Comparison on Incidence, Radiological Features and Outcome of Skull Base Versus Non-Skull Base Meningioma in General Hospital Kuala Lumpur: A 5-year Retrospective Study

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PUM 0163/13

Dissertation Submitted in Partial Fulfillment Of The Requirements For the Master Of Surgery (Neurosurgery)

THESIS PRODUCED ACCORDING TO NEW USM FORMAT

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Acknowledgement

To my mentor and father-figure, Datuk Dr Mohammed Saffari Mohammed Haspani, who has been very supportive since I reported duty under your tutelage in June 2014, I would not have made it this far without you. My sincere utmost gratitude to you for teaching me patience and humility; and for moulding my hands into those of a surgeon's. To my in-campus supervisor Professor Zamzuri Idris, Head of Neuroscience Department, Universiti Sains Malaysia, a million thanks to you for your guidance in helping me in completing my thesis.

To my Universiti Sains Malaysia teachers Professor Dato Dr Jafri Malin Abdullah, founding Director of the Centre for Neuroscience Services and Research, Universiti Sains Malaysia; Professor John Tharakan, Dato' Dr Abdul Rahman Izaini Ghani, Dr Badrisyah Idris, Dr Regunath Kandasamy and Dr Tan Yew Chin, Neurosciences lecturers of Universiti Sains Malaysia, thank you for the patience and continual education and guidance. Not forget to thank Professor Kamarul, statistician from Universiti Sains Malaysia for statistical advice.

To my teachers in Hospital Kuala Lumpur: Mr Azmi Alias, Mr Gurmit Singh, Mr Kantha Rasalingam, Mr Saiful Razman, Madam Siti Suriyati Buang, and especially Mr Thinesh, whom I also see as a friend and mentor, my greatest gratitude to all.

Not forget to thank specialists in Hospital Sungai Buloh: Mr Azmin Kass, head of Neurosurgery Department, Mr Saiful Azli, Mr Liew Boon Seng, Miss Cheah Pooi Pooi, Mr Mah Jon Kooi, Miss Ailani Ab. Ghani and Miss Ng Wei Ping in guiding me in both academic and clinical works.

To my beloved wife Dr Bong Yee Tian, thank you for your unconditional love and support at all time. Special thanks to my parents, my son and daughter as well. I would not have made it this far without my family; you are my everything.

This study was registered under National Institute of Health, Ministry of Health Malaysia with ID NMRR-14-1676-23330.

Authors note: This manuscript was prepared for submission to The Malaysian Journal of Medical Sciences (MJMS)

Abstrak

Tajuk abstrak

Perbandingan antara kejadian, ciri-ciri radiologi serta hasil pembedahan bagi kumpulan Meningioma Asas Tengkorak dan kumpulan Meningioma Bukan Asas Tengkorak di Hospital Besar Kuala Lumpur: Kajian retrospektif selama 5 tahun.

Latar Belakang

Meningioma adalah pertumbuhan otak yang biasa, didapati di United Kingdom sebanyak 24 hingga 30% daripada pesakit barah otak menghidapi meningiomas. Di Amerika pula dianggarkan sebanyak 2 hingga 3% daripada penduduknya mempunyai meningioma, sungguhpun tiada tanda-tanda klinikal pada peringkat awal, dan dilaporkan insiden tahunan meningioma sebanyak 2 kes setiap 100,000 orang. Sebanyak 30% meningiomas berada di asas tengkorak. Kawasan asas tengkorak ini amat sukar dibedah. Ini kerana meningioma asas tengkorak biasanya dekat dengan struktur-struktur penting seperti saraf-saraf kranial penting dan pembuluh darah utama. Sungguhpun meningioma biasanya dijumpai di Malaysia, kita masih kekurangan data tempatan di Malaysia.

Prosedur kajian

Seramai 1149 pesakit yang mempunyai pertumbuhan otak telah dibedah di Hospital Besar Kuala Lumpur dari bulan Januari 2010 hingga bulan Disember 2014. Sebanyak 199 pesakit yang dibedah didiagnosis meningioma dan memenuhi syarat-syarat kajian kami. Pesakit-pesakit tersebut dikategorikan dalam kumpulan meningioma asas tengkorak dan kumpulan meningioma bukan asas tengkorak. Data demografi, ciri-ciri tumor serta hasil pembedahan dikaji. Ujian-ujian

seperti ‘Kaplan-Meier survival curve’, ‘univariate and multivariate cox hazard regression’ telah dianalisasikan

Keputusan:

Meningioma WHO gred I jauh lebih banyak (n = 194; 97.5%) berbanding dengan WHO gred II, dan keputusan ini serasi dengan kajian lain. Kajian kami tiada kes baru meningioma yang dikategorikan dalam kumpulan WHO gred III. Kebanyakannya pesakit meningioma adalah wanita (67.3%), hanya 32.7% pesakit ialah pesakit lelaki. Kebanyakan pesakit daripada kaum Melayu, iaitu seramai 138 orang (69.3%) berbanding dengan kaum lain. 27% daripada semua pesakit mempunyai meningioma di asas tengkorak (n = 54) dan majoriti meningioma adalah WHO gred I (n = 52, 96.3%). Sebanyak tujuh puluh peratus pesakit dalam kumpulan meningioma asas tengkorak adalah perempuan (38 orang). Min umur untuk mereka dikesani mempunyai meningioma adalah lebih muda jika dibandingkan dengan kumpulan lain, iaitu 51.7 tahun (SD 11.01) bagi mereka yang mempunyai meningioma asas tengkorak, manakala min umur untuk kumpulan meningioma bukan asas tengkorak adalah 54.1 tahun (SD 9.4).

Kedua-dua kumpulan meningioma mempunyai pesakit kebanyakannya dalam lingkungan umur 40-60. Lebih daripada sembilan puluh peratus pesakit kedua-dua kumpulan ini menghadapi masalah sakit kepala yang menyebabkan mereka berjumpa doktor. Lima puluh satu pesakit dengan meningioma asas tengkorak (94.4%) mempunyai ciri-ciri radiologi otak bengkak; 30 kes (55.6%) mempunyai bukti hyperotosi dan 16 pesakit (29.6%) mempunyai kalsifikasi. Meningioma asas tengkorak berkaitan dengan hasil pembedahan yang lebih membimbangkan (n = 23; 42.6% nilai $p < 0.01$) dan sebanyak 63% meningioma asas tengkorak tidak dapat dikeluarkan sepenuhnya.

Kajian kami menunjukkan pesakit meningioma asas tengkorak hidup lebih pendek, iaitu selama 37.6 bulan (SD 20.94) sahaja berbanding dengan 47.8 bulan (SD 18.2) bagi mereka yang mempunyai meningioma di luar asas tengkorak dengan nilai-p 0,187. Di samping itu, kajian kami mendapati pesakit meningioma asas tengkorak yang mengalami pembedahan adalah berisiko 4 kali ganda untuk mati berbanding kumpulan bukan asas tengkorak. Keputusan ini diselaraskan dengan jantina, penyakit-penyakit kronik, WHO gred dan tahap meningioma dikeluarkan samaada sepenuhnya ataupun tidak, dan didapati nilai p bererti. (HR 4.22; 95% CI 1,53-11,66; nilai-p 0.005).

Kesimpulan:

Pesakit meningioma dapt disembuhkan sepenuhnya jika pertumbuhan dapat dikeluarkan sepenuhnya. Meningioma asas tengkorak biasanya susah dikeluarkan sepenuhnya melalui pembedahan. Kajian kami mempamerkan hasil pembedahan bagi kumpulan meningioma asas tengkorak tidak menggalakkan. Kebanyakan meningioma asas tengkorak juga tidak dapat dikeluarkan sepenuhnya melalui pembedahan. Ini amat berbeza dengan pesakit dalam kumpulan meningioma bukan asas tengkorak. Selain itu, kajian kami menunjukan bahawa pesakit meningioma asas tengkorak berisiko 4 kali ganda untuk mati berbanding dengan pesakit meningioma bukan asas tengkorak. Dengan adanya lebih banyak latihan dalam pembedahan asas tengkorak serta peningkatan tahap teknologi dalam bidang ini, diharapkan risiko dapat dikurangkan demi kebaikan pesakit . Kami ingin mengesyorkan lebih banyak kajian dibuat khususnya dalam bidang mengkaji meningioma asas tengkorak, dengan harapan hasil pembedahan dapat diperbaiki.

Kata-kata penting: *meningioma, asas tengkorak, WHO, hasil pembedahan*.

Abstract

a. Article title

Comparison on Incidence, Radiological Features and Outcome of Skull Base Versus Non-skull Base Meningiomas in General Hospital Kuala Lumpur: A 5-year Retrospective Study.

Chan Chee Kong[1, 2], Saffari Haspani[2], Zamzuri Idris[1]

[1]Centre for Neuroscience Services and Research as Department of Neuroscience, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

[2]Department of Neurosurgery, Hospital Kuala Lumpur (HKL), Wilayah Persekutuan Kuala Lumpur, Malaysia.

Background: Meningiomas are the most common intracranial tumours, accounting for 13-26% of all the primary intracranial tumours. In the United States, an estimated 2–3% of the population has an incidental asymptomatic meningioma, and annual incidence of symptomatic meningioma is 2 cases per 100,000 individuals. Skull base meningiomas comprise 30% of meningiomas and are one of the most difficult intracranial tumours to be managed surgically because of the difficulty in approaching the lesions and their proximity to vital structures such as cranial nerves and major blood vessels. Meningiomas are commonly seen in Malaysia, however there is minimal local data published. The main purpose of our study was to identify the demographic data, tumours characteristic and surgical outcome of patients with meningiomas operated in GHKL.

Methods: A total of 199 patients with histologically proven meningiomas were operated from January 2010 till December 2014 in General Hospital Kuala Lumpur. They were categorized into skull base and non-skull base groups. Demographical data, tumour characteristics and patients' outcome were studied. Kaplan-Meier overall survival curve and Cox hazard univariable and multivariable regression for possible predictors of survival were analyzed.

Results: There was 199 patients included in the study, 97.5% of the patients (n=194) had WHO grade I meningioma Only 5 patients had WHO grade II meningiomas. However, no new WHO grade III meningiomas diagnosed throughout the study period. Majority of our patients were female (n=134; 67.3%) with only 65 patients were male (32.7%). Malay ethnicity has the highest incidence (n=138; 69.3%).

Skull base meningioma (n=54) comprised 27.1 % of all the intracranial meningioma. Majority of the skull base meningiomas were histopathologically WHO grade I (n=52, 96.3%). Seventy percent of the skull base meningioma group was female (n=38) with mean age at diagnosis was 51.7 (SD 11.01), as compared to non-skull base group with mean age of diagnosis at 54.1 (SD 9.4). Both categories showed highest prevalence in age group 40-60 with skull base group (n=33; 61.1%) and non-skull base group (n=91; 62.8%). Majority of the patients in both skull base and non-skull base group presented with clinical feature of headache, with 94.4% (n=51) and 91% (n=132) respectively. Radiologically, ninety four percent of the patients with skull base meningioma (n=51) had radiological evidence of oedema; 30 cases (55.6%) had hyperotosis and 16 patients (29.6%) had calcification as reported by radiologists.

Skull base meningioma was related to poorer outcome with poor discharge condition (n=23; 42.6% p value < 0.01) and higher possibility of incomplete resection (n=34; 63% p value < 0.01). In contrast, 88% (n=128) patients in non-skull base meningiomas group were discharged well and only 11 cases out of the total 145 patients were incompletely resected. Our study showed a shorter median survival of 37.6 months (SD 20.94) for skull base group as compared to 47.8 months (SD 18.2) in the non-skull base group with p-value 0.187.

Multivariate cox hazard regression test showed skull base meningioma group had 4 times the chance to succumb to death as compared to non-skull base group (Adjusted HR 4.22; 95% CI 1.53-11.66; p-value 0.005), adjusted with gender, comorbidities, WHO grading and extends of meningioma.

Conclusion: The primary treatment for symptomatic meningioma is surgery, which can be curative if the tumour is completely removed. Skull base meningiomas are widely accepted as being more technically challenging to achieve gross total resection. Our study has showed skull base meningiomas operated locally had higher rate of incomplete resection and poorer surgical outcome as compared to non-skull base group. Patients with skull base meningioma had 4 times higher risk to succumb to death as compare to non-skull base group. More studies need to be carried out locally to look into skull base meningioma seriously for the improvement of surgical outcome.

Key words: Meningiomas, skull base, WHO, clinical feature, Kaplan Meier survival curve, predictor, outcome.

Introduction and Literature review

Meningiomas are the most common non-glial primary intracranial tumour. (1) Hospital-based brain tumour series indicate that the incidence of meningiomas is approximately 20% of all intracranial tumours, whereas autopsy-based studies indicate an overall incidence of 30%.(1, 2) Meningiomas occur with an annual population incidence of 6.0 per 100,000 persons per year, and have recently surpassed gliomas as the most common primary brain and central nervous system tumour in the United State, accounting for 36.8% of all tumour (2). Fonkem et al (2016) reported the incidence among females is shown to be 2.3 times that of males (3).

Yusoff et al reported the incidence of brain tumour among Kelantan and Terengganu Population in 1996 was 0.44 per 100,000 population per year. (4, 5) Report of National Cancer Registry (2007) revealed that the crude incidence of brain tumour and nervous system including spine and peripheral nervous tumour was 2.0 for male and 1.7 for female per 100,000 population per year. (6) Globocan 2012 estimated Malaysia brain tumours and other nervous system age standardized incidence to be 2.8 per 100,000 population per year with cumulative rate 0.3%. (7) Two prospective studies by General Hospital Sarawak Neurosurgical unit published in 2002 and 2014 showed an average two meningiomas case were done a month (8) and thirty to thirty five percent of the operated cases were meningiomas (4, 8). General Hospital Kuala Lumpur (GHKL), being our national neurosurgical referral center in Peninsular Malaysia, has been providing neurosurgical services for many years. The main purpose of our study was to identify the demographic data of the patients with meningiomas and were operated in GHKL. Besides, the tumour characteristics, radiological features and surgical outcome would be studied as well.

Meningiomas of the cranial base account for approximately 25% of all meningiomas, with a reported ratio of calvarial-to-skull base distribution of 2.3:1. (9) Skull base meningiomas are difficult to be managed surgically because of the difficulty in approaching the lesions and their proximity to vital structures such as cranial nerves and major blood vessels. (9, 10) Literature reviews showed skull base meningioma is more surgically demanding and challenging (10, 11). Many countries have developed skull base neurosurgery as a distinct neurosurgery subspecialty (10).

Previous two local prospective studies to-date from General Hospital Sarawak lacked grouping of meningiomas into skull base and non-skull base for comparison. (4, 8). It is therefore important to establish the prevalence in local settings and to analyze skull base meningiomas versus non-skull base in term of demographic data, radiological features and surgical outcome. Only with local data available, we could compare ours with other international studies available. These helps in identifying any possible factors affecting the surgical outcome especially, for the betterment of neurosurgical care in Malaysia.

Study Protocol

i. Ethical approval letter

JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
KEMENTERIAN KESIHATAN MALAYSIA
d/aInstitut Pengurusan Kesihatan
Jalan Rumah Sakit, Bangsar
59000 Kuala Lumpur
Tel. : 03 2282 9082/03 2282 9085
03 2287 4032/03 2282 0491
Faks: 03 22828072/03 2282 0015

Ruj. Kami: (6) KKM/NIHSEC/P15-288
Tarikh : 8hb Jun 2015

DR CHAN CHEE KONG
HOSPITAL UNIVERSITI SAINS MALAYSIA

Tuan/Puan,

NMRR-14-1676-23330 (IIR)
Surveillance of Typical, Atypical and Malignant Meningiomas in two neurosurgical centres: A comparative Study on Incidence, Radiological Features and Outcome

Lokasi Kajian : Hospital Kuala Lumpur Dan Hospital Sultanah Aminah

Dengan hormatnya perkara di atas adalah dirujuk.

2. Jawatankuasa Etika & Penyelidikan Perubatan (JEPP), Kementerian Kesihatan Malaysia (KKM) tiada halangan dari segi etika ke atas pelaksanaan kajian tersebut. JEPP mengambil maklum bahawa kajian tersebut tidak mempunyai intervensi klinikal ke atas subjek dan hanya menggunakan **kajian pemerhatian** sahaja untuk mengumpul data kajian.

3. Segala rekod dan data subjek adalah **SULIT** dan hanya digunakan untuk tujuan kajian ini dan semua isu serta prosedur mengenai *data confidentiality* mesti dipatuhi. Kebenaran daripada Pegawai Kesihatan Daerah/Pengarah Hospital dan Ketua-Ketua Jabatan atau pegawai yang bertanggung jawab disetiap lokasi kajian di mana kajian akan dijalankan mesti diperolehi sebelum kajian dijalankan. Tuan/Puan perlu akur dan mematuhi keputusan tersebut.

4. Adalah dimaklumkan bahawa kelulusan ini adalah sah sehingga **8hb Jun 2016**. Tuan/Puan perlu menghantar dokumen-dokumen seperi berikut selepas mendapat kelulusan etika . Borang-borang berkaitan boleh dimuat turun daripada laman web MREC (http://www.nih.gov.my/mrec).

I. *'Continuing Review Form'* selewat-lewatnya 2 bulan sebelum tamat tempoh kelulusan ini bagi memperbaharui kelulusan etika.
II. Laporan tamat kajian pada penghujung kajian.
III. Laporan mengenai *"All adverse events, both serious and unexpected"/Protocol Deviation* atau *Violation* kepada Jawatankuasa Etika & Penyelidikan Perubatan, KKM jika berkenaan.
IV. Memaklumkan jika terdapat pindaan keatas sebarang dokumen kajian.

5. Sila ambil maklum bahawa sebarang urusan surat-menyurat berkaitan dengan penyelidikan ini haruslah dinyatakan nombor rujukan surat ini untuk melicinkan urusan yang berkaitan.

Sekian terima kasih.

BERKHIDMAT UNTUK NEGARA

Saya yang menurut perintah,

DATO' DR CHANG KIAN MENG
Pengerusi
Jawatankuasa Etika & Penyelidikan Perubatan
Kementerian Kesihatan Malaysia

Cc

Pengarah
Hospital Kuala Lumpur

Pengarah
Hospital Sultanah Aminah

Clinical Research Centre
Hospital Kuala Lumpur

Clinical Research Centre
Hospital Sultanah Aminah

ii. Amendment from approved of study protocol and its justification

- Small amendment was performed to modify the study title to ‘comparison on Incidence, Radiological Features and Outcome of Skull base versus Non-skull base meningiomas in General Hospital Kuala Lumpur: A 5-year Retrospective Study’ after discussed with consultant neurosurgeons during 6 monthly assessments, in view the progress in data collection in single hospital was convincing. The main purpose of the study was to emphasize on the incidence of meningioma in Malaysia as well as its radiological features and surgical outcome, comparison between two neurosurgical centers has minimal added value over the prevalence and outcome of meningioma in Malaysia as a whole. Besides, grouping meningiomas based on location- skull base versus non-skull base highlighted the purpose of the study which was to explore, and hopefully to establish the need for subspecialty in skull base neurosurgery in Malaysia, as literature reviews showed skull base meningioma is surgically more demanding and challenging.
- Aim to include multicenter for data collection was initiated, however, due to time constraints, was advised to continue data collection in multicenter neurosurgical centers later as phase II study. Amendment for title modification was sent to NMRR and approved.

Body

Abstract

a. Article title

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Introduction

Meningiomas are the most common non-glial primary intracranial tumour. (1) Hospital-based brain tumour series indicate that the incidence of meningiomas is approximately 20% of all intracranial tumours, whereas autopsy-based studies indicate an overall incidence of 30%.(1, 2) Meningiomas occur with an annual population incidence of 6.0 per 100,000 persons per year, and have recently surpassed gliomas as the most common primary brain and central nervous system tumour in the United State, accounting for 36.8% of all tumour (2). Fonkem et al (2016) reported the incidence among females is shown to be 2.3 times that of males (3).

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Methodology:

Patient population and initial evaluation

A retrospective review of all intracranial tumour patients operated in Neurosurgical Department General Hospital Kuala Lumpur from January 2010 to December 2014 was carried out and all operated meningioma cases were identified. We analyzed the demographic data, radioimaging reports (in the form of initial X-rays, CT Scans, and MRI), histopathological findings, surgical outcome and follow-up review in the patients' medical records. Inclusion criteria were newly diagnosed meningiomas operated between the study periods and was histo-pathologically proven

according to World Health Organization (WHO) Grading system 2007 and 2016. (12, 13) Exclusion criteria includes recurrent meningiomas, extracranial meningioma and patients with incomplete data or records.

Grouping

Patient with meningiomas operated were divided into skull base and non-skull base group, based on their tumour location as listed by Brokinkel et al. 2012 for skull base group. (1, 9, 14-16). Skull base meningiomas included olfactory groove (n=15), sphenoid ridge (n=22), tuberculum sellae or sellar (n=4), cerebellopontine angle (n=8) and petroclival or clivus (n=5). Non-skull base meningiomas (n=152) included convexity, falx, parasagittal, supra-tentorial and infra-tentorial meningiomas apart from skull base locations.

Imaging characteristics

The MRI and CT brain reports by radiologists were reviewed. Maximal diameter of meningioma documented was used to indicate the size of the tumour. (8, 17) ABC/2 was conducted as follows: A= maximum tumour diameter, B= diameter of the tumour perpendicular to A, and C= maximum height of the tumours as reported on MRI scan or CT scan (17). Besides, other radiological features as reported by the radiologists such as presence of oedema, hyperotosis and calcification for meningiomas were reviewed, as suggested by Ben et al (2016). (18)

Surgical and pathological review

Operative notes and both pre- and post-operative imaging were reviewed to determine the tumour characteristics and completeness of resection as per Simpsons grading. The extents of

resection were classified as gross total resection (GTR) or subtotal resection (STR) corresponding to EORTC/RTOG definition as related to Simpson 1-3 and Simpsons 4 respectively, as been quoted in Jenkinson et al. 2015. (19, 20) Besides, GTR was defined as no intraoperative evidence of residual tumour and no evidence of residual tumour and no evidence of contrast enhancement on post-operative scan. (19, 20) When either of these criteria was not satisfied, the extent of surgery was classified as subtotal. (20)

All meningiomas were graded as per World Health Organization (WHO) histopathological grade. (12, 13)

Outcome of surgery

Surgery was the sole modality of treatment. Post-operative complications including those required re-surgery reviewed. Functional outcome was categorized as well, partially dependent, fully dependent and death post-surgical intervention and follow-up based on Modified Rankin Scale. (11, 21)

Follow-up

The periods between the first complaints and diagnosis was registered as symptoms duration. Follow-up MRS data were collected through clinical records in 3 months, 6 months, 12 months and 18 months thereafter. (21) Overall survival (OAS) was calculated from the date of diagnosis to the date of death or the last follow-up for survival analysis. (9, 22, 23)

Statistical Analysis

Descriptive analysis was performed using Strata version 22 and SPSS version 24. Categorical data were expressed as proportions while continuous data were presented in mean ± Standard deviation (SD). Gender differences and age were assessed using α test and Student's t-test, respectively. Tumour maximum diameter and calculated tumour volume were represented as mean ± SD. Overall survival (OAS) was calculated from the date of diagnosis to the date of death or last follow-up, Kaplan Meier survival curve were plotted to estimate the survival. (24) Univariable and multivariable cox regression analysis was used to identify predictors for poor outcome. P-value of < 0.05 is considered significant.

Results:

Descriptive analysis prior grouping

A total of 1149 intracranial brain tumour cases were operated from January 2010 and December 2014. 199 patients were newly diagnosed meningioma and these patients were recruited. Majority of the patients had WHO grade I meningioma (n=194, 97.5%) and only 5 patients had WHO grade II meningioma. No newly diagnosed WHO grade III meningioma patients during the study period. Female predominated (n=134; 67.3%) with 2: 1 ratio to male. Malay was most commonly affected race (n=138; 69%). Highest incidence at age group 40-60 years noted (n=124; 62.3%).