TITLE: COGNO Patterns of Care Study in Neuro-oncology in Australia
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Executive Summary
This is the report of the initial phase of the *Patterns of Care Study in Neuro-oncology in Australia* conducted in April 2010. Key findings were:

1. The number of patients is largely a guesstimate (⅔ of respondents), most likely due to lack of an electronic database which can be readily queried retrospectively based on ICD coding in order to access data for retrospective studies or audits.
2. There is a lack of/insufficient neuro-oncology expertise (e.g. neurosurgeons, multidisciplinary teams, MRI, clinical trials staff) and supportive services (palliative care, psycho-oncology) in regional cancer centres. This has several implications. For example, rural patients may need or are more inclined to travel to metropolitan cancer centre and spend months away from home and families. A lower patient number at regional centres can also translate to lower levels of clinical trial participation.
3. Where good evidence exists (e.g. EORTC/Stupp protocol in GBM), it is universally adopted regardless of where or by whom the patients are being treated. This highlights the importance of establishing new standards of care through randomised trials e.g. CABARET trial.
4. Even in areas where clinical trials are needed (e.g. anaplastic tumours or low grade gliomas), Australia alone is unlikely to have sufficient numbers to conduct a phase III randomised study. Such research will need collaboration with international groups in order to achieve accrual target. An example is COGNO's CATNON trial which is part of an international collaborative effort with the EORTC.
5. Of the remaining 12 sites that had not returned the survey, some provided helpful feedback about the survey including:
    - Too many details were required and some information was difficult to obtain (e.g. patient numbers)
    - Lack of available time to complete the survey during working hours
    - Do not wish to give a dogmatic answer as neuro-oncology treatments are highly variable and individualised
    - No significant benefit to the clinician or institution to participate in the survey
    - Survey form is more targeted towards adult brain tumours than paediatric brain tumour therefore data from the paediatric centres may bias the results.

    Based on these findings, a second phase of the survey will be conducted to capture information from additional hospitals and identify common patterns of care and potential research gaps. This will involve the COGNO research fellow conducting 15-minute face-to-face or telephone interviews with relevant COGNO contacts at 12 neuro-oncology centres.

Background
COGNO conducted a pattern of care study in April 2010 across 27 Australian Cancer Centres with COGNO memberships. Eleven centres from New South Wales, 6 from Victoria, 4 from Queensland, 3 from South Australia, 1 each from Australian Capital Territory, Western Australia and Tasmania were asked to participate. A COGNO member was identified (generally a medical oncologist) from each centre who would complete the survey. While most centres are tertiary university teaching hospitals for adults (where most brain tumour patients will be treated), 2 regional centres and 3 children's hospitals were asked to participate in the survey in order to capture a broader range of patient demographics.

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This was based on a 2007 pilot survey from 4 neuro-oncology sites (Royal Melbourne Hospital; Sir Charles Gairdner Hospital in Perth; Royal Prince Alfred Hospital and Prince of Wales Hospital in Sydney) which were also included in the latest survey. The pilot survey form was re-designed to a more comprehensive 5-page questionnaire, which consisted of 10 questions (each led to a number of sub-questions). The information COGNO tried to collect included:

- Total number, age and gender breakdown of patients with the following brain tumours diagnosis: glioblastoma multiforme (initial and recurrent); anaplastic tumours (astrocytoma, oligodendroglioma, oligoastrocytoma and ependymoma); low grade gliomas; and medulloblastomas treated in 2009
- Level of neuro-oncology services e.g. number of neurosurgeons and oncologists; on site chemotherapy and radiotherapy facilities; radiology capabilities; establishment of multi-disciplinary meetings; supportive care services etc
- Treatment protocols for the above mentioned primary brain tumours at initial diagnosis and at recurrence
- Use of supportive therapy such as steroids, anti-convulsants, anti-coagulation, antibiotics etc
- Clinical trials participation.

To date, fifteen sites have returned their survey (see Table 1 & 2 below) - 5 from NSW; 1 from ACT; 4 from VIC; 2 from QLD; 1 from SA, 1 from WA and 1 from TAS).

Table 1. Breakdown by locations

	Sent	Returned
NSW	11	5
ACT	1	1
QLD	4	2
VIC	6	4
SA	3	1
WA	1	1
TAS	1	1
Total	**27**	**15**

Table 2. Breakdown by types of hospital

	Sent	Returned
Metropolitan adult hospitals	22	11
Children's hospitals	3	2
Regional centres	2	2

Findings

In 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 was only one major neuro-oncology centre in the entire state. The lowest numbers belonged to the 2 paediatric hospitals (18 & 26 patients). In regional centres, the patient numbers ranged from 10 to 33. Glioblastomas generally account for the majority of patients (~50-70%) seen in adult neuro-oncology centres, followed by low grade gliomas and anaplastic tumours (~10-15%). In children, low grade gliomas were the most common followed by medulloblastoma.

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Table 3. Patient numbers over a 12 months period in 15 neuro-oncology centres (de-identified)

Tumour types	NSW/ACT						QLD	
	H01	H02	H03	H04	H05	H06	H07	H08
GBM initial	27	2	29	8	7	18	n/a	2
GBM recurrence	7	1	29	17	0	8	n/a	2
Anaplastic tumours (AA, AOD, AOA, AE)	4	4	7	8	2	10	n/a	4
LGG	9	8	5	4	1	6	n/a	10
Medulloblastoma	0	3	1	0	0	2	n/a	8
Total	47	18	71	37	10	44	n/a	26

Tumour types	VIC				SA	WA	TAS
	H09	H10	H11	H12	H13	H14	H15
GBM initial	65	30	55	40	15	96	11
GBM recurrence	35	n/a	25	40	10	65	10
Anaplastic tumours (AA, AOD, AOA, AE)	21	3	11	21	8	33	3
LGG	24	0	2	10	5	15	2
Medulloblastoma	2	0	1	1	1	2	1
Total	147	63	94	112	39	211	27

Our surveys showed access to specialist services appears consistent in metropolitan tertiary hospitals with 2-9 neurosurgeons per centre and ~80% having dedicated a neuro-oncology medical and radiation oncologist. All centres had access to on-site chemotherapy and ~80% had radiotherapy on-site. The level of supportive services (palliative care, psycho-oncology, rehabilitation) is also consistent except the availability of a dedicated neuro-oncology clinical nurse coordinator (CNC) which was lacking in 6 of 15 centres. The number of clinical trial staff ranged from 2-20 (median of 6). The majority of centres have a neuro-pathologist and hold regular multidisciplinary meetings (weekly to monthly).

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Table 4. Level of neuro-oncology service

		N	(%)
Neurosurgeons on site			
	Y	13	(87%)
	N	2	(13%)
No. of neurosurgeons			
	0-3	3	(20%)
	4-6	11	(73%)
	7 or more	1	(7%)
Neuro-onc medical oncologist			
	Y	11	(73%)
	N	4	(37%)
No. of neuro-onc medical oncologist			
	1	4	(27%)
	2	6	(40%)
	3 or more	1	(7%)
Neuro-onc radiation oncologist			
	Y	13	(87%)
	N	2	(13%)
No. of neuro-onc radiation oncologist			
	1	6	(40%)
	2	5	(33%)
	3 or more	2	(13%)
Refer externally for RT			
	Y	3	(20%)
	N	12	(80%)
Neuro-pathologist			
	Y	12	(80%)
	N	3	(20%)
% of cases referred externally			
	0-25%	12	(80%)
	>25%	2	(13%)
	n/a	1	(7%)
Neuro-oncology MDM			
	Y	3	(20%)
	N	12	(80%)

The lack of neuro-oncology services in regional centres was evident in our survey, where both regional respondents stated a lack of on-site neurosurgeons; lack of dedicated neuro-oncologist; lack of palliative care nurses and specialist and lack of psycho-oncology for counselling. One regional centre also cited a lack of public-funded magnetic resonance imaging (MRI) facility in their cancer centre.

Treatment protocols are virtually identical (all opted for EORTC/Stupp) in the initial management of glioblastoma multiforme (GBM). The only difference was that 2 centres apply an age cut-off and exclude older patients (>65 years old) when using EORTC/Stupp protocol. However, our surveys showed only 60-80% of patients are fit enough to receive such intense treatments. For the remaining patients, most clinicians favoured using radiotherapy alone although 30% would like to enrol patients on clinical trials e.g. TROG elderly GBM trial which is co-badged by COGNO.

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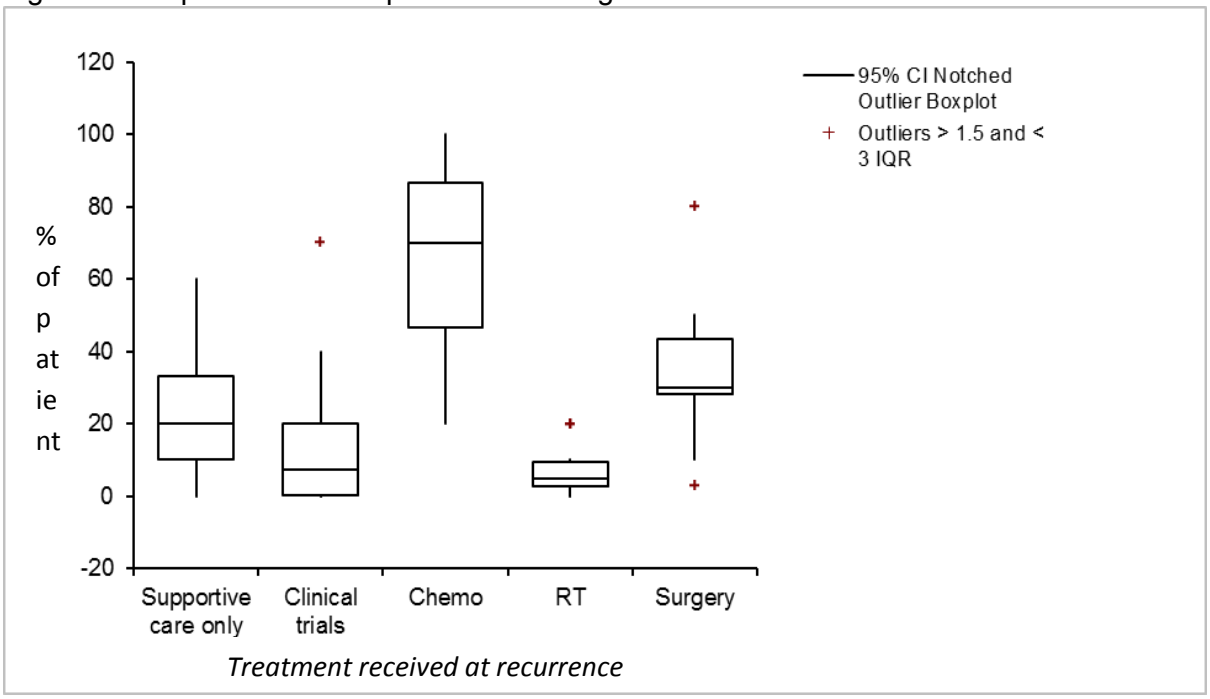
The treatments of recurrent GBM were less dogmatic and responses varied, confirming the lack of standard therapy. This is of particular relevance because an upcoming COGNO clinical trial (CABARET) is designed to answer this question. Centres will have few competing trials as our survey showed less than 20% of patients with recurrent GBM were enrolled in clinical trials in the last 12 months.

Chemotherapy is the most common salvage treatment, followed by further surgery (Figure 1). Several chemotherapy regimens were nominated by respondents including metronomic temozolomide (TMZ), carboplatin, etoposide, and procarbazine. Despite not being listed on the Pharmaceutical Benefits Scheme, 9 of 15 centres nominated bevacizumab as either 1st or 2nd line chemotherapy for recurrent GBM. They cited bevacizumab can be accessed on pharmaceutical company sponsored trials or alternatively, available to patients who can self-fund the costs. Its popularity reflects emerging positive evidence from overseas trials (leading to the registration of bevacizumab as a single agent with the FDA in the USA) and it will also be tested in COGNO's randomised CABARET trial. Lastly, very few patients are eligible for further radiation as recurrences are usually within the area that had already received high dose radiation. A significant proportion of patients would only receive supportive care due to deteriorating performance status.

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



In terms of supportive treatments, dexamethasone was the universal steroid of choice but none of the centres have a specific protocol (Table 5). All clinicians reported using "clinical judgments" in selecting a starting dose and to wean patients of steroids. 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 e.g. 0.5mg when the patients have been receiving dexamethasone for a prolonged period at the lower end of the dose level).

Half the respondents reported using prophylactic anti-convulsant after surgery despite the lack of evidence supporting such practice. 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.

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Our survey showed DVT prophylaxis was routine in adult hospitals but rarely practised in paediatric settings. Enoxaparin was more commonly used than heparin (60% vs 40%). In the event of venous thromboembolism, most clinicians recommend at least 6 months of enoxaparin and in fact half will continue this indefinitely. The use of prophylactic anti-ulcer therapy was prevalent (74%) and proton pump inhibitors (PPIs e.g. omeprazole, pantoprazole) were preferred over histamine H2-receptor antagonist (e.g. ranitidine). One in 4 respondents would not use prophylactic antibiotics routinely during chemoradiotherapy for GBM including one clinician who would base their decision on whether the patient was on concurrent steroids. Bactrim DS 2-3 times a week is the prophylactic antibiotic of choice but there is wide variability as to when antibiotics should be stopped. Some would stop the antibiotic when the lymphocyte count is above 0.5; some stop after the combined phase of Stupp protocol and some stop at the end of adjuvant TMZ.

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Table 5. Pattern of use in supportive therapy

Steroid therapy			
	Dexamethasone	15	(100%)
	Other	0	(0%)
Anticonvulsant			
Routine prophylaxis			
	Y	8	(53%)
	1st line		
	Phenytoin	8	(100%)
	Other	0	(0%)
	2nd line		
	Levetiracetam	5	(71%)
	Carbamazepine		2
	Valproate		(25%)
	N	1	(12%)
	n/a (no neurosurgical service)	6	(40%)
			1
Anticoagulants			(7%)
Routine prophylaxis			
	Y		
	Enoxaparin		
	Heparin		11
			(74%)
	N	7	(64%)
	n/a (no neurosurgical service)	4	(36%)
Anti-ulcer therapy			3
Routine prophylaxis			(20%)
	Y		1
	PPI		(7%)
	Ranitidine		
	Others*		
	N		
			11
Antibiotics therapy			(74%)
Routine prophylaxis peri-op		8	(73%)
	Y	2	(18%)
	N	1	(9%)
	n/a (no neurosurgical service)		4
Routine prophylaxis during chemoradiotherapy			(26%)
	Y		
	N**		
			8
			(53%)
			6
			(40%)
			1
			(7%)
			11
			(74%)
			4
			(26%)

*varies according to situation

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

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Biomarkers are increasingly being used to either predict response to a particular treatment (hence reserve expensive drug treatment for selected patient who will gain the most benefit) or to prognosticate (to forecast what will happen to the tumour/patient in the future). Several biomarkers have been demonstrated in CNS tumours e.g. MGMT methylation and more are likely to emerge in future research. Since it could be difficult or dangerous (potentially unethical) to obtain brain tumour specimen simply for the purpose of testing for biomarkers, increasingly, brain tumours that are removed today are being stored in tissue banks for future testing. Our survey showed 7 of 15 centres have such facilities. For example, NSW and WA collaborated through the AGOG (Australian Genomics and Clinical Outcomes of Glioma) project collecting tumour and blood samples for genetic analysis. Victoria has a state funded project called Victorian Cancer Biobank which acts as a central consortium to improve coordination and research access between 4 existing independent biobanks. In Queensland, 1 respondent used the Queensland Institute of Medical Research (QIMR) for tumour banking. Respondents from ACT, Tasmania and South Australia had no tissue banking facility. However, researchers from those states can potentially access biospecimen data via a nationwide data linkage system called BioGrid Australia.

In terms of clinical trials, only 3 centres were not currently involved in neuro-oncology trials at the time of this survey. The potential reasons could be these are regional (hence smaller) cancer centres with less patients and also less clinical trial staff (median number of 2-3 compared to 5-6 in metropolitan centres) available. However, all centres have expressed an interest to participate in clinical trials as part of a cooperative trials group.

Conclusion

Our survey identified several key issues.

1. The number of patients is largely a guesstimate (⅔ of respondents), most likely due to lack of an electronic database which can be readily queried retrospectively based on ICD coding in order to access data for retrospective studies or audits.
2. There is a lack of/insufficient neuro-oncology expertise (e.g. neurosurgeons, multidisciplinary teams, MRI, clinical trials staff) and supportive services (palliative care, psycho-oncology) in regional cancer centres. This has several implications. For example, rural patients may need or are more inclined to travel to metropolitan cancer centre and spend months away from home and families. A lower patient number at regional centres can also translate to lower levels of clinical trial participation.
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- Survey form is more targeted towards adult brain tumours than paediatric brain tumour therefore data from the paediatric centres may bias the results

Based on the above feedback, a second phase of the survey will be conducted. The COGNO research fellow will arrange a semi-structured 15 minutes face-to-face or phone interview with the relevant COGNO contacts in the remaining 12 neuro-oncology centres. This is a more efficient use of clinician's time and allows us to prioritise more important questions in the survey.

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