation was performed between the 1st of January 1963 and the 30th of April 1967. The randomization was carried out as follows: Patients who were born on even dates should only be operated upon, while patients born on uneven dates should in addition receive postoperative irradiation.

The irradiation was given as soon a possible after the operation, that is, when the wound had healed and the general condition of the patient permitted it. In most cases the irradiation began less than two weeks after the operation and was given with a cobalt unit. Two parallel opposing fields were used, one on each side of the head and in most cases the entire intracranial content was irradiated. In single cases in which the tumour seemed to be more localised only the tumour area and a reasonable surrounding area was irradiated. A tumour dose of 45 Gy in $4\frac{1}{2}$ to 5 weeks was administered with 5 or 6 fractions a week. A higher dose was never used to assure certain avoidance of cerebral necrosis. This treatment regimen was generally well tolerated.

Material

The material consisted of 108 patients. The distribution according to the year of treatment appears in Table 1 and the age and sex distribution in Fig. 1. The malignant glioma grade 4 is most common in the 6th and 7th decade of life and is twice as frequent in males as in females.

All histologic specimens were evaluated by the same neuropathologist. Gliomas

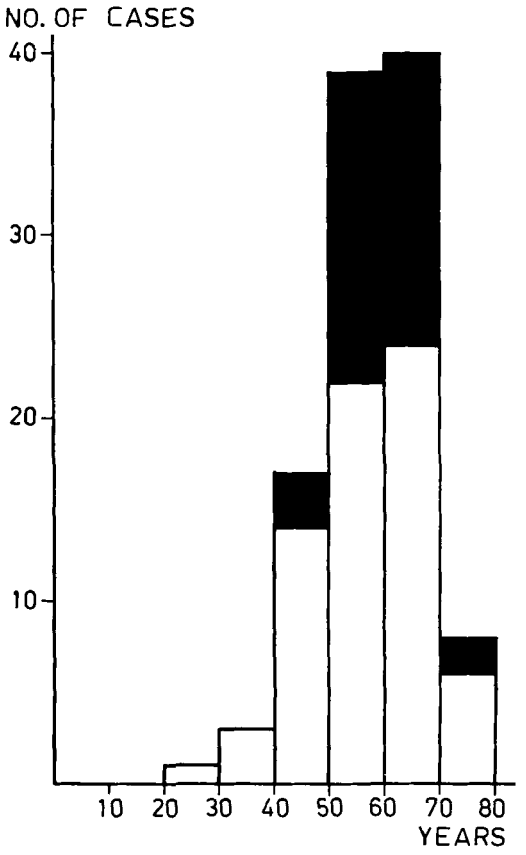


Fig. 1. Distribution by age (years) and sex. ■ Females (39 cases). □ Males (69 cases).

of lower grade than grade 4 are not included in the material, nor in cases in which a primary biopsy had shown astrocytoma while a later biopsy in connection with recurrence and re-operation had shown glioblastoma. All cases were controlled at regular intervals and the follow-up was complete. All survival curves are calculated as crude survival and the date of operation is used as the beginning of the observation period.

Results

Total material. The survival curve for the total material (Fig. 2) indicates that the primary mortality is considerable, i.e., 25 per cent of the patients died within one month and only 6 per cent survived one year. The separate survival curves for males and females (Fig. 3) show that no difference between the sexes exists. A comparison between patients older and younger than 60 years appears in Fig. 4. The most important difference between the two groups is found in the primary mortality

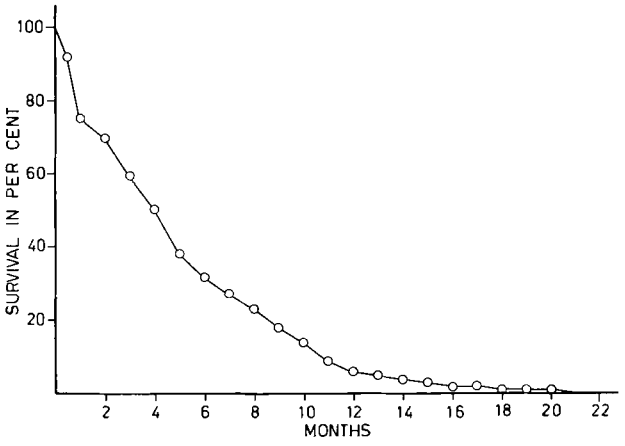


Fig. 2. Crude survival of total material (108 cases).

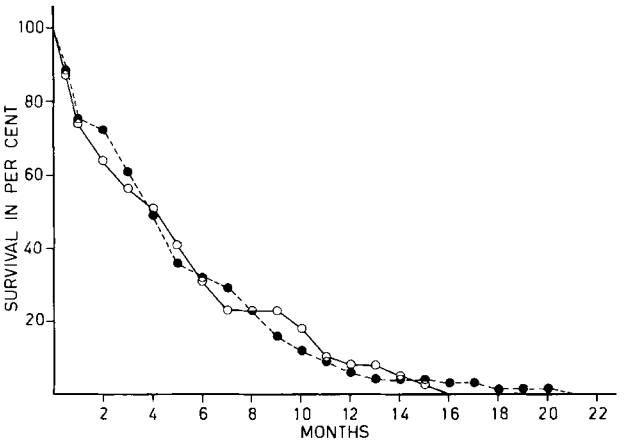


Fig. 3. Crude survival according to sex: ○ females (39), ● males (69).

within the first two months. After that time the curves are nearly parallel, with a tendency to converge against one year.

The group of glioblastomas indicates several subgroups, with differing microscopic appearance. The number of cases in the present material does not permit a comparative evaluation of these subgroups. The differentiation of these subgroups is also a matter of dispute, but it is generally accepted that the angionecrotic type is the most malignant and has the poorest prognosis. Therefore, a comparative evaluation was made between this and the other types (Fig. 5). This comparison confirmed the opinion that the angionecrotic type is the most serious; a closer analysis revealed, however, that the greatest difference is found in the primary mortality and that the difference in number of long term survivors is less marked.

Value of postoperative irradiation. The survival curves for the two randomized groups are given in Fig. 6. Patients born on even dates should belong to the irradiated

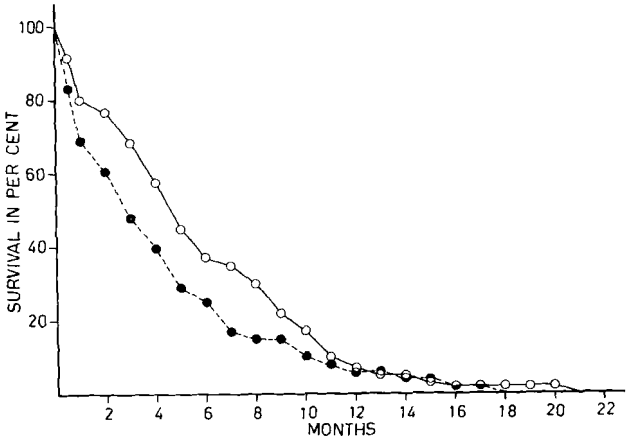


Fig. 4. Crude survival according to age groups: ● over (60 cases), ○ under 60 years (48 cases).

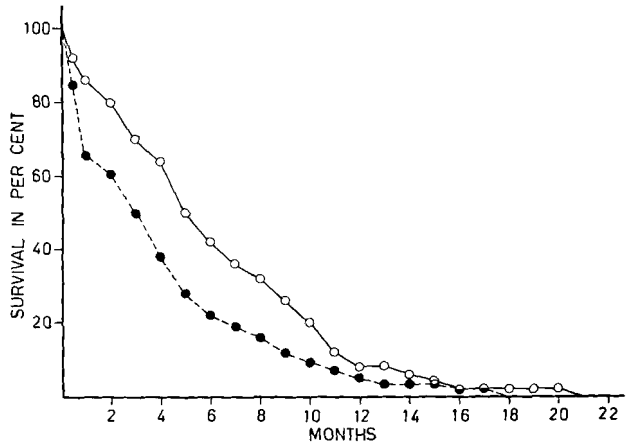


Fig. 5. Crude survival according to type of tumours: ● angionecrotic (58 cases), ○ other types of glioblastoma (50 cases).

group but, nevertheless 11 patients did not receive any irradiation. This was due either to a general condition too poor for irradiation or to the fact that death occurred in connection with the operation. The two curves follow each other during the first two months after the operation, but then diverge. Six months after the operation the difference between the two groups is significant at the 5 per cent level ($p < 0.05$).

A better evaluation of the value of the irradiation is obtained if all cases which have not survived 2 months are excluded (Fig. 7).

The irradiated group, then, consisted of 36 cases (28 males, 8 females) and the non-irradiated group of 39 (22 males, 17 females). However, in the irradiated group only 30 were given the intended dose because 4 patients were in too poor a general condition, and in 2 cases the patients' families wished the treatment to be discontinued.

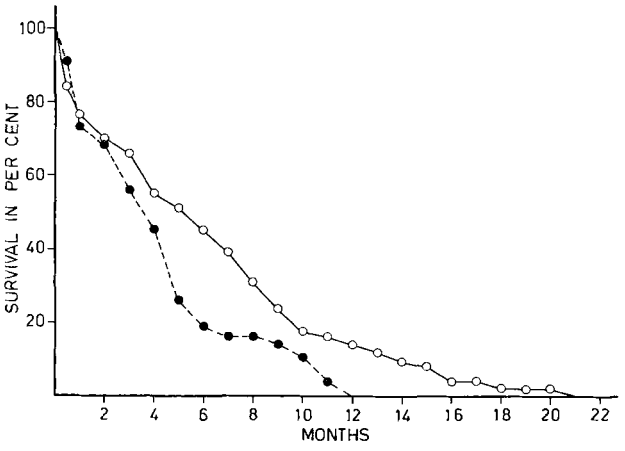


Fig. 6. Crude survival according to irradiated (○, 51 cases), non-irradiated (●, 57 cases).

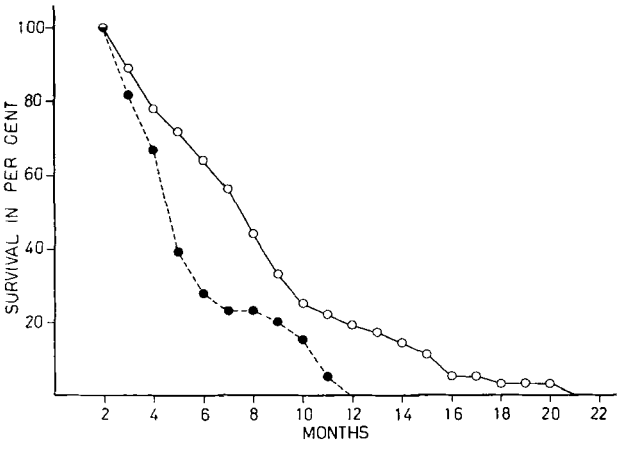


Fig. 7. Crude survival of the irradiated group (○, 36 cases) compared with the non-irradiated group (●, 39 cases). Patients who survived less than 2 months after operation excluded.

From Fig. 7 it is evident that the irradiation improved the prognosis. The difference between the two groups 6 months after the operation is significant at the 0.5 per cent level ($p < 0.005$). Furthermore, only patients from the irradiated group survived one year (7 patients).

The two groups were compared with regard to age and microscopic type (Tables 2, 3). The distribution is equal in these respects but there were more females in the non-irradiated group. However, no difference in the general prognosis was found between males and females (Fig. 3), and therefore this fact can scarcely be of importance for the difference between the two groups.

Discussion

The results seem to indicate that postoperative irradiation improves the prognosis, which, however, is still very poor.

Table 2

Irradiated and non-irradiated groups divided according to age (patients not surviving 2 months excluded)

Age	20–29	30–39	40–49	50–59	60–69	70–79	Total
Irradiated group	0	2	7	12	13	2	36
Non-irradiated group	1	1	7	16	12	2	39

Table 3

Irradiated and non-irradiated groups divided according to microscopic type (patients not surviving 2 months excluded)

Microscopic type	Angionecrotic	Others	Total
Irradiated group	16	20	36
Non-irradiated group	19	20	39

Some factors which may influence the evaluation of the value of the irradiation must be considered. The system of randomizing used made it possible for the neurosurgeon, in advance, to know to which group the patient belonged. In principle this is not correct, but it seems to be irrelevant for the conclusions drawn.

Another factor which could be of importance is that patients in the irradiated group had been under medical care 4 to 6 weeks longer than the non-irradiated group. However, the majority of patients in the non-irradiated group were sent for medical care in local hospitals, especially if the patient's general condition was unsatisfactory.

A repeat operation because of recurrence was performed in 7 of the 108 patients, 6 being in the 4th and 5th decade of life. Of the re-operated patients, 6 belonged to the irradiated group and one to the non-irradiated. On average these patients survived $7\frac{1}{2}$ weeks after the re-operation and it is doubtful whether this operation prolonged the survival time.

No accurate evaluation of the grade of recovery was made, but no essential difference seems to exist between the two groups.

The present results are not so encouraging as those reported by others. BOUCHARD (1966) reported a 1- and 3-year survival of 44 and 13 per cent, respectively; LINDGREN (1965) 42 and 12 per cent, respectively. STENBERG & MOBERG (1971) found in their series 4 of 13 surviving one year but none two years, and ONOYAMA et coll. (1976) found in a series of 127 cases 52 per cent surviving one year, 19 per cent 3 and 12 per cent 5 years. In all these series operation was combined with irradiation.

The explanation of these considerable differences in treatment results is probably to be found in differences in the microscopic classification. Some classify these lesions to microscopic type and others to the degree of malignancy. The term glioblastoma multiforme has without doubt in many cases been used as a general term

to include all malignant gliomas. The present cases belong to the most malignant type (grade 4), which may explain the present results.

SHELINE (1977) found considerable differences in the prognosis between irradiated (1 year: 24 %, 3 years: 6 %) and non-irradiated (1 year: 8 %, 3 years: 0 %) in the four collected series. The present difference between the irradiated and non-irradiated group is smaller.

The treatment technique or the dose level used may also be of importance when considering the treatment results. In most cases the entire skull was irradiated as recommended by CONCANNON et coll. (1960) and KRAMER as post mortem examinations have shown that the extent of the tumour is often underestimated (LINDGREN 1969).

More limited fields, although with generous margins and only in a few cases 'whole brain irradiation', were used by UIHLEIN et coll., STERNBERG & MOBERG, CALDWELL & ARISTIZABAL (1975), MARSA et coll. (1975) and ONOYAMA et coll. It seems that their results are not poorer than those reported by others.

The intended dose level was 45 Gy/4½–5 weeks. This level may be too low because these tumours are relatively insensitive to radiation. However, TAVERAS et coll. could not find significant differences between cases receiving from 40 to 55 Gy and those receiving from 30 to 39 Gy. On the other hand, ONOYAMA et coll. report that a tumour dose of more than 60 Gy (or 1 700 ret) is necessary to improve the prognosis significantly, while LEGRÉ et coll. (1969) found the dose optimum should be in the range of 50 to 70 Gy. The results from CALDWELL & ARISTIZABAL do not suggest that high doses are necessary to obtain maximum survival. However, they found a probable benefit from doses of approximately 50 Gy.

It is to be hoped that newer types of radiation, use of radiosensitizers, or chemotherapy can improve the prognosis in the future.

Conclusion

The results seem to indicate that the survival rate is improved if operation is combined with postoperative irradiation. However, the prognosis is very poor and irradiation must be considered as palliative.

The indication for postoperative irradiation cannot be considered as absolute. On the one hand the survival time may be prolonged by a few months, but on the other hand the fact must be recognised that irradiation in many cases is uncomfortable for the patient and demands a prolonged stay at hospital during a period when survival time in most cases can be counted in months.

SUMMARY

A material of 108 patients with glioblastoma is presented. The series was randomized in two groups: cases only operated upon and cases with postoperative irradiation in addition. Patients dead within 2 months after operation were excluded in estimating the real value of

the postoperative irradiation. The irradiated cases had a 6-month survival rate of 64 per cent and a one-year survival rate of 19 per cent; the non-irradiated cases a 6-month survival rate of 28 per cent and a one-year survival rate of 0 per cent.

ZUSAMMENFASSUNG

Ein Material von 108 Patienten mit Glioblastoma wird beschrieben. Die Serie wurde in zwei Gruppen eingeteilt: Patienten die nur operiert wurden und Patienten die zusätzlich postoperative Bestrahlung erhielten. Die Patienten, die innerhalb von 2 Monaten nach der Operation gestorben waren, wurden ausgeschlossen um den wirklichen Wert der postoperativen Bestrahlung festzustellen. Die bestrahlten Patienten hatten eine 6-Monate Überlebensrate von 64 Prozent und eine ein-Jahr Überlebensrate von 19 Prozent. Die nicht bestrahlten Patienten hatten eine 6-Monate Überlebensrate von 28 Prozent und eine ein-Jahr Überlebensrate von 0 Prozent.

RÉSUMÉ

L'auteur présente une série de 108 malades atteints de glioblastome. Cette série a été répartie de façon aléatoire en deux groupes : les cas qui ont été seulement opérés et ceux qui ont subi en plus une irradiation post-opératoire. Les malades décédés dans les deux mois après l'opération ont été exclus pour estimer l'intérêt réel de l'irradiation post-opératoire. Les cas irradiés ont eu un taux de survie à 6 mois de 64 pour-cent et un taux de survie à 1 an de 19 pour-cent. Les cas non irradiés ont eu un taux de survie à 6 mois de 28 pour-cent et un taux de survie à 1 an de 0 pour-cent.

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