Application of the MRC brain tumour prognostic index to patients with malignant glioma not managed in randomised control trial

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Abstract

Objectives—The MRC brain tumour prognostic index, which uses clinical variables to place patients in different outcome categories, has not been evaluated on a cohort outside a randomised controlled trial. The aims of this study were to (a) determine in a large cohort of patients, derived solely from one centre and not in a clinical trial, whether the MRC prognostic index stratified patients for outcome; (b) compare actual outcomes with those obtained in the original studies; and (c) examine whether neuropathological diagnosis was an independent prognostic variable.

Methods—The MRC prognostic index was calculated for 236 patients with either glioblastoma or anaplastic astrocytoma managed at a dedicated neuro-oncology clinic in Edinburgh between 1989 and 1995.

Results—For this mixed population of malignant glioma the median survival was 8.6 months. Two year survival was 72.2% for patients with an MRC index score of 1–10; 36.3% for those with an index score of 11–15; 25.1% for those scoring 16–20; 20.4% with those scoring 21–25; 4.8% with those scoring 26–33; and 0% for those scoring 34–38. Exclusion of 79 patients who would not have been eligible for the MRC studies from which the index was derived, because they were either too old or did not receive radiotherapy, still resulted in a similar pattern of stratification but with significantly improved median survival times for the lowest two categories. Multivariate analysis of prognostic variables in the Edinburgh cohort showed that patients with anaplastic astrocytoma did significantly better than those with glioblastoma ($p < 0.001$).

Conclusions—Although there were some differences in median survival times between the patients in the original MRC studies and the Edinburgh cohort in similar prognostic categories and a tendency to improved two year survivorship in the Edinburgh cohort these differences have arisen because (a) the Edinburgh cohort was accrued about 10 years later than the MRC cohorts and thus had optimal radiotherapy; and (b) many Edinburgh patients were included in experimental and other chemotherapy studies on relapse. This

study has shown that even outside the setting of a prospective controlled trial and with relaxed inclusion criteria the Medical Research Council (MRC) prognostic index is a robust predictor of outcome in patients with malignant glioma. Survival clearly declines as the prognostic index increases. Moreover, the prognostic model can be substantially improved by the addition of histology data, although there is some evidence that this will require complex modelling procedures.

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Patients with malignant glioma, glioblastoma or anaplastic astrocytoma, have a poor prognosis with most prospective randomised controlled trials showing median survival times of around 10 months.^{1–5} It is pertinent to note that these series report patients who are selected for optimal treatment and by no means reflect the overall outcome of patients with malignant glioma. An audit of practice in south east Scotland, which is served by a dedicated neuro-oncology service, showed that only 39% of patients with malignant glioma receive surgery or radiotherapy.⁶ The reasons for this selection are multifactorial⁷ but are largely determined by clinicians' perceptions of likely outcomes in certain categories of patients. The identification of clinical prognostic variables was modelled in the Medical Research Council (MRC) brain tumour prognostic index (appendix) which was described in 1990.⁵ This study confirmed the importance of advanced patient age, poor performance status, no history of seizures, and limited surgical resection of the tumour as all being independent, significant poor prognostic variables. These four variables are easily measured in routine practice, making the MRC index an attractive prognostic aid. The importance of some of these variables has been confirmed in other studies. The main areas of controversy concern the importance of the extent of surgery and of neuropathological diagnosis.^{1–5, 8–10} Some series have not found the extent of surgery to be a significant variable,^{4, 5} and others have found that patients with anaplastic astrocytoma do significantly better than those patients with glioblastoma.^{8, 9}

The data for the MRC brain tumour prognostic index were derived from one prospective randomised controlled trial (MRC study of misanidazole, accrued 1979–83) and

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Table 1 Data for all patients (n=236) treated in Edinburgh between 1989 and 1995 with malignant glioma grouped according to MRC prognosis score

Category	n	Survival time (weeks) median	(95% CI)	Survival for 2 y (%)	(95% CI)
1-10	24	Not reached	—	72.2	(55-94)
11-15	27	86	(55.3-128)	36.3	(21-64)
16-20	39	43	(33-90)	25.2	(14-44)
21-25	39	35	(27-74.6)	20.4	(11-39)
26-33	69	30	(24-41)	4.8	(0-14)
34-38	38	9	(6.4-19.3)	0.0	—

then validated in another prospective study (BR-2 a study of different radiotherapeutic treatments in malignant glioma, accrued 1983-6).^{3,11} The authors in their paper suggested that the generalisability and validity of the index should be checked in patients not managed on MRC protocols and where primary treatment may be different.⁶ The aims of this study were therefore (a) to determine whether the MRC prognostic index stratified outcomes for patients with malignant glioma managed at a dedicated neuro-oncology clinic, (b) to compare these outcomes with those predicted by the MRC prognostic index, and (c) to evaluate the significance of neuropathological diagnosis and the extent of surgery as independent prognostic variables.

Methods

PATIENT COHORT

The case files on all patients diagnosed as having a glioblastoma or anaplastic astrocytoma in the Department of Clinical Neurosciences, Edinburgh, between 1 January 1989 and 30 November 1995 were reviewed. Data retrieved from the case files and neuropathology database include patient age, sex, performance status before surgery with the World Health Organisation (WHO) scale, presence and duration of preoperative seizures, date of surgery, type of surgery (biopsy, partial resection, or macroscopic resection), tumour neuropathology, death within 30 days of diagnosis, radiotherapy and chemotherapy, and date of death. From these data the MRC prognostic index of each patient was calculated. The tumour neuropathology had been reviewed by a neuropathologist (JWI) who has taken part in MRC brain tumour trials. The WHO tumour

grading system was used and in particular if no necrosis was found in the tumour specimen it was termed an anaplastic astrocytoma.^{8,9}

STATISTICAL METHODS

Median survival and survival curves within each MRC prognosis group were estimated by the Kaplan-Meier method for (a) all patients; and (b) only those within the original MRC criteria. Two year survival was compared with that reported in the original paper.⁵ A Cox's regression model was used to assess the influence of year of referral, sex, radiotherapy, and histology after controlling for the effects of case mix incorporated into the MRC score, with time dependent covariates modelled as appropriate.¹² All analysis was carried out with Splus for Windows, StatSci Europe, Oxford, UK.

Results

During the period encompassing the study 236 patients (147 male; 89 female) had a malignant glioma, 158 had a glioblastoma, and 78 had an anaplastic astrocytoma. Surgery performed included 99 stereotactic biopsies and 137 craniotomy and resection. Resections were considered macroscopic in 64 patients and partial in 73. Thirty day mortality was 12 patients (4.9%). One hundred and twenty seven patients had radical radiotherapy (60 Gy in 30 fractions) and 31 had palliative radiotherapy (30 Gy in six fractions). The cohort includes 79 patients who were either aged over 70 years or who did not have radiotherapy (both these categories would have been excluded from the MRC trial data).

When all the Edinburgh patients were analysed the MRC brain tumour prognostic index proved to be a highly significant predictor of survival (log rank test, $p < 0.001$) with a clearly increasing hazard ratio for progressive categories (table 1). The figure shows the Kaplan-Meier survival curve estimates for each category of MRC prognostic index. Clearly the index stratifies patients in terms of survival, although there may be some difficulty in distinguishing the groups from 16-20, 21-25, and 26-33 during the first year.

When the index was applied to only those patients eligible for inclusion in the MRC trial (n=157) a similar pattern of stratification was attained but outcomes were significantly better in the poorest two prognostic categories (table 2). This occurred as the greater proportion of excluded patients (no radiotherapy or age >70) were from the worst two outcome categories.

When the median survival times in each of the prognostic categories of the MRC BR-2 study, which was accrued from 1983-6, were

Kaplan-Meier survival curves for all patients (n=236) stratified by MRC prognostic index score.

Table 2 Data for patients ($n = 157$) treated in Edinburgh with malignant glioma (1989–1995) who would have been eligible for the MRC brain tumour trial protocols are included in this table (patients > 70 years and not receiving radiotherapy have been excluded)

MRC score	<i>n</i>	Survival time (weeks) median	(95% CI)	Survival for 2 y	(95% CI)
1–10	19	Not reached	—	77.0	(60–100)
11–15	25	85	(55–128)	37.0	(21–65)
16–20	28	67	(40—)	36.0	(21–60)
21–25	33	41	(30–91)	24.0	(13–45)
26–33	43	44	(40–54)	3.9	(1–23)
34–38	9	28	(19—)	0.0	—

The comparative outcomes from the BR-2 study are; MRC score 1–10, median survival time 80 weeks, 2 year survival 39%; score 11–15, 76 weeks, 33%; score 16–20, 46 weeks, 16%; score 21–25, 33 weeks, 7%; score 28 weeks, 0%; and score 34–38, 19 weeks, 0%.

compared with the respective eligible Edinburgh cohorts the median survival times were very similar, but consistently higher for the Edinburgh cohort in all prognostic categories. However, formal statistical testing of whether this is significant would require access to individual patient data from the MRC database.

A Cox's regression model was fitted to the full dataset, with the six categories of the MRC prognostic index as a case mix adjusting variable. The effect of year of referral (1989–91, 1992–4, or 1995), histology (anaplastic astrocytoma or glioblastoma), and sex were assessed by adding these variables to this model simultaneously. Both year of referral ($\chi^2=16.0$, $p=0.0003$) and histology ($\chi^2=21.9$, $p<0.0001$) were independently significant, but sex was not ($\chi^2=2.44$, $p=0.118$). Checking of the proportional hazards assumption, however, suggested that the hazard ratio for patients with glioblastoma relative to those with anaplastic astrocytoma was not constant over time (Grambsch-Therneau test¹³, $p = 0.005$). Diagnostic plots suggest that the hazard ratio of glioblastoma relative to anaplastic astrocytoma is increasing over time. To approximate this behaviour, a time dependent covariate which modelled the hazard ratio as an increasing step function was used. Thus the hazard ratio was assumed to be constant from zero to 12 months, from 12 to 24 months, and from 24 months onwards, but differed between intervals. Continually varying time dependent covariates require highly specialised software to implement, and we thought that this solution was both adequate for our purposes and simple to interpret. The choice of times at which the hazard ratio "jumps" is essentially arbitrary, but the use of one year periods seems preferable to a more data dependent strategy. Table 3 shows the estimated hazard ratios and associated 95% confidence intervals (95% CIs) for this model.

The MRC prognostic index shows a clearly increasing hazard ratio with increasing index score. Similarly both the year of referral and histology are important prognostic factors for this dataset. After adjusting for these factors, there was no evidence that survival was in any way related to sex.

Discussion

The MRC prognostic index was derived and validated by statistical analysis of patient data in two MRC trials that accrued patients between 1979 and 1986. Unlike several other studies,^{1 8 9} including this one, it did not predict

that patients with anaplastic astrocytoma did significantly better than those with glioblastoma. The explanation for this finding related to differences of opinion about actual tumour diagnosis (anaplastic astrocytoma v glioblastoma) between the three neuropathologists reviewing the histology.⁵ In contrast all tumours in the Edinburgh series were reviewed by one neuropathologist who had previously worked on MRC trials. The two MRC studies also showed that the diagnosis of anaplastic astrocytoma was more common in biopsy specimens than resection specimens. Because patients with biopsy fared worse than those with resection the beneficial effect of lower grade tumour was diminished. The median survival times for patients with anaplastic astrocytoma in the two MRC studies were only 33 weeks (misonidazole) and 43 weeks (BR-2) which are significantly less than the 90 weeks in our cohort that included elderly patients and some patients who did not have radiotherapy, and two to three years in other prospective randomised controlled trials.^{8 9}

There are several explanations for the differences in survival in the best (score 1–10) and worst (score 34–38) prognostic categories between the total Edinburgh cohort and the MRC BR-2 findings.¹¹ The fact that the patients with a poor prognosis in the Edinburgh cohort had poorer survival than the original group may be explained by the number of patients over 70 years and the many patients who did not have radiotherapy. Both these factors, which are associated with a bad outcome, would have been exclusion criteria for the MRC study. Exclusion of these patients from

Table 3 Cox regression model fitted to all patients ($n=236$) with malignant glioma showing effect of each prognostic variable after adjusting for all others

Covariate	Hazard ratio (95% CI)	<i>p</i> Value
MRC score:		
1–10	1	<0.0001
11–15	5.00 (1.94–12.9)	
16–20	6.54 (2.65–16.1)	
21–25	7.30 (2.92–18.2)	
26–33	11.2 (4.59–27.6)	
34–38	35.8 (13.9–92.0)	
Year:		
1989–91	1	0.0002
1992–94	0.65 (0.48–0.88)	
1995	0.28 (0.12–0.62)	
GBM v AA:		
0–1 y	1.84 (1.19–2.88)	<0.0001
1–2 y	3.65 (1.80–7.42)	
>2 y	26.4 (5.35–130)	
Male v female	1.27 (0.93–1.73)	0.132

p Values shown are based upon the likelihood ratio test for the deletion of each covariate from the full model. GBM = glioblastoma; AA = anaplastic astrocytoma.

the analysis led to a dramatic improvement in survival times of poor grade patients in the Edinburgh cohort. The substantially better outcome in the patients with the most favourable prognosis and improved two year survivorship probably emanates from the fact that the Edinburgh cohort was accrued 10 years after the MRC cohort.³⁻¹¹ In particular many patients in the two MRC studies received <60 Gy which is now regarded as appropriate radiotherapy for malignant glioma. The benefit of this higher dose of radiotherapy is also apparent in the two MRC studies where a significant improvement in the top two outcome categories occurred.⁵ Another factor contributing to better outcome in the Edinburgh patients with a good prognosis may have been that all the patients were managed at a multidisciplinary and dedicated neuro-oncology clinic. As a result of this focused care 75 of these patients were included in either conventional (procarbazine, CCNU, and vincristine) or experimental (phase II TCNU study; intraoperative carboplatin and TCNU studies; phase II carboplatin and RMP-7 studies) chemotherapy protocols after relapse.¹⁴⁻¹⁵ A previous MRC meta-analysis has shown that chemotherapy can significantly increase the percentage of patients surviving for 18 months but this treatment does not significantly increase median survival times.¹⁶ This improvement may also reflect the benefits of better neuroimaging, technical advances, improved postoperative nursing care, physiotherapy, and rehabilitation. Moreover, >73% of the Edinburgh resections were performed by one surgeon (IRW) and there was more uniform reporting of the estimated extent of surgical resection when compared with the inherent variability associated with many surgeons contributing to a multicentre trial.

This apparent temporal improvement is confirmed by the regression model. When the MRC index is used as a surrogate variable for case mix adjustment, more recent diagnosis and treatment is independently associated with a significantly better outcome. Furthermore, tumour histology (anaplastic astrocytoma or glioblastoma) was also a highly important prognostic factor in the Edinburgh cohort. Indeed, although the contribution of the extent of surgical resection to survival time remains controversial for both anaplastic astrocytoma and glioblastoma there is mounting evidence that the tumour subtype should be considered when modelling prognostic factors to determine outcome. None the less the excellent stratification obtained by the MRC index with specific or relaxed patient entry criteria is testimony to its robustness and validity outside the setting of a prospective randomised controlled

trial. The MRC index can therefore be used as one measure to adjust for case mix when comparing data from non-randomised clinical studies.

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Appendix:

The MRC brain tumour prognostic index

Prognostic factor	Score
Age:	0
<45	6
45-59	12
>60	
Clinical performance status:	
0-1	1
2	4
3-4	8
Extent of neurosurgery:	
Complete resection	0
Partial resection	4
Biopsy	8
History of fits:	
>3 months	0
<3 months	5
None	10

Index = sum of scores for each factor.

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