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Therapy of Glioblastoma Multiforme: A Cumulative Experience of 10 Years

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Summary

Purpose: Comparison of the effect of different therapeutic modalities on survival time of patients with glioblastoma multiforme operated on during the last decade (1980–1990).

Patients and methods: The records of 157 consecutive patients with the histological diagnosis of glioblastoma multiforme were analysed for survival with respect to age of patients, extent of surgery, influence of re-operation and adjuvant postoperative treatment. The latter included fractionated radiotherapy, chemotherapy (BCNU, CCNU with Vincristine) and photodynamic therapy (PDT).

Results: Analysis of variance showed a significant effect for survival after macroscopically radical surgery ($p = 0.005$), postoperative radiotherapy ($p < 0.001$), chemotherapy ($p < 0.01$). Low age ($p < 0.05$) and a postoperative Karnofsky performance score (KPS) ≥ 60 ($p < 0.001$) had a positive influence; the site of tumour and pre-operative presence of seizures had no significant influence ($p > 0.1$) on survival time.

Conclusion: We conclude that the current adequate management of glioblastoma multiforme should include surgical resection followed by adjuvant treatment such as radiotherapy and chemotherapy.

Keywords: Glioblastoma; survival; surgery; radiotheraphy; chemotherapy.

Introduction

Prognosis of patients with glioblastoma multiforme is almost uniformly fatal [27]. Despite reports on long-term survivors [1, 10, 21] and development of various adjuvant treatments [15, 20, 22] there is no significant improvement in outcome over the last decade [15]. In agreement with other authors [8, 23] we believe that operation with gross tumour removal constitutes the first step in the treatment of a high grade glioma. Adjuvant therapy in our institution is tailored to the needs of each patient after careful analysis of the extent of residual tumour in postoperative imaging. Additionally age and postoperative clinical state are major factors in treatment planning.

Over a decade this approach has generated a quite heterogenous assembly of treatment groups which, we suspect, represents the glioblastoma population in many centres. In this retrospective analysis we compared the effect of surgery and various adjuvant therapeutical strategies on survival of our patients operated on for glioblastoma multiforme by the use of a multivariate analysis.

Patients and Methods

Clinical Characteristics

Between 1980 and 1990 157 patients fulfilled the criteria for the diagnosis of supratentorial grade 4 glioma. Tumour grading was performed according to Kernohan and coworkers [1, 2].

Nine patients undergoing operation for glioblastoma multiforme had a known brain tumour classified as low-grade astrocytoma or as oligodendroglioma by surgery 6 months to 7 years earlier.

The records of all patients were evaluated and age, sex, history, neurological symptoms prior to surgery and tumour location were recorded. Extent of tumour resection was obtained from the operation notes and postoperative CT scan. Data concerning the postoperative course was gathered from our outpatient records and from correspondence. The date of death was obtained from the family doctor or the registration office. In 3 cases of foreign patients data were lost to follow up and excluded from the study.

Three patients with a histological diagnosis of glioblastoma multiforme were still alive at the time of our investigations (1993). All showed a postoperative survival longer than 5 years and were also excluded from our analysis.

A total of 151 patients (64 female, 87 male) with a mean age of 57,5 years was entered into the study. No attempt was made to distinguish between disease-related and not disease-related death.

Treatment

Extent of tumour resection was classified as subtotal or total, according to the macroscopic aspect at the time of surgery, supported by a postoperative CT scan after contrast enhancement.

Radiation therapy was applied in a conventional fractionated dose by an electron beam (LINAC, Siemens, 1.7–2.0 Gy/day, 5 days/week). Three groups were distinguished: no irradiation

(n = 54), less than 50 Gy (n = 10), more than 50 Gy (range 50–65 Gy) (n = 87).

Chemotherapy (n= 41) consisted of BCNU 80 mg/sqm intravenously on 3 successive days every 6–8 weeks or CCNU 200 mg orally with Vincristine 1.5 mg/sqm every 6–8 weeks.

Photodynamic therapy (PDT) was performed after the parenteral sensitisation with the photosensitizer haematoporphyrin activated by an argon-dye laser (n = 9) [16].

Thirty-three patients underwent *re-operation* of a recurrent glioblastoma. When established therapeutic modalities were exhausted, we applied *experimental treatment modalities*, such as PDT [16] and intra-operative radiotherapy (n = 3) [13]. Treatment protocols for inclusion of PDT (photodynamic treatment) and intra-operative radiotherapy in the therapy of recurrent glioblastoma were approved by the committee on ethics in medical research at our institution.

Statistics

The survival time was taken as duration from time of biopsy or resection until death. Survival analysis was performed with the program SPSS.

To analyse the shared influence of all treatment modalities, we used a simple factorial analysis of variance (ANOVA) model, with days of survival as dependent variable. The natural logarithm of survival days was used to obtain a normal distribution. Factors were extent of surgery (subtotal vs. total), radiotherapy (no therapy, <50 Gy, >50 Gy), chemotherapy (no therapy, <3 times, ⩾3 times), PDT (no, yes). Covariates were age, KPS (<60, ⩾60), site of tumour (lobar, midline) and pre-operative presence of seizures.

Different therapeutic groups were additionally compared by means of the Mann-Whitney-U test. All p-values less than 5% were considered as significant.

Results

Three patients died in the first postoperative week (peri-operative mortality 2%). This figure corresponds well with the data recently reported [3, 8]. 21 patients had a poor postoperative outcome with a KPS lower than 60 and were not considered for further adjuvant therapy. Resection was considered to be total in 111 patients by the criteria mentioned under Patients and Methods. Of these, 97 received radiotherapy, 41 chemotherapy (10 patients less than 3 times) and 9 patients received additional intra-operative PDT following tumour resection. Mean survival time of all patients entered in this study was 355 days.

33 patients were operated on for recurrent glioblastoma within 371 days after the first operation. These

Table 1. *Mean Survival Time with Range and Numbers of Each Subgroup for Different Therapeutic Strategies*

Extent of surgery	Chemotherapy	Radiotherapy	Data		
			Number	Mean	Range (days)
Partial resection	no	no radioth.	15	78	3–292
		<50 Gy	4	256	24–359
		>50 Gy	15	258	67–498
	no total		34	178	3–498
	<3 times	<50 Gy	1	32	32–32
		>50 Gy	2	628	460–795
	<3 times total		3	429	32–795
	⩾3 times	no radioth.	1	327	327–327
		>50 Gy	2	499	219–778
	⩾3 times total		3	441	219–778
Partial resection total			40	217	3–795
Total resection	no	no radioth.	34	180	6–649
		<50 Gy	3	85	41–155
		>50 Gy	39	462	126–1216
	no total		76	321	6–1216
	<3 times	<50 Gy	1	365	365–365
		>50 Gy	6	397	170–771
	<3 times total		7	393	170–771
	⩾3 times	no radioth.	4	832	349–1797
		<50 Gy	1	703	703–703
		>50 Gy	23	600	122–1992
	⩾3 times total		28	637	122–1992
Total resection total			111	405	6–1992
Grand total			151	355	3–1992

patients had a mean survival time of 597 days and 226 days after the second operation.

Table 1 shows the survival time (number of patients, mean and range) of patients assigned to different treatment groups. Patients who did not receive any adjuvant therapy after tumour removal lived on the average for 78 days if removal was subtotal (n = 15) and for 180 days (n = 34) if removal was total ($p<0.05$, Mann-Whitney-test).

All patients with partial excision and radiation of lower than 50 Gy (n = 4) and higher than 50 Gy (n = 15) demonstrated a mean survival of 256 days and 258 days, respectively.

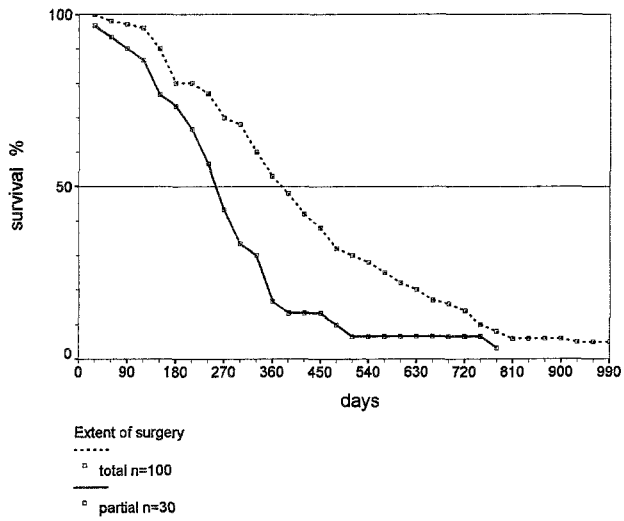

Fig. 1. Survival time with regard to extent of surgery

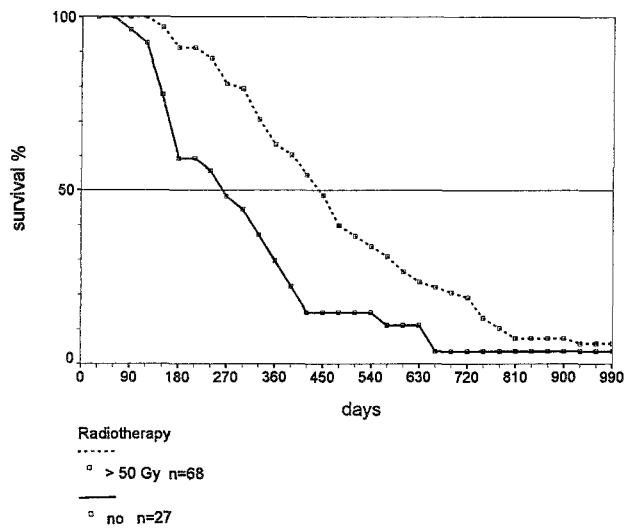

Fig. 2. Subgroup (total resection) of Fig. 1 with regard to radiotherapy

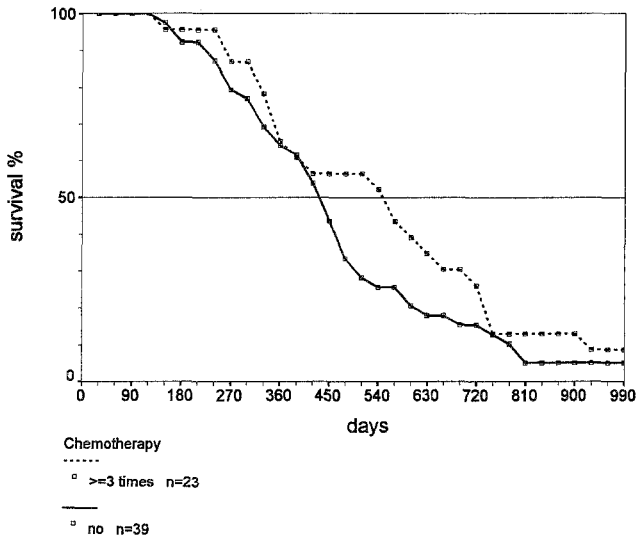

Fig. 3. Subgroup (with radiotherapy >50 Gy) of Fig. 2 with regard to chemotherapy

In contrast patients with radical excision and only radiation of lower than 50 Gy (n = 3) and higher than 50 Gy (n = 39) demonstrated a mean survival of 85 days and 462 days, respectively.

Patients with and without radical excision plus chemotherapy alone lived on average 832 (n = 4) and 327 (n = 1) days.

Patients with a combined treatment modality of radiation and chemotherapy with and without radical excision lived on average 600 days (n = 23) and 499 (n = 2) days, respectively.

The overall results in all patients with or without adjuvant therapy was in the radical excision group 405 days and 217 days in subtotally resected patients.

Cumulative survival rates with regard to extent of surgery, radiotherapy and chemotherapy after irradiation are given in Figs. 1–3. Figure 1 compares the survival time of patients with total vs. partial resection. All patients had a KPS of $\geqslant 60$. Figure 2 is a subgroup analysis of patients after total resection with regard to radiotherapy. Figure 3 compares survival rates of patients after total resection and radiotherapy with respect to chemotherapy. Each additional treatment provides an increase in survival time, although the effect of adjuvant chemotherapy is the least dramatic.

Analysis of variance showed significant differences in survival related to extent of surgery ($p = 0.005$), irradiation ($p< 0.001$) and chemotherapy

($p < 0.01$). Young age ($p < 0.05$) and KPS ≥ 60 ($p < 0.001$) had a positive influence. The influence of PDT ($p = 0.092$), pre-operative seizures and location ($p > 0.1$) were not statistically significant.

In 21 patients with a poor postoperative KPS (<60) extent of surgery had no significant influence upon postoperative survival time. (Mann-Whitney-U: $p > 0.3$).

Discussion

The aim of this report is to evaluate the efficacy of current treatment modalities in consecutive patients with the histopathological diagnosis of glioblastoma multiforme by survival analysis. Due to the small number of patients in some subgroups no meaningful statistical data can be obtained, however, tendencies can be demonstrated. We were able to demonstrate that a combined approach consisting of macroscopically total resection, postoperative irradiation and polychemotherapy leads to a substantially longer survival, and even more so if the patient is young and in a good postoperative condition.

Surgery is one cornerstone in the management of glioblastoma multiforme [15]. Surgery not only allows physicians to establish an accurate diagnosis, but adds the effect of cytoreduction. As recently published by Simpson *et al.* [23] and Höllerhage *et al.* [8] extent of surgery is an important factor in lengthening survival. Some authors, however, have recommended biopsy followed by irradiation and chemotherapy or other treatments without surgical resection [17]. We could show that the mean survival time of our patients increased (322 vs. 503 days) if we compared partial versus total resection in all irradiated patients (Mann-Whitney-u: $p = 0.003$). This was also true in our patients without adjuvant therapy.

Postoperative radiation is the established therapeutic method in glioblastoma management [15, 17]. In our retrospective analysis the efficacy of radiation with 50 to 65 Gy was confirmed. In our data we also saw, that patients with interrupted radiation <50 Gy had a shorter mean survival time (238 vs. 463), but we have to note that this effect may be due to observer bias.

The role of *chemotherapy* is discussed in the literature. In the seventies The Brain Tumour Study Group [26], and later also other authors [2, 18], proved an increase of survival time by supportive treatment of BCNU or other nitrourea compounds. In later years many attempts were made to find other application routes and new agents [19, 22]. Kornblith *et al.* [14] summarized some publications concerning this issue and conclude, that the role of chemotherapy is adjunctive and that interpretation of data is rather difficult [14, 15]. Our study showed a positive effect of chemotherapy ($p < 0.01$), however, the positive effect of chemotherapy alone may be greater than we observed due to the fact that almost all patients had been additionally irradiated ($n = 25$), so the chemotherapy effect is overlapped by the effect of radiation. The effect of radiation alone ($n = 54$) seems to be equal to that of chemotherapy ($n = 5$), but the small number in this subgroup does not allow a statistical evaluation.

Like other authors [9, 17, 23] we could confirm that a younger patient and a high KPS have a positive influence on survival.

Like other investigators [4, 7] we found that *re-operation for recurrent glioblastoma* seems to be useful. Our patients had a mean postoperative survival time after re-operation of 226 days which is more than the mean survival time after the first operation without supportive treatment. This suggests that a second effort to reduce the tumour volume is rewarding, with benefit for the patients.

Many *other therapeutic attempts* like PDT [11, 16], brachytherapy [24], immunologically-directed therapy [6, 25], hyperthermia [5], and various combinations did not improve the prognosis of glioblastoma.

Conclusions

We conclude from our results that complete tumour resection combined with postoperative radiotherapy and chemotherapy is the best treatment for glioblastoma at the moment. Re-operation of recurrences also improved the survival. We doubt that it is ethically acceptable to neglect any therapeutic possibilities in the management of malignant brain tumours.

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