COMPARING MONOMODALITY TREATMENTS OF LOW-GRADE INTRACRANIAL ARTERIOVENOUS MALFORMATION AT HOSPITAL KUALA LUMPUR BETWEEN 2008 AND 2011: A RETROSPECTIVE STUDY

BY

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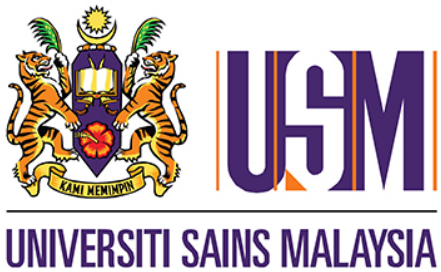
DISSERTATION SUBMITTED IN FULFILMENT OF THE PARTIAL REQUIREMENT FOR THE DEGREE OF MASTER OF SURGERY (NEUROSURGERY)



UNIVERSITI SAINS MALAYSIA

2015

Bismillah hir rahman nir rahim

(In the name of Allah, Mercy abundant, Mercy Eternal)

ACKNOWLEDGEMENTS

Alhamdulillah, praise be to Allah for steering my path in this particular direction. The roads I have traversed have not always been smooth, but by His Grace, the journey remains an interesting and an educational one.

To my mentor and father-figure, Datuk Dr Mohammed Saffari Mohammed Haspani, who has ever been supportive of my career from the day I reported to work under your tutelage in July 2006, I would not have made it this far without you. For teaching me patience and humility, for moulding my hands into those of a surgeon's, I offer my utmost gratitude.

To my teachers Professor Jafri Malin Abdullah, founding Director of the Centre for Neuroscience Services and Research, Universiti Sains Malaysia; Associate Professor Zamzuri Idris, Head of Neuroscience Department, Universiti Sains Malaysia; Professor John Tharakan, Dato' Dr Abdul Rahman Izaini Ghani, Dr Badrisyah Idris & Dr Regunath Kandasamy, Neurosciences lecturers of Universiti Sains Malaysia, thank you for the patient and continual education and guidance.

To my teachers at Hospital Kuala Lumpur: Mr Azmi Alias, Mr Gurmit Singh, Mr Kantha Rasalingam, Mr Saiful Razman, Ms Siti Suriyati Buang, and especially to Mr Mohamed Azman Mohamad Raffiq, whom I also see as a friend and mentor, as well as to specialists who used to work at Hospital Kuala Lumpur: Mr N Ramesh, Mr Mohd Hafiz Mohamad Zain, Mr Rahmat Harun @ Haron, Mr Cheang Chee Keong, Mr Azhari Omar, and other teachers who have played a big part in guiding me: Mr Pulivendhan Sellamuthu, Dr Lau Jia

Him, Dr Vanitha Sivanaser, Dr Zarina Abu Kasim, and Dr Hui Mun Tsong, no words, no actions can ever express my gratitude enough for shaping me into what I am today.

To my friends Faizul Hizal Ghazali, Ailani Ab Ghani, Low Siaw Nee, Shiraz Qamil, Siti Azleen Mohamad, Kanmani Devi Ganeson, Ginelle Genista Low, Breanna Teintze, Izwan Johari, Lim Mei Sin, Tan Shze Ee, Adlina Mustafa Kamal and the rest of the crew, thank you for your support, your understanding, and for the food and laughter when I need them the most.

And to my family: my mother Puan Aishah Mohd Tahir, my sister Ellisha Johanabas Rosli, my brother Faizalishah Johanabas Rosli, my brother-in-law Azrin Haris Mohd Yusoff, my sister-in-law Ili Aris, and the little ones Aryanna Arwen Johanabas Azrin Haris and Ayden Haris Johanabas Azrin Haris, I would not have made it this far, I would not be here, writing this, without you. You are my all, my everything.

For those of you who are reading this, I hope that this dissertation will be of benefit to you as much as it has benefited me, *insyaAllah*.

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LIST OF ABBREVIATIONS

AVM: arteriovenous malformation

AVMs: arteriovenous malformations

cm: centimetres

CT: computed tomography

CTA: computed tomography-angiography

GCS: Glasgow Coma Scale

GOS: Glasgow Outcome Score

Gy: Grey

ICH: intracranial haemorrhage

IVH: intraventricular haemorrhage

mL: millilitre

MRI: magnetic resonance imaging

MRA: magnetic resonance angiography

mRS: modified Rankin Scale

NA: not applicable/not available

SMG: Spetzler-Martin grading

SRS: stereotactic radiosurgery

ABSTRAK

Pengenalan

'Arteriovenous Malformation' (AVM) merupakan sambungan yang tidak normal antara arteri dan vena yang memintas sistem kapilari. Walaupun ia boleh muncul di mana-mana lokasi, anomali vaskular ini lebih dikenali dengan kehadirannya di dalam sistem saraf pusat. Kehadiran AVM adalah satu per sepuluh daripada kes aneurisme otak. Kadar pendarahan bagi pesakit yang tidak dirawat adalah antara 2 hingga 4 peratus setahun, dengan kadar kematian sebanyak 5 hingga 10 peratus.

Terdapat beberapa kaedah rawatan untuk AVM: pembedahan, embolisasi dan radiosurgeri stereotaktik (SRS). Pembedahan masih kekal sebagai rawatan pilihan untuk AVM gred rendah yang mudah dicapai. Namun, AVM yang dalam, sebagai contoh di dalam talamus atau akar otak, merupakan cabaran terapeutik.

Objektif

Mewujudkan kefahaman samada SRS atau embolisasi dapat mencapai penghapusan AVM secara memuaskan berbanding pembedahan, dan untuk mencari komplikasi rawatan seperti pendarahan dan kerosakan saraf kekal selepas rawatan, sehingga 3 tahun.

Kaedah

Kajian ini adalah kajian retrospektif rekod maklumat pesakit. Data yang diperoleh dari nota kes pesakit yang menjalani satu daripada tiga jenis rawatan untuk AVM gred Spetzler-

Martin I hingga III di Hospital Kuala Lumpur antara tahun 2008 dan 2011. Pesakit mendapat rawatan susulan dengan pengimejan sehingga 3 tahun dari tarikh rawatan. Seramai 81 pesakit telah dimasukkan ke dalam kajian ini, di mana 30 telah menjalani pembedahan, 27 telah mendapat rawatan embolisasi, dan 24 telah menjalani SRS.

Keputusan

Jumlah penghapusan AVM telah dicapai 96.2% pesakit yang menjalani pembedahan, 8.7% pesakit yang menjalani embolisasi dan 79.2% pesakit yang menjalani SRS. 4 pesakit yang menjalani pembedahan meninggal dunia (3 berkait secara lansung dengan pembedahan), dan 4 pesakit yang mendapat embolisasi meninggal duina (3 berkait secara lansung dengan tatacara), manakala tiada kematian dilihat dalam kumpulan SRS. 'Modified Rankin Scale' (mRS) bagi ketiga-tiga kumpulan rawatan menunjukkan peningkatan, dengan kumpulan pembedahan menunjukkan peningkatan terbaik (menunjukkan skala mRS yang menggalakkan, daripada 70% pada bulan ketiga kepada 92.3% pada tahun ketiga).

Kesimpulan

Penghapusan AVM bagi setiap kumpulan rawatan adalah setara dengan analisis-meta yang diterbitkan pada tahun 2011, di mana penghapusan AVM berjaya dicapai dalam 96% (julat 0%-100%) pesakit selepas pembedahan, 38% (julat 0%-75%) selepas SRS dan 13% (julat 0%-94%) selepas embolisasi. Setiap tatacara mempunyai komplikasi yang tersendiri; namun, kebanyakan pesakit di ketiga-tiga kumpulan menunjukkan peningkatan atau keadaan statik pada skala mRS pada akhir tahun ketiga rawatan susulan. Oleh kerana kami dapat mencapai penghapusan AVM dengan baik menggunakan pembedahan dan SRS, adalah wajar sekiranya kaedah-kaedah ini diteroka dan dimajukan dengan lebih lanjut. Walau bagaimanapun, embolisasi masih memainkan peranan penting dalam kes-kes rumit (kawasan fasih/'eloquent' dan AVM yang besar).

ABSTRACT

Title

Comparing Monomodality Treatments of Low-Grade Intracranial AVM at Hospital Kuala Lumpur between 2008 and 2011: A Retrospective Study

Authors

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Introduction

Arteriovenous malformation (AVM) is an abnormal connection between arteries and veins, which bypasses the capillary system. Although it can appear in any location, this vascular anomaly is widely known due to its occurrence in the central nervous system.

AVMs are one-tenth as common as saccular aneurysms. The rate of haemorrhage in untreated patients is between 2 to 4 percent per year, with a mortality rate of 5 to 10 percent.

There are several treatment modalities for AVMs: microsurgery, endovascular embolization and stereotactic radiosurgery (SRS). Surgical excision remains the gold standard treatment

for accessible, low-grade AVM. However, resection of deep-seated AVMs, such as within the thalamus and the brainstem, remains a therapeutic challenge.

Objectives

To establish an understanding whether SRS or embolization can achieve satisfactory obliteration of AVM nidi for patients as opposed to microsurgical excision, and to look for incidence of complications such as haemorrhage and permanent neurological deficit following treatment, for up to 3 years.

Methods

This is a retrospective review of records study. The data is acquired from case notes of patients with intracranial AVM of Spetzler-Martin grades I to III who underwent monomodality treatment at Hospital Kuala Lumpur between 2008 and 2011. The patients were followed-up with imaging for up to 3 years from the date of treatment. A total of 81 patients were recruited in this study, where 30 underwent microsurgical treatment, 27 underwent embolization, and 24 underwent SRS.

Results

Total obliteration of AVM nidus was achieved in 96.7% of patients who underwent microsurgery, 8.7% of patients who underwent embolization and 79.2% of patients who underwent SRS. 4 patients who underwent microsurgery passed away (3 directly related to surgery), and 4 patients who underwent embolization passed away (3 directly related to procedure), whereas no mortality was seen in the SRS group. The modified Rankin Scale (mRS) for all three groups showed an improving trend, with the microsurgery group showing the best improvement (from 70% at 3 months to 92.3% at 3 years showing favourable mRS scores).

Conclusion

The AVM nidus obliteration for each treatment group is comparable to the meta-analysis published in 2011, where successful AVM obliteration was achieved in 96% (range 0% - 100%) after microsurgery, 38% (range 0% - 75%) after SRS and 13% (range 0% - 94%) after embolization. Each modality had its own set of complications; however, most of the patients in all three groups had either static or improved modified Rankin Scale (mRS) at the end of the 3-year follow-up. As we can achieve good AVM nidus obliteration using microsurgery and SRS, it will be good to explore and develop these treatment options further. Embolization, however, still plays a vital role in complicated cases (eloquent regions, large AVM).

Keywords

Arteriovenous malformation, brain AVM, intracranial AVM, microsurgery, endovascular embolization, stereotactic radiosurgery, SRS, Spetzler-Martin grades I, II and III, monomodality therapy for AVM, management of AVM in Malaysia

INTRODUCTION

Arteriovenous malformation (AVM) is an abnormal connection between arteries and veins, which bypasses the capillary system. Although it can appear in any location, this vascular anomaly is widely known due to its occurrence in the central nervous system.

Arteriovenous malformations (AVMs) are one-tenth as common as saccular aneurysms and about equally frequent in males and females (Ropper and Samuels, 2009). Bleeding or seizures are the main presentations. The rate of haemorrhage in untreated patients is between 2 to 4 percent per year, with a mortality rate of 5 to 10% and a 50% risk of serious neurological morbidity with each haemorrhage (Reyns *et al.*, 2007; Ropper and Samuels, 2009).

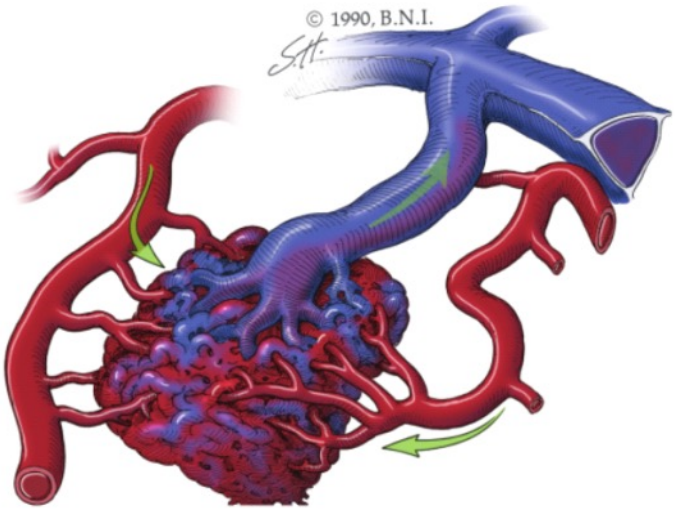

Figure 0-01: Diagrammatic representation of an AVM

adapted from *Neurovascular Surgical Techniques* (Jabbour, 2013)

AVMs are commonly graded using the Spetzler-Martin Grade (SMG) system, which categorizes AVMs based on size (less than 3cm, 3 to 6cm, more than 6cm), eloquence of adjacent brain tissue (eloquent areas include the brainstem, thalamus, hypothalamus, cerebellar peduncles, sensorimotor cortex, language cortex, or primary visual cortex), and the presence of deep venous drainage (Spetzler and Martin, 1986). However, Spetzler in 2011 proposed a 3-tiered grading system to simplify the original 5-tiered system as the differences in surgical results between the newly paired grades were small (A: SMG I & II, B: SMG III, C: SMG IV-V) (Spetzler and Ponce, 2011).

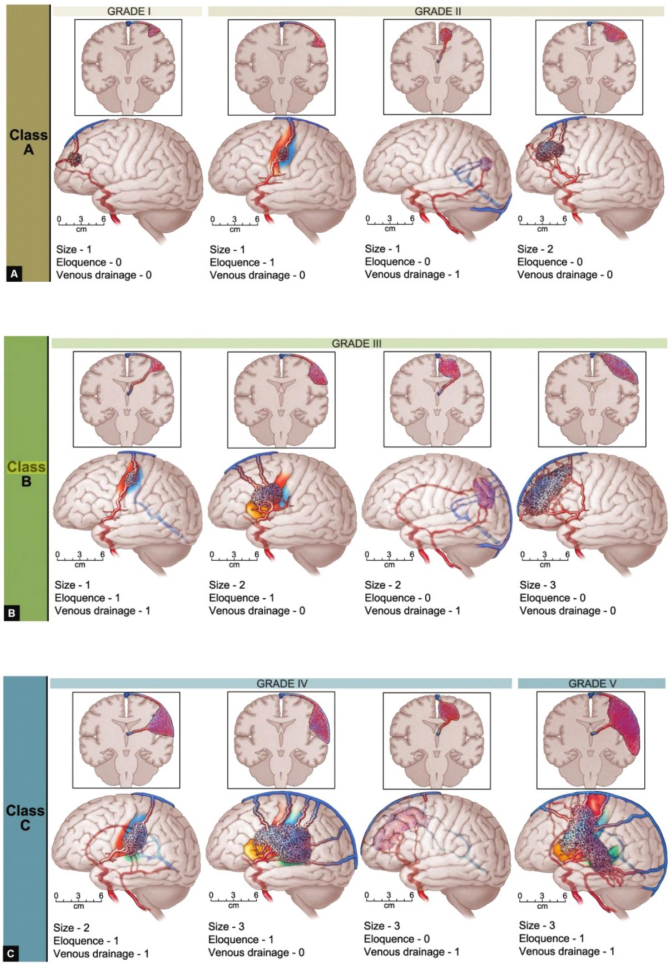

Figure 0-02: Spetzler-Martin Grading (SMG) of intracranial AVM adapted from *Neurovascular Surgical Techniques* (Jabbour, 2013)

There are several treatment modalities for AVMs: microsurgery, endovascular embolization and stereotactic radiosurgery (SRS). Surgical excision remains the gold standard treatment for accessible, low-grade AVM. In a meta-analysis of 6 journals between January 2000 and March 2011 by van Beijnum et al, successful AVM obliteration was achieved in 96% (range 0% - 100%) after microsurgery, 38% (range 0% - 75%) after SRS and 13% (range 0% - 94%) after embolization (van Beijnum *et al.*, 2011).

However, resection of deep-seated AVMs, such as within the thalamus and the brainstem, remains a therapeutic challenge. In a long-term outcome study by Tomoyuki Koga et al, the annual haemorrhage rate before SRS was 14%, but with treatment, the obliteration rate was 82% at 5 years after treatment, and the annual haemorrhage rate after SRS dropped to 0.36% (Koga *et al.*, 2010).

This is a retrospective review of records study to ascertain the efficacy of microsurgery, embolization and SRS for patients with AVMs of SMG I, II and III in Hospital Kuala Lumpur between 2008 and 2011, and in determining their outcome up to a period of 3 years post treatment.

CHAPTER 1: INTRACRANIAL ARTERIOVENOUS MALFORMATIONS

1.01: PATHOLOGY

Arteriovenous malformations (AVMs) are lesions defined by the presence of arteriovenous shunting through a nidus of coiled and tortuous vascular connections between feeding arteries and draining veins. Seen under the microscope, cells within the nest show chronic reactive changes and are thought to be non-functioning. The vessels retain the characteristic feeding artery and draining vein components, though without capillaries in between, thus creating a direct arteriovenous shunting. Arterial and venous elements show luminal hypertrophy. The elastic lamina of the arterial intimal layer is mostly intact, but it might show some degradation. The arterialized veins can be recognized by their size and by the absence of elastic staining. If bleeding has occurred, the surrounding parenchyma will show gliosis and hemosiderin staining.

1.02: EMBRYOGENESIS

Yasargil postulated in 1987 that AVMs might be a “proliferative capillaropathy” instead of a simple structural connection between arterial and venous systems (Fleetwood and Steinberg, 2002). This suggestion is supported by several case reports and two theories.

Most theories state that AVMs are congenital lesions, attributed with either a persistent primitive arteriovenous connection, or a development of this connection after its initial closure. However, in 1996, Mullan and colleagues showed that AVMs are impossible to identify in utero or with perinatal ultrasound, which suggests that they are either too small to be detected in those early stages, or that they develop after birth (Mullan *et al.*, 1996). They speculated that the origins of AVMs might be related to sequential formation and absorption of surface veins that occur in the 40- to 80-mm length interval of human embryonic development. However, persistent AVM growth is possible even after birth. In 1997, Lasjaunias speculated that AVMs are the result of biological dysfunction of the remodelling process at the junction of capillaries and veins from genetically-controlled maintenance and homeostasis, rather than as congenital structural anomalies (Lasjaunias, 1997).

1.03: NATURAL HISTORY AND CLINICAL PRESENTATION

53% of patients with AVMs will present with haemorrhage. In a meta-analysis of nine natural history studies with 3923 patients, the overall annual haemorrhage rate was 3.0%. For patients with unruptured AVMs, the annual rate of haemorrhage was 2.2%, whereas for patients with ruptured AVMs, the rate was 4.5%. Deep-seated AVMs, AVMs with previous haemorrhage, AVMs that have exclusive deep venous drainage, as well as AVMs with associated aneurysms were also found to have higher annual haemorrhage rates compared to their counterparts (Gross and Du, 2013). The risk of haemorrhage goes up to 6.0-6.9% within the first year after a rupture, but returns to the baseline annual risk of haemorrhage thereafter. Morbidity after an AVM rupture has been recorded to be as high as 53.0-81.0%, and mortality after the initial rupture is 10.0-16.6% (Fleetwood and Steinberg, 2002).

Table 1-01: Natural history studies for arteriovenous malformations

Author (year)	Study Type	Number of Patients	Average Years of F/U	Annual Haemorrhage Rate
Graf et al. (1983)	Retrospective	164	4.8	2-3%; 6% at first year, then 2%/year
Crawford et al. (1986)	Retrospective	217	10.4	2%; 36% cumulative risk with previous haemorrhage & 17% without haemorrhage at 10 years
Brown (1988)	Retrospective	168	8.2	2.2%
Ondra et al. (1990)	Retrospective	160	23.7	4% overall; 3.9% with haemorrhage; 4.3% with seizures
Mast et al. (1997)	Prospective	139	1.0	2.2% without haemorrhage; 17.8% with haemorrhage
Halim et al. (2004)	Retrospective	790	4.0	7% for the first year, then 3%/year
Gross & Du (2013)	Meta-analysis	3923	18,423 patient-years	3% overall; 2.2% without haemorrhage; 4.5% with haemorrhage;

The size of the nidus can influence the risk of haemorrhage, as the intranidal pressure of small AVMs is higher to that of larger AVMs. Typically, the haemorrhage is intraparenchymal; however, intraventricular and subarachnoid bleeding may also occur. Vasospasm rarely follows an AVM rupture as opposed to an aneurysmal rupture.

The second most common presentation is seizures, which occur in 10-30% of patients (Jabbour, 2013). Others include headaches and focal neurological deficits, the latter presumably from direct mass effect on the eloquent brain or relative hypoperfusion from the vascular steal phenomenon.

7% of patients with AVMs have aneurysms, and 75% of these aneurysms are found on major feeding arteries, likely from the increased flow. These arterial aneurysms can be classified into 5 types, as shown in *Table 1-02*. Aneurysms may also be found within the nidus or on draining veins (Greenberg, 2010).

Table 1-02: Categories of aneurysms associated with AVMs

Type	Aneurysm Location
I	Proximal on ipsilateral major artery feeding the AVM
IA	Proximal on major artery related to but contralateral to AVM
II	Distal on superficial feeding artery
III	Proximal or distal on deep feeding artery
IV	On artery related to AVM

1.04: EPIDEMIOLOGY AND DEMOGRAPHICS

From the Cooperative Study of Intracranial Aneurysms and Subarachnoid Haemorrhage and early autopsy series, the prevalence of intracranial AVMs are estimated at 140-500 per 100,000 people, affecting 0.14-0.50% of the population (McCormick, 1966; Perret and Nishioka, 1966). Hofmeister et al, in a review of 1289 patients, observed a mean age at diagnosis of 31.2 years, with 45% of the patients being female (Hofmeister *et al.*, 2000). However, intracranial AVMs can present in patients of any age, and the distribution between sexes is equal (Choi and Mohr, 2005).

1.05: DIAGNOSTIC EVALUATION

For patients presenting with neurologic sequelae of AVMs, computed tomography (CT) scan is the initial screening tool, which will show the location of the lesion, the acute haemorrhage, and the presence of intraventricular haemorrhage and/or hydrocephalus. On a plain CT, unruptured AVMs may appear as irregular hyperdense areas with or without calcifications. Contrast-enhanced CTs may show the nidus and feeding vessels or dilated draining veins (Geibprasert *et al.*, 2010).

Magnetic resonance imaging (MRI) can delineate details of the architecture of the AVM where features like the anatomic relationships of the feeding arteries, nidus and draining veins, and the topography between the AVM and adjacent brain can be appreciated. AVMs can bee seen as sponge-like structures with patchy flow voids on T2-weighted images (T2WI). However, magnetic resonance angiography (MRA) cannot replace conventional cerebral angiography, and in ruptured AVMs, the hematoma may obscure the AVMs on an MRI (Morris *et al.*, 2009).

Cerebral angiogram is an obligatory step in the preoperative evaluation of patients with AVMs, and is a gold standard for these lesions (Farhat, 2011). Not only can it localize the nidus, feeding arteries and draining veins, it can also detect associated aneurysms and other AVM-related factors associated with a high risk of haemorrhage.

In cases where the AVM is close to or on the eloquent areas of the brain (sensory, motor, language and visual cortex, hypothalamus and thalamus, internal capsule, brainstem), the use of positron emission tomography or functional MRI (fMRI) may be useful in determining the appropriate treatment modalities.

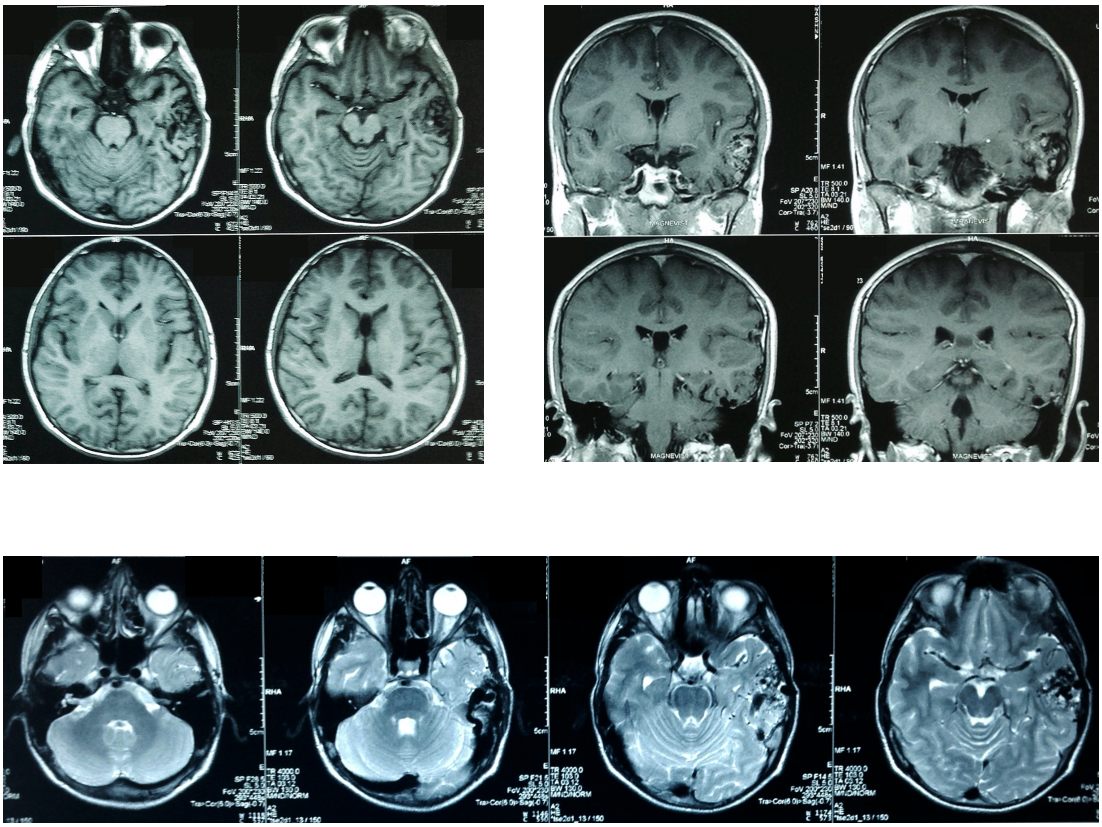

Figure 1-01A: Axial and coronal views of T1WI (above) and axial view of T2WI of MRI showing vascular flow voids at the posterior left temporal region. A dilated draining vein that connects to the left sigmoid sinus can easily be seen on T2WI.

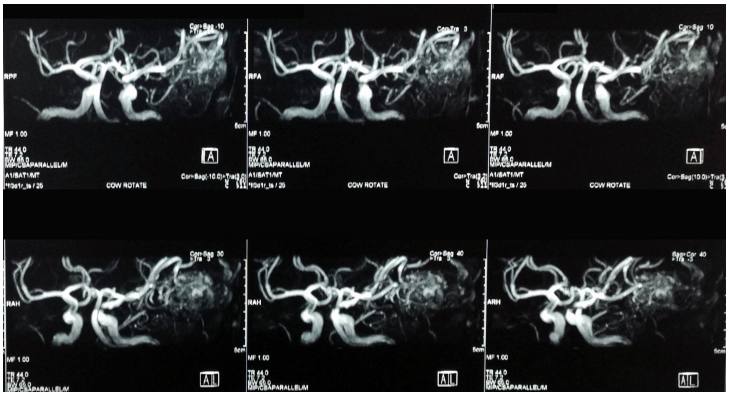

Figure 1-01B: MRA showing the same left temporal AVM in 3-dimensional views.

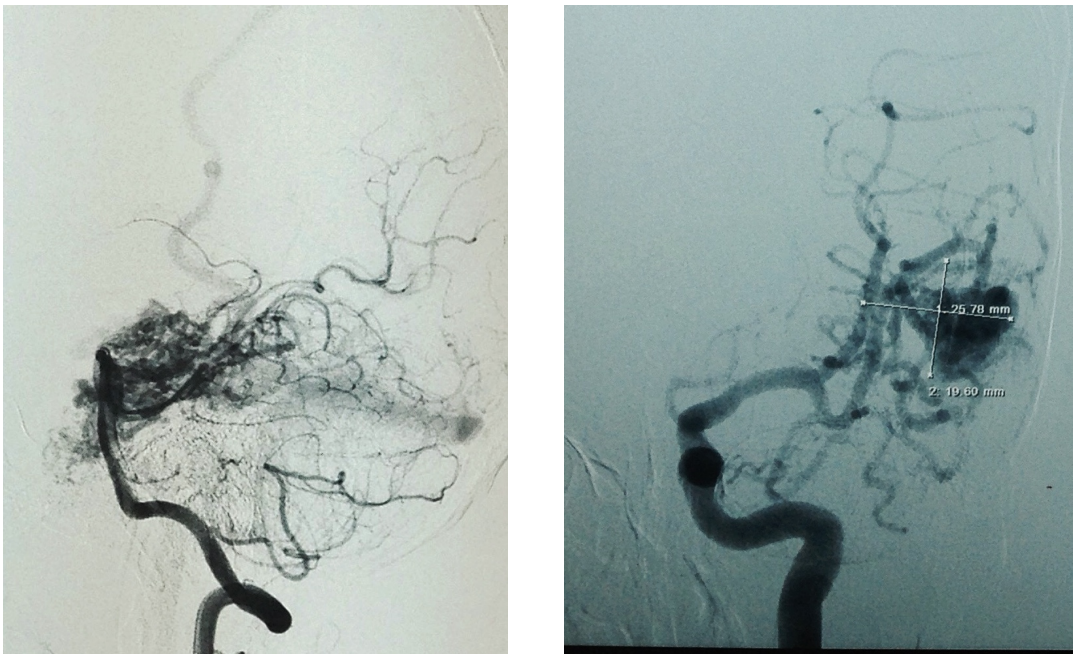

Figure 1-02: left vertebral artery run of cerebral angiogram shows a small left temporal AVM, whose feeders come from branches of the distal posterior cerebral artery (PCA) and posterior communicating artery (PCA), and whose draining veins flow superficially (SMG I).

1.06: CLASSIFICATION

In 1977, Luessenhop and Gennarelli proposed a classification system based on the number of arterial supply of AVMs. Grades I through IV were given corresponding to the number of feeding arteries from one vascular territory; no additional grade was assigned if the number exceeded 4, and the lesion was deemed inoperable. It did not take into consideration the draining veins or whether the lesions were located in the eloquent areas of the brain (Luessenhop and Spence, 1960; Quinones-Hinojosa, 2012). Luessenhop and Rosa published a grading scale in 1984 based on the size of the AVM; however, it was not practical for

surgical purposes, as it also did not consider draining veins and association with eloquent areas of the brain (Stieg and Batjer, 2006).

In 1986, Shi and Chen a classification based on the size, location, arterial supply and drainage of an AVM. AVMs were graded according to these parameters (Stieg and Batjer, 2006):

1. Size—largest diameter of the nidus on angiogram (excluding distal parts of the draining veins). Grades 1 to 4 are given based on size of less than 2.5cm, 2.5 to 5cm, 5 to 7.5cm, and greater than 7.5cm, respectively.
2. Location and depth—superficial versus deep, "functional" versus "non-functional", corpus callosum, brain stem, diencephalon. Grades 1 to 4 are assigned on the basis of increasing anatomic complexity and "functionality".
3. Arterial supply—grade 1 for single superficial feeder (MCA/ACA), grade 2 for multiple superficial feeders (MCA/ACA), grade 3 for branches of PCA or deep MCA/ACA branches or vertebral artery, and grade 4 for main branches of all three territories or vertebrobasilar system.
4. Venous drainage—single superficial (grade 1), multiple superficial (grade 2), deep (grade 3), deep with aneurysmal venous dilatation (grade 4).

The final grade is determined by a simple algorithm and matched with the highest grade(s) if at least two criteria are in that grade. Grade IV patients are not subjected to surgery. However, it is a complex classification and difficult to remember.

Spetzler and Martin proposed their classification in the same issue of the *Journal of Neurosurgery* as Shi and Chen in 1986, based on the size of the nidus, the pattern of venous drainage, and the association with eloquent areas of the brain. This classification turned out to be the most practical one due to its simplicity and the low inter-observer variability, thus

became widely accepted, and is still applicable today (Spetzler and Martin, 1986; Quinones-Hinojosa, 2012).

Table 1-03: Spetzler-Martin Scale for Grading Arteriovenous Malformations

Variable	Points
Size	
<3cm	1
3-6cm	2
>6cm	3
Venous drainage	
Superficial	0
Deep	1
Brain region	
Non-eloquent	0
Eloquent	1

The scale consists of 5 grades with 12 possible combinations, as shown in *Figure 0-02*. Lesions in which surgical resection would invariably lead to death or major deficit, such as very large AVMs within eloquent areas such as the thalamus or brain stem, a separate grade (grade 6, or inoperable) is given.

Several other authors have proposed different classifications for AVMs, including Pertuiset et al. in 1991, Höllerhage et al. in 1992, and Malik et al. in 1994. To note, Malik et al. proposed a system based for the first time on AVM volume, location, and nature of arterial feeders (Malik *et al.*, 1994; Stieg and Batjer, 2006).

1. Volume is approximated by using the formula of (length x width x height)/2. Volumes are then divided into six grades.
2. Location is divided into 4 categories following the scheme of Shi and Chen.
    - Cortical simple: non-eloquent cortex (including visual cortex);
    - Cortical functional: sensorimotor/speech;
    - Deep non-vital: insula, basal ganglia, anterior limb of internal capsule, corpus callosum, medial temporal lobe, intra- and periventricular, and cerebellar nuclei;
    - Deep vital: genu and posterior limb of internal capsule, thalamus and hypothalamus, and brain stem.
3. Arterial feeders are divided into superficial or deep, including lenticulostriate arteries, thalamo-perforator arteries, choroidal arteries, and brain stem perforators.

The final grade is determined by characterizing the type of location followed by size. If any of the arterial feeders are deep, an "A" is attached.

With the application of the Spetzler-Martin grading (SMG) system, it became clear that AVMs of SMG III presented different difficulties in treatment and prognosis. Several authors have proposed modifications to this classification. de Oliveira et al. further divides SMG III into IIIA (large) and IIIB (small, in eloquent areas) (de Oliveira *et al.*, 1998). However, SMG classification is still the most commonly used, and treatment criteria are mostly based on it. Although the classification proposed by Malik et al. has not yet been

clinically tested, it introduces a valuable addition by implementing volume instead of the more imprecise measurement of maximum diameter.

1.07: TREATMENT

When dealing with AVMs, Drake proposed five options for neurosurgeons (Drake, 1979):

- Expectant behaviour;
- Surgery;
- Endovascular therapy;
- Radiotherapy (radiosurgery);
- Combination of the above options.

Although it was published in 1979, the options for treatments are still applicable today. Once a complete resection of an AVM is done, with no angiographic evidence of remaining lesions, the patient can be deemed cured. Nevertheless, AVM relapses have been reported (Quinones-Hinojosa, 2012). Advances in neuroimaging and in neuro-anaesthesia with brain protection allow for complex surgeries to be safer and less harmful.

Microsurgery is reported to have a low risk of complications for SMG I and II, with immediate cure. However, surgery is invasive. SRS can be effective for lesions smaller than 3.5 cm, but complete obliteration requires between 1 and 3 years after treatment, and may not always be obtained. Embolization is used to obliterate small malformations or to make larger malformations amendable for microsurgery or SRS. AVMs of SMG IV or V generally require multimodality treatment (van Beijnum *et al.*, 2011).

Patient factors must also be considered in decision-making. Age, presentation, medical comorbidities, as well as functional status and social factors have to be addressed. Elderly patients with multiple comorbidities and an incidental finding of an unruptured AVM may be treated conservatively, but young patients should be worked up for treatment in view of the cumulative risk of haemorrhage. Assuming an annual haemorrhage rate of 2-4%, with an average life expectancy of 70 years, the cumulative risk (in percentage) of an AVM to rupture can be estimated using this formula (Brown, 2000; Farhat, 2011):

Lifetime risk (%) = 105 – patient's age in years.

Patients with a ruptured AVM should be stabilized first and be allowed to recover neurological function before the AVM is tackled. In cases where the hematoma is causing a mass effect, the clots may be evacuated first, before revisiting the lesion later in a controlled, elective environment.

CHAPTER 2: LITERATURE REVIEW

2.01: A 3-TIER CLASSIFICATION OF CEREBRAL ARTERIOVENOUS MALFORMATIONS (SPETZLER AND PONCE, 2011)

As mentioned in the previous chapter, Spetzler and Martin had proposed a grading system for intracranial AVMs in 1986 based on the size of the nidus, the location of the AVM whether it is in an eloquent area of the brain, and the presence of deep venous drainage. The Spetzler-Martin grading (SMG) classification has since been widely accepted and applied. Since the management of AVMs at the Barrow Neurological Institute practices a treatment paradigm where SMG I and II are managed in a similar fashion, as are SMG IV and V, the authors have proposed a system consisting of 3 classes (please also refer to *Figure 0-02*):

Table 2-01: Proposed 3-tier classification of cerebral AVMs with treatment paradigm, adapted from "A 3-tier Classification of Cerebral Arteriovenous Malformations"

Class	Spetzler-Martin Grade (SMG)	Management
A	I & II	resection
B	III	multimodality treatment
C	IV & V	no treatment*

* Exceptions for treatment of Class C AVMs include recurrent haemorrhages, progressive neurological deficits, steal-related symptoms, and AVM-related aneurysms.

7 surgical series were considered in this study, and the authors found no significant difference between the outcomes of SMG I and II or SMG IV and V AVMs. The authors recommended microsurgical resection as the management of Class A AVMs, as a study by Davidson and Morgan reported a 0.7% risk of adverse surgery-related outcomes for this group of patients.

For Class B AVMs, the management is more individualized and tailored to suit the patient's situation, although it typically requires a multimodality approach. de Oliveira et al, when subdividing SMG III into IIIA (large) and IIIB (small, in eloquent areas), recommended embolization followed by microsurgery for IIIA, and radiosurgery alone for IIIB (de Oliveira *et al.*, 1998).

Medical management is recommended for Class C AVMs except for cases with repeated haemorrhages or progressive neurological deficits in view of the high reported rates of morbidity associated with surgery and possible risk of haemorrhage associated with radiation or partial embolization.

2.02: MEDICAL MANAGEMENT WITH OR WITHOUT INTERVENTIONAL THERAPY FOR UNRUPTURED BRAIN ARTERIOVENOUS MALFORMATIONS (ARUBA): A MULTICENTER, NON-BLINDED, RANDOMIZED TRIAL (MOHR *ET AL.*, 2014)

This study was aimed to compare the risk of death and symptomatic stroke in patients with an unruptured brain arteriovenous malformation who were either treated medically alone (experimental study group), or medical management with interventional therapy (standard treatment). It recruited patients at 39 clinical sites in nine countries, starting from April 4, 2007.

Randomization was stopped on April 15, 2013 due to the superiority of the medical management group (log-rank Z statistic of 4.10, above the pre-specified boundary value of 2.87). At that point, outcome data for 223 patients were available, where 114 patients (51.1%) had been assigned to interventional therapy and 109 patients (48.9%) to medical management. Patients with SMG I-IV were included in this study, and most (62%) had scores of II or less.

35 out of 114 patients from the interventional study (30.7%) reached the study's endpoint of death or stroke (25 patients developed haemorrhagic stroke, 9 patients developed ischemic stroke, and 3 patients died). As for the medical management group, 11 out of 109 patients

(10.1%) reached the endpoint (6 patients developed haemorrhagic stroke, 3 patients developed ischemic stroke, and 2 patients died). The hazard ratio (instantaneous risk) was significantly less in the medical management group (HR 0.27, 95%CI 0.14-0.54) as compared with the interventional therapy group (p <0.0001).

2.03: TREATMENT OF BRAIN ARTERIOVENOUS MALFORMATIONS: A SYSTEMATIC REVIEW AND META-ANALYSIS (VAN BEIJNUM *ET AL.*, 2011)

In 2011, van Beijnum et al. published a meta-analysis on 137 observational studies with a total of 13,698 patients and 46,314 patient-years of follow-up. This study measured the outcomes following treatment of arteriovenous malformations (AVMs) with microsurgery, embolization, stereotactic radiosurgery (SRS), or a combination of treatment modalities. The study was aimed to assess the rates of successful obliteration of brain AVMs, rates of case fatality, long-term risk of haemorrhage and complications following interventional treatment.

In this study, the primary outcome was all-cause case fatality during treatment and follow-up. The secondary outcome was intracranial haemorrhage beyond 30 days of treatment, as haemorrhage within 30 days was considered a complication of treatment. The tertiary outcomes were treatment complications and successful obliteration of the AVMs.

From the 137 articles reporting on 142 cohorts, 41 cohorts (29%) reported on microsurgery, 14 (10%) reported on embolization, 69 (48%) reported on SRS, 7 (5%) reported on fractionated radiotherapy, while 11 (8%) described either multimodality treatment, various treatments within 1 article, or another treatment such as intraoperative embolization.

Table 2-02: Primary, Secondary and Tertiary Outcome measures Adapted from "Treatment of Brain Arteriovenous Malformations: A Systematic Review and Meta-analysis" (van Beijnum *et al.*, 2011)

	No. (%) of Cohort [Study Sample Size]	Estimate (95% CI) per 100 Person-Years	Median (Range), %
Overall			
Case fatality	142 [13,698]	0.68 (0.61-0.76)	1.5 (0-29)
Haemorrhage	142 [13,698]	1.4 (1.3-1.5)	3.6 (0-46)
Follow-up, person-years	142 [13,698]		157 (3.5-3900)
Follow-up, mo	124 [11,287]		30 (2.0-123)
Microsurgery			
Case fatality	41 [2549]	1.1 (0.87-1.3)	0.67 (0-13)
Haemorrhage	41 [2549]	0.18 (0.10-0.30)	0 (0-11)
Complications, %			
Acute	33 (80) [1655]		29 (1.5-54)
Severe	24 (30) [1252]		7.4 (0-40)
Obliteration, %	34 (85) [1837]	96 (0-100)	
Follow-up, person-year	41 [2549]	72 (3.5-2063)	
Follow-up, mo	35 (85) [2309]	17 (2.0-98)	
SRS			
Case fatality	69 [9436]	0.50 (0.43-0.58)	1.1 (0-12)
Haemorrhage	69 [9436]	1.7 (1.5-1.8)	5.8 (0-21)
Complications, %			
Acute	33 (48) [3290]		0 (0-16)
Acute severe	32 (46) [2558]		0 (0-4.8)
Late	63 (91) [6914]		13 (0-63)
Late severe	35 (51) [2862]		5.1 (0-21)
Obliteration, %	57 (83) [7996]		38 (0-75)
Follow-up, person-year	69 [9436]		202 (21-3900)
Follow-up, mo	68 (99) [7501]		35 (8.0-94)

	No. (%) of Cohort [Study Sample Size]	Estimate (95% CI) per 100 Person-Years	Median (Range), %
Embolization			
Case fatality	14 [1019]	0.96 (0.67-1.4)	2.5 (0-12)
Haemorrhage	14 {1019]	1.7 (1.3-2.3)	1.9 (0-14)
Complications, %			
Acute	18 (100) [1201]		25 (7.6-55)
Severe	16 (89) [818]		6.6 (0-28)
Obliteration, %	13 (72) [786]		13 (0-94)
Follow-up, person-year	14 [1019]		137 (7.5-931)
Follow-up, mo	11 (79) [926]		27 (5.3-78)

In this study, obliteration was achieved in 96% (range, 0%-100%) of patients who underwent microsurgery, in 38% (range, 0%-75%) after SRS, and in 13% (range, 0%-94%) after embolization. Complications leading to death or permanent neurological deficits occurred in a median of 7.4% (range, 0%-40%) after microsurgery, 5.1% (range, 0%-21%) after SRS, and 6.6% (range, 0%-28%) after embolization.

It was also noted that complete obliteration was obtained in a high proportion of patients who underwent microsurgery, whereas embolization as a monotherapy was achieved in a minority of patients. SRS was reported to be associated with a low case fatality, but at the expense of a low obliteration rate. The authors commented that the 2-year obliteration rate after SRS is probably in the range of 40% as opposed to the commonly cited 80%.

2.04: WHEN TO TREAT AN AVM

When an AVM has bled, it has to be treated. The same goes for AVM-related epilepsy refractory to medical treatment. Unruptured AVMs that show no clinical manifestation but with imaging evidence of intranidal aneurysms, stenosis of the feeding arteries or significant venous stenosis should also be treated. The following guideline can be used based on the SMG scale (Quinones-Hinojosa, 2012).

Grades I and II AVMs

Grade I AVM should always be treated. As they do not, in principle, pose any difficulty for the surgeon, microsurgery without prior endovascular treatment is the indicated and curative procedure. For unruptured SMG I AVMs, SRS is another option; however, the AVM may bleed during the time it takes to disappear. Endovascular option would be the last for this group, for even though there is angiographic evidence of lesion disappearance, non-visible pedicles may exist that may cause the nidus to reappear.

SMG I AVM

1. Surgery
2. Radiosurgery
3. Endovascular therapy
4. Do nothing

As with SMG I AVMs, SMG II should be treated, as the natural risks are higher than those of treatment complications. Microsurgery is the first-line treatment for SMG II. Endovascular therapy may be of help prior to surgery. It is possible to achieve angiographic total obliteration of AVM via endovascular therapy alone, but it is also likely that non-visible pedicles may still exist. Radiosurgery as a monotherapy is not indicated. It has been

proven that the area to be radiated does not include the entire nidus, and that areas treated endovascularly may not be included, thus leading to lesion reproduction.

SMG II AVM

1. Surgery
2. Endovascular therapy + surgery
3. Endovascular therapy
4. Radiosurgery
5. Surgery + radiosurgery

Grade III AVM

SMG III AVMs must always be treated, but management may be problematic in view of the variants that appear in this group (S1E1D1, S2E1D0, S2E0D1, S3E0D0). Endovascular therapy becomes essential in these situations by progressively occluding the afferent vessels without causing a sudden redistribution of flow prior to surgery. A time of no less than 4 to 5 days should be given before proceeding with surgery. Direct microsurgery can be done, but pre-embolized SMG III AVMs will bleed less. Endovascular therapy with SRS and SRS alone are also valid treatment options.

SMG III AVM

1. Endovascular therapy + surgery
2. Surgery
3. Endovascular therapy + surgery + SRS
4. Endovascular therapy + radiosurgery
5. SRS

Grade IV AVMs

Unruptured SMG IV AVMs that do not have intranidal aneurysms should be controlled clinically and with imaging evaluation. The mortality and morbidity rates of treatment are higher than that of the AVM's natural history. However, if there is presence of haemorrhage, these lesions should be treated in view of the higher risk of rebleed. Treatment should always be a combination of techniques, starting from endovascular therapy, which may take at least 2 sessions. Once the endovascular treatment has been completed, and enough time has elapsed, surgery is the next step. If post-surgery angiography shows any remnant, the treatment is completed with radiosurgery.

SMG IV AVM

1. Do nothing
2. Endovascular therapy + surgery
3. Endovascular therapy + surgery + SRS
4. Endovascular therapy + SRS (palliative)
5. Endovascular therapy (palliative)

Grade V AVMs

In principle, SMG V AVMs are not treated. Cure is possible, but the complication rates are high. If they cause recurrent bleedings, treatment should be tried, though it will always be palliative, with endovascular therapy as the mainstay of the management plan.

SMG V AVM

1. Do nothing
2. Endovascular therapy + SRS
3. Endovascular therapy