BRAIN TUMOURS IN RURAL NORTH EAST MALAYSIA

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SUMMARY: Reliable data on the epidemiology of brain tumours is essential for planning health services and research. The objectives of this study are to determine the epidemiologic distribution and the incidence of brain tumours less than 4 cm in diameter and to identify factors associated with poor outcome. All cases of brain tumour admitted to Hospital University Sains Malaysia between 1st January 1990 and 31st December 1996 were included. Computerized Tomographic (CT) scan of the brain was done on all patients. The tumours were diagnosed based on their appearance on CT scan, and clinical course with or without tissue diagnosis. The size of the brain tumour was measured manually from the axial CT scan films using the ABC/2 technique. The classification of brain tumours was based on the recent World Health Organization classification. The incidence of brain tumours in this region was low (0.4 per 100.000 population), with no significant gender preponderance. Neuroglial tumours (35%) were the most common brain tumours followed by meningiomas (33%), medulloblastomas (12%) and schwannomas (6%). The incidence of brain tumour with a size less than 4 cm in diameter and less than 30 cc in volume was 68.2% and 58.7% respectively. The incidence of brain tumours located in eloquent areas was 21.7%. One-year survival rate in this study was better with combination of treatment modalities (surgery and radiotherapy), and Karnofsky performance scale was identified as the only important prognostic factor for the survival outcome. In conclusion, the incidence of brain tumours in this region (Kelantan and Terengganu) is low and the size of brain tumours less than 4 cm is common.

Key Words: Brain Tumours.

INTRODUCTION

Brain tumours are the most dramatic form of human illness, and among the most rapidly fatal of all cancers. Only about half of the patients with brain tumours are still alive one year after diagnosis (1). They are the most common solid tumours and the second most common malignancy of childhood (2-4). Among adults, primary brain tumours rank between 6th and 8th in frequency of all neoplasms (2-4). The management of brain tumours has been improved due to technological advancement in the diagnosis and localization of brain tumours using Magnetic Resonance

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Imaging (MRI) and Computerized Tomographic (CT) scan of the brain (5).

Most brain tumours need to be operated and completely resected. This may be followed by other modalities of treatment such as radiotherapy, chemotherapy or immunotherapy. Some tumours are too small for open surgery or situated in remote, or inoperable sites, thus, suitable for alternative treatment such as radiosurgery. Unfortunately, this service is too expensive to be set up in a developing area like in North East Malaysia. The main objective of this study is to establish the incidence of brain tumours of less than 4 cm in diameter which are suitable for radiosurgery. The other objectives are to study the epidemiology of the disease and prognostic factors that influence the outcome of brain tumour treatment.

MATERIALS AND METHODS

All cases of brain tumour admitted to Hospital University Sains Malaysia (HUSM) between 1st January 1990 and 31st December 1996 were included in this retrospective study. Computerized Tomographic (CT) scan of the brain was done on all patients and the date of the first abnormal CT scan was considered as the date of diagnosis. Patients with a purely clinical diagnosis of intracranial tumour without neuroradiological or histological examinations were excluded as were spinal tumours, vascular malformation or fistula, primary tumours of the retina, and those with recurrent brain tumours. The classification of brain tumours into nine categories was based on recent second World Health Organization (WHO) classification (6). If histology was not available, then the tumours were diagnosed based on their clinical examination and appearance on CT scan of the brain. In the case of pituitary tumours, the endocrine abnormality was appropriately investigated. Tumour margins were hand traced and measurements were performed manually. ABC/2 technique was applied such that a representative slice at (A) in cm was multipled by the maximum width (B) in cm and the maximum depth (C) in cm. The depth (C) was determined by multiplying the number of slices on which tumour was visible by the slice thickness on CT scan. The volume (in cm^3) was obtained by dividing the final product by two (7).

Socio-economic status was assigned to each patient on the basis of the total monthly family income and was classified into three social classes: low (below RM1000 per month), middle (RM1000-3000) and high (>RM3000) (8).

Data was collected from the hospital registry using coded the International Disease Classification. The case notes, CT scan and histology reports of all patients were traced and carefully reviewed to ensure that the diagnosis of brain tumour was correct, and the diagnosis was made during the study period. Relevant demographic, clinical, histological, mode of treatment and outcome data were extracted. Glasgow coma score was defined as mild when the score was 13 and above, and moderate when the score was less than 9. Clinical evaluation after treatment was assessed by neurological examination and performance status was rated according to the Karnofsky scale (1). The outcome was assessed according to age, sex, socio-economic status, duration of symptoms, tumour size and volume, histological types, Karnofsky performance status and modes of treatment.

The population of Kelantan and Terengganu during the study period (total 2.298.300, Annual Report 1995, Ministry of Health) was taken as the average of the mid year estimates for 1990 to 1996. The annual incidence rate was calculated as the average rate over the seven study years. Crude incidence rates were calculated from the total numbers of cases over the total population of both states above and were expressed as the number of cases per 100.000 population per year.

Statistical analyses were performed using microsoft Excel and Epi Info. Associations between categorical variables, evaluated by chi-square test on contingency tables and Fisher's exact test. The survival estimates were obtained and analyzed by the Kaplan-Meier method.

RESULTS

Seventy patients with brain tumours confirmed by CT scan were admitted to HUSM during the study period. The crude incidence of brain tumours in this study was 0.44 per 100.000 population per year.

93% of patients were Malays and 71% belonged to the low socio-economic group. Age (range 4 months and 70 years). Distribution of brain tumours is shown in Table 1. Most patients presented with multiple symptoms, of which headache was the most common (Table 2). Duration of symptoms (interval from the onset of first symptom to the date of presentation) ranged from one day to more than three years, with 57.1% presenting within three months. Over half of the patients presented with papilloedema.

Table 1: Incidence of brain tumours by histological types versus age and survival outcome.

	Age				Survival outcome			
Type of tumor	number	< 15 years	15-44 years	> 45 years	age < 1 years	1-3 years	> 3 years	Defaulted
Astrocytoma	7 (10 %)	4 (5.7 %)	2 (2.9%)	1 (1.4 %)	3 (4.3 %)	0 (0 %)	3 (4.3 %)	1 (1.4 %)
Oligodendro glioma	2 (2.9 %)	0 (0 %)	2 (2.9%)	0 (0 %)	0 (0 %)	1 (1.4 %)	1 (1.4 %)	0 (0 %)
Glioblastoma multiforme	8 (11.4 %)	1 (1.4 %)	6 (8.6 %)	1 (1.4 %)	3 (4.3 %)	2 (12.9 %)	1 (1.4 %)	2 (2.9 %)
Meningioma	16 (22.9 %)	1 (1.4 %)	9 (12.9 %)	6 (8.6 %)	6 (8.6 %)	7 (10 %)	2 (2.9 %)	1 (1.4 %)
Medullo-blastoma	6 (8.6 %)	5 (7.1 %)	1 (1.4 %)	0 (0 %)	3 (4.3 %)	2 (2.9 %)	1 (1.4 %)	0 (0 %)
Nerve sheat tumour	3 (4.3 %)	0 (0 %)	2 (2.9 %)	1 (1.4 %)	2 (12.9 %)	0 (0 %)	1 (1.4 %)	0 (0 %)
Other specified tumour	7 (10 %)	1 (1.4 %)	5 (7.1 %)	1 (1.4 %)	2 (2.9 %)	3 (4.3 %)	1 (1.4 %)	1 (1.4 %)
Not microscopically confirmed	21 (30 %)	4 (5.7 %)	10 (14.3 %)	7 (10 %)	8 (11.4 %)	1 (1.4 %)	0 (0 %)	12 (17.1 %)
Total	70 (100 %)	16 (22.8 %)	37 (52.9 %)	17 (24.2 %)	27 (38.5 %)	16 (22.9 %)	10 (14.3 %)	17 (52.9 %)

Table 3 presents the details of the CT scan findings of the brain tumours with regard to size, site and volume.

Of the 70 patients admitted over the study period, 49 had histopathological confirmation of type of brain tumour (Table 1). 96% were primary brain tumours and the remainder (4%) were metastatic cancer. Neuroglial tumours were the most common (35%), followed by meningioma (33%), medulloblastoma (12%) and schwannomas (6%). In children younger than 15 years of age, medulloblastoma was the most common variety encountered (41.7%), followed by other specific tumours (18.3%), astrocytoma (8.3%), and meningioma (8.3%).

Fourteen cases (20%) refused hospital treatment. Of the remainder, 32 had surgical resection, 18 received radiotherapy following surgery, 4 were administered chemotherapy following surgery and one received chemotherapy alone. Only one patient was treated with a combination of all three modalities. Surgical treatment followed by radiotherapy which gave a better outcome.

The shortest follow-up was six months, and the longest follow-up was 80 months. The general outcome of brain tumours in HUSM was as follows: six months survival rate 70.6%, one year survival rate 55%, two years 35.3% and three years 23.5%. Outcome was studied in relation to various parameters: histological type (Table 1), age, sex, socio-economic status and duration of symptoms (Table 4), tumour characteristics (Table 5) and Karnofsky status (Table 6).

DISCUSSION

This retrospective study of the epidemiology and prognostic factors of brain tumours was carried out at HUSM, a relatively new teaching hospital, in Kelantan.

Table 2: Chief symptoms and signs

Symptoms and signs	Number of patients
Headache	54 (77.1%)
Seizures	16 (22.9%)
Vomiting	39 (54.9%)
Visual disturbances	28 (36.6%)
Altered consciousness level	7 (10%)
Changes in personality	8 (11.4%)
Neurological deficit	20 (28.6%)
Papilloedema	41 (58.6%)
Altered mentation	10 (14.3%)
Cranial nerve lesion	20 (28.6%)
Paresis	17 (24.3%)
Cerebellar signs	5 (7.1%)

HUSM served as a regional referral centre for both Kelantan and Terengganu states.

The crude incidence of brain tumours in this study was 0.44 per 100.000 population per year. This was one third of the incidence encountered at the Institute of Neurology in Kuala Lumpur where the incidence was three times more than the 1.4/100.000 incidence rate (a national referral centre). This discrepancy may arise from different methodologies, since the present study was retrospective and difficulties were encountered in tracing the cases notes and CT scans of some patients with possible tumours. General practitioner's records were not used to identify patients and therefore, some patients who were admitted to neither HUSM nor any hospital outside the study region may not have been included. Other possible reasons may be poor health education (32.8% of patients refused any form of hospital treatment and preferred traditional healer) and low socio-economic status (70% of patients in present study). Asymptomatic brain tumours may have been missed due to low autopsy rates in this region.

There were too few patients with each tumour type to reliably determine the relative incidences according to sex, race and age. Generally, there seemed to be little difference between the sexes. This present study showed however, that the incidence of brain tumours in general was more common in males than females. This finding was similar to that of Institute of Neurology in Kuala Lumpur (ratio 2:1) and those of other studies (10-12) but the latter were mainly studies on primary neoplasms of the brain. However, in our study meningiomas and nerve sheath tumours occurred more frequently in women than in men. Studies done by Walker AE (10) and Nakasu (13) also showed the same findings.

The incidence rate by age was low in the teens; this rose steadily to a peak in the fourth decade and then declined somewhat after the age of 60. This data was the same when compared with other reports where the incidence rates consistently increased with age and then decreased in the very old patients (10-12). This decrease could be an artefact. Elderly patients may not present themselves to a doctor if they have symptoms of a brain tumour, and may also be less likely to be referred for CT scan or have an autopsy done if they die.

Although only 70% of patients had been confirmed histologically, it was unlikely that this study included many patients who did not, in fact, have brain tumours. All CT scan films were reviewed by a radiologist and a neurosurgeon to confirm the diagnosis and the patient's notes were reviewed to make sure no other diagnosis came to light during follow up. A previous study showed that about 3% of those with a CT scan diagnosis of an intracranial tumour had some other pathology on biopsy (14). In the present study, about 6% of patients (data not shown) had incorrect radiological diagnosis after histological confirmation. Hence, if no histology is available, the brain tumours may be diagnosed on the basis of their appearance on CT scan and clinical course. No doubt, histological diagnosis of brain tumours allows rational treatment and helps assessment of prognosis. In selected patients, surgery is done without preoperative tissue diagnosis. Decisions to operate depend on the patient's clinical condi-

Table 3: Size, volume and site of tumours

Type of tumour	Size of brain tumours (cm) n=70		Volume (cm^3) n=70		Eloquent areas
	≤ 4	> 4	< 30 cm^3	≥ 30 cm^3	
Astrocytoma	9 (12.8%)	2 (2.9%)	9 (12.9 %)	2 (2.9%)	4 (5.7%)
Oligodendroglioma	1 (1.4%)	1 (1.4%)	1 (1.4%)	1 (1.4%)	0 (0%)
Glioblastoma	3 (4.3%)	5 (7.1%)	3 (4.3%)	5 (7.1%)	2 (2.9%)
Meningioma	14 (20%)	3 (4.3%)	12 (7.1%)	5 (7.1%)	4 (5.7%)
Medulloblastoma	3 (4.3%)	1 (1.4%)	1 (1.4%)	3 (4.3%)	0 (0%)
Nerve sheath tumour	3 (4.3%)	0 (0%)	3 (4.3 %)	0 (0%)	0 (0%)
Other specified tumour	5 (7.1%)	2 (2.9%)	4 (5.7%)	3 (4.3%)	4 (5.7%)
Not microscopically confirmed	12 (17.1%)	6 (8.6%)	11 (15.7%)	7 (10%)	5 (7.1%)
Total	50 (71.4%)	20 (8.6%)	44 (62.8%)	26 (7.1%)	19 (27.1%)

tion, consent and the site and size of the lesion. Radical excision of brain tumours reduces mass (mechanical cytoreduction), lowers intracranial pressure by internal decompression (14), and yields material for accurate tissue diagnosis. The patient may then be more confidently referred for additional intervention (e.g. adjunctive chemotherapy or radiotherapy). For the small tumour situated in an eloquent area stereotactic biopsy is beneficial (15).

The distribution of pathologically confirmed cases by histologic type agrees with those of other previous studies (1,10-12,16-18). The most common primary brain tumour was neuroglial tumour, followed by meningiomas. In children the most common was astrocytoma and medulloblastoma.

Radiosurgery refers to single-fraction, high-dose irradiation of a limited target volume of tissue. Similar to other neurosurgical procedures, it is a precisely

Table 4: Age, sex, socio-economic status and duration of symptoms versus survival outcome.

		Survival Outcome			
		< 1 year	1-3 years	> 3 years	Defaulted
Age	≤ 15	3 (4.3%)	5 (7.1%)	8 (11.4%)	5 (7.1%)
	≥ 15	22 (31.4%)	12 (17.1%)	20 (28.6%)	13 (18.6%)
Sex	Male	12 (17.1%)	8 (11.4%)	4 (5.7%)	12 (17.1%)
	Female	13 (18.6%)	9 (12.6%)	6 (8.6%)	6 (8.6%)
Socio-economic	Low	19 (27.1%)	7 (10%)	6 (8.6%)	18 (25.7%)
	Middle	6 (8.6%)	8 (11.4%)	4 (5.7%)	0 (0%)
	High	0 (0%)	2 (2.9%)	0 (0%)	0 (0%)
Duration of Symptoms %	< 6 months	17 (24.3%)	12 (17.1%)	5 (7.1%)	14 (20%)
	6 -12 months	7 (10%)	2 (2.9%)	3 (4.3%)	0 (0%)
	> 12 months	1 (1.4%)	2 (2.9%)	2 (2.9%)	3 (4.3%)

Table 5: Tumour size, volume and site versus survival outcome.

		Survival Outcome			
		< 1 year	1-3 years	> 3 years	Defaulted
Tumour size	< 4 cm	13 (18.6%)	14 (20%)	9 (12.9%)	10 (14.3%)
	≥ 4 cm	11 (15.7%)	3 (4.3%)	1 (1.4%)	5 (7.1%)
Volume	≤ 30 cm^3	15 (21.4%)	9 (12.9%)	7 (10%)	9 (12.9%)
	≥ 30 cm^3	9 (12.6%)	8 (11.4%)	3 (4.3%)	6 (8.6%)
Site	Frontal	5 (7.1%)	6 (8.6%)	0 (0%)	6 (8.6%)
	Temporal	3 (4.3%)	1 (1.4%)	0 (0%)	0 (0%)
	Parietal	2 (2.9%)	1 (1.4%)	3 (4.3%)	3 (4.3%)
	Occipital	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)
	Cerebellar	5 (7.1%)	3 (4.3%)	5 (7.1%)	3 (4.3%)
	Eloquent	3 (4.3%)	4 (5.7%)	1 (1.4%)	4 (5.7%)
	Others	0 (0%)	2 (2.9%)	1 (1.4%)	1 (1.4%)

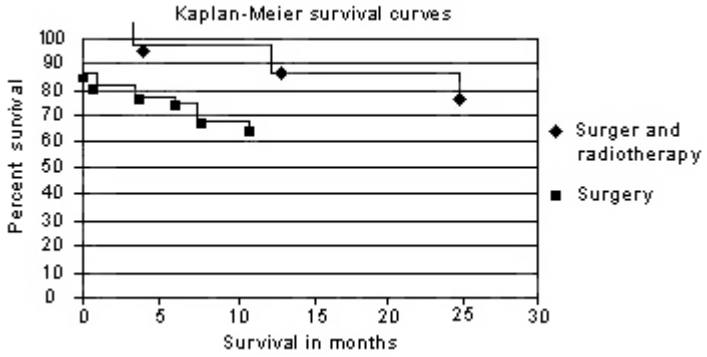
localized, ablative procedure limited to a well-defined volume. It is a noninvasive method and seems to provide results that are similar to those of surgical resection. It is suitable for small tumours (less than 4 cm in diameter) and those situated in eloquent areas. From this study the incidence of brain tumours located in the eloquent areas was common (21.7%). Rutigliano *et. al.* (19) did a study on cost effectiveness of stereotactic radiosurgery compared to resection in the treatment of solitary metastatic brain tumours. He found that radiosurgery had a lower total cost per procedure (by 25.8%) and was more cost effective (by 22.5%) than surgical resection. Another study done by Pollock *et. al.* (20) also showed that radiosurgery was a more cost-effective management strategy. However, anatomical and radiobiological considerations of normal tissue tolerance are thouhgt to limit effective radiosurgery to targets no larger than 3 to 4 cm in maximum dimension (21) or a volume that is less than 30 cm3 (21). The present study shows that the incidence of brain tumours suitable for radiosurgery is 60% by size and 21% by volume (22). Based on this and the cost effectiveness, a radiosurgery facility is strongly recommended.

Survival can be influenced by a variety of patient characteristics and tumour variables. Prognostic factors such as age, histological grade, tumour location and size, specific neurological findings, extent of

Table 6: Karnofsky status versus survival outcome.

Karnofsky status	< 1 year	1-3 years	> 3 years	Defaulted
< 30	10 (14.3%)	0 (0%)	0 (0%)	1 (1.4%)
30 - 40	1 (1.4%)	0 (0%)	0 (0%)	1 (1.4%)
50 - 60	2 (2.9%)	2 (2.9%)	2 (2.9%)	0 (0%)
70 - 80	4 (5.7%)	7 (10%)	7 (10%)	5 (7.1%)
90 - 100	3 (4.3%)	9 (12.9%)	9 (12.9%)	1 (1.4%)
Total	20 (28.6%)	18 (25.8%)	18 (25.8%)	8 (11.3)

Figure 1: Influence of mode of treatment on survival. Kaplan-Meier curves are presented for surgical treatment (■) and surgery and radiotherapy (◆).



tumour resection and postoperative functional status have been regarded as influential by some investigators and relatively unimportant by others. Among prognostic factors that are agreed upon by many investigators are age, histological types, performance status and the extent of surgery and tumour volume (23-26). Analysis of the present study showed that there was no statistical significance found for associated prognostic factor versus the survival outcome except for Karnofsky performance scale. The samples of the study were too small to be statistically significant. Survival rates have been said to vary considerably according to histological type and age. Studies done by Salmon et. al. (23) and Law *et. al.* (26) found that the patient's age was a strong prognostic factor ($p<0.0001$) for survival. The relative 5-year survival rate in children ages 0 to 14 years, who, overall, tend to develop less aggressive tumours than adults, is now 59% compared with 35% 20 years ago (27). The Children's Cancer Group studies (28) showed that survival was significantly correlated with age and metastatic stage. Progression-free survival was better at 5 years in children with no dissemination. The histological types are also an important factor that influence the survival outcome. Nerve sheath tumours, other specific tumour category (mostly haemangiomas and gangliogliomas), and meningiomas, all of which are predominantly benign, have the best prognosis; more than 90% survive for 5 years. Patients with glioblastoma multiforme have the poorest prognosis, about 5% survive for 5 years (29). The extent of surgery is important in predicting length of survival. A study done by Philippon *et. al.* (30) on supratentorial low-grade astrocytoma showed that 80% of patients with total removal of tumours were alive at 5 years compared with 50% with incomplete surgery and 45% with biopsy. In contrast to age, residual tumour is an important factor in outcome, which can be controlled by neurosurgeons.

Mode of treatment is an important variable for patient survival. The combination of treatment as shown in this study had a good outcome in general. The influence of mode of treatment on survival was shown by Kaplan-Meier survival curves (Figure 1). One-year survival rate of patients treated by surgery alone was about 60% compared to those who were treated with surgery and radiotherapy, in which the one-year survival rate was more than 85%. This may well have some clinical importance, even though it was not statistically significant in both age groups. The validity of the above results however, depends on other patient's characteristic factors such as age, histological features, performance status and the extent of surgery. To achieve an accurate result regarding the influence of mode of treatment on the outcome, bias should be excluded by performing multivariate analysis. The samples of this study however were too small to exclude all the above bias and to show statistical significance.

CONCLUSION

The epidemiological description of this study was similar to those of previous studies (1,10-12,18) except that the general incidence of brain tumours in this study was lower. Primary brain tumours were more common in male than female except meningiomas and nerve sheath tumours, which were more common in the female. In this study, the incidence of brain tumours declined after an early peak at age 10 and then rose again after the age of 25 years. Headache, vomiting, papilloedema, and cranial nerve deficits were the common presenting features.

This study showed that brain tumours smaller than 4 cm in diameter were common. It is therefore feasible to set up a radiosurgical programme in Malaysia. The programme is associated with less morbidity and is cost effective.

Karnofsky performance scale is an important prognostic factor for survival outcome. Other prognostic factors, which were shown to influence the outcome by many other authors, were found not to influence the outcome in this study. Surgical treatment followed by radiotherapy has a better survival outcome in general compared to surgery alone as shown by Kaplan-Meier survival curves but this was not statistically significant.

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