Management of glioma in Victoria (1998–2000): retrospective cohort study

Mark A Rosenthal, Katharine J Drummond, Michael Dally, Michael Murphy, Lawrence Cher, David Ashley, Vicky Thursfield and Graham G Giles

ABSTRACT

Objective: To describe the management of and outcomes in a population-based cohort of patients with newly diagnosed glioma.

Design, setting and patients: Retrospective cohort study of patients with glioma newly diagnosed over the period 1998–2000 in Victoria. Patients were identified from the population-based Victorian Cancer Registry (VCR). Doctors involved in managing the patients were surveyed by a questionnaire sent out in 2003. The cohort was followed until the end of 2004 to obtain at least 4 years' follow-up data on all patients.

Main outcome measures: Reported treatment, referral patterns and survival rates.

Results: Over the study period, 992 cases of glioma were identified; 828 completed surveys on eligible patients were obtained (response rate, 93%); 473 patients (57%) had glioblastoma multiforme (GBM); 105 patients (13%) diagnosed with "glioma" had had no histological confirmation. Complete macroscopic resection was performed in 209 patients (25%); 612 patients (74%) were referred for radiotherapy and 326 (54%) for chemotherapy; 39 (5%) were enrolled on a clinical trial. Median survival was 9.2 months for all patients and 7.4 months for patients with GBM.

Conclusions: This is the largest reported glioma management survey in the world to date. Much of the patient demographics and approach to treatment were as expected and represent a reasonable "standard of care". However, there are some areas for improvement, including the absence of histological diagnosis in some patients, lack of multidisciplinary care, low clinical trial enrolment and poor use of ancillary services.

MJA 2006; 184: 270–273

In Victoria in 2003, there were 346 cases of primary brain and central nervous system cancers with 341 deaths, making it the eighth most common cause of cancer-related death in Victoria.[1] The majority of these cancers are high-grade gliomas: glioblastoma multiforme (GBM), anaplastic astrocytoma and mixed anaplastic astrocytoma/oligodendroglioma. For patients with glioma, poorer prognosis is associated with increasing tumour grade, older age, worse performance status and residual disease after surgical resection.[2-4]

The standard approach to treatment of gliomas depends on the tumour grade. There are published US and European management guidelines for gliomas, but there are no Australian guidelines.[5,6] Further, little is known about current treatment practices in Australia. A recent study of glioma management across 52 US institutions demonstrated wide variation in the therapeutic approach to high-grade gliomas.[7]

In the largest study of gliomas ever reported, the Victorian Cooperative Oncology Group, in collaboration with the Victorian Cancer Registry (VCR), undertook to examine patterns of care for patients with glioma over a 3-year period. We report the results of the study here.

METHODS

Questionnaire

A population-based sample of all patients with glioma diagnosed in Victoria during 1998, 1999 and 2000 was identified from the VCR. Treating clinicians were identified by registry staff and sent a questionnaire relating to the management of each patient. The survey was sent out in 2003 and the sample followed until December 2004 to obtain outcome details for a minimum of 4 years' follow-up. The questionnaire was developed by a multidisciplinary steering committee with expertise in managing gliomas and included neurosurgeons, radiation oncologists, neurologists and medical oncologists. Eligible patients were those over 16 years of age diagnosed with glioma, including low-grade gliomas, anaplastic tumours and GBM.

The questionnaire was designed to confirm patient eligibility and to obtain specific details including patient demographics; referral patterns; and surgical, radiation and chemotherapy management. The questionnaire did not evaluate presenting symptoms and signs or diagnostic imaging practices. If the clinician indicated that the patient had been referred to another clinician (eg, medical oncologist, radiation oncologist), additional treatment details were sought from the other clinician.

Three weeks after the initial approach, registry staff contacted each non-responding clinician and offered assistance with completion of the questionnaires. Returned questionnaire responses were de-identified and scrutinised by the clinical investigators. Registry staff followed up to resolve any ambiguities in responses. Completed and checked questionnaires were coded and computerised by registry staff before statistical analysis.

Royal Melbourne Hospital, Melbourne, VIC.
Mark A Rosenthal, MB BS, FRACP, PhD, Medical Oncologist; Katharine J Drummond, MB BS, FRACS, Neurosurgeon.
William Buckland Radiotherapy Centre, Alfred Hospital, Melbourne, VIC.
Michael Dally, MB BS, FRANZCR, Radiation Oncologist.
St Vincent's Hospital, Melbourne, VIC.
Michael Murphy, MB BS, FRACS, MD, Neurosurgeon.
Austin Health, Melbourne, VIC.
Lawrence Cher, MB BS, FRACP, Neurologist.
Royal Children's Hospital, Melbourne, VIC.
David Ashley, MB BS, FRACP, PhD, Paediatric Oncologist.
Cancer Epidemiology Centre, Cancer Council of Victoria, Melbourne, VIC.
Vicky Thursfield, BSc, GradDipAppl Stats, Epidemiologist; Graham G Giles, MSc, PhD, Director.
Reprints will not be available from the authors. Correspondence:
Associate Professor Mark A Rosenthal, Royal Melbourne Hospital, Parkville, VIC 3055.
mark.rosenthal@mh.org.au

1 Number of completed responses to primary questionnaire and reasons for non-inclusion in our study*

	Number (%)
Ineligible	102 (10%)
No treatment information	30 (3%)
Not glioma	23 (2%)
Not a Victorian resident	19 (2%)
Outside study interval	11 (1%)
Concurrent malignancy	9 (1%)
Duplicate record	1 (< 1%)
Other	9 (1%)
Excluded	62 (7%)
Survey not returned	43 (4%)
Doctor died or retired	2 (< 1%)
Unable to locate doctor	6 (< 1%)
Record unavailable or lost	11 (1%)
Number of completed eligible surveys	828 (93%)

* Based on 992 cases identified from the Victorian Cancer Registry. ◆

2 Characteristics of the 828 eligible patients

Characteristic	Number (%)
Male	470 (57%)
Age (years)	
< 40	141 (17%)
40–60	253 (31%)
> 60	434 (52%)
Tumour site	
Frontal lobe	241 (29%)
Temporal lobe	170 (20%)
Parietal lobe	133 (16%)
Cerebrum	48 (6%)
Occipital lobe	38 (5%)
Other or not specified	198 (24%)
Side of tumour	
Left	374 (45%)
Right	351 (42%)
Bilateral	54 (7%)
Central	23 (3%)
Not specified	26 (3%)
Tumour grade	
I	8 (1%)
II	34 (4%)
III	139 (17%)
IV (GBM)	473 (57%)
Glioma but grade unknown	69 (8%)
No biopsy	105 (13%)

GBM = glioblastoma multiforme. ◆

The pathology results reported here represent the primary pathology report. All pathology reports were de-identified by registry staff.

Statistical analysis

Descriptive statistics were analysed using SPSS 13.0 release 10.0.1 (SPSS Inc, Chicago, Ill, USA).

Ethical approval

The Cancer Council of Victoria Institutional Ethics Committee approved the study.

RESULTS

Over the period 1998–2000, 992 glioma cases were identified from the VCR, of which 890 were eligible for our study. Completed questionnaires were obtained for 828 (93%) of the eligible cases (Box 1), with 695 (84%) of questionnaires completed by the survey data manager from clinicians' medical histories.

Patient characteristics

Patient characteristics are summarised in Box 2. There was a slight male preponderance. Just over half the patients were aged over 60 years, 264 (32%) over 70 years and 92 (11%) over 80 years. The median age of all patients was 72 years (range, 16–85 years). Tumour grade was determined in 654 patients (86%) who underwent biopsy or resection. A further 69 patients (8%) had a diagnosis of glioma without a grade specified. A significant proportion of ungraded tumours were the result of inadequate samples being taken from critical areas (including spinal cord and brainstem). Seventy-one per cent of tumours that were graded were GBM. Not all reports were from specialist neuropathologists.

Patients with no histological diagnosis

Of the eligible patients, 105 (13%) did not have a histological diagnosis. In such cases, the diagnosis of glioma was based on the clinical and radiological features of the illness. The reasons reported for no histological diagnosis included advanced age, anatomical location of the lesion, comorbidities and patient refusal. Only five of these patients (5%) received either radiotherapy or chemotherapy, with the remaining 100 patients receiving no therapy at all. This represents 12% of all cases of glioma reported in our study.

Management (Box 3)

Treatment for the most common glioma, GBM, included histological diagnosis, attempt at macroscopic resection, postoperative radiotherapy and chemotherapy (given either in an adjuvant fashion or at disease recurrence).

Among the 190 patients (23%) who underwent a biopsy procedure only, the major reasons included location of the lesion, extensive disease, multifocal disease and patient age.

Of the 256 patients who underwent craniotomy, 209 achieved a gross macroscopic resection and 247 a partial resection. Reported reasons for failure to achieve a gross macroscopic resection included location or extent of the lesion and involvement of cerebral vessels. There was no apparent change in surgical approach noted over the 3 years.

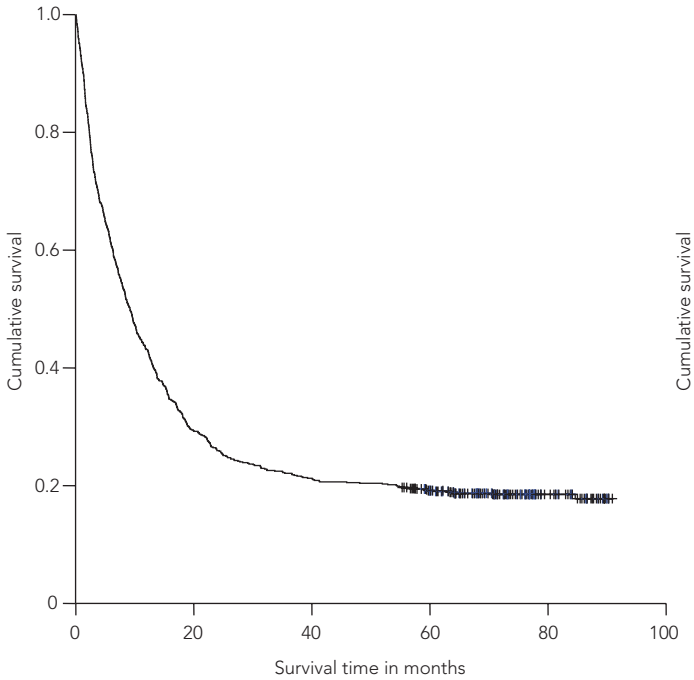
3 Management of gliomas

	Number (%)
Resection	
Complete	209 (25%)
Less than complete	247 (30%)
Biopsy only	190 (23%)
No biopsy	105 (13%)
Not specified	77 (9%)
Referral pattern	
To radiation oncologist at initial diagnosis	
All patients	612 (74%)
GBM	406 (86%)
To neuro-oncologist at initial diagnosis	
All patients	326 (54%)
GBM	147 (31%)
Clinical trial enrolment	39 (5%)
Radiotherapy given	
All patients	506 (61%)
GBM	322 (68%)
Chemotherapy given	
All patients	
Neoadjuvant or adjuvant	123 (15%)
At recurrence	175 (21%)
GBM patients	
Neoadjuvant or adjuvant	67 (14%)
At recurrence	198 (42%)

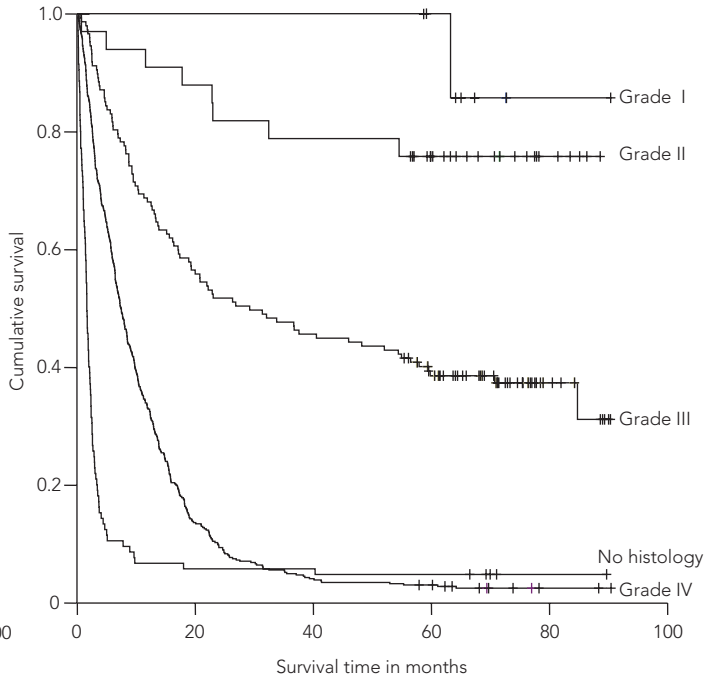
GBM = glioblastoma multiforme. ◆

4 Survival outcome

A: For all patients



B: According to tumour grade



Completed radiotherapy and chemotherapy questionnaires were obtained for 506 (83%) and 250 (77%) patients, respectively. Sixty-four patients (14%) were not referred to either a radiation oncologist or neuro-oncologist. Thirty-nine patients (5%) were enrolled onto clinical trials; 70 (8%) were referred for rehabilitation; and two were referred to either a psychiatrist or a psychologist.

A variety of radiotherapy set-ups, planning and field techniques were used. Most commonly, this involved a head immobilisation shell, computed tomography planning and a multifield technique using a variety of dose and fractionation schedules. For patients receiving chemotherapy, a broad range of agents and schedules were applied.

Survival

The overall survival times for all patients and for patients according to tumour grade are shown in Box 4. The median survival was 9.2 months (range, 0–84+ months) overall and 7.4 months (range, 0–84+ months) in patients with GBM. The 5-year survival rate was 19% for the entire cohort and 3% for patients with GBM.

DISCUSSION

Our retrospective cohort study examined the management of 828 patients with gliomas treated over a 3-year period. Gliomas represent a small but significant component of cancer incidence and mortality in Western societies. Over 50% are GBM with a median survival of 12 months. There have been incremental improvements in the treatment of these cancers, but management strategies are not well defined.

Our study documents many expected features in this patient group. At least half the patients were over 60 years of age and the majority had high-grade gliomas. As the Australian population ages, it is likely that more elderly patients with gliomas will be diagnosed. However, most management strategies have been based on younger patients and may not be appropriate for older patients because of more severe side-effects in older people.[5,6]

The general approach to management conformed to recent standards of care. That is, histological diagnosis was obtained, a macroscopic resection was performed (if feasible), patients were referred for radiotherapy and then received chemotherapy, either in an adjuvant fashion or at disease recurrence.[4,8-10]

However, several observations were of concern. Firstly, 13% of patients did not have a histological diagnosis and 23% had only a biopsy performed. The reasons for this were explored and generally reflected the patient's age, comorbidities, location of the lesion and patient refusal. Secondly, only 74% of patients were referred after initial diagnosis to a radiation oncologist and only 54% were referred to a neuro-oncologist. Thirdly, 12% of patients had no active anticancer therapy such as surgery, radiotherapy or chemotherapy. Fourthly, it appeared that few patients were referred for rehabilitation, allied health evaluation/support or psychiatric/psychological assessment. Finally, only 5% of patients were enrolled onto a clinical trial. This is similar to the overall rate of about 6% for all cancer types in the state of

5 Comparison of our GBM data with those from a US study[7]

	US study	Our study
Number of patients with GBM	418	473
Age > 60 years	49%	57%
Male	60%	58%
Macroscopic resection	46%	31%
Biopsy only	19%	21%
Radiotherapy	89%	68%
Chemotherapy	54%	56%

GBM = glioblastoma multiforme. ◆

Victoria (Susan Fitzpatrick, Executive Officer, Centre for Clinical Research in Cancer, Cancer Council of Victoria, personal communication) but lower than the 15% rate observed in the US Glioma Outcomes Project.[11]

Chang and colleagues recently reported a "patterns of care" survey similar to ours for 565 patients with malignant gliomas[7] — to date the largest such survey reported. A comparison of their findings with ours (Box 5) demonstrates very similar outcomes in the group of patients with GBM, apart from a lower rate of radiotherapy in our patients.

Our study has several limitations. Firstly, the very nature of the study design, a retrospective cohort study, will result in some biases and inaccuracies. Secondly, not all questionnaires were returned and we cannot speculate on the data relating to unreported patients. Thirdly, a proportion of patients who never had a biopsy confirmation of glioma may have had a non-glioma disease. Fourthly, the accuracy of the extent of resection estimated by the surgeon is unreliable.[12] Fifthly, there may be considerable under-reporting of the number of patients referred to allied health professionals. Finally, the cohort represents a period of 3 years, during which management practice may have changed. Indeed, it is now over 8 years since some of these patients were diagnosed and treated. However, we believe this is an important body of information regarding glioma management in Australia. It also establishes the "standard of care" during this period and will allow us to observe changes in practice.

The management of gliomas has become even more complex since the completion of our study, with a number of significant changes in treatment practice. The role of palliative chemotherapy (temozolomide) for recurrent high-grade gliomas has been established.[13-15] Concurrent radiotherapy and temozolomide therapy has now become the standard treatment for patients with newly diagnosed GBM.[16] In addition, the technology available to both surgeons and radiation oncologists has improved significantly. Furthermore, clinicians now have access to improved imaging techniques such as early postoperative magnetic resonance imaging and magnetic resonance spectroscopy, thallium scanning and positron emission tomography.

Management of gliomas requires a multidisciplinary approach by clinicians with an interest and expertise in the field. Just as important is the provision of ancillary services, including rehabilitation, allied health services, nurse coordinators, psychosocial support and community groups. Finally, the field of neuro-oncology must embrace clinical trials if we are to improve the care of our patients.

ACKNOWLEDGEMENTS

We gratefully acknowledge the support of the Cancer Council of Victoria, the Neuro-Oncology Committee of the Victorian Cooperative Oncology Group, the Victorian Cancer Registry, and the clinicians who completed the survey.

COMPETING INTERESTS

None identified.

REFERENCES

1 Thursfield V, Farrugia H, Billiet D, Giles G, editors. Cancer in Victoria 2003. Melbourne: The Cancer Council Victoria, 2004. (Canstat Series No. 41.)
2 Burton EC, Prados MD. Malignant gliomas. *Curr Treat Options Oncol* 2000; 1: 459-468.
3 Lacroix M, Abi-Said D, Fourney D, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg* 2001; 95: 190-198.
4 Sawaya R. Extent of resection in malignant glioma: a critical summary. *J Neurooncol* 1999; 42: 303-305.
5 National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. 2005. Available at: http://www.nccn.org/professionals/physician_gls/default.asp (accessed Feb 2006).
6 Stupp R, Pavlidis N, Jelic S; European Society of Medical Oncology Guidelines Task Force. ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up of malignant glioma. *Ann Oncol* 2005; 16 Supp l: i64-i65.
7 Chang SM, Parney IF, Huang W, et al. Patterns of care for adults with newly diagnosed malignant glioma. *JAMA* 2005; 293: 557-564.
8 Stewart LA. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002; 359: 1011-1018.
9 Laws ER, Parney IF, Huang W, et al. Survival following surgery and prognostic factors for recently diagnosed malignant glioma: data from the Gliomas Outcome Project. *Neurosurgery* 2004; 54: 358-366.
10 Laperriere N, Zuraw L, Cairncross G; Cancer Care Ontario Practice Guidelines Initiative Neuro-Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. *Radiother Oncol* 2002; 64: 259-273.
11 Chang SM, Barker FG, Schmidt MH, et al. Clinical trial participation among patients enrolled in the Glioma Outcomes Project. *Cancer* 2002; 94: 2681-2687.
12 Albert FK, Forsting M, Sartor K, et al. Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on re-growth and prognosis. *Neurosurgery* 1994; 34; 45-61.
13 Harris MT, Rosenthal MA, Ashley DL, Cher L. An Australian experience with temozolomide for the treatment of recurrent high-grade gliomas. *J Clin Neurosci* 2001; 8: 325-327.
14 Yung KA, Albright R, Olson J, et al. A phase II study of temozolomide vs procarbazine in glioblastoma multiforme at first relapse. *Br J Cancer* 2000; 83: 588-593.
15 MacDonald DR, Kiebert G, Prados M, Yung A, Olson J. Benefit of temozolomide compared with procarbazine in treatment of glioblastoma multiforme at first relapse: effect on neurological functioning, performance status, and health related quality of life. *Cancer Invest* 2005; 23: 138-144.
16 Stupp R, Mason WP, van den Bent ML, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; 352: 987-996.

(Received 29 Nov 2005, accepted 5 Jan 2006) ❑