UNIVERSITY OF LIVERPOOL

Residual meningioma: Volumetric growth and progression following surgical resection

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Contents

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Abstract

Introduction: Meningiomas are the most common primary brain tumour, with the primary management strategy being surgery. A residual tumour is identified in approximately 25% of operated meningioma. They have a higher progression rate than if no residual is present. The precise growth rates of these tumours on long-term follow up, using accurate and verified 3D volume measuring tools, remains unclear. This uncertainty has implications for patient management, and stratification of treatment paradigms. Previous literature has used small sample sizes, and different definitions to define an increase in meningioma volume after surgery. There is a need for a large study delineating the volumetric growth of residual meningioma, using uniform progression definitions. The aims of this thesis were to conduct a systematic review, followed by a highly powered study measuring the volumetric growth of residual meningioma.

Methods: A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, using six scientific databases. After audit approval, a retrospective cohort study of 236 patients with residual meningioma was completed, analysing the tumour volume using manual segmentation at every MRI follow up scan, and conducted non-linear regression analysis of the growth trajectories of residual tumour.

Results: The systematic review revealed only four studies available in the literature, with variable growth rates and factors associated with growth identified. The retrospective study revealed a low rate of tumour growth after surgery, both in absolute and relative tumour volume (0.11cm^3 and 4.3% per year respectively). More than half patients (55.9%) on long-term follow up demonstrated sufficient volumetric growth to satisfy a definition of tumour progression, and most patients were managed conservatively for this (73.7%). Multivariable analysis revealed skull base location (Hazard ratio [HR] 1.58, 95% Confidence interval (CI) 1.02-2.44), adjuvant *f*RT (HR 1.72, 95% CI 1.03-2.89) and elevated Ki-67 index (HR 3.62, 95% CI 1.25-10.48) to be associated with high volumetric growth. Regression analysis revealed that most residual tumours exhibit exponential, logistic, and gompertz growth patterns.

Conclusions: Residual meningioma is a commonly encountered clinical entity, but volumetric growth rates are scarcely reported. In our retrospective cohort of 236 meningiomas, the absolute and relative growth rate was low, yet over a long period of follow up most met a Response Assessment in Neuro-Oncology (RANO) definition of progression. Further clinical studies of WHO grade 2 meningiomas, and studies that use a uniform growth definition are required to delineate growth rates, and substantiate the findings of this work.

Dissemination

Conferences and meetings:

1. December 2020- Brain Tumour North West Annual Retreat (Virtual)- Oral presentation
2. September 2021- Pharmacology Postgraduate Seminar day (Virtual)- Oral presentation
3. September 2021- European Association of Neuro-Oncology 16th Annual meeting (Virtual)- E-poster presentation.

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AD	Autosomal dominant
AGR	Absolute growth rate
ATK1	v-akt murine thymoma viral oncogene homolog 1
CNAs	Copy Number Alterations
CNS	Central nervous system
CT	Computed tomography
DVT	Deep vein thrombosis
EANO	European Association of Neuro-Oncology
ECA	External carotid artery
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-1308	European Organisation for Research and Treatment of Cancer-1308 trial
FDA	Food and drug administration
FLAIR	Fluid-attenuated inversion recovery
GTR	Gross-total resection
Gy	Grey
HRQoL	Health related Quality of Life
HR	Hazard ratio
HRT	Hormone replacement therapy
Ki-67	Marker Of Proliferation Ki-67
KLF4	Kruppel-like factor 4
mTOR	mammalian Target Of Rapamycin
Merlin	Moesin-Ezrin-Radixin-Like Protein
MMA	Middle meningeal artery
MRI	Magnetic resonance imaging
nBCA	n-butyl cyanoacrylate
NF2	Neurofibromatosis type 2

NGS	Next Generation Sequencing
LOH	Loss of Heterozygosity
PACS	Picture archive and communications system
PE	Pulmonary embolism
PI3K	Phosphatidylinositol-3-kinase
PVA	Polyvinyl alcohol
QoL	Quality of Life
ROAM	Radiation versus Observation following surgical resection of Atypical Meningioma
RCT	Randomised Control Trial
RFS	Recurrence free survival
RGR	Relative Growth rate
RR	Relative risk
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
RTK	Receptor Tyrosine Kinase
SRS	Stereotactic Radiosurgery
STR	Sub-total resection
TERT	Telomerase reverse transcriptase
TRAF	Tumor necrosis factor (TNF) receptor associated factor 7
UK	United Kingdom
VOMIT	Victims of modern imaging technology
VTE	Venous thromboembolism
WHO	World Health Organisation

Chapter 1: Introduction to meningiomas, residual, and volumetrics

1.1. Background

First described by American Neurosurgeon Harvey Cushing in a 1922 publication in the journal *Brain*, a meningioma describes tumours that originate from the meningeal (dural) coverings of the brain and spinal cord[1, 2]. Meningiomas are the most common primary intracranial tumour and of the central nervous system (CNS), and account for 38.3% of primary brain tumours[3-5]. Surgery is the first-choice treatment strategy for symptomatic meningioma. Some meningioma are unable to be completely removed during surgery. This is referred to as a 'subtotal resection', leaving residual solid tumour. Dynamic changes in meningioma size over time can be ascertained by undertaking precise measurements of tumour volume, referred to as 'volumetrics'.

1.2. Incidence

Meningioma has a reported incidence of 8.3 per 100,000 in the last decade, although this varies considerably based on specific population registries from as low as 1.3 to 8.3 per 100,000[6-8]. The overall incidence of meningioma has increased in recent decades[9]. The reasons for this are multifactorial, including the result of an ageing population, increased use of sensitive modern imaging techniques leading to increased frequency of meningioma discovery[10], and greater classification in tumour registries and histological confirmation[9]. Subclinical (undiscovered) meningioma has been identified in up to 2.8% of the general population at autopsy[11, 12]. Such meningiomas, discovered with the patient being asymptomatic (having no clinical symptoms), are described as 'incidental', and account for 30% of all new meningioma diagnoses[13-15].

1.3. Meningioma and age

Meningiomas mainly affect adults, with a median age at diagnosis of 66 years of age[16]. Incidence increases with age, with there being a notable increase in meningioma after the age of 65 (23.9 cases per 100,000 if aged 65-69, compared to 50.3 cases per 100,000 if over age 85)[17]. Meningioma is rare in children, and paediatric populations account for 1-3% of all meningioma diagnoses[18]. Many elderly patients with meningioma display normal life expectancies in comparison with the standard population or age matched controls, and similar surgical outcomes to younger patients[19].

Patients over the age of 65 are more likely to present with higher grade tumours (with 15% of all meningioma in these patients displaying more aggressive histology, compared to 8% of meningioma in patients under the age of 65)[20], and physical frailty and comorbidities may pose a serious issue when considering medical or surgical intervention in these groups[21]. Discerning exact outcomes in this group

are also less clear due to the utilisation of different definitions of an 'elderly' patient across clinical studies (with age 65, 70, and 75 all being used)[22-24].

1.4. Meningioma and sex

Meningioma is more prevalent in females, with a female: male ratio of 2-4:1[25]. The reasons for this predominance have not been fully elucidated. Nevertheless, it has been observed that meningioma exhibits a higher prevalence in females, and an increase in size and symptomatology in pregnancy which subsequently ameliorates post-partum[25-27]. Meningiomas have been shown to express oestrogen and progesterone receptors[28, 29], and hormone replacement therapy (HRT) has been shown to increase the risk of meningioma[30-32, 33]. The use of other steroid hormones such as Cyproterone acetate (CPA) increases the risk of developing a meningioma, with a strong dose-effect relationship observed in large cohorts[34-36].

1.5. Meningioma and ionising radiation

Exposure to ionising radiation is a risk factor for meningioma development. This was first demonstrated in a 1974 retrospective cohort study of 11,000 Israeli adults, which identified a significantly higher risk of head and neck tumours in those treated with low dose scalp irradiation for tinea capitis as children[37,38]. These tumours are often described as 'Radiation-induced meningiomas (RIM)'. RIMs can also arise in adults who received cranial, craniospinal or whole body radiotherapy for the treatment of childhood brain tumours or leukaemia[39]. Patients with RIM are more likely to have multiple[40], clinically aggressive meningiomas[41]. They display higher recurrence after surgery[42-44], with reduced five and ten year survival compared to sporadic meningioma controls[45]. There is no sex difference reported in comparison to sporadic meningioma, which is more commonly reported in females[44].

1.6. Meningioma clinical presentation

Over 90% of meningiomas are benign, asymptomatic tumours that grow slowly, and many meningiomas are now discovered incidentally[46, 47]. This discovery often leads to difficult management decisions, patient anxiety and uncertainty regarding the impact of the diagnosis. These patients have been labelled 'victims of modern imaging technology (VOMIT)'[48], and there is controversy in the literature regarding how they should be optimally managed[49].

The most common symptomatic presentation of meningioma is with headaches (33-37%), focal cranial nerve deficit (29-31%), seizures (17-25%) (which can be partial or secondary generalised), cognitive dysfunction (14%), vertigo/dizziness (10%), ataxia (6%), and sensory disturbance (6%)[50-52]. Focal

neurological defects may also be present, and are largely dependent on the anatomical site of the tumour.

Less commonly reported symptoms include those of obstructive hydrocephalus, personality change, cranial nerve defects, trigeminal dysaesthesias, or progressive visual loss for meningiomas affecting the optic sheath[53]. Personality change, confusion, and altered level of consciousness can also be seen, most commonly in frontal or parasagittal meningiomas. Petroclival meningiomas may also cause axial and cranial neuropathies[54].

Spinal meningiomas can cause slowly progressive paraparesis with or without radicular or nocturnal pain[55]. The most common location for spinal meningioma is the cervical spine, followed by the craniocervical junction, thoracic and lumbar regions[56]. Less commonly, spinal meningiomas may present acutely with a sudden spinal event, due to acute compromise of the spinal cord vascular supply[56].

1.7. Pathophysiology, genetic and molecular factors

Many mutated genes have been associated with meningioma development[57]. The most common of these is the Neurofibromatosis Type 2 (NF2) mutation. An autosomal dominant (AD) condition with an incidence of 1 in 33,000 in the United Kingdom (UK)[58], approximately 50% of patients with NF2 will develop intracranial meningiomas, 60% vestibular schwannomas, and 20% spinal meningiomas[59]. The pathognomonic hallmark of NF2 is bilateral vestibular schwannomas (acoustic neuromas)- a tumour of schwann cells. The NF2 gene is located on the long arm of chromosome 22 (chr22q), and is caused by inactivation and subsequent reduction of its gene product, moesin-ezrin-radixin-like protein (merlin)- a tumour suppressor gene postulated to link the actin cytoskeleton with plasma membrane proteins, that causes contact-dependent inhibition of proliferation[60]. The subsequent pathways affected include the hippo pathway, receptor tyrosine kinases (RTKs), and mammalian target of rapamycin (mTOR)/PI3K/AKT pathway. Over half of patients affected by NF2 have multiple meningiomas with differing growth trajectories and velocities, ranging from syndromic meningiomas that do not grow, to those that appear de novo and grow more rapidly, with a variety of histological subtypes exhibited[61]. This suggests that NF2 inactivation may be a critical event in development of some meningioma subtypes.

Other potential mutated genes have been identified, mainly due to advances in next generation sequencing (NGS) technology. NGS is a high-throughput technique that involves sequencing DNA to help identify variations in coding genes (such as mutations and deletions)[62,63].

Such genetic alterations include KLF4, TRAF7, ATK1, SMO, POLR2A, SMARCB1, PRC2 and DREAM[64-71]. Of these mutations, approximately a fifth of meningiomas express TRAF7 (Tumour necrosis factor [TNF] receptor associated factor 7), linked to induction of apoptosis and activation of cellular stress pathways, ubiquitinylation of multiple cellular targets, and induction of apoptosis[72]. ATK1 (v-akt murine thymoma viral oncogene homolog 1) is controlled by phosphatidylinositol-3-kinase (PI3K)-where it appears to suppress apoptosis, with mutations occurring in 10% of meningiomas, and Kruppel-like factor 4 (KLF4) is a regulator of cell proliferation, with activation mutations associated with tumour cell growth. Specific mutations are also observed in WHO grade 1 meningioma, specific histological subtypes, location and those with a poor prognosis[73].

The hedgehog (Hh) pathway has also been implicated in meningioma development, via mutations in Smoothened (SMO) and suppressor of fused homolog (SUFU) genes[74]. More recently, attention has turned to non-coding regions of gene expression, and, specifically in meningioma, the role of the telomerase reverse transcriptase (TERT) promoter. Mutations in the promoter region increase TERT expression, and can lead to immortalisation of cancer cells[75]. TERT has been associated to be an adverse prognostic marker in predicting meningioma recurrence independent of WHO grade (4.8 times higher in WHO-1 and WHO-2 TERT-alt patients) and more aggressive histological grade, occurring in 4.7% of WHO grade 1, 7.9% of WHO grade 2 and 15.4% of WHO grade 3 meningiomas. A TERT-alt type mutation indicates reduced recurrence free survival and overall survival[76].

Copy number alterations (CNAs) are highly involved in meningioma tumourigenesis due to dysregulation of tumour suppressor gene and oncogene activity[77]. In a CNA, parts of a chromosome can become duplicated or deleted. Specific examples are the loss of chromosome 22, and loss of heterozygosity (LOH) specifically on 22q, which is lost in 60-70% of sporadic meningiomas, and are highly expressed in aggressive meningiomas[78, 79].

1.8. WHO grade

Meningiomas are categorised according to the 2016 World Health Organisation (WHO) grading system as Benign (WHO grade 1), Atypical (WHO grade 2), and Anaplastic (WHO grade 3)[80, 81]. The current 2016 classification is outlined below. An updated classification is projected to be introduced at the end of 2021[82]. Histological grade remains the most important factor for meningioma growth, recurrence, and overall survival[83].

Table 1.1. WHO grades of meningioma

Meningioma type	WHO Grade	Percentage (%) of meningiomas
Benign	1	81.1
Atypical	2	16.9
Anaplastic	3	1.7

Table 1.2. 2016 WHO classification of meningioma

Grades	Appearance	Mitotic figures	Brain invasion*
1	Meningothelial, Fibrous (fibroblastic), Transitional (mixed), Psammomatous, Angiomatous, Microcystic, Secretory, Lymphocyte rich, Metaplastic	<4/10 HPF	Absent
2	Atypical, Clear cell, Chordoid	4-19/10 HPF	Present OR three of: Spontaneous necrosis, sheeting, prominent nucleoli, high cellularity, small cells
3	Anaplastic, Rhabdoid, Papillary, Or frank sarcomatous carcinomatous histology	>20/10 HPF	Present

***Previously not a criterion for WHO grade 2 in 2007 classification, HPF= High power field.**

1.9. Meningioma location

The most common locations for meningiomas are parasagittal, convexity, sphenoid wing, and anterior cranial fossa (Table 1.3). Less common locations for meningioma include the optic sheath (0.5-3% cases), choroid plexus (0.5-3% cases) and sella turcica[84]. Approximately 10% of meningiomas arise in the spine. Very rarely, they may be extracalvarial, with locations such as the mediastinum, temporal bone and lung[56].

Table 1.3. Most common meningioma locations	
Meningioma location	**Percentage of all meningioma (%)**
Parafalcine, parasagittal	25%
Convexity	20%
Sphenoid wing	20%
Olfactory groove	10%
Suprasellar	10%
Posterior fossa	10%
Intraventricular	2%
Intraorbital	<2%
Spinal	2-10%
Source: BrainScience Foundation	

Meningioma location can be classified according to the International Consortium on Meningiomas (ICOM) classification[85].

Table 1.4. International Consortium on Meningioma (ICOM) meningioma location classification.			
Main category	**Subcategories**		
convexity	anterior[1]	posterior[1]	
parasagittal	anterior[1]	posterior[1]	falco-tentorial
parafalcine	anterior[1]	posterior[1]	falco-tentorial
sphenoid wing	lateral	medial (including ACP)	
anterior midline	cribriform plate or olfactory groove[2]	planum	Tuberculum and diaphragma sellae
post fossa - midline	clival	petro-clival	anterior foramen magnum[4]
post fossa – lateral & posterior	petrous	squamous occipital	posterior foramen magnum[4]
tentorial	supratentorial	infratentorial	
intraventricular			
pineal region[5]			
[1]The main attachment is located anterior or posterior, respectively, to the coronal suture			
[2]Arising between the crista galli and the fronto-sphenoid suture			
[3]Arising between the fronto-sphenoid suture and the limbus sphenoidale			
[4]The main attachment is located anterior or posterior, respectively, to the hypoglossal canal			
[5]No obvious tentorial attachment			

1.10. Diagnosis- imaging and investigations

Meningioma are diagnosed with Magnetic Resonance Imaging (MRI) scanning and Computed Tomography (CT)[86]. MRI is most commonly used, due to its superior soft tissue capabilities compared to CT, and superiority for long-term follow up due to the absence of radiation exposure[87]. Most typically appear on MRI as solitary, well circumscribed tumours arising from the dura mater with homogenous contrast enhancement (Figure 1.1). Meningioma usually appear isointense on T1-weighted imaging, isointense on fluid-attenuated inversion recovery (FLAIR), and with uniform, homogenous enhancement post administration of gadolinium contrast. There may also be thickening of the adjacent dura mater located around the tumour. This is called the 'dural tail'- and reflects neoplastic dural infiltration, reactive vascularity, or both draining into adjacent dura[88, 89]. T2 and FLAIR can be used to assess peritumoural oedema.

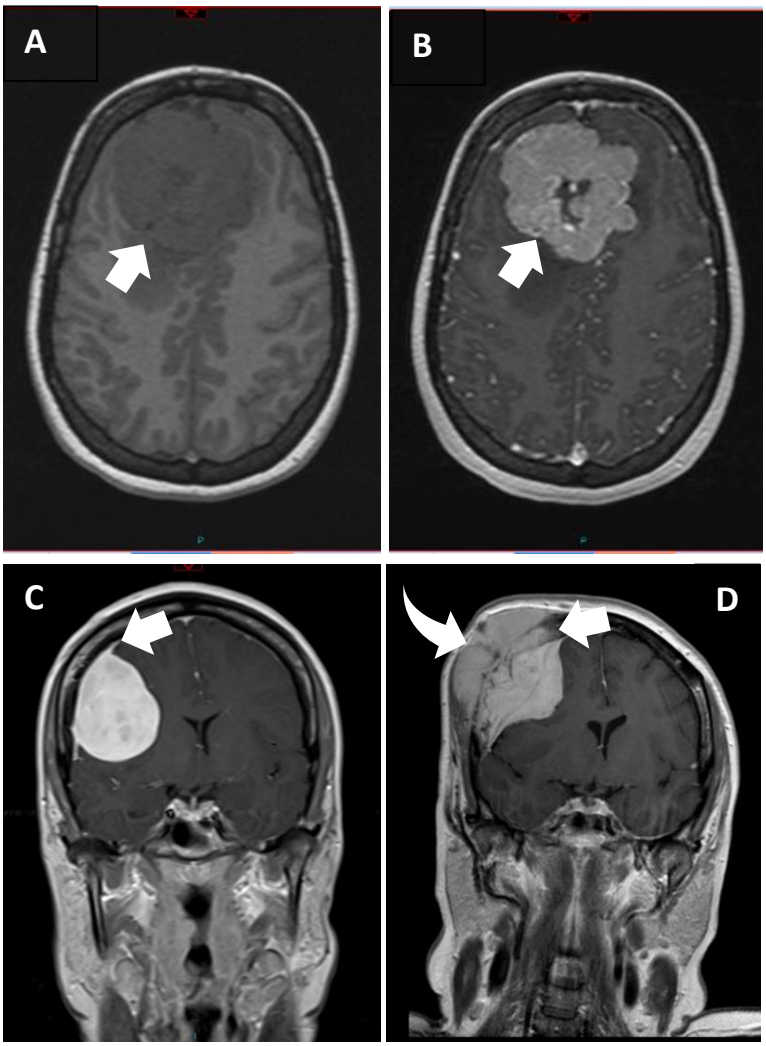


Figure 1.1. MR brain scans of various intracranial meningiomas. (A) and (B) Axial gadolinium enhanced pre and post contrast T1 sequence demonstrating an anterior cranial fossa meningioma before (A) and after (B) administration of gadolinium contrast (white arrows). (C) A coronal T1-weighted MRI showing Right sided convexity meningioma with enhancement of the 'dural tail' (white arrow). (D) Coronal gadolinium enhanced post contrast T1 sequence MRI demonstrating right sided intraosseous meningioma. There is hyperostosis (straight white arrow) and bone invasion (curved white arrow).

Meningiomas can display varying signal intensities on T2-weighted MRI sequences. They can appear brighter than (hyperintense), similar intensity to (isointense), or darker than (hypointense) cortical grey matter (Figure 1.2). It is suggested meningioma signal intensity on T2-weighted MRI may have an adverse prognostic value[90, 91]. On CT scanning, the appearances reflects the density of the tissue and can be 'hyperdense', 'isodense', and 'hypodense' respectively, with most tumours appearing isodense to cortical grey matter[92].

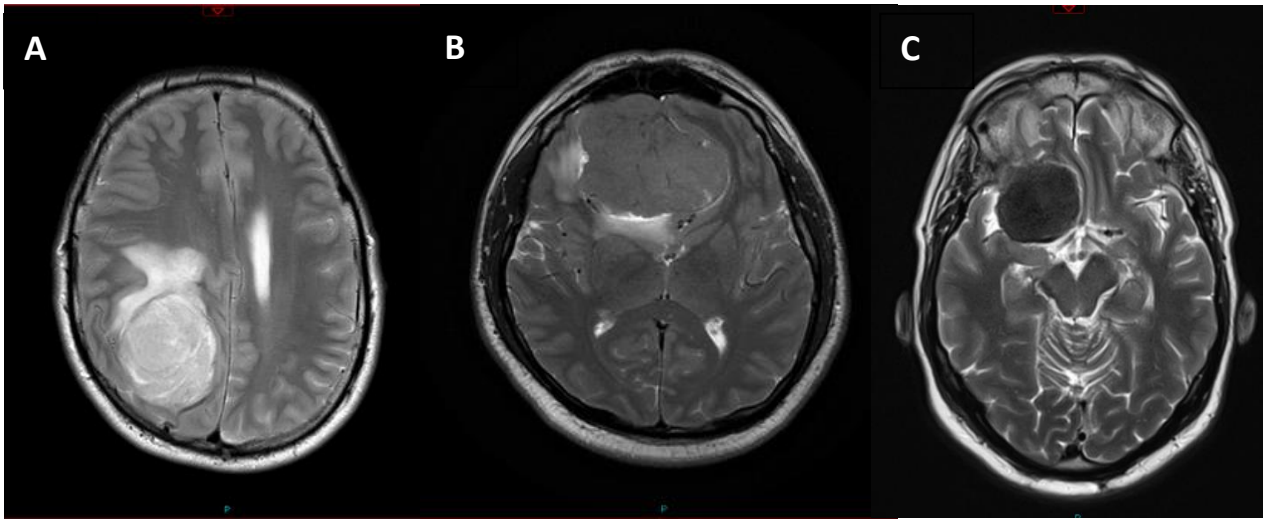


Figure 1.2. Selection of axial T2- weighted MRI studies demonstrating three meningioma of varying T2 signal intensity compared to cortical grey matter (A) Hyperintense (B) Isointense (C) Hypointense.

CT is useful at assessing hyperostosis of adjacent bone and assessing calcification within the tumour (occurring in approximately 25% of meningiomas[87]), and any intraosseous tumour involvement (Figure 1.3).

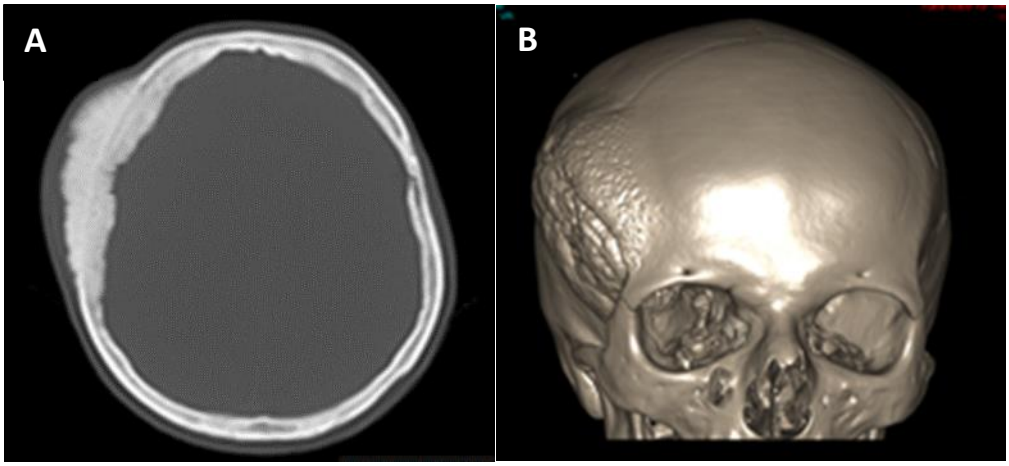


Figure 1.3. Axial CT scan (with bone window) showing (A) Hyperostosis and bone invasion in an intraosseous meningioma with (B) 3D reformats demonstrating a visible skull deformity arising secondary to the hyperostosis.

Cerebral angiography is not used for diagnostic purposes, but can be used to plan treatment, including pre-operative embolisation, which may help to reduce blood loss intraoperatively[93]. In cases of complex skull base meningiomas, expression of somatostatin receptor 2 can be used to differentiate healthy tissue from meningioma, through the utilisation of peptide ligands such as 68Ga- Dotatate or 90Y-Dotatoc as PET tracers[94, 95], although this remains primarily a research tool. MR spectroscopy can be used to evaluate metabolite concentrations in a given meningioma region of interest, and characteristically shows an alanine peak at 1.3-1.5 ppm[96], but again, this is not used routinely clinically.

1.11. Management- guidelines

Management guidelines exist for meningiomas, such as guidelines produced by the European Association of Neuro-Oncology (EANO)[86], National Institute for Health and Care Excellence (NICE)[97], and Society for Neuro-Oncology (SNO)[98], but the general principles for meningioma management are outlined below[86].

1. If imaging strongly suggests meningioma, a histological diagnosis is not required.
2. The diagnostic role of molecular profiling still needs to be established.
3. Surgery is the first-choice treatment for symptomatic meningioma, with the aim of a Simpson grade 1 resection.
4. Post-operative MRI should be performed 48 hours after surgery or after 3 months to avoid artefacts.

5. Stereotactic radiosurgery (SRS) can be offered for small tumours that have been incompletely resected- but this is low grade evidence.

6. The combination of radiotherapy (RT) and subtotal resection is associated with similar survival rates to gross total resection. Intensity modulated RT (IMRT) and fractionated SRS are increasingly used to spare sensitive neurovascular structures.

7. After therapy, annual MRI follow up should be employed for 5 years followed by biannual follow ups.

8. Pharmacotherapy is experimental in any grade of meningioma.

9. Growth kinetics of those undergoing subtotal resection are unclear.

The guidelines identify several areas of possible further research, such as pharmacotherapies, combination surgery and radiation therapy or Stereotactic radiosurgery (SRS), but another area identified is how to manage meningiomas with unclear growth kinetics. Understanding this by conducting studies of meningioma volumetric growth may aid in scientific understanding and clinical decision making.

1.11.1 Management- conservative

Many asymptomatic meningiomas demonstrate a decreased growth rate and can be managed conservatively with a combination of observation and periodic imaging. EANO recommends annual observation (using clinical and/or MRI tests) after an initial observation interval of 6 months. Recent NICE guidelines published in 2018 do not make any recommendations regarding this management[97].

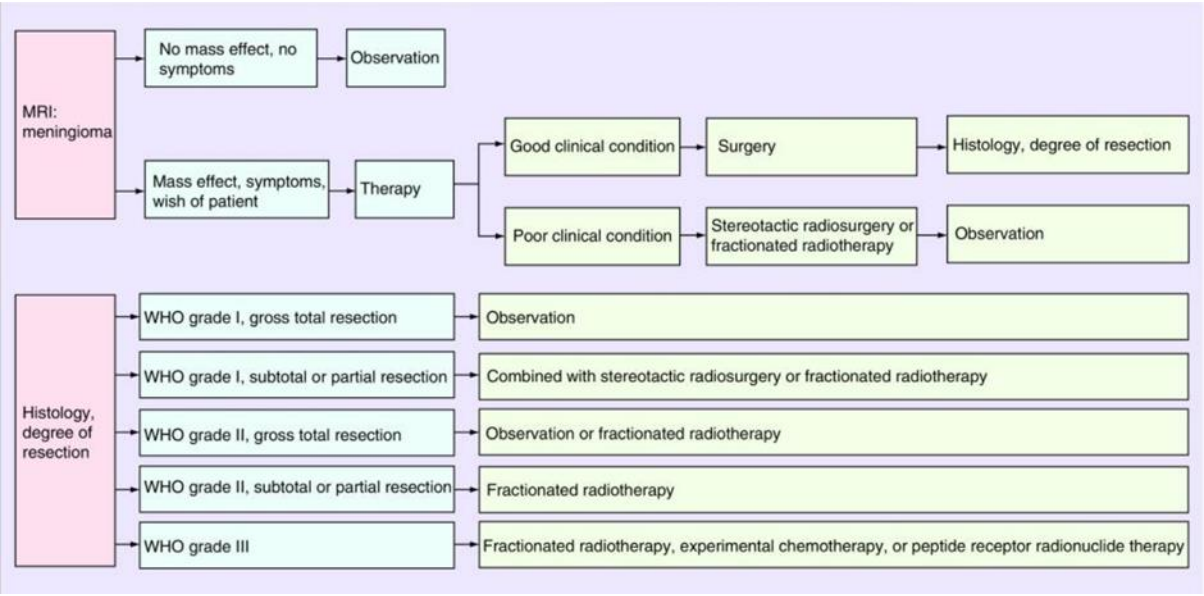


Figure 1.4. Summary of European Association of Neuro-Oncology (EANO) meningioma guidelines[99].

1.11.2 Management- surgical

Surgery is the first-line treatment for most meningioma. Indications for surgery include symptomatic presentations, tumour growth on serial interval scans, or the development of symptoms in patients with incidental meningioma. Surgery can also be considered in scenarios where there is diagnostic uncertainty based on the imaging (e.g dural-based metastases). The aim of surgery is complete removal (resection) of the tumour including any involved dura and bone. The extent of resection should be confirmed by a post-operative MRI scan completed within 48 hours after surgery, or after 3 months to avoid imaging artefacts.

Due to surgery being an important component of meningioma management, predicting risk of progression (either recurrence of a completely resected tumour or regrowth of a residual tumour) following surgery is a highly pertinent issue. This can be predicted in a myriad of ways, such as by tumour location and presence of symptoms[100], but the most established way to predict progression is to stratify by the extent of surgical resection[101].

The Simpson grading system, first introduced in 1957 by Donald Simpson, is used for this purpose[102], and is widely utilised in clinical practice nationally and internationally[103-105]. This can also be used to predict the rate of symptomatic recurrence at 10 years after surgery, which relies on the operating surgeon's assessment, and is briefly outlined below[106]. The Simpson grading system has five categories, each reflecting the extent of surgical resection.

Table 1.5. Simpson's grades of resection (Based on Simpson 1957 paper)

Grade	Description	Extent of resection (EOR)	Estimated symptomatic recurrence at 10 years (%)
1	Macroscopically complete removal of tumour, with excision of its dural attachment, and of any abnormal bone. Includes resection of venous sinus if involved	Gross total resection (GTR)	9
2	Macroscopically complete removal of tumour and its visible extensions with coagulation of its dural attachment		19
3	Macroscopically complete removal of the intradural tumour, without resection or coagulation of its dural attachment or its extradural extensions		29
4	Partial removal, leaving intradural tumour in situ	Subtotal resection (STR)	44
5	Simple decompression, with or without biopsy		100

A Simpson grade zero (0) is not part of the classification but is occasionally reported by surgeons, and is a Simpson grade 1 resection, but with an additional dural margin of 2cm adjacent to the tumour removed[107]. This additional resection does not appear to confer any further advantage to reduce recurrence risk, but can lead to an increase in morbidity[108]. Grades 1-3 are defined as 'complete, gross total, or macroscopic resection', and can be collectively referred to as a 'gross total resection (GTR)'[109]. This grouping is often used in meningioma clinical trials[110-112].

Grade 4 and 5 are defined as a 'subtotal or incomplete resection (STR)', and these tumours are historically associated with an increased rate of recurrence, and reduced progression free survival[103, 113]. The rate of recurrence following a GTR at 5, 10 and 15 years are 7%, 20%, and 32% respectively[114]. In contrast, rate of local recurrence with STR at 5 years is 47%[115].

Reasons for performing a sub-total resection include: large size of meningioma, difficult/unexpected intra-operative location or unexpected complications, skull base location precluding complete resection, and most commonly to preserve critical neurovascular structures and neurological function[116]. Subtotal resections is seen in 10-23% of all meningioma operations[106, 113, 117]. Depending on location, some centres have reported figures as high as 32.3%[118], and one centre 58% for a series of skull base meningiomas[119]. Gross total resection of Simpson grade 1-3 also increases recurrence free survival compared to STR. This is more pronounced for convexity tumours than for parasagittal, parafalcine or skull base tumours, and those with a high proliferation index (MIB-1 labelling index >3%)[104].

1.11.3 Simpson grade controversy/debate

Several notes, concerns and assessments have been made regarding Simpson's grading of resection since it's inception[103, 104, 120, 121]. First, the Simpson grading is based on the surgeon's assessment of the degree of resection, which is susceptible to observer bias. Studies completed in the last decade have also demonstrated little difference in recurrence rates between Simpson grades 1-3, indicating the scoring system's significance may be diluted in the modern surgical era[104, 122, 123]. One study also found that the 5-year recurrence/progression free survival of WHO grade 1 meningioma after resection for Simpson grades 1, 2, 3, and 4 to be 95%, 85%, 88% and 81% respectively, suggesting patients with Simpson grade 4 resection may have lower recurrence rates than originally postulated[124].

Secondly, the accuracy of the grading system has been called into question. Some studies have identified that on multivariable analysis, Simpson grade was not a predictor for recurrence, but post-operative residual volume was significant[125]. Therefore, clinicians should consider the residual volume and not the Simpson grading to be the most significant predictor. Despite this, some authors have not corroborated this finding[121].

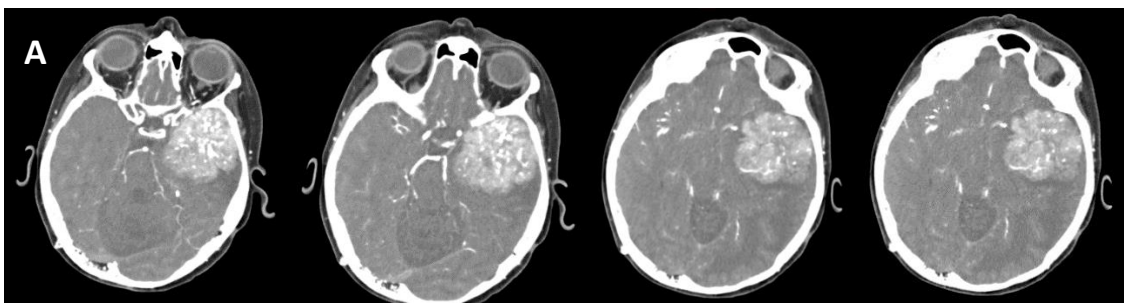
Thirdly, the Simpson grading system predated modern imaging such as CT and MRI (as it was first described in 1957) and some studies have identified that residual tumour may still be present on post-operative MRI imaging after a gross total resection, in some cases between 8 and 10% of cases[125]. This has led authors to question the additional benefit of achieving maximal Simpson resection in comparison to utilising modern treatment paradigms and active surveillance methods[120].

Finally, a recent study utilising postoperative SSTR-PET-CT using DOTATATE/PET-CT scans revealed that surgeons impression of Simpson Grade 1 and 2 resections were estimated discordantly in approximately 30% of cases, and in particular, the Simpson grade may tend to underestimate tumour remnants[126]. This is supported by another study that found Simpson grade to be overestimated compared to the true actual grade in 20% of cases, although this was more pronounced in skull base meningiomas specifically[127].

In contrast, many authors have retorted by arguing that Simpson grading retains its prognostic value for recurrence and recurrence free survival in modern day cohorts[103, 113, 128, 129]. A recent systematic review and meta-analysis reported that Simpson grade still predicts risk of recurrence even when stratified by WHO grade[130], and is a viewpoint shared by many clinicians, including the authors of the 2016 EANO guidelines[104]. Thus, while controversial, Simpson grading remains relevant in modern day meningioma management as an indicator of recurrence, and survival[86, 128, 131].

1.11.4. Pre-operative embolisation

Pre-operative embolisation is an interventional radiology technique occasionally used as an adjunctive therapy before meningioma surgery, and is thought to reduce intraoperative complications by reducing operation time and blood loss[132]. Embolisation using an embolic agent such as polyvinyl alcohol (PVA) particles or n-butyl cyanoacrylate (nBCA)[133] leads to devascularisation of the lesion, which induces necrosis and may enhance tumour resection through tumour softening[134].



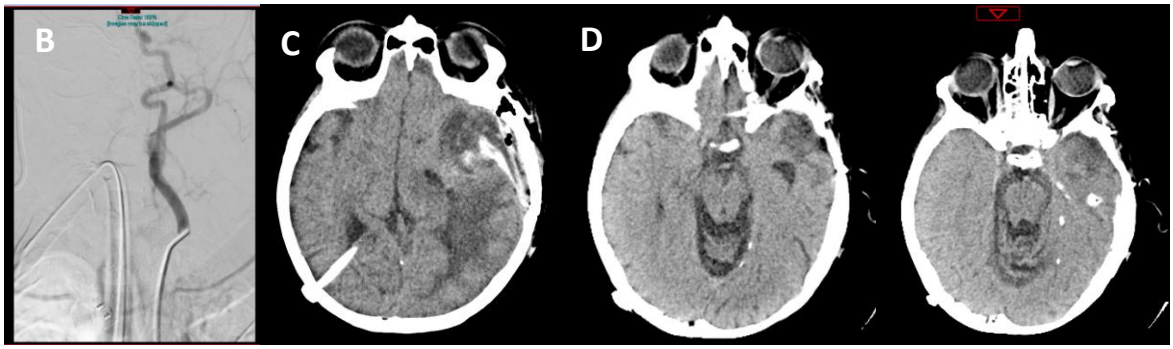


Figure 1.5. Axial CT angiography (CTA) scan demonstrating (A) Large, vascular sphenoid wing meningioma. The patient underwent successful pre-operative embolisation of the left common carotid artery (B). Pathology revealed a WHO grade 1 meningioma; post-operative axial non-contrast CT scan showing a small collection of blood in the resected area (C), and follow up CT scan 6 months after surgery demonstrating bleeding resolution (D).

1.11.5. Complications of surgery

Complications after meningioma surgery are in part related to the anatomical location, for instance visual loss in a meningioma in close proximity to or invading the optic nerve. General complications after meningioma surgery include transient or permanent neurological deficit, new seizures, haematomas, infection, and venous thromboembolism (VTE)[109]. Complications are more common in older adults (over age 65) undergoing meningioma surgery[135, 136]. Rates of medical complication after meningioma are rare and estimated at 5-10% (6.8%)[137], and include pneumonia, renal dysfunction, arrythmias, and VTE.

1.11.6. Management- Radiotherapy and Stereotactic radiosurgery

Radiation therapy (RT) is the only nonsurgical standard of care treatment option for meningiomas[99]. The use of RT includes both fractionated radiotherapy (*f*RT) and Stereotactic radiosurgery (SRS). SRS refers to higher dose per fraction RT that is delivered with precise 3-dimensional localisation systems, typically within one session[138]. The use of both *f*RT and SRS is equivocal in meningioma, with many recommendations based on observational, retrospective studies. There are no randomised studies comparing different RT modalities, and treatment is often individualised based on tumour location, and previous treatments[2]. The role of RT and SRS can be best examined at the level of different WHO grades of meningioma, and studies that are available indicate that RT can utilised to achieve local control in numerous settings[98].

1.11.6.1. WHO grade 1

While the definitive management of WHO grade 1 meningioma remains gross total resection (GTR), multiple retrospective studies have demonstrated that RT and SRS can provide improved local control in selected meningioma patients, both when used as adjunctive therapy and as primary treatment[139]. Radiotherapy can be used in two clinical settings: after subtotal resection, and as primary therapy for inoperable tumours. SRS refers to higher dose per fraction RT that is delivered with extremely precise 3- dimensional localisation systems, typically within a single session. SRS can be offered for small tumours, typically those less than 3cm in diameter or 10cm^3 in volume (as efficacy is based on tumour size)[140], after incomplete surgical resection, if the patient is elderly (>65 years), or the patient has a tumour not amenable to surgery[86]. Most clinicians use 14-17 Gy with single fraction SRS, and 25 Gy in 5 fractions for multifraction radiosurgery[141]. WHO grade 1 tumours are typically treated with 50-54 Gy with a 0-5mm clinical target volume (CTV) margin[142].

Fractionated radiotherapy and SRS are often successfully employed for control of local tumour growth. Primary SRS has showed a 5-year progression free survival (PFS) of 86-100%[2]. Fractionated radiotherapy has control rates of 75-92% when used as a primary therapy, for example, for optic sheath or skull base meningiomas not amenable to surgical resection[143, 144], and combining *f*RT and subtotal resection results in progression rates similar to patients who undergo gross total resection[145-147].

Radiotherapy, when used in the post-operative adjuvant setting, primarily when surgery is not an option, or following recurrence can achieve long term control in 68-100% of patients at 5-10 years, for tumours in difficult to access surgical locations, inoperable for medical reasons or patients who choose RT over surgery[148-155].

1.11.6.2. WHO grade 2

The role of RT as adjuvant therapy in WHO grade 2 meningioma is still unclear. As WHO grade 2 meningioma has a higher rate of recurrence and progression following surgery, RT and SRS would be more highly indicated. However, there is no prospective data on this in the published literature, and retrospective studies have come to differing conclusions, with some reporting benefit and others no difference in recurrence rates[156-158]. In a recent systematic review, no included study was able to demonstrate a statistically significant improvement in clinical outcomes with adjuvant RT for atypical meningioma[159]. Reports for SRS in grade 2 meningioma are almost exclusively reserved for recurrent tumour, with rates of control at 2 years varying from 0-90%, with most between 50 and 80%[158, 160-162].

1.11.6.3. ROAM trial

The ROAM/EORTC-1308 trial (Radiation versus Observation following surgical resection of Atypical Meningioma) is a multi-centre, prospective, randomised clinical trial (RCT) designed to stratify atypical meningiomas after gross total resection to receive either adjuvant RT (60 Gy in 30 fractions) or active observation and treatment at recurrence, and determine whether early adjuvant radiotherapy reduces the risk of tumour recurrence, and if the potential side-effects of RT are justified[163]. The trial has completed recruitment of 157 patients and is in follow-up, with results expected in 2026.

For Grade 2 meningiomas undergoing subtotal or incomplete resection, adjuvant RT of 54-60 Gy given in 1.8-2.0 Gy per fraction should be considered[86]. Long-term toxicity is the most significant risk after radiotherapy and occurs in approximately half of cases treated with RT at 10 years[159]. The long-term, overall survival rates using this treatment are poorly reported in the literature[164].

1.11.6.4. WHO grade 3 meningioma

Anaplastic (WHO grade 3) meningiomas are more aggressive than WHO grade 1 and 2 meningiomas, have a high recurrence rate and metastasise more frequently, with median overall survival reported to be less than 2-3 years[165, 166], but they are rare and account for only 1-3% of newly diagnosed meningiomas. There are no randomised trials assessing RT in grade 3 meningioma, but some retrospective studies have shown measurable benefit, using varied meningioma populations[143, 167]. It is recommended that following surgical resection all patients should receive fractionated RT, at least 54 Gy in 1.8-2 Gy fractions, although the precise dose is unclear at present[168, 169]. This is currently being investigated in the RTOG 0539 and EORTC 22042-26042 trials respectively[112, 170]. RT has been associated with significant improvement in progression free survival (PFS) at 24 months (from 50% to 80% compared to surgery alone)[169], and has been found to be a significant positive prognostic factor in this group[171]. Recommendations are for a total *f*RT dose of 60 Gy administered after the initial complete resection, with a 4cm margin for the initial 50 Gy. Despite this, outcomes overall are poor in groups treated with adjuvant RT (5-year Overall survival [OS] of 35% and PFS of 29%)[159]. SRS is generally not recommended for anaplastic meningioma[172-174].

1.11.7. Management- Chemotherapy and systemic therapies

Chemotherapy is less commonly utilised in meningioma, and is seldom used in WHO grade 1 tumours. Some retrospective studies have assessed the use of treatments including bevacizumab, hydroxycarbamide, megestrol acetate, octreotide, nivolumab, imatinib, erlotinib, gefitinib, vatalanib, and sunitinib in grade 2 and 3 tumours[175, 176]. When used in combination with RT and surgery, survival was increased in many of these studies, most promisingly with bevacizumab, valatinib, and sunitinib[177]. It is thought this is linked to angiogenesis and the action of these drugs in inhibiting it,

disrupting the tumour blood supply and subsequent growth, but prospective data confirming their efficacy is lacking[178]. An ongoing, phase 2 trial (Alliance trial) of targeted therapies specifically is ongoing[179]. Future treatments targeting the genetic abnormalities in meningioma, such as AKT inhibitors, PI3K inhibitors, Hedgehog pathway inhibitors, and drugs that target the NF2 mutation are promising developments[177, 180-183].

1.12. Recurrence/Progression

There is yet to be an established definition of recurrence in meningioma, and many definitions have been utilised in clinical studies. The response assessment in neuro-oncology (RANO) group is currently seeking to establish a uniform definition to utilise in clinical trials and prospective studies[2]. It can be used to describe radiological progression of current or residual tumour, transformation from a lower to higher WHO grade, and volumetric growth. There is currently no standard definition for what constitutes volumetric growth or progression.

1.13. Meningioma prognosis- overall survival

Many patients with meningiomas discovered incidentally that do not grow or require surgical intervention have a normal life expectancy, and meningioma prognosis has improved in recent decades[184]. Estimated 10-year overall survival for meningioma is 57.1%, and 77.7% for younger patients (age 20-44 years at diagnosis). Grade 2 and 3 tumours have a higher rate of recurrence (50% for Grade 2 and 90% for grade 3), and ten-year survival rates are significantly lower for these patients (53% for grade 2 and almost 0% for grade 3 despite maximum treatment)[3].

1.14. Meningioma prognosis- quality of life

A recent study demonstrated that 40% of patients that undergo surgery for meningioma have long-term cognitive or psychological dysfunction after the surgery, such as anxiety or symptoms of depression[185]. There is paucity in the literature regarding the exact impact a meningioma diagnosis has on overall quality of life (QoL), but studies available suggest that QoL is worse in patients before intervention compared to healthy controls, improves significantly after surgery which is maintained, and improves transiently in most patients after RT, but declines to pre-intervention levels within 2 years[186,187]. Larger, long term studies are needed to assess the true burden of meningioma on quality of life[188].

1.15. Meningioma volume calculation

A meningioma is a 3-dimensional (3D) structure, and therefore the tumour volume is reflective of the exact size of the tumour, usually measured in cm^3. As many meningiomas are considered ellipsoid (spherical) structures, the use of ABC/2 formula can be used to estimate meningioma tumour volume

in cm^3. This can be defined by measuring the maximum diameter in the axial plane (A), then measuring the diameter perpendicular to this (B), followed by the maximum height on a coronal or sagittal planes (C). When it is not possible to measure maximum height (for example if coronal or sagittal planes are not available), the height can be approximated by utilising the axial slice thickness of the CT/MRI scanner. Dural tails, an area of thickened dura that often has a 'string' appearance on imaging and is not considered part of the meningioma itself, is often omitted from volume calculation[189]. An example of how to perform this in a meningioma is outlined in Figure 1.6 below:

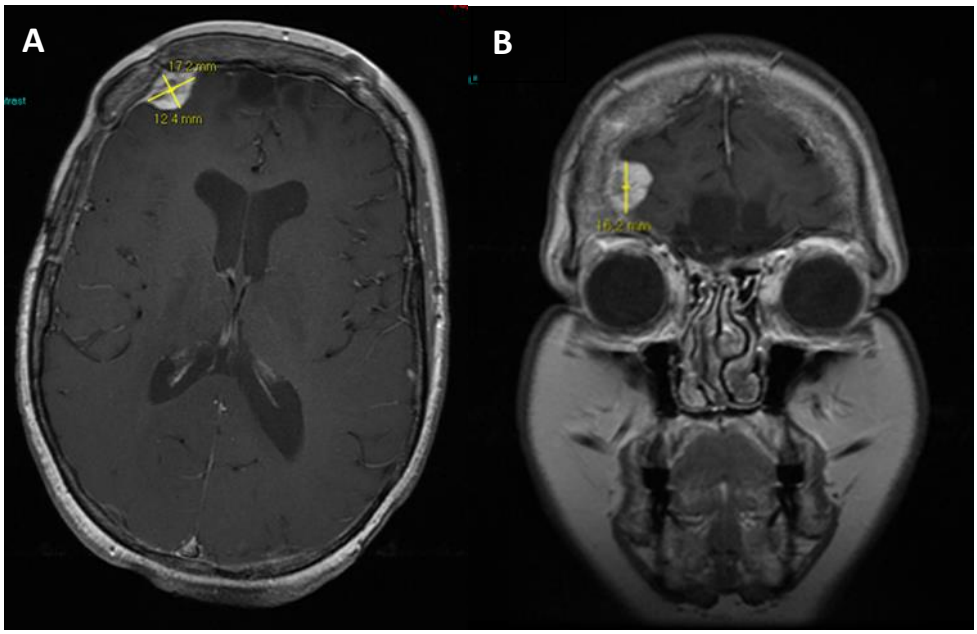


Figure 1.6. Diagram showing calculation of meningioma volume using ABC/2 method (A= maximum meningioma diameter on axial plane, B=diameter perpendicular to A, and C= maximum height on coronal or sagittal plane)[190].

This is an estimated volume that assumes an ellipsoid shape to the meningioma, and thus the more the lesion deviates from this morphology, the more inaccurate the calculated volume will be. This formula has been examined and validated at approximating volume of other tumours such as vestibular schwannomas[191, 192], and has now been validated in meningioma[193] as a viable method of volume calculation compared to more complex methods[194].

It is important to note, not all meningiomas are ellipsoid in shape, and therefore calculating precise volumes when possible and considering the individual shape of meningioma will lead to more precise measurements, and theoretically, a better estimation of volume. This has led to the development of

tools that aid tumour volume calculation, and these have been utilised in studies to calculate tumour volume for meningioma[195].

1.15.1. Volume calculation- Semi-automated methods

There are three methods for conducting precise volumetric measurements of meningioma: manual segmentation, semi-automated, and fully automated. Manual segmentation involves measuring each slice of tumour volume on an axial, coronal, or sagittal view, and can be done in most software programmes. A semi-automated method is the Picture archiving and communication system (PACS), a widely available, international, Food and drug administration (FDA) validated tool used to access patient imaging records such as CT and MRI scans. Using a freehand tool to draw around the edges of the tumour using the cursor, then progressing through each axial slice. The semi-automatic tool will then calculate the volume of segments in between, for instance if an observer measures the first and last slice of volume, the tool will calculate the volume of segments in between. This tool calculates a precise measurement, and is readily available to clinicians worldwide. Nonetheless, this technique has disadvantages in that it is time consuming (as the measurer must trace around each slice to achieve full segmentation) and expensive. Fully automated methods do not rely on manual interpolation, and employ a combination of software, artificial intelligence (AI) and machine learning methods.

Slicer™ is an imaging software programme that can be used to perform volumetric measurements of brain tumours either manually via slice by slice segmentation, or semi-automatically using the GrowCut function, a preset algorithm accessible as part of the software. In GrowCut, the images are labelled with at least two different colours (region of interest) and surrounding area. The tumour is then automatically segmented using the function based on pixels or intensities of the scans. This only works for tumours with well-defined margins. Slicer™ is not approved by the food and drug administration (FDA) in the US or in the UK for clinical use, and should be used for medical research purposes only. NIH Image J is a software tool that uses a similar method to Slicer™ for volume calculation, and is also not FDA approved.

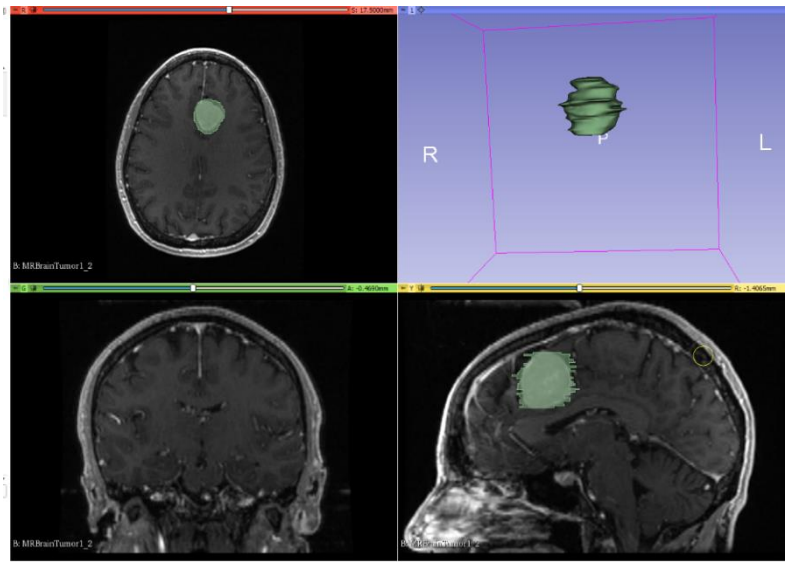


Figure 1.7. Example of manual segmentation using Slicer™ of a parafalcine meningioma. The 3D representation of the tumour is demonstrated in the top right image.

Brainlab™ is a privately-owned company specialising in software-based technology for use in medical and surgical fields. A component of this software is Smartbrush™ (Smartbrush 2.0, Brainlab AG, Feldkirchen, Germany). By using the brush tool, the system will utilise an algorithm to detect the presence of tumour, and will outline the tumour precisely according to this, based on the brain tumour software package recognition tool. A slice in one view is outlined (such as axial), and then another slice in a separate view (such as coronal) is conducted. Smartbrush™ then creates a 3D tumour image, which can be reviewed in a 3x3 view. The software creates a volumetric report for each tumour.

For the 3D interpolation method, the user segments the tumour in one slice, which is ideally as centrally as possible. Then, segmentation of the desired structure in a plane perpendicular to that segmented slice is carried out. The 3D- interpolation automatically detects the three dimensional region of interest (ROI) and segments the area three dimensionally with a region-growing algorithm[196]. If required, the result of 3D interpolation can quickly be adjusted manually. Smartbrush™ is FDA approved as a tool to use in clinical practice, but is only available in a select number of Neuro-Oncology units, and are often only located in surgical theatre operating rooms in the UK.

1.15.2. Volume calculation- automated segmentation software

Of the programmes available, only one software programme offers fully automated tumour segmentation. Brain Tumour Image Analysis (BraTumIA) is a software enabling fully automated tumour segmentation. The user uploads T1W, postcontrast T1W, T2W, and FLAIR sequences to the program interface. The images are processed, aligned, healthy and non-healthy tissue is delineated, and classification using a support vector machine classifier to determine, on the features of each voxel, delineation of healthy and non-healthy tissue. Then spatial recognition is conducted, and tumour volume given[197]. BraTumIA is not currently FDA approved.

1.16. Summary of volume calculation tools

PACS and Smartbrush™ are the only tools with FDA approval for clinical use, meaning the measurements and their preciseness are validated for use in clinical practice, and not just research studies. PACS is also the most utilised volume measurement tool in the literature. There have been few direct comparisons between tools to assess validity and reliability of measurements, but some studies exist. One study compared Smartbrush™ to an automatic software programme (Brain tumour image analysis [BT]) for imaging of glioblastoma (GBM), and found a slight difference in tumour volume differentiation in favour of BT[197]. A study anecdotally described the use of Smartbrush™ in 38

patients with keratocystic odontogenic tumours, with results suggesting that Smartbrush™ was a significantly faster process with comparable accuracy[196].

A recently published study compared the use of Smartbrush™ with BraTumIA in 58 pre and post-operative scans of patients with high grade glioma and found that although automated software reduced time to calculate volume and was reliable for preoperative tumour images, it was less reliable than the other methods for postoperative quantification of residual volume[198]. There have been no studies directly comparing multiple software programmes in meningioma volume measurement.

1.17. Meningioma- volumetric studies

There is no consensus on what constitutes a definition of meningioma volumetric growth. Table 1.6 lists the varying definitions utilised by authors, stratified by differing definitions. Some have used an arbitrary cut-off to define 'high' growth rates, others simply defined 'growth'. Some have used absolute growth that is not defined over time, such as >2mm absolute increase in any diameter[199], others a 15% overall volume increase[200, 201]. Some researchers have argued that growth rate should be graded in proportion with time, as time has been highlighted to be an important factor in determining meningioma growth velocity when incorporated into studies[202].

In addition, calculating growth rates by using an absolute cut off that does not include time as a variable assumes that meningiomas all exhibit a linear growth pattern, something that has been disproved in many studies that suggest meningioma growth can resemble power, exponential, linear or gompertz curves[203-205]. More recent studies have used definitions that take this into account, such as absolute growth rate (AGR) or relative growth rate (RGR) per year[202, 206].

Table 1.6. Different volumetric growth definitions used in meningioma studies

Author and year	Growth definition	Population studied	% of meningiomas that met the study-specific growth definition (n/total)
Islim et al., 2020* [207]	AGR ≥2cm^3/year or AGR ≥1cm^3/year and RGR ≥30% per year	Incidental meningioma	7.5% (29/385)
Materi et al., 2020 [206]	AGR>1.28cm^3/year	Sub-totally resected meningioma	NA
Behbahani et al., 2019 [199]	Volume increase >15% Volume increase >8.2%	Incidental meningioma	70.6% (72/102) 79.4% (81/102)
Lee et al., 2017 [208]	AGR ≥2cm^3/year	Untreated meningioma (incidental and symptomatic)	25.4% (59/232)
Lee et al., 2017* [209]	AGR ≥2cm^3/year or AGR ≥1cm^3/year and RGR ≥30% per year	Untreated meningioma (incidental and symptomatic)	29.7% (69/232)
Hunter et al., 2017 [210]	Volume increase >20%	Sub-totally resected petroclival meningioma	66.7% (15/23)
Hashimoto et al., 2012 [200]	Volume increase >15%	Incidental meningioma	62.8% (71/113)
Nakasu et al., 2011 [211]	Volume increase >8.2%	Incidental and residual/recurrent meningioma	84.6% (44/52)
Oya et al., 2011 [212]	Volume increase >8.2%	Untreated meningioma (incidental and symptomatic)	44% (120/273)
Hashiba et al., 2009 [201]	Volume increase >15%	Incidental meningioma	62.9% (44/70)

AGR= Absolute growth rate per year, RGR= Relative growth rate per year

Some authors have used linear mixed models to define their growth definition[202, 213]. In comparison, others have self-reported growth definitions based on the specific study population, for instance defining any growth over the median growth rate observed in the study as 'high'[206]. There is marked heterogeneity between studies reporting meningioma growth and growth rates and there is a need to have an agreed definition, that is applicable to the type of tumour of interest, for example, incidental meningiomas, subtotally resected meningioma, and untreated meningiomas.

1.18. Volumetrics- residual meningioma

Although meningiomas undergoing a subtotal resection are associated with a higher rate of recurrence clinically and radiologically, there has never been a detailed, highly powered study analysing the specific volumetric growth patterns and trajectory of all residual meningioma following surgery. Currently, EANO have highlighted that the volumetric growth of meningioma after subtotal resection is unclear. Such a study could be used to stratify management, develop prognostic models and improve clinical decision making. This would also improve understanding in a field that is relatively unexplored. In addition, considerable ambiguity and a lack of consensus exists among clinicians as to how pertinent Simpson grading is at predicting progression, with wide discrepancy in recurrence rates amongst smaller growth studies focusing on single meningioma locations, such as petroclival meningiomas[113, 116, 214].

Volumetric studies in meningioma in general are lacking, with a recent systematic review highlighting only four pertinent studies in meningioma, each with differing conclusions[215]. Some were underpowered, with all having heterogenous conclusions[203, 216, 217]. In addition, none of these studies have focused exclusively on sub-total resection, instead favouring to prognosticate meningiomas undergoing complete resection, and many have utilised Computed Tomography (CT) scanning over more detailed MRI scanning to conduct and calibrate volumetric measurements.

The course of residual meningioma is clearly an important clinical problem. The volumetric growth of tumours undergoing subtotal resection, and progression rates according to standardised criteria are unclear. There is a need to delineate this, in order to best stratify management, and the existing literature on this topic is sparse. The aims of this thesis, therefore, were to conduct a systematic review of the literature, and a large, retrospective cohort study delineating the volumetric growth of residual meningioma, with analysis of important prognostic factors for tumour regrowth.

Chapter 2: Volumetric growth of residual meningioma - a systematic review

2.1. Abstract

Background: Resection of meningioma leaves residual solid tumour in over 25% of patients. Selection for further treatment and follow-up strategy may benefit from knowledge of volumetric growth and factors associated with growth. The aim of this review was to evaluate volumetric growth and variables associated with growth in patients that underwent incomplete resection of a meningioma without the use of adjuvant radiotherapy.

Methods: A systematic review was conducted in accordance with the PRISMA statement and registered a priori with PROSPERO (registration number: CRD42020177052). Six databases were searched up to September 2020. Full text articles analysing volumetric growth rates in at least 10 patients who had residual meningioma after surgery were assessed.

Results: Four single-centre, retrospective studies totalling 238 patients were included, of which 99% of meningioma were WHO grade 1. The absolute tumour growth rate ranged from 0.09cm^3 to 4.94 cm^3 per year. The relative growth rate ranged from 5.11% to 14.18% per year. Varying methods of volumetric assessment and definitions of growth impeded pooled analysis. Pre-operative and residual tumour volume, sex and hyperintensity on T2 weighted MRI were identified as variables associated with residual meningioma growth, but this was inconsistent across studies. Risk of bias was high in almost all studies. Radiological regrowth occurred in 42-67% of cases.

Conclusions: Volumetric growth of residual meningioma is scarcely reported. Sufficiently powered studies are required to delineate volumetric growth and prognostic factors to stratify management.

Keywords: Meningioma; Prognostic factors; Simpson grade; Subtotal resection; Systematic review; Volume.

2.2. Introduction

Meningiomas account for over a third of primary central nervous system tumours, and are the most common primary intracranial neoplasm[5]. The first line management strategy for symptomatic meningiomas is surgery. Risk of recurrence is correlated with the extent of resection, and is typically classified according to the Simpson grading system[218]. Simpson grades 4-5 are often defined as an 'incomplete' or 'subtotal' resection, leaving residual tumour, which has an increased risk of regrowth following surgery[103, 113]. A subtotal resection may be performed due to proximity of the meningioma to critical neurovascular structures, restricted surgical corridors (most commonly in skull base meningiomas), and unexpected intraoperative complications[116]. Residual tumour is present after approximately 25% of meningioma operations, although some studies report this to be significantly higher[118, 119, 219].

Following complete resection, patients with WHO grade 1 meningiomas are usually managed with surveillance imaging. Following subtotal resection, fractionated radiotherapy (*f*RT) or Stereotactic radiosurgery (SRS) can be used to optimise local disease control[220-222]. Adjuvant radiotherapy is not always utilised following subtotal resection, due to patient preference, or favourable histological features, and the growth rates of these residual meningioma is an important clinical problem. Volumetric assessments can delineate tumour change over time, and ascertain rates of growth[215]. Data relating to volumetric growth of residual meningioma, and its association with clinical outcomes is lacking.

2.3. Review Question

In patients who have a residual meningioma after surgery, what is the volumetric growth rate of the residual tumour?

2.4. Objectives

The primary objective of this systematic review was to evaluate the volumetric growth rate of residual meningioma. Secondary objectives were to search for variables associated with regrowth of residual meningioma (if reported) and delineate overall survival (OS) and progression free survival (PFS), or recurrence free survival (RFS).

2.5. Material and methods

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[223], A systematic review critical appraisal tool (AMSTAR-2)[224], and Risk of Bias Assessment Tool for Systematic Reviews (ROBIS)[225]. The study was registered with PROSPERO (registration number: CRD42020177052).

2.5.1. Search strategy

A literature search, last updated 13/09/2020, was carried out from inception in the following study databases and registries: Medline (Ovid), Embase (Ovid), CINAHL Plus (EBSCO), Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform and UK Clinical Trials Gateway. The search strategy utilised for Embase can be found in Appendix 1. The search strategy was adapted for the other electronic registries (Appendix 2), and trial registries were searched using the term 'meningioma'. Bibliographies and reference lists of included articles were scanned to identify additional studies in the review. Papers were limited to English language due to the feasibility of translation.

2.5.2. Study screening and selection

Articles identified from the search were transferred to the online platform Rayyan, a repository to facilitate de-duplication and independent screening of potential records[226]. After removal of duplicates, titles were screened against the population, intervention, comparison, outcome, and study design (PICOS) criteria defined in Table 2.1 by two independent, blinded reviewers (CSG and BAT). Following this, abstracts were screened, followed by full-text articles using the same process to identify manuscripts eligible for inclusion.

If any disagreements occurred, an attempt was made to resolve this between two review authors (CSG and BAT), and if discussion failed to lead to consensus, the senior author was consulted for clarification (MDJ). If any data was not present or available in the articles identified, corresponding authors were contacted via email to request the data.

Table 2.1. PICOS inclusion criteria

Review question	In patients who have undergone subtotal resection of intracranial meningioma, what is the volumetric growth rate of meningioma and how does this impact on clinical management and outcome?	
Population	Adults ≥16 years with an operated meningioma. Studies with less than 10 patients/cases, NF2 or Radiation induced meningiomas, and patients that underwent adjuvant radiotherapy after surgery were excluded.	
Intervention	Sub-total resection + active monitoring	
Comparator	Not required	
Outcomes	**Primary**	**Secondary**
	Growth rates	**Survival**
	Absolute growth rate (AGR)	Progression free survival (PFS)
	Relative growth rate (RGR)	Recurrence free survival (RFS)
	Tumour doubling time	Overall survival (OS)
	Growth period/follow-up	Variables associated with growth
Setting	Studies taking place in any neurosurgical department or centre	
Study design	Phase 2, 3 or 4 trials, prospective case series and cohort studies with >10 adult patients	
Follow-up	Post-operative follow-up of at least one year	

2.5.3. Data extraction and synthesis

Data extraction was conducted independently and in duplicate by two authors (CSG and BAT) using a standardised pre-piloted data collection proforma (Appendix 3). Data extracted included baseline patient demographics, imaging and tumour characteristics, volumetric growth (both absolute growth rate [AGR] and relative growth rate [RGR]), and variables associated with growth. The primary outcome measure was volumetric meningioma growth rate. The secondary outcome measures were variables associated with growth, OS and PFS or RS. The data is presented for all studies separately. Data was incorporated into a Microsoft Excel spreadsheet, and exported to SPSS Version 25.0 for analysis.

2.5.4. Statistical analysis

Study level data was collected and presented as number, mean or median based on the type of data reported by authors. Variables assessed were reported based on the statistical test used. Due to heterogeneity of study outcomes, and patient characteristics varying considerably, the decision was made not to undertake a meta-analysis.

2.5.5. Quality assessment

The level of reporting of included studies was assessed by two authors independently (CSG and BAT) using the Quality in Prognostic Studies (QUIPS) tool. The following were evaluated: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain was studied and each score was used to produce an overall rating based on Scottish Intercollegiate Guidelines Network (SIGN) criteria with consensus between the two authors[227].

2.6. Results

2.6.1. Study selection process

Figure 2.1 describes the study selection process. The initial number of studies included was four. The corresponding authors for five additional studies were contacted to request additional data. A duration of two months was allowed for responses after which follow up emails were sent. One response was received; however, the data returned was unsuitable for inclusion. Therefore, the final number of studies analysed was four[206, 210, 228, 229]. A list of all full text articles screened and the reasons for their exclusion are provided in Appendix 4.

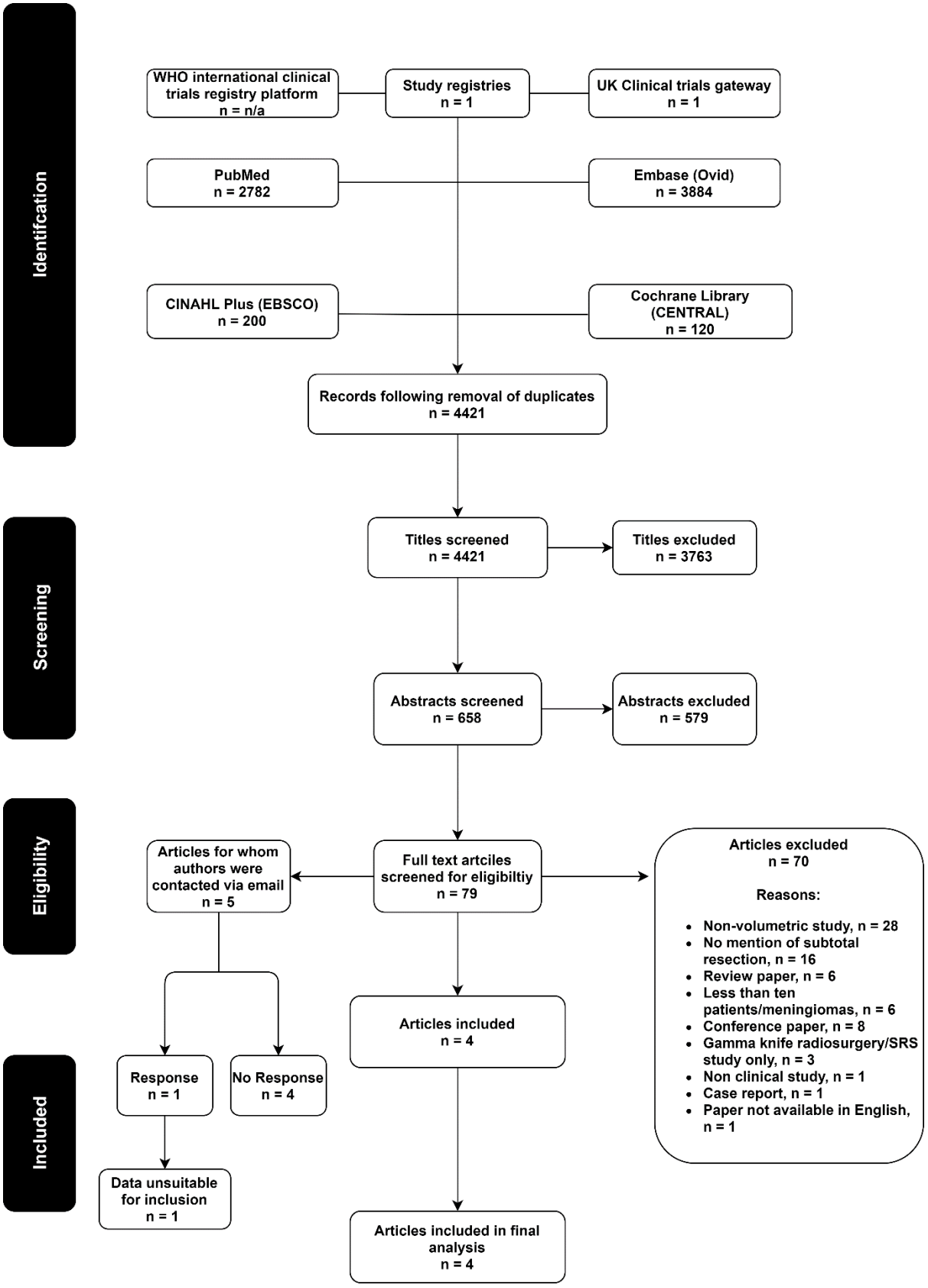


Figure 2.1. PRISMA flow chart

2.6.2. Study and patient characteristics

The study characteristics are outlined in Table 2.2. After screening, four studies comprising 238 patients with residual meningioma, with volumetric growth rates were included. All included articles were retrospective, single-centre studies. Two studies analysed meningiomas in multiple locations, while two studies only assessed petroclival meningiomas[210, 229]. Most patients included were female (range 67.9%-72.2%), mean age ranged from 53-57 years, and 235/238 (99%) of meningiomas were WHO grade 1. One study included three WHO grade 2 meningiomas[228]. One study defined extent of resection using the Simpson grade[206]. All other studies dichotomised extent of resection as the presence or absence of residual meningioma (Table 2.3). The majority of eligible patients were included in their study analysis (reported eligible population range 74.2-100%). No study used the same monitoring intervals after surgery (Table 2.3).

Table 2.2. Baseline characteristics of included studies.

Author (year)	Study design	Single center?	Population size/number of meningiomas	Main Inclusion and exclusion criteria	Mean Age (years)	Sex (% female)	WHO Grade	WHO Grading system	Tumour Location	Follow up (months)
Materi (2020)	Retrospective	Single	141	WHO Grade 1 meningioma Excluded: NF2 Radiation-induced meningioma Recurrent, spinal meningioma WHO grade 2 or 3 <3 months follow up Postoperative radiation	56.55 (SD 12.76)	Females: 101 (72%) Males: 40 (28%)	1	2007	9% Convexity (12) 17% Parasagittal (24) 12% Falcine (17) 23% Sphenoid wing (34) 7% Olfactory groove (10) 15% Planum sphenoidale (21) 10% Suprasellar (14) 9% Tentorial (13) 21% Posterior fossa (29) 14% Cerebellopontine angle (20) 3% Foramen magnum (4)	Median: 45 (IQR 22-72)
Hunter (2017)	Retrospective	Single	23	Excluded: NF2 SRS/RT before/after surgery Radiological follow up <2 MRI scans WHO grade 2 or 3	54 (30-73)	Females: 16 (67.9%) Males: 7 (32.1%)	1	*NS*	100% Petroclival (23)	Mean: 22.7 (0.1-70.4, SD 26.9)
Nakamura (2005)	Retrospective	Single	36	Included subtotal tumour resection meningioma Exclusion: *NS*	53.14 (33-79)	Females: 26 (72.2%) Males: 10 (27.8%)	33 Grade 1, 3 Grade 2	*NS*	33% Sphenoid wing (11) 21% Petroclival (7) 12% Tuberculum sellae (4) 6% Cerebellopontine angle (2) 6% Convexity (2) 6% Frontobasal (2) 6% Parasagittal (2) 3% Tentorium (1) 3% Jugular foramen (1) 3% Optic nerve sheath (1)	Mean: 37.5 (4-122)
Jung (2000)	Retrospective	Single	38	*NS*	*NS*	*NS*	*NS*	*NS*	100% Petroclival (38)	Median: 30 Mean: 47.5 (6-141)

SD= Standard deviation; IQR= Interquartile range; *NS*= Not stated/defined.

Table 2.3. Definition and measurements

Author (year)	Type of scans used for measurements	Measurement tool	Formula used for volume measurement	ICC or inter observer reliability reported?	Simpson grade of resection	WHO classification and diagnosis	Growth definition	Monitoring intervals
Materi (2020)	T1 weighted MRI with gadolinium contrast	Freehand	Semi-automated PACS, Z Dimension	✗	4	Senior neuropathologist, 2016	High growth: >1.28cm^3/year	48 hrs after surgery, 3-month follow-up scan
Hunter (2017)	T1 weighted MRI with gadolinium contrast	Freehand	NIH Image J software, manual tracing and interpolation	✗	*NS*	*NS*	20% volume change for 'growth' or 'shrinkage'	1 day after surgery, *NS*
Nakamura (2005)	MRI scans with contrast, 1 patient CT	Freehand/planimetry	NIH Scion (Image) J software	✗	*NS*	*NS*	*NS*	Continuously followed up with imaging studies, frequency not defined.
Jung (2000)	CT scans with contrast	Freehand	Ellipsoid formula: $V = \left(\frac{4\pi ABC}{3}\right) * 2^3$	✗	*NS*	*NS*	'Regrowth on follow up CT or MRI images'	*NS*

***NS*= Not stated/defined, ICC= Intraclass correlation coefficient, NIH= National institutes of health**

2.6.3. Volumetric measurement method and definition

The method of volumetric measurement varied between studies (Table 2.3). Two studies determined mean volumes from three measurements using the National Institutes of Health (NIH) Scion Image J programme with either automatic[228] or manual interpolation[210]. Two studies used the ellipsoid formula, and one used the oval formula ($V=4/3\pi$ ABC/2)[228, 229]. One study used the Picture archiving and communication system (PACS) semi-automatic tool with manual measurements[206]. No studies reported the use of inter, intra-rater reliability or Intraclass correlation coefficient (ICC). Two studies did not categorise change in meningioma volume as "growth" or "stable disease". One study defined "high" growth rate as >1.28cm^3/year[206], and another defined a 20% minimum volume change as "growth"[210].

2.6.4. Volumetric growth rates

All four studies reported absolute growth rates per year (Table 2.4). The median growth rates ranged from 0.09-2.82cm^3/year, and one study reported a mean growth rate of 4.94cm^3/year. The same study reported that 3 WHO grade 2 meningiomas had higher growth rates than 33 WHO grade 1 meningiomas (mean 25.3cm^3/year vs 1.51cm^3/year)[228]. Two studies reported relative growth rates per year (RGR). One study reported a median RGR of 5.11% per year, and another a mean RGR of 14.18% per year[206, 228]. Two studies reported the mean tumour doubling time (2906 days and 1908 for WHO grade 1)[228, 229].

Table 2.4. Growth and recurrence rates

Author (year)	Residual volume (cm^3)	Growth definition	Growth rate per year (cm^3)	Growth rate per year (%)	Absolute growth rate (AGR)	Tumour doubling time	Recurrence definition	Clinical/radiological	Recurrence of cohort (n)	Time to recurrence (months)	Recurrence or progression-free survival
Materi (2020)	Median: 2.31 (IQR 0.98-5.16)	'High growth': >1.28cm^3/year	Median 0.09 (IQR 0-1.39)	Median 5.11 (IQR 0-37%)	*NS*	*NS*	Definitive growth of residual assessed by a neuroradiologist	Radiological	52% (74)	Median: 14 (IQR 6-34)	Recurrence free survival: 41% (5 years)
Hunter (2017)	Mean: 6.9 (0.1-27.3)	20% volume change for 'growth' or 'shrinkage'	Median: 2.82 (IQR 0.34-22.1)	*NS*	*NS*	*NS*	*NS*	Radiological	67% (15)	*NS*	*NS*
Nakamura (2005)	Mean: 10.79 (0.1-45.04)	*NS*	Mean WHO grade 1: 1.51 (0.009-7.19) grade 2: 25.3	Median WHO grade 1: 14.18 (0.45-90.94%) WHO grade 2: 246.13	*NS*	Median WHO grade 1: 5.2 yrs (1.0-155.4) grade 2: 0.56 yrs	*NS*	*NS*	*NS*	*NS*	*NS*
Jung (2000)	*NS*	'Regrowth on follow up CT or MRI images'	Mean: 4.94	*NS*	*NS*	2906 days	Regrowth on follow up CT scans or MRI with or without aggravation of clinical symptoms or signs	Radiological	42% (16)	Median: 36 Months	Progression free survival: 60% (5 years)

IQR= Interquartile range, NS= Not stated

2.6.5. Prognostic factors

The included studies analysed several variables associated with regrowth and recurrence in their analysis (Table 2.5 and 2.6). Two studies identified residual tumour volume as a significant variable for tumour regrowth (P<0.001)[206, 210]. One study identified pre-operative tumour volume as a significant variable for regrowth (P=0.008)[206]. Sex was not found to be a significant variable in all studies. Younger age (<60 and <50) was reported as a significant variable for growth by two studies (P=0.041 and P=0.040 respectively)[228, 229]. Meningioma hyperintensity on T2 weighted MRI was identified as a significant variable for regrowth in one study of 36 meningiomas (P=0.024)[228], but not in another study of 23 meningiomas (P=0.061)[210, 228]. Other variables reported as significantly associated with regrowth included absence of calcification, tumour location, cranial nerve palsies, and menopausal status (Table 2.6).

Table 2.5. Variables associated with tumour growth and recurrence

Author (year)	Age	Test used, effect size	P value	Sex	Test used and effect size	P value	Pre-op tumour volume/size	Test used, effect size	P value	Residual tumour volume	Test used, effect size	P value
Materi (2020)	*NS*	-	-	✗[G] (male)	Cox regression, OR 1.67 (0.69-4.07)	0.262	✓[R]	Cox regression, HR 1.01 (1.00-1.01)	0.008	✗[R]	Cox hazard regression, HR 1.01 (0.97-1.07)	0.531
							✗[G]	Cox regression, OR 1.01 (1.00-1.02)	0.111	✓[G]	Cox regression, OR 1.18 (1.08-1.28)	<0.0001
Hunter (2017)	✗[G]	Spearman Rank, 0.30	0.313	✗[G]	Mann-Whitney U test	0.733	*NS*	-	-	✓[G]	Spearman rank, 0.86	<0.001
Nakamura (2005)	✓[G] (<60 vs ≥60)	Student's t test	0.041	✗[G]	Student's t test	0.09	-	-	-	-	-	-
Jung (2000)	✓[G] (<50 vs ≥50)	Wilcoxon rank-sum	0.040	✗[G] (Male vs female)	Wilcoxon rank-sum	0.114	✗[G] (<4.5 vs ≥4.5)	Wilcoxon rank-sum	0.391	*NS*	-	-
	✗[R] (<50 vs ≥50)	Wilcoxon rank-sum	0.1916	*NS*	-	-	✗[R]	Wilcoxon rank-sum	0.7370	*NS*	-	-

HR: Hazard ratio, OR: Odds ratio, ✓= Factor identified as significant, ✗= Factor identified as not significant, *NS*: Not stated, -= Factor not analysed, [R] Risk factor for recurrence, [G] Risk factor for tumour growth

Table 2.6. Other prognostic factors reported.

Author (year)	Calcification	Test used, effect size and p value	Tumour location	Test used, effect size and p value	T2 hyperintensity	Test used, effect size and p value	Other tests used	Test used, effect size and p value
Materi (2020)	*NS*		✗[G] Falcine	Cox regression, OR 2.15 (0.68-6.80), p=0.262	*NS*	-	✓[R] African American race	Cox regression, HR 1.81 (1.04-3.15), p=0.044
			✓[R] Falcine	Cox regression, HR 2.22 (1.18-4.16), p=0.021				
			✗[G] Tentorial	Cox regression, OR 2.10 (0.47-9.34), p=0.339				
			✓[R] Tentorial	Cox regression, HR 2.41 (1.20-4.83), p=0.024			✗[G] African American race	Cox regression, OR 0.30 (0.09-1.10), p=0.056
			✗[G] Sphenoid wing (medial)	Cox regression, OR 1.68 (0.57-4.92), p=0.352				
Hunter (2017)	✗[G]	Mann-Whitney, p>0.999	*NS*	-	✗[G]	MW, p=0.061	✓[G] CNVI palsy	(MW) 0.03
							✓[G] EOR	(S) 0.018
							✗[G] BMI	(S) 0.484
							✗[G] Pre-op growth rate	(S) 0.919
							✗[G] Peritumoural oedema	(MW) >0.999
							✗[G] CNIII, CNVII, or CNX palsy	(MW) 0.889, 0.864, 0.571
							✓[G] Pial-cortical blood supply	(MW) 0.031
Nakamura (2005)	✓[G]	(S), p=0.01 (AG), p=0.007 (RG)	-	-	✓[G]	S, p=0.024	✗[G] Pathology subtypes	(S) Not significant (no p value)
Jung (2000)	-	-	-	-	-	-	✓[G] Before menopause	(WRS) 0.034
							✓[G] Radiation	(WRS) 0.021
							✗[G] Sx <12 months	(WRS) 0.626
							✗[G] CN Palsy initial symptoms	(WRS) 0.589
							✗[G] Brainstem oedema	(WRS) 0.558
							✗[R] Sx<12 months	(WRS) 0.0973
							✗[R] Tumour size>4.5cm	(WRS) 0.7370

✓= Factor identified as significant, ✗= Factor identified as not significant, NS/-: Not reported, EOR: Extent of resection, AG: Absolute growth, RG: Relative growth, BMI: Body Mass Index, IICP: Increased intracranial pressure (ICP), MW: Mann-Whitney test, S: Spearman rank, WRS: Wilcoxon-Rank Sum, [R]Risk factor for recurrence, [G]Risk factor for tumour growth, OR: Odds Ratio, HR: Hazard ratio, NS: Not stated/defined.

2.6.6. Progression-free and overall survival

Three studies defined progression as radiological meningioma regrowth[228], with two studies defining this as definitive radiological growth assessed by a neuroradiologist or tumour regrowth on follow up CT scans or MRI[206, 229]. The median time to progression ranged from 14-36 months (table 2.4). One study reported a PFS of 60% at 5 years[229]. One study reported PFS rates at 1, 2, 3, and 5 years after surgery as 72%, 63%, 51%, and 41% respectively[206]. Two studies did not report PFS[210, 228]. No studies reported overall survival.

2.6.7. Quality assessment and risk of bias

All papers were recorded as high risk of bias. All studies scored high risk for study participation, confounding, and three studies for statistical analysis and reporting. The clinical heterogeneity of the four included studies was low, and the methodological diversity was high. This was because many studies used different growth definitions, statistical tests, and methods of measuring meningioma volume. Only one study included multivariable analysis. Two studies declared no conflicts of interest[206, 210], one declared no conflicts of interest and research grant funding[229], and one study did not provide a clear report of potential conflicts of interest[228, 229]. No disagreements were reported between the two authors, and the summary is outlined in Appendix 5.

2.7. Discussion

This review provides limited evidence of volumetric growth rates of residual meningioma, with radiological regrowth rates close to 50% with MRI surveillance. Studies included suggest that the absolute and relative growth rate of residual meningioma vary. The growth rate of WHO grade 2 meningioma is unclear, as only three were included in the review. Survival data were not available in any of the studies included.

The latest EANO guidelines recommend consideration of either *f*RT or SRS for residual WHO grade 1 meningioma, but this is not employed universally, for example due to patient or clinician preference, or discovery of residual meningioma on imaging many months after the original surgery. The guidelines recommend an individualised approach to meningioma management[86]. A large residual meningioma volume was identified as a significant variable in the two studies that included it[206, 210], and recently, authors have reported post-operative tumour volume on MRI imaging to be more influential than Simpson grading at predicting recurrence[125].

The Simpson grading system is still used worldwide, as advocated by international guidelines[86]. Despite this, recent studies highlight its inferiority in comparison to objectively assessed residual volume on post-operative MRI[230, 231]. Moreover, Simpson grade is over estimated in as many as one-third of meningioma operations[232].

There was no consensus between studies on the effect of other variables such as the patient's clinical characteristics, and imaging features including calcification, tumour location, and signal intensity. Sufficiently powered studies are needed to elucidate the effect of these variables.

Certain molecular characteristics have been found to be predictive of regrowth of residual meningioma. The use of DNA methylation profiling has been used to predict disease progression more accurately than WHO grade and histology, and has been incorporated alongside Simpson grading in the development of meningioma recurrence calculators[233, 234]. Methylation based molecular classifications were not included in any of the studies in this systematic review, but should be examined as a potential prognostic factor for regrowth in future studies[235]. Other possible molecular factors that influence the regrowth of residual meningioma include telomerase reverse transcriptase (*TERT*) promoter and BRAF V600E mutations, although it is important to note they are only present in a small proportion of meningiomas[76, 236]. Likewise, the strong association of v-akt murine thymoma viral oncogene homolog 1 (AKT1), Tumour necrosis factor (TNF) receptor associated factor 7 (TRAF7)/ Kruppel-like factor 4 (KLF4), and Smoothened (SMO) with skull base meningiomas, which demonstrate a more favourable clinical course, may be used to stratify treatment strategies after subtotal resection[77].

The review was limited by the level of evidence in included articles, with four retrospective cohort studies analysed. This highlights the lack of studies available in the literature, and severely limits the findings of this manuscript. Heterogeneity of volume measurements and calculations, as well as different definitions and cut-offs for meningioma regrowth prevented pooled analysis of the data. There is no standardised definition of volumetric growth in meningioma, which undoubtedly leads to discrepancies in reporting, with some authors choosing time dependent definitions, and others using the absolute growth rate[199, 202, 206, 210]. None of the studies utilised the same statistical methods to demonstrate outcomes. No studies used inter- or intra-observer reliability, or ICC to ensure congruity of volumetric measurements. In addition, some variables identified with growth may be confounders by indication, for instance cranial nerve involvement and location may mean meningiomas are less amenable to radical resection. Furthermore, many of the variables were identified using univariate analysis, and the prognostic effect of these variables is still unknown.

2.8. Conclusions

Volumetric growth of residual meningioma is uncommonly reported. Residual and pre-operative meningioma volume may be associated with higher risk of re-growth, which needs to be confirmed in higher quality studies due to high risk of bias in many reported studies. Uniform, standardised or categorical definitions are required to assess the extent of regrowth of residual meningioma.

2.9. Acknowledgments

Basel A. Taweel (BAT), intercalating Master of Philosophy (MPhil) student at the University of Liverpool, was second reviewer and co-authored this chapter. Professor Michael D. Jenkinson (MDJ) was senior author.

Chapter 3: Volumetric growth of residual meningioma: outcomes and factors associated with progression

3.1. Introduction

When meningioma are resected, in approximately 75% of cases, a complete resection of solid enhancing tumour is achieved- meaning in 25%, there is solid residual tumour[206, 237]. The volumetric growth of the residual meningioma after incomplete resection is currently unknown, with only low powered studies existing in the literature[210, 228]. The prognostic factors and predictors of regrowth of a residual meningioma, namely WHO grade and administration of post-operative fractionated radiotherapy (*f*RT) is also yet to be established.

Understanding the factors that influence growth rate of residual meningioma would help to support clinical decision making after surgery. For example, variables that are associated with progression of the residual tumour could be used to justify initiating early adjuvant radiotherapy, rather than starting active surveillance with MRI. Furthermore, it is unclear from the literature how many patients present with "radiological" progression, in which a patient's residual tumour grows on MRI without provoking clinical symptoms, and "clinical" progression, when the patient develops new or worsening neurological symptoms[238]. The pattern of growth that residual meningioma exhibit remains unexplored in residual meningioma, with no studies available.

There is a need for a high-quality study that investigates growth rates in residual meningioma to either support or disprove previous studies[206, 210, 228]. Understanding the growth pattern and trajectory of these tumours could aid in clinical decision making and understanding, and help indicate the growth patterns of meningioma subject to long-term follow-up without intervention.

3.2. Objectives

3.2.1. Primary objectives

1. Delineate the volumetric growth of residual tumour for meningiomas undergoing subtotal resection.
2. Identify variables associated with meningioma regrowth and progression.

3.2.2. Secondary objectives

1. Establish the rate of radiological regrowth (progression) in patients with residual meningioma.
2. Compare growth rates of meningioma that have received adjuvant fractionated radiotherapy (*f*RT), to those that did not receive any adjuvant treatment for the residual meningioma.
3. Identify the best growth curve to simulate residual meningioma growth.

3.3. Methods

3.3.1. Study design

This was a retrospective, single-centre cohort study conducted at the Walton Centre NHS Foundation Trust. Patients were eligible for the study if they were: ≥18 years of age, and had surgery for meningioma with residual tumour (equivalent to a Simpson grade 4 or 5 resection) operated between 1st January 2004 and 1st February 2019. This study was approved by the Walton Centre NHS Foundation Trust clinical audit group on 19th February 2020. Patients who underwent surgery were consented to the Walton Research Tissue bank. All tissue, imaging and clinical information were available for use under this ethics approval.

3.3.2. Study setting and participants

The Walton Centre NHS Foundation Trust is a tertiary Neuroscience centre, with a catchment area of 3.5 million people. Patients who underwent surgery for meningioma between 1st January 2004 and 1st February 2019 that also had residual tumour were identified. Residual meningioma was identified from either confirmed operation notes by the operating surgeon, or on the baseline post-operative MRI within 3 months of surgery. Patients recorded by the operating surgeon as having undergone a 'Simpson grade 4' resection were eligible for analysis. Patients ineligible were those that did not have subtotal resection confirmed by radiological imaging, syndromic meningioma, and those undergoing a repeat surgery (re-operation). Patients with less than 3 follow up scans were excluded from the volumetric component of the study.

3.3.3. Meningioma database

To identify eligible patients, a large meningioma database was constructed and captured all meningioma patients diagnosed at the Walton Centre between 01/01/2004 and 31/12/2019. The database was compiled by three intercalating medical students (see acknowledgments for details). 1850 patients with meningioma were entered. This database was searched for every patient categorised as having a residual meningioma, or a Simpson grade IV-V resection, and included in this study.

3.3.4. Baseline characteristics

Baseline characteristics recorded included date and age at diagnosis, sex, ethnicity, if the meningioma was associated with radiation, pregnancy or exogenous hormone use, if the patient had a clinical syndrome that predisposes to meningioma development, if the meningioma was discovered incidentally compared to being symptomatic, the symptoms at presentation, indication for surgery (presence of symptoms, radiological growth or patient choice/preference), WHO performance status (Table 3.1) and Age adjusted Charlson comorbidity index preoperatively (ACCI) (Table 3.2),

meningioma location according to the International Consortium for Meningioma (ICOM) classification, presence of calcification within the tumour, meningioma signal intensity on T2-weighted MRI imaging, peritumoural oedema on T2-weighted MRI imaging (measured using manual slice segmentation in cm^3), bone invasion, hyperostosis, proximity to venous sinuses (stratified into 3 categories- separate, direct contact and invading [Figure 3.1]), and involvement of critical neurovascular structures including cranial nerves, arteries and veins. Surgical variables included the pre-operative tumour volume in cm^3, extent of resection according to Simpson grade, WHO grade, Ki-67 index (where available), presence of residual tumour, residual tumour location, and volume of residual tumour. Adjuvant treatments collected were *f*RT/Stereotactic radiosurgery (SRS) if received, the doses and fractionations, and time of adjuvant therapy. A patient was deemed to have received adjuvant *f*RT if it was delivered within 6 months of the original surgery. Follow up data included WHO performance status (PS), Karnofsky performance status (KPS) and ACCI at 6 months, 12 months, 5 years after surgery, and at last follow up.

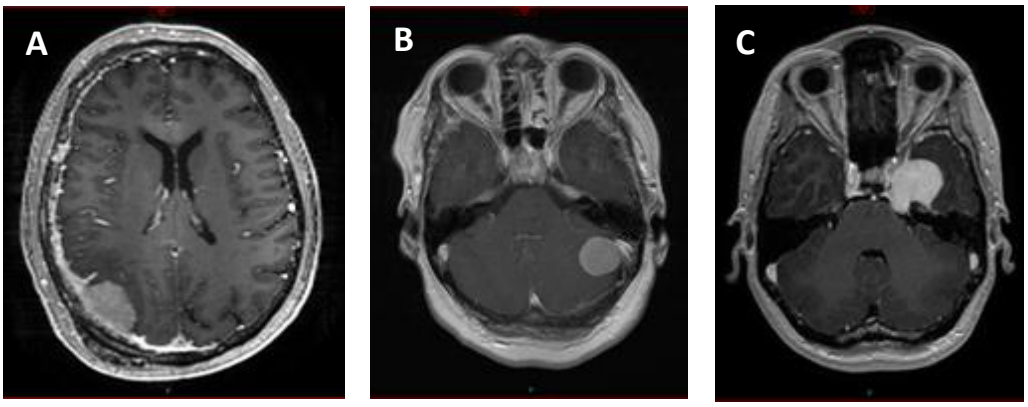


Figure 3.1. Axial, gadolinium enhanced post contrast T1 MR brain scans of various intracranial meningiomas. (A) Convexity meningioma with no evidence of sinus invasion. (B) Infratentorial meningioma in direct contact with the left transverse sinus. (C) Sphenoid wing meningioma invading the cavernous sinus.

Table 3.1. WHO performance status classification.

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Table 3.2. Age adjusted Charlson comorbidity index.

Condition	Weight
Myocardial infarction	**1**
Congestive heart failure	**1**
Peripheral vascular disease	**1**
Hemiplegia	**2**
Cerebrovascular disease	**1**
Pulmonary disease	**1**
Diabetes	**1**
Diabetes with end organ damage	**2**
Renal disease	**2**
Liver disease (mild)	**1**
Liver disease (severe)	**3**
Peptic ulcer disease	**1**
Any cancer	**2**
Cancer with metastatic spread	**6**
Dementia	**1**
Connective tissue disease	**1**
Acquired immunodeficiency syndrome (AIDS)	**6**
Hypertension	**1**
Skin ulcers or cellulitis	**2**
Taking Warfarin	**1**
Depression	**1**
Age (years)	
<50	**0**
50-59	**1**
60-69	**2**
70-79	**3**
≥80	**4**

Clinical progression or radiological regrowth were also noted if they occurred, and subsequent treatments for this (such as repeat surgery, *f*RT or SRS) were recorded. Follow up variables recorded were the follow up time after surgery (in months), date of last follow up, patient mortality, if mortality was secondary to meningioma, and the number of follow up MRI scans in total. Growth variables recorded were the absolute growth, absolute growth rate per year, relative growth rate, and mean tumour doubling time. In accordance with departmental policy, patients were followed up with a variety of different scan strengths on MRI, ranging from 0.35T to 3T. Data collection took place between 1st January 2021 and 1st April 2021.

3.3.5. Data sources

- Baseline demographics: Patient's medical records.
- ICOM location: Carestream Vue Patient archiving and communications system (PACS) MRI scans version 12.
- Surgical variables: Surgeon's operative notes/surgical logbooks.
- Adjuvant therapy/radiation treatment details: Clatterbridge Cancer Centre Oncology clinic letters/clinical notes.
- Overall outcome (discharged, still under follow up, KPS at last follow up): Medical records and NHS Spine.

3.3.6. Quantitative analysis

Statistical analysis was carried out using SPSS statistics version 26 (IBM, Armonk, NY, USA) and figures were created using R version 4.0.2. Continuous variables were analysed using mean (standard deviation [SD]), or median (interquartile range [IQR]), dependent on a histogram, normal distribution curve, and Kolmogorov-Smirnov test of normality. Statistical significance for baseline characteristic differences were assessed using the Chi-squared test for categorical variables, and a student's t test or Mann-Whitney U test was used for continuous data as appropriate. Differences were considered statistically significant if $P < 0.05$.

3.3.7. Volumetric measurements

Tumour volume was measured using the patient archiving and communications system (PACS) semi-automatic volume measurement tool. Tumour volume was measured by manually tracing around each slice in the axial, coronal and sagittal dimensions. The tool has two features: a semi-automatic measurement that allows the user to measure the first and last slices appearing on a sequence. The tool will then estimate and measure the tumour in between slices, and approximate a total volume based on these measurements. The approximated measurements for each slice can be modified using the tools. For this study, each slice was manually contoured to ensure an optimal measurement, then

all of the slices combined to calculate the volume. In most cases, the axial view was used for this purpose. In cases when this was not available, a coronal or sagittal view was used. A diagram of how the tool was used can be found below (Figure 3.2).

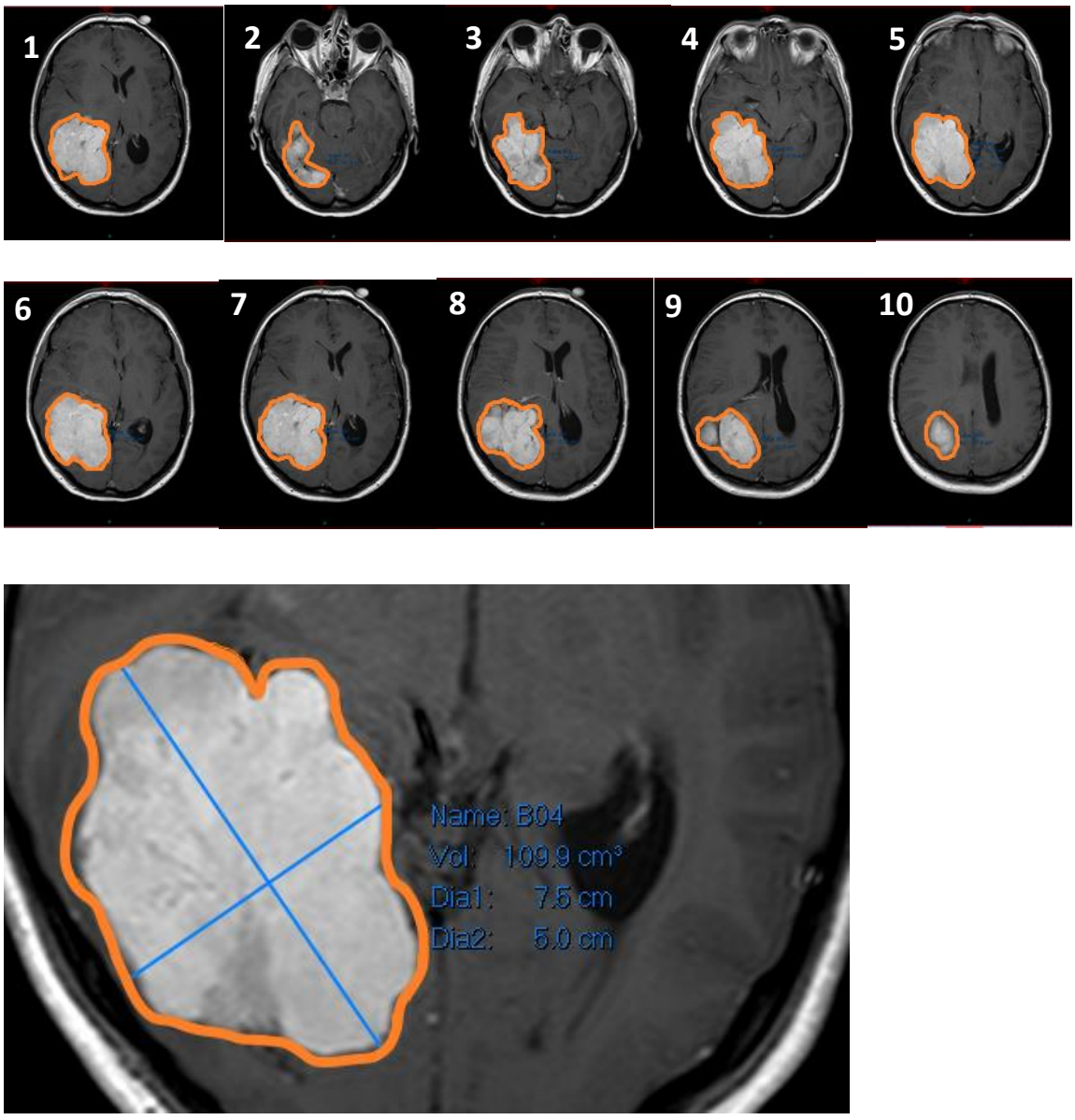


Figure 3.2. Figure demonstrating the PACS semi-automated measuring tool for volumetric analysis. Manual tracing is performed for each axial slice of tumour, and the volume calculated.

In total, 1034 measurements of residual tumour were completed (Figure 3.3). 190 oedema volumes on T2-weighted sequences were measured (Figure 3.4), and 193 pre-operative tumour volumes were available and measured. Each tumour volume was measured, both pre-operatively and post-

operatively, and then measured at each interval scan using the same method. Volume measurements were carried out even if radiotherapy was given, and after repeat surgeries, but these patients were censored from the volumetric growth analysis at point of commencement of these treatments. Volumetric growth was determined using a linear-mixed effects model, which included both the random intercept and slope, with 100 iterations. We measured the absolute growth rate (AGR) in cm^3, and measured the relative growth rate (RGR) in cm^3. AGR was defined as $\left(\left(\frac{V2-V1}{time(months)}\right) \text{x } 12\right)$ (increase in volume [V] per year), whilst RGR was defined as $\left(\left(\frac{\frac{(V2-V1)}{V1}}{time\ (months)}\right) \text{x } 12 \text{ x } 100\right)$ (percentage increase in volume per year). The tumour doubling time (TDT) was defined as the time required for a tumour to double in size. Tumour progression (regrowth) was defined according to RANO criteria, which was an absolute increase in volume over 40% at any point during the follow up period. A second observer (GER/MAM- intercalating Master of Research [MRes] students) independently assessed radiological parameters (T2-weighted MRI signal intensity, calcification, venous sinus invasion and residual tumour volume), and an intra-class correlation coefficient (ICC) was calculated to assess observer agreement.

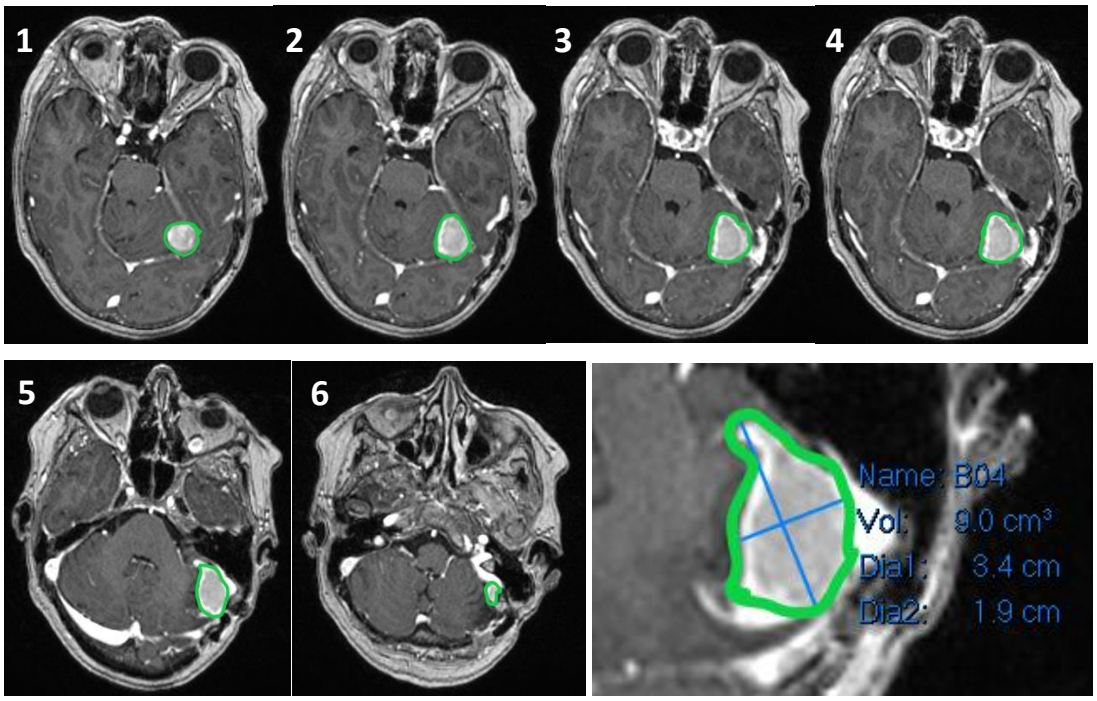


Figure 3.3. Figure demonstrating the PACS semi-automated measuring tool for residual tumour volume measurement. Manual tracing is performed for each axial slice of tumour, and the volume calculated.

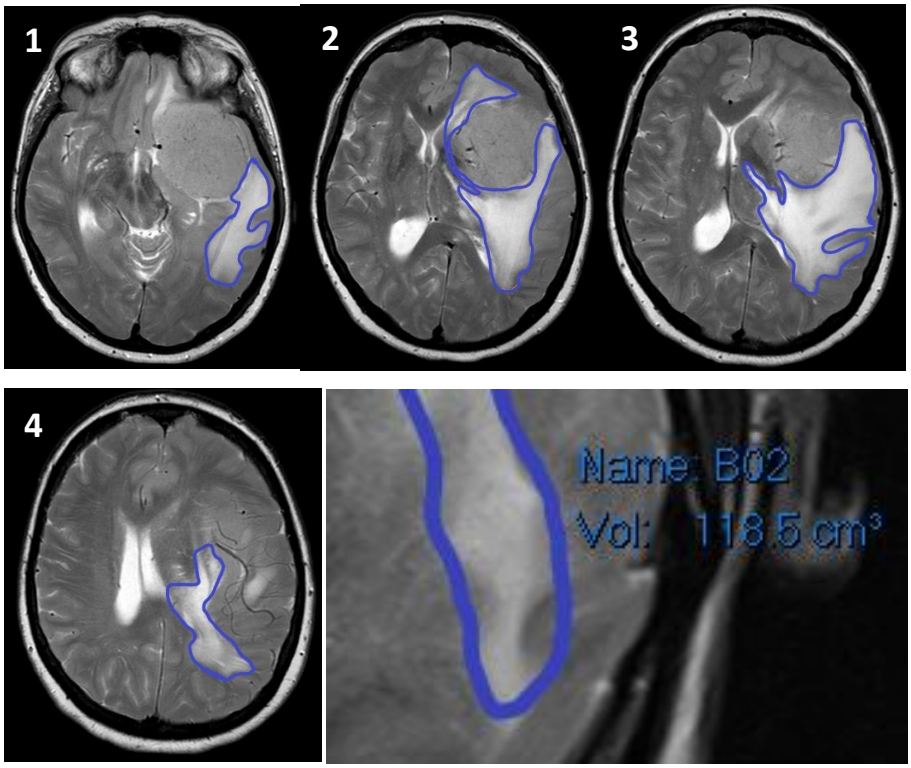


Figure 3.4. Figure demonstrating the PACS semi-automated measuring tool for oedema measurement. Manual tracing is performed for each axial slice that oedema is present, and the volume calculated.

3.3.8. Growth curve analysis

Of all meningiomas identified in the cohort, the growth curve for each individual tumour was estimated. Meningiomas were excluded if they underwent intervention before having four post-operative follow up MRI scans (such as *f*RT, SRS or repeated surgery), as there would not be sufficient data points to estimate the growth curves accurately. The volume of meningioma was plotted on a volume time curve, and the non-linear regression, growth curve estimation function in SPSS V26 was used to approximate the best curve fit. Meningioma growth was assessed against 6 established growth trajectories: linear, logarithmic, power, exponential, and logistic curves. The R and R^2 values were derived from each meningioma to assimilate the best curve estimation for each meningioma. Quartiles were estimated by linear interpolation between neighbouring sample values as necessary. Overall values were combined with the median R^2 value for each meningioma showcased. The constant was included in the equation, meaning that the starting volume of each tumour was considered in curve estimation, rather than starting at zero. Data analysis was conducted using SPSS V26.

3.3.9. Survival/progression analysis

Progression was estimated by cox regression analysis, using the RANO criteria as an endpoint[239], time from surgery until progression (in months) as the time, and assessed variables associated with progression using univariable and multivariable analysis. Variables with P<0.1 on univariable analysis were incorporated into the cox regression model for multivariable analysis. Factors were considered significant if P<0.05.

3.4. Results

3.4.1. Study population and baseline characteristics

Figure 3.3 describes the study population selection process. In total, 238 patients met the initial inclusion criteria. After exclusion of two patients with syndromic meningioma (both patients had NF2), 236 patients were included. The baseline characteristics are shown in Table 3.3. The median age at diagnosis was 56.8 years (IQR 46.5-67.5 years). Most patients were female (n=174, 73.1%), and the female: male ratio was approximately 3:1. 93.2% of patients were of “White British” ethnicity (n=220). Three patients had previously received craniospinal radiation (radiation-induced meningioma), and three patient’s meningioma was linked to pregnancy/hormone replacement therapy (HRT).

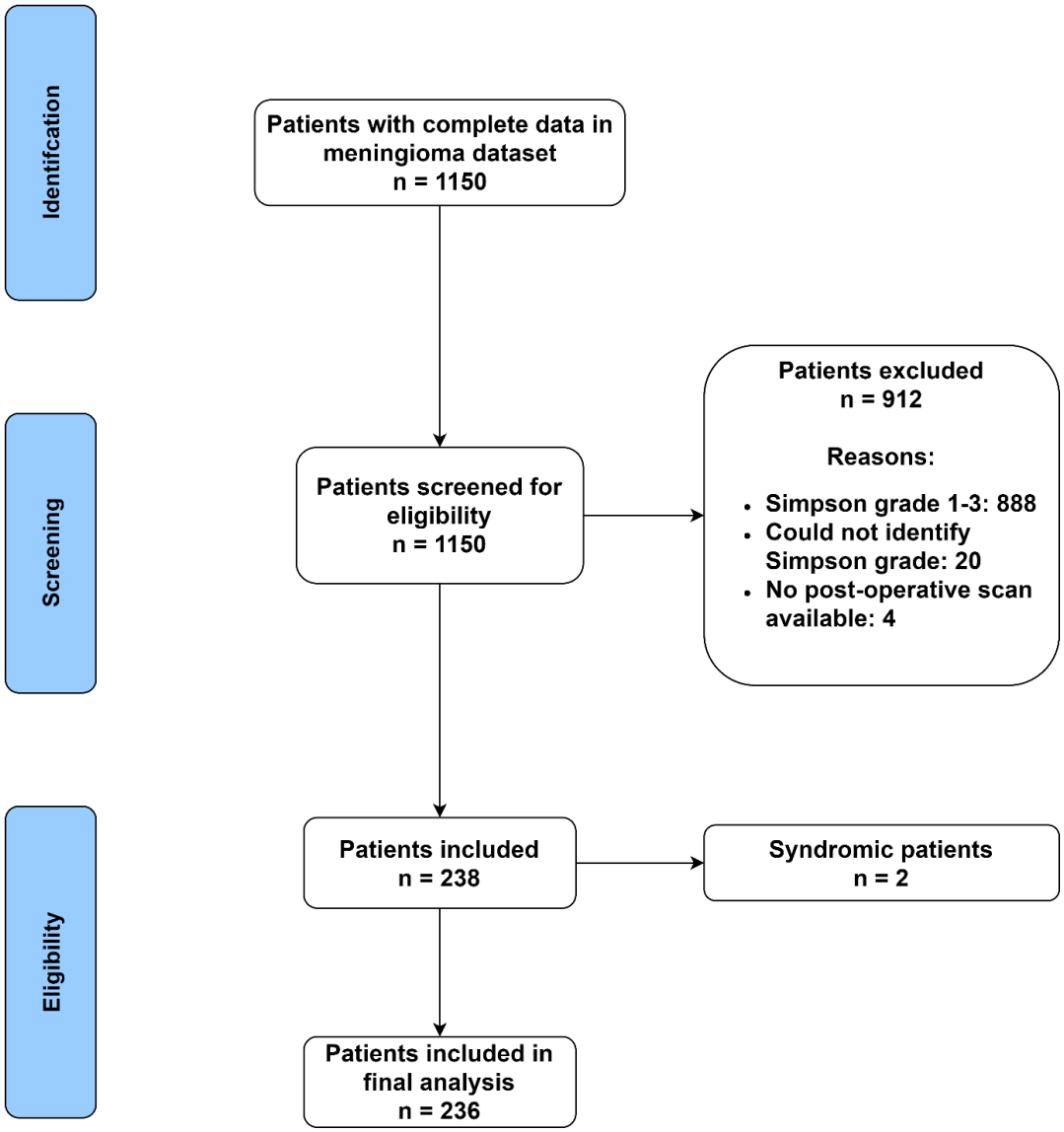


Figure 3.5. Patient selection process.

Table 3.3. Baseline demographics and clinical characteristics

Characteristic		**N (%)**
Age	Mean (SD)	56.3 (13.7)
	<40	29 (12.3)
	40-49	47 (19.9)
	50-59	55 (23.3)
	60-69	61 (25.8)
	70-79	38 (16.1)
	≥80	6 (2.5)
Sex	Male	62 (26.3)
	Female	174 (73.7)
Ethnicity	White British	220 (93.2)
	White- 'Other'	6 (2.5)
	White- 'European'	2 (0.8)
	Indian	2 (0.8)
	Chinese	2 (0.8)
	Asian other 'Cantonese'	1 (0.4)
	Arabic	1 (0.4)
	White other 'South American'	1 (0.4)
	Unknown	1 (0.4)
Radiation induced	No	233 (98.7)
	Yes	3 (1.3)
Pregnancy/HRT	No	233 (98.7)
	Yes	3 (1.3)
Incidental	Yes	32 (13.6)
	No	204 (86.4)
Symptoms	Headache	65
	Seizures	41
	CN deficit(s)	77
	CN 2	62
	Other CN deficit	19
	Limb weakness	30
	Limb sensory disturbance	12
	Altered GCS	12
	Cognitive deficit	22
	Ataxia	17
WHO Performance status (pre-op)	Median (IQR)	0 (0-1)
	0-1	190 (80.5)
	2-4	46 (19.5)
ACCI (pre-op)	Median (IQR)	2 (1-3)
	0-2	160 (66.4)
	3-5	62 (26.4)
	>5	17 (7.2)

SD= Standard deviation, IQR= Inter-quartile range, HRT= Hormone replacement therapy, CN= Cranial nerve, GCS= Glasgow Coma Scale.

3.4.2. Clinical features

Most patients were symptomatic from their meningioma (86.4%, n=204), and 32 meningiomas were discovered incidentally. The most common presenting symptoms were cranial nerve deficit (32.6%, n=77), headache (27.5%, n=65), and seizures (17.4%, n=41). Forty-two presented with limb weakness or limb sensory symptoms, twenty-two presented with a cognitive deficit, seventeen with ataxia, sixteen with nausea and/or vomiting, twelve presented with altered GCS, nine presented with psychiatric symptoms, and eight presented with expressive dysphasia. The most common cranial nerve deficits were optic nerve (76.5%, n=62) and vestibulocochlear nerve (8.6%, n=3).

3.4.3. Radiological features

Radiological characteristics of the cohort are shown in Table 3.4. The distribution of meningioma locations was 96 right sided, 94 left sided, and 46 located in the midline. The most frequently occurring ICOM locations were sphenoid wing (23.9%, n=56), anterior midline (22.0%, n=52), and parafalcine (14.0%, n=33) (Table 3.4). Most meningiomas were located in the skull base (59.3%, n=140). Seventy meningiomas displayed calcification, with 45 being partial, and 25 diffuse. One hundred and twenty meningiomas were hyperintense on T2 MRI, fifty were isointense, and nineteen were hypointense.

Of 195 patients with a T2-weighted pre-operative MRI scan available to assess peritumoural oedema, 120 had any oedema present (61.5%). The median oedema volume was 39.1cm^3 (IQR 6.5-85.6, range 223.5), and the most common extent of oedema relative to tumour volume in cm^3 was '100% and greater' (n=47, 40.5%). The median oedema index (volume of oedema relative to tumour volume) was 0.72 (IQR 0.15-1.74, range 8.82), and the median volume of oedema relative to tumour volume was 72.2% (IQR 14.8%-174.3%). Sixty-seven patients had evidence of bone invasion, and 59 patients had evidence of hyperostosis on pre-operative scanning.

One hundred and ten (46.6%) meningiomas displayed evidence of sinus involvement. Of these, 35 (31.8%) were in direct contact with the sinus, and 75 (68.2%) were invading. In total, 83 meningiomas were compressing/encasing a critical neurovascular structure. Overall, 138 meningiomas (58.5%) were either in direct contact with, invaded a sinus, or compressed/encased a critical neurovascular structure. The median pre-operative tumour volume before surgery was 34.0cm^3 (IQR 16.0-63.0, range 276.0). The median mean tumour diameter was 22.7mm (IQR 10.6-42.0, range 1.0-184.0), and the median maximum tumour diameter in a single measurement was 49.0mm (IQR 36.0-60.0).

Table 3.4. Radiological characteristics of the cohort		
Characteristic		**N (%)**
Tumour Laterality	Left	94 (39.8)
	Right	96 (40.7)
	Midline	46 (19.5)
Skull base	Yes	140 (59.3)
	No	96 (40.7)
Calcification	Absent	139 (66.5)
	Partial	45 (21.5)
	Diffuse	25 (12.0)
Tumour signal intensity	Hyperintense	120 (63.5)
	Isointense	50 (26.5)
	Hypointense	19 (10.0)
Peritumoural oedema	Yes	120 (61.5)
	No	75 (38.5)
Peritumoural oedema relative to tumour volume (%)	0-5	14 (12.1)
	6-33	26 (34.5)
	34-66	17 (14.7)
	67-100	12 (10.3)
	>100%	47 (40.5)
Oedema volume (cm^3)	Median (IQR)	39.1 (6.5-85.6)
Oedema grade	1	12 (10.3)
	2	35 (30.2)
	3	69 (59.5)
Oedema index	Median (IQR)	0.7 (0.1-1.7)
Bone invasion	Yes	67 (33.2)
	No	135 (66.8)
Hyperostosis	Yes	59 (29.2)
	No	143 (70.8)
Sinus invasion	Separate	103 (48.4)
	Direct contact	35 (16.4)
	Invading	75 (35.2)
Compressing critical neurovascular structures	Yes	83 (38.6)
	No	132 (61.4)
Pre-operative tumour volume (cm^3)	Median (IQR)	34.0 (16.0-63.0)
Pre-operative tumour diameter (mm)	Median (IQR)	22.7 (10.6-42.0)

3.4.4. Surgery and residual tumour volume

The median time to surgery was 1.4 months after diagnosis (IQR 0.5-4.4 months, range 0-103 months, Table 3.5). The most common indication for surgery was presence of symptoms (86.0%, n=203), followed by patient preference (7.2%, n=17), and radiological progression (6.8%, n=16). There were 195 WHO grade 1 (82.6%), 40 WHO grade 2 (16.9%), and 1 WHO grade 3 meningiomas. The most common histopathological subtypes were meningothelial (46.2%, n=85), transitional (20.7%, n=38), and atypical (15.8%, n=29). Twenty patients had a recorded Ki-67 index (median 7.0, IQR 4.3-11.5). The median residual tumour volume was 2.0cm^3 (IQR 0.8cm^3-5.2cm^3, range 0-66.1), and the median percentage tumour resected at first surgery was 92.0% (IQR 77.5%-97.5%). In total, 180 patients had a Simpson grade 4 resection according to the operating surgeon. 56 patients had a complete resection recorded in the operation note, but on the baseline MRI at 3 month follow up scans had residual meningioma identified (initial extent of resection recorded was 12 Simpson grade 1, 32 Simpson grade 2, and 11 Simpson grade 3).

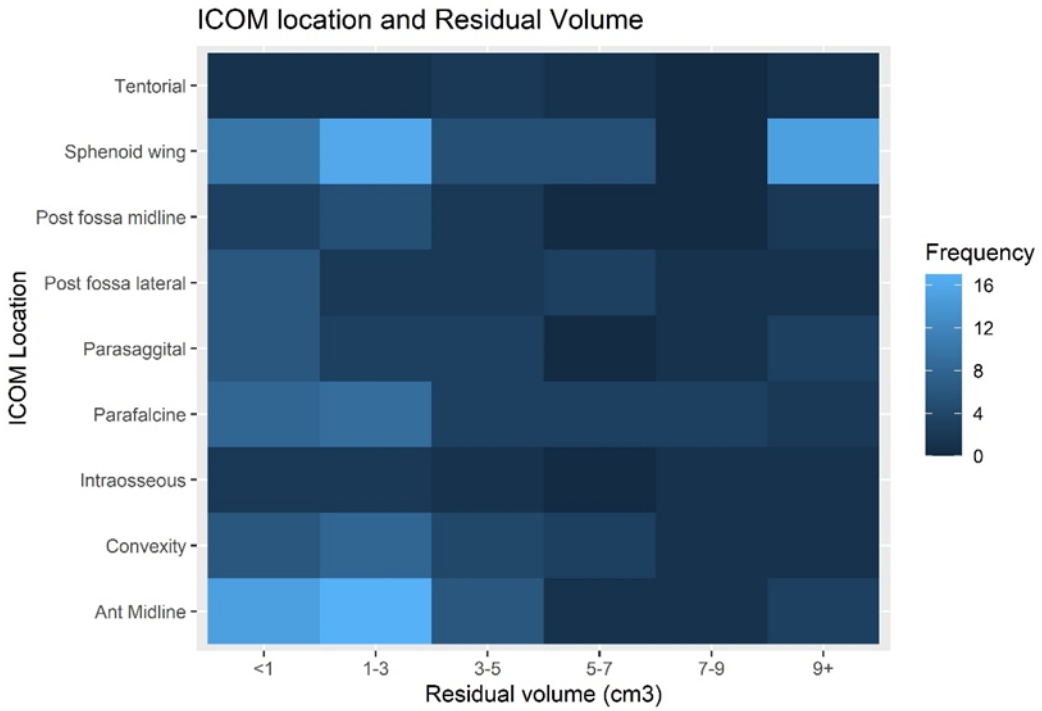


Figure 3.6. Heatmap demonstrating ICOM location, and residual tumour volume, with density representing number of cases.

Table 3.5. Surgical and adjuvant treatments of the cohort		
Characteristic		**N (%)**
Time to surgery (months)	Median (IQR)	1.4 (0.5-4.4)
WHO grade	1	195 (82.6)
	2	40 (16.9)
	3	1 (0.4)
Ki-67 index	Median (IQR)	7.0 (4.3-11.3)
Residual tumour volume (cm^3)	Median (IQR)	2.0 (0.8-5.2)
Percentage of original tumour resected (%)	Median (IQR)	92.1 (77.5-97.5)
Percentage of original tumour remaining (%)	Median (IQR)	7.9 (2.5-22.5)
Additional treatments	No treatment	156 (66.1)
	*f*RT	68 (28.8)
	SRS	12 (5.1)
Time to *f*RT (months)	Median (IQR)	10.9 (4.0-44.9)
Adjuvant* *f*RT?	Yes	36 (15.3)
	No	200 (84.7)
***Adjuvant *f*RT defined as patient receiving *f*RT within 6 months of the original surgery.**		

3.4.5. Adjuvant treatment and follow-up

Most patients underwent initial MRI surveillance (n=200). Sixty-eight patients received *f*RT, and 12 patients received SRS. Of these, 36 received treatment in the adjuvant setting (within 6 months of surgery), and 44 received treatment after 6 months. Patients who received SRS had doses of 12.5Gy (n=9) or 15Gy (n=3) in one fraction, and patients who received *f*RT either had 54 Gy in 30 fractions (n=55) or 60 Gy in 30 fractions (n=10). The median time from surgery to *f*RT or SRS was 10.9 months (IQR 4.0 months-44.9 months). The mean number of follow up scans available per patient was 8.5 (SD 3.9, range 1-24). The median follow-up time after surgery was 64.4 months (IQR 41.7 months-103.5 months).

3.4.6. Volumetric growth and progression

The volumetric growth of residual tumours is shown in Table 3.6. In all patients post-operatively, the median annual relative growth rate and absolute growth rate were 4.3% (IQR 1.4%-14.7%), and 0.11 cm^3/year (IQR 0.03-0.68cm^3/year) respectively. The median relative and absolute growth over the study period were 82.5% (IQR 26.9%-284.0%) and 2.2cm^3 (IQR 0.6-12.3) respectively. Growth plots of all residual meningioma are shown in figure 3.5. In total, one hundred and thirty-two (56.0%) tumours satisfied the RANO criteria for progression[239] (increase in volume of over 40% during follow up [Table 3.6]). Of the cohort, 13 patients demonstrated clinical progression (5.5%). The most common

symptoms of progression were visual field loss/progression of existing visual field deficit (n=6) and headache (n=4). The median time to progression was 45.5 months after surgery (IQR 28.4-76.8 months [Figure 3.6 and Figure 3.7]).

Table 3.6. Volumetric growth and progression observed among the cohort of 236 residual meningiomas

Growth Characteristic		**N (%)**
Absolute growth (cm^3)	Median (IQR)	2.2 (0.6-12.3)
AGR (cm^3)	Median (IQR)	0.11 (0.03-0.68)
Relative growth (%)	Median (IQR)	82.5 (26.9-284.0)
RGR (%)	Median (IQR)	4.3 (1.4-14.7)
Progression as per RANO criteria	Yes	132 (55.9)
	No	97 (41.1)
Clinical progression	Yes	13 (5.5)
	No	223 (94.5)
Symptoms of progression	Visual field progression	6 (42.9)
	Headache	4 (28.6)
	Sensory disturbance	1 (7.1)
	Lump re-appearance	1 (7.1)
	Bilateral arm pain	1 (7.1)
	Fatigue	1 (7.1)
Time to progression (months)	Median (IQR)	45.5 (28.4-76.8)

AGR= Absolute Growth Rate; RGR= Relative Growth rate; RANO= Response Assessment in Neuro-Oncology.

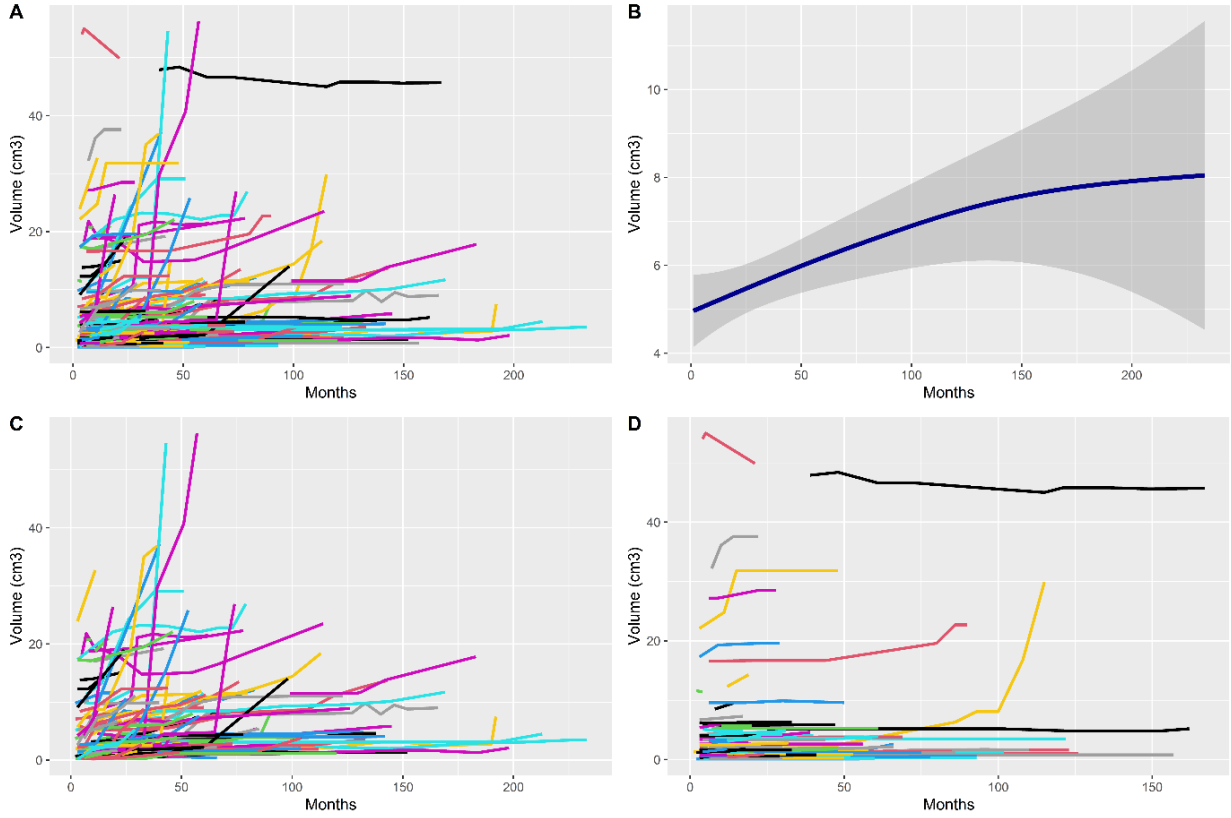


Figure 3.7. Volume-time growth plots demonstrating (A) All volumetric growth of meningioma in the study, (B) Smooth conditional means plot demonstrating overall residual tumour growth (with shading representing 95% confidence intervals), (C) Meningiomas that progressed according to RANO criteria, and (D) Meningiomas that did not progress according to RANO criteria.

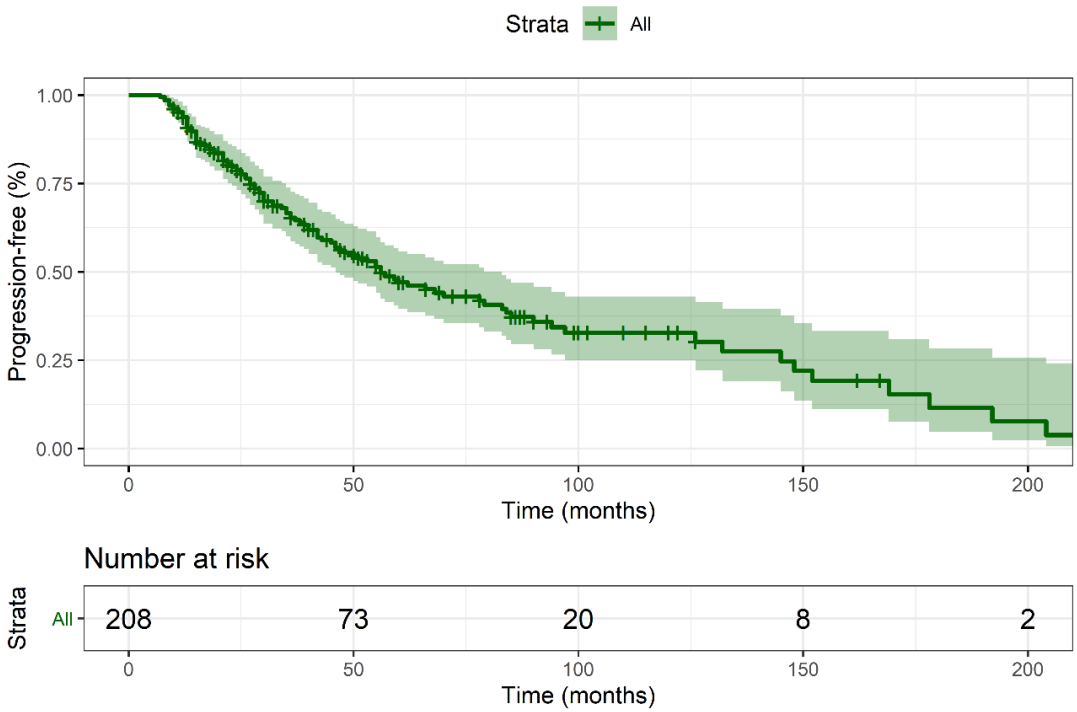


Figure 3.8. Kaplan-Meier curve demonstrating progression-free survival (PFS) in the cohort.

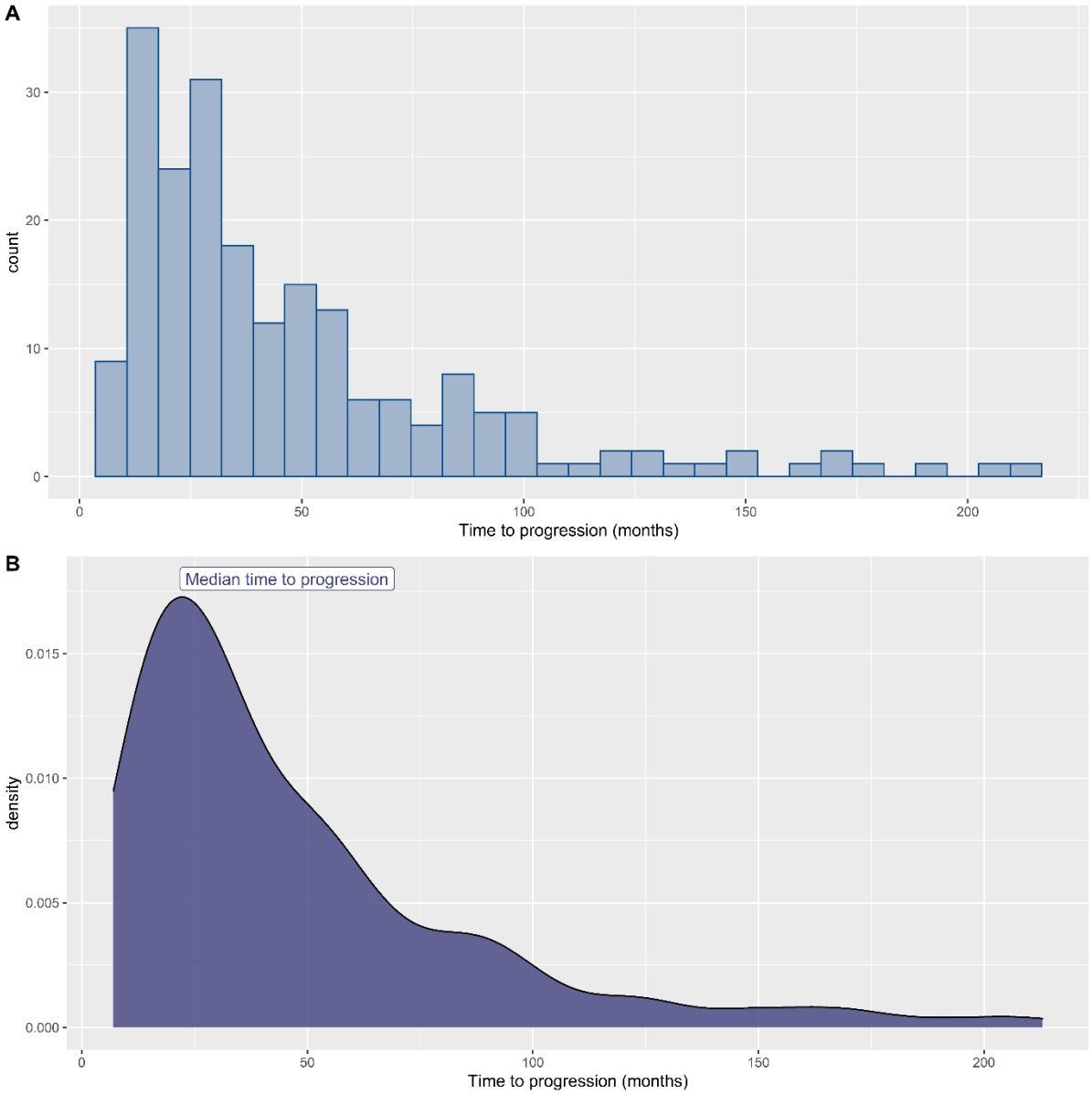


Figure 3.9. (A) Histogram and (B) Density plot of time to progression (in months) of residual meningioma in the cohort.

3.4.7. Treatment strategies for progression

The treatment strategies for patients whose meningioma progressed are outlined in Figure 3.8. In total, forty-nine patients (36.3%) were treated for progression of their residual meningioma, with eighty-six managed conservatively (73.7%). Nineteen patients were treated with *f*RT, fifteen with repeat surgery alone, ten with SRS, and five with surgery plus adjuvant *f*RT. Of these patients, only eight (16.3%) progressed further, with six progressing after repeat surgery, and two progressing after SRS. Seven patients were treated further, with one managed conservatively (three with *f*RT,

three repeat surgery, and one with SRS). Only one patient progressed after a third surgery, and was treated with SRS, with no further progression at last follow up.

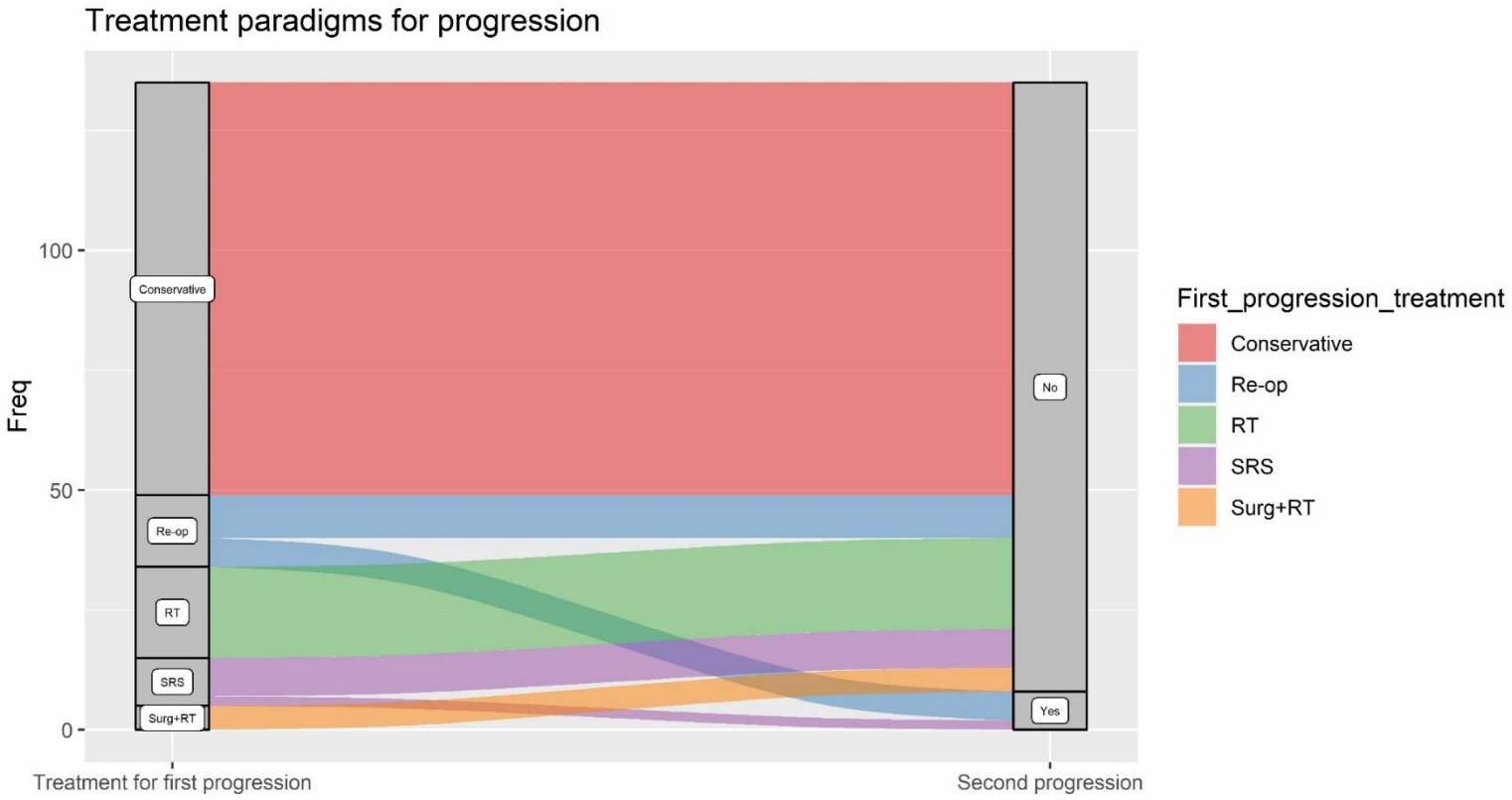


Figure 3.10. Alluvial plot outlining different treatment paradigms for meningiomas that progressed according to RANO criteria.

3.4.8. Factors associated with progression of residual tumour

The cox regression analysis for univariable and multivariable analysis is shown in Table 3.7 and Table 3.8. On univariable analysis, factors identified as significant were ethnicity, if the meningioma was associated with radiation, skull base location, presence of calcification, adjuvant *f*RT, and increased Ki-67 index. These were incorporated into the cox regression model on multivariable analysis. On multivariable analysis, factors associated with progression were skull base location (HR 1.58 [95% CI 1.02-2.44], *P*=0.040), Adjuvant *f*RT (HR 1.72 [95% CI 1.03-2.29], *P*=0.040), and Ki-67 Index (HR 3.62 [95% CI 1.25-10.48], *P*= 0.018]. Factors not associated with progression on multivariable analysis were ethnicity (HR 1.05 [95% CI 0.78-1.41], *P*=0.761), and presence of calcification (HR 1.44 [0.95-2.17], *P*=0.086).

Table 3.7. Univariable analysis of variables associated with progression.

Risk factor	Hazard ratio (HR)	95% CI	P value*
Age	1.01	0.99-1.02	0.454
Ethnicity (White- other)	10.88	1.45-81.59	**0.020***
Radiation-Induced	10.46	1.35-80.93	**0.025***
Female sex	0.86	0.54-1.37	0.521
Pregnancy/HRT	0.82	0.11-5.68	0.815
Presentation with symptoms	1.30	0.77-2.20	0.322
T2 hyperintensity	0.72	0.47-1.10	0.129
Any Oedema	0.98	0.63-1.52	0.910
Oedema (cm^3)	1.00	0.99-1.00	0.630
Bone invasion	0.80	0.51-1.25	0.324
Hyperostosis	0.80	0.51-1.27	0.348
Any calcification	1.50	0.99-2.26	**0.056***
Sinus invasion	0.75	0.50-1.13	0.167
Compressing a critical neurovascular structure	0.90	0.59-1.37	0.628
Skull base location	1.51	1.02-2.23	**0.039***
Pre-operative tumour volume	1.00	0.99-1.00	0.648
WHO grade (2)	0.97	0.54-1.73	0.965
Ki-67	3.33	1.28-8.67	**0.014***
Residual tumour volume	1.00	0.98-1.02	0.981
% of original tumour remaining	1.00	0.99-1.00	0.479
Adjuvant *f*RT	1.86	1.11-3.10	**0.018***

Table 3.8. Multivariable analysis of variables associated with progression.

Risk factor	Hazard ratio (HR)	95% CI	P value*
Ethnicity (White- other)	1.05	0.78-1.41	0.761
Radiation-Induced	10.72	1.37-83.89	**0.024***
Skull base location	1.58	1.02-2.44	**0.040***
Any calcification	1.44	0.95-2.17	0.086
Adjuvant *f*RT	1.72	1.03-2.89	**0.040***
Ki-67	3.62	1.25-10.48	**0.018***

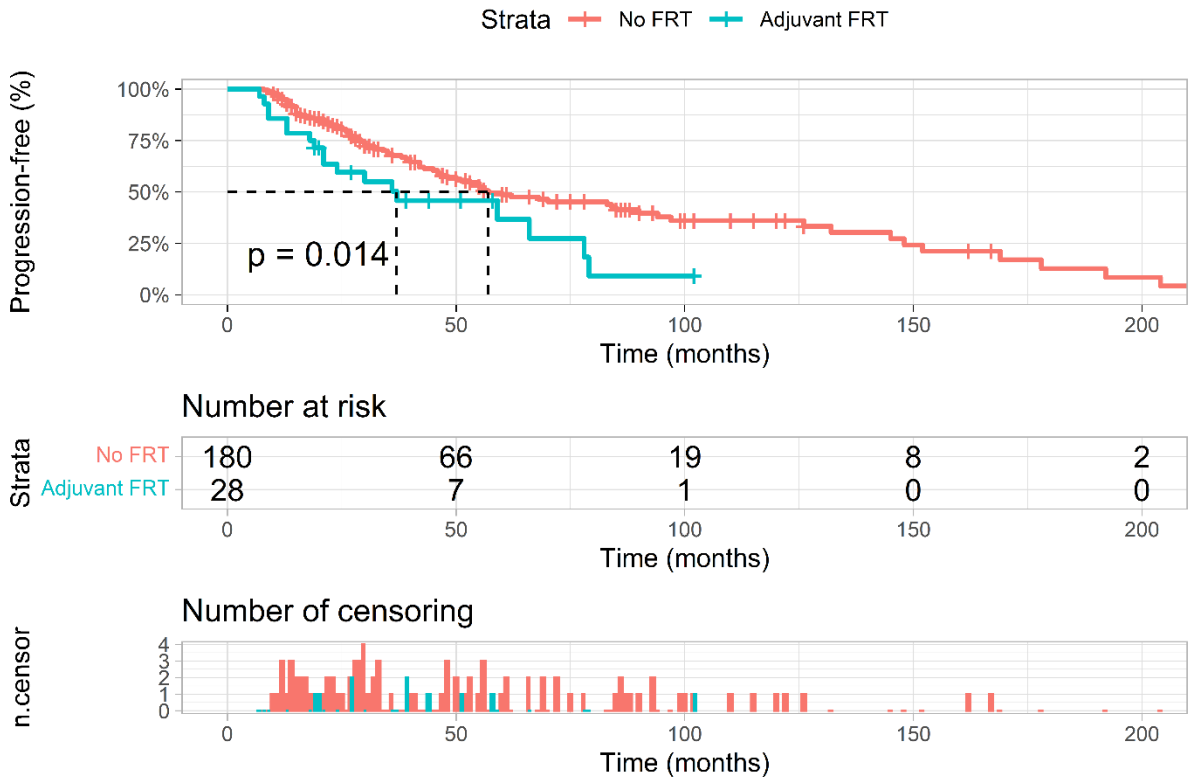


Figure 3.11. Kaplan-Meier curve of progression stratified by adjuvant *f*RT. The log-rank test was significant (*P*=0.014).

3.4.9. Kaplan-Meier analysis

The mean survival of the cohort was 216 months (95% CI 199-232 months) (Figure 3.10). Median survival was not reached. There was no difference between *f*RT, SRS and no adjuvant treatment groups in overall survival (*P*=0.230). The group that received adjuvant *f*RT had worse overall survival (*P*=0.006). Most patients were alive at latest follow up (92.4%, n=218). Of the 18 patients that died, 12 died due to their meningioma. The majority of patients were still under active follow up at the end of the study period (75.8%, n=179).

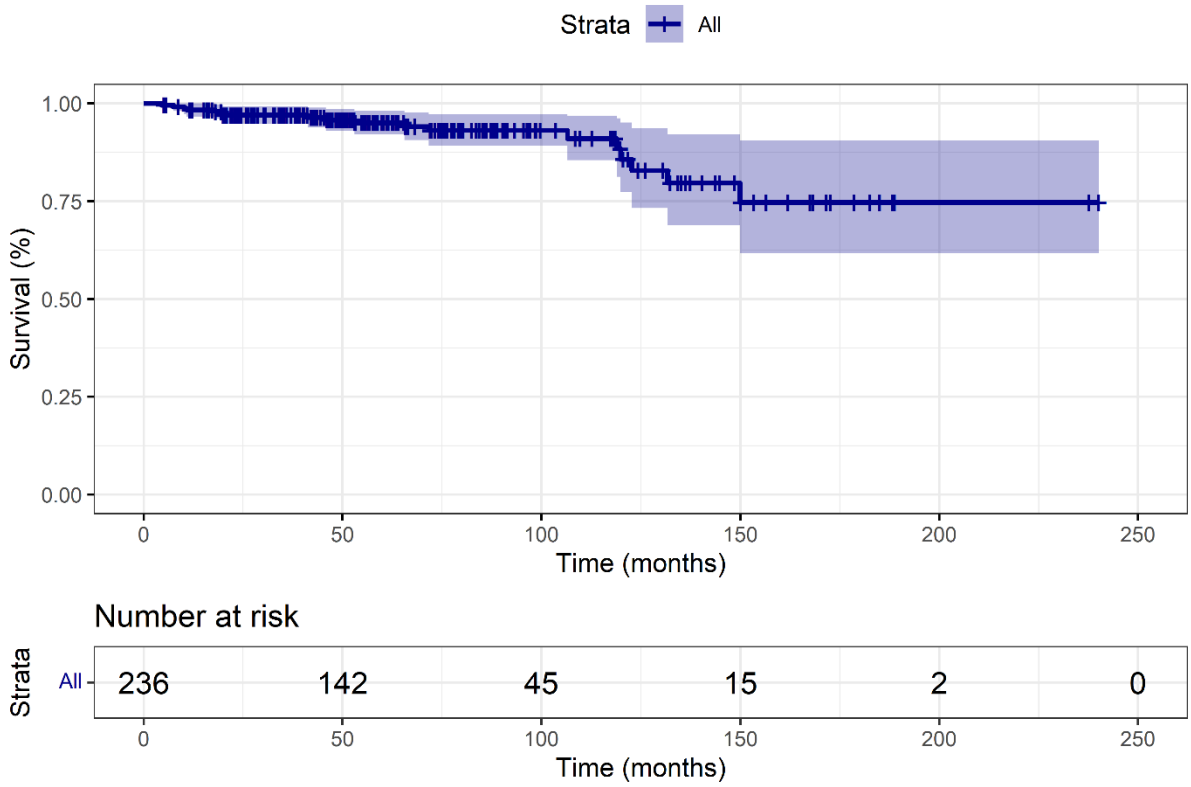


Figure 3.12. Kaplan-Meier curve of overall survival of the cohort.

3.4.10. Data validity

Both inter and intra-observer variability of all radiological factors reached at least a good level of agreement. The independent measurements between CSG and another independent observer (GER or MAM) are outlined in Figure 3.11. Residual volume measures between the primary and secondary raters were consistent (intra-observer ICC 0.988 [95% CI 0.972-0.995], inter-observer ICC 0.984 [95% CI 0.963-0.993]). Weighted kappa for agreements between the two raters for peritumoural signal intensity, calcification, and sinus invasion were all between 0.61 and 0.8, indicating a good level of agreement. For the intra-observer categorical variables, all but sinus invasion had a kappa value of >0.8, indicating a very good level of agreement.

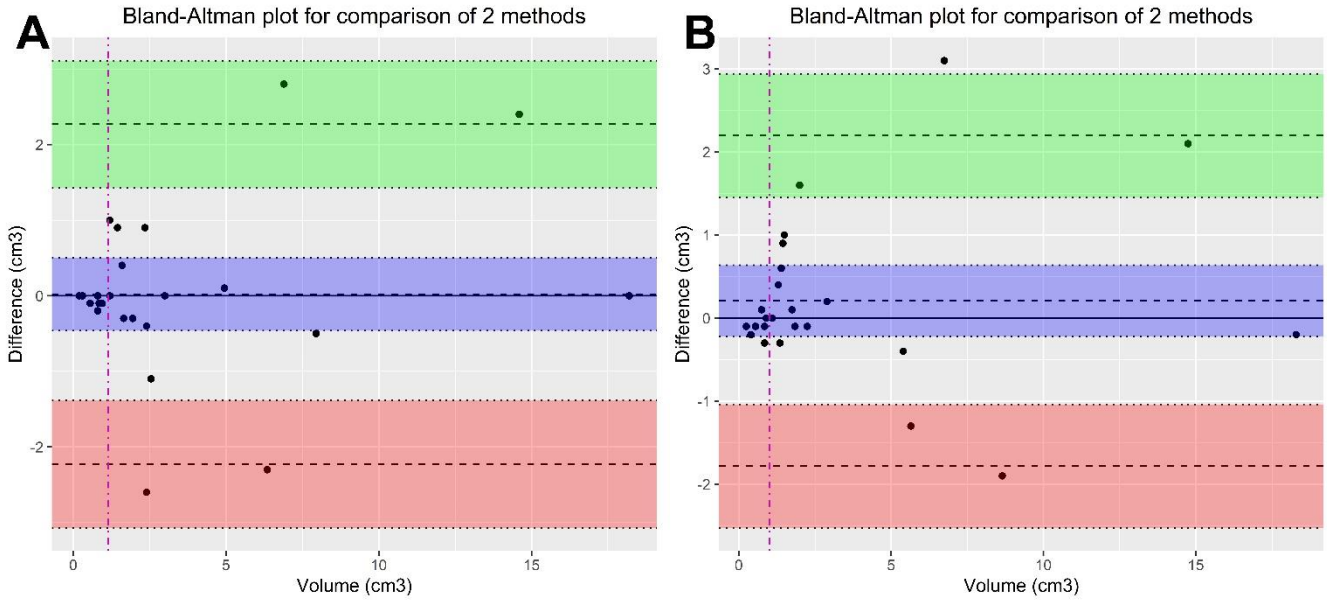


Figure 3.13- Bland-Altman plot with mean residual volume intercept (1.15cm^3) for interobserver variability (A) and intra-observer variability (B). All points are within the 95% CI indicating a good level of agreement.

Table 3.9. Weighted Kappa values assessing the inter- and intra-observer variability among variables

	Weighted Kappa (95% CI)	
Parameter	Inter-observer variability	Intra-observer variability
Calcification	0.747 (0.416-1.000)	0.908 (0.731-1.000)
Tumour signal intensity	0.714 (0.424-1.000)	0.822 (0.587-1.000)
Residual tumour volume	0.984 (0.963-0.993)	0.988 (0.972-0.995)
Sinus invasion	0.673 (0.400-0.949)	0.660 (0.360-0.959)
	ICC (95% CI)	
	Inter-rater variability	Intra-rater variability
Residual tumour volume	0.984 (0.963-0.993)	0.988 (0.972-0.995)

3.4.11. Growth curve estimation

Of 236 patients included in the overall study, only 96 had four follow up scans available before intervention to analyse the growth rates (Figure 3.12). This was mainly because patients ended up having an intervention (such as *f*RT after a meningioma growth) precluding any subsequent scans, or had less than 4 follow up scans after surgery before being discharged.

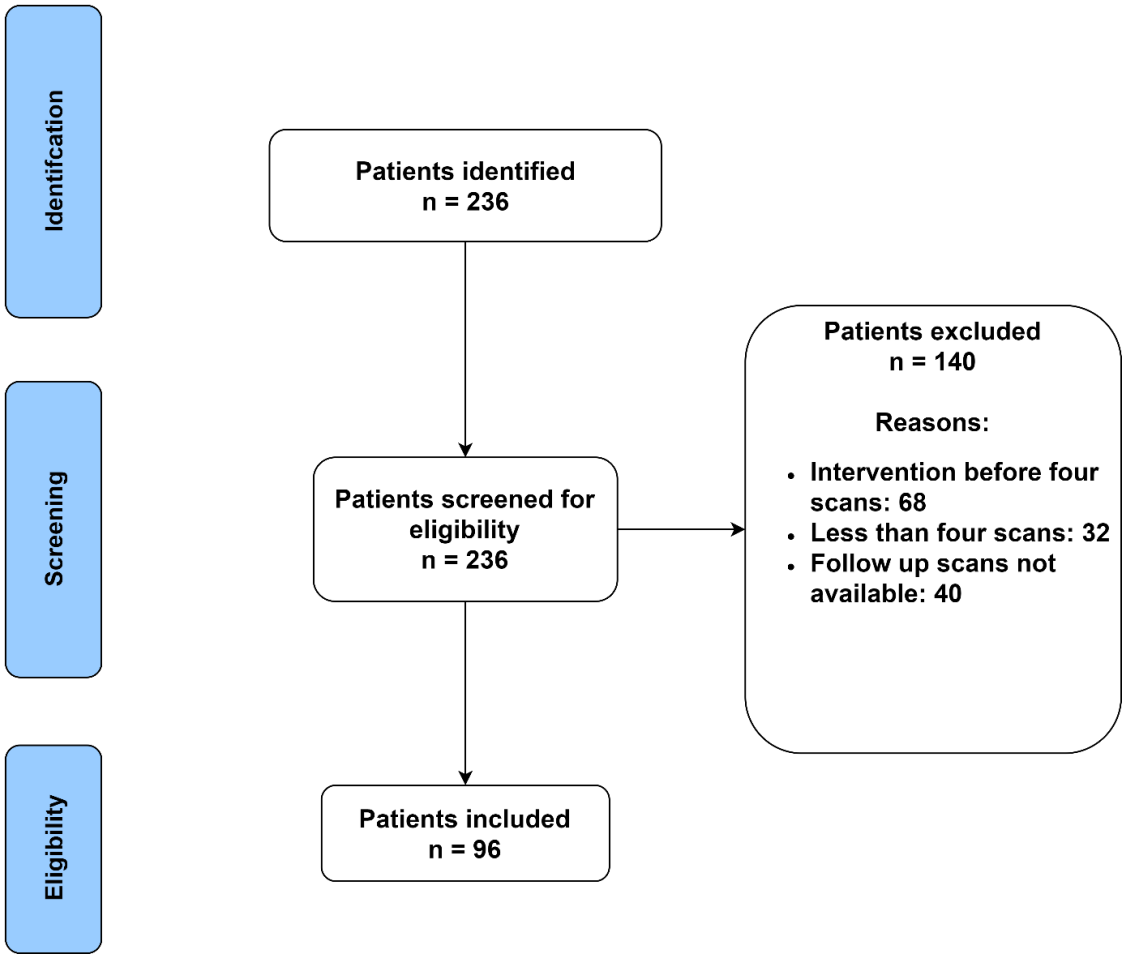


Figure 3.14. Patient flow chart demonstrating number of meningiomas with growth curve data analysed, and reasons for exclusion.

Results are shown in Table 3.10. The most frequently occurring best fit curve for growth was the logistic and exponential curve (38.5%, n=37), followed by Gompertz (36.5%, n=35). Other growth curves occurred much less frequently. The best curve for estimation of all meningiomas were the logistic and exponential curves (median R^2 value 0.84 [IQR 0.60-0.90]) (Figure 3.13).

Table 3.10. Coefficients of determination (all meningiomas, n = 96)			
Regression model	**Percentile**		
	25th	50th (median)	75th
Linear	0.57	0.82	0.91
Logarithmic	0.58	0.76	0.92
Power	0.63	0.77	0.92
Gompertz	0.49	0.72	0.94
Exponential	0.60	**0.84**	0.90
Logistic	0.60	**0.84**	0.90
Highest curve estimations		**N (%)**	
Exponential and Logistic		37 (38.5)	
Gompertz		35 (36.5)	
Tie (linear, exponential and logistic)		7 (7.3)	
Power		7 (7.3)	
Logarithmic		6 (6.3)	
Linear		4 (4.2)	

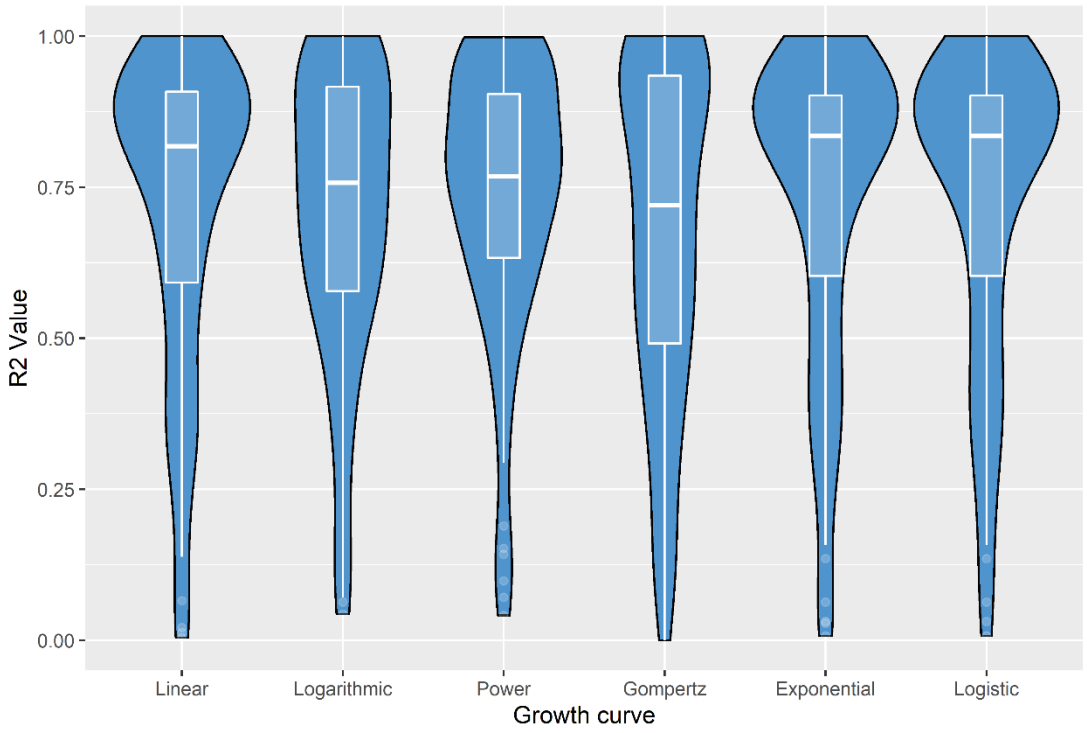


Figure 3.15. Violin plot (with internal boxplot) of the overall R^2 values for all meningioma growth curves, stratified by type of growth curve model. The wider the sections for each 'violin', the more meningioma R^2 values are located around this. No differences were detected in the comparisons between the models (Table 3.10).

3.5. Discussion

3.5.1. Key findings

The objectives of this study were to evaluate the volumetric growth of residual meningioma, and identify prognostic factors for progression. The study identified that the absolute and relative growth rate per year after subtotal resection are low (0.11cm^3 and 4.3% respectively). However, over half meningiomas meet the RANO criteria for progression within a median follow up period of 5 years. In addition, it was observed that adjuvant *f*RT, skull base location, and increased Ki-67 index were associated with volumetric progression according to RANO criteria. Most patients that progressed were successfully managed conservatively, with most patients not requiring further treatment. It was hypothesised that based on previously published studies examining untreated meningiomas[204, 240], the best curve overall for estimating meningioma growth would be the Gompertz curve. In the study, this demonstrated the smallest median R^2 value overall. Exponential and logistic curves were found to be the joint highest overall median R^2 value, and the highest frequency for the best curve for each individual meningioma.

3.5.2. Possible mechanisms and explanations

As meningiomas are slow growing tumours, with many exhibiting a slow rate of growth over many years, it is reasonable to assume that any residual tumour after surgery would have a similarly slow growth rate[241]. This supports the results in our study, as the relative growth rate is high, leading to RANO defined progression after 5 years, despite the absolute growth rate per year being low. Most tumours in the cohort were WHO grade 1, so the less rapid absolute growth trajectory is largely in keeping with tumour histology[242]. The results are in concordance with Simpson's original paper, which reported a recurrence rate of 50% at 10 years after surgery for a Simpson grade 4 resection[102, 243]. Furthermore, recent studies have identified that Simpson grade is over-estimated in as much as 33% of cases[244]. This is similar to our study results, which showed that 23.3% of residual meningiomas were actually discovered after surgery, despite the surgeon having an impression of a complete or macroscopic resection.

With regards to the prognostic factors for growth, the findings that *f*RT and skull base location were predictive of progression, are in contrast to the existing literature[245, 246]. For example, skull base meningiomas are known to contain a higher frequency of SMO and ATK1 mutations, indicating a less clinically aggressive course[247, 248]. Meningiomas that are treated with adjuvant *f*RT are also historically associated with a reduced risk of recurrence, with rates reported to be similar to meningioma undergoing a complete macroscopic resection[143, 238]. One possible causative explanation could be that more tumours that are receiving adjuvant *f*RT are WHO grade 2, and thus are more likely to progress,

although there was no difference in the WHO grades of patients who had adjuvant radiotherapy in the cohort (*P*=0.912). These tumours may therefore be predisposed to progression based on histopathological and molecular characteristics.

Ki-67 was identified as a strong factor for progression, and is a marker of increased tumour proliferation[249, 250]. This has not been investigated before in residual meningioma, but has been established as a marker of progression after complete resection in previous studies, and was identified on multivariable analysis on a recent study to be a predictor of reduced survival in surgically managed meningiomas[251]. Despite this, these results should be interpreted with caution since Ki-67 was only available in 8.5% of cases, and is not part of the diagnostic criteria for meningioma[252]. There is also possible selection bias in the cohort, in the sense that meningiomas that were subtotally resected are by default, more likely to progress due to being more problematic lesions.

It is also notable that certain prognostic factors were not identified as being associated with progression (including residual volume, WHO grade, and signal hyperintensity on T2-weighted MRI). These were previously identified in the literature as significant factors- this may be due to the smaller sample size in the previous studies, in addition to a lack of multivariable analysis[210, 228]. Another reason may be because for this study, growth was defined according to RANO approved criteria, while none of the other studies used this definition[239]. Other studies defined progression according to a smaller volume increase, or a neuroradiologist report, leaving them susceptible to selection bias. One study did identify these factors, but they defined recurrence as per a neuroradiologist's report, with no defined volumetric cut-off for progression, although they did define high growth as meningiomas growing more than 1.28cm^3/year[206]. It would be useful to compare the factors associated with progression in these studies, if a 40% increase in volume of residual tumour was used, in accordance with RANO guidelines.

Furthermore, the lack of significant findings may reflect a heterogeneity in tumour behaviour, and despite having 236 patients included, no previously identified factors were included as significant. WHO grade and residual volume have been identified to be significant by several studies, and it makes plausible sense that the larger the residual, the higher chance of progression[206]. It is important to note that we used a progression definition that is dependent on the original residual volume, therefore larger tumours may not have grown by 40% or met the cut-off for progression by the time they received further treatment, despite growing considerably in absolute terms.

A surprising finding was that exponential and logistic both had the same median R^2 values. The only previous report of meningioma growth curve analysis is a study of fifty-two patients with a combination of symptomatic and incidental meningiomas; the study demonstrated exponential and

logistic to have different R^2 values[204]. Possible reasons for this are that the populations were different; The study examined a mixed population of both incidental, symptomatic, and operated meningiomas, and compared WHO grade 1 to WHO grade 2 tumours, in comparison to our analysis of the growth curves of residual meningioma only[204]. The previous surgical intervention could have meant that meningiomas had already grown past the inflection point, and therefore may be less likely to exhibit power or gompertz shaped distributions. If a primary meningioma exhibits growth, it may encounter an inflection point, due to being an extra-axial tumour, and having to grow in a closed space. This would indicate that growth rates would decrease after an initial period of growth- a gompertz curve. A residual tumour may therefore exhibit growth without reaching its inflection point- with this effect increased if the meningioma is small. This would make residual meningioma more likely to express exponential growth patterns, as shown in the cohort.

3.5.3. Comparison with relevant findings from other published studies

Comparing the study with previously published work, the results are similar to a study of 141 WHO grade 1 residual meningioma[206]. The absolute and relative growth rate were similar, with not much difference observed. Notable differences were observed in the prognostic factors and variables associated with growth and recurrence. Different definitions of growth and progression were used for both studies, which may explain some of the differences. This study is the largest cohort of residual meningioma in comparison to existing literature, and therefore adds significantly to the existing knowledge base. The suggestion that there may be few statistically significant factors associated with volumetric growth, is also important.

3.5.4. Limitations of the study

This study has several limitations. Firstly, this is a retrospective cohort of patients from a single centre, with limited ethnic diversity. Therefore, surgical practice, initiation of adjuvant treatment, and monitoring practice may vary considerably both nationally and internationally. Secondly, volumetric analysis was only carried out using a single programme (PACS). This was used since it is Food and Drug Administration (FDA) validated, and was easily accessible on hospital trust computers. Thirdly, the median follow-up time was only five years after surgery. A longer follow up time could detect more progressions, as evidence now suggests that many meningiomas recur upwards of ten years after initial surgery/treatment[238, 253].

Fourthly, different WHO classification systems were used during the study period (2004-2019)[81, 254, 255]. Whilst there was no change in the criteria for diagnosing grade 2 meningioma between 2007 and 2016, it is possible that some patients diagnosed with a grade 1 meningioma according to the 2000 classification[255], could be reclassified as WHO grade 2 according to the 2007 or 2016 classification[81,

[254]. Furthermore, not all patients had sufficient number of scans or follow up available to measure for progression. Finally, only 36 patients were identified as having received adjuvant post-operative *f*RT. Therefore, another 22 patients had *f*RT that was not considered as adjuvant, and this forced censoring of patient's volumetric measurements, as it was counted as an intervention for those patients.

3.5.3. Implications for practice and future research

This study has implications for current clinical practice, such that in patients who do not receive any adjuvant radiotherapy, the volumetric growth of residual meningioma is low in absolute and relative terms, and even when they progress, this is mainly radiological, and therefore in the absence of clinical progression most can be successfully managed with continued MRI monitoring. This is the only study to the author's knowledge, examining the growth curves of residual meningioma, in a large cohort of patients. The findings have also not been demonstrated in previous work.

Future studies should investigate different growth rates of residual meningioma, using uniform, standardised definitions, in order to ensure comparability across datasets. It is also hoped that future research in this area specifically identifies prognostic factors for progression according to RANO criteria.

3.6. Conclusions

The volumetric growth rate of residual meningioma is low in absolute and relative terms. Most patients who do progress according to RANO criteria, can be successfully managed with active monitoring. Variables associated with progression are difficult to ascertain, but adjuvant *f*RT, skull base location, and elevated Ki-67 index may be associated with increased risk of progression after surgery. Most residual meningioma exhibit exponential and logistic growth patterns.

3.7. Acknowledgments

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Chapter 4: Future research and closing remarks

A residual meningioma is identified in ~25% of meningioma surgeries, and their management after surgery is an important clinical problem. NICE and EANO guidelines recommend an individualised approach to meningioma management, but data to support the choice of MRI scan frequency is lacking, and there are very few studies reporting the volumetric growth rates, progression rates, and prognostic factors for progression. This is confirmed with the results of the systematic review[237], which identified limited studies available, and few prognostic factors for volumetric growth, with very little multivariable analysis conducted.

The results in this thesis suggest that although the absolute and relative growth rate of residual meningioma is low, radiological progression, when defined according to RANO criteria, remains high. Most patients continue to be managed conservatively after progression with a low mortality rate, and only 5% of patients develop neurological symptoms indicative of clinical progression. The factors related to progression were treatment with adjuvant *f*RT, skull base location and elevated Ki-67 index.

There are many aspects of residual meningioma that warrant further research. The most important areas include DNA methylation and other molecular profiling as a factor for progression, further exploration of volume calculations to delineate what the most accurate software is, and the most pragmatic software with the highest clinical utility. Further focal points of future research encapsulate the best growth definitions, scanning methods and intervals, and the overall place of Simpson grading and its clinical importance. Psychological effects of having a residual tumour, and subsequent monitoring of patients with residual tumour also needs to be ascertained.

In conclusion, this thesis achieved its original aims as set out in the protocol, whilst highlighting areas of residual meningioma work that warrant further research. Residual meningioma is inevitable in some cases despite our best efforts, and we need to understand how to optimally stratify management for these patients going forward.

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Appendices

Appendix 1. Embase search strategy

Search	Query
1	'meningioma'/de
2	meningioma*
3	#1 OR #2
4	((subtotal* or sub-total* or incomplete* or partial*) NEAR/1 (resect* or remov*))
5	(Simpson NEAR/2 ('4' or '5' or IV or V))
6	(residual* or recurren*)
7	(volume*)
8	#4 OR #5 OR #6 OR #7
9	(observ* or conservative* or follow-up or natural history or grow*)
10	#3 AND #8 AND #9
11	Limit #10 to English Language

Appendix 2. Search strategies for each database included in systematic review

Medline	
Search	**Query**
1	meningioma/
2	meningioma*.tw
3	1 OR 2
4	((subtotal* or sub-total* or incomplete* or partial*) adj1 (resect* or remov*)).tw
5	(Simpson adj2 ('4' or '5' or IV or V)).tw
6	(residual* or recurren*).tw
7	(volume*).tw
8	4 OR 5 OR 6 OR 7
9	(observ* or conservative* or follow-up or natural history or grow*).tw
10	3 AND 8 AND 9
11	Limit 10 to English Language

PubMed	
Search	**Query**
1	meningioma[mh]
2	meningioma*[tw]
3	#1 OR #2
4	(subtotal resect*[tw] or subtotal remov*[tw] or sub-total resect*[tw] or sub-total remov*[tw] or incomplete resect*[tw] or incomplete remov*[tw] or partial resect*[tw] or partial remov*[tw])
5	('Simpson 4'[tw] or 'Simpson 5'[tw] or Simpson IV[tw] or Simpson V[tw] or ‘Simpson grade 4’[tw] or ‘Simpson grade 5’[tw] or Simpson grade IV[tw] or Simpson grade V[tw])
6	(residual*[tw] or recurren*[tw])
7	(volume*[tw])
8	#4 OR #5 OR #6 OR #7
9	(observ*[tw] or conservative*[tw] or follow-up[tw] or natural history[tw] or grow*[tw])
10	#3 AND #8 AND #9
11	Limit #10 to English Language

Embase	
Search	**Query**
1	'meningioma'/de
2	meningioma*
3	#1 OR #2
4	((subtotal* or sub-total* or incomplete* or partial*) NEAR/1 (resect* or remov*))
5	(Simpson NEAR/2 ('4' or '5' or IV or V))
6	(residual* or recurren*)
7	(volume*)
8	#4 OR #5 OR #6 OR #7
9	(observ* or conservative* or follow-up or natural history or grow*)
10	#3 AND #8 AND #9
11	Limit #10 to English Language

CINAHL Plus	
Search	**Query**
1	MH meningioma
2	meningioma*
3	S1 OR S2
4	((subtotal* or sub-total* or incomplete* or partial*) N1 (resect* or remov*))
5	(Simpson N2 ('4' or '5' or IV or V))
6	(residual* or recurren*)
7	(volume*)
8	S4 OR S5 OR S6 OR S7
9	(observ* or conservative* or follow-up or natural history or grow*)
10	S3 AND S8 AND S9
11	Limit S10 to English Language

Cochrane library	
Search	**Query**
1	Mh ‘meningioma’
2	meningioma*
3	#1 OR #2
4	((subtotal* or sub-total* or incomplete* or partial*) NEAR/1 (resect* or remov*))
5	(Simpson NEAR/2 ('4' or '5' or IV or V))
6	(residual* or recurren*)
7	(volume*)
8	#4 OR #5 OR #6 OR #7
9	(observ* or conservative* or follow-up or natural history or grow*)
10	#3 AND #8 AND #9
11	Limit #10 to English Language

Appendix 3. Data extraction proforma

Authors:		**Publication date:**
Title:		**Journal:**
Study design:	**Population size:**	**Number of meningiomas:**
Characteristics		
Baseline characteristics	Age	
	Sex	
Clinical demographics pre-op	Symptom profile	
Radiological demographics pre-op	Tumour volume (cm^3)	
	Tumour intensity	
	ICOM classification	
	Calcification	
	Perilesional oedema	
Intervention	Simpson grade	
	Residual tumour volume (cm^3)	
	Growth definition and measurement	
Outcomes	Growth rate	
	Recurrence	
	Prognostic factors	
	Survival	
Prognostic factors	Age	
	Sex	
	WHO grade	
	Preop/residual tumour volume	
	Tumour intensity	

Appendix 4. Non-eligible studies and reasons for exclusion

No volumetric analysis conducted (28)
Abdel Aziz, K. M.; Froelich, S. C.; Dagnew, E.; Jean, W.; Breneman, J. C.; Zuccarello, M.; Van Loveren, H. R.; Tew Jr, J. M.; Delfini, R.; Sekhar, L. N.; Lunsford, L. D.: Large sphenoid wing meningiomas involving the cavernous sinus: Conservative surgical strategies for better functional outcomes. **Neurosurgery** 54(6): 1375-83, 2004.
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Appendix 5. Quality in prognostic studies (QUIPS tool) summary for each paper included in systematic review.

Paper/Author name	Domain 1: Study participation	Domain 2: Study attrition	Domain 3: Prognostic factor measurement	Domain 4: Outcome measurement	Domain 5: Study confounding	Domain 6: Statistical analysis and reporting	Overall rating*
Materi et al	High	Low	Moderate	Low	High	Moderate	+
Hunter et al	High	Moderate	Moderate	Low	High	High	+
Jung et al	High	Low	Moderate	Low	High	High	+
Nakamura et al	High	Low	Low	Low	High	High	+
***Low quality (+): Either most criteria not met, or significant flaws relating to key aspects of study design. Acceptable (++): Most criteria met. Some flaws in the study with an associated risk of bias, Conclusions may change in the light of further studies. High quality (+++): Majority of criteria met, little or no risk of bias.**							

Appendix 6. Embase search strategy

(Conducted 12th September 2020)

Search ID#	Search terms	Search options	Last run via	Results
1	*'meningioma'/de*	*Advanced search*	*Ovid*	33284
2	*meningioma**	*Advanced search*	*Ovid*	28226
3	*#1 OR #2*	*Advanced search*	*Ovid*	38248
4	*((subtotal* or sub-total* or incomplete* or partial*) NEAR/1 (resect* or remov*))*	*Advanced search*	*Ovid*	28618
5	*(Simpson NEAR/2 ('4' or '5' or IV or V))*	*Advanced search*	*Ovid*	132
6	*(residual* or recurren*)*	*Advanced search*	*Ovid*	1090348
7	*(volume*)*	*Advanced search*	*Ovid*	972481
8	*#4 OR #5 OR #6 OR #7*	*Advanced search*	*Ovid*	2022921
9	*(observ* or conservative* or follow-up or natural history or grow*)*	*Advanced search*	*Ovid*	7806326
10	*#3 AND #8 AND #9*	*Advanced search*	*Ovid*	4214
11	*Limit #10 to English Language*	*Advanced search*	*Ovid*	3884