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Clinical study

Prognostic factors for high-grade malignant glioma: Development of a prognostic index

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Summary

Although the prognosis of high grade malignant glioma patients is generally poor, it is possible to identify groups of patients with varying prognoses. Basing our results on the first MRC glioma study, multivariate methods were used to identify prognostic factors independently associated with the length of survival. Young age, the presence of fits, especially of long duration, extensive surgical removal of tumour and good clinical performance status were found to be the most important predictors of longer survival. The effect of tumour grade (3 or 4) was not significant, being considerably diluted by an association with extent of neurosurgery. A prognostic index was derived which split the patients into 6 groups of varying prognoses, with 2-year survival rates of between 1 and 32%. The results were verified in patients entered into a subsequent MRC trial. The successful identification of different prognostic groups suggests the use of this index as an aid in making treatment decisions for individual patients, and in interpreting the results of uncontrolled phase II studies.

Introduction

The results of treatment of patients with high grade supratentorial astrocytomas are poor. Prospective randomised studies have confirmed the benefit of postoperative radiotherapy [1–3]. Adjuvant chemotherapy usually with a nitrosourea drug is of less well proven value but is frequently employed [4]. Even with the best results median survival times of around 9 months and two year survival rates of 5–10% are reported [5]. This has led to some expression of the view that it is unjustified to treat patients with grade 3, 4 and glioblastoma multiforme tumours once a diagnosis is established. The identification of groups of patients with favourable prognostic factors should therefore be an advantage in deciding on treatment strategies.

Several groups have described analyses on the influence of prognostic variables in their studies (BTSG [3, 4] ECOG/RTOG [6], EORTC [7]). Important factors which have been identified include age of patient, performance status, duration of symptoms and tumour grade. Other factors have been reported as being possibly related to survival such as blood group, pretreatment white cell and platelet counts and the level of consciousness after

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surgery [8]. In this paper an analysis of prognostic factors identified in two Medical Research Council (MRC) postoperative radiotherapy studies for high grade glioma is presented. The first study [9] investigated the effect of adding the radiosensitizer misonidazole to postoperative radiotherapy of 45 Gy in 20 fractions over 4 weeks. The second study, still in progress, is comparing the effect of the previously used radiation dose regime with that of a higher dose.

In structuring our investigation of prognostic factors we have taken advantage of these two studies. A full analysis of prognostic factors in the misonidazole study including multivariate methods is used to derive a prognostic index which separates patients into groups of varying prognosis. The ability of this prognostic index to predict length of survival is then tested on the patients in the second study.

Patients and methods

The main results on prognostic factors presented in this paper are drawn from the group of eligible patients entered into the MRC study of misonidazole. This was a multicentre double-blind, randomised study which aimed to assess the value of the radiosensitizer misonidazole in combination with radiotherapy for the treatment of malignant gliomas, grade 3 and 4.

Patients were eligible for the study only if:

1. Histological proof of supratentorial astrocytoma grade 3 or 4 was available and later confirmed by a central panel of 3 pathologists.
2. Their age was between 18 and 70 years on the day of entry.
3. No previous treatment had been given except aspiration, biopsy, surgical removal, corticosteroids or anticonvulsants.
4. They were not pregnant.
5. They had no previous or concurrent malignancy (except basal or squamous cell carcinoma of the skin).
6. Their neurological and mental function was not so seriously impaired as to make radiotherapy undesirable.
7. They had no other serious condition likely to prejudice treatment or to complicate the assessment of progress.
8. Their blood urea was within normal limits.
9. They had no significant liver damage as judged by clinical and biochemical examination.

Patients were allocated by randomisation to receive capsules of either misonidazole or placebo with radiotherapy. Radiotherapy was scheduled to be given within 3 weeks of neurosurgery, the prescribed minimum tumour dose being 4500 cGy. This was to be given in 20 equal-dose fractions, 5 days per week for 4 weeks.

The study commenced in January 1979 and patient entry was closed in September 1982. During this period, 482 patients were entered into the study from 19 centres. Of these, 417 patients were eligible.

To verify the prognostic factor results obtained from the misonidazole study, we used the data from the group of eligible patients entered into the subsequent MRC study. This study, the MRC radiotherapy dose study (BR2), was ongoing at the time of analysis, having commenced patient entry in April 1983. Its aim is to evaluate the effect of two radiotherapy dose levels in the treatment of malignant glioma grade 3 and 4.

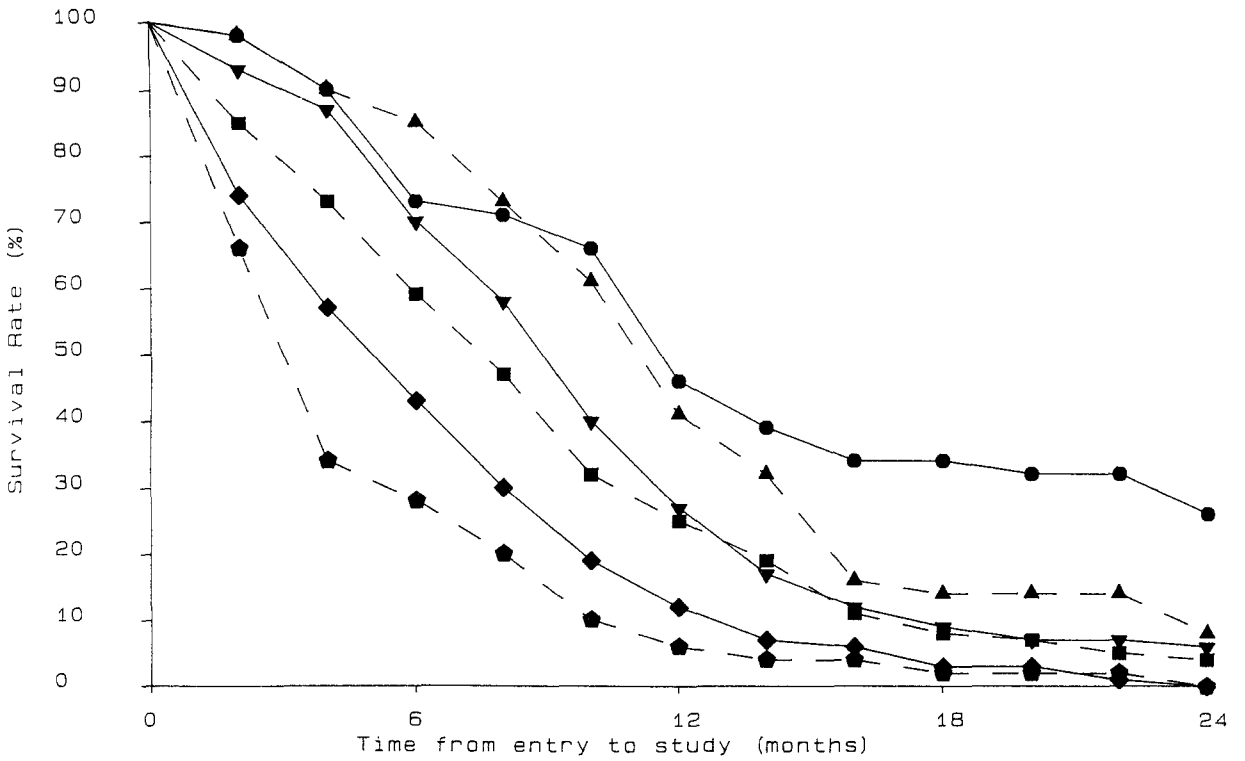
Eligible patients were randomised to receive either 4500 cGy in 4 weeks: 20 × 225 cGy fractions to brain

or

6000 cGy in 6 weeks: 20 × 200 cGy fractions to brain, followed by a 2000 cGy boost to the tumour in 10 × 200 cGy fractions.

The eligibility criteria were the same as for the misonidazole trial. Between April 1983 and September 1986, 311 patients were entered into this study, of whom 22 were subsequently found ineligible.

Results on prognostic factors were based on the analysis of survival times from date of entry to the study. The actuarial method [10] was used to calculate survival rates based on deaths grouped into monthly intervals. Linear interpolation from the actuarial survival curves was used to calculate median survival.



MRC Misonidazole study: Prognostic index

Group 1: Index in range 0–10
Group 2: Index in range 11–15
Group 3: Index in range 16–20
Group 4: Index in range 21–25
Group 5: Index in range 26–33
Group 6: Index in range 34–38

To assess the importance of individual prognostic factors, the logrank test [10] was used to examine overall differences in survival curves. However, in assessing factors associated with prognosis, it is important to apply multivariate techniques, so that the joint effects of prognostic variables acting simultaneously can be determined. Correlations between different prognostic variables may exist. The multivariate analysis is able to select out the variables which are independently most closely related to prognosis. Thus two variables which are highly correlated are unlikely both to be selected as important by a multivariate analysis, since one will, at least in part, replicate the information provided by the other. Cox's proportional hazards regression model [11] was used for our study.

Results

A number of pretreatment factors were investigated for their possible prognostic value:

1. Age;
2. Clinical performance status before radiotherapy as measured on the WHO scale (see appendix);
3. Neurological status;
4. Extent of neurosurgery;
5. Previous history of fits (yes or no);
6. Length of history of fits;
7. Sex;
8. Tumour grade;
9. Dexamethasone dose.

Of these, only sex and tumour grade (see below) were not individually significantly related to surviv-

Table 1. Tumour grades given by three pathologists in the misonidazole study

Tumour grade	Pathologist 1	Pathologist 2	Pathologist 3
Ineligible	8%	13%	16%
3	33%	69%	21%
4	59%	18%	63%

Table 3. Tumour grade by extent of neurosurgery

Extent of neurosurgery	Consensus tumour grade		Total
	3	4	
Biopsy	95 (57%)	73 (43%)	168
Partial resection	65 (41%)	95 (59%)	160
Complete resection	11 (16%)	57 (84%)	68

al. Neurological status was highly correlated with clinical performance status. Dexamethasone was prescribed at the individual clinician's discretion, and in view of its dependence on the individual management policy, dexamethasone dosage was not considered a reliable prognostic factor and was not considered further.

Tumour grading

The grade of tumour was assessed, according to the Kernohan and Sayre criteria [12], by a panel of 3 pathologists. They assessed the slides as ineligible pathology, grade 3 or grade 4 tumour (thus this classification would include those tumours described by other systems as glioblastoma multiforme, and anaplastic astrocytomas).

There was considerable divergence of opinion. Thus, Table 1 shows the proportions of the 482 patients assigned to the various grades by the different pathologists. Pathologist 2 assigned grade 3 more frequently than the others – the percentage of cases in which pathologist 2 agreed with pathologist 3 was 42% and with pathologist 1 was 47%. In contrast, there was 65% agreement between pathologist 1 and 3.

Pathologist 2 was the only one involved in both studies. In the BR2 study, the level of agreement was higher and more consistent than in the earlier one, with 61% agreement between 1 and 2, 62% between 1 and 3, and 61% between 2 and 3.

The tumour grade was taken to be the majority decision of the 3 pathologists. Based on this, 41 patients in the Misonidazole study were found pathologically ineligible. Of the 417 eligible patients, 171 had grade 3 tumours and 225 grade 4. In the remaining 21 cases each pathologist gave a different assessment.

The actuarial survival rates for consensus tumour grade in the misonidazole study at 6, 12, 18 and 24 months are given in Table 2. The survival curves are not significantly different ($X^2 = 0.13$ on 1 d.f., $P = 0.72$) and for grades 3 and 4, the median survival times are 33 and 36 weeks respectively. Similar results are obtained using tumour grade as assessed by any one of the 3 individual pathologists instead of the consensus grade.

Of 263 eligible patients in the BR2 study, 91 were given consensus grade 3, 156 grade 4 and in 16 no majority decision was reached. In this study the

Table 2. Tumour grade related to survival rates

	Consensus tumour grade	Survival rates (%)			
		6 month	12 month	18 month	24 month
Misonidazole study	3	55	23	13	7
	4	60	24	6	4
BR2 study	3	70	42	31	23
	4	68	30	14	8

Table 4. Tumour grade and extent of neurosurgery related to 2-year survival rates in the misonidazole study

Consensus tumour grade	Extent of Neurosurgery			Total
	Biopsy	Partial resection	Complete resection	
Grade 3	4%	15%	27%	10%
Grade 4	4%	2%	10%	5%

tumour grade assessed by 2 of the 3 individual pathologists was significantly related to survival time, with patients having grade 3 tumours faring better. This was reflected in the survival rates for the consensus tumour grade, given in Table 2 and in the median survival time – 43 weeks for grade 3 patients and 38 for grade 4.

A possible contributory reason for the apparent lack of association between tumour grade and survival in the misonidazole study, was the evident association between tumour grade and extent of neurosurgery (Table 3). A significantly greater proportion of patients having biopsy were diagnosed as grade 3 compared to those having partial or complete resection ($X^2 = 32.9$ on 2 d.f., $P < 0.001$). This relationship would distort any direct relationship between tumour grade and survival, because patients with biopsy tend to have a shorter survival than those following more extensive surgery (see Table 5).

A stratified analysis was carried out in order to examine the possible masking of a tumour grade effect. Table 4 shows the 2-year survival rates by grade, stratifying by extent of neurosurgery. It shows that in patients on whom more extensive neurosurgery was performed, survival of patients with grade 3 tumours is improved over those with grade 4. Such a difference was not apparent amongst patients having biopsy only who form nearly half the study group. Overall, a stronger relationship between grade and survival emerges, although still not statistically significant: the unadjusted logrank X^2 is 0.13 on 1 d.f. ($P = 0.72$); after adjusting for extent of neurosurgery the logrank X^2 becomes 2.24 on 1 d.f. ($P = 0.13$).

Table 5. Prognostic factors found to be important in the misonidazole study

		No. patients	Median survival (weeks)	Survival rates (%)			
				6 month	12 month	18 month	24 month
Age	< 45	95	48	76	36	23	17
	45–59	193	36	60	23	6	3
	> 59	129	19	40	12	3	1
Clinical performance status	0–1	201	41	67	30	13	8
	2	73	35	62	22	7	3
	3–4	143	22	41	13	4	1
Extent of neurosurgery	Biopsy	178	23	44	14	8	4
	Partial resection	168	38	65	25	10	7
	Complete resection	71	45	69	38	14	9
History of Fits	None	306	30	54	20	6	3
	< 3 months	55	30	59	24	10	6
	≥ 3 months	56	49	69	39	23	17

A similar association between grade and extent of neurosurgery was found in the BR2 study.

Prognostic index

Cox's proportional hazards regression model was used to identify the factors which should be included in the prognostic index. Age, extent of neurosurgery, length of history of fits, presence or absence of fits, clinical performance status, neurological status, and tumour grade were initially included in the model. Both forward and backward stepwise variable selection procedures identified age, performance status, length of history of fits and extent of neurosurgery as the only independently important variables. The actuarial survival rates for the above 4 factors at 6, 12, 18 and 24 months are presented in Table 5. In the BR2 radiotherapy dose study, these factors were also found to be of prognostic importance with a similar strength of relationship to length of survival as in the Misonidazole study. Using this moded leads to the result that the log hazard rate of each patient is incremented by an amount:

$$\beta 1 \times \text{age group} + \beta 2 \times \text{clinical performance status} + \beta 3 \times \text{type of neurosurgery} + \beta 4 \times \text{history of fits} \quad (1)$$

where each factor is measured on a 3-point scale and the values of $\beta 1$, $\beta 2$, $\beta 3$, $\beta 4$ are the estimated regression coefficients from the model (Table 6).

The expression [1] was then simplified to define a prognostic index:– each level of each of the 4 factors was given a 'score', related to the relative magnitude of its estimated regression coefficient. The individual factor scores thus indicate the relative importance of the prognostic factor (Table 6). The scores of the four factors are added to give the value of the prognostic index for an individual patient. A high score on the composite index indicates a worse prognosis than a low one.

The index was calculated for each of the 417 eligible patients in the misonidazole study. The patients were then divided, by score, into 6 subgroups. The survival curves of these subgroups are shown in figure 1. Two-year survival rates and median survival times are shown in Table 7. One group, those with index in the range 1–10 was identified as having a particularly good prognosis – a median survival of 12 months, and a two-year survival rate of 32%. However, this subgroup accounted for only 41 patients, 10% of the total.

When the same procedure was applied to patients in the BR2 study, the predictive ability of the prognostic index was confirmed. The second prognostic group, those with an index in the range 11–15 had nearly as good a prognosis as the first group,

Table 6. Definition of index

Prognostic factor	Category	Coefficient (SE)	Score
Age	< 45		0
	45–59	0.33 (0.07)	6
	⩾ 60		12
Clinical performance status	0–1		0
	2	0.21 (0.06)	4
	3–4		8
Extent of neurosurgery	complete resection		0
	partial resection	0.23 (0.07)	4
	biopsy		8
History of fits	⩾ 3 months		0
	< 3 months	0.26 (0.07)	5
	none		10

Index = sum of scores for each factor.

and these two top groups comprised nearly 30% of patients (Table 8). These patients had a median survival of around 18 months, and a two-year survival rate of about 35%. In addition it was confirmed that the groups of patients with an index greater than or equal to 26 had a very poor prognosis, with a median survival of less than 6 months. In the BR2 study there were no survivors in these groups after 2 years.

Table 8. Survival according to prognostic index score in the BR2 study

Prognostic index score	Number of patients	Median survival	2-year survival
0–10	29 (11 %)	80 weeks	39 %
11–15	46 (17 %)	76 weeks	33 %
16–20	56 (21 %)	46 weeks	16 %
21–25	43 (16 %)	33 weeks	7 %*
26–33	53 (20 %)	28 weeks	0 %
34–38	38 (14 %)	19 weeks	0 %

* Follow-up to 21 months only.

Discussion

Our analysis has identified 4 factors of independently significant prognostic value:– age, clinical performance status, extent of neurosurgery and length of history of fits. These results are in general agreement with previous studies, all of which confirm the importance of age and performance status – measured on various scales – as prognostic factors. Evidence concerning extent of neurosurgery is conflicting. No relationship with prognosis was found by Brisman [13] and Eyre [14], whereas Gehan [15] and Chang [6] found a strong relationship, as we have done. The fact that its significance has been confirmed in successive multicentre MRC trials suggest that, for wide range of U.K. neurosurgical practice at least, it is an important prognostic factor. The length of history of fits, in itself, does not appear the have been studied elsewhere, although presence or absence of fits, and duration of symptoms have. These have generally been found to be of prognostic importance, with one exception [15]. A possible explanation of the relationship of symptoms of fits to length of survival is that they lead to earlier detection of the tumour and hence a longer period between detection and death [16].

The question of prognostic importance of tumour grade is debatable. Other studies [6, 13, 14] have also found no prognostic value in dividing high grade gliomas into Kernohan grade 3 or 4. Nelson's classification [17] of malignant glioma based on the presence or absence of tumour necrosis, has been found more useful in terms of predicting prognosis [6]. The observation that tumour grading is related to extent of neurosurgery has not been made before. This could account for some of the failures to discover an important relation between grading and survival. It would be of interest to investigate whether other studies have found this relationship and particularly whether it applies also to Nelson's classification. The most likely explanation of the relationship between grading and extent of neurosurgery is that the more extensive sampling, possible in tumours which have been partially or completely removed, enables the pathologist to discover areas of higher grade tumour.

A number of other factors have been proposed

Table 7. Survival according to prognostic index score in the misonidazole study

Prognostic index score	Number of patients	Median survival	2-year survival
0–10	41 (10 %)	53 weeks	32 %
11–15	41 (10 %)	51 weeks	11 %
16–20	92 (22 %)	41 weeks	7 %
21–25	73 (18 %)	35 weeks	4 %
26–33	120 (28 %)	23 weeks	1 %
34–38	50 (12 %)	16 weeks	2 %

Table 9. Other factors with possible prognostic values

a.	ABO blood type[8]
b.	WBC count[8]
c.	Platelet count[8]
d.	Consciousness level after surgery[8]
e.	Involvement of cranial nerves II, III, IV, VI.[15]
f.	Location of tumour[15]
g.	Personality changes[4]
h.	Speech impairment, visual disturbance[6]
i.	Other pathological criteria[15]

for their possible prognostic value – these are listed in Table 9. None of these were documented in the MRC misonidazole study. These factors need to be studied further to confirm their importance, since when large numbers of factors are considered, it is possible that some will be found significant by chance. In addition, these features may be replicating information provided by other, more established prognostic factors. However, Green, Byar and Walker [8] found ABO blood type, WB count, platelet count and consciousness level after neurosurgery to be of importance independent of age, histologic grade and clinical performance status.

The prognostic index described here was successful in identifying distinct groups of patients with varying prognoses. This suggests the use of the index to gain some broad indication of the likely course of the disease for an individual patient which may be of some help in patient counselling. Further, it may possibly be used as an aid to decide on a course of treatment. For example one might perhaps adopt a more innovative regime undergoing phase II investigation for a patient with an otherwise very poor prognosis.

While the index has been tested and verified on a second independent set of patients, it would be useful to check it on a series of patients not entered on MRC protocols, where primary therapy may not be exactly the same or where some of the prognostic factors may be assessed in a different manner.

The clear separation between 'good' and 'bad' prognosis patients, based on 4 prognostic factors, indicates the misleading results which could be obtained if differences in prognostic factors are not allowed for in treatment comparisons. Knowledge of prognostic factors should be utilised to interpret treatment results, particularly in uncontrolled trials. When random allocation to treatment is employed in a trial prognostic factors will on average be balanced between treatment groups but in small trials substantial imbalances can occur. For example in a randomised trial of CCNU versus no chemotherapy for malignant glioma, reported by Garrett and co-workers [18], the considerable differences in survival between the two groups were found to have been greatly enhanced by an age imbalance between them.

The need to record prognostic factors, and to refine treatment comparisons, particularly in phase II trials but also in other studies with small numbers of patients should therefore be emphasised.

Appendix

Clinical Performance Status: WHO Scale

0 Able to carry out all normal activity without restriction
1 Restricted in physically strenuous activity but ambulatory and able to carry out light work
2 Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours
3 Capable only of limited self-care; confined to bed or chair more than 50% or waking hours
4 Completely disabled; cannot carry out any self-care; totally confined to bed or chair

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