Introduction

Primary brain tumours are a complex and heterogeneous group of diseases representing less than 2% of all cancers diagnosed annually in Australia. In 2005, 1422 people in Australia were diagnosed with a malignant primary brain tumour[1]. Standard management for many primary brain tumours remains ill-defined due to a paucity of large Phase III clinical trials examining treatment modalities. This includes the management of patients with recurrent glioblastoma multiforme (GBM), anaplastic astrocytoma, oligodendroglioma and rare brain tumours such as medulloblastomas and ependymomas. In contrast, the management of newly diagnosed GBM for particular patient groups is well established[2]. However, there is no consensus regarding the treatment of newly diagnosed elderly patients with GBM or those of poor performance status.

Patterns of Care studies have previously been conducted examining the management of Brain tumours. These include several large International studies[3,4,5] and an Australian study confined to Victoria[6]. All studies documented significant variation in a number of parameters including: referral patterns, multi-disciplinary care, treatment strategies, as well as elements of supportive care.

The Cooperative Trials Group for Neuro-Oncology (COGNO) was established in 2007 as a central mechanism to provide a coordinated approach to the management of national neuro-oncology trials in Australia. In 2007, COGNO conducted a pilot survey of neuro-oncology practices in four metropolitan Australian hospitals with large neuro-surgical services. In April 2010, the survey was expanded to an additional 24 Australian Cancer Centres. The aim of the study is to identify variations in the level of neuro-oncology services and patterns of care in Australian cancer centres. This is the first national patterns of care assessment undertaken in the field of neuro-oncology.

Methods and materials

The survey comprised 10 questions that included a variety of demographic and clinical elements regarding patients treated at a Cancer Centre in 2009. The questions included information about pathology subtype (glioblastoma multiforme, anaplastic tumours, low grade gliomas, medulloblastomas); access to neuro-oncology services (neurosurgeons and oncologists; on-site chemotherapy and radiotherapy facilities; radiology capabilities; presence of multi-disciplinary meetings (MDM) and supportive care services); treatment protocols, supportive care (corticosteroids, anti-convulsants, anti-coagulation and antibiotics) and clinical trial participation

A COGNO member was identified (either a medical or radiation oncologist) from 28 Australian cancer centres to complete the survey including: Twelve centres from New South Wales, six from Victoria, four from Queensland, three from South Australia, 1 each from Australian Capital Territory, Western Australia and Tasmania. Twenty-two centres were tertiary university teaching adults hospitals, three were regional cancer centres and three were specialist Children's hospitals. The survey responses were meant to represent a consensus opinion of the neuro-oncology multi-disciplinary team

Twenty-one sites (75%) have returned their survey (Table 1). This analysis included a description of the returned survey data. Quantitative variables were expressed by the mean, standard deviation, quartiles, and extreme values. Qualitative variables were expressed by the numbers and percentages.

Results

For the 12 metropolitan centres, the total number of patients seen in 2009 from each centre ranged from 18 to 211. The highest number came from WA, where there is only one major neuro-oncology centre for the entire state. The lowest numbers belong to the two paediatric hospitals (18 & 26 patients respectively). In regional centres, the patient numbers ranged from 10 to 33. GBM accounted for the majority of patients (50-70%) seen in adult neuro-oncology centres, followed by low grade gliomas and anaplastic tumours (10-15%). In the paediatric centres, low grade gliomas were the most common followed by medulloblastoma.

Access to neuro-oncology services appeared consistent in metropolitan tertiary hospitals with a median of 5 neurosurgeons per centre (range 2-10) and at least 80% having dedicated neuro-oncology medical and radiation oncologist attending the neuro-oncology multi-disciplinary meeting and who treats the majority of neuro-oncology patients in their institution. All centres had access to on-site chemotherapy and 86% had radiotherapy on-site. The median number of clinical trial staff was six (range 2-20). The majority of centres have a neuro-pathologist and holds a regular multidisciplinary meetings (ranging from weekly to monthly). Regional centers have less access to on site neurosurgeons and palliative care staff and are less likely to have sub-specialization of pathologists, oncologists and clinical nurse consultants (Table 3).

Treatment protocols are virtually identical in the initial management of GBM with all centres using the EORTC/Stupp[2] approach of radiotherapy with concurrent and adjuvant temozolomide (TMZ). The only difference was that four centres exclude older patients (>65 years old) when using such protocol. In most centres, an estimated 60-80% of the adult patients would receive the Stupp protocol. In paediatric centres, all paediatric patients would receive such treatment. For less fit patients or those

older than 65-70, most clinicians favour using hypofractionated radiotherapy alone; 16% would consider temozolomide alone as alternative and 42% would enrol patients on a current Trans-Tasman Radiation Oncology Group (TROG 08.02) and NCIC clinical trial[7].

The treatment of recurrent GBM was less standardised and responses varied (Figure 1). On average, 70% of patients would receive chemotherapy, most commonly modified schedule temozolomide; but procarbazine, carboplatin, etoposide or combination thereof were offered. Half of the cancer centres surveyed offered bevacizumab either via industry sponsored trials or self-funded by patients. Approximately, 30% of recurrent GBMs patients had further surgery; 20% received best supportive care only; 10% were enrolled into clinical trials and only 5% received further radiotherapy.

For the initial treatment of anaplastic astrocytomas, the majority of centres recommend radiotherapy alone, 30% of respondents would use the Stupp protocol, 10% of clinicians would adopt sequential radiotherapy and chemotherapy if patients had macroscopic residual disease post surgery and 10% would enrol patients into clinical trial. At recurrence, all clinicians nominated TMZ as the chemotherapy of choice. All clinicians would recommend adjuvant radiotherapy alone for anaplastic ependymoma but the answers varied greatly for recurrent disease including half who gave no response, citing they see too few cases. For adjuvant management of low grade gliomas, radiotherapy was the most common response (40%), followed by enrolment into a specific international low grade glioma clinical trial[8] (30%) which is now closed to recruitment. Chemotherapy was rarely used as initial adjuvant treatment except in the two paediatric centres where carboplatin and vincristine are preferred over radiotherapy

Patterns of supportive treatments are shown in Table 5. Dexamethasone was the universal steroid of choice but there was no specific dosing protocol. All clinicians reported using “clinical judgments” in

selecting a starting dose and to wean patients of corticosteroids. Most suggested a gradual dose reduction of 25-50% or by 2mg over a period of 5-10 days (with occasionally even smaller decrements mentioned). Half the respondents reported using prophylactic anti-convulsants. Phenytoin was universally used as the 1st line agent, followed by levetiracetam and carbamazepine. Most clinicians would stop anti-convulsants after 3 months if there were no seizures. Deep vein thrombosis (DVT) prophylaxis was routine in adult hospitals at the time of surgery but not used in paediatric setting. Enoxaparin was more commonly used than heparin. In the event of venous thromboembolism, most clinicians recommend at least six months of enoxaparin but half will continue this indefinitely in GBM patients (Figure 2).

The use of prophylactic anti-ulcer therapy was prevalent (74%) and proton pump inhibitors (PPIs) were preferred over histamine H2-receptor antagonist. In the Stupp[2] study, routine prophylactic antibiotics were recommended due to significant lymphopenia noted with the protocol and the risk of *pneumocystis carinii* (now called *pneumocystis jirovecii*) pneumonia. One in four respondents do not use prophylactic antibiotics routinely during chemoradiotherapy for GBM including one clinician who would base their decision on whether patient was on concurrent steroids. Sulfamethoxazole-trimethoprim combination is the preferred choice but there is wide variability as to when antibiotics should be stopped (Figure 3).

76% of centres have active neuro-oncology trials at the time of the survey and all centres expressed interest in participating in national neuro-oncology trials. Fifty-two percent of surveyed centres have access to tissue banking facilities for research.

Discussion

This survey is the first Australian "Patterns of Care" study in the field of neuro-oncology. Our survey identified several key issues. First, there is no electronic database to document demographics, diagnosis, types of treatment and survival outcome that can be readily queried for retrospective studies or audits. A central national registry would be an ideal platform to conduct epidemiological studies and compare practice patterns and patient outcome across different regions. Such information could be used to inform government on future neuro-oncology resources allocations and target areas of need.

Secondly, there is discrepancy of neuro-oncology expertise across cancer centres including metropolitan and regional cancer centres. This includes the presence or absence of neuro-surgeons, neuro-pathologists, medical and radiation oncologists with sub-speciality expertise, palliative care services as well as regular Multi-disciplinary meetings. This has several implications. For example, rural patients may need to travel to metropolitan cancer centre to access neurosurgical services at a time when their driving privileges had been removed as a result of their brain tumour diagnosis. Patients then return to their local cancer centres to be reviewed by oncologists without neuro-oncology sub-specialty expertise and might be less likely to receive second-line therapy although this was not specifically explored with this survey. Similarly, a low patient number at regional centres may also translate to lower level of clinical trial participation.

Third, treatment for newly diagnosed GBM was consistent across centres with the routine use of the EORTC/Stupp protocol. However, there appears to be substantive centre to centre variation in the treatment of recurrent GBM, anaplastic tumours and rare tumours such as medulloblastoma and ependymoma. Similarly, there is significant variation in supportive care elements such as: anti-coagulation, prophylactic anti-convalescents and prophylactic antibiotics. Not surprisingly, the treatment of newly diagnosed GBM follows clear Phase III clinical trial evidence and is

recommended in the Australian guidelines[9]. In contrast, the variations in therapy observed generally represent areas of clinical management that are not well characterised due to a lack of Phase III clinical trial data.

Fourth, the Australian Cancer Network/Cancer Council Australia produced a guideline[10] for the management of adult gliomas in 2009, recognising the controversy and variation in clinical practices in neuro-oncology. It aims to "improve level of practice" for medical practitioners and provide a "documented benchmark" for consumers to check if their treatments conform to standard therapies. There are two noteworthy differences between the published guidelines and our survey results. Firstly, the guideline does not recommend the Stupp approach in the management of anaplastic astrocytoma yet 30% of our respondents would use such treatments. Secondly, 50% of centres continue to use prophylactic anti-seizure medication despite a lack of evidence supporting its use. Of interest, , this is similar to the North American patterns of care study[3] where 89% of patients received anti-convulsants despite only 32% presented with seizures. In contrast, in other areas of supportive care therapy, the survey results closely conformed to national guidelines[9]. For example, peri-operative thromboprophylaxis with a low molecular weight heparin is recommended (alternatively unfractionated heparin) for most glioma patients as the incidence of DVT was reported to range from 24-33%[11]. In our survey, 84% respondents used such thromboprophylaxis, much higher than the 7% reported in the North American study.

Clinical trial options now exist for Australian patients. Indeed, both anaplastic astrocytomas and recurrent GBM are the subject of two clinical trials currently open in Australia. For rare tumours such as ependymoma and medulloblastoma national randomised clinical trial are not feasible but options may be to join existing international trials or alternatively, develop common treatment protocols to harmonise patient care in such rare brain tumours.

Several international patterns of care studies on patients with GBM have been published both Europe[4,5] and North America[3]. The main difference compared to our study is that the international studies all had a prospectively collected central national database which allowed detailed and accurate analysis of patient demographics, treatment received and survival outcomes. Our study relied on COGNO affiliated clinicians to access their own departmental database therefore the quality and quantity of data is more variable. Hence we chose to focus on departmental treatment protocols and provision of neruo-oncology resources rather than emphasising the demographic statistics highlighted in previous patterns of care reports. Of interest, the use of salvage chemotherapy at GBM recurrence in our survey (70%) is similar to Italian study by Scoccianti et al (68%). and higher than the French study (37%) with TMZ being the most common regime used. However, clinicians in our survey commonly discussed or used bevacizumab as salvage treatment, which was not observed in previous patterns of care studies. This is largely due to a timeline difference as the bevacizumab efficacy data[12] was published after completion of those international studies.

Our study has several limitations. Only 21 cancer centres returned the survey therefore our results may not represent the views of oncologists in other centres. Several reasons were cited for not participating in the survey including: too many details required and clinician has limited time to do the survey; neuro-oncology treatments are highly variable and individualised and clinicians were hesitant to provide a dogmatic answer or were concerned that the answer may not always represent the view of the multi-disciplinary team. Another potential issue affecting participation is that perhaps there were no perceived significant benefits to the clinician or institution to participate in the survey, leading to 25% of centre not returning their survey.

In addition, information such as overall patient numbers and demographics were based on estimates rather than exact figures in a number of responses. Therefore the answers given may represent an

ideal scenario of what treatments the clinician would do or like to do rather than what happens in day-to-day clinical practice.

Conclusion

This is the first Australian-wide patterns of care study of centres involved in the management of GBM. There is general consensus on the use of the EORTC protocol and the use of chemotherapy for recurrent GBM. This survey highlights variation in the following: (1) treatment of the "elderly" GBM patient; (2) choice of chemotherapy at GBM recurrence and provision of bevacizumab; (3) duration of prophylactic antibiotics and therapeutic anti-coagulation; (4) use of prophylactic anti-convulsants despite guidelines. There is low rate of clinical trial enrolment, which is similar to other cancer sites[13]. However, there is broad interest in national trials participation and more patients would be enrolled if such trials become available.

Acknowledgement

This project received funding from the Australian government through Cancer Australia

Table 1. Cancer Centre Demographics

	N = 21 (%)
Neurosurgeons on site	
Yes	19 (90%)
No	2 (10%)
Number of neurosurgeons	
0-3	4 (19%)
4-6	15 (71%)
7 or more	2 (10%)
Number of neuro-oncology medical oncologists	
0	4 (19%)
1	8 (38%)
2	8 (38%)
3 or more	1 (5%)
Number of neuro-oncology radiation oncologists	
0	2 (10%)
1	9 (43%)
2	6 (29%)
3 or more	4 (19%)
On site radiotherapy	
Yes	18 (86%)
No	3 (14%)
On site Neuro-pathologist	
Y	16 (76%)
N	5 (24%)
Cases referred externally	
0-25%	17 (81%)
>25%	3 (14%)
n/a	1 (5%)
Neuro-oncology MDM	17 (81%)
Yes	4 (19%)
No	
Neuro-oncology clinical nurse consultant (CNC)	
Yes	14 (67%)
No	7 (33%)

Table 2. Comparison between metropolitan and regional cancer centres

	Metropolitan cancer centres	Regional cancer centres
On site neurosurgeons	100%	33%
Neuro-oncology medical oncologists	89%	33%
Neuro-oncology radiation oncologists	94%	67%
Neuro-pathologists	89%	0%
Neuro-oncology Clinical Nurse Consultant	72%	33%
Neuro-oncology Multi-Disciplinary Meeting	89%	33%
On site palliative care nurses & physicians	100%	33%

Table 3. Pattern of use in supportive therapy

Type of supportive therapy				Number (%)	
Dexamethasone				21	(100%)
Anticonvulsant					
	Routine prophylaxis				
		Y		10	(48%)
			1st line		
				Phenytoin	10 (100%)
				Other	0 (0%)
			2nd line		
				Levetiracetam	7 (70%)
				Carbamazepine	2 (20%)
				Valproate	1 (10%)
		N		9	(43%)
		n/a (no neurosurgical service)		2	(9%)
Anticoagulants					
	Routine prophylaxis				
		Y		16	(77%)
			Enoxaparin	12	(75%)
			Heparin	4	(25%)
		N		3	(17%)
		n/a (no neurosurgical service)		2	(9%)
Anti-ulcer therapy					
	Routine prophylaxis				
		Y		17	(81%)
			PPI	15	(88%)
			Ranitidine	1	(6%)
			Others*	1	(6%)
		N		4	(19%)
Antibiotics therapy					
	Routine prophylaxis peri-op				
		Y		9	(43%)
		N		10	(47%)
		n/a (no neurosurgical service)		2	(10%)
	Routine prophylaxis during chemoradiotherapy				
		Y		15	(71%)
		N**		6	(29%)

*varies according to situation

**one clinician would change their decision and use prophylaxis if patient is on concurrent steroid

Figure 1. Proportion of GBM patients receiving treatments at first recurrence

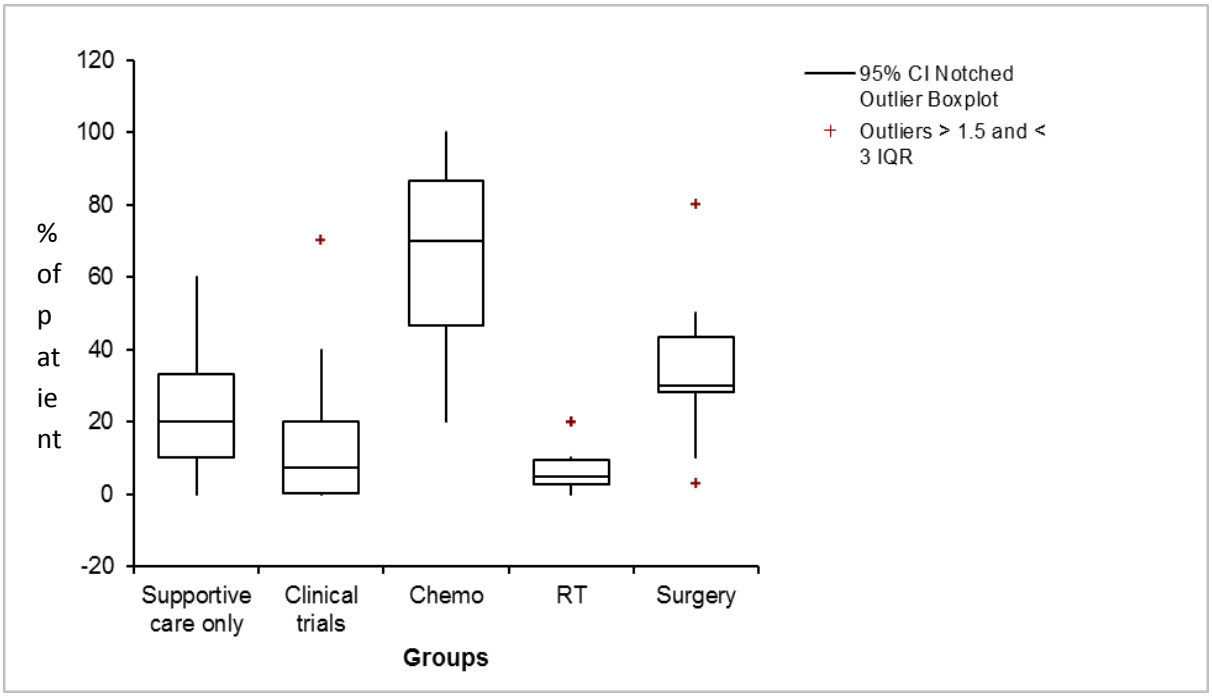


Figure 2. Duration of therapeutic anti-coagulation for proven DVT

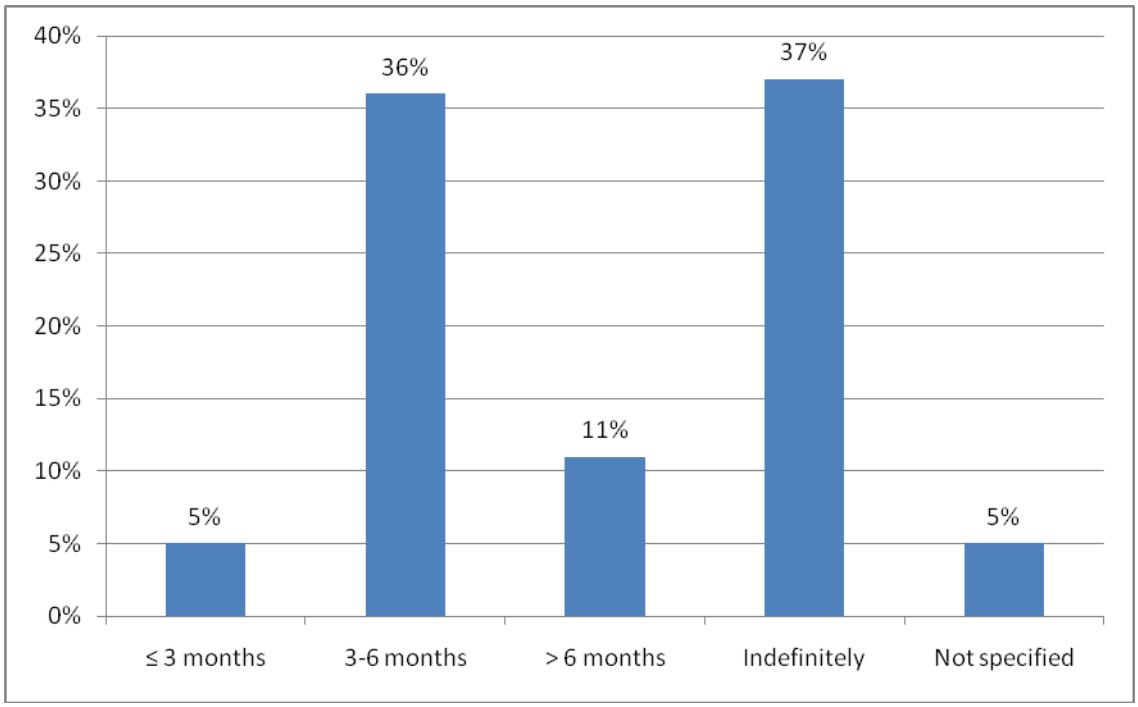
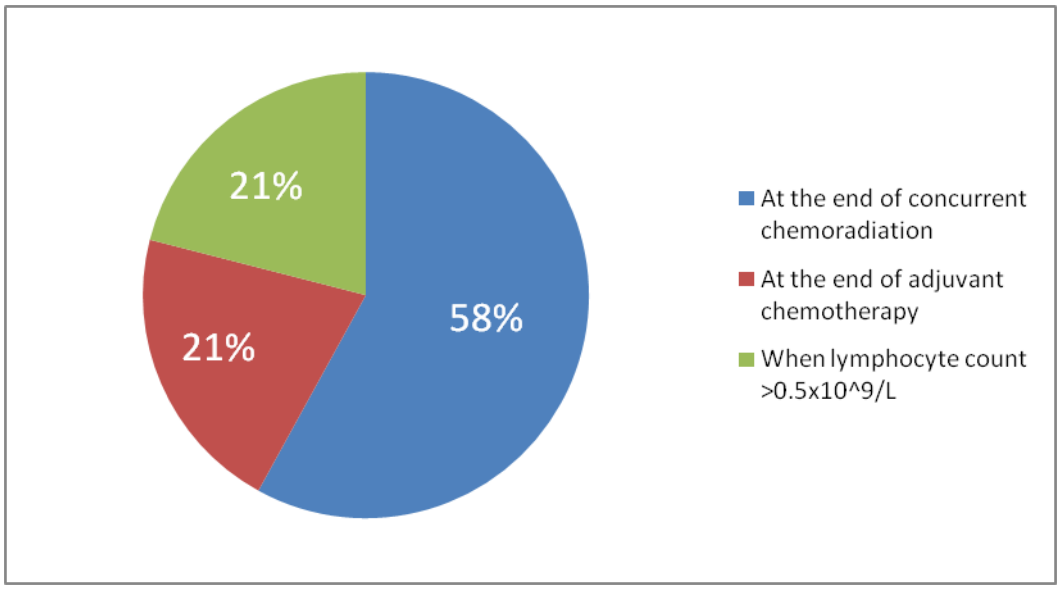


Figure 3. When to cease prophylactic antibiotics during Stupp protocol



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