An anatomical investigation of intracranial meningiomas

by

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DECLARATION

I, Mr Ezra Earl Anirudh, declare that:

i. That the work described in this thesis has not been submitted to UKZN or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

ii. This dissertation does not contain another person's data, graphs, tables, or other information unless specifically acknowledged as being sourced from other persons.

iii. This dissertation does not contain another person's writing unless specifically acknowledged as being sourced from other persons. Where other written sources have been quoted, the information used has been referenced accordingly.

iv. The research reported in this thesis unless where otherwise indicated, is my original work. My contribution to the project was as follows:

Development and design of research topic and protocol.
Conduction of research methodology.
Collection and analysis of data.
Interpretation of data obtained.
Formulation of manuscript.
Write-up of the final thesis.

v. The contribution of others to this project was as follows:

Prof L. Lazarus (supervisor), Dr R. Harrichandparsad (co-supervisor):

Development and refining of the research design and plan.
Assistance with analysis of data and statistical analysis.
Review of manuscript and thesis before submission.

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03 December 2021

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ABBREVIATIONS AND ACRONYMS

CT	Computed tomography
DSA	Digital subtraction angiography
ECA	External carotid artery
ICA	Internal carotid
MMA	Middle meningeal artery
MRI	Magnetic resonance imaging
POI	Preoperative imaging
TSA	Total surface are
WHO	World Health Organization

ABSTRACT

Meningiomas are generally benign, highly vascularised, slow-growing tumours arising from the arachnoid cap cells of the arachnoid villi. The clinical presentation of these tumours is usually location dependant due to the vast expanse covered by the meninges. Resection of a meningioma is generally performed after preoperative embolisation. A feeder vessel is selected and embolised in an attempt to reduce excessive blood loss and postoperative complications. However, embolisation requires a sound knowledge of the vasculature of the meninges since these vessels supply portions of the cranial nerves. Literature consulted have investigated anatomical features of meningioma's; however, there is a scarcity of studies investigating patients specifically referred for preoperative embolisation. Therefore, this study aimed to investigate the anatomical features, namely the location, histology, volume and vascularity of intracranial meningiomas referred for preoperative embolisation.

This entailed using Magnetic resonance imaging (MRI), Digital subtraction angiography (DSA), and the histological reports obtained from the data bank at the central regional hospital in Durban, South Africa. A retrospective chart review yielded 103 patients that met the inclusion criteria, of which 98 patients (subset 1) presented with a single meningioma and 5 patients (subset 2) presented with multiple meningiomas. The average age of patients (at the time of diagnosis) was reported within the 40–49-year group and primarily within the female population (subset 1: 67.3%; subset 2: 80%). The benign grade of meningiomas was reported as the most common (70.4%), of which the meningothelial subtype (48%) was predominant. Meningiomas were mostly observed within the supratentorial region (subset 1: 57.2%; subset 2: 91.7%) with almost equal incidences in subset 1 and a majority on the right side in subset 2. Regarding tumour volume, subset 1 revealed the largest meningiomas within the supratentorial region (90.9 cm^3), and subset 2 revealed an average tumour volume of 43.9 cm^3. In terms of meningioma vascularity, within the supratentorial region, the external carotid arteries were noted to be a common primary feeder vessel, for the skull base region the primary arterial supply is the internal carotid artery.

This study provides insight into the anatomical basis of intracranial meningiomas within a select South African population as it has introduced a novel methodology of meningioma vascularity. This may assist endovascular surgeons in assessing the feeder vessel contributions of meningiomas and understand the prevalence of these anatomical parameters in this population.

CHAPTER 1

INTRODUCTION

1.1 Introduction

The meninges are a distinct triple layer of membranes that envelop the brain and spinal cord (Gray and Standring, 2016). Its core function involves the enclosure and support of the vascular components of the central nervous system in addition to protection of the brain from infections, allowing for the efficient functioning of the brain (Adeeb, Mortazavi and Tubbs et al., 2012). Embryologically, the paraxial mesoderm forms the meninges caudal to the mesencephalon whilst the neural crest cells form the meninges located rostrally (Gray and Standring, 2016; Sadler, 2012). These meningeal layers, as arranged from superficial to deep, are the dura (endosteal and meningeal layer), arachnoid, and pia mater (Adeeb, Mortazavi and Tubbs et al., 2012; Patel and Kirmi, 2009).

The meninges are supplied arterially by vessels that course deep to the endosteal layer of the dura mater (Adeeb, Mortazavi and Tubbs et al., 2012; Gray and Standring, 2016). Since the meninges envelop the entire central nervous system, the blood supply varies depending on its anatomical location (Gray and Standring, 2016; Patel and Kirmi, 2009). The internal and external carotid system of arteries, together with the vertebral arteries, form an anastomotic plexus that supply the meninges within the cranial region (Adeeb, Mortazavi and Tubbs et al., 2012; Patel and Kirmi, 2009).

The anterior and posterior ethmoidal arteries are responsible for the arterial supply to the medial aspect of the meninges within the anterior cranial fossa (Hiramatsu, Sugiu, Hishikawa et al., 2020). The posterior meningeal artery, which is derived from the occipital or vertebral arteries supplies portions of the posterior cranial fossa (Gray and Standring, 2016). However, the most significant contributor to the vascular supply of the meninges is from the middle meningeal artery (MMA), derived from the maxillary artery (Gray and Standring, 2016; Patel and Kirmi, 2009).

A meningioma is described as a highly vascularised, usually benign tumour that arises from the arachnoid cap cells of the arachnoid villi (Dubel, Ahn and Soares, 2013; Martin, Cha, Higashida et al., 2007; Pistolesi, Boldrini, Gisfredi et al., 2004). This type of tumour is rare in relation to

tumours of the entire body with its incidence accounting for less than 3% in autopsy studies; however, it is the most common form of tumour in the head region (Dubel, Ahn and Soares, 2013; Pistolesi, Boldrini, Gisfredi et al., 2004).

When a meningioma grows beyond its current vascular supply and requires additional arterial feeders, angiogenesis occurs (Martin, Cha, Higashida et al., 2007; Pistolesi, Boldrini, Gisfredi et al., 2004). Angiogenesis is the process in which new blood vessels are formed to supply a new region or accommodate a growing structure (Buerki, Horbinski, Kruser et al., 2018). Accompanied with the high degree of vascularity of the meninges, meningiomas have the potential to grow exponentially and occlude or interrupt the functioning neurovascular structures situated deep to the meninges (Huang, Bi, Griffith et al., 2019; Oya, Sade and Lee, 2011). Approximately three-quarters of meningioma blood supply is derived from dural feeders whilst some meningiomas may even parasitise the pial network of arteries adjacent to it (Huang, Bi, Griffith et al., 2019).

Preoperative tumour embolisation has proven to be a critical advantage in ensuring a safe surgical outcome with minimal blood loss (Martin, Cha, Higashida et al., 2007; Raper, Starke, Henderson et al., 2014; Shah, Choudhri, Jung et al., 2015). The process of tumour embolisation involves isolating a feeder vessel using micro-catheterisation and injection of embolic agents such as polyvinyl alcohol particles, detachable coils or fibrin glue to reduce blood flow to the meningioma (Raper, Starke, Henderson et al., 2014; Shah, Choudhri, Jung et al., 2015). However, this procedure warrants a thorough understanding of the vascularity of the tumour and the surrounding regions since these vessels also supply portions of the cranial nerves (Chan and Thompson, 1984; Dubel, Ahn and Soares, 2013). Post-operative embolisation complications such as epilepsy, cerebrospinal fluid leaks, hemiparesis and other neurological deficits have been reported and investigated due to the misidentification of the vascular territories (Dubel, Ahn and Soares, 2013; Martin, Cha, Higashida et al., 2007; Shah, Choudhri, Jung et al., 2015). An understanding of the anatomical basis of intracranial meningiomas including its vascular supply is warranted in a South African population due to the paucity of these studies in the literature. This study, therefore, aimed to explore the anatomy of intracranial meningiomas referred for preoperative embolisation within a South African population.

Aim: To investigate the anatomical basis of intracranial meningiomas referred for preoperative embolisation within a select South African cohort.

Objectives:

1) To investigate the demographic profile of patients with intracranial meningiomas referred for preoperative tumour embolisation in terms of age, sex and race.

2) To document the histological grade and subtypes of intracranial meningiomas referred for preoperative tumour embolisation.

3) To calculate and compare the volume of intracranial meningiomas referred for preoperative tumour embolisation against its anatomical location (supratentorial, cranial base or posterior fossa).

4) To document vascular territories of intracranial meningiomas referred for preoperative embolisation.

Research question: What are the anatomical features of intracranial meningiomas referred for preoperative embolisation in terms of anatomical location, histology, volume and arterial supply?

1.2 Literature review

1.2.1 Gross anatomy

The meninges have been described as three membranous layers surrounding the central nervous system, namely dura (endosteal and meningeal), arachnoid and pia mater (Gray and Standring, 2016; Last, 2011). These layers function to protect the brain as well as participate in the formation of the blood-brain barrier (Adeeb, Mortazavi and Tubbs et al., 2012; Gray and Standring, 2016).

The dura mater is the most superficial layer of the meninges and comprises of two sublayers namely an endosteal layer that is thick, fibrous and adherent to the osseous structures, and a meningeal layer that is fibrous and related to the underlying neurovascular systems (Patel and Kirmi, 2009). The meningeal dural layer acts as a tubular sheath for the emerging cranial nerves through the cranial foramina (Gray and Standring, 2016). It reflects inwards forming septations such as the falx cerebri, which separates the left and right cerebral hemispheres, the falx cerebelli, which separates the cerebellar hemispheres, the tentorium cerebelli, which separates the cerebrum from the cerebellum, as well as the diaphragma sellae, which separates the pituitary gland from the cerebrum (Moore, Dally and Agur, 2014).

1.2.2 Meningioma anatomy

Described as a highly vascularised tumour and usually benign, meningiomas originate from the leptomeninges, specifically the arachnoid cap cells of the arachnoid villi (Dubel, Ahn and Soares, 2013; Martin, Cha, Higashida et al., 2007; Shah, Choudhri, Jung et al., 2015). The meninges provide a vast expanse of possible sites for occurrence, ranging from the spinal dural segments to the dura mater lining the cranial vault (Buerki, Horbinski, Kruser et al., 2018). Depending on the location of the tumour and the neurological region affected, the symptoms may differ between patients (Shah, Choudhri, Jung et al., 2015).

The term multiple meningiomas has been used to describe the presentation of more than a single meningioma that are independent of each other in the same patient (Salvati, Caroli, Ferrante et al., 2004). These multiple tumours may occur either concurrently or after a period, although, recurrent meningioma formation from the same anatomical location is not considered as multiple meningiomas (Salvati, Caroli, Ferrante et al., 2004). These are usually common in patients with congenital tumour predisposition syndromes such as neurofibromatosis type 2 and Cowden syndrome (Gray and Kalamarides, 2010). Other causes for the formation have been attributed to fertility treatment, which is based on the presence of progesterone receptors on the surface of meningiomas (Shahin, Magill, Dalle et al., 2019).

Meningiomas act like parasites that ‘steal’ the arterial supply from the intracranial and extracranial arteries (Buerki, Horbinski, Kruser et al., 2018). Meningeal arteries supply the central portion of the meningioma, while the capsule of the tumour receives a pial or cortical supply (Dubel, Ahn and Soares, 2013). Furthermore, the arterial supply to a meningioma is location-specific (Shah, Choudhri, Jung et al., 2015).

Therefore, meningiomas identified in the convexity, parasagittal, sphenoidal wing and clinoidal region are supplied mainly by the MMA; whilst meningiomas of the olfactory groove are supplied by dural branches of the internal carotid (ICA), ethmoidal and ophthalmic arterial branches (Dubel, Ahn and Soares, 2013). The cavernous portion of the ICA, MMA and the tentorial artery are responsible for meningiomas' vascularisation in the tentorium and clival regions (Shah, Choudhri, Jung et al., 2015). Branches of the ascending pharyngeal, occipital, posterior meningeal and vertebral arteries are responsible for the blood supply to meningiomas in the posterior fossa (Dubel, Ahn and Soares, 2013). Choroidal arteries supply meningiomas found intraventricularly (Shah, Choudhri, Jung et al., 2015).

Due to the slow growth rate of meningiomas, detection usually occurs in the later stages of the patient's life (Hashiba, Hashimoto, Izumoto et al., 2009). However, some cases have been reported in young individuals, but these are primarily due to the size and location of the tumour within the brain (Buerki, Horbinski, Kruser et al., 2018; Huang, Bi, Griffith et al., 2019). According to the World Health Organization (WHO), meningiomas are classified into three grades: Grade I, is a benign tumour that grows at a slow rate; Grade II is an atypical meningioma with a more rapid growth; and Grade III is a rare, malignant tumour which shows exponential growth (Buerki, Horbinski, Kruser et al., 2018; Pistolesi, Boldrini, Gisfredi et al., 2004).

1.2.3 Aetiology

Harvey Cushing first described the term 'meningioma' in 1922 in the early works of meningioma surgery (Shah, Choudhri, Jung et al., 2015). These tumours are intra-dural, which grow into the meningeal layers compressing certain areas of the brain (Dubel, Ahn and Soares, 2013; Pistolesi, Boldrini, Gisfredi et al., 2004). Previous studies revealed high incidences of meningiomas in relation to other intracranial tumours (Christensen, Kosteljanetz and Johansen, 2003; Dubel, Ahn and Soares, 2013). The aetiology of meningiomas is unknown, though multiple studies have investigated possible causes.

A minor contributor to the aetiology of intracranial meningiomas is hereditary factors such as abnormalities of chromosome 22 and neurofibromatosis type 2, which have been associated with the formation of intracranial meningiomas (Klaeboe, Lonn, Scheie et al., 2005).

Studies done by Sadamori, Shibata, Mine et al. (1996) and Shintani, Hayakawa, Hoshi et al. (1999) investigated the incidence of intracranial meningiomas in Nagasaki and Hiroshima atomic bomb survivors and concluded that ionising radiation is a contributor to meningioma formation. Low dose radiotherapy has also been attributed to the increase in intracranial tumours in children; however, the findings from these studies were inconclusive (Christensen, Kosteljanetz and Johansen, 2003). Advancements in radiographic imaging were also noted to be a significant contributor to the rise in intracranial meningiomas in countries such as Denmark, Finland, Norway and Sweden during the periods of 1968–1997 (Hashiba, Hashimoto, Izumoto et al., 2009; Klaeboe, Lonn, Scheie et al., 2005).

1.3 Arterial supply of meninges

1.3.1 Anterior cranial fossa

Within the anterior cranial fossa, the dura is supplied by meningeal branches of the anterior and posterior ethmoidal arteries, a recurrent meningeal branch of the ophthalmic artery, and the anterior branch of the MMA (Shah, Choudhri, Jung et al., 2015). The falcine artery, an extension of the anterior ethmoidal artery, is responsible for vascular irrigation of the anterior parts of the falx cerebri (Gray and Standring, 2016). Vascularisation of the meninges of the anterior basal surface of the anterior cranial fossa are mainly supplied by the recurrent meningeal artery (Dubel, Ahn and Soares, 2013). The MMA and the anterior falcine artery supply anterior parasagittal and high convexity meningiomas (Dubel, Ahn and Soares, 2013). All of these blood vessels resulted in the incorporation of the external carotid artery (ECA) and ICA in a highly vascularised network supplying the meninges (Gray and Standring, 2016).

1.3.2 Middle cranial fossa

The MMA and accessory meningeal arteries are responsible for the vascularisation of the middle cranial fossa and the bulk of the meningeal layers within the anterior and posterior cranial fossae (Moore, Dally and Agur, 2014). Other branches of the maxillary artery, including the Vidian artery and the artery of foramen rotundum, aids these principle arteries (Dubel, Ahn and Soares, 2013). The Vidian artery may also arise, in some cases, from the petrous segment of the ICA (Dubel, Ahn and Soares, 2013). Originating from the first part of the maxillary artery, the MMA enters the cranial cavity via the foramen spinosum, where it divides into frontal, parietal and petrosal branches (Gray and Standring, 2016). Distal to the MMA, the accessory meningeal artery begins its course through the foramen spinosum to enter the cranial vault (Last, 2011). Dubel, Ahn and Soares (2013) stated that the MMA likely vascularises meningiomas in the sphenoidal wing and clinoidal regions.

1.3.3 Posterior cranial fossa

The posterior meningeal artery varies in origin, arising from either the occipital, ascending pharyngeal arteries or the suboccipital region of the vertebral artery (Dubel, Ahn and Soares, 2013). However, in most cases, it originates as a branch of the occipital artery, arising from the posterior surface of the external carotid artery and enters the cranium through either the jugular or mastoid foramen (Gray and Standring, 2016).

1.4 Morphological and morphometric variations

1.4.1 Morphological variation

1.4.1.1 Location of the meningioma

Meningiomas originate from the arachnoid cap cells and are found intra-durally (Shah, Choudhri, Jung et al., 2015). Since meninges envelop the central nervous system, it provides a large area for the formation of a meningioma (Gray and Standring, 2016). As described by Chan and Thompson (1984), a classification system that divides the regions of the intracranial portion of the skull into three broad regions, was used in studies as early as 1984. These three regions comprise the supratentorial region, which encompasses the meninges above the tentorium cerebelli (parasagittal, falcine, convexity, intraventricular regions); the skull base, which consists of the floor of the anterior and middle cranial fossa (sphenoidal ridge, olfactory groove, tuberculum sellae, clinoidal processes, petrosal, intraorbital and cavernous sinus regions); and the posterior fossa, which comprises the area at the floor of the posterior cranial fossa (cerebellopontine angle, cerebellar convexity, foramen magnum, jugular foramen, clivus, tentorial regions) (Bhat, Wani, Kirmani et al., 2014).

The literature indicates that the most common location of intracranial meningiomas is the cerebral convexity, as reported by Rohringer, Sutherland, Louw et al. (1989), Fang, He, Li et al. (2015) and Jensen-Kondering, Helle, Lindner et al. (2019). However, Bhat, Wani, Kirmani et al. (2014) concluded that the majority of intracranial meningiomas occurred in the parasagittal region (31.14%) compared to the cranial convexity (16.05%).

Within the skull base region, the incidence varies amongst the different subregions. However, areas such as the sphenoid wing are usually predominant, as reported by Bhat, Wani, Kirmani et al. (2014) and Kang, Wei and Toh (2019), who documented incidences of 15.50% and 15.69%, respectively. Interestingly, Oya, Sade and Lee (2011) conducted a study and revealed variations in the tuberculum sellae (14.29%) and petrosal (14.81%) regions as predominant in relation to the sphenoid wing (4.76%). This revealed variation within this region as the tuberculum sellae and petrosal sites are rare points of origin for skull base meningiomas (Tables 1.1, 1.2 and 1.3).

1.4.1.2 Multiple meningiomas

Table 1.4 illustrates the incidence of multiple meningiomas, which range from 2.8% to 8.6% in the literature. Furthermore, it is also noted that the average age of patients presenting with multiple meningiomas ranged from 52.4 to 58 years old. Regarding multiple meningioma presentation in terms of anatomical location, it is evident that the supratentorial region is most likely to harbour meningiomas. However, Huang, Buhl, Hugo et al. (2005) and Tsermoulas, Turel, Wilcox et al. (2018) reported higher incidences of meningiomas within the skull base and posterior fossa regions compared to Salvati, Caroli, Ferrante et al. (2004) and Pereira, de Almeida, de Aguiar et al. (2019) (Table 1.4).

Table 1.1 Review of the anatomical location of intracranial meningioma's in the supratentorial region

Author (Year)	Population	Modality	Sample size	Supratentorial (%)				
				Parasagittal	Falcine	Convexity	Intraventricular	Other
Chan and Thompson (1984)	Canadian	CT	257		80 (31.13%)	53 (20.62%)	4 (1.56%)	-
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	43 (22.38%)	-	67 (34.71%)	10 (5.18%)	1 (0.52%)
Lieu and Howng (1999)	Taiwanese	POI	222		51 (22.97%)	81 (36.49%)	-	8 (3.60%)
Oya, Sade and Lee (2011)	North American	MRI	189	23 (12.2%)	17 (9.0%)	43 (22.75%)	-	10 (5.29%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	2 (9.52%)	1 (4.76%)	4 (19.05%)	-	-
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	146 (20.0%)	81(11.1%)	117 (16.05%)	23 (3.16%)	-
Raper, Starke, Henderson et al. (2014)	North American	POI	490	88 (18.0%)	-	187 (38.2%)	9 (1.8%)	-
Fang, He, Li et al. (2015)	Chinese	POI	157		20 (12.73%)	69 (43.95%)	2 (1.27%)	7 (4.45%)
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65	5 (7.7%)	15(23.3%)	13 (20%)	-	-
Ishi, Terasaka, Yamaguchi et al. (2016)	Japanese	POI	83	35 (42.17%)				
Magill, Young, Chae et al. (2018)	North American	POI	1113	540 (48.52%)				
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42		2 (4.76%)	11 (26.19%)	1 (2.38%)	-
Kang, Wei and Toh (2019)	Korean	POI	51	17 (33.33%)	-	22 (43.14%)	2 (3.92%)	-
Klae, Safi, Stavrinou et al. (2019)	German	POI	58	11 (18.97%)	-	20 (34.48%)	-	-
Lagman, Ong, Nguyen et al. (2018)	North American	MRI	21			11 (52.38%)	-	-
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	-	6 (17%)	12 (34%)	-	-

*POI: Preoperative imaging, combined use of Magnetic resonance imaging (MRI) and Computed tomography (CT) angiograms

Table 1.2 Review of the anatomical location of intracranial meningioma's in the skull base region

Author (Year)	Population	Modality	Sample size	Skull base (%)					
				Sphenoid ridge	Olfactory groove/ Anterior cranial fossa	Tuberculum sellae	Petrosal	Intra-orbital	Cavernous sinus
Chan and Thompson (1984)	Canadian	CT	257	35 (13.62%)	20(7.78%)	12 (4.70%)	10 (3.89%)	2 (0.78%)	-
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	33 (17.09%)	6 (3.11%)	7 (3.63%)	-	4 (2.07%)	-
Lieu and Howng (1999)	Taiwanese	POI	222	18 (8.11%)	8 (3.60%)	26(11.71%)	-	-	-
Oya, Sade and Lee (2011)	North American	MRI	189	9 (4.76%)	6 (3.17%)	27(14.29%)	28(14.81%)	-	11(5.82%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	5 (23.81%)	-	1 (4.76%)	2 (9.52%)	-	-
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	113(15.50%)	58(7.96%)	35 (4.80%)	22 (3.02%)	11 (1.51%)	7 (0.96%)
Raper, Starke, Henderson et al. (2014)	North American	POI	490	66 (13.5%)	27 (5.5%)	42 (8.6%)	12 (2.4%)	1 (0.2%)	5 (1.0%)
Fang, He, Li et al. (2015)	Chinese	POI	157	10 (6.37%)	7 (4.45%)	13 (8.28%)	3 (1.91%)	-	-
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65	7 (10.8%)	8 (12.3%)	-	4 (6.2%)	-	-
Ishi, Terasaka, Yamaguchi et al. (2016)	Japanese	POI	83	27 (32.53%)					
Magill, Young, Chae et al. (2018)	North American	POI	1113	343 (30.82%)					
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42	14 (33.3%)	-	4 (9.52%)	-	1 (2.38%)	-
Kang, Wei and Toh (2019)	Korean	POI	51	8 (15.69%)	-	-	-	-	-
Kauke, Safi, Stavrinou et al. (2019)	German	POI	58	8 (13.79%)	3 (5.17%)	6 (10.34%)	-	-	-
Lagman, Ong, Nguyen et al. (2018)	North American	MRI	21	3 (14.28%)	1 (4.76%)	1 (4.76%)	2 (9.52%)	1 (4.76%)	-
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	5 (14.3%)	4 (11%)	-	2 (6%)	-	-

*POI: Preoperative imaging, the use of MRI, CT angiograms, digital subtraction angiograms

Table 1.3 Review of the anatomical location of intracranial meningioma's in the posterior fossa region

Author (Year)	Population	Modality	Sample size	Posterior fossa (%)					
				Cerebello-pontine angle	Cerebellar convexity	Foramen magnum	Jugular foramen	Clival	Tentorial
Chan and Thompson (1984)	Canadian	CT	257						41 (15.95%)
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	4 (2.07%)	9 (4.66%)	1 (0.52%)	-	1 (0.52%)	7 (3.62%)
Lieu and Howng (1999)	Taiwanese	POI	222	20 (9.00%)	-	-	10 (4.50%)	-	-
Oya, Sade and Lee (2011)	North American	MRI	189	-	-	7 (3.70%)	-	-	8 (4.23%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	1 (4.76%)	1 (4.76%)	-	1 (4.76%)	2 (9.52%)	1 (4.76%)
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	26 (3.57%)	21 (2.88%)	10 (1.37%)	2 (0.27%)	9 (1.23%)	48 (6.58%)
Raper, Starke, Henderson et al. (2014)	North American	POI	490	10 (2.0%)			41 (8.4%)	2 (0.4%)	-
Fang, He, Li et al. (2015)	Chinese	POI	157	8 (5.10%)		18 (11.47%)			-
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65			13 (20.0%)			
Ishi, Terasaka, Yamaguchi et al. (2016)	Japanese	POI	83			21 (25.30%)			
Magill, Young, Chae et al. (2018)	North American	POI	1113			230 (20.66%)			
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42					6 (14.28%)	3 (7.14%)
Kang, Wei and Toh (2019)	Korean	POI	51	-	-	-	-	1 (1.96%)	1 (1.96%)
Kauke, Safi, Stavrinou et al. (2019)	German	POI	58						10 (17.24%)
Lagman, Ong, Nguyen et al. (2018)	North American	MRI	21	-	1 (4.76%)	-	-	-	1 (4.76%)
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	-	-	-	-	-	6 (17%)

*POI: Preoperative imaging, the use of MRI, CT angiograms, digital subtraction angiograms

Table 1.4 Review of multiple meningioma incidence according to the anatomical location

Author (year)	Population	Sample size	Age (years)	Incidence (%)	Anatomical location			
					Supratentorial	Skull base	Posterior fossa	Other
Salvati, Caroli, Ferrante et al. (2004)	Italian	1250	52.4	2.80%[1]	93 (60.50%)	18(11.80%)	13 (8.60%)	28 (18.40%)
Huang, Buhl, Hugo et al. (2005)	German	456	57.9	8.55%[1]	63 (66.32%)	32 (33.68%)[2]		-
Tsermoulas, Turel, Wilcox et al. (2018)	Canadian	133	58	-	294 (74.00%)	101 (26.00%)[2]		-
Pereira, de Almeida, de Aguiar et al. (2019)	Brazilian	629	55.8	3.30%[1]	50 (86.21%)	8 (13.79%)[2]		-

[1]*Percentage indicated as part of the total sample size investigating meningiomas*
[2]*Incidence reported as combination of the anterior, middle and posterior cranial fossae*

Table 1.5 Review of histological grades of meningiomas

Author (year)	Population	Modality	Sample size	Incidence			
				Grade I	Grade II	Grade III	Other
Lieu and Howng (1999)	Taiwanese	Histological	222	190 (85.6%)	12 (5.40%)	-	20 (9%))
Pistolesi, Boldrini, Gisfredi et al. (2004)	Italian	Histological	40	31 (77.5%)	7 (17.5%)	2 (5%)	-
Kasuya, Kubo, Tanaka et al. (2006)	Japanese	Histological	342	296 (86.5%)	28 (8.2%)	18 (5.3%)	-
Bhat, Wani, Kirmani et al. (2014)	Indian	Histological	729	651 (89.30%)	43 (5.90%)	35 (4.80%)	-
Raper, Starke, Henderson et al. (2014)	North American	Histological	504	344 (74.8%)	98 (21.3%)	18 (3.9%)	108 (21.4%)
Fang, He, Li et al. (2015)	Chinese	Histological	157	122 (77.7%)	33 (21%)	2 (1.3%)	-
Magill, Young, Chae et al. (2018)	North American	Histological	1113	905 (81.31%)	208 (18.69%)	-	-
Kang, Wei and Toh (2019)	Korean	Histological	51	40 (78.4%)	8 (15.7%)	3 (5.9%)	-
Kauke, Safi, Stavrinou et al. (2019)	German	Histological	58	49 (85%)	9 (15%)	-	-
Lagman, Ong, Nguyen et al. (2018)	North American	Histological	51	36 (71%)	15 (29%)	-	-
Catapano, Whiting, Mezhera et al. (2020)	North American	Histological	35	24 (69%)	11 (31%)		-

1.4.1.3 Histological grading

Since meningiomas are generally benign, it is expected that the WHO Grade I would be the most prevalent. This is further strengthened by previous studies conducted by the incidences in Table 1.5 whilst the WHO Grade III is the least prevalent histological grade.

1.4.2 Morphometric variations

1.4.2.1 Volume of meningioma

The growth of skull base meningiomas has been documented to be smaller than non-skull base meningiomas (Kauke, Safi, Stavrinou et al., 2019). Factors such as the location and grade of the tumour may be implicated in the growth and volume of meningioma (Kauke, Safi, Stavrinou et al., 2019). Ishi, Terasaka, Yamaguchi et al. (2016) conducted a study in the Japanese population and documented a variation in the volumes of meningiomas in the supratentorial (41.0 cm^3), skull base (28.75 cm^3), and posterior fossa regions (18.2 cm^3). These findings, when compared against a similar study done by Kauke, Safi, Stavrinou et al. (2019), induced variability of the volumes of meningiomas in that their findings were larger in the supratentorial region (49.19 cm^3) and smaller in the skull base (9.33 cm^3) and posterior fossa (8 cm^3) regions. Hashiba, Hashimoto, Izumoto et al. (2009) noted that a thorough understanding of a meningioma's volumetric aspect and growth rate is imperative in the preoperative planning for surgical excision. Tables 1.6 and 1.7 illustrates a review of the mean volume of location-specific meningiomas in the literature, highlighting the variability in meningioma volumes.

1.4.2.2 Vascularity of meningioma

Jensen-Kondering, Helle, Lindner et al. (2019) conducted a non-invasive semiquantitative investigation of the vascularity of intracranial meningiomas using a super-selective arterial spin labelling modality. It was noted that 40% of the tumours received less than 50% of arterial supply from the ICA, and 24% of the tumours received less than 50% of blood from the ECA (Jensen-Kondering, Helle, Lindner et al., 2019).

Table 1.6 Review of intracranial meningioma volume (cm^3) in terms of anatomical location

Author (year)	Population	Modality	Sample size	Mean tumour volume (cm^3)		
				Supratentorial	Skull base	Posterior fossa
Hashiba, Hashimoto, Izumoto et al. (2009)	Japanese	MRI	44	11.39 cm^3 (0.8 - 77.3)	36.03 cm^3 (1.3 - 92.3)	5.9 cm^3 (5.9)
Ishi, Terasaka, Yamaguchi et al. (2016)	Japanese	MRI	83	41.0 cm^3 (± 38.1)	28.75 cm^3 (± 28.65)	18.2 cm^3 (± 13.1)
Jensen-Kondering, Helle, Lindner et al. (2019)	German	CT/MRI	42	86.33 cm^3 (±52)	29 cm^3 (±4)	31 cm^3 (±46)
Kang, Wei and Toh (2019)	Korean	MRI	51	64.2 ± 46.7 cm^3		
Kauke, Safi, Stavrinou et al. (2019)	German	MRI	58	49.19 cm^3 (3 - 133)	9.33 cm^3 (1 - 67)	8 cm^3 (4 - 48)
Lagman, Ong, Nguyen et al. (2018)	North American	MRI	51	73 cm^3 (±102)		

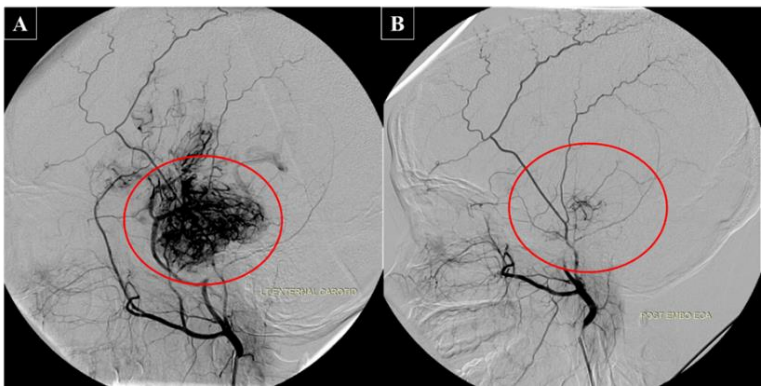
Table 1.7 Review of intracranial meningioma size (maximum tumour diameter - cm) with regards to anatomical location

Author (year)	Population	Modality	Sample size	Tumour diameter (cm)		
				Supratentorial	Skull base	Posterior fossa
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	5.37 cm	5.29 cm	4.57 cm
Raper, Starke, Henderson et al. (2014)	North American	MRI	504	38.7 cm (5-89)		
Fang, He, Li et al. (2015)	Chinese	MRI	157	5.60 cm (1.3 -10.1)		
Magill, Young, Chae et al. (2018)	North American	MRI	1113	12 cm	6.6 cm	3.0 cm
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	4.9 cm (±1.3)		

1.5 Clinical relevance

1.5.1 Preoperative embolisation

The preoperative embolisation of intracranial meningiomas involves the insertion of a microcatheter into the arterial feeder of the tumour (Dubel, Ahn and Soares, 2013; Geibprasert, Pongpech, Armstrong et al., 2009; Shah, Choudhri, Jung et al., 2015). This microcatheter will release an embolic agent namely liquid embolic agents such as glue and onyx or particles such as gel foam powder and polyvinyl alcohol particles (Geibprasert, Pongpech, Armstrong et al., 2009). This procedure aids the clinician in preventing excessive blood loss during tumoral resection, as depicted in Figure 1.1 (Shah, Choudhri, Jung et al., 2015). These embolising particles and liquids have varying sizes, which, if not released as proximal to the tumour as possible, may result in retrograde flow of the embolic agents or embolism of the arteries that supply portions of the cranial nerves (Geibprasert, Pongpech, Armstrong et al., 2009). Thus, a strong understanding of the vascular territories and anastomoses is needed for these procedures (Dubel, Ahn and Soares, 2013; Geibprasert, Pongpech, Armstrong et al., 2009). The ideal outcome of this procedure is a loss or decrease in the intensity of the tumoral blush as depicted in Figure 1.1. Studies have reported the effectiveness of preoperative embolisation in the surgical resection of meningiomas and as a solution to treat high-risk patients (Dubel, Ahn and Soares, 2013; Shah, Choudhri, Jung et al., 2015). However, this procedure has its risks and requires an in-depth knowledge of the vascular anatomy of the meninges and the neurological structures related to it (Dubel, Ahn and Soares, 2013).



Key: A – Preoperative image showing the tumoral blush outlined in red; B – Postoperative image showing a decrease in tumoral blush.

Figure 1.1 Digital subtraction angiography (DSA) of the left ECA showing the effect of preoperative embolization on an intracranial meningioma.

1.5.2 Neural compression

Meningiomas are not specific in their growth patterns as some may grow rapidly, while others may grow very slowly or not at all (Pistolesi, Boldrini, Gisfredi et al., 2004). Depending on the location of the variant tumour, its growth will interact and compress neurological structures in relation to it (Chan and Thompson, 1984; Lieu and Howng, 1999). Furthermore, primary ischaemia may result from mechanical compression of other arterial systems in the area (Tatagiba, Mirzai and Samii, 1991). However, paresis and seizures are more common symptoms associated with meningiomas (Chan and Thompson, 1984; Rohringer, Sutherland, Louw et al., 1989). A study by Lieu and Howng (1999) concluded that epilepsy was common in patients with meningiomas in the supratentorial region due to tumour compression on the brain. and that removing the tumour eliminated the condition. Thus, by assessing the vascular anatomy of meningiomas in a local population, the surgeon may determine and plan an effective methodology in treatment of intracranial meningiomas.

1.6 Materials and methods

1.6.1 Methodology

This study employed the use of MRI, DSA, along with the surgical and histological reports obtained from the data bank at the Inkosi Albert Luthuli Central Hospital, Durban, South Africa. Data obtained was anonymised and statistically analysed to determine if any relationship existed between the meningioma anatomy and the demographic groups. Since this study was a retrospective chart review, individual patient consent was not required as patient identifiers were anonymised and only demographic factors such as age, sex and race were incorporated into the study.

1.6.1.1 Inclusion criteria

Preoperative radiographic images comprising MRIs and DSAs conducted on-site (Inkosi Albert Luthuli Central Hospital) for intracranial meningiomas that were referred for preoperative embolisation showing no disturbances or other pathologies affecting the meningioma were included in this study. Furthermore, MRI scans that consisted of a T1 post-contrast fine slice (1 mm–2 mm slice thickness) series were included. DSA's that depicted a coronal and sagittal view of the vascular contributions were utilised. Tumours that presented with a clear tumoral blush in the early arterial phase of the DSA were included in this study.

1.6.1.2 Exclusion criteria

Preoperative radiographic images comprising MRIs and DSAs of intracranial meningiomas that illustrated disturbances and unclear borders of the tumour were excluded. MRI scans that did not consist of a T1 post-contrast series were not included. DSAs that did not show a clear tumoral blush as well as have coronal and sagittal views of the tumour vascularity were also excluded.

1.6.2 Histological grade and anatomical location of meningiomas

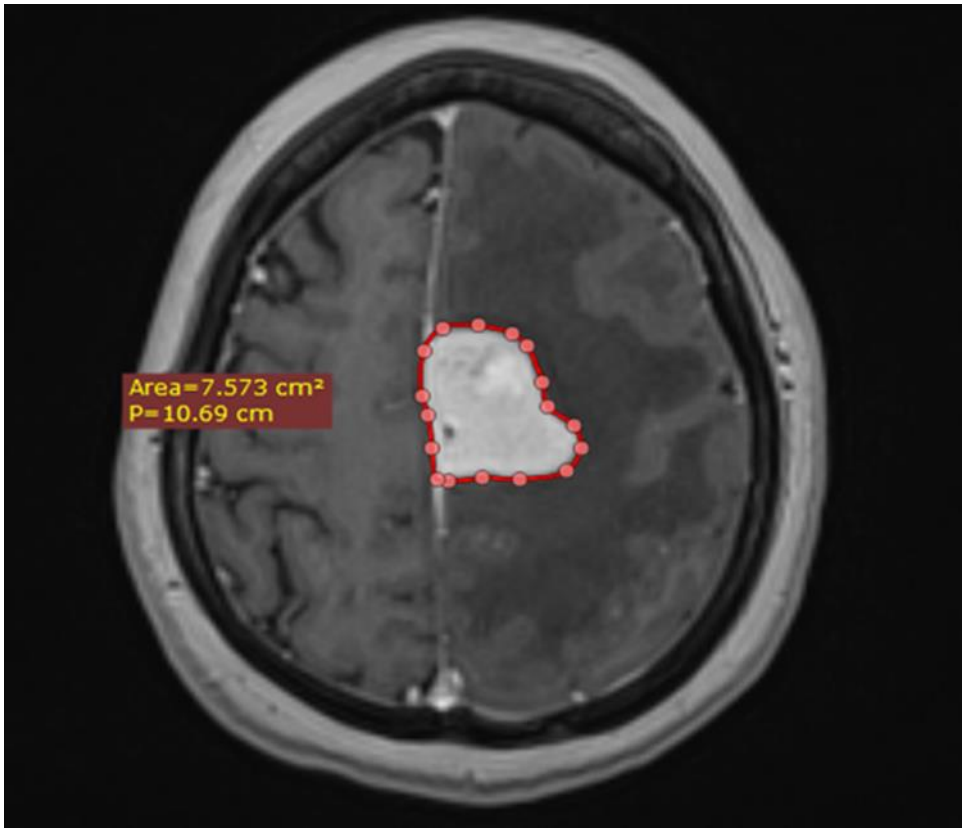
Histological reports detailing the WHO Grade and subtype of the meningioma were obtained and categorised according to the various demographic and anatomical parameters namely. sex, race and anatomical location. MRI images of the meningioma were analysed, and the incidence of the dural attachment was noted and categorised into three broad anatomical locations namely supratentorial, skull base and posterior fossa. Thereafter, it was further divided into subregions. The parasagittal, falx, parafalx, cerebral convexity and intraventricular regions formed the supratentorial region; the sphenoidal wing, olfactory groove, tuberculum sellae, petrosal, intra-orbital, cavernous sinus and the suprasellar regions formed the skull base area; and the cerebellopontine angle, cerebellar convexity, foramen magnum, jugular foramen, clival, tentorium cerebelli and the falco-tentorial regions created the posterior fossa location.

1.6.3 Volume of meningiomas

The volume of a meningioma was calculated employing a mathematical formula using measurements obtained from thin slice (1.0–2.0 mm slice thickness) transverse (axial) MRI images as described by Hashiba, Hashimoto, Izumoto et al. (2009) and Ishi, Terasaka, Yamaguchi et al. (2016). T1 weighted post-contrast images were used to prevent misidentification of the meningioma boundaries in terms of peri-tumoral oedema (Figure 1.2). The formula involves the summation of the total surface area (TSA) of the tumour in each axial slice that was multiplied by the vertical distance determined from the slice thickness (Formula 1.1). The tumour volumes were then compared to various anatomical and demographic parameters to assess whether any significant statistical correlation exists.

$$(Tumour\ Volume) = \left(TSA^{Slice\ 1} + TSA^{Slice\ 2} \ldots TSA^{nth}\right) \times Slice\ Thickness$$

Formula 1.1 Tumour volume calculation

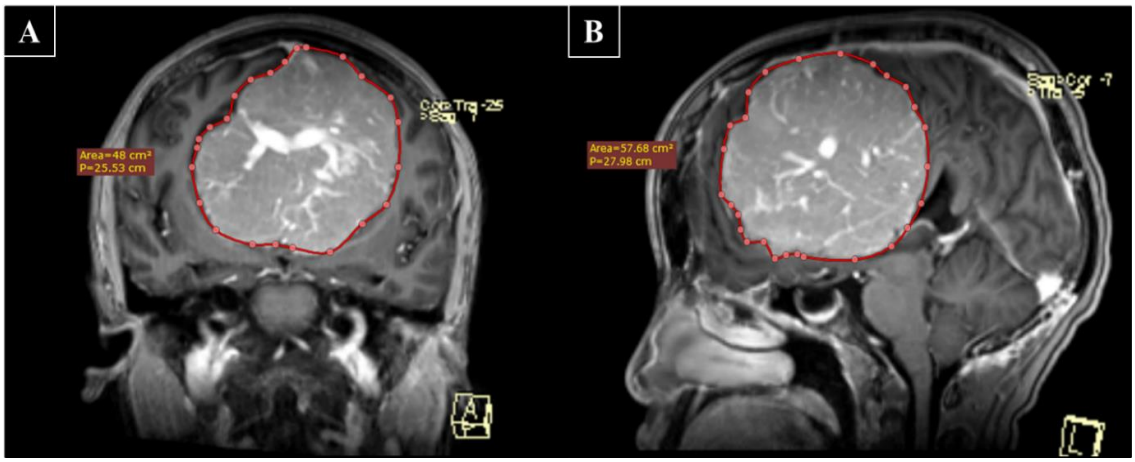


Key: Tumoral border outlined, and surface area calculated

Figure 1.2 Axial (transverse) MRI slice (T1 post contrast, 1mm slice thickness) indicating a portion of a supratentorial meningioma outlined in the determination of tumour volume

1.6.4 Vascularity of meningiomas

The vascular territories of a meningioma were determined using DSA images in which contrast dye was injected into the principle arterial vessels (ICA, ECA and vertebral system), and the perfusion of the meningioma was noted. The quantification of the vascular territory was ascertained through proportionality of the tumoral blush (obtained from the DSA) in relation to the maximum tumour diameter (obtained from the MRI) as depicted in Formulae 1.2 and 1.3. The T1 weighted post-contrast images (1 mm–2 mm slice thickness) were used for neuro-navigation and were only available on an axial or transverse series. This meant that this series needed to be translated into coronal and sagittal series using multi-planar reconstruction to acquire a precise image (Figure 1.3).



Key: A – Coronal view of the tumour; B – Sagittal view of the tumour; Red – Tumour outlined in calculation of the maximum tumour surface area (cm3)

Figure 1.3 Multiplanar reconstruction images of a patient presenting with a supratentorial meningioma (obtained from T1 post contrast, 1 mm slice thickness axial MRI)

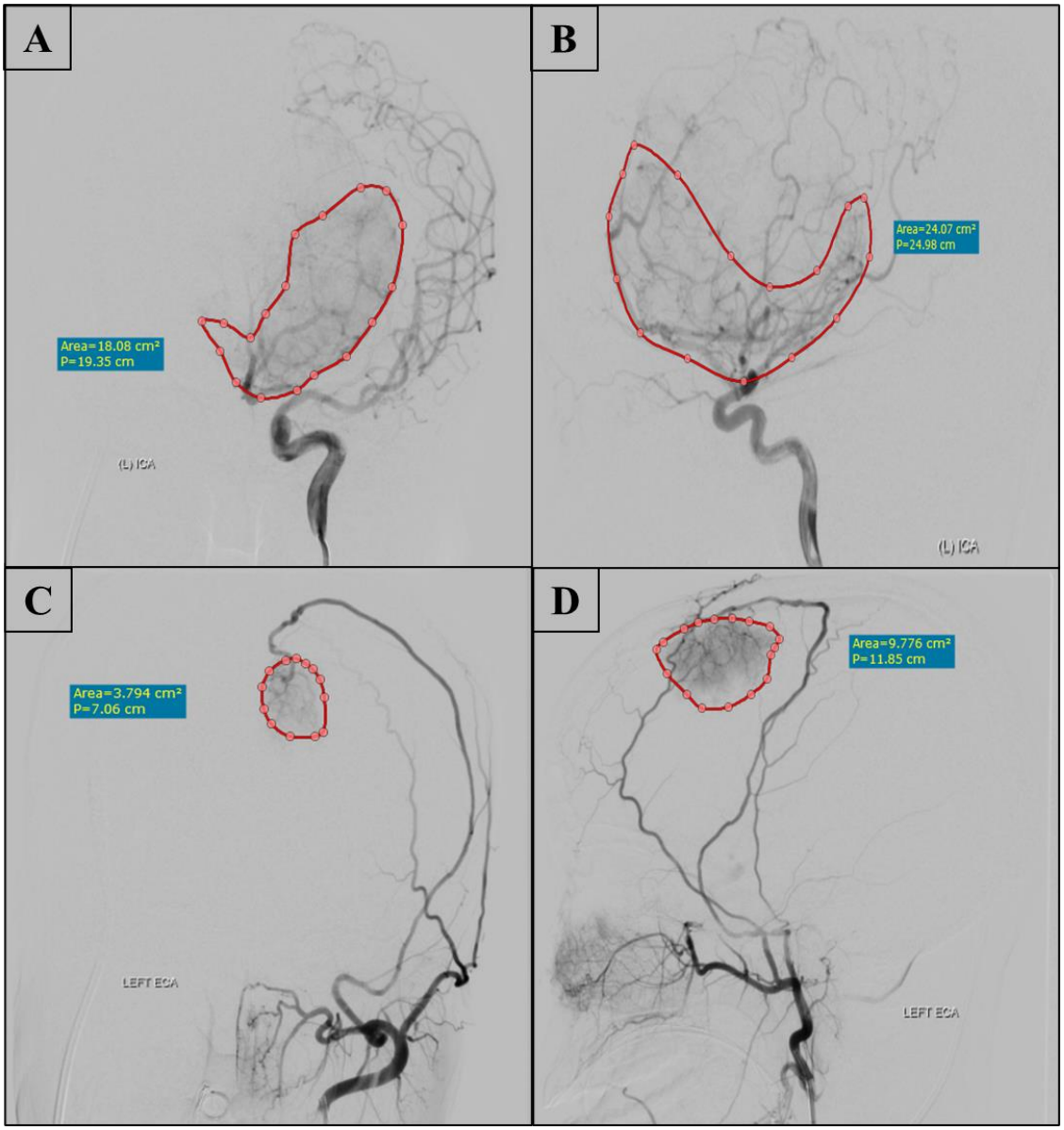
Due to the varying morphology of meningiomas, the tumour shape varies on the anatomical structures in relation to it, it proved vital to quantify the vascularity of the meningioma on a three-dimensional basis. This entailed calculating the vascular contribution on the coronal and sagittal planes. An average of the coronal and sagittal contribution was calculated and grouped according to two classes: minor contribution (secondary feeder) (X < 0.50) and major contribution (primary feeder) (X > 0.50) (Figure 1.4).

$$Vascular\ Contribution\ (Coronal\ plane) = \frac{TSA\ of\ the\ tumor\ blush\ (DSA)}{TSA\ of\ the\ tumour\ (MRI)}$$

Formula 1.2 Vascular contribution of the tumour in the coronal plane

$$Vascular\ Contribution\ (Sagittal\ plane) = \frac{TSA\ of\ the\ tumour\ blush\ (DSA)}{TSA\ of\ the\ tumour\ (MRI)}$$

Formula 1.3 Vascular contribution of the tumour in the sagittal plane



Key: A – Coronal view of left ICA; B – Sagittal view of left ICA; C – Coronal view of left ECA; D – Sagittal view of left ECA; Red – outline of vascular contribution in the early arterial phase

Figure 1.4 DSA images showing vascular contributions from the left ICA (images A and B) and left ECA (images C and D) in relation to the meningioma shown in Figure 1.3

1.7 Ethical considerations

Ethical approval was granted from the Biomedical Resource Ethics Committee of the University of KwaZulu-Natal regarding the data collection and analysis (reference number: BREC/00001934/2020). Gatekeeper permission and ethical clearance was obtained from the Inkosi Albert Luthuli Central Hospital and the Department of Health.

1.8 Variables

1.8.1 Demographic factors

Demographic factors such as age, sex and race were documented. Information was retrieved from the patient records, and factors such as age were recorded on the date that the radiographic imaging was performed. Variations regarding incidence, volume and anatomical location in the different demographic groups were documented.

1.8.2 Side location of the meningioma

Incidences of meningioma occurrence in relation to the midline, left and right cranial hemispheres were documented. MRI scans were analysed, and the tumour was categorised according to the site of the dural attachment. The parasagittal and parafalx regions were classified as midline tumours, provided that the tumour progressed to both sides of the falx cerebri. These incidences were statistically compared to sex, race and anatomical location.

1.8.3 Sample size

The proposed study entailed a retrospective chart review of intracranial meningiomas referred for preoperative embolisation at the Inkosi Albert Luthuli Central Hospital from January 2011 to December 2020. The files of patients with a diagnosis of meningioma who were referred for pre-operative embolisation were reviewed. Only cases that met the inclusion criteria were incorporated into the study. This revealed one hundred and three (n = 103) patients that met the inclusion criteria. Further categorisation of this sample into patients presenting with single and multiple intracranial meningiomas revealed 98 patients presented with single tumours and five patients presented with multiple meningiomas (more than a single meningioma at the same time). These two subsets have been investigated and analysed separately in an attempt to highlight variables that may affect the presentation of single or multiple cases of meningiomas.

1.9 Statistical analysis

Descriptive statistics were used to summarise the data. Frequencies and percentages were used for categorical data, such as location with regard to demographic factors. Frequency distributions of numeric data were checked for normality and means. Standard deviations or medians (interquartile range) were used as appropriate. Subgroup comparisons of categorical variables such as the location of the meningioma and gender were done using Chi-square or Fisher's exact

test as appropriate. Numeric variables such as meningioma volume were compared using t-tests, Mann Whitney or Anova tests as appropriate. Data were analysed using R statistical computing software, version 3.63 (R Studio, Boston, MA, USA).

1.10 Structure of the thesis

This Master's thesis was prepared according to the guidelines outlined by the College of Health Sciences, University of KwaZulu-Natal, South Africa. The manuscripts have been structured and formatted according to the guidelines of the respective scientific journals. The structural outline of the thesis is as follows:

1. **Chapter 1: Introduction**

   This chapter provides insight into intracranial meningiomas as well as a comprehensive literature review and an overview of the study. The aims, objectives, research question and detailed methodology are included in this chapter.

2. **Chapter 2: Scientific manuscript 1**

   This chapter comprises an original scientific manuscript entitled: Anatomical basis for preoperative embolisation of intracranial meningiomas: A retrospective chart review. This manuscript investigated the demographic profile in terms of age, sex and race as well as anatomical parameters in terms of histological grades, anatomical location, tumour volume and vascularity in patients presenting with a single intracranial meningioma (n=98). This manuscript was submitted to the Heliyon journal and is currently under review (Manuscript number: HELIYON-D-21-10408).

3. **Chapter 3: Scientific manuscript 2**

   This chapter comprises an original scientific manuscript entitled: The anatomical basis of multiple meningiomas: A case series. This manuscript presented five case reports of multiple meningiomas and the anatomical features in terms of anatomical location, tumour volume and vascularity. This manuscript was submitted to the Radiology Case Reports journal and is currently under review (Manuscript number: 211202-013988)

4. Chapter 4: Synthesis, limitations, recommendations and conclusion

This chapter discusses the findings of Chapters 2 and 3 and provides a synthesis of the findings of the anatomy of intracranial meningiomas in this study. Limitations encountered and recommendations for future research have been outlined and highlighted.

Following this chapter are the appendices.

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CHAPTER 2

SCIENTIFIC MANUSCRIPT 1

Interface

Chapter 1 provided an overview into the anatomy of intracranial meningiomas as well as the areas of scarcity of this tumour. This chapter described the clinical relevance and overview of the methodology.

Contributions of this chapter

This chapter comprises two scientific manuscripts that investigated the anatomical features of intracranial meningiomas referred for preoperative embolisation in two subsets. The following manuscript outlines the results obtained from subset one of patients presenting with a single meningioma. The results were compared on the basis of demographic variables and the anatomical location. The manuscript was formatted according to the guidelines of the journal. The following manuscript was submitted and is currently under review by the scientific journal:

Title:	Anatomical basis for preoperative embolisation of intracranial meningiomas: A retrospective chart review
Authors:	E.E. Anirudh, R. Harrichandparsad, L. Lazarus
Journal:	Heliyon
Manuscript Number:	HELIYON-D-21-10408

TITLE PAGE

Title: Anatomical Basis for Preoperative Embolisation of Intracranial Meningiomas: A Retrospective Chart Review

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Running head: The anatomy of intracranial meningiomas

LIST OF ABBREVIATIONS:

CV:	Coefficient of variation
DSA:	Digital Subtraction Angiography
ECA:	External carotid artery
IALCH:	Inkosi Albert Luthuli Central Hospital
ICA:	Internal carotid artery
MRI:	Magnetic Resonance Imaging
SD:	Standard deviation
VA:	Vertebrobasilar system of arteries
WHO:	World Health Organization

Abstract

Meningiomas are described as intracranial, extra-axial tumours arising from the arachnoid cap cells of the meninges. Due to the vast expanse of the meninges, variation in its clinical presentation varies. Treatment of this pathology involves surgical resection of the tumour. Preoperative tumour embolisation has proven to reduce blood loss during resection, however, misidentification of the vascular territory may lead to various post-operative complications such as cranial nerve palsies. The present study aimed to investigate the anatomy of intracranial meningiomas, referred for preoperative embolisation at the Inkosi Albert Luthuli Central Hospital, South Africa. Patient demographics, histological reports, Magnetic Resonance Images and Digital Subtraction Angiography images were utilised to analyse the study's objectives. We report a high incidence of meningiomas in the female population with a smaller tumour volume in relation to males. The Grade I meningioma was the most common with the meningothelial subtype being predominant. Regarding the blood supply, the internal carotid arteries were noted to be the primary feeders in the skull base region whilst the left external carotid artery was noted to be a primary feeder in the supratentorial region. The results from this investigation provided insight into the variable anatomy of intracranial meningiomas within a select South African population. Key outcomes from this study support the female predisposition for meningiomas along with the high incidences of meningiomas of the WHO Grade I and in the supratenorial region. Further research should be carried out as a comparative study in patients that were not referred for preoperative embolisation.

Keywords: Intracranial meningioma; Meningioma vascularity; Meningioma volume; Preoperative embolisation; Meningioma blood supply

2.1 Introduction

Meningiomas are described as intracranial, extra-axial tumours and are documented as the most frequent form of brain tumours, accounting for approximately a third of all neurological tumours (Uetani, Akter, Hirai et al., 2013; Huang, Bi, Griffith et al., 2019). These tumours, which arise from the arachnoid cap cells, are located in the subdural space and are classified according to the dural point of origin and may be further subdivided according to its histological grade (Dubel, Ahn and Soares, 2013; Huang, Bi, Griffith et al., 2019). Varying in their attachments, meningiomas may present as either a broad-based dural attachment or as a vast 'sheet-like' appearance (Huang, Bi, Griffith et al., 2019). Common sites of meningioma occurrence include the dural linings of the calvarium and cranial base, whilst the spinal cord, choroid plexus and optic nerve sheath are considered to be less frequent areas of incidence (Dubel, Ahn and Soares 2013; Buerki, Horbinski, Kruser et al., 2018). Clinical presentation of this tumour is generally location specific depending on the tumour's interaction with other tissue as well as its size (Dubel, Ahn and Soares 2013; Buerki, Horbinski, Kruser et al., 2018). However, common symptoms include headache, generalised or partial seizures and focal neurological deficits (Dubel, Ahn and Soares, 2013; Buerki, Horbinski, Kruser et al., 2018). Incidental meningiomas were previously discovered during diagnostic imaging in patients; thereby, due to the increased use of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) in routine neurological exams, an increase in tumour incidence has been reported (Hashiba, Hashimoto, Izumoto et al., 2009).

The meninges consist of three membranous layers surrounding the central nervous system (Moore, Dally and Agur, 2014). Their embryological origin varies in that the caudal portions of the head (inferior to the mesencephalon) and spinal cord arise from paraxial mesoderm whilst the rostral part (superior to the mesencephalon) arises from neural crest cells (Gray and Standring, 2016). These layers, located superficial to deep, are the fibrous dura mater, avascular arachnoid mater and the highly vascular pia mater (Patel and Kirmi, 2009; Gray and Standring, 2016). Innervation to these membranes is derived from a large number of nerves, including all branches of the trigeminal nerve, glossopharyngeal, vagus and the first three spinal nerves (Patel and Kirmi, 2009). Arterial supply to the meninges is derived from an anastomotic plexus with branches from the internal and external carotid as well as the vertebral arteries (Patel and Kirmi, 2009). The bulk of this supply is primarily sourced from the middle meningeal artery originating from the external carotid artery (ECA) (Dubel, Ahn and Soares, 2013). Meningiomas have been reported to be primarily supplied by these dural feeders that vascularise the central portion of the tumour whilst

the supply to the outer part is derived from the parasitic interaction with the pial system of arteries (Dubel, Ahn and Soares, 2013; Huang, Bi, Griffith et al., 2019).

Surgical procedures in the treatment of this pathology involve resection of the tumour; however, due to the high degree of vascularity, excessive blood loss is a typical result, which may lead to complications during surgery (Pistolesi, Boldrini, Gisfredi et al., 2004). Preoperative embolisation of a meningioma has proven to be of great importance in preventing excessive blood loss (Martin, Cha, Higashida et al., 2007; Dubel, Ahn and Soares, 2013). However, neurological deficits have been reported post-embolisation due to misidentification of the vascular territories since these arteries supply portions of cranial nerves as well (Martin, Cha, Higashida et al., 2007). Thus, a thorough understanding of the meningioma vasculature is imperative to the surgeon to prevent post-operative complications such as epilepsy, cerebrospinal fluid leaks, hemiparesis, and other neurological deficits (Martin, Cha, Higashida et al., 2007; Dubel, Ahn and Soares, 2013; Shah, Choudhri, Jung et al., 2015). This study aimed to investigate the anatomical basis of intracranial meningiomas within a select South African population. This entailed describing the incidence of meningiomas with regards to the anatomical location and its histological Grade and reporting on the volume and arterial supply in relation to the anatomical location of the tumour.

2.2 Materials and methods

A retrospective chart review of patients admitted to the Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa, presenting with an intracranial meningioma referred for preoperative embolisation within the past ten years (January 2011–December 2020) were examined in order to investigate the current study's objectives. Ethical clearance was obtained from the institutional ethics review committee (Biomedical Resource Ethics Committee - Reference number: BREC/00001934/2020). MRI's, Digital Subtraction Angiographies (DSA's), and histology reports were critically analysed, and cases that met the inclusion criteria were utilised in this study. Individual patient consent was not required as this study employed a retrospective chart review which anonymised patient details, only demographic factors such as age, sex, and race were recorded.

Inclusion criteria: Patients presenting with intracranial meningiomas with MRI's and DSA's that were conducted on-site (IALCH) and showed clear borders with no macroscopic disturbances of the tumour were included. Additionally, MRI series that consisted of a T1 post-contrast fine slice (1 mm–2 mm slice thickness) series were included in the present study (which eliminated the misidentification of peritumoral oedema as part of the tumour volume). DSA's that depicted a

coronal and sagittal view of the vascular supply with a clear tumoral blush were included in the present study.

2.2.1 Data processing

Data was analysed using the RadiAnt DICOM Viewer software, in which both the MRI and DSA images were analysed. The anatomical location of the tumour was initially separated into three (3) broad anatomical regions *viz.* supratentorial, cranial base and posterior fossa. The supratentorial area included the parasagittal, parafalx, cerebral convexity, and intraventricular subregions. The cranial base encompassed the sphenoidal wing, olfactory groove, tuberculum sellae, petrosal, intra-orbital, cavernous sinus and suprasellar regions. The posterior fossa consisted of the cerebellopontine angle, cerebellar convexity, clival, tentorium cerebelli and the falco-tentorial areas. The World Health Organization (WHO) outlined a histological grading system which was used in the present study. A Grade I tumour represented the benign, slow-growing tumours, Grade II, which included the atypical tumours that presented a faster growth rate and Grade III, which represented the rare malignant group with a rapid growth rate. The volume of the tumour was quantified using the planimetry method described by Hashiba, Hashimoto, Izumoto et al. (2009) and Ishi, Terasaka, Yamaguchi et al. (2016), which was determined by calculating the product of the summation of the total surface area of the tumour on each MRI slice and the slice thickness (Formula 2.1; Figure 2.1).

$$(Tumour\ Volume) = \left(TSA^{Slice\ 1} + TSA^{Slice\ 2} \ldots\ TSA^{nth}\right) \times Slice\ Thickness$$

Formula 2.1 Tumour volume calculation

Figure 2.1

In the assessment of the vascular contribution to the meningioma, DSA images of the possible feeder vessels were critically analysed, and contributions measured. The quantification of the of the vascular contribution was measured by calculating the total surface area of the tumoral blush. This contribution was then compared against the maximum tumour surface area obtained from the MRI (Figure 2.2). Since the vascular contribution is three-dimensional, an average of the vascular proportions in the sagittal and coronal planes was used to accurately depict the blood supply (Formula's 2.2 and 2.3). Vascular proportions were then grouped according to either: minor contribution ($X < 0.50$) and major contribution ($X > 0.50$).

$$Vascular\ Contribution\ (Coronal\ plane) = \frac{TSA\ of\ the\ tumor\ blush\ (cm^2)(DSA)}{TSA\ of\ the\ tumour\ (cm^2)(MRI)}$$

Formula 2.2 Vascular contribution of the tumour in the coronal plane

$$Vascular\ Contribution\ (Sagittal\ plane) = \frac{TSA\ of\ the\ tumour\ blush(cm^2)\ (DSA)}{TSA\ of\ the\ tumour\ (cm^2)(MRI)}$$

Formula 2.3 Vascular contribution of the tumour in the sagittal plane

Figure 2.2

2.2.2 Statistical analysis

Statistical analysis was performed using R statistical computing software, version 3.63 (R Studio, Boston, MA, USA). A statistically significant value of $p < 0.05$ was set. Analysis of the means was utilised for data identified as normal, and the medians of the data were used for data classified as abnormal. Relevant statistical tests were performed, which included: Fisher's exact test, Chi-Square test, Ranksum and Kruskal-Wallis tests.

2.3 Results

A 10-year (Jan 2011–Dec 2020) retrospective chart review yielded 98 patients (n = 98) presenting with intracranial meningiomas were included. Histological confirmation was unavailable for 5 patients; however, these cases were confirmed as a meningioma by the neurosurgeon (RH) using the radiographic imaging criteria outlined by Buerki, Horbinski, Kruser et al. (2018), Huang, Bi, Griffith et al. (2019) and Jensen-Kondering, Helle, Lindner et al. (2019). Intra-rater reliability tests revealed a high reliability ($p < 0.001$) of the numerical measurements (ICC = 1). Inter-rater reliability tests resulted in the following interclass coefficients (95% confidence interval): volume (ICC = 0.99), vascular proportionality (ICC = 0.98).

2.3.1 Demographics

The sample size (n = 98) yielded the incidence of intracranial meningiomas within the various demographic parameters such as sex, race and age (Table 2.1). The age range of patients was 15 to 77 years old (average age = 48 years old). Table 2.1 illustrates a high incidence of meningiomas

within the female population (67.3%). Ethnic categorisation revealed the following incidences of the tumour *viz.* African (74.5%), Indian (18.4%), Coloured (2%) and Caucasian (5.1%).

Table 2.1 Demographic profile of intracranial meningiomas referred for preoperative embolisation

Parameter				
Sex	**Male**		**Female**	
	32(32.7%)		66(67.3%)	
Ethnicity	**African**	**Coloured**	**Indian**	**Caucasian**
	73 (74.5%)	2 (2%)	18 (18.4%)	5 (5.1%)
Age	**Mean ± SD (CV%)**	**Median (Q1-Q3)**	**Min–Max**	
	48.1 ± 14.0 (29.2)	49 (38–58)	15–77	

Table 2.2 Categorisation of the histological and anatomical parameters investigated in terms of histological grading, side location, anatomical location according to sex

Aspect	**Male**	**Female**	***p-value***	**Total**
Histological grade				
Total	**32 (32.7%)**	**66 (67.3%)**	*0.001*[1]	**98 (100%)**
Grade I	**15 (15.3%)**	**54 (55.1%)**	*0.003*[1]	**69 (70.4%)**
Meningothelial	*11 (11.2%)*	*36 (36.7%)*	-	*47(48%)*
Fibroblastic	*1 (1%)*	*5 (5.1%)*		*6(6.1%)*
Transitional	*3 (3.1%)*	*11 (11.2%)*		*14(14.3%)*
Microcystic	-	*2 (2%)*		*2(2%)*
Grade II	**11 (11.2%)**	**8 (8.2%)**	*0.041*[1]	**19 (19.4%)**
Atypical	*10 (10.2%)*	*5 (5.1%)*	-	*16(16.3%)*
Choroidal	-	*1 (1%)*		*1(1%)*
Clear cell	*1 (1%)*	*1 (1%)*		*2(2%)*
Grade III	**3 (3.1%)**	-	-	**3 (3.1%)**
Anaplastic	*3 (3.1%)*	-	-	*3(3.1%)*
No histology	**3 (3.1%)**	**4 (4.1%)**	-	**7(7.1%)**
Side location of meningioma				
Total	**32 (32.7%)**	**66 (67.3%)**	***0.276***[2]	**98 (100%)**
Left	*10 (10.2%)*	*26 (26.5%)*	-	*36 (36.7%)*

Right	*16 (16.3%)*	*22 (22.4%)*		*38 (38.8%)*
Midline	*6 (6.1%)*	*18 (18.4%)*		*24 (24.5%)*
Anatomical location and subregions				
Total	**32 (32.7%)**	**66 (67.3%)**	*0.012*[2]	**98 (100%)**
Supratentorial	**24 (24.5%)**	**32 (32.7%)**	*0.033*[2]	**56 (57.2%)**
Convexity	*12 (12.2%)*	*17 (17.3%)*	-	*29 (29.6%)*
Intraventricular	*1 (1%)*	*2 (2%)*		*3 (3.1%)*
Parafalx	*6 (6.1%)*	*8 (8.2%)*		*14 (14.3%)*
Parasagittal	*5 (5.1%)*	*5 (5.1%)*		*10 (10.2%)*
Skull base	**4 (4.1%)**	**28 (28.6%)**	*0.008*[2]	**32 (32.7%)**
Intraorbital	*1 (1%)*	-	-	*1 (1%)*
Olfactory groove	*1 (1%)*	*12 (12.2%)*		*13(13.3%)*
Sphenoid wing	*2 (2%)*	*13 (13.3%)*		*15(15.3%)*
Spheno-orbital	-	*1 (1%)*		*1 (1%)*
Suprasellar	-	*1 (1%)*		*1 (1%)*
Tuberculum sellae	-	*1 (1%)*		*1 (1%)*
Posterior fossa	**4 (4.1%)**	**6 (6.1%)**	*0.724*[2]	**10 (10.2%)**
Cerebellar Convexity	-	*1 (1%)*	-	*1 (1%)*
Cerebellopontine angle	-	*1 (1%)*		*1 (1%)*
Falco-tentorial	*1 (1%)*	-		*1 (1%)*
Petroclival	*1 (1%)*	*1 (1%)*		*2 (2%)*
Tentorial	*2 (2%)*	*3 (3.1%)*		*5 (5.1%)*

[1]Fischer's exact test (performed on a dataset of histologically confirmed meningiomas only; n = 91; since absence of histological grading does not count as a WHO grade)

[2]Chi-square test

Table 2.3 Categorisation of the histological and anatomical parameters investigated in terms of histological grade, side location and anatomical location according to ethnicity

Aspect	African	Coloured	Indian	Caucasian	*p-value*	Total
Histological grade						
Total	**73(74.5%)**	**2(2%)**	**18(18.4%)**	**5(5.1%)**	***0.866[1]***	**98(100%)**
Grade I	**49(50.1%)**	**1(1%)**	**14(14.3%)**	**5(5.1%)**	***0.569[1]***	**69(70.4%)**
Meningothelial	*34(34.7%)*	-	*8(8.2%)*	*5(5.1%)*	-	*47(48%)*
Fibroblastic	*2(2%)*	-	*4(4.1%)*	-		*6(6.1%)*
Transitional	*11(11.2%)*	*1(1%)*	*2(2%)*	-		*14(14.3%)*
Microcystic	*2 (2%)*	-	-	-		*2(2%)*
Grade II	**15(15.3%)**	**1(1%)**	**3(3.1%)**	**-**	***1.000[1]***	**19(19.4%)**
Atypical	*12(12.2%)*	*1(1%)*	*3(3.1%)*	-	-	*16(16.3%)*
Choroidal	*1(1%)*	-	-	-		*1(1%)*
Clear cell	*2(2%)*	-	-	-		*2(2%)*
Grade III	**3(3.1%)**	**-**	**-**	**-**	**-**	**3 (3.1%)**
Anaplastic	*3(3.1%)*	-	-	-	-	*3(3.1%)*
No histology	**6(6.1%)**	**-**	**1(1%)**	**-**	**-**	**7(7.1%)**
Side location of meningioma						
Total	**73(100%)**	**2(100%)**	**18(100%)**	**5(100%)**	*0.931[2]*	**98(100%)**
Left	26 (35.6%)	1 (50.0%)	7 (38.9%)	2 (40.0%)	-	*36(36.7%)*
Right	28 (38.4%)	1 (50.0%)	8 (44.4%)	1 (20.0%)		*38 (38.8%)*
Midline	19 (26.0%)	-	3 (16.7%)	2 (40.0%)		*24 (24.5%)*
Anatomical location and subregion						
Total	**73(74.5%)**	**2(2%)**	**18(18.4%)**	**5(5.1%)**	***0.170[3]***	**98(100%)**
Supratentorial	**42 (42.9%)**	**1 (1%)**	**13 (13.3%)**	**-**	***0.655[3]***	**56(57.1%)**
Convexity	*23(23.5%)*	-	*6(6.1%)*	-	-	*29 (29.6%)*
Intraventricular	*2(2%)*	-	*1(1%)*	-		*3 (3.1%)*
Parafalx	*9(9.2%)*	*1(1%)*	*4(4.1%)*	-		*14 (14.3%)*
Parasagittal	*8(8.2%)*	-	*2(2%)*	-		*10 (10.2%)*
Skull base	**25 (25.5%)**		**3 (3.1%)**	**4(4.1%)**	***0.253[3]***	**32(32.7%)**

Intraorbital	*1(1%)*	-	-	-		*1 (1%)*
Olfactory groove	*10(10.2%)*	-	*1(1%)*	*2(2%)*		*13(13.3%)*
Sphenoid wing	*11(11.2%)*		*2(2%)*	*2(2%)*	-	*15(15.3%)*
Spheno-orbital	*1(1%)*	-	-	-		*1 (1%)*
Suprasellar	*1(1%)*	-	-	-		*1 (1%)*
Tuberculum sellae	*1(1%)*	-	-	-		*1 (1%)*
Posterior fossa	**6 (6.1%)**	**1 (1%)**	**2 (2%)**	**1(1%)**	***0.294*[3]**	**10(10.2%)**
Cerebellar Convexity	-	-	*1(1%)*	-		*1 (1%)*
Cerebellopontine angle	-	*1(1%)*	-	-	-	*1 (1%)*
Falco-tentorial	*1(1%)*	-	-	-		*1 (1%)*
Petroclival	*2(2%)*	-	-	-		*2 (2%)*
Tentorial	*3(3.1%)*	-	*1(1%)*	*1(1%)*		*5 (5.1%)*

[1]Fischer's exact test (performed on a dataset of histologically confirmed meningiomas only; n = 91; since absence of histological grading does not count as a WHO grade)

[2]Chi-square test

[3]Fischer's exact test

2.3.2 Histological grading

A retrospective chart review of the histological reports was also conducted and revealed a high incidence of the Grade I meningioma (70.4%) and the meningothelial subtype (48%) (Table 2.2 and 2.3). The WHO Grade III (Anaplastic) type of tumour was found in males only in this study (Table 2.2). Ethnic categorisation into the various population groups indicated a high prevalence of the Grade I (50.1%) and II (15.3%) meningiomas within the African population, respectively. Most Grade I meningiomas were supratentorially located (39.8%) and these were found primarily in the African population. The atypical subtype was found predominantly in males (10.2%). Grade I tumours were found in all the anatomically classified regions as opposed to Grade III which was found only in the supratentorial region (3.1%) as illustrated in Table 2.4.

Table 2.4 Categorisation of the histological grades in terms of the anatomical location

Aspect	Supratentorial	Skull base	Posterior fossa	*p-value*	Total
WHO Grade and histological subtype					
Total	**56(57.1%)**	**32(32.7%)**	**10(10.2%)**	*0.040*[1]	**98(100%)**
Grade I	**39 (39.8%)**	**25 (25.5%)**	**5 (5.1%)**	-	**69(70.4%)**
Meningothelial	*22(22.4%)*	*21(21.4%)*	*4(4.1%)*	-	*47(48%)*
Fibroblastic	*6(6.1%)*	-	-		*6(6.1%)*
Transitional	*9(9.2%)*	*4(4.1%)*	*1(1%)*		*14(14.3%)*
Microcystic	*2(2%)*	-	-		*2(2%)*
Grade II	**13 (13.3%)**	**4 (4.1%)**	**2 (2%)**	-	**19(19.4%)**
Atypical	*12(12.2%)*	*2(2%)*	*2(2%)*	-	*16(16.3%)*
Choroidal		*1(1%)*	-		*1(1%)*
Clear cell	*1(1%)*	*1(1%)*	-		*2(2%)*
Grade III	**3 (3.1%)**	-	-	-	**3 (3.1%)**
Anaplastic	*3(3.1%)*	-	-	-	*3(3.1%)*
No histology	**1(1%)**	**3(3.1%)**	**3(3.1%)**	-	**7(7.1%)**

[1]Fischer's exact test (performed on a dataset of histologically confirmed meningiomas only; n = 91; since absence of histological grading does not count as a WHO grade)

2.3.3 Side location of the meningioma

Intracranial meningiomas were observed to be almost equal with regards to laterality (Right hemisphere: 38.8%; left hemisphere: 36.7%). Within the male population, it was noted that meningiomas were primarily found in the right hemisphere (16.3%). Almost equal prevalence of meningiomas in the left and right hemispheres were noted among the African and Indian population as illustrated in Table 2.3.

2.3.4 Anatomical location

Categorising the incidence of intracranial meningiomas according to the three broad anatomical locations *viz.* supratentorial, skull base and posterior fossa revealed a high incidence of these tumours in the supratentorial region (57.2%) for both the male (24.5%) and female (32.7%) populations (Table 2.2; Figure 2.3). It was also noted that the female population reported a high incidence of meningiomas within the skull base region as well (28.6%). Patients of Caucasian descent were observed to form meningiomas primarily in the skull base region (Table 2.3).

More specifically, a high incidence of meningiomas were found in the convexity (29.6%), sphenoidal wing (15.3%) and parafalx (14.3%) regions. Within the male population, the following were documented as the 3 regions with highest prevalence: convexity (12.2%), parafalx (6.1%) and parasagittal (5.1%). The female population revealed the following as the most common sites for meningioma occurrence: convexity (17.3%), sphenoidal wing (13.3%) and olfactory groove (12.2%).

Figure 2.3

2.3.5 Tumour volume

Males reported a larger median volume (102 cm^3) than females (81.3 cm^3). Ethnic categorisation of the tumour volume reported the African population group having the largest tumour volume at 100 cm^3 (Table 2.5). Meningioma's located in the midline were noted to be the largest occupying 90.3 cm^3 (Table 2.5). Categorisation based on anatomical region revealed that the largest tumours were found in the supratentorial region (90.9 cm^3), and the smallest tumour volume was found in the posterior fossa (65.8 cm^3).

Table 2.5 Volume of meningiomas in relation to demographic and anatomical parameters

Aspect					*p – value*
Sex	Male		Female		*0.001*[1]
Volume(cm^3) (Q1–Q3)	102[1] (64.1–149)		81.3[1] (49.7–115)		
Ethnicity	African	Coloured	Indian	Caucasian	*0.001*[2]
Volume(cm^3) (Q1–Q3)	100[1] (69.8–143)	57.7[1] (24.4–91.2)	46.9[1] (31.1–64.3)	86.4[1] (49.4–102)	
Side location	Left	Midline	Right		*0.122*[2]
Volume(cm^3) (Q1–Q3)	87.0[1] (60.5–142)	90.3[1] (64.1–130)	77.0[1] (47.8–115)		
Anatomical location	Supratentorial	Skull base	Posterior fossa		*0.061*[2]
Volume(cm^3) (Q1–Q3)	90.9[1] (54.8–135)	83.2[1] (52.9–122)	65.8[1] (43.4–102)		

[1]Ranksum test

[2]Kruskal-Wallis test

2.3.6 Vascularity of the meningioma

The vascularity of an intracranial meningioma was determined by quantifying the tumour's vascular proportionality in relation to the maximum tumour volume (Figure 2.2; 2.4; 2.5; 2.6). The vascular contributions have been described below in terms of the three anatomical regions (Table 2.6). Due to a single meningioma receiving blood from either one or multiple feeders, the incidences of vascular contribution do not necessarily sum up to 100% or the total number of tumours in the anatomical region.

Within the supratentorial region, the left ECA was noted as a common primary feeder vessel supplying 12 (21.4% of supratentorial meningiomas) meningiomas. It was also noted that nine (16.1%) tumours received blood from the vertebral system of arteries. Regarding a minor (less than 50%) supply, the left ICA was identified as the most common feeder vessel supplying 20 meningiomas (35.7% of supratentorial meningiomas).

In the skull base region, a majority of tumours received blood from the internal carotid system of arteries (21 (65.6%) meningiomas supplied by the right ICA and 19 (59.4%) meningiomas supplied by the left ICA).

Within the posterior fossa region, the main arterial feeder was observed to be the vertebra-basilar system of arteries supplying nine (90%) of the tumours. The external carotid system of arteries was also a significant contributor in this region, with four (40%) tumours being supplied by the left ECA and four (40%) tumours being supplied by the right ECA.

Table 2.6 Vascularity of intracranial meningiomas in relation to the anatomical region

Blood supply		Anatomical region		
Blood vessel	**Vascular contribution**	**Supratentorial (n = 56)**	**Skull base (n = 32)**	**Posterior fossa (n = 10)**
Right ICA	*Minor*	16 (28.6%)	11 (34.4%)	-
	Major	12 (21.4%)	10 (31.3%)	2 (20%)
Left ICA	*Minor*	20 (35.7%)	9 (28.1%)	3 (30%)
	Major	13 (23.2%)	10 (31.3%)	1 (10%)
Right ECA	*Minor*	16 (28.6%)	3 (9.4%)	4 (40%)
	Major	10 (17.9%)	6 (18.8%)	-
Left ECA	*Minor*	18 (32.1%)	8 (25%)	4 (40%)
	Major	12 (21.4%)	1 (3.1%)	-
Vertebral	*Minor*	6 (10.7%)	1 (3.1%)	4 (40%)
	Major	3 (5.4%)	-	5 (50%)

[1]Percentages are in relation to the total number of meningiomas within the anatomical region.

[2]The categories are not exclusive, due to intracranial meningiomas receiving blood from more than one vessel, the total number of meningiomas may not summate to the total number of tumours within the anatomical region.

Figure 2.4, 2.5 and 2.6

2.4 Discussion

Generally considered as a benign tumours, meningiomas grow from the arachnoid cap cells of the meninges into the subdural region (Buerki, Horbinski, Kruser et al., 2018). Due to the vast area covered by the meninges, the clinical presentation varies, and diagnosis can only be made after the symptoms arise. Treatment commonly used is preoperative embolisation of the meningioma. Due to the high degree of vascularity of the meningioma coupled with the arterial relations to other vital neurological structures, post-embolisation related pathologies have sparked investigations into the arterial supply of the meningioma. The present study aimed to address the question relating to the arterial supply and various anatomical features of intracranial meningiomas referred for preoperative embolisation within a South African setting. Understanding the incidences of intracranial meningiomas within the study population can assist in identifying the prevalence and predispositions of this tumour in relation to demographic and location-specific factors. The analysis of the arterial supply aimed to provide a deeper

understanding of the feeder vessels of meningiomas thus, providing insight into potential vascularity assessment methods of meningiomas.

2.4.1 Demographics

An initial objective of the present study was to investigate the demographic profile of intracranial meningiomas. Due to the generally slow growth rate of meningiomas, diagnosis of this tumour is usually reported in the later stages of a patient's life (Hashiba, Hashimoto, Izumoto et al., 2009). The present study reports the average age of patients presenting with intracranial meningiomas (at the time of diagnosis) to be 48 years old, which was noted to be lower than studies conducted by Oya, Sade and Lee (2011) (59.1-years-old), Hoefnagel, Kwee, van Putten et al. (2014) (56.2-years-old) and Jensen-Kondering, Helle, Lindner et al. (2019) (61-years-old) in North American, Dutch and German populations, respectively.

Previous studies investigating meningioma incidence have been consistent in establishing a female predisposition (Fang, He, Li et al., 2015; Ostrom, Cioffii, Gittleman et al., 2019; Kang, Wei and Toh 2019; Kauke, Safi, Stavrinou et al., 2019). Ostrom, Cioffii, Gittleman et al. (2016) and Kauke, Safi, Stavrinou et al. (2019) conducted studies investigating intracranial meningiomas and reported female predominance ratios of 2.27:1 and 3.83:1, respectively. The present study reported a female predominance of 2.06:1, agreeing with these studies. Pravdenkova, Al-Mefty and Sawyer et al., (2006) investigated the various receptors found on meningiomas and reported 68% of meningiomas had a progesterone receptor. This suggests that in patients that receive treatment that increase the progesterone levels (such as infertility treatment) or produce high levels of progesterone would be more likely to develop meningiomas (Shahin, Magill, Dalle et al., 2019).

Anzalone, Glasgow and van Gompel et al. (2018) investigated the racial prevalence of intracranial meningiomas within the North American population. Results from this study revealed a high prevalence of meningiomas within patients of European ancestry accounting for 68.6%, whilst only 11% of the meningiomas were reported in patients of African ancestry. Contrary to Anzalone, Glasgow and van Gompel et al. (2018), the present study revealed a high incidence among the African population (74.5%) as compared to the Caucasian population (5.1%).

The trends of meningioma prevalence in the present study may be attributed to a combined effect of several factors. External factors such as increased exposure to ionising radiation from various sources and the rise in use of MRI and CT imaging in 'accidentally' identifying meningiomas may

be attributed to the fluctuating prevalence in tumour incidence within the present study (Hashiba, Hashimoto, Izumoto et al., 2009; Shintani, Hayakawa, Hoshi et al., 1999; Klaeboe, Lonn, Scheie et al., 2005). Internal factors such as genetic abnormalities on chromosome 22 may also affect the prevalence of meningioma presentation (Klaeboe, Lonn, Scheie et al., 2005). Since the present study is a retrospective chart review, genetic testing and patient interviews could not be conducted to investigate the aetiology of the trends observed. The general asymptomatic behaviour of intracranial meningiomas may also be attributed to the prevalence noted in the present study (Buerki, Horbinski, Kruser et al., 2018).

2.4.2 Histological grading

The Grade I meningioma is slow-growing and benign, usually only detected in the late stages of a patient's life (Buerki, Horbinski, Kruser et al., 2018). Harvey Cushing first termed the word meningioma in 1915 with four histological variants, *viz.* meningothelial, fibroblastic, angioblastic and osteoblastic (Bhat, Wani, Kirmani et al., 2014). Other histological subtypes were added in the WHO standardised classification based on the interactions of the meningioma with relating tissue (Bhat, Wani, Kirmani et al., 2014). Table 2.7 depicts the prevalence of the WHO histological Grades and subtypes of intracranial meningiomas compared to the present study. The Grade I meningioma was noted to be prevalent overall with a weighted mean of 82.8%. The findings in this study are consistent with the literature, in that the Grade I type was the most common type in 75.8% of the histologically confirmed patients. Furthermore, the Grade II meningioma (20.9%) was notably higher than the weighted average of 12.6% (Table 2.7). The meningothelial and transitional subtypes were reported to be prevalent in previous studies, as stated in studies conducted by Lieu and Howng (1999) (Meningothelial: 53.6%; Transitional: 13.1%) and Bhat, Wani, Kirmani et al. (2014) (Meningothelial: 57.8%; Transitional: 10.4%). The present study supports these findings in terms of the meningothelial (51.6%) and transitional (15.4%) subtypes. Interestingly, we report a high incidence of the atypical subtype (WHO Grade II) in 17.6% which was notably higher than studies listed in Table 2.7. Categorisation of the histological grades according to sex revealed that the Grade II and III meningiomas were predominantly found within the male population accounting for 43.8% of the male subset in comparison to 12.1% of the female subset. Statistical tests revealed a *p-value* of <0.001, indicating a statistically significant relationship between the WHO Grade and sex. More specifically, between the Grade I and sex ($p = 0.003$) and Grade II and sex ($p = 0.041$). Due to the high incidence of meningiomas within the African population, it was noted that this group displayed a greater amount of variation among the histological subtypes (Table 2.3).

Table 2.7 Review of WHO Grades of intracranial meningiomas in relation to the present study's findings

Author (year)	Population	Sample size	Incidence							
			Grade I				Grade II			Grade III
			Meningothelial	*Fibroblastic*	*Transitional*	*Microcystic*	*Atypical*	*Choroidal*	*Clear cell*	*Anaplastic*
Lieu and Howng (1999)	Taiwanese	222	119(53.0%)	8(3.6%)	29(13.1%)	-	12(5.4%)			-
Pistolesi, Boldrini, Gisfredi et al. (2004)	Italian	40	8(20%)	2(5%)	16(40%)	1(2.5%)	7(17.5%)	-	-	2(5%)
Nakamura, Roser, Michel et al. (2005)	German	36	33(91.7%)				3(8.3%)			-
Kasuya, Kubo, Tanaka et al. (2006)	Japanese	342	134(39.2%)	80(23.4%)	56(16.4%)	1(0.3%)	27(7.9%)	1(0.3%)	-	15(4.4%)
Bhat, Wani, Kirmani et al. (2014)	Indian	729	421(57.8%)	81(11.1%)	76(10.4%)	2(0.3%)	25(3.4%)	10(1.4%)	8(1.1%)	10(1.4%)
Hoefnagel, Kwee, van Putten et al. (2014)	Dutch	581	465(80%)				87(15%)			29(5%)
Raper, Starke, Henderson et al. (2014)	North American	460	344(74.8%)				98(21.3%)			18(3.9%)
Fang, He, Li et al. (2015)	Chinese	157	122(77.7%)				33(21%)			2(1.3%)
Lagman, Ong, Nguyen et al. (2018)	North American	51	36(71%)				15(29%)			-
Kang, Wei and Toh (2019)	Korean	51	40(78.4%)				8(15.7%)			3(5.9%)
Kauke, Safi, Stavrinou et al. (2019)	German	58	49(85%)				9(15%)			-
Weighted mean		**2727**	**82.8%**				**12.6%**			**3.9%**
Present study	**South African**	**91**	**69(75.8%)**				**19(20.9%)**			**3(3%)**
			47(51.6%)	6(6.6%)	14(15.4%)	2(2.2%)	16(17.6%)	1(1.1%)	2(2.2%)	3(3.3%)

The categorisation of the WHO Grades according to the three anatomical locations agreed with the Grade I being prevalent in all three regions as illustrated in Table 2.4. Bhat, Wani, Kirmani et al. (2014) reported common sites for malignant tumours in the skull base, posterior fossa and intraventricular regions. These findings did not agree with the results of the present study which reported a majority of atypical and malignant tumours in the supratentorial region (17.6%). Statistical tests revealed a *p-value* of 0.040 when comparing the WHO Grade against the anatomical location, indicating a statistically significant relationship between these two parameters.

A possible basis behind the high incidence of meningiomas in the supratentorial region may be linked to the quantity of arachnoid cap cells in these regions. Since meningiomas grow from the arachnoid cap cells, a common site for meningioma formation would be areas in which these cells are numerous (Bhat, Wani, Kirmani et al., 2014). Areas such as the dural venous sinuses (superior sagittal sinus and inferior sagittal sinus) as well as along the cranial sutures (fronto-ethmoidal suture and spheno-frontal suture) are generally sites for the presence of the arachnoid cap cells; thus, areas for meningioma formation (Bhat, Wani, Kirmani et al., 2014).

2.4.3 Side location of the meningioma

The site location of the meningioma was determined by observing the location of the tumour relative to the midline. A meningioma was classified as a midline only in the parasagittal, parafalx and olfactory groove tumours provided that the tumour invaded the surrounding regions on either side. We report an almost equal incidence of meningiomas on the left (36.7%) and right (38.8%) cranial hemispheres. These findings concur with Inskip, Tarone, and Hatch et al. (2003), who reported an almost equal incidence of meningiomas (Left: 44.7%; right: 41.1%) indicating no evident predisposition regarding tumour incidence in terms of laterality (Inskip, Tarone, and Hatch et al., 2003).

Categorisation according to sex revealed that in the male subset, half (16 cases) of the meningiomas were reported in the right hemisphere whilst only 10 cases (31.2% of males) were reported in the left hemisphere. These findings did not agree with Inskip, Tarone, and Hatch et al. (2003), who reported almost equal incidences in the left (20 cases) and right (19 cases) hemispheres in the male subset (Inskip, Tarone, and Hatch et al., 2003).

Inter-hemispheric balance in the brain is maintained in a healthy brain in terms of mass and volume (Mainio, Hakko and Niemela et al., 2003). However, the introduction of a tumour such

as a meningioma may affect this form of equilibrium. Activities such as perception and motor functions may become affected depending on the location of the meningioma in relation to the brain (Mainio, Hakko and Niemela et al., 2003). Due to the vast expanse that the meninges cover, its effects are location specific. Mainio, Hakko and Niemela et al. (2003) stated that patients with a primary supratentorial tumour (such as a meningioma, glioma) on the right hemisphere are likely to experience higher anxiety levels due to the disruption of the interhemispheric balance.

2.4.4 Anatomical location

Meningiomas may vary in morphological shape as either a broad-based dural attachment or a vast 'sheet-like' appearance and are categorised according to the anatomical dural attachment within the cranial vault (Huang, Bi, Griffith et al., 2019). As shown in Table 2.8, a review of previous studies revealed a commonality regarding meningioma incidence. The supratentorial region harboured the most meningiomas with a weighted average of 52.9%, whilst the skull base contained a weighted mean of 31%. The posterior fossa usually holds the least number of tumours with a weighted average of 16.2%. The present study agrees with these results regarding the skull base meningiomas, however a larger incidence of supratentorial meningiomas and lower incidence of posterior fossa meningiomas have been observed.

Categorisation according to sex and ethnicity revealed that the supratentorial region was the most common area for meningioma formation. More specifically, it was noted that a large portion of the male population (24 cases: 75% of males) harboured supratentorial meningiomas. Statistical analysis of the anatomical location and sex revealed a *p-value* of 0.012, which indicated a statistically significant relationship amongst these two groups. Further investigation into these groups revealed statistically significant differences between sex and the supratentorial meningiomas ($p = 0.033$) and sex and skull base meningiomas ($p = 0.008$).

Further investigations into the specific areas of the three broad anatomical regions were carried out to identify any sites classified as a 'meningioma hotspot'. The cerebral convexity was noted as a ‘meningioma hotspot’ with an incidence of 29.6%; the most common in the supratentorial region and amongst all subregions. This is supported by studies done by the weighted mean calculated in Table 2.9. This was the highest in the supratentorial region as well as in all anatomical subregions.

Table 2.8 Review of literature showing the anatomical location of meningiomas in relation to the present study's findings

Author (year)	Population	Modality	Sample size	Anatomical location		
				Supratentorial	Skull base	Posterior fossa
Chan and Thompson (1984)	Canadian	CT	257	137 (53.3%)	79 (30.7%)	41 (16%)
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	121 (62.7%)	50 (25.9%)	22 (11.4%)
Lieu and Howng (1999)	Taiwanese	POI	222	140 (63.1%)	52 (23.4%)	30 (13.5%)
Oya, Sade and Lee (2011)	North American	MRI	189	93 (49.2%)	81 (42.9%)	15 (7.9%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	7 (33.3%)	8 (38.1%)	6 (28.6%)
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	367 (50.3%)	246 (33.7%)	116 (15.9%)
Raper, Starke, Henderson et al. (2014)	North American	POI	490	284 (58%)	153 (31.2%)	53 (10.8%)
Fang, He, Li et al. (2015)	Chinese	POI	157	98 (62.4%)	33 (21%)	26 (16.6%)
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65	33 (50.8%)	19 (29.2%)	13 (20%)
Ishi, Terasaka, Yamaguchi et al. (2016)	Japanese	POI	83	35 (42.1%)	27 (32.5%)	21 (25.3%)
Lagman, Ong, Nguyen et al. (2018)	North American	MRI	21	11 (52.4%)	8 (38.1%)	2 (9.5%)
Magill, Young, Chae et al. (2018)	North American	POI	1113	540 (48.5%)	343 (30.8%)	230 (20.7%)
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42	14 (33.3%)	19 (45.2%)	9 (21.4%)
Kang, Wei and Toh (2019)	Korean	POI	51	41 (80.4%)	8 (15.7%)	2 (3.9%)
Kauke, Safi, Stavrinou et al. (2019)	German	POI	58	31 (53.5%)	17 (29.3%)	10 (17.2%)
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	18 (51.4%)	11 (31.4%)	6 (17.1%)
Weighted mean			**3726**	**52.9%**	**31%**	**16.2%**
Present study	**South African**	**MRI**	**98**	**56 (57.1%)**	**32 (32.70%)**	**10 (10.20%)**

*POI: Preoperative Imaging, Combined use of Magnetic Resonance Imaging and Computed Tomography Angiograms

Table 2.9 Review of meningioma incidence in relation to the supratentorial subregion in relation to the present study's findings

Author (year)	Population	Modality	Sample size	Supratentorial			
				Parasagittal/Parafalx	Convexity	Intraventricular	Other
Chan and Thompson (1984)	Canadian	CT	257	80 (31.1%)	53 (20.6%)	4 (1.6%)	-
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	43 (22.3%)	67 (34.7%)	10 (5.2%)	1 (0.5%)
Lieu and Howng (1999)	Taiwanese	POI	222	51 (23%)	81 (36.5%)	-	8 (3.6%)
Oya, Sade and Lee (2011)	North American	MRI	189	40 (21.2%)	43 (22.8%)	-	10 (5.3%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	3 (14.3%)	4 (19%)	-	-
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	227 (31.1%)	117 (16%)	23 (3.2%)	-
Raper, Starke, Henderson et al. (2014)	North American	POI	490	88 (18%)	187 (38.2%)	9 (1.8%)	-
Fang, He, Li et al. (2015)	Chinese	POI	157	20 (12.7%)	69 (43.9%)	2 (1.3%)	7 (4.5%)
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65	20 (30.8%)	13 (20%)	-	-
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42	2 (4.8%)	11 (26.2%)	1 (2.4%)	-
Kang, Wei and Toh (2019)	Korean	POI	51	17 (33.3%)	22 (43.1%)	2 (3.9%)	-
Kauke, Safi, Stavrinou et al. (2019)	German	POI	58	11 (19%)	20 (34.5%)	-	-
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	6 (17.1%)	12 (34.3%)	-	-
Weighted mean			**2509**	**24.2%**	**27.9%**	**2%**	**1%**
Present Study (2021)	**South African**	**MRI**	**98**	**24 (24.5%)**	**29 (29.6%)**	**3 (3.1%)**	**-**

*POI: Preoperative Imaging, Combined use of Magnetic Resonance Imaging and Computed Tomography Angiograms

Table 2.10 Review of meningioma incidence in relation to the skull base subregion in relation to the present study's findings

Author (year)	Population	Modality	Sample size	Skull base					
				Sphenoid wing	Olfactory groove/ Anterior cranial fossa	Tuberculum sellae	Petrosal	Orbital	Cavernous sinus
Chan and Thompson (1984)	Canadian	CT	257	35 (13.6%)	20 (7.8%)	12 (4.7%)	10 (3.9%)	2 (0.8%)	-
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	33 (17.1%)	6 (3.1%)	7 (3.6%)	-	4 (2.1%)	-
Lieu and Howng (1999)	Taiwanese	POI	222	18 (8.1%)	8 (3.6%)	26 (11.7%)	-	-	-
Oya, Sade and Lee (2011)	North American	MRI	189	9 (4.8%)	6 (3.2%)	27 (14.3%)	28 (14.8%)	-	11 (5.8%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	5 (23.8%)	-	1 (4.8%)	2 (9.5%)	-	-
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	113(15.5%)	58 (8%)	35 (4.8%)	22 (3%)	11(1.5%)	7 (1%)
Raper, Starke, Henderson et al. (2014)	North American	POI	490	66 (13.5%)	27 (5.5%)	42 (8.6%)	12 (2.4%)	1 (0.2%)	5 (1%)
Fang, He, Li et al. (2015)	Chinese	POI	157	10 (6.4%)	7 (4.5%)	13 (8.3%)	3 (1.9%)	-	-
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65	7 (10.8%)	8 (12.3%)	-	4 (6.2%)	-	-
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42	14 (33.3%)	-	4 (9.5%)	-	1 (2.4%)	-
Kang, Wei and Toh (2019)	Korean	POI	51	8 (15.7%)	-	-	-	-	-
Kauke, Safi, Stavrinou et al. (2019)	German	POI	58	8 (13.8%)	3 (5.2%)	6 (10.3%)	-	-	-
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	5 (14.3%)	4 (11.4%)	-	2 (5.7%)	-	-
Weighted mean			**2509**	**13.2%**	**5.9%**	**6.9%**	**3.3%**	**0.8%**	**0.9%**
Present Study (2021)	**South African**	**MRI**	**98**	**15 (15.3%)**	**13 (13.3%)**	**1 (1%)**	**-**	**1 (1%)**	**-**

*POI: Preoperative Imaging, Combined use of Magnetic Resonance Imaging and Computed Tomography Angiograms

Regarding skull base meningiomas, the sphenoid wing has been noted to produce a large number of meningiomas, as evident by the weighted mean of 13.2% calculated in Table 2.10. These studies corroborate the results of the present study which reports the sphenoid wing as the most common site in the skull base region (15.3%). Additionally, we also report on a high incidence of olfactory groove meningiomas in relation to consulted literature with an incidence of 13 cases (13.3%) as compared to the weighted average of 5.9% (Table 2.10). In the present study, categorisation of the skull base subregions according to sex, the female population was noted to harbour most of the meningiomas in the sphenoidal wing (13 cases; 19.7% of the female population) and olfactory groove (12 cases; 18.2% of the female population) subregions.

Due to the low incidence of meningiomas in the posterior fossa, a weighted mean could not be calculated. Additionally, previous studies have referred to the posterior fossa as a whole region which proved difficult to calculate the weighted mean (Table 2.11). The tentorium cerebelli has been reported as the most frequent site of meningioma formation in the posterior fossa region as reported in studies by Oya, Sade and Lee (2011) (4.2%), Bhat, Wani, Kirmani et al. (2014) (6.6%) and Jensen-Kondering, Helle, Lindner et al. (2019) (7.1%). The findings of this study agree with these studies with a total of five cases (5.1%) of meningiomas in the posterior fossa region. Incidences of meningiomas were mainly reported as single cases in the various subregions with the exception of tentorial meningiomas in terms of sex and race.

One possible explanation for this tumour spread among these three anatomical regions could be attributed to the overall area covered by these regions. The supratentorial region covers the largest surface area of the cranial vault in comparison to the skull base and posterior fossa regions. The incorporation of the large falx cerebri may also add to the overall sites for meningioma formation.

The cerebral convexity, sphenoidal wing and tentorial subregions were noted as areas for meningioma formation. The convexity region has been described in previous studies and anatomical texts as having numerous arachnoid cap cells which increases the likelihood of meningioma formation in this region (Bhat, Wani, Kirmani et al. 2014). These cap cells are also noted to be present along the suture lines as evident by the spheno-frontal suture resulting in the prevalence of meningiomas in the sphenoidal wing as well as the fronto-ethmoidal suture and its relationship to olfactory groove meningiomas (Bhat, Wani, Kirmani et al. 2014). Subregions associated with the dural venous sinuses have also been noted to produce meningiomas, as evident by the parasagittal (10 cases; 10.2%) and parafalx (14 cases; 14.3%) subregions which are associated with the superior and inferior sagittal sinuses, respectively. Although these tumours

are noted to produce more meningiomas, it may prove difficult to resect these tumours since the meningioma may invade the venous sinus and hinder total resection of the tumour. In cases in which the meningioma has occluded the venous sinus, a portion of the meningioma is not removed to prevent complications such as air embolism, excessive blood loss or acute postoperative sinus thrombosis (Buerki, Horbinski, Kruser et al. 2018).

2.4.5 Tumour volume

Studies encountered in our literature search represented the maximum tumour diameter rather than a calculated volume. Since meningiomas are not necessarily spherical in shape, it proved more accurate to determine the tumour volume on a three-dimensional basis. The meningioma volume was calculated using the planimetry method (described in the methodology).

In the present study, it was noted that within the supratentorial region, the average size of a meningioma was calculated to be 90.9 cm^3 which supported the findings of Jensen-Kondering, Helle, Lindner et al. (2019) who reported the tumour volume to be 86.3 cm^3 in the same region (Jensen-Kondering, Helle, Lindner et al. 2019). Hashiba, Hashimoto, Izumoto et al. (2009) reported a tumour volume of 11.4 cm^3 and Kauke, Safi, Stavrinou et al. (2019) reported a volume of 49.2 cm^3 in the supratentorial region (Table 2.12).

Regarding the skull base meningiomas, we report a tumour size of 83.2 cm^3 which was higher than the meningiomas reported by Hashiba, Hashimoto, Izumoto et al. (2009) (36 cm^3) and Ishi, Terasaka, Yamaguchi et al. (2016) (28.8 cm^3). The tumour size of the posterior fossa meningiomas in this study was 65.8 cm^3 which was also far higher than studies by Ishi, Terasaka, Yamaguchi et al. (2016) (18.2 cm^3) and Jensen-Kondering, Helle, Lindner et al. (2019) (31 cm^3) as illustrated in Table 2.12.

A possible basis behind these varying results may be due the select cohort that was included in the present study. Only patients that were referred for preoperative embolisation were included in the present study. This criterion may have excluded patients that presented with smaller, asymptomatic meningiomas that did not require embolisation. Thus, only severe cases that required an endovascular intervention were included.

From the results obtained and consulted literature it is established that females are more likely to develop meningiomas with a male to female ratio in the present study of 1:2.06. Although females are predisposed for meningioma formation, the present study reports that the average size of

tumours in females (81.3 cm^3) was significantly lower than the tumour size of males (102 cm^3). Statistical tests yielded a *p-value* of 0.001 (Ranksum test) indicating a statistically significant relationship between sex and tumour volume. Furthermore, categorisation of meningioma volume according to race revealed a larger tumour size in the African subset (100.00 cm^3) in comparison to the Indian subset (46.9 cm^3). Statistical tests revealed a *p-value* (Kruskal-Wallis) of 0.001 when investigating the statistical relationship between these 2 population groups.

2.4.6 Vascularity of the meningioma

Blood supply to the meningioma is normally location-specific, with contributions from the ECA, ICA and VA (Dubel, Ahn and Soares 2013). Surgical resection of the meningioma is often performed, however, due to its high degree of vascularity, excessive blood loss is a common complication (Shah, Choudhri, Jung et al. 2015). Preoperative tumour embolisation has proven to reduce complications in surgical resection of these tumours. Although embolisation is accepted as adjuvant therapy to ease the tumour resection procedure, identifying vessels that, if embolised, would reduce the overall blood loss and prevent damage to adjacent neurological structures requires a thorough understanding of the vascular contribution of the feeder vessel/s. Meningiomas may receive arterial blood from single or multiple arteries of varying contributions. The present study aimed to quantify the vascular contributions of intracranial meningiomas in relation to their anatomical location.

Within the supratentorial region, it was noted that the common primary feeders were the right ICA (12 tumours; 21.4% of supratentorial meningiomas) and the left ECA (12 tumours; 21.4% of supratentorial meningiomas). These findings corroborate the results of Jensen-Kondering, Helle, Lindner et al. (2019) who reported three meningiomas (21.4% of supratentorial meningiomas) primarily supplied by the right ICA and three meningiomas (21.4% of supratentorial meningiomas). However, the right ECA was noted to be most common primary feeder reported by Jensen-Kondering, Helle, Lindner et al. (2019).

Table 2.11 Review of meningioma incidence in relation to the posterior fossa subregion in relation to the present study's findings

Author (year)	Population	Modality	Sample size	Posterior fossa					
				Cerebello -pontine angle	Cerebellar convexity	Foramen magnum	Jugular foramen	Clival	Tentorial
Chan and Thompson (1984)	Canadian	CT	257	41 (16%)					
Rohringer, Sutherland, Louw et al. (1989)	Canadian	CT	193	4 (2.1%)	9 (4.7%)	1 (0.5%)	-	1 (0.5%)	7 (3.6%)
Lieu and Howng (1999)	Taiwanese	POI	222	20 (9%)	-	-	10 (4.5%)	-	-
Oya, Sade and Lee (2011)	North American	MRI	189	-	-	7 (3.7%)	-	-	8 (4.2%)
Uetani, Akter, Hirai et al. (2013)	Japanese	MRI	21	1 (4.8%)	1 (4.8%)	-	1 (4.8%)	2 (9.5%)	1 (4.8%)
Bhat, Wani, Kirmani et al. (2014)	Indian	POI	729	26 (3.6%)	21 (2.9%)	10 (1.4%)	2 (0.3%)	9 (1.2%)	48 (6.6%)
Raper, Starke, Henderson et al. (2014)	North American	POI	490	10 (2%)	41 (8.4%)			2 (0.4%)	-
Fang, He, Li et al. (2015)	Chinese	POI	157	8 (5.1%)	18 (11.5%)				-
Jadid, Feychting, Hoijer et al. (2015)	Swedish	POI	65	13 (20%)					
Jensen-Kondering, Helle, Lindner et al. (2019)	German	MRI	42					6 (14.3%)	3 (7.1%)
Kang, Wei and Toh (2019)	Korean	POI	51	-	-	-	-	1 (2%)	1 (2%)
Kauke, Safi, Stavrinou et al. (2019)	German	POI	58	10 (17.2%)					
Catapano, Whiting, Mezhera et al. (2020)	North American	MRI	35	-	-	-	-	-	6 (17%)
Present Study (2021)	**South African**	**MRI**	**98**	**1 (1%)**	**1 (1%)**	**-**	**-**	**2 (2%)**	**5 (5.1%)**

*POI: Preoperative Imaging, Combined use of Magnetic Resonance Imaging and Computed Tomography Angiograms

Table 2.12 Review of literature regarding meningioma volume in relation to anatomical location

Author (year)	Population	Modality	Sample size	Mean volume (cm^3)		
				Supratentorial	Skull base	Posterior fossa
Hashiba, Hashimoto, Izumoto et al. (2009)	Japanese	MRI	44	11.4 cm^3 (0.8–77.3)	36 cm^3 (1.3–92.3)	5.9 cm^3 (5.9)
Ishi, Terasaka, Yamaguchi et al. (2016)	Japanese	MRI	83	41 cm^3 (± 38.1)	28.8 cm^3 (± 28.65)	18.2 cm^3 (± 13.1)
Lagman, Ong, Nguyen et al. (2018)	North American	MRI	51	73 cm^3 (±102)		
Jensen-Kondering, Helle, Lindner et al. (2019)	German	CT/MRI	42	86.3 cm^3 (±52)	29 cm^3 (±4)	31 cm^3 (±46)
Kang, Wei and Toh (2019)	Korean	MRI	51	64.2 cm^3 (± 46.7)		
Kauke, Safi, Stavrinou et al. (2019)	German	MRI	58	49.2 cm^3 (3–133)	9.3 cm^3 (1–67)	8 cm^3 (4–48)
Present Study	**South Africa**	**MRI**	**98**	**90.9 cm^3 (54.8–135)**	**83.20 cm^3 (52.9–122)**	**65.8 cm^3 (43.4–102)**

With regard to the skull base region, we report a high incidence of meningiomas primarily supplied by the internal carotid arterial system (right ICA: 10 tumours; 31.3% of skull base meningiomas; left ICA: 10 tumours; 31.3% of skull base meningiomas). These findings agreed with studies done by Uetani, Akter, Hirai et al. (2013) (5 tumours supplied by the ICA; 23.8%) and Jensen-Kondering, Helle, Lindner et al. (2019) (right ICA: 10 tumours; 52.6%; left ICA: 3 tumours; 15.8%). We report a single meningioma (3.1% of skull base meningiomas) receiving a minor supply from the vertebral system of arteries.

The posterior fossa harboured a total of ten meningiomas of which five (50%) were primarily supplied by the vertebral system of arteries and four (40%) received a minor contribution from the vertebral system. These findings did not agree with Jensen-Kondering, Helle, Lindner et al. (2019) who reported only three meningiomas (33.3% of posterior fossa meningiomas) receiving a minor supply from the vertebrobasilar system and no cases of a primary supply from this system. Instead, arterial supply to posterior fossa meningiomas was derived from the external carotid system of arteries (right ECA: 2 tumours; 22.2% of posterior fossa meningiomas; left ECA: 1 tumour; 11.1% of posterior fossa meningiomas). However, the present study reports minor (less than 50%) contributions from the ECA (left ECA: 4 tumours; 40% of posterior fossa meningiomas; right ECA: 4 tumours; 40% of posterior fossa meningiomas) as well as from the left ICA (3 tumours; 30% of posterior fossa meningiomas).

The identification of primary arterial feeders highlighted possible vessels to identify; based on the anatomical location; that if embolised would reduce the tumoral blush significantly to ensure safer resection reducing the chances of post-operative complications. From the observed results, we can conclude that within the supratentorial regions, embolisation of the left ECA as well as the right ICA would be most effective in reducing tumoural blush whilst in the skull base regions, embolisation of the ICA system would be most effective. The basis behind the skull base region being associated with the ICA may be attributed to the location of the ICA in this region. The ICA forms the cerebral arterial circle of Willis in the middle cranial fossa and branches off into various regions of the brain. Meningiomas that grow in the skull base region have the potential to parasitise this vascular rich bed of vessels.

Uetani, Akter, Hirai et al. (2013) employed the use of Magnetic Resonance Angiography in an attempt to investigate less invasive procedures to assess the meningioma vascularity (Uetani, Akter, Hirai et al. 2013). However, this proved unsatisfactory results in comparison to DSA's. The present study analysed the vascular supply to intracranial meningiomas using the

proportionality of the tumoral blush (obtained from DSA's) in relation to the meningioma maximum surface area (obtained from fine slice post-contrast MRI scans) in the respective anatomical plane. This methodology has not been encountered in the literature consulted, however it provides a scientific framework in quantifying and evaluating meningioma vascularity. Selecting a secondary feeder vessel to embolise should be considered in light of the relative location of the meningioma to other neurological structures. The assessment of the arterial supply in both the sagittal and coronal plane has provided insight into the 3-Dimensional arterial characteristics of meningiomas.

2.5 Limitations and recommendations

The present study investigated the anatomy of intracranial meningiomas referred for preoperative embolisation at the IALCH. This medical institution is a regional public hospital where socio-economic factors may have skewed the demographic data obtained as evident by the large population of patients of African descent. Additionally, the present study only included patients that were referred for preoperative embolisation, indicating that the results from the present study are an indication of cases in which an endovascular intervention was possible which may not represent the true prevalence of intracranial meningiomas within the region. To develop a full picture of meningiomas within a South African setting, additional studies could investigate a subset of patients presenting with intracranial meningiomas that have not been referred for preoperative embolisation at both public and private health care institutions to evaluate the variant anatomy present in these two subsets.

2.6 Conclusion

The aim of the current study was to investigate the anatomical basis behind intracranial meningiomas referred for preoperative embolisation. The study supports the basis of a female predisposition for the formation of intracranial meningiomas as well as predominance of the WHO Grade I meningiomas and the meningothelial histological subtype. In light of this, it was interesting to note that the malignant WHO Grades (II and III) were predominant in the male population. Additionally, the supratentorial region (more specifically, the convexity and parasagittal subregions) is noted as a common region for meningioma formation. Whilst females are noted to be more likely to develop a meningioma, the overall volume of the meningioma is significantly smaller in comparison to the male population. We also note a significantly larger tumour size in all three anatomical regions (supratentorial, skull base and posterior fossa). Arterial supply to meningiomas within the supratentorial region is usually derived from the left ECA with

the right ICA, whilst the ICA system is a major feeder to skull base meningiomas. These results have provided a clearer understanding into the anatomy of intracranial meningiomas and may assist neurosurgeons in the region to plan and assess cases of intracranial meningiomas referred for preoperative embolisation adding to the scarce body of literature present.

2.7 Author contributions

E. Anirudh: Project Development, Data collection, Data analysis, Manuscript writing and editing.

R. Harrichandparsad: Project development, Data analysis, Manuscript editing.

L. Lazarus: Project development, Data analysis, Manuscript editing.

2.8 Conflicts of interest

The authors declare that they have no conflicts of interest to report.

2.9 Ethical approval

The present study has been reviewed and approved by the institutional ethics committee of the University of KwaZulu-Natal (Biomedical Resource Ethics Committee -Reference number: BREC/00001934/2020). Ethical approval was dependant on review by the medical institution (Inkosi Albert Luthuli Central Hospital) as well as the Department of Health of South Africa. Individual patient consent was not required since the present study is a retrospective chart review with patient identifiers anonymised and only the age, sex and race of the patients recorded.

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2.12 Figures

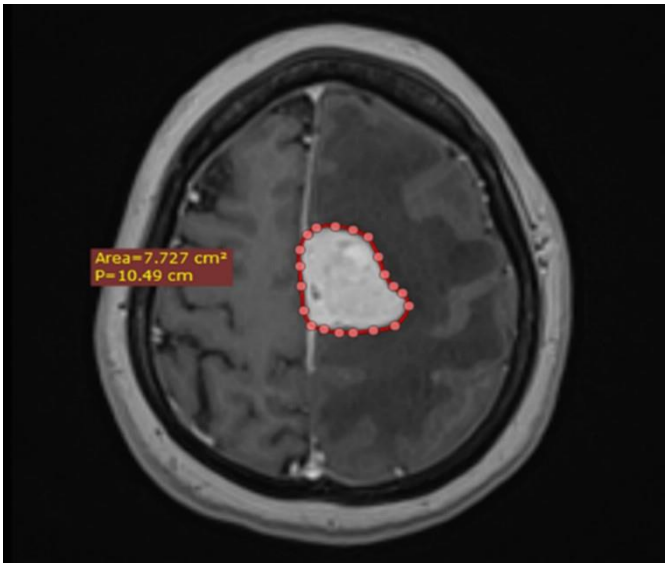


Figure 2.1 MRI fine slice (1 mm slice thickness) on a post contrast T1 weighted image used to measure the total surface area of the meningioma in conjunction with the tumour volume calculation.

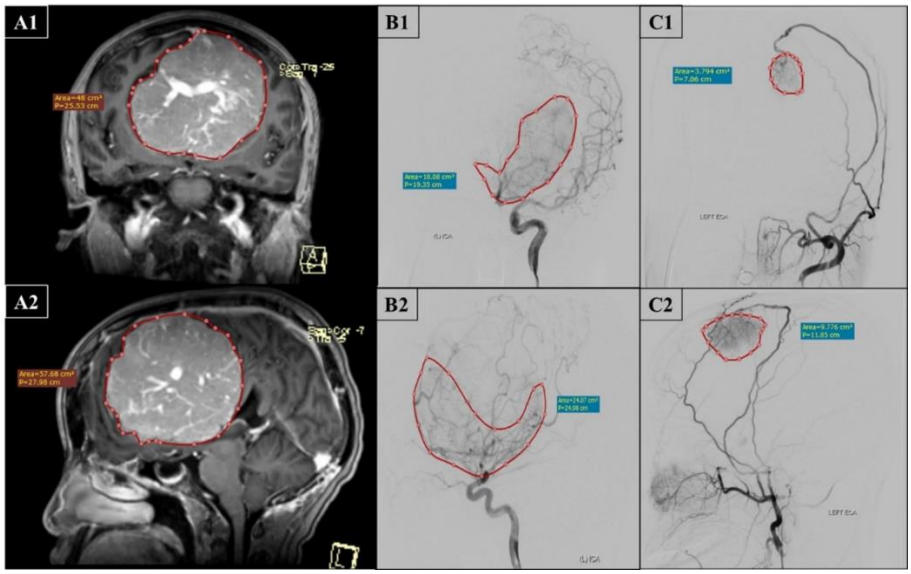


Figure 2.2 MRI (Images A1 and A2, multiplanar reconstruction transposed from T1 weighted post contrast axial images) and DSA (Images B and C) series of a patient presenting with a supratentorial meningioma and the vascular contributions (Coronal view: Image B1 and C1; Sagittal view: Image B2 and C2) of the left ICA (Images B1 and B2) and left ECA (Images C1 and C2).

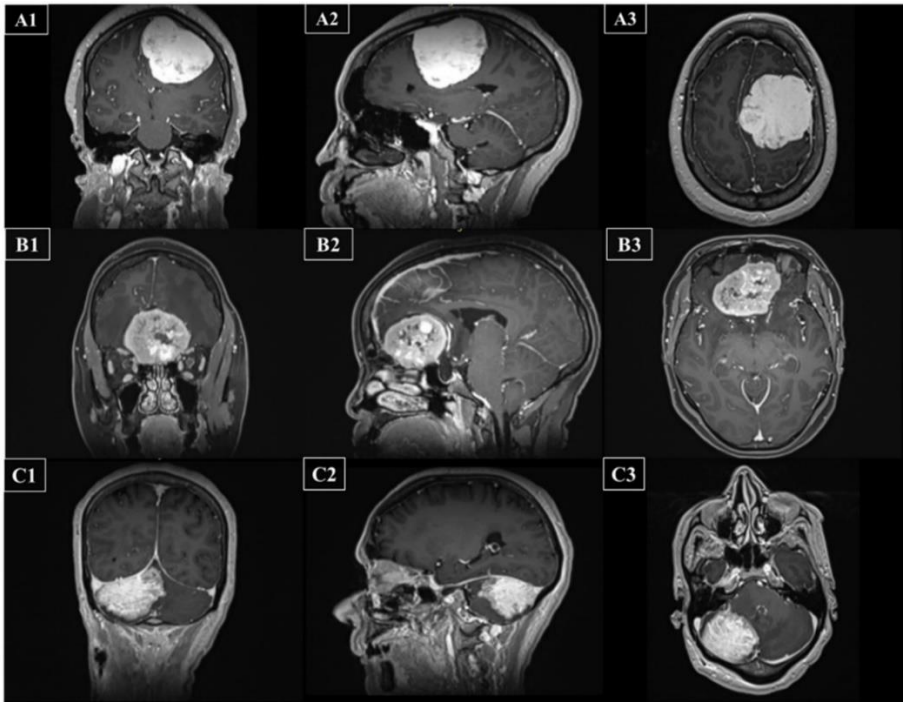
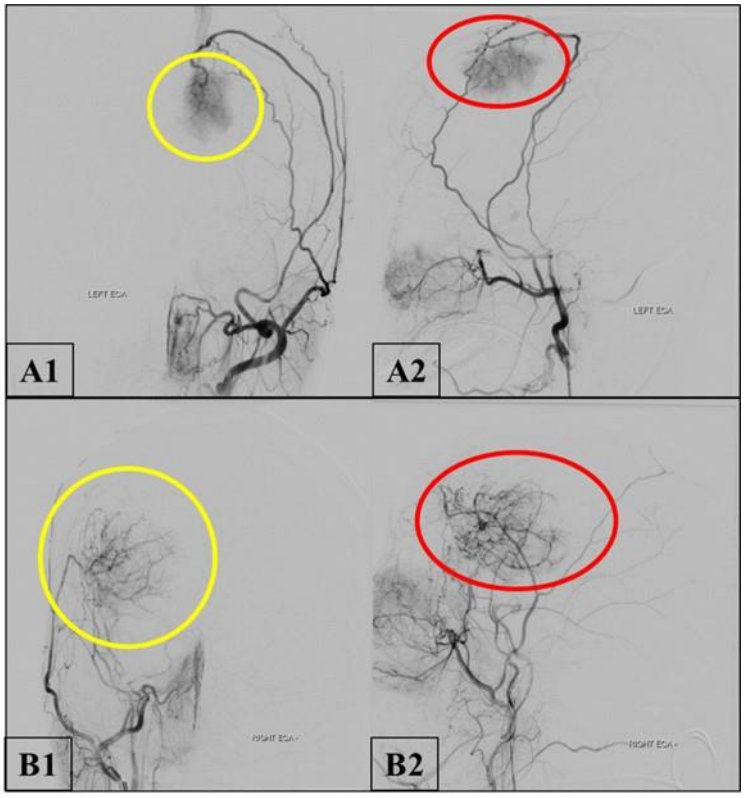
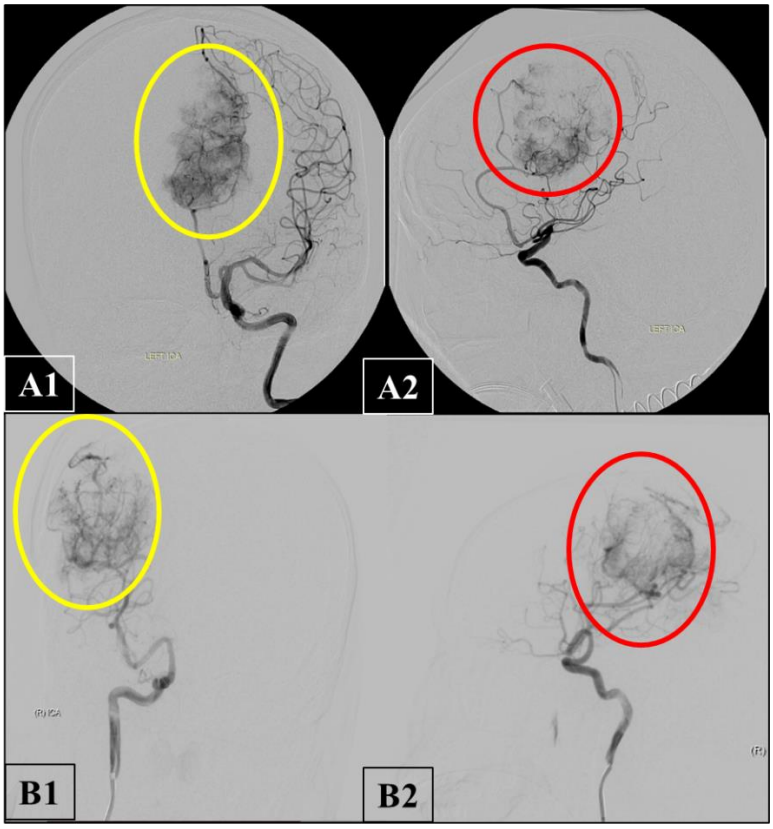


Figure 2.3 MRI series showing coronal (Image A1, B1 and C1), sagittal (Image A2, B2 and C2) and transverse/axial (Image A3, B3 and C3) sections of three independent patients that presented with a supratentorial (Image A), skull base (Image B) and posterior fossa (Image C) intracranial meningioma referred for preoperative embolisation.



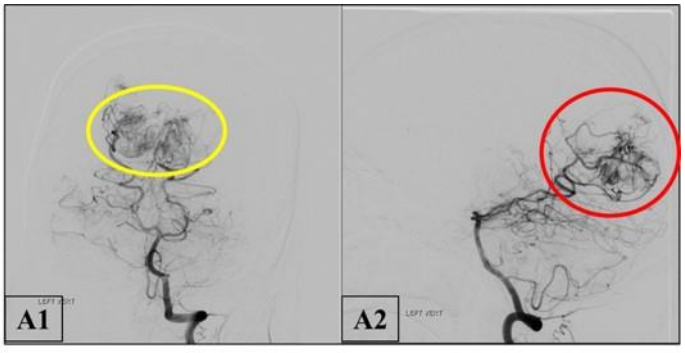
Legend: Image A1 and A2: Left ECA; Image B1 and B2: Right ECA; Yellow: Tumoral blush in coronal view; Red: Tumoral blush in sagittal view

Figure 2.4 DSA showing vascular contributions of the ECA to intracranial meningiomas viewed from a coronal (A1 and B1) and sagittal (A2 and B2) view.



Legend: Image A1 and A2: Left ICA; Image B1 and B2: Right ICA; Yellow: Tumoral blush in coronal view; Red: Tumoral blush in sagittal view

Figure 2.5 DSA showing vascular contributions of the ICA to intracranial meningiomas viewed from a coronal (A1 and B1) and sagittal (A2 and B2) view.



Legend: Image A1: Coronal view of VA; A2: Sagittal view of VA; Yellow: Tumoral blush in coronal view; Red: Tumoral blush in sagittal view

Figure 2.6 DSA showing vascular contributions of the vertebral system to intracranial meningiomas viewed from a coronal and sagittal view.

CHAPTER 3
SCIENTIFIC MANUSCRIPT 2

Interface

Chapter 1 provided a foundation in terms of the anatomy of intracranial meningiomas as well as a comprehensive literature review highlighting areas where there appears to be a dearth of information. Chapter 2 investigates the anatomical features of single cases of intracranial meningiomas.

Contributions of this chapter

This chapter investigated the anatomical parameters of intracranial meningiomas in patients that presented with multiple meningiomas (subset 2). The results were compared to the literature available. Due to the paucity of studies investigating the anatomy of multiple meningiomas, the present study aimed to add to the body of literature available. The following manuscript has been formatted according to the guidelines outlined by the journal.

Title: The anatomical basis of multiple meningiomas: A case series

Authors: E.E. Anirudh, R. Harrichandparsad, L. Lazarus

Journal: Radiology Case Reports

Manuscript Number: 211202-013988

TITLE PAGE

Title: The anatomical basis of multiple meningiomas: A case series

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Running head: The anatomy of multiple meningiomas

Number of figures: 2

Number of tables: 1

Author contributions

E. Anirudh: Project development, data collection, data analysis, manuscript writing and editing.

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L. Lazarus: Project development, data analysis, manuscript editing.

Conflicts of interest

The authors declare that they have no conflicts of interest to report.

Ethical approval

The present study has been reviewed and approved by the institutional ethics committee of the University of KwaZulu-Natal (Biomedical Resource Ethics Committee -Reference number: BREC/00001934/2020). Ethical approval was dependant on review by the medical institution (Inkosi Albert Luthuli Central Hospital) as well as the Department of Health of South Africa. Individual patient consent was not required since the present study is a retrospective chart review with patient identifiers anonymised and only the age, sex and race of the patients recorded.

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List of abbreviations:

Ant.:	Anterior
DSA:	Digital subtraction angiography
ECA:	External carotid artery
IALCH:	Inkosi Albert Luthuli Central Hospital
ICA:	Internal carotid artery
Mid.:	Middle
MRI:	Magnetic resonance imaging
Post.:	Posterior

Abstract

Introduction: Meningiomas are the most common primary intracranial tumours arising from the arachnoid cap cells of the arachnoid villi. These tumours are generally benign, highly vascularised and may be caused by a host of factors consisting of genetic mutations, hormonal imbalances and exposure to ionising radiation. In most cases, the meningioma forms as a single tumour; however, rare cases of multiple meningiomas have been reported. Multiple meningiomas represent less than 10% of diagnosed meningiomas and may form simultaneously or at different times.

Methods: This study aimed to investigate the anatomical parameters of multiple meningiomas within a select South African population. A retrospective chart review was conducted using Magnetic Resonance Imaging and Digital Subtraction Angiographies obtained from the data bank at a central regional hospital in KwaZulu-Natal, South Africa over the period of 2011 to 2020.

Results: Five cases of multiple intracranial meningiomas were found primarily in females and in the supratentorial region. A high incidence of meningiomas within the right hemisphere was observed. The meningiomas were calculated to have an average volume of 43.9 cm^3 (range: 9.1 cm^3–127.5 cm^3). Regarding its arterial supply, the external carotid system of arteries was noted to be the most common primary arterial feeder to these tumours.

Conclusion: Findings of this study have described the anatomical features of multiple meningiomas within a select South African population adding to the scarce literature available. Additionally, this study investigated the arterial supply using a proportionality methodology to quantify the vascular contributions.

Key words: Multiple meningioma, meningioma vascular supply, meningioma anatomy

3.1 Introduction

Considered as one of the most common primary intracranial tumours, meningiomas are highly vascularised, generally benign tumours arising from the arachnoid cap cells of the arachnoid villi (Buerki, Horbinski, Kruser et al. 2018). These cells are usually found along the dural venous sinuses and the suture lines of the skull (Bhat, Wani, Kirmani et al. 2014). Studies have reported that the superior sagittal sinus, convexity and sphenoidal ridge as potential sites for meningioma formation (Bhat, Wani, Kirmani et al. 2014). However, hereditary genetic mutations, exposure to radiation or hormonal imbalances may result in multiple meningiomas formation (Tsermoulas, Turel, Wilcox et al. 2018). Multiple meningiomas are rare, occurring in less than 10% of diagnosed meningiomas (Pereira, de Almeida, de Aguiar et al. 2019). This pathology is diagnosed based on the presence of two or more meningiomas that are independent of each other anatomically in the same patient (Salvati, Caroli, Ferrante et al. 2004). They may form simultaneously or differently due to the varying vasculature and histological grade (Buerki, Horbinski, Kruser et al. 2018).

Preoperative embolisation is considered necessary in reducing blood loss during meningioma resection (Buerki, Horbinski, Kruser et al. 2018). Misidentification of the vascular territories, retrograde flow of the embolite or tumour swelling may lead to neurological deficits post-embolisation (Martin, Cha, Higashida et al. 2007). Ideally, embolisation should reduce the arterial supply significantly whilst also preserving the vascular system present (Martin, Cha, Higashida et al. 2007; Buerki, Horbinski, Kruser et al. 2018).

There exists a considerable amount of literature investigating single cases of meningiomas. However, the knowledge regarding the anatomical features of multiple meningiomas is rare. The present study aimed to investigate the anatomical variations present in patients with more than one intracranial meningioma. This was achieved by investigating the demographic profile, side location of the meningioma, anatomical origin, tumour volume and vascularity of each meningioma within a select South African population.

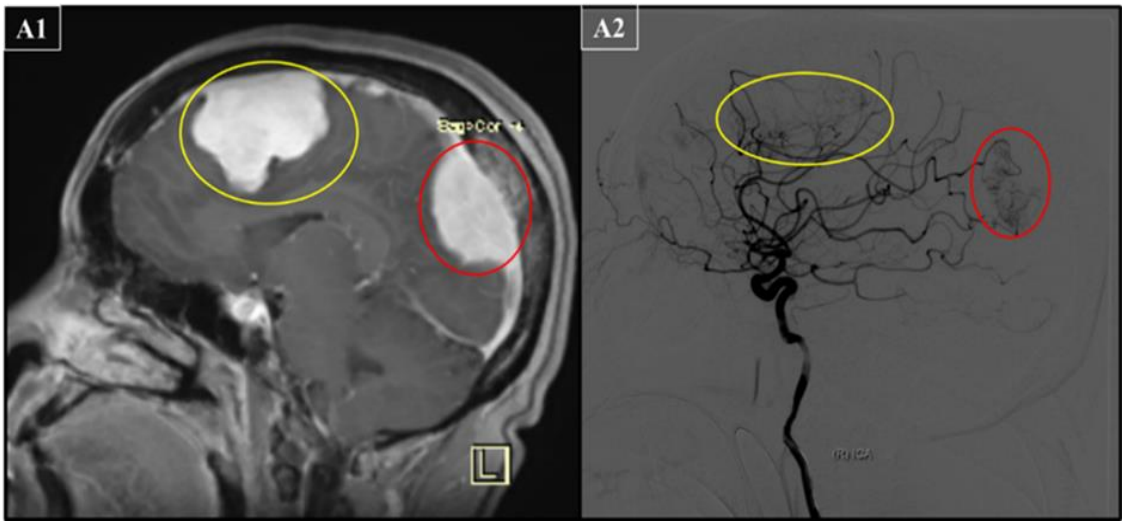
3.2 Materials and methods

The present study comprised a retrospective chart review of patients admitted to the Inkosi Albert Luthuli Central Hospital (IALCH) over the past 10 years (Jan 2011–Dec 2020) who were referred for preoperative embolisation. Ethical clearance was obtained from the relevant institutional ethics committees (Biomedical Resource Ethics Committee – Reference number:

BREC/00001934/2020). Magnetic Resonance Imaging (MRI) and Digital Subtraction Angiography (DSA) of patients presenting with intracranial meningiomas were critically analysed. Patient details were anonymised, and only the age, sex and race of the patient was recorded.

Inclusion criteria: Patients presenting with more than one meningioma in which visible clear borders between each tumour were included. Only patients referred for preoperative embolisation of at least one of the meningiomas were included in the present study. Patients that presented with MRI scans of a T1 post-contrast (1 mm fine slice) series of images and DSA's showing the sagittal view of the meningiomas were considered in this study.

Analysis of the radiographic data was conducted on the RadiAnt DICOM Viewer software. The anatomical location of the meningioma was categorised according to their dural attachment, and the tumour volume was calculated using the planimetry method (product of the sum of the total surface area and the slice thickness) described by Ishi, Terasaka, Yamaguchi et al. (2016). The vascularity of the meningioma was quantified by means of the proportionality of the tumoral blush (obtained from the surface area on the DSA) in relation to the maximum tumour surface area (obtained from the post-contrast fine slice MRI) observed in the sagittal plane (Figure 3.1). The proportionality was categorised according to the following groups: minor contribution (less than 0.5) and major contribution (greater than 0.5). This study did not incorporate the coronal aspect of the arterial supply due to the superimposition of multiple meningiomas' arterial blushes, especially in the supratentorial region.



Legend: Yellow – Anterior meningioma shown on the MRI (A1) and DSA (A2) highlighting a minor arterial; Red – Posterior meningioma shown on the MRI (A1) and DSA (A2) indicating a major supply in relation to the maximum tumour area

Figure 3.1 Sagittal view of an MRI (A1) showing 2 intracranial meningiomas and the corresponding sagittal view of a DSA (A2) of the right ICA showing the tumoral blush of each meningioma.

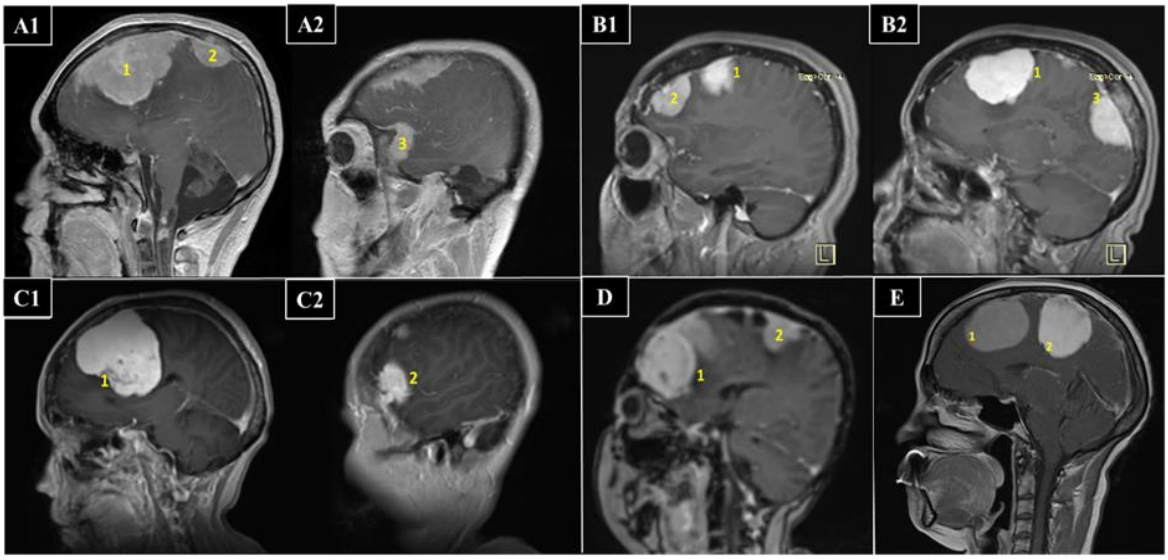
3.3 Case series

The retrospective chart review yielded 103 patients of which five patients (n = 5) met the inclusion criteria (incidence of 4.9%). Patients ranged from 34 to 52 years old (average age – 44 years old) at the time of diagnosis (Table 3.1; Figure 3.2). The presence of triple intracranial meningiomas was documented in 2 patients whilst the presence of a double intracranial meningioma was noted in 3 patients. In this case series, four patients presented as multiple meningiomas and these were observed in the female population. Half of the meningiomas within this series were observed in the right hemisphere of the skull. A large majority of meningiomas were observed in the supratentorial region (91.7%). The average tumour volume amongst all meningiomas was measured at 43.9 cm^3. The external carotid artery (ECA) is reported as a common primary arterial feeder within this subset supplying the five meningiomas.

Table 3.1 Demographic and anatomical description of patients presenting with multiple meningiomas (n =5)

Patients	Demographics			Anatomical parameters				
	Age	Sex	Ethnicity	Side location	Anatomical region	Anatomical subregion	Volume (cm^3)	Vascularity
Patient 1 *(Figure 3.2A)*	40	Indian	Male	Right	Supratentorial	Ant. $^2/_3$ parafalx	127.5	Right ICA: major Right ECA: major
				Right	Supratentorial	Mid $^1/_3$ parafalx	9.1	Right ICA: minor Right ECA: minor
				Right	Skull base	Sphenoidal wing	6.5	Right ICA: major
Patient 2 *(Figure 3.2B)*	52	Indian	Female	Right	Supratentorial	Ant. $^1/_3$ parasagittal	44.5	*
				Right	Supratentorial	Ant. $^1/_3$ convexity	10.4	*
				Midline	Supratentorial	Post. $^1/_3$ parasagittal	27.2	Right ICA: major Right ECA: major
Patient 3 *(Figure 3.2C)*	34	Indian	Female	Left	Supratentorial	Ant. $^1/_3$ parasagittal	117.9	Left ICA: minor Left ECA: major
				Left	Supratentorial	Ant. $^1/_3$ convexity	13.7	Left ECA: major
Patient 4 *(Figure 3.2D)*	44	Indian	Female	Right	Supratentorial	Ant. $^1/_3$ convexity	34.6	Right ICA: minor Right ECA: major
				Left	Supratentorial	Mid. $^1/_3$ parasagittal	18.5	Right ICA: minor
Patient 5 *(Figure 3.2E)*	49	Caucasian	Female	Left	Supratentorial	Ant. $^1/_3$ convexity	42.5	Left ICA: minor
				Midline	Supratentorial	Mid. $^1/_3$ parafalx	37.3	Left ICA: major Right ECA: minor

* Tumours 1 and 2 were observed in close proximity with unclear tumoral blushes and were therefore excluded from the arterial supply analysis



Legend: Figure 3.2A: Patient 1 (1: Tumour 1; 2: Tumour 2; 3: Tumour 3)
Figure 3.2B: Patient 2 (1: Tumour 1; 2: Tumour 2; 3: Tumour 3)
Figure 3.2C: Patient 3 (1: Tumour 1; 2: Tumour 2)
Figure 3.2D: Patient 4 (1: Tumour 1; 2: Tumour 2)
Figure 3.2E: Patient 5 (1: Tumour 1; 2: Tumour 2)

Figure 3.2 Sagittal MRI (T1 post-contrast fine slice) images showing the multiple meningiomas in the case series.

3.4 Discussion

Five case reports of patients presenting with multiple meningiomas have been reported. The purpose of this study was to highlight the anatomy of intracranial meningiomas based on the presence of multiple tumours. We report an incidence of multiple meningiomas referred for preoperative embolisation of 4.9% which supports the incidence reported in previous studies done by Salvati, Caroli, Ferrante et al. (2004) and Pereira, de Almeida, de Aguiar et al. (2019) who report incidences (as part of larger studies investigating meningiomas) of 2.8% and 3.3%, respectively. Several reports have shown that the average age of multiple meningioma presentation was in the fifth decade of a patient's life (Salvati, Caroli, Ferrante et al. 2004; Pereira, de Almeida, de Aguiar et al. 2019; Tsermoulas, Turel, Wilcox et al. 2018). Interestingly, our study did not concur with these findings, reporting an average age of diagnosis to be 44 years old (range 34–52 years old). The inconsistency in the literature may be attributed to the location-specific features coupled with the larger sizes of the meningiomas, which may have resulted in the earlier presentation of symptoms.

The present study also supports the idea of a female prevalence of multiple meningiomas accounting for 80% of this subset as evident in studies conducted by Salvati, Caroli, Ferrante et al. (2004) (71.40%); Pereira, de Almeida, de Aguiar et al. (2019) (76.19%); and Tsermoulas, Turel, Wilcox et al. (2018) (78%). A possible explanation for this prevalence has been linked to progesterone receptors on meningiomas (Shahin, Magill, Dalle et al. 2019). Other factors that may affect the female population's hormonal levels, such as fertility treatment or pregnancy, may increase the incidence of multiple meningiomas, specifically the convexity and falx regions, as stated by Shahin, Magill, Dalle et al. (2019). The present study reports a high incidence of multiple meningiomas within the Indian population group (80.0%) with no cases from the African or Coloured population. Although IALCH is a medical institution in the public health sector, it caters to a diverse population within the KwaZulu-Natal region. The 10-year retrospective chart review yielded only 5 patients that presented with multiple intracranial meningiomas. Considering these factors, it may be suggested that an ethnic basis of multiple meningiomas may exist, however, further research investigating cases of multiple meningiomas within both the private and public health sectors would be required.

Combined analysis of meningiomas revealed a total of 12 meningiomas, half of which were located in the right hemisphere of the skull. Literature consulted on multiple meningiomas did not report on any form of laterality regarding multiple meningiomas. These findings do not indicate that the associated symptoms would be observed on the left side of the body since factors such as the location and volume of the meningioma should be considered in identifying the tumour responsible for the symptoms. In patients presenting with multiple meningiomas, more specifically in the supratentorial region, there is a shift in the inter-hemispheric balance of the cerebrum (Mainio, Hakko and Niemela et al. 2003). This would result in displacement of structures in the cerebrum which may lead to a host of associated pathologies.

The present study found 11 (91.67%) cases of meningiomas within the supratentorial region and only a single case within the skull base region. These findings agreed with those of Tsermoulas, Turel, Wilcox et al. (2018), who reported the supratentorial region harbouring the most cases of multiple meningiomas (74.0%). Closer inspection of the supratentorial region highlighted the parasagittal (33.33%) and convexity (33.33%) regions as common sites for meningioma formation. These findings are corroborated by the investigations of Salvati, Caroli, Ferrante et al. (2004) (convexity: 38.2%; parasagittal: 22.30%) and Tsermoulas, Turel, Wilcox et al. (2018) (Convexity: 39%). This study supports the findings of Salvati, Caroli, Ferrante et al. (2004) who reported a similar incidence of 6.66% of meningiomas originating from the sphenoidal wing. A

possible basis behind these meningioma "hotspots" may be attributed to the vast amount of arachnoid cap cells in these regions (convexity, parasagittal and sphenoid wing) since major dural venous sinuses and cranial sutures are found in this region (Bhat, Wani, Kirmani et al. 2014).

Volumetric measurements of the meningioma were calculated using fine slice T1 post-contrast images which reduced the misidentification of peritumoral oedema as part of the volume. The current study reports an average volume of 43.9 $cm^{3,}$ with the smallest tumour measuring 6.5 cm^3 and the largest being 127.5 cm^3. The literature investigated did not reveal calculated volumes of patients with multiple meningiomas but rather categorised the tumours according to the maximum tumour diameter on a transverse (axial) section. Additionally, it was interesting to note the variation in the overall size of the meningiomas in each patient. Most patients (except for patient 2 and 5) harboured a single relatively large meningioma (tumour volume greater than 40.0 cm^3) and additional meningiomas that were less than half its size. This is further supported by findings from Tsermoulas, Turel, Wilcox et al. (2018), in which 67.00% of the multiple meningiomas were categorised as small meningiomas (cross-sectional diameter of <2 cm) as opposed to large meningiomas (cross-sectional diameter of >4 cm) in 11.00% of the sample size (Tsermoulas, Turel, Wilcox et al. 2018). This variance of the meningioma volume may be attributed to the phase of the meningiomas. In three of the cases reported (patient 1, 3 and 4), there was only a single meningioma in the vascular phase of growth, in which neo-angiogenesis occurred resulting in the rapid growth of the single meningioma, whilst the additional meningiomas were in the avascular phase only accessing the blood that was parasitised from adjacent blood vessels (Pistolesi, Boldrini, Gisfredi et al. 2004).

Regarding the arterial supply within this series, the meningioma vascularity was only measured on the sagittal view. This was due to the high presence of supratentorial tumours with tumoral blushes that were superimposed upon coronal view. Case 2 represented three meningiomas independent of each other, however tumours 1 and 2 were in close proximity when viewed on the DSA with the arterial supply indistinguishable and was therefore excluded from the analysis of the tumour vascularity. Within the supratentorial region, the right ICA and ECA were noted to supply most of the tumours, which was expected due to the high incidence of meningiomas within the right hemisphere. The ECAs were observed as common primary feeders to meningiomas within this region (right ECA: 3 meningiomas; left ECA: 2 meningiomas). This may be due to the course of the dural branches of the ECA in this region, *viz.* the anterior and middle branches of the middle meningeal artery and the accessory meningeal artery. Embolisation of these branches (as proximal to the meningiomas as possible) would be favourable as these vessels do

not supply portions of the cerebrum; however, caution should still be taken since these ECA branches also supply parts of the cranial nerves. Misidentification or the release of the embolite further away from the tumour may increase the risk for cranial nerve palsies.

3.5 Conclusion

This study aimed to investigate the anatomical features of multiple meningiomas. The findings suggest a prevalence of multiple meningiomas within the female population and in the supratentorial region, more specifically the parasagittal and cerebral convexity regions. It is also important to note that cases of multiple meningiomas were mainly reported in the Indian population. The ECA is noted as a leading contributor to meningiomas found in the supratentorial region. A limitation of this study experienced was that the cases reported were obtained from patients referred for preoperative embolisation, which did not account for all patients presenting with multiple meningiomas. However, the results of this study have provided evidence in terms of the anatomical basis of multiple meningiomas referred for preoperative embolisation. It is recommended that future research investigating multiple meningiomas consider using multi-institutional data banks with patients from the private and public health sectors.

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CHAPTER 4
SYNTHESIS

Interface

Chapters 1, 2 and 3 provided a foundational and structural framework of intracranial meningiomas referred for preoperative embolisation. Chapter 1 investigated the relevant literature, highlighting the gaps present and an overview of the methodology. Chapters 2 and 3 investigated the anatomical features of intracranial meningiomas within the two subsets.

Contributions of this chapter

The following chapter critically analyses and discusses the findings of the study and its potential impact. Comparisons between the two subsets and relevant literature are discussed as well. Limitations encountered during the study as well as possible areas for future research are outlined.

4.1 Introduction

This retrospective chart study investigated the anatomical basis of intracranial meningiomas by investigating the demographic profile, anatomical location (in terms of subregions and side), tumour volume and the arterial supply to these tumours. Due to the paucity of literature within the South African population, this study aimed to explain the anatomical features of meningiomas referred for preoperative embolisation. Surgical resection of meningiomas has the possibility for many vascular-related complications due to the high degree of vascularity present. Preoperative embolisation has proven vital in reducing this risk by preventing excessive blood loss during resection (Buerki, Horbinski, Kruser et al., 2018). We reported a total of 98 (n = 98) cases of a single meningioma and 5 (n = 5) cases of multiple meningiomas. Histological reports, MRI and DSA images were used to investigate the anatomy of the meningioma.

4.2 Demographics

Regarding the tumour incidence, it was noted that within subset 1, the average age of patients at the time of diagnosis was 48 years old, whilst subset 2 noted an average age of 44 years old. The average age of patients in both subsets was noted to be much lower than other studies in the consulted literature (Jensen-Kondering, Helle, Lindner et al., 2019; Oya, Sade and Lee, 2011). Due to the slow growth rate of meningiomas, its clinical presentation appears in the later years of the patient's life (Hashiba, Hashimoto, Izumoto et al., 2009). This suggests that there may be potential external or internal factors within the sample population that would require further research into the aetiology of meningioma presentation.

This study supports the female predisposition reported in the literature (Kang, Wei and Toh, 2019). Within both subsets, it was observed that meningiomas were predominantly found in the female population (subset 1: 67.3%; subset 2: 80%). Ethnic categorisation revealed a high incidence of meningiomas in the African population within subset 1, contrary to subset 2, which reported a high incidence within the Indian population. This suggests that there may be an ethnic predisposition in terms of single and multiple meningiomas; however, due to the small sample size and specificity of the inclusion criteria, there is insufficient evidence to propose an ethnic basis.

4.3 Histological grading

As reported in the literature, the Grade I meningioma are the most common histological grade (Table 2.7; page 46; Chapter 2). The present study agreed with the literature reporting an incidence of 75.8 % of subset 1. Additionally, we report a high incidence of atypical and malignant grade meningiomas within the male population. This suggested that although females are more susceptible to developing meningiomas, these are more likely to be benign, however malignant meningiomas are more common in males. Statistical tests (Fisher's exact test) revealed statistically significant relationships between WHO Grade I and sex ($p = 0.003$) as well as Grade II and sex ($p = 0.041$). In terms of categorising the histological grade according to anatomical location, it was evident that due to the large number of meningiomas within the supratentorial region, this region would display a large amount of variation amongst the histological subtypes. It was interesting to note that the malignant subtype was solely found in the supratentorial region. The findings reported may be due to factors such as the number of arachnoid cap cells in the supratentorial region and the superior and inferior sagittal sinuses (Bhat, Wani, Kirmani et al. 2014).

4.4 Anatomical location

Within both subsets, it was noted that meningiomas were found mainly in the supratentorial region (subset 1: 57.2%; subset 2: 91.7%). Both subsets agreed with the literature reviewed, which reported high incidences of meningiomas within the supratentorial region (Table 2.8; page 48; Chapter 2) (Pereira et al., 2019). In terms of categorisation according to sex, within subset 1, it was observed that the male population harboured mostly supratentorial meningiomas (75% of males). The posterior fossa has been reported as the least common site for meningioma formation, with a weighted mean of 16.2% (Table 2.8; page 49; Chapter 2). The present study noted no cases of multiple meningiomas within the posterior fossa in subset 2 and 10.2% in subset 1. This lower percentage may be attributed to the specificity of the inclusion criteria or due to location-based factors of the meningioma, such as interactions with the surrounding neurovascular structures in relation to it. Anatomical subregions identified as meningioma 'hotspots' included the convexity, parafalx and sphenoidal wings within subset 1. Subset 2 reported the convexity and parasagittal subregions as areas for potential multiple meningioma formation. A possible basis behind these sites may be due to the overall area covered by these regions as well as the number of arachnoid cap cells present (Bhat, Wani, Kirmani et al., 2014).

4.5 Side location of the meningioma

Regarding the side locations, within subset 1, there was an almost equal incidence of meningiomas in the left (36.7%) and right (38.8%) sides observed, whilst subset 2 noted meningiomas found mainly in the right side of the cranial vault. Within subset 1, it was observed that the male population reported 50% of the meningiomas to be located on the right side as opposed to the left side, reporting only 31.2%. This suggests that symptoms of meningiomas in males (such as poor motor function or absence of touch) may be more likely observed in the left side of the body due to the contralateral control of the brain resulting from compression of the brain (Mainio, Hakko, Niemela et al., 2003).

4.6 Tumour volume

Meningioma volume was calculated utilising the planimetry method outlined by Ishi, Terasaka, Yamaguchi et al. (2016), which calculated the sum of the surface area of each MRI slice showing the meningioma multiplied by the slice thickness (1 mm). This methodology provided a more accurate representation of the tumour since the meningiomas are not necessarily spherical in certain regions (meningiomas observed in the skull base region and along the calvarium were noted to grow around the osteological structures), which would prove measurements using a spherical volume or maximum tumour diameter as an appropriate volume method calculation.

When categorising the meningioma volume according to anatomical location, the present study notes meningiomas that were larger than the literature reviewed (Table 1.6; page 14; Chapter 1). This may be primarily attributed to the specificity of the inclusion criteria, which only investigated patients referred for preoperative embolisation, which only included patients presenting with meningiomas that were symptomatic and required endovascular intervention. Comparisons according to sex revealed that the male population reported significantly larger tumour volumes than females (Ranksum test; $p = 0.001$). This, coupled with the observations regarding the histological grading, highlighted that although females are more likely to develop meningiomas; these tumours are usually benign and smaller in comparison to males. Ethnic categorisation revealed a statistical difference between tumour volume in the African and Indian populations (Kruskal-Willis test; $p = 0.001$). However, due to the smaller sample size of the Indian population (n = 18) in relation to the African population (n = 73), an ethnic basis behind meningioma volume is not suggested. Subset 2 revealed a smaller tumour volume of 43.9 cm^3 compared to subset 1. This may be attributed to the difference in sample sizes between the two subsets. It was noted that in the cases of multiple meningiomas, there usually was a single large tumour (volume greater

than 40.0 cm^3), and the additional meningiomas were smaller (except for patient 5). However, these may be due to the anatomical location of the meningiomas.

4.7 Vascularity of the meningioma

The vascularity of the meningiomas was quantified using measurements taken from the sagittal and coronal sections of the fine slice (1 mm slice thickness) post-contrast MRI and DSA. The borders of tumoral blush (observed in the early arterial phase of the DSA) were measured, and the surface area was proportionate to the maximum surface area of the meningioma (observed in the MRI images). As mentioned previously, since the meningiomas observed are not necessarily spherical, it proved vital to measure the blood supply on a three-dimensional basis. This methodology has not been encountered before in the literature to compare the vascularity of the meningioma; however, studies conducted by Jensen-Kondering, Helle, Lindner et al. (2019) and Uetani, Akter, Hirai et al. (2013) investigated the arterial supply of meningiomas using arterial spin labelling and three-dimensional magnetic resonance angiography, respectively.

Within subset 1, the common arterial feeders observed in the supratentorial region was the right ICA (21.4% of supratentorial meningiomas) and left ECA (21.4% of supratentorial meningiomas). The skull base meningiomas were observed to be primarily supplied by the ICAs (right ICA: 31.3% of skull base meningiomas; left ICA: 31.3% of skull base meningiomas). These findings supported the findings of Jensen-Kondering, Helle, Lindner et al. (2019) and Uetani, Akter, Hirai et al. (2013).

The arterial supply to meningiomas in subset 2 was only measured in the sagittal plane due to the superimposition of the tumoral blush observed in the coronal plane. This subset is comprised mainly of meningiomas in the supratentorial region as well as on the right side. Therefore, it was expected that the arterial supply would primarily be sourced from the ECAs (right ECA: 3 meningiomas; left ECA: 2 meningiomas). These findings agreed with the results from subset 1.

The results highlighted in the present study may be likely due to the relation of these feeder vessels in relation to the meningiomas. The ICAs enter the cranial cavity in the petrous portion of the temporal bone before forming the arterial circle of Willis (Moore, Dally and Agur 2014). Within this region of the middle cranial fossa, tumours would be more likely to parasitise the arterial supply from the ICA rather than the ECA (more specifically, the middle meningeal artery and dural branches of the occipital artery), which branches travel along the calvarium (Gray and Standring, 2016). The large number of feeder vessels noted may be likely due to the larger tumour

volumes noted. Once a tumour enters a neovascular phase of growth, there is an increase in angiogenesis in which there is a rapid growth of the tumour due to access to the host arterial supply (Pistolesi, Boldrini, Gisfredi et al., 2004).

4.8 Limitations

This study investigated the anatomical basis of intracranial meningiomas referred for preoperative embolisation. Patient data were obtained from the Inkosi Albert Luthuli Central Hospital, which is a regional public hospital in the KwaZulu-Natal province.

Due to the small sample size, there was insufficient evidence to investigate and describe the anatomical features of meningiomas within the posterior fossa (n = 10). The commonalities have been described in the study in an attempt to add to the body of literature present.

Another limitation experienced was the patient cohort extending to 2011. An older software was used for radiographic imaging; some of the DSAs did not clearly depict the exact branches of the principle vessels that supplied meningiomas. This resulted in the present study only reporting on the vascularity of the meningiomas in terms of either the ICA, ECA or vertebral system of arteries.

4.9 Recommendations

Due to the large cohort of patients from the public health sector at the Inkosi Albert Luthuli Central Hospital, further studies using a sample population from both private and public medical institutions may shed more light on the demographic profile and anatomy of meningiomas within South Africa.

A greater focus on the arterial supply of meningiomas would prove useful in future studies. A prospective study using imaging modalities with more precise image quality, focussing on the exact branches of the feeder vessels of meningiomas, would provide precise quantification of the vascularity of meningiomas.

Since the present study only investigated patients referred for preoperative embolisation, a cohort of patients not referred for preoperative embolisation could be studied in conjunction with the patients referred for preoperative embolisation. Findings from a study of this calibre have the potential to highlight similarities and differences that may exist between these two subsets in terms of the anatomy and vascularity of meningiomas within a South African setting.

Due to the rarity of posterior fossa meningiomas, future research could possibly increase the sample size or investigate specifically the anatomy of the posterior fossa and possibly the other skull base meningiomas.

The possible impact of meningiomas on the feeder vessel anatomy in terms of vessel diameter would also be an area of interest in future research. This would entail an investigation into meningiomas that are found in either the left or right cranial hemisphere and the feeder vessel diameter. The vessel diameter would then be compared to the same vessel on the contralateral side as well as after the surgical resection. The finding from a study of this nature may quantify the effect of meningiomas on the vascular system during meningioma presentation and after surgical resection.

4.10 Conclusion

Preoperative embolisation of intracranial meningiomas has been proven to lower the risk of intraoperative and postoperative complications during tumour resection. This highlights the importance of a strong understanding of the vasculature of meningiomas. The present study aimed to investigate the anatomical features of intracranial meningiomas referred for preoperative embolisation focussing on the variations present in terms of the anatomical location, laterality, tumour volume and the associated blood supply. Additionally, this study proposes a methodology of quantifying the vasculature of the meningioma in an attempt to assess the primary and secondary feeders. Results from this investigation within a select South African population has the potential to assist the endovascular surgeon and clinician by providing a reference framework of the variant anatomy present.

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ANNEXURE A
PROVISIONAL ETHICAL APPROVAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

12 November 2020

Mr Ezra Earl Anirudh (216007050)
School of Lab Medicine & Medical Science
Westville

Dear Mr Anirudh,

Protocol reference number: BREC/00001934/2020
Project title: An anatomical investigation of intracranial meningiomas
Degree: Bachelor of Medical Science Masters

PROVISIONAL APPROVAL – Expedited Application

A sub-committee of the Biomedical Research Ethics Committee has noted and considered your application received on 18 September 2020.

The study is given PROVISIONAL APPROVAL pending:

- Gatekeeper permissions.

Only when full ethical approval is given, may the study begin. Full ethics approval has not been given at this stage. **PLEASE NOTE:** Provisional approval is valid for 6 months only – should we not hear from you during this time – the study will be closed and reapplication will need to be made. Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

Yours sincerely

[redacted]

.....

Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx
Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

ANNEXURE B
SITE PERMISSION

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

DIRECTORATE:
Office of The Medical Manager
IALCH

17 November 2020

Mr E E Anirudh (216007050)
School of Lab Medicine & Medical Science
Westville

Dear Mr Anirudh

Re: Approved Research: Ref No: BREC/00001934/2020: An anatomical investigation of intracranial meningiomas.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr L P Mtshali
Medical Manager

pp Dr A Harichandpersad
Clinical Care Manager

Fighting Disease, Fighting Poverty, Giving Hope

ANNEXURE C
KWAZULU-NATAL
DEPARTMENT OF HEALTH APPROVAL

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202011_025

Dear Mr EE Anirudh
(UKZN)

Approval of research

1. The research proposal titled **'An anatomical investigation of intracranial meningiomas'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely
([redacted])
Dr E Lutge
Chairperson, Health Research Committee
Date: 27/11/2020.

ANNEXURE D
FULL ETHICAL APPROVAL

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

14 December 2020

Mr Ezra Earl Anirudh (216007050)
School of Lab Med & Medical Sc
Westville

Dear Mr Anirudh,

Protocol reference number: BREC/00001934/2020
Project title: An anatomical investigation of intracranial meningiomas
Degree: MMedSci

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 14 December 2020. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site. Updated ethics certificates must be submitted to BREC by 31 March 2021.

This approval is subject to national and UKZN lockdown regulations dated 10th November 2020, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Lockdown_Level_1_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 14 December 2020. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 09 February 2021.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

INSPIRING GREATNESS

ANNEXURE E
ETHICS CERTIFICATES

TRREE

Zertifikat
Certificat
Certificado
Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Ezra Earl Anirudh

a complété avec succès - has successfully completed

Introduction to Research Ethics

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

[redacted]

October 11, 2018

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH Continuing Education Program (5 Credits)
Programme de Formation Continue (5 Crédits)

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[REV : 20170310]

TRREE

Zertifikat
Certificat
Certificado
Certificate

Promouvoir les plus hauts standards éthiques dans la protection des participants à la recherche biomédicale
Promoting the highest ethical standards in the protection of biomedical research participants

Clinical Trials Centre
The University of Hong Kong

Certificat de formation - Training Certificate

Ce document atteste que - this document certifies that

Ezra Earl Anirudh

a complété avec succès - has successfully completed

South Africa

du programme de formation TRREE en évaluation éthique de la recherche
of the TRREE training programme in research ethics evaluation

[redacted]

Release Date: 2019/01/15

Professeur Dominique Sprumont
Coordinateur TRREE Coordinator

FMH Continuing Education Program (5 Credits)
Programme de Formation Continue (5 Crédits)

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[REV : 20170310]

ANNEXURE F
STATISTICAL ANALYSIS

Subset 1:

Descriptive statistics

	Overall (N=98)
Age	
Mean±SD(CV%)	48.1±14.0 (29.2)
Median(Q1–Q3)	49.0 (38.0–58.0)
Min-Max	15.0–77.0
Sex	
Female	66 (67.3%)
Male	32 (32.7%)
Race	
African	73 (74.5%)
Coloured	2 (2.0%)
Indian	18 (18.4%)
White	5 (5.1%)
Anatomical location	
Posterior fossa	10 (10.2%)
Skull base	32 (32.7%)
Supratentorial	56 (57.1%)
Laterality	
Left	36 (36.7%)
Midline	24 (24.5%)
Right	38 (38.8%)
Subregion	
Cerebellar convexity	1 (1.0%)
Cerebellopontine Angle	1 (1.0%)
Convexity (Ant 1/3)	15 (15.3%)
Convexity (Mid 1/3)	11 (11.2%)
Convexity (Post 1/3)	3 (3.1%)
Falco-tentorial	1 (1.0%)

	Overall (N=98)
Intraorbital	1 (1.0%)
Intraventricular (periventricular)	1 (1.0%)
Intraventricular (Posterior horn)	1 (1.0%)
Intraventricular (trigone)	1 (1.0%)
Olfactory Groove	13 (13.3%)
Parafalx (Ant 1/3)	4 (4.1%)
Parafalx (Mid 1/3)	7 (7.1%)
Parafalx (Post 1/3)	3 (3.1%)
Parasagittal (Ant 1/3)	2 (2.0%)
Parasagittal (Mid 1/3)	4 (4.1%)
Parasagittal (Post 1/3)	4 (4.1%)
Petroclival	2 (2.0%)
Spheno-Orbital	1 (1.0%)
Sphenoid Wing	15 (15.3%)
Suprasellar	1 (1.0%)
Tentorial	5 (5.1%)
Tuberculum Sellae	1 (1.0%)

Inter-rater reliability

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  ICC1: Each target is rated by a different judge and the
        judges are selected at random.
  ICC2: A RANDOM sample of k judges rate each target.The
        measure is one of absolute agreement in the ratings.
  ICC3:  A FIXED set of k judges rate each target. There is
        no generalization to a larger population of judges.
  ICC1k, ICC2k, ICC3K reflect the means of k raters.
  Reliability interpretation:  <0.5         -Poor
                               0.5-<0.75    -Moderate
                               0.75-<0.9    -Good
                               >=0.90       -Excellent

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Intraclass correlations
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Call: ICC(x = data.Interraters.wide, missing = TRUE, alpha = 0.05,
    lmer = TRUE, check.keys = FALSE)

Intraclass correlation coefficients
                         type  ICC   F df1 df2       p lower bound upper bound
Single_fixed_raters      ICC3 0.99 342  29  29 6.7e-30        0.99           1

 Number of subjects = 30     Number of Judges =  2
-----
```

```
RATED:
Interobserver & Ezra
-----
```

Intra-rater reliability

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Intraclass correlations
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
Call: ICC(x = data.Interraters.wide, missing = TRUE, alpha = 0.05,
    lmer = TRUE, check.keys = FALSE)

Intraclass correlation coefficients
                         type ICC    F df1 df2        p lower bound upper bound
Single_fixed_raters      ICC3   1 7230  97 194 2.7e-307           1           1

 Number of subjects = 98     Number of Judges =  3
-----
RATED:
Volume_cm3_Time.1, Volume_cm3_Time.2 & Volume_cm3_Time.3
-----
```

Categorisation according to sex

Sex	Female (N=66)	Male (N=32)	p-value	Overall (N=98)
Anatomical location			0.012	
Posterior fossa	6 (9.1%)	4 (12.5%)	Chisq.	10 (10.2%)
Skull base	28 (42.4%)	4 (12.5%)		32 (32.7%)
Supratentorial	32 (48.5%)	24 (75.0%)		56 (57.1%)
Laterality			0.276	
Left	26 (39.4%)	10 (31.2%)	Chisq.	36 (36.7%)
Midline	18 (27.3%)	6 (18.8%)		24 (24.5%)
Right	22 (33.3%)	16 (50.0%)		38 (38.8%)
Volume cm3			0.001	
Median(Q1–Q3)	81.3 (49.7–115)	102 (64.1–149)	Ranksum	87.0 (53.7–128)
Min-Max	2.94–271	13.5–325		2.94–325

P-values based on non-missing cases only | Ranksum test | Kruskal-Wallis test | Chisq. test | Fisher's exact test

Categorisation according to race

Race	African (N=73)	Coloured (N=2)	Indian (N=18)	White (N=5)	p-value	Overall (N=98)
Anatomical location					0.017	
Posterior fossa	6 (8.2%)	1 (50.0%)	2 (11.1%)	1 (20.0%)	Fisher's	10 (10.2%)
Skull base	25 (34.2%)	0 (0%)	3 (16.7%)	4 (80.0%)		32 (32.7%)
Supratentorial	42 (57.5%)	1 (50.0%)	13 (72.2%)	0 (0%)		56 (57.1%)
Laterality					0.931	
Left	26 (35.6%)	1 (50.0%)	7 (38.9%)	2 (40.0%)	Fisher's	36 (36.7%)
Midline	19 (26.0%)	0 (0%)	3 (16.7%)	2 (40.0%)		24 (24.5%)
Right	28 (38.4%)	1 (50.0%)	8 (44.4%)	1 (20.0%)		38 (38.8%)
Volume cm3					<0.001	
Mean±SD (CV%)	109±61.9 (56.5)	58.1±36.9 (63.5)	55.2±33.3 (60.3)	78.2±51.5 (65.8)	delete row	96.9±60.7 (62.7)
Median (Q1–Q3)	100 (69.8–143)	57.7 (24.4–91.2)	46.9 (31.1–64.3)	86.4 (49.4–102)	Kruskal	87.0 (53.7–128)
Min–Max	11.7–325	24.3–93.1	12.2–157	2.94–152		2.94–325

P-values based on non-missing cases only | Ranksum test | Kruskal-Wallis test | Chisq. test | Fisher's exact test

Tumour volume according to anatomical location

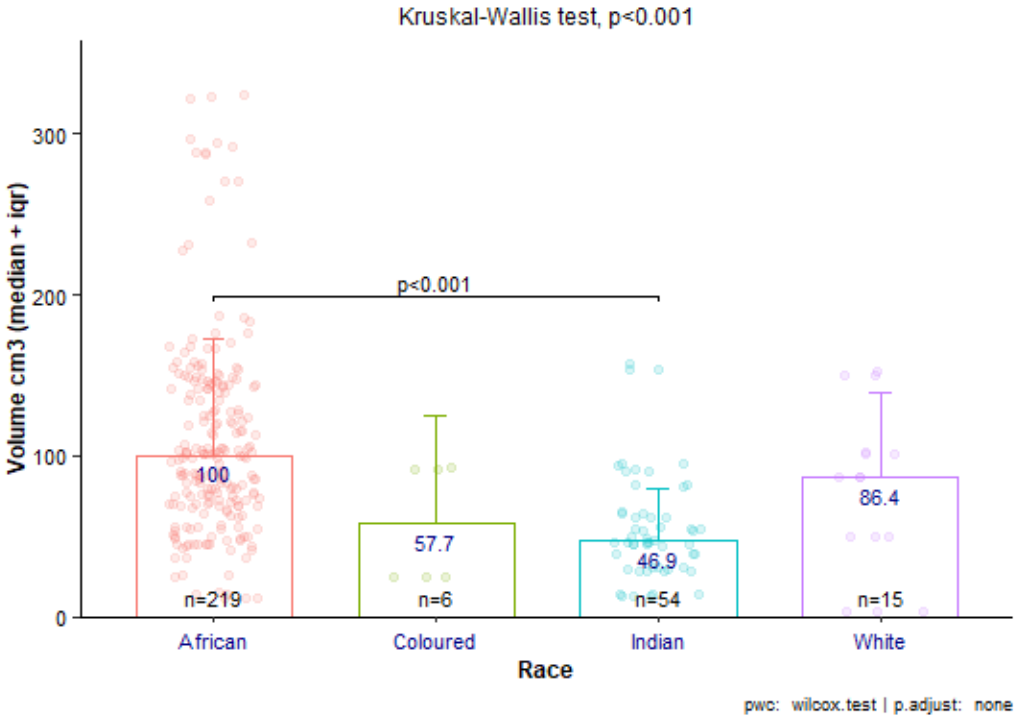
Anatomical location	Posterior fossa (N=30)	Skull base (N=96)	Supratentorial (N=168)	p-value	Overall (N=294)
Volume cm3				0.061	
Median (Q1–Q3)	65.8 (43.4–102)	83.2 (52.9–122)	90.9 (54.8–135)	Kruskal	87.0 (53.7–128)
Min–Max	24.3–146	2.94–289	12.2–325		2.94–325

P-values based on non-missing cases only | Ranksum test | Kruskal-Wallis test | Chisq. test | Fisher's exact test

Tumour volume according to laterality

Laterality	Left (N=108)	Midline (N=72)	Right (N=114)	p-value	Overall (N=294)
Volume cm3				0.122	
Median (Q1–Q3)	87.0 (60.5–142)	90.3 (64.1–130)	77.0 (47.8–115)	Kruskal	87.0 (53.7–128)
Min–Max	2.94–296	11.7–289	13.5–325		2.94–325

P-values based on non-missing cases only | Ranksum test | Kruskal-Wallis test | Chisq. test | Fisher's exact test


Kruskal-Wallis test, p<0.001
Volume cm3 (median + iqr)
300
200
100
0
p<0.001
100
57.7
46.9
86.4
n=219
n=6
n=54
n=15
African
Coloured
Indian
White
Race
pwc: wilcox.test | p.adjust: none

Meningioma vascularity

Blood Vessel + Contribution	Left ECA		Left ICA		Right ECA		Right ICA		Vertebral		Overall	
	Major	Minor	Major	Minor	Major	Minor	Major	Minor	Major	Minor	Major	Minor
	(N=13)	(N=30)	(N=24)	(N=32)	(N=16)	(N=23)	(N=24)	(N=27)	(N=8)	(N=11)	(N=85)	(N=123)
Age												
Mean±SD (CV%)	51.5±13.0 (25.2)	49.0±11.1 (22.7)	47.5±14.3 (30.2)	51.6±12.7 (24.6)	45.9±14.1 (30.7)	44.9±14.4 (32.1)	44.8±16.0 (35.6)	47.4±15.5 (32.7)	46.4±13.4 (28.8)	40.8±14.5 (35.5)	46.9±14.3 (30.5)	47.8±13.6 (28.5)
Median (Q1–Q3)	54.0 (45.0–57.0)	50.0 (43.3–56.5)	49.5 (37.0–57.3)	51.0 (42.8–-61.0)	49.5 (37.0–55.8)	47.0 (36.0–55.0)	42.5 (36.3–56.5)	48.0 (39.0–56.5)	49.0 (39.3–56.3)	42.0 (32.0–50.0)	49.0 (37.0–57.0)	48.0 (39.5–57.5)
Min–Max	28.0–76.0	15.0–72.0	15.0–77.0	27.0–76.0	16.0–65.0	15.0–70.0	15.0–71.0	16.0–77.0	25.0–62.0	15.0–61.0	15.0–77.0	15.0–77.0
Sex												
Female	8 (61.5%)	21 (70.0%)	16 (66.7%)	23 (71.9%)	12 (75.0%)	11 (47.8%)	16 (66.7%)	18 (66.7%)	6 (75.0%)	4 (36.4%)	58 (68.2%)	77 (62.6%)
Male	5 (38.5%)	9 (30.0%)	8 (33.3%)	9 (28.1%)	4 (25.0%)	12 (52.2%)	8 (33.3%)	9 (33.3%)	2 (25.0%)	7 (63.6%)	27 (31.8%)	46 (37.4%)
Race												
African	11 (84.6%)	20 (66.7%)	18 (75.0%)	25 (78.1%)	10 (62.5%)	20 (87.0%)	20 (83.3%)	18 (66.7%)	4 (50.0%)	10 (90.9%)	63 (74.1%)	93 (75.6%)
Coloured	1 (7.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.4%)	1 (0.8%)
Indian	1 (7.7%)	8 (26.7%)	4 (16.7%)	5 (15.6%)	4 (25.0%)	2 (8.7%)	2 (8.3%)	7 (25.9%)	3 (37.5%)	1 (9.1%)	14 (16.5%)	23 (18.7%)
White	0 (0.0%)	2 (6.7%)	2 (8.3%)	1 (3.1%)	2 (12.5%)	1 (4.3%)	1 (4.2%)	2 (7.4%)	1 (12.5%)	0 (0.0%)	6 (7.1%)	6 (4.9%)
Location												
Posterior fossa	0 (0.0%)	4 (13.3%)	1 (4.2%)	3 (9.4%)	0 (0.0%)	4 (17.4%)	2 (8.3%)	0 (0.0%)	5 (62.5%)	4 (36.4%)	8 (9.4%)	15 (12.2%)
Skull base	1 (7.7%)	8 (26.7%)	10 (41.7%)	9 (28.1%)	6 (37.5%)	3 (13.0%)	10 (41.7%)	11 (40.7%)	0 (0.0%)	1 (9.1%)	27 (31.8%)	32 (26.0%)
Supratentorial	12 (92.3%)	18 (60.0%)	13 (54.2%)	20 (62.5%)	10 (62.5%)	16 (69.6%)	12 (50.0%)	16 (59.3%)	3 (37.5%)	6 (54.5%)	50 (58.8%)	76 (61.8%)

Subset 2:

Patient demographics

Aspect	Subset 2 (N = 5 patients)
Age	
Mean ± SD	44 ± 6.41
Median (Q1–Q3)	45.0 (40.0–50.0)
Min–Max	34.0–52.0
Sex	
Male	1 (20.0 %)
Female	4 (80.0 %)
Race	
Indian	4 (80.0 %)
White	1 (20.0 %)

ANNEXURE G
RAW DATA

SUBSET 1

No.	Patient ID	Age	Sex	Race	Anatomical location	Laterality	Subregion	Volume (cm3)
1	KZ 00001	64	F	Indian	Supratentorial	Left	Convexity (Ant 1/3)	31,07
								31,05
								31,17
								31,10
2	KZ 00002	36	F	African	Skull base	Left	Sphenoid Wing	164,34
								170,75
								167,17
								167,42
3	KZ 00003	37	F	African	Skull base	Midline	Olfactory Groove	64,33
								65,64
								66,54
								65,50
4	KZ 00004	47	M	Indian	Supratentorial	Midline	Parasagittal (Post 1/3)	95,18
								94,51
								94,06
								94,58
5	KZ 00005	42	F	African	Skull base	Midline	Suprasellar	11,73
								11,86
								12,07
								11,89
6	KZ 00006	21	F	African	Skull base	Midline	Olfactory Groove	173,17
								176,54
								176,53
								175,41
7	KZ 00007	65	F	African	Supratentorial	Right	Convexity (Ant 1/3)	79,74
								79,65
								79,45
								79,61
8	KZ 00008	43	F	African	Supratentorial	Left	Convexity (Mid 1/3)	55,55
								55,23
								54,88
								55,22
9	KZ 00009	61	M	African	Posterior fossa	Left	Falco-tentorial	141,93
								142,93
								143,47
								142,78
10	KZ 00010	55	F	African	Skull base	Right	Sphenoid Wing	45,39
								44,63
								44,53
								44,85

11	KZ 00011	63	F	African	Skull base	Left	Sphenoid Wing	79,10 77,75 76,72 77,85
12	KZ 00012	38	F	African	Supratentorial	Right	Convexity (Ant 1/3)	150,94 149,84 149,16 149,98
13	KZ 00013	51	F	White	Skull base	Right	Sphenoid Wing	151,79 150,15 150,33 150,76
14	KZ 00014	38	M	African	Skull base	Midline	Olfactory Groove	288,58 287,67 288,30 288,18
15	KZ 00015	27	M	African	Supratentorial	Right	Convexity (Ant 1/3)	153,18 154,03 154,40 153,87
16	KZ 00016	48	F	African	Skull base	Right	Spheno-Orbital	41,42 43,08 44,72 43,07
17	KZ 00017	15	F	African	Supratentorial	Midline	Parafalx (Ant 1/3)	258,04 270,57 270,60 266,40
18	KZ 00018	62	F	Indian	Posterior fossa	Right	Cerebellar convexity	38,68 38,43 38,94 38,68
19	KZ 00019	63	M	African	Supratentorial	Right	Convexity (Mid 1/3)	121,05 124,82 126,75 124,20
20	KZ 00020	23	M	African	Posterior fossa	Midline	Petroclival	41,39 43,22 44,09 42,90
21	KZ 00021	71	F	Coloured	Posterior fossa	Right	Cerebellopontine Angle	24,32 24,58 24,38 24,43
22	KZ 00022	58	M	African	Supratentorial	Left	Convexity (Ant 1/3)	149,65 147,32 147,30 148,09
23	KZ 00023	53	M	African	Supratentorial	Midline	Parafalx (Ant 1/3)	49,47 48,43 47,94 48,61

24	KZ 00024	57	F	African	Supratentorial	Left	Convexity (Mid 1/3)	106,00 105,06 106,53 105,87
25	KZ 00025	67	F	African	Skull base	Midline	Olfactory Groove	82,98 85,84 82,99 83,94
26	KZ 00026	43	F	African	Skull base	Midline	Olfactory Groove	83,90 83,32 85,46 84,23
27	KZ 00027	18	F	African	Skull base	Midline	Tuberculum Sellae	82,61 85,21 85,65 84,49
28	KZ 00028	28	M	African	Skull base	Left	Sphenoid Wing	101,08 103,95 104,52 103,19
29	KZ 00029	43	F	African	Supratentorial	Right	Intraventricular (periventricular)	98,63 98,22 98,11 98,32
30	KZ 00030	39	F	African	Skull base	Left	Sphenoid Wing	72,75 72,82 73,91 73,16
31	KZ 00031	54	M	African	Supratentorial	Midline	Parafalx (Ant 1/3)	89,10 90,88 89,22 89,74
32	KZ 00032	58	M	African	Posterior fossa	Right	Tentorial	68,75 68,24 68,83 68,61
33	KZ 00033	57	F	African	Supratentorial	Left	Parafalx (Mid 1/3)	25,42 25,12 25,29 25,28
34	KZ 00034	57	M	Indian	Posterior fossa	Midline	Tentorial	45,92 45,74 46,03 45,90
35	KZ 00035	42	F	African	Posterior fossa	Midline	Tentorial	144,33 145,02 145,58 144,98
36	KZ 00036	34	F	African	Skull base	Right	Sphenoid Wing	74,64 74,40 72,94 73,99

37	KZ 00037	44	F	African	Supratentorial	Right	Convexity (Mid 1/3)	98,70 99,99 101,06 99,91
38	KZ 00038	57	F	African	Supratentorial	Left	Convexity (Ant 1/3)	134,33 134,23 133,92 134,16
39	KZ 00039	25	F	African	Supratentorial	Right	Intra-ventricular (Posterior horn)	47,59 47,84 49,14 48,19
40	KZ 00040	55	F	African	Skull base	Right	Sphenoid Wing	69,93 70,20 71,15 70,43
41	KZ 00041	41	F	African	Supratentorial	Left	Convexity (Mid 1/3)	119,01 118,69 120,31 119,33
42	KZ 00042	55	F	African	Posterior fossa	Midline	Petroclival	62,01 62,71 63,34 62,69
43	KZ 00043	37	F	African	Supratentorial	Left	Convexity (Fronto-Mid 1/3)	142,20 142,16 142,51 142,29
44	KZ 00044	30	M	African	Supratentorial	Right	Convexity (parieto-Post 1/3)	324,69 323,60 322,29 323,53
45	KZ 00045	59	F	African	Supratentorial	Left	Convexity (Mid 1/3)	69,59 70,20 71,34 70,37
46	KZ 00046	58	F	African	Supratentorial	Right	Parasagittal (Ant 1/3)	102,74 103,78 104,37 103,63
47	KZ 00047	45	M	African	Supratentorial	Left	Parasagittal (Mid 1/3)	67,53 68,50 68,59 68,21
48	KZ 00048	77	F	White	Skull base	Midline	Olfactory Groove	49,60 49,36 49,47 49,47
49	KZ 00049	41	M	African	Supratentorial	Right	Convexity (Mid 1/3)	101,02 101,70 101,73 101,48

50	KZ 00050	49	M	African	Supratentorial	Left	Convexity (Post 1/3)	227,25 232,27 230,90 230,14
51	KZ 00051	51	F	African	Supratentorial	Left	Parasagittal (Post 1/3)	154,33 158,00 158,35 156,89
52	KZ 00052	66	M	African	Supratentorial	Right	Parafalx (Mid 1/3)	51,16 50,08 50,02 50,42
53	KZ 00053	72	F	African	Skull base	Midline	Olfactory Groove	123,52 125,41 125,79 124,90
54	KZ 00054	61	F	African	Supratentorial	Midline	Parafalx (Ant 1/3)	186,53 186,06 183,31 185,30
55	KZ 00055	51	M	African	Supratentorial	Right	Convexity (Ant 1/3)	127,80 127,93 128,35 128,03
56	KZ 00056	55	M	African	Supratentorial	Right	Convexity (Ant 1/3)	88,24 87,91 88,57 88,24
57	KZ 00057	30	M	African	Supratentorial	Left	Parasagittal (Mid 1/3)	74,45 75,01 75,98 75,15
58	KZ 00058	31	F	African	Posterior fossa	Right	Tentorial	100,93 101,55 100,40 100,96
59	KZ 00059	61	F	African	Skull base	Midline	Olfactory Groove	146,21 146,27 146,58 146,35
60	KZ 00060	69	F	Indian	Supratentorial	Left	Parafalx (Mid 1/3)	14,21 14,49 14,45 14,38
61	KZ 00061	38	M	African	Supratentorial	Right	Convexity (Ant 1/3)	137,61 138,65 139,24 138,50
62	KZ 00062	33	M	Indian	Supratentorial	Right	Convexity (Post 1/3)	152,97 156,81 153,46 154,41

63	KZ 00063	72	F	Indian	Supratentorial	Left	Parafalx (Post 1/3)	82,20 81,83 80,94 81,66
64	KZ 00064	52	F	White	Skull base	Left	Olfactory Groove	3,04 3,00 2,94 3,00
65	KZ 00065	50	F	Indian	Skull base	Left	Sphenoid Wing	54,69 54,03 55,34 54,69
66	KZ 00066	53	M	African	Supratentorial	Left	Convexity (Mid 1/3)	87,49 87,72 88,58 87,93
67	KZ 00067	29	M	Indian	Skull base	Right	Sphenoid Wing	45,55 44,88 43,86 44,77
68	KZ 00068	61	F	Indian	Supratentorial	Right	Convexity (Mid 1/3)	64,38 64,09 65,02 64,50
69	KZ 00069	45	F	African	Skull base	Left	Sphenoid Wing	144,42 144,18 141,97 143,53
70	KZ 00070	56	M	Indian	Supratentorial	Right	Intra-ventricular (trigone)	27,70 28,29 28,15 28,04
71	KZ 00071	70	F	African	Supratentorial	Right	Parasagittal (Mid 1/3)	115,50 115,08 113,32 114,63
72	KZ 00072	49	F	Indian	Skull base	Midline	Olfactory Groove	91,28 90,25 90,31 90,61
73	KZ 00073	36	M	African	Supratentorial	Right	Parasagittal (Ant 1/3)	166,93 167,44 168,23 167,53
74	KZ 00074	36	F	African	Skull base	Left	Sphenoid Wing	157,09 155,72 154,27 155,69
75	KZ 00075	49	M	African	Supratentorial	Right	Parafalx (Post 1/3)	113,39 114,08 113,84

								113,77
76	KZ 00076	48	F	African	Skull base	Right	Sphenoid Wing	44,98 45,08 45,00 45,02
77	KZ 00077	20	M	African	Skull base	Right	Intraorbital	14,89 13,53 13,79 14,07
78	KZ 00078	40	F	African	Skull base	Midline	Olfactory Groove	101,88 102,71 103,29 102,63
79	KZ 00079	65	F	Indian	Supratentorial	Left	Parasagittal (Mid 1/3)	45,36 45,13 45,08 45,19
80	KZ 00080	50	F	African	Skull base	Left	Sphenoid Wing	94,65 96,01 98,01 96,22
81	KZ 00081	51	F	Indian	Supratentorial	Left	Parafalx (Mid 1/3)	12,34 12,50 12,24 12,36
82	KZ 00082	51	F	African	Supratentorial	Left	Convexity (Mid 1/3)	36,41 37,14 37,00 36,85
83	KZ 00083	50	M	African	Supratentorial	Left	Convexity (Ant 1/3)	104,12 105,02 103,94 104,36
84	KZ 00084	76	F	Coloured	Supratentorial	Left	Parafalx (Post 1/3)	93,05 90,91 91,29 91,75
85	KZ 00085	42	F	White	Posterior fossa	Midline	Tentorial	101,49 100,72 102,35 101,52
86	KZ 00086	45	F	White	Skull base	Left	Sphenoid Wing	86,32 86,43 86,56 86,43
87	KZ 00087	58	F	African	Supratentorial	Left	Parafalx (Mid 1/3)	81,50 81,19 80,05 80,91
88	KZ 00088	62	F	Indian	Supratentorial	Right	Convexity (Ant 1/3)	47,76 49,95 48,90

								48,87
89	KZ 00089	44	M	African	Supratentorial	Left	Parasagittal (Post 1/3)	292,42 293,81 296,49 294,24
90	KZ 00090	36	F	African	Supratentorial	Right	Parasagittal (Post 1/3)	55,30 53,89 53,96 54,39
91	KZ 00091	69	F	African	Skull base	Midline	Olfactory Groove	77,13 75,54 76,30 76,32
92	KZ 00092	37	M	African	Supratentorial	Left	Parafalx (Mid 1/3)	148,82 149,08 150,68 149,52
93	KZ 00093	38	F	African	Supratentorial	Right	Convexity (Ant 1/3)	87,53 87,71 88,72 87,99
94	KZ 00094	48	F	Indian	Supratentorial	Left	Convexity (Mid 1/3)	62,23 62,18 62,16 62,19
95	KZ 00095	41	F	Indian	Supratentorial	Right	Convexity (Ant 1/3)	28,18 28,95 29,05 28,73
96	KZ 00096	50	M	Indian	Supratentorial	Right	Parafalx (Mid 1/3)	53,99 53,70 53,28 53,66
97	KZ 00097	16	F	African	Supratentorial	Right	Convexity (Ant 1/3)	56,80 55,50 54,45 55,58
98	KZ 00098	46	F	African	Skull base	Midline	Olfactory Groove	120,86 121,58 120,34 120,93

Meningioma Vascularity

Patient ID	Age	Sex	Race	Location	Blood Vessel	Contribution
KZ00001	64	Female	Indian	Supratentorial	Left ICA	Minor
		Female	Indian	Supratentorial	Right ICA	Minor
KZ00002	36	Female	African	Skull base	Left ICA	Minor
		Female	African	Skull base	Left ECA	Minor
KZ00003	37	Female	African	Skull base	Right ICA	Major
		Female	African	Skull base	Left ICA	Major
KZ00004	47	Male	Indian	Supratentorial	Vertebral	Minor
		Male	Indian	Supratentorial	Left ICA	Minor
		Male	Indian	Supratentorial	Left ECA	Minor
		Male	Indian	Supratentorial	Right ICA	Minor
		Male	Indian	Supratentorial	Right ECA	Minor
KZ00005	42	Female	African	Skull base	Right ICA	Major
		Female	African	Skull base	Left ICA	Minor
KZ00006	21	Female	African	Skull base	Right ICA	Major
	65	Female	African	Supratentorial	Right ICA	Major
KZ00007		Female	African	Supratentorial	Right ECA	Major
KZ00008	43	Female	African	Supratentorial	Left ICA	Minor
		Female	African	Supratentorial	Left ECA	Minor
KZ00009	61	Male	African	Posterior fossa	Left ICA	Minor
		Male	African	Posterior fossa	Vertebral	Minor
KZ00010	55	Female	African	Skull base	Right ICA	Major
		Female	African	Skull base	Right ECA	Minor
KZ00011	63	Female	African	Skull base	Left ICA	Major
		Female	African	Skull base	Left ECA	Minor
KZ00012	38	Female	African	Supratentorial	Right ICA	Major
		Female	African	Supratentorial	Right ECA	Major
KZ00013	51	Female	White	Skull base	Right ICA	Major
		Female	White	Skull base	Right ECA	Major
KZ00014	38	Male	African	Skull base	Right ICA	Major
KZ00015	27	Male	African	Supratentorial	Vertebral	Minor
		Male	African	Supratentorial	Right ICA	Minor
		Male	African	Supratentorial	Right ECA	Major
		Male	African	Supratentorial	Left ICA	Minor
KZ00016	48	Female	African	Skull base	Right ICA	Minor
		Female	African	Skull base	Right ECA	Major
KZ00017	15	Female	African	Supratentorial	Vertebral	Minor

		Female	African	Supratentorial	Right ECA	Minor
		Female	African	Supratentorial	Right ICA	Major
		Female	African	Supratentorial	Left ECA	Minor
		Female	African	Supratentorial	Left ICA	Major
KZ00018	62	Female	Indian	Posterior fossa	Vertebral	Major
KZ00019	63	Male	African	Supratentorial	Right ICA	Major
		Male	African	Supratentorial	Right ECA	Minor
KZ00020	23	Male	African	Posterior fossa	Vertebral	Minor
		Male	African	Posterior fossa	Left ICA	Major
KZ00021	71	Female	Coloured	Posterior fossa	Right ICA	Major
KZ00022	58	Male	African	Supratentorial	Right ECA	Major
		Male	African	Supratentorial	Left ICA	Major
		Male	African	Supratentorial	Left ECA	Minor
KZ00023	53	Male	African	Supratentorial	Right ICA	Minor
		Male	African	Supratentorial	Left ICA	Major
		Male	African	Supratentorial	Left ECA	Major
KZ00024	57	Female	African	Supratentorial	Left ICA	Major
		Female	African	Supratentorial	Left ECA	Major
KZ00025	67	Female	African	Skull base	Left ICA	Major
KZ00026	43	Female	African	Skull base	Right ICA	Major
		Female	African	Skull base	Left ICA	Minor
KZ00027	18	Female	African	Skull base	Right ICA	Major
		Female	African	Skull base	Right ECA	Minor
KZ00028	28	Male	African	Skull base	Left ICA	Minor
		Male	African	Skull base	Left ECA	Major
KZ00029	43	Female	African	Supratentorial	Vertebral	Major
KZ00030	39	Female	African	Skull base	Vertebral	Minor
		Female	African	Skull base	Left ICA	Minor
KZ00031	54	Male	African	Supratentorial	Right ICA	Minor
		Male	African	Supratentorial	Right ECA	Major
		Male	African	Supratentorial	Left ICA	Minor
		Male	African	Supratentorial	Left ECA	Major
KZ00032	58	Male	African	Posterior fossa	Vertebral	Minor
		Male	African	Posterior fossa	Right ECA	Minor
KZ00033	57	Female	African	Supratentorial	Left ECA	Major
		Female	African	Supratentorial	Left ICA	Minor
KZ00034	57	Male	Indian	Posterior fossa	Vertebral	Major
		Male	Indian	Posterior fossa	Left ECA	Minor
KZ00035	42	Female	African	Posterior fossa	Left ECA	Minor

		Female	African	Posterior fossa	Vertebral	Minor
KZ00036	34	Female	African	Skull base	Right ICA	Major
		Female	African	Skull base	Right ECA	Major
KZ00037	44	Female	African	Supratentorial	Right ICA	Minor
		Female	African	Supratentorial	Right ECA	Major
KZ00038	57	Female	African	Supratentorial	Left ECA	Major
		Female	African	Supratentorial	Left ICA	Minor
KZ00039	25	Female	African	Supratentorial	Vertebral	Major
		Female	African	Supratentorial	Right ICA	Minor
KZ00040	55	Female	African	Skull base	Right ICA	Minor
		Female	African	Skull base	Right ECA	Major
KZ00041	41	Female	African	Supratentorial	Left ICA	Minor
		Female	African	Supratentorial	Left ECA	Major
KZ00042	55	Female	African	Posterior fossa	Right ECA	Minor
		Female	African	Posterior fossa	Vertebral	Major
		Female	African	Posterior fossa	Left ICA	Minor
		Female	African	Posterior fossa	Left ECA	Minor
KZ00043	37	Female	African	Supratentorial	Left ICA	Major
		Female	African	Supratentorial	Left ECA	Minor
KZ00044	30	Male	African	Supratentorial	Right ICA	Major
		Male	African	Supratentorial	Right ECA	Minor
KZ00045	59	Female	African	Supratentorial	Left ECA	Minor
		Female	African	Supratentorial	Left ICA	Minor
KZ00046	58	Female	African	Supratentorial	Right ECA	Minor
KZ00047	45	Male	African	Supratentorial	Left ICA	Minor
		Male	African	Supratentorial	Left ECA	Major
KZ00048	77	Female	White	Skull base	Right ICA	Minor
		Female	White	Skull base	Left ICA	Major
KZ00049	41	Male	African	Supratentorial	Right ICA	Minor
		Male	African	Supratentorial	Right ECA	Minor
KZ00050	49	Male	African	Supratentorial	Right ICA	Major
		Male	African	Supratentorial	Vertebral	Minor
		Male	African	Supratentorial	Left ICA	Major
		Male	African	Supratentorial	Left ECA	Minor
KZ00051	51	Female	African	Supratentorial	Vertebral	Minor
		Female	African	Supratentorial	Left ICA	Minor
		Female	African	Supratentorial	Left ECA	Minor
KZ00052	66	Male	African	Supratentorial	Right ICA	Major
		Male	African	Supratentorial	Right ECA	Minor
KZ00053	72	Female	African	Skull base	Left ICA	Minor

KZ00054	61	Female	African	Supratentorial	Left ICA	Minor
		Female	African	Supratentorial	Left ECA	Minor
KZ00055	51	Male	African	Supratentorial	Right ECA	Minor
		Male	African	Supratentorial	Right ICA	Major
KZ00056	55	Male	African	Supratentorial	Right ICA	Minor
		Male	African	Supratentorial	Right ECA	Minor
KZ00057	30	Male	African	Supratentorial	Left ECA	Major
		Male	African	Supratentorial	Left ICA	Major
KZ00058	31	Female	African	Posterior fossa	Vertebral	Major
		Female	African	Posterior fossa	Right ICA	Major
		Female	African	Posterior fossa	Right ECA	Minor
KZ00059	61	Female	African	Skull base	Left ICA	Minor
		Female	African	Skull base	Left ECA	Minor
		Female	African	Skull base	Right ICA	Major
KZ00060	69	Female	Indian	Supratentorial	Right ICA	Major
		Female	Indian	Supratentorial	Left ICA	Minor
KZ00061	38	Male	African	Supratentorial	Left ICA	Major
		Male	African	Supratentorial	Right ICA	Major
		Male	African	Supratentorial	Right ECA	Minor
KZ00062	33	Male	Indian	Supratentorial	Right ICA	Minor
		Male	Indian	Supratentorial	Right ECA	Minor
KZ00063	72	Female	Indian	Supratentorial	Left ICA	Minor
		Female	Indian	Supratentorial	Left ECA	Minor
KZ00064	52	Female	White	Skull base	Right ICA	Minor
		Female	White	Skull base	Right ECA	Major
KZ00065	50	Female	Indian	Skull base	Left ICA	Major
		Female	Indian	Skull base	Left ECA	Minor
KZ00066	53	Male	African	Supratentorial	Left ICA	Minor
		Male	African	Supratentorial	Left ECA	Minor
KZ00067	29	Male	Indian	Skull base	Right ICA	Minor
		Male	Indian	Skull base	Right ECA	Major
KZ00068	61	Female	Indian	Supratentorial	Right ICA	Minor
		Female	Indian	Supratentorial	Right ECA	Major
KZ00069	45	Female	African	Skull base	Left ICA	Major
		Female	African	Skull base	Left ECA	Minor
KZ00070	56	Male	Indian	Supratentorial	Vertebral	Major
KZ00071	70	Female	African	Supratentorial	Right ICA	Minor
		Female	African	Supratentorial	Right ECA	Minor
KZ00072	49	Female	Indian	Skull base	Right ICA	Minor
		Female	Indian	Skull base	Left ICA	Major

KZ00073	36	Male	African	Supratentorial	Right ECA	Minor
		Male	African	Supratentorial	Left ICA	Major
		Male	African	Supratentorial	Left ECA	Minor
KZ00074	36	Female	African	Skull base	Left ICA	Major
		Female	African	Skull base	Left ECA	Minor
KZ00075	49	Male	African	Supratentorial	Right ICA	Major
		Male	African	Supratentorial	Right ECA	Minor
KZ00076	48	Female	African	Skull base	Right ICA	Minor
		Female	African	Skull base	Right ECA	Minor
KZ00077	20	Male	African	Skull base	Right ICA	Minor
KZ00078	40	Female	African	Skull base	Right ICA	Minor
KZ00079	65	Female	Indian	Supratentorial	Left ECA	Minor
		Female	Indian	Supratentorial	Left ICA	Major
KZ00080	50	Female	African	Skull base	Left ICA	Major
		Female	African	Skull base	Left ECA	Minor
KZ00081	51	Female	Indian	Supratentorial	Left ICA	Major
		Female	Indian	Supratentorial	Left ECA	Minor
KZ00082	51	Female	African	Supratentorial	Left ICA	Minor
		Female	African	Supratentorial	Left ECA	Major
KZ00083	50	Male	African	Supratentorial	Left ICA	Major
		Male	African	Supratentorial	Left ECA	Minor
KZ00084	76	Female	Coloured	Supratentorial	Left ICA	Minor
		Female	Coloured	Supratentorial	Left ECA	Major
KZ00085	42	Female	White	Posterior fossa	Vertebral	Major
		Female	White	Posterior fossa	Left ECA	Minor
		Female	White	Posterior fossa	Left ICA	Minor
		Female	White	Posterior fossa	Right ECA	Minor
KZ00086	45	Female	White	Skull base	Left ICA	Major
		Female	White	Skull base	Left ECA	Minor
KZ00087	58	Female	African	Supratentorial	Right ICA	Minor
		Female	African	Supratentorial	Left ICA	Major
		Female	African	Supratentorial	Left ECA	Major
KZ00088	62	Female	Indian	Supratentorial	Right ICA	Minor
		Female	Indian	Supratentorial	Left ECA	Major
		Female	Indian	Supratentorial	Right ECA	Major
KZ00089	44	Male	African	Supratentorial	Left ICA	Minor
		Male	African	Supratentorial	Left ECA	Minor
KZ00090	36	Female	African	Supratentorial	Right ECA	Minor
KZ00091	69	Female	African	Skull base	Left ICA	Minor
		Female	African	Skull base	Right ICA	Minor

KZ00092	37	Male	African	Supratentorial	Vertebral	Minor
		Male	African	Supratentorial	Left ICA	Minor
KZ00093	38	Female	African	Supratentorial	Right ICA	Minor
		Female	African	Supratentorial	Right ECA	Minor
KZ00094	48	Female	Indian	Supratentorial	Left ICA	Minor
		Female	Indian	Supratentorial	Left ECA	Minor
KZ00095	41	Female	Indian	Supratentorial	Right ICA	Major
		Female	Indian	Supratentorial	Right ECA	Major
KZ00096	50	Male	Indian	Supratentorial	Left ECA	Minor
KZ00097	16	Female	African	Supratentorial	Right ICA	Minor
		Female	African	Supratentorial	Right ECA	Major
KZ00098	46	Female	African	Skull base	Right ICA	Minor
		Female	African	Skull base	Left ICA	Minor

SUBSET 2

No.	Patient ID	Age	Sex	Race	Anatomical location	Laterality	Sub-region	Volume (cm3)	Blood Vessel	Contribution
1	KZ02001	45	F	Indian	Supratentorial	Right	Convexity (Ant 1/3)	34,63	Right ICA	Intermediate
								34,57		
								34,46	Right ECA	Intermediate
								34,55		
					Supratentorial	Left	Parasagittal (Mid 1/3)	17,60	Right ICA	Intermediate
								18,66		
								19,16	Right ECA	Intermediate
								18,47		
2	KZ02002	49	F	White	Supratentorial	Left	Convexity (Ant 1/3)	42,53	Left ICA	Minor
								42,31		
								42,59		
								42,48		
					Supratentorial	Mid-line	Parafalx (Mid 1/3)	37,29	Right ECA	Minor
								37,18		
								37,56	Left ICA	Intermediate
								37,34		

3	KZ02003	40	M	Indian	Skull base	Right	Sphenoid Wing	6,45	Right ICA	Major
								6,57		
								6,39		
								6,47		
					Supratentorial	Right	Parafalx (Post 1/3)	9,74	Right ICA	Major
								10,02		
								7,58	Right ECA	Intermediate
								9,12		
					Supratentorial	Right	Parafalx (Ant 1/3)	126,77	Right ICA	Intermediate
								126,96		
								128,68	Right ECA	Major
								127,47		
4	KZ02004	52	F	Indian	Supratentorial	Right	Parasagittal (Ant 1/3)	44,38	Right ICA	Intermediate
								44,60		
								44,46	Right ECA	Intermediate
								44,48		
					Supratentorial	Right	Convexity (Ant 1/3)	10,40	Right ICA	Intermediate
								10,28		

								10,42	Right ECA	Major
								10,37		
					Supratentorial	Mid-line	Parasagittal (Post 1/3)	25,71	Right ICA	Intermediate
								28,08	Right ECA	Major
								27,78	Vertebral	Intermediate
								27,19		
5	KZ02005	34	F	Indian	Supratentorial	Left	Parasagittal (Ant 1/3)	118,12	Left ICA	Minor
								117,64		
								117,79	Left ECA	Intermediate
								117,85		
					Supratentorial	Left	Convexity (Temporal)	13,57	Left ECA	Major
								13,76		
								13,82		
								13,72		

ANNEXURE H
TURNITIN ORIGINALITY REPORT

An anatomical investigation of intracranial meningiomas

ORIGINALITY REPORT

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