UNIVERSITY OF LIVERPOOL

Incidental Meningioma: Modelling Growth Characteristics and Predicting Failure of Monitoring

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy

by

Abdurrahman Islim

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Abstract

Meningiomas are the commonest primary intracranial tumours. With the increased access to neuro-radiological investigations, there has been a tremendous increase in the number of incidental findings. Incidental meningioma accounts for 10% of these findings and for 30% of newly-diagnosed meningiomas. International guidelines advise that these tumours are best managed using active clinical-radiological monitoring, however, duration of surveillance and intervals in between scans, remain unspecified. This uncertainty has economic implications and causes patient anxiety. Previous literature has focused primarily on radiological prognostication with little attention to the effect of clinical factors such as comorbidity and performance status on prognosis of incidental meningiomas. Moreover, the temporal relationship between these factors and progression remains poorly defined.

The aims of this thesis therefore were to investigate the prognostic relationship between radiological factors and the timing of progression and to examine how this is augmented by clinical factors including patient age, comorbidity and performance status. Moreover, a predictive model of progression was built based on these factors and used to inform duration of follow-up and appropriate time-points for scans.

Radiological factors included in the model were: increasing tumour volume, peritumoural signal change, MR FLAIR/T2 hyperintense meningiomas and proximity to critical neurovascular structures. Patients were stratified into low, medium and high-risk groups and rates of disease progression at 5-years were 3%, 28% and 75% respectively. Low-risk patients had non-oedematous, small iso/hypointense meningiomas, distant from neurovascular structures. Older patients with co-morbidities were 15-times more likely to die than to receive intervention at 5-years following diagnosis, regardless of risk-group. After 5-years of follow-up the probability of disease progression plateaued in all risk groups. Active monitoring strategies based on these results were formulated. These have the potential to reduce the cost burden of incidental meningiomas. Prospective studies are needed to validate the model.

Dissemination

Conferences and meetings:

- December 2017 – Brain Tumour North West Annual Retreat – Preston, UK. Oral presentation
- May 2018 – British-Irish Meningioma Society Meeting – Haywards Heath, UK. Oral presentation
- June 2018 – Pharmacology Postgraduate Seminar Day – Liverpool, UK. Oral presentation
- July 2018 – British Neuro-Oncology Society Conference – Winchester, UK. Oral presentation

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List of abbreviations

2DRT	Conventional two-dimensional radiotherapy
3DRT	Conformal three-dimensional radiotherapy
^{68}Ga-DOTATATE	Gallium-68 DOTA-DPhe1, Tyr3-octreotate
ACCI	Age-adjusted Charlson comorbidity index
AGR	Absolute growth rate
AMF	Active monitoring failure
AUC	Area under the curve
CART	Classification and regression tree
CCG	Clinical Commissioning Groups
CI	Confidence interval
CIR	Cumulative incidence rate
CNS	Central nervous system
CRIS	Computerised radiological information system
CS	Cavernous sinus
C-statistic	Concordance statistic
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DDFU	Dead during follow-up
EANO	European Association of Neuro-Oncology
ECM	Extracellular matrix
EOR	Extent of resection
EORTC	European Organisation for Research and Treatment of Cancer
FLAIR	Fluid-attenuated inversion recovery
FSRT	Fractionated stereotactic radiotherapy

GOS	Glasgow outcome scale
GTR	Gross total resection
Gy	Grey
HD	Hospital discharge
hFSRT	Hypofractionated stereotactic radiotherapy
HPF	High-power field
HR	Hazard ratio
ICA	Internal carotid artery
ICC	Intraclass correlation coefficient
ICOM	Society for Neuro-oncology International Consortium on Meningioma
IMPACT	Incidental meningioma: prognostic analysis using patient comorbidity and MR-Tests
iMRI	Intraoperative MRI
IMRT	Intensity-modulated radiotherapy
IQR	Interquartile range
KPS	Karnofsky performance status
LINAC	Linear accelerator
LMM	Linear mixed model
LQ	Linear quadratic
LTFU	Lost to follow-up
Merlin	Moesin-ezrin-radixin-like protein
MLC	Multileaf collimator
MMP-9	Matrix Metalloproteinase-9
MRI	Magnetic resonance imaging
MTD	Mean tumour diameter
mTORC1	Mammalian target of rapamycin complex 1
NCCN	National Comprehensive Cancer Network

NCF	Neurocognitive function
NF2	Neurofibromatosis-2
NHS	National Health Service
NIH	National Institutes of Health
NSB	Non-skull base
OA	Optic apparatus
OR	Odds ratio
OS	Overall survival
PACS	Picture archiving and communication system
PET	Positron emission tomography
PFS	Progression-free survival
PH	Proportional hazards
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROSPERO	International prospective register of systematic reviews
PS	Performance status
PVA	Polyvinyl alcohol
QoL	Quality of life
RANO	Response Assessment in Neuro-Oncology Group
RGR	Relative growth rate
ROC	Receiver operating characteristic curve
RS	Radiosurgery
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SB	Skull base
SD	Standard deviation
SF-36	Short Form (36) health survey

SPECT	Single-photon emission computed tomography
SRS	Stereotactic radiosurgery
SS	Sigmoid sinus
SSS	Superior sagittal sinus
STR	Sub-total resection
T1	T1-weighted
T2	T2-weighted
TS	Transverse sinus
UK	United Kingdom
VASARI	Visually accesable rembrandt images
VEGF-A	Vascular endothelial growth factor A
VOMIT	Victims of modern imaging technology
WHO	World Health Organisation

Chapter 1: An Introduction to Meningiomas

Meningioma, a term first used by Cushing in 1922, is an extra-axial tumour that arises from the arachnoid cap cells (1). It represents more than a third of intracranial and intraspinal primary tumours and can manifest in a variety of symptoms depending on its location. With the extensive application of neuro-imaging modalities for purposes such as diagnostics and research, more of these tumours are being discovered whilst in a clinically dormant state. These are referred to as incidental meningiomas.

1.1. Epidemiology and natural history

Meningiomas have the highest incidence rate amongst all primary central nervous system (CNS) tumours. Descriptive studies from Europe and North America suggest this rate to be between 4.20 and 7.86 per 100,000 individuals. Their incidence increases with age and peaks between the 5th and 7th decades of life. The female to male ratio is approximately 2:1 (2-4).

These descriptive studies do not make the distinction between cerebral and spinal tumours. They are additionally limited by inclusion of only histologically-verified meningiomas. This means that the aforementioned rates might be underestimated as they do not account for radiologically-diagnosed meningiomas that remain asymptomatic until death. This is evident in autopsy studies which report an undiagnosed meningioma prevalence of 0.3-2.3% (5-7).

The natural history of untreated meningiomas has been well described in the literature; most exhibit indolent growth rates and some, followed for a number of years, prove to be static (8, 9). In addition, several factors that contribute to increased growth rates have been identified. These include absence of calcification within the tumour, increased signal intensity on T2-weighted (T2) magnetic resonance imaging (MRI) and tumour size (10). Multiplicity does not seem to have an impact on growth potential (11).

1.2. Location and clinical presentation

The majority of meningiomas are found supratentorially, most commonly along the dural venous sinuses in the cerebral convexity, and along the falx cerebri. These localisations account for approximately 60% of cerebral meningiomas. Less common sites include the ventricles. They could also be found in the skull base alongside structures such as the olfactory groove, sphenoid wing and the clivus. The distribution of locations can be found in Table 1.1 (12, 13). These meningiomas, if sizeable or oedematous, can present with headaches, seizures or focal neurological deficits such as unilateral weakness, speech disturbance and personality changes (14, 15).

Table 1.1. The distribution of intracranial meningioma location

Location	Percentage (%)
Cerebral convexity	20-34
Parasagittal and parafalcine	18-22
Sphenoid and middle cranial fossa	17-25
Anterior midline	10
Posterior fossa	9-15
Intraventricular	2-5
Orbital	1-2

Thoracic meningiomas constitute roughly 60% of intradural extramedullary spinal meningiomas. Symptoms on presentation include motor and sensory deficits, sphincter dysfunction and gait ataxia. Lumbar meningioma is uncommon (16, 17).

An increasing number of meningiomas is still asymptomatic when discovered, particularly those within the cranium (18). These will be the main topic of discussion in this thesis.

1.3. Grading and histology

The World Health Organisation (WHO) classifies meningiomas into three groups (19):

- Benign meningioma (grade I).
- Atypical meningioma (grade II).
- Anaplastic meningioma (grade III).

The latest 2016 classification reported the addition of brain invasion as a sole criterion for diagnosis of atypical meningioma. This in addition to other histological diagnostic parameters can be found in Table 1.2.

Table 1.2. The WHO classification of meningiomas

Grades	**I**	**II**	**III**
Diagnostic parameters	4 mitoses/10 hpf	4–19 mitoses/10 hpf OR 3 of the following 5: sheet-like growth, spontaneous necrosis, high nuclear to cytoplasmic ratio, prominent nucleoli, and increased cellularity OR **brain Invasion**	≥20 mitoses/10 hpf OR frank anaplasia OR rhabdoid/papillary histology
Histological subtypes	meningothelial, fibroblastic, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic	Atypical, clear cell and chordoid	Anaplastic, rhabdoid and papillary
Frequency (%)	80-90	5-10	1-5
Abbreviations: hpf= high-power field			

This change is likely to increase the proportion of atypical meningiomas. It will also have an impact on clinical outcomes; however, comparative reports are still in process.

1.4. Aetiology

Although most meningiomas are hypothesised to occur sporadically, cytogenetic and molecular studies imply that chromosome 22 aberrations are involved in up to 70% of tumours (20, 21). This is in keeping with the association between neurofibromatosis-2 (NF2) and the increased incidence of meningiomas. NF2, a rare genetic syndrome, predisposes its carriers to benign intracranial tumours. The cardinal feature is the development of bilateral

vestibular schwannomas. Meningioma is the second most frequent tumour type affecting up to half of patients. The tumour suppressor *NF2* gene is located on the long arm of Chromosome 22 (22q12.2); 50% of mutations are familial inherited in an autosomal dominant manner whilst the rest are sporadic (22-24). Other genes such as *SOD*, *DAL1*, *AKT1, SMO* and *TRAF7* are implicated but to a lesser extent (25, 26). Whilst these mutations, particularly of the *NF2* gene, are consistently observed in benign grade I meningiomas, high grade tumours exhibit a different variety of genetic karyotypes. This suggests that beyond meningioma development, *NF2* might have a limited role in malignant progression (27).

Meningiomas have also been observed to occur as a result of ionizing radiation (28). This observation is supported by large-scale studies done on 11,000 Israeli adults irradiated for tinea capitis during childhood, and Hiroshima and Nagasaki survivors (29-32). Based on radiation dose, these meningiomas can be split into 3 categories: low-dose (<10 Grey (Gy)), medium-dose (10-20 Gy) and high-dose (>20 Gy) (33). High-dose meningiomas demonstrate a shorter latency period as opposed to low-dose meningiomas. Clinical and histopathological aggressiveness also correlates with the amount of radiation administered (28).

Researchers have additionally investigated the relationship between endogenous or exogenous hormone exposure and meningiomas. This is due to the following observations:

- A female preponderance particularly amongst those of reproductive age.
- Expression of hormone receptors in meningioma cell lines.
- A link with breast cancer.
- Changes in the size of meningiomas during periods of hormone fluctuations such as pregnancy and menopause.

These investigations have been inconclusive (34-36).

1.5. Pathogenesis

Neoplastic meningioma cells like their normal counterparts exhibit some degree of overlap with mesenchymal and epithelial cells. Encapsulating the brain and the spine are three meningeal layers: the dura mater, arachnoid mater and pia mater. Histologically, the arachnoid mater is composed of arachnoid cap cells which cytologically resemble meningioma tumour cells. Therefore, it is widely accepted that these cap cells represent the most likely site of origin (37, 38). The process of tumorigenesis is highly linked to a protein named Moesin-Ezrin-Radixin-Like Protein. This is often referred to as Merlin. This protein, which is encoded by the frequently mutated *NF2* gene in meningiomas, has been demonstrated to regulate several processes; these include cell migration and proliferation (39). It has also been shown to be implicated in regulating the mammalian target of rapamycin complex 1 (mTORC1) which is dysfunctional in several human cancers (40, 41). The process of malignant transformation, likely to be independent of *NF2* as previously discussed, is linked to several candidate chromosomes. These include: 1, 9, 10 and 14, amongst several others (42, 43).

Meningiomas are highly variable in regard to vascularity and peritumoural oedema, which have been shown to influence prognosis (44). Vascular endothelial growth factor A (VEGF-A) has been suggested to regulate both processes via pathological angiogenesis of cerebral-pia

blood vessels (45). Bone invasion or hyperostosis is also characteristic of many meningiomas, particularly those found along skull base structures (46). Potential candidate regulating proteins include osteoblast stimulating factors such as alkaline phosphatase (47, 48). Brain invasion, which reflects a more aggressive nature amongst meningiomas, is driven by extra-cellular matrix (ECM) proteins such as matrix metalloproteinase-9 (MMP-9) (49, 50). This is similar to other aggressive malignancies (50).

These genetic alterations increase the susceptibility of individuals to develop meningiomas (51); therefore, molecular and genetic characterisation is vital as to enable the use of personalised medicine in managing these patients (52).

1.6. Diagnosis

The majority of meningiomas can be confidently diagnosed using the combination of MRI and computed tomography (CT) (53). MRI sequences performed for this purpose include T1-weighted (T1), T2 and fluid-attenuated inversion recovery (FLAIR). Meningiomas are typically isointense on T1 and iso/hyperintense on the latter. The addition of a contrast agent such as gadolinium to T1 leads to a vivid enhancing appearance; it also frequently demonstrates the typical “dural tail” feature, which is thickening of the dura mater adjacent to the tumour. T2 and FLAIR are useful for detecting peritumoural oedema (54). CT is an important adjunct as to further characterise tumour calcification and hyperostosis (55).

Although once the modality of choice for diagnosis (56), cerebral angiography has now become outdated; however, it is important that MRI venography is performed as to establish venous patency for meningiomas in proximity of major dural sinuses and veins (57).

Nuclear imaging modalities such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) could also be used for the purpose of diagnosis (58). Several radiotracers could be employed; these include 1-11C-Acetate and gallium-68 DOTA-DPhe1, Tyr3-octreotate (^{68}Ga-DOTATATE). The majority of meningiomas have been shown to express somatostatin receptor subtype 2 (SSTR2) which is highly affinitive for ^{68}Ga-DOTATATE; therefore, its diagnostic use in delineating meningioma cells from tumour-free tissue is promising (59).

The utility of those previous imaging modalities has also been investigated for predicting meningioma grade and recurrence rates; however, histopathological diagnosis, as outlined by the WHO classification, remains the gold standard (60).

1.7. Prognosis

Although most meningiomas are benign in nature, overall survival does seem to be shorter in those affected. Historic population-based studies from Europe demonstrated 10-year relative survival rates between 86% and 92% when compared to matched populations (61, 62). These studies however are outdated.

Studies have also addressed the influence of patient and clinical characteristics, imaging findings and choice of intervention on prognosis. Several factors are implicated including tumour grade, surgical resection and patient age (60, 63, 64). The attention has however now shifted towards studying the impact of molecular and genetic alterations in meningiomas

which most likely will uncover more aspects to prognosis and subsequently management (65).

Moreover, due to increasingly effective treatment approaches over the past decades, we are now observing prolonged treatment journeys for meningioma patients. As a result, studies have attempted to assess their effect on quality of life (QoL) and neurocognition function (NCF). Two recent systematic reviews concluded that meningioma patients suffer with dysfunction in several cognitive domains, and that meningioma patients fare worse in regards to QoL than healthy controls (66, 67); this merits further studies assessing the impact of previously investigated factors on QoL and NCF alongside conventional clinical measures such as progression and survival.

1.8. Management strategies

Meningiomas are heterogeneous tumours ranging in spectrum from small, slow-growing lesions, to large progressive masses, invading brain parenchyma and engulfing cranial nerves. Therefore, treatment should be personalised with patient, clinical and radiological factors being considered.

Management options include surgery, radiotherapy and active monitoring. Surgical trials pose many methodological challenges and thus up to this date, there have been no randomised controlled trials comparing these modalities (68); hence, the majority of recommendations are based on retrospective and prospective observational studies.

1.8.1. Symptomatic meningiomas

1.8.1.1. Surgery

Ever since the inception of Simpson's score for resection, meningioma surgery has been the mainstay treatment for most symptomatic tumours (69). Over the past thirty years or so, intraoperative navigation, microscopic surgery and minimally invasive endoscopes have revolutionised the world of neurosurgery and have helped introduce a vast number of novel surgical techniques. Meningioma surgery, however, is still primarily underpinned by key principles which are early tumour devascularisation and internal debulking followed by peripheral dissection (70). The main objectives are to achieve safe maximal resection, without inflicting any significant neurological deficits, relieve mass effect and subsequently alleviate symptoms; there's also the added benefit of diagnostic verification and histopathological characterisation (69).

Preoperatively, patients with significant peritumoural oedema and associated neurological deficits should be offered steroids (71). Certain meningiomas could also be subjected to embolisation, where certain materials such as polyvinyl alcohol (PVA) particles and porous cellulose beads, delivered via microcatheters, are used to obliterate the corresponding blood supply (72). The potential advantages include reduced intraoperative blood loss, and softening of the tumour, all of which could facilitate a technically less difficult surgery and increase the likelihood of achieving a more complete resection (73). Embolization, however, carries risks including infarction and cranial nerve palsies with an incidence rate ranging from as high as 12.6% to approximately 3.0% (74). Moreover, evidence does not suggest better outcomes in comparison to non-embolised meningiomas and there's no consensus regarding

the specific indications (75). As a result, whether to embolise or not, remains a matter of personal preference and prospective controlled trials are needed to better define indications and outcomes. Neurosurgeons frequently also prescribe prophylactic antiepileptic drugs in aim of reducing the rate of postoperative seizures following excision of intracranial meningiomas (76), however, recent systematic reviews demonstrated that these should not be given routinely and that again randomised trials are needed to shape clinical practice (77).

Recurrence rates following extirpation of grade I tumours depend mainly on extent of resection (EOR). This is usually defined using Simpson's grading (78); Table 1.3, which despite being previously challenged for its use as a prognostic factor (79, 80), still maintains its relevance as shown by more recent series (81, 82).

A previous investigation observed no significant difference in recurrence rates amongst grades 1, 2 and 3 of resection and another extended this observation to include grade 4. More recent studies however have challenged this notion; Table 1.4. These observational variations might stem from methodological differences, and distinct follow-up times and sample sizes; whist those in favour of Simpson's criteria uniformly classified all cases according to the 2007 WHO grading system (82), other authors did not specify whether this was carried out for meningiomas diagnosed prior to 2007 (79, 80).

Table 1.3. Simpson's grades of meningioma resection

Grade	Description	
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)
2	Macroscopically complete removal of tumour and its visible extensions with coagulation of its dural attachment	
3	Macroscopically complete removal of the intradural tumour, without resection or coagulation of its dural attachment or its extradural extensions	
4	Partial removal, leaving intradural tumour in situ	Subtotal resection (STR)
5	Simple decompression, with or without biopsy	

Additionally, the follow-up times were relatively shorter than the average time of 62 months between surgery and confirmation of recurrence in Simpson's report. This disparity might have also been due to the subjective variability amongst surgeons in intraoperative assessment of resection, and as such the European Association of Neuro-Oncology (EANO) advocates confirmation of this by postoperative MRI (69). Regardless, in recognition of this issue, EOR could be classified into gross total resection (GTR) or subtotal resection (STR). GTR is described as Simpson I-III, while STR corresponds to Simpson IV-V. These definitions have been endorsed by both the European Organisation for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) (83).

Furthermore, tumour location was previously thought to have an impact on prognosis (84, 85); more recent series however, have nullified this demonstrating the effect of new surgical technologies and techniques on EOR and consequently recurrence rates (81, 82).

Table 1.4. Meningioma recurrence rates (%) associated with Simpson's 5 grades of resection in 5 selected studies

Authors and year	N. of patients	Follow-up time	1	2	3	4	5
Simpson, 1957 (78)	265	62 months*	9	19	29	44	100
Sughrue et al., 2012 (86)	373	44.4 months†	5	15	13	19	-
Oya et al., 2012 (80)	240	-	2.4	12.3	15.9	53.2	-
Gallagher et al., 2016 (81)	145	60 months†	3.2	0	-	17.6	100
Nanda et al., 2017 (82)	458	54 months‡	5	22	31	35	-

* The average time between primary operation and confirmation of recurrence
† Median follow-up time
‡ Mean follow-up time

There has also been a shift now in the management of cranial base and venous sinus meningiomas moving away from radical resection and towards conservative surgery, where residual tumour could be left to avoid devastating neurological deficits. This residual could be monitored postoperatively with serial MRI or may be treated with adjuvant radiotherapy (87). This will be elaborated upon in the next section.

WHO grade II and III meningiomas are more aggressive and they exhibit a significant predisposition to recur following surgery. Indeed, the 5-year recurrence rates are quoted at approximately 40% and 55% respectively (88-93). These rates again, similarly to grade I tumours, largely depend on EOR. Other factors' prognostic effect including age, gender, Ki-67 status and tumour size is debatable with studies demonstrating conflicting results (90, 94-96). Lastly, whilst adjuvant radiotherapy has been shown to influence progression and recurrence following resection of anaplastic meningiomas, its role is yet to be defined for atypical meningioma (97).

Since EOR has been consistently observed to impact recurrence rates, intraoperative technologies such as fluorescence guided surgery and intra-operative MRI (iMRI) have been developed to aid this. A recent Cochrane review however showed that current evidence is of a low quality and that the application of these technologies in routine meningioma practice is yet to be established (98).

1.8.1.2. Radiotherapy

The anti-tumour activity of radiation is due to double-strand-DNA damaging free radicals which lead to multiple consequences including cell death (99). The application of this in meningioma practice has evolved greatly over the past decades; from being historically considered a radioresistant entity to its resurgence becoming the topic of multiple investigations, now available to us are several ways of delivery, these include: external beam radiation therapy (RT) and radiosurgery (RS) (100, 101).

1.8.1.2.1. RT

RT primarily relies on the radiobiologic linear-quadratic (LQ) model. In this model, the response of normal or tumour tissue to radiation is dictated by a single clinical parameter: the α/β ratio; α refers to the cell's "intrinsic radiosensitivity" whilst β reflects its "repair

mechanisms" (99, 102). This ratio is important as to establish the number of fractions and total dose needed to achieve tumour control whilst minimizing normal tissue toxicity. CNS cells have an accepted ratio of 2 Gy whilst meningiomas have a higher value 3.76 Gy (103, 104). RT is planned and delivered via the conventional two-dimensional (2DRT), conformal three-dimensional (3DRT) or intensity-modulated (IMRT) techniques (105), and can be used in the following situations:

- Meningiomas not amenable to surgery.
- Following STR of benign meningiomas.
- Following GTR/STR of atypical and anaplastic meningiomas.
- Recurrent meningiomas.

Location might preclude some meningiomas from resection and in such cases, RT offers an alternative option. One example is meningiomas of the skull-base, and particularly the cavernous sinus, which the internal carotid artery (ICA) and 4/12 cranial nerves traverse; namely the oculomotor, trochlear, trigeminal and abducens. Therefore meningiomas seated within the sinus present a surgical challenge and neurovascular outcomes could be unforgiving (106, 107). One previous paper reported on 28 treated cavernous sinus meningiomas of which 21 received primary 2DRT or 3DRT. Control rates were excellent with an 8-year PFS of 81% (108). A more recent report described outcomes following 3DRT in 53 patients harbouring meningiomas; 28 as first-line treatment, and again control rates were impressive with a 10-year PFS of 95.8% (109). Mean doses in the two studies were similar: 53.1 and 52.9 Gy respectively. Permanent morbidly such as persistent nerve palsies occurred in 3 patients across these two studies (7.1% versus (vs.) 1.9% respectively) which in addition to the improvement in PFS could theoretically reflect the betterment of RT techniques over the years.

IMRT is an advanced technique of external beam radiation that aims to deliver precise treatment. This is achieved using the multi-leaf collimator (MLC). In IMRT treatment, the leaves of MLC move during radiation and thus ensure that the appropriate dose is targeted to treatment areas whilst sparing neighbouring normal tissue (110). Outcomes following IMRT are similar to those of 2DRT and 3DRT with local control rates ranging between 93% at 5 years and 100% at 3 years. One series assessed IMRT in a population of 40 meningiomas; 15 were prescribed it as definitive treatment. Fifteen percent of lesions were skull-based, and the median dose was 50.4 Gy. PFS at 5 years was 93% (111). Another series included 30 patients treated for radiologically-diagnosed meningiomas of which mostly were situated along the sphenoid wings. Median dose was 57.6 Gy and after an estimated 23-month longer median follow-up period, five-year PFS was 94.8% (112). Although evidently yielding excellent results, it should be noted that on average, follow-up times in IMRT series are relatively shorter than those papers of conventional techniques (~34 vs. ~66 months) (108, 109, 111-115). Therefore, studies with longer follow-ups are warranted. Grades 3 and 4 toxic effects (as classified by Radiation Therapy oncology Group (RTOG)) were observed in 4.5% of patients included (111, 112, 116).

Meningiomas of the optic nerve sheath, which comprise <2% of intracranial meningiomas, also provide a significant body of literature regarding outcomes following RT. The reason

being that it has now become the primary treatment of choice, due to the high rates of surgery-associated blindness observed over the years (117). Overall, these studies demonstrate stability or regression in 95-100% of patients and prevention of visual deterioration in up to 96% of patients (118-120).

RT could also be utilised following STR of benign WHO grade I meningiomas to attain better control rates. Previous case series demonstrated an adequate 10-year PFS off 77% and in other retrospective studies those rates following RT + STR were comparable to PFS rates following GTR (121). Of those, one study compared outcomes in 4 different treatment groups: Surgery alone (GTR, n=174 vs. STR, n=55), STR + RT (n=21), RT alone (n = 7) and radiosurgery alone (n = 5). Fifteen-year control rates for GTR and STR + RT were 76% and 87% respectively; much improved rates in comparison to 30% following STR alone (122). A more recent study has exhibited a similar pattern; the 5-year PFS rates in patients treated with GTR and STR + RT were 77 and 91%, respectively. Patients treated with STR alone had an inferior PFS rate of 38% (123). Those selected studies however are limited by their retrospective nature and by inclusion of patients across long periods of time (e.g. 1953-2001) which have witnessed marked changes in practices and WHO grading systems.

The more aggressive nature of WHO grade II and III meningiomas means that adjuvant RT could potentially be necessary even following GTR. Several systematic reviews have addressed this topic and agreed on the following (97, 124, 125):

- Anaplastic meningiomas should postoperatively receive RT regardless of EOR.
- Atypical meningioma patients post STR should receive RT.
- Atypical meningioma patients post GTR benefit from RT; however, the timing of administration could not be confidently defined considering the current evidence.

Those reviews highlighted as a result the need for randomised controlled studies as to enable a better definition of RT timing for completely excised WHO II tumours. The ROAM/EORTC 1308 and NRG-BN003 trials, which are currently in process of recruiting patients, should provide class I evidence on this issue (126, 127).

Recurrence of meningiomas could indicate malignant transformation and a more aggressive course (128, 129). Thus, its management is challenging with a need to incorporate multiple treatment modalities, including RT. Evidence suggests better salvage rates with surgery + RT vs. surgery alone (130-132), however, meningiomas primarily treated with radiotherapy demonstrate resistance to re-irradiation and as a result further systemic therapies might be required (133); these are beyond the merit of the thesis and won't be discussed.

Other RT studies that are noteworthy include the NRG Oncology RTOG 0539 trial that has recently been published (134). This phase II study allocated patients to 1 of 3 prognostic arms: low risk, intermediate risk and high risk. The intermediate-risk group comprised of newly diagnosed WHO Grade II meningioma that had been treated with GTR or recurrent WHO Grade I meningioma. Recruitment ended in 2011 and 52 eligible patients were administered RT; 44 patients (84.6%) received IMRT and 8 (15.4%) received 3DRT. The 3-year actuarially PFS primary endpoint was 93.8%. The authors concluded that those results support the use of postoperative RT for newly diagnosed gross-totally resected WHO Grade

II or recurrent WHO Grade I meningioma irrespective of resection and that comparison with historical control data suggests it to be superior to active observation. This study although informative regarding an efficacious radiation protocol (total dose=54 Gy and number of fractions=30) lacks the comparative "observation" arm and thus the results of ongoing randomised controlled trials (ROAM and NRG-BN003) are needed to assess the efficacy of such protocols vs. active observation.

1.8.1.2.2. RS

The use of stereotaxy in neurosurgery goes back to 1908, when Sir Victor Horsley and Robert H. Clarke depicted the use of an apparatus to delineate cerebellar nuclei in monkeys (135). This apparatus was referred to as being "stereotactic"; a term they coined from the Greek words *stereos* meaning "3D"and *taxis* meaning "orderly arrangement". This apparatus underwent multiple modifications the years after and in 1949, Professor Lars Leksell described an arc-based stereotactic system which he utilised in 1951 to introduce the concept of radiosurgery (136, 137). Leksell defined stereotactic radiosurgery (SRS) as "*a technique for the non-invasive destruction of intracranial tissues or lesions that may be inaccessible or unsuitable for open surgery*" (138). The principle of SRS treatment is cross-firing of the target with narrow beams of radiation whilst surrounding normal tissue is spared. The succeeding years observed marked progress in techniques of delivery and now accessible for use are several technologies including Gamma Knife, Cyber Knife and other Linear Accelerator (LINAC)-based devices. These could be used to administer one single beam to lesions and this modality of treatment is known as SRS, however, if delivered over fractions, then it's referred to as fractionated stereotactic radiotherapy (FSRT).

The radiobiologic mechanisms underlining SRS and FSRT are quite different to those of conventional external beam radiotherapy (139). Additionally, whist the LQ model is still considered applicable for use in RT modalities of treatment, its utility in radiosurgical methods has been the topic of several studies which highlight its inappropriateness (140-142), therefore, clinical outcomes following SRS and FSRT have been elected to be discussed separately in this thesis.

A recent systematic review on the use of SRS in intracranial meningioma demonstrated an overall PFS between 78.0% and 98.9% at 5 years across 34 selected papers (143). The most commonly treated meningiomas were either grade I lesions (adjuvant) or radiologically-diagnosed (primary). This indicates that atypical and anaplastic meningiomas, which tend to be infiltrative and uncircumscribed, might not be a suitable for SRS treatment. The majority of meningiomas selected for treatment were those located within the skull-base, which might have been inaccessible surgically or only could be subjected to STR. The median meningioma volume ranged between 3 and 17.5 cm^3 and the weighted rate of toxicity was 8.1%. A higher morbidity rate was observed among meningiomas >10 cm^3.

Patients with meningiomas >10 cm^3 are thought to be safer undergoing FSRT. This could be conventionally planned and delivered in multiple daily fractions of 1.8-2.0 Gy or in a "hypofractionated" manner consisting of higher-dose fractions delivered over a fewer number of sessions. One report of 52 skull base meningiomas, measuring >4 cm in greatest dimension, demonstrated a 93% PFS at the median follow-up point of 42 months. Eighteen

(34.6%) received FSRT (total dose=50 Gy and number of fractions=30) after STR whilst the rest were treated for recurrence (n=34, 56.4%) (144). Histologically all meningiomas were classified as WHO grade I. Late toxic effects such as cranial nerve deficits were observed in 3 patients (5.5%). Another study of outcomes in 136 patients with grade I meningiomas or a radiological diagnosis showed 5-year PFS to be likewise excellent at 93.8%. Median dose was 56.95 Gy delivered in 30-33 fractions (145). No patients suffered from any serious late toxic effects however 51 (37.5%) showed grade 1 and 2 symptoms such as fatigue, headache and vertigo.

Hypofractionated FSRT (hFSRT) regimens have also been the topic of recent investigations, which exhibited control rates between 89.4% and 100%. All meningiomas were located in the skull-base. Median follow-up time ranged between 24.5 and 53 months and sample size ranged from 22 to 143 (146-148). Example of a hypofractionated protocol as depicted by the previous three studies is 25-30 Gy over 3-5 fractions.

A relative contraindication to all modalities of RS is the presence of peritumoural oedema, which has been shown to be an independent predictive factor of post-radiation oedema and consequent neurological symptoms (149).

No studies have attempted to compare outcomes of RT and RS prospectively, however the excellent control rates demonstrated over the years have led the Clinical Commissioning Groups (CCG) of the National Health Service in England (NHS England) to issue a statement policy in 2013 (reference: NHS ENGLAND D05/P/e) on radiosurgical management of intracranial meningiomas. The policy describes indications for RS as well as clinical conditions that need to be met for the service to be NHS funded.

1.8.1.3. Active monitoring strategy

Not all meningiomas warrant an immediate intervention; for patients with minimally symptomatic small tumours who might suffer from multiple co-morbidities, an active monitoring strategy can be adopted (69). A meta-analysis of 22 retrospective studies amounting to 675 untreated meningiomas, of which 39% had symptoms on presentation, showed that the majority of meningiomas did not demonstrate any tangible growth over a median follow-up period of 4.6 years (150). However, the authors found tumour size to be a significant discriminating factor in that regard. Whilst 2.2% of meningiomas measuring <2 cm grew and went on to worsen or initiate symptoms, those measuring >2 cm, coupled with tumour signal hyperintensity; demonstrated an increased tendency to grow, but still again very few caused or worsened symptoms. The authors conclude by highlighting the need for systematic efforts to predict the disease progression during observation, which is what has been done in a recent retrospective study (151). Endpoints comprised:

- Aggravation or development of neurological symptoms.
- Significant tumour growth (absolute growth rate (AGR) ≥2 cm^3/year or AGR ≥1 cm^3/year + relative growth rate ≥30%/year).
- SRS becoming inappropriate if tumour volume exceeds 10 cm^3 after observation.
- Invasion of surgically-inaccessible spaces such as the cavernous and superior sagittal sinuses.

Two hundred and thirty-two patients were included in the analysis of which 32 exhibited pre-existing neurological symptoms. After a median follow-up period of 46.9 months, 77 (33.2%) patients met at least one of the previous criteria and were subsequently deemed to have progressed. Predisposing factors included absence of calcification, hyperintense signal and larger tumours, in concordance with the findings of the meta-analysis, as well as pre-existing neurological symptoms. This of course puts the option of active monitoring for symptomatic tumours into question. However, similarly to previous studies reporting on outcomes of untreated meningiomas, the authors failed to incorporate important patient factors such as performance status (PS) and the presence of co-morbid conditions, which are likely to influence any management decision made.

1.8.2. Asymptomatic incidental meningiomas

As briefly aforementioned, the discovery of meningiomas whilst still asymptomatic is becoming a more frequently occurring phenomenon (152). Asymptomatic meningiomas diagnosed during radiological examination for unspecific symptoms or other diseases, are often referred to as "incidental meningiomas". Incidental findings are frequently encountered in clinical settings, where patients presenting with headache, amongst other unspecific symptoms, undergo neuro-imaging which might reveal unrelated pathologies. An examination of 3000 CT scans carried out following head trauma found meningioma to be the most common incidental finding following cisterna magna (10% of findings) (153). Persisting audiovestibular symptoms such as tinnitus can also lead clinicians to request MR images of the brain, and again this could uncover a range of incidental findings including meningiomas (154, 155). The increased use of brain imaging modalities for research also yields a significant number of Incidental neurological findings. The Rotterdam Scan study, the Alzheimer and Families study, and the Older Australian Twins study are all perfect examples of this with an average rate of 16.1% of incidental findings; meningiomas comprised 6.5-26.0% of those (156-158). More epidemiological studies are soon to follow; these include the UK Biobank imaging study and the National Institutes of Health's (NIH) BRAIN Initiative (159). An influx of incidental findings, including meningiomas, therefore is to be expected.

Patients affected by such incidental findings have been previously described as **V**ictims **O**f Modern **I**maging **T**echnology (VOMIT) in a personal view, highlighting the overwhelming anxiety that such discoveries are bound to generate (160). Nonetheless, whether in a healthcare or a research setting, qualitative data suggests that most individuals involved would like to be informed of these findings and from an ethical and a legal perspective, our duty is to do so (161, 162).

Data also indicates that those individuals expect rapid access to experts as to be counselled about these findings (163), which in the case of incidental meningiomas would be a neurosurgeon, a neurologist or a clinical oncologist.

A recent meta-analysis, comprising 9 articles, demonstrated how two meningioma factors, signal intensity and calcification status, could be used to guide individual patient management. For example, if a patient has meningioma calcification or a low T2 signal on MRI, a follow-up observation with neuroimaging and clinical monitoring can be preferentially considered. The follow-up interval can be as long as 6 months or 1 year. However, if the

imaging examination is less favourable in its characteristics, the possibility of rapid growth exists and as such, shorter intervals could be opted for. The latest meningioma guidelines, published by EANO and the National Comprehensive Cancer Network (NCCN), support this notion; however, EANO fail to define the optimum duration of follow-up whilst NCCN suggest indefinite surveillance, which clearly has economic implications (69, 164). Moreover, a recent survey of UK neurosurgery practice demonstrated that whilst most neurosurgeons considered patient factors and tumour location in optimising management, those previous radiological features were not taken into account as often (165). This highlights the need for studies modelling growth patterns and subsequent management based on patient demographics, performance status, co-morbidity, as well as established radiological factors.

1.9. Aims and outline of the thesis

It is suggested that common incidental findings should be managed proportionately, sensitively, and economically (166). The aim of this thesis is to devise a management strategy for incidental meningiomas which could inform clinical practice whist satisfying the first two factors. This will be presented in the form of 2 chapters with each encompassing a different study. Chapter 2 describes a systematic literature review of papers reporting incidental meningiomas and chapter 3 describes a retrospective cohort with the aim of modelling management strategies.

Chapter 2: Incidental Intracranial Meningiomas: A Systematic Review to Evaluate Management Strategies and Outcomes

Acknowledgements: Dr Midhun Mohan (MM), academic foundation doctor at the University of Liverpool, was second reviewer and co-authored this chapter. Dr Richard Moon, academic foundation doctor at the University of Liverpool, co-authored this chapter.

2.1. Introduction

Meningiomas arise from the arachnoid cap cells in the linings of the brain (19). With an estimated annual incidence rate of five per 100,000 person-years in the UK, they account for almost a third of all primary intracranial neoplasms (2). Their incidence increases with age and peaks between the ages of 40 and 60 (167). The World Health Organisation (WHO) classifies these tumours into three groups: benign meningioma (grade I), atypical meningioma (grade II) and anaplastic meningioma (grade III) (19).

Asymptomatic meningiomas constitute 30% of these tumours (168). In recent years, with the extensive application and noticeable advancement in neuroimaging modalities, incidental intracranial findings are becoming more prevalent (169). Meningiomas comprise 3.0-26% (153, 170-173). These incidental findings cause significant patient anxiety and distress which are compounded by the uncertainty faced by clinicians in their ongoing management.

The management of incidental intracranial meningiomas consists of surgery, radiotherapy and active monitoring. Recent consensus guidelines published by the European Association of Neuro-Oncology (EANO) suggest active monitoring to be the best management strategy. However, the frequency and duration of follow-up are not specified (69). This leads to a variety of different follow-up strategies which has economic implications and is of uncertain patient benefit (165).

Furthermore, there is a paucity in the literature with regards to outcomes following each management strategy. Thus, the aim of this systematic review is to evaluate the outcomes of current management strategies of incidental intracranial meningiomas with particular emphasis on active monitoring and the timing of meningioma progression during follow-up.

2.2. Objectives

The aim of this systematic review was to evaluate the outcomes of alternate strategies currently in clinical use for the management of incidental intracranial meningiomas.

2.3. Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (174). The protocol was registered with the international prospective register of systematic reviews (PROSPERO) under the following ID: CRD42017077928 (175).

2.3.1. Search strategy

A literature search, last updated September 24, 2017, was performed from inception in the following electronic databases and study registries:

i. Medline (Ovid): Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and 1946 to Present.
ii. Embase (Ovid): 1974 to present.
iii. Cochrane Library: Central Register of Controlled Trials.
iv. CINAHL Plus (EBSCO).
v. World Health Organization – International Clinical Trials Registry Platform (WHO ICTRP).
vi. UK Clinical Trials Gateway.

The search strategy utilised for Medline (Ovid) and Embase (Ovid) can be found in Table 2.1. The strategy adopted for the other databases was altered appropriately and the search term "meningioma" was used in isolation to explore the study registries.

Table 2.1. Search strategy for Medline (Ovid) and Embase (Ovid)

Search	Query
1	exp meningioma/
2	((central nervous system or CNS or brain* or cerebral* or intracranial or intra-cranial) adj3 (cancer* or tumo?r* or malignan* or neoplas*)).mp.
3	1 or 2
4	(glioma* or glial* or glioblastoma* or GBM* or astrocytoma* or ependym* or subependym* or neurocytoma* or pineal* or pineo* or chordoma* or hamartoma* or pituitary* or craniopharyngioma* or neuroblastoma* or medulloblastoma* or lymphoma* or metastat*).mp.
5	((lung* or breast* or skin* or blood* or h?ematolg* or dermatolog* or renal* or genitourinary*) adj3 (cancer* or tumo?r* or malignan* or neoplas*)).mp.
6	(leuk?emia* or myeloma* melanoma*).mp.
7	4 or 5 or 6
8	3 not 7
9	(asymptomatic or incidental or small or untreated).mp.
10	(surgery or radiotherapy or radiosurg* or observ* or conservative treatment or follow-up or natural history or growth).mp.
11	8 and 9 and 10
12	Limit 11 to English

The bibliographies for each included record were scanned for additional studies that could have met the eligibility criteria.

2.3.2. Paper selection

Initially, the titles of all results were screened independently by AII and MM. Abstracts were reviewed with titles that mentioned Incidental/asymptomatic/small meningioma in combination with surgical/radiosurgical/radiotherapy/active monitoring outcomes or anything of similar construct. Full-text articles were inspected for abstracts which alluded to outcomes being available for more than 10 incidental/asymptomatic/small meningioma

patients. Decisions were blinded, and articles identified were only included upon mutual agreement; when disagreements occurred, authors discussed the disparities and attempted to resolve them. If these could not be resolved amongst AII and MM, the senior authors were consulted. Full-text article were subjected to the following population, intervention, comparison and outcomes (PICO) inclusion criteria outlined in Table 2.2.

Relevant registered trials were categorised, based on recruitment status, into concluded or on-going. If concluded, disseminated results were examined. If yet to be disseminated, investigators were contacted for data involving incidental meningioma patients. On-going trials were excluded.

Table 2.2 PICO inclusion criteria

Population	Patients ≥16 years of age diagnosed radiologically with an incidental/asymptomatic intracranial meningioma/s. NF2-associated and radiation-induced meningiomas were excluded.	
Intervention	Surgical resection, SRS, FRT, active monitoring or hospital discharge after the first inpatient/outpatient appointment.	
Outcomes	**Primary**	**Secondary**
	Post-intervention complications (surgery, SRS and FRT)	Quality of life
	Progression free survival (PFS)	Neurocognitive function
	Time to intervention (active monitoring)	
	Meningioma-related readmissions (hospital discharge)	
Duration of Follow-up	≥12 months	
Study design	Randomised controlled trials and retrospective and prospective case series and cohort studies with < 10 adult patients (≥ 16 years). Case reports were excluded	

2.3.3. Data Extraction

A standardised pre-piloted proforma (appendix 1) was used to extract individual patient data per included study by AII and MM independently. In the event that a study's population comprised in part of incidental meningiomas patients, corresponding authors of the studies in question were contacted via email to obtain their data. Data sets that subsequently remained incomplete were handled using the following imputation approach:

i. Studies in which incidental meningioma patients comprised ≥90% of the cohort, weighted averages were quoted and used for quantitative analysis.
ii. Studies with a lower percentage were excluded.

Data was inputted into a Microsoft Excel for Window version 16.0 spreadsheet before being exported to SPSS version 24.0 for statistical analysis.

2.3.4. Data synthesis

Meningioma location was categorised into non-skull base and skull-base. Further subdivisions according to the Society for Neuro-oncology International Consortium on Meningioma (ICOM) classification system (unpublished material, appendix 4) was carried out when appropriate. Meningioma size was recorded as noted in each individual study. Volumetric measurements were converted to one-dimension diametric measurements using the equation *Mean tumour diameter (MTD) = (2 × V)* $^{(1/3)}$ and vice versa. Diametric measurements were used for prognostication whereas changes in tumour size over time

were performed using volumetry. Post-intervention complications and presenting symptoms were grouped into hierarchical domains where appropriate.

2.3.5. Statistical analysis

Data was analysed using SPSS version 24.0 (IBM, Armonk, NY, USA). Baseline patient demographics are expressed using descriptive statistics with non-weighted statistical differences for categorical variables assessed using the Chi-square test or Fisher's exact test as appropriate. Continuous string variables were examined using the Mann-Whitney U test or Student's t-test. Differences were considered to be statistically significant at 0.05. Pooling of raw individual patient data pertaining to all tested variables was carried out whenever possible and subsequent statistical significance was assessed on a non-weighted multivariate level.

2.3.6. Quality assessment of the included studies

Although all study types were eligible for inclusion, the literature available on this topic was observational and of retrospective nature. Therefore, the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used (appendix 2, accessible using: accessible using: http://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort). This was carried out, independently, by AII and MM. Results were compared and in the case of discrepancies, the senior authors were asked to review before comparing results again.

2.4. Results

2.4.1. Literature search

Fig. 2.1. shows the study selection process. The total number of unique pooled records was 4750. Of titles screened, 4479 were deemed to be irrelevant and so were subsequently excluded. The abstracts of the remaining 271 records were screened and a total of 126 full-text articles were examined for eligibility. The initial number of articles included and excluded was 20 and 95. The corresponding authors for an additional 11 records were contacted on 21/11/2017. A duration of 3 months was allowed for responses and follow-up emails were sent to those expressing interest in providing data. However, none were received. Thus, the final number of articles included was 20.

2.4.2. Study characteristics

The characteristics of the 20 included studies are summarised in Table 2.3. Four of these were published prior to 2000 (176-179). All were retrospective observational studies (176-194) apart from one cross-sectional paper which investigated quality of life (QoL) and neurocognitive function (NCF) (195). Fifteen were single-centred studies whilst 5 were multi-centred. There were no prospective observational or randomised controlled trials.

2.4.3. Patient demographic and clinical characteristics

The overall number of incidental meningioma patients was 2130. Eighteen studies comprising of 2061 (96.8%) patients were examined for quantitative analysis (176-192, 194). The remaining two studies, comprising 69 patients, were used for a narrative review of QoL and NCF (193, 195). Age was reported in 12 studies for a combined total of 814 (39.5%) patients. The mean age was 63.1 years (SD = 6.9). Sex was reported in all studies with 1531

being female and 399 males (4:1). Co-morbidities and performance status were noted in only one study. Baseline clinical features are summarised in Table 2.4.

2.4.4. Baseline radiological characteristics

Indications for brain imaging were neurological deficit (n=107), headache (n=101), audiovestibular symptoms (n=88), head injury (n=77) and miscellaneous (n=163). These symptoms were all deemed unrelated to the meningiomas discovered. Thirty-two meningiomas were identified during follow-up for other diseases, while 97 were found on voluntary imaging or routine health check-ups. Reasons for scan were not reported for the remaining 1385 (67.2%) patients. Location was available for 1465 meningiomas of which 69.1% were non-skull base. The mean diameter for 888 meningiomas was 2.14 cm. The remainder of baseline imaging characteristics are outlined in Table 2.4.

2.4.5. Treatment groups

At initial presentation, four management strategies were identified; surgery, stereotactic radiosurgery (SRS), clinical-radiological active monitoring and clinical active monitoring. Eleven patients were discharged without clinical or radiological data and thus were excluded from subsequent analysis. The two active monitoring strategies aforementioned were combined. Five hundred and sixty (27.3%) patients had surgery, 450 (22.0%) had SRS while 1040 (50.7%) patients were conservatively managed with regular clinical or clinical-radiological monitoring. The differences in characteristics amongst the three management groups are summarised in Table 2.3.

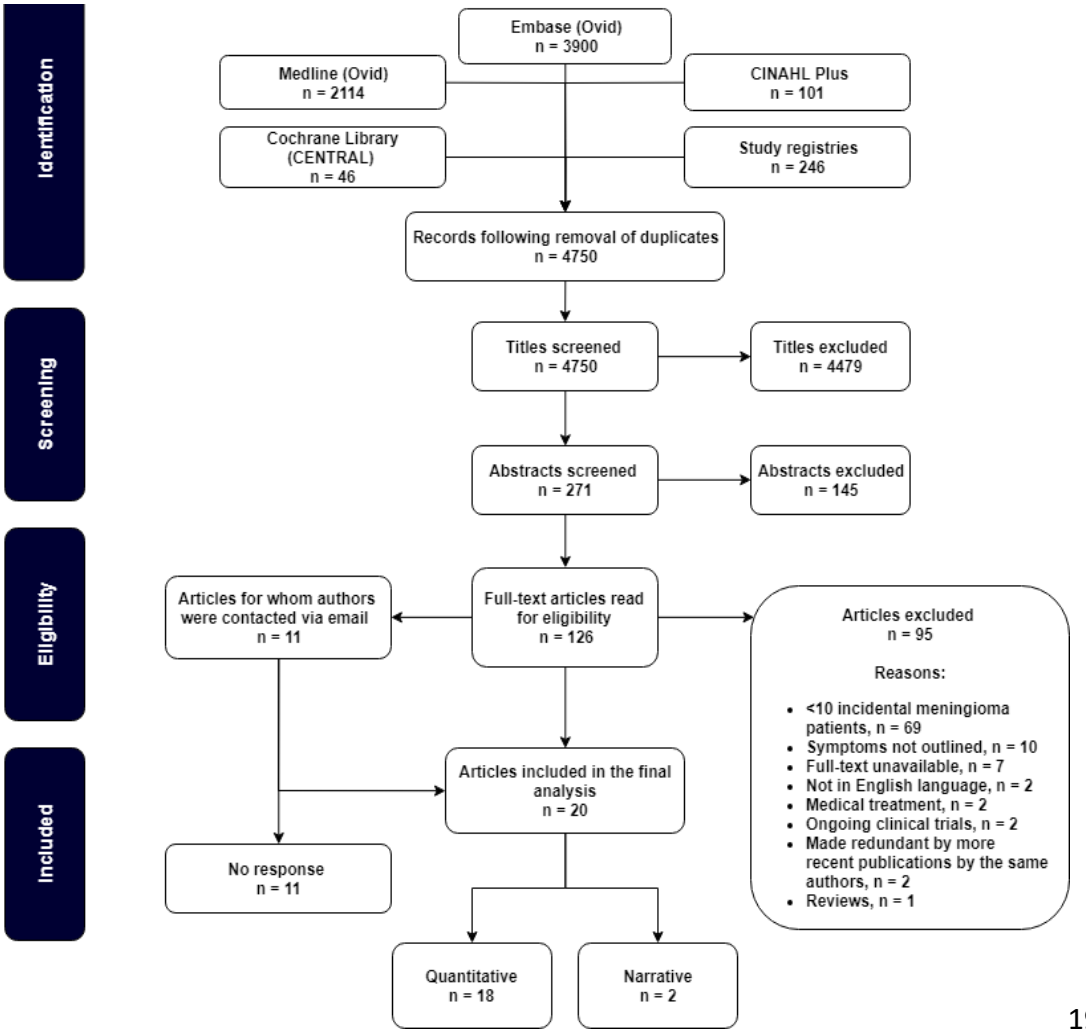


Fig. 2.1. The study selection process

Table 2.3. Summary of the Study characteristics of the 20 included studies

Study authors	Publication date	Study design	Setting	N. of incidental meningioma patients	Median/mean age (yrs.)	Female	Male	Intervention					
								Active monitoring		Surgery	SRS	FSRT	Hospital discharge
								C	CR				
Firsching et al. (176)	1990	Retro	Single-centre	15	68/64.7	12	3	0	15	0	0	0	0
Olivero et al. (179)	1995	Retro	Single-centre	60	NA/66	45	15	15*	45	0	0	0	0
Go et al. (177)	1998	Retro	Multi-centre	33	NA	NA	NA	6*	27	0	0	0	0
Nishizaki et al. (178)	1999	Retro	Multi-centre	108	64.7/NA	85	23	0	33*	75	0	0	0
Niiro et al. (180)	2000	Retro	Multi-centre	40	NA/76.1	32	8	0	40	0	0	0	0
Yoneoka et al. (181)	2000	Retro	Single-centre	71	NA/61	61	10	0	37*	23	0	0	11*
Nakamura et al. (182)	2003	Retro	Single-centre	47	59/60.1	42	5	0	47	0	0	0	0
Sonoda et al. (183)	2004	Retro	Single-centre	16	75/74.8	7	9	0	11	5	0	0	0
Yano et al. (185)	2006	Retro	Multi-centre	603	NA	489	114	0	351 (171)	191	61	0	0
Reinert et al. (184)	2006	Retro	Single-centre	102	NA	NA	NA	0	0	102	0	0	0
Hashiba et al. (186)	2009	Retro	Single-centre	70	NA/61.6	61	9	0	70	0	0	0	0
Jo et al. (187)	2010	Retro	Single-centre	154	NA/59.2	121	33	0	77	8	69	0	0
Rubin et al. (194)	2011	Retro	Single-centre	54	NA	NA	NA	0	54	0	0	0	0
Kasuya et al. (188)	2012	Retro	Single-centre	69	NA	55	14	0	19	50	0	0	0
Van Nieuwenhuizen et al. (195)	2013	CS	Single-centre	21	NA/63.4	17	4	0	21	0	0	0	0
Jadid et al. (9)	2014	Retro	Single-centre	65	68/66.6	41	24	0	65	0	0	0	0
Hoe et al. (189)	2015	Retro	Single-centre	320	56/NA	260	60	0	0	0	320	0	0
Liu et al. (191)	2015	Retro	Single-centre	122	NA/58.6	83	39	0	104	18	0	0	0
Zeng et al. (192)	2015	Retro	Single-centre	112	53/NA	88	24	0	24*	88	0	0	0
Butts et al. (193)	2017	Retro	Multi-centre	48	80/NA	32	16	0	48	0	0	0	0

Abbreviations: C=clinical; CR=clinical-radiological; SRS=stereotactic radiosurgery; FSRT=fractionated stereotactic radiotherapy; Retro=retrospective; CS=cross-sectional
*outcomes not available
() outcomes available for a part of this group

Table 2.4. Baseline clinical and radiological characteristics

N. of studies informing characteristic	N. of valid cases informing characteristic (%)	Characteristics		Total	Surgery	SRS	Active monitoring	P
18	2050	**N. of patients, N (%)**		2050	560 (27.3)	450 (22.0)	1040 (50.7)	
12	803 (39.2)	**Mean age (SD)**		63.1 (6.9)	61.5 (4.7)	54.9 (NR)**	64 (6.9)	<0.001
17	1919 (93.6)	**Sex, N (%)**	Female	1526	294 (19.3)	375 (24.6)	857 (56.2)	<0.001
			Male	393	164 (41.7)	75 (19.1)	154 (39.2)	
16	1465 (71.5)	**Location, N (%)***	Non-skull base	1012	269 (26.6)	233 (23.0)	510 (50.4)	<0.001
			Convexity	484	129	86	269	
			Parafalcine	247	55	71	121	
			Parasagittal	153	40	36	77	
			Tentorial	61	11	28	22	
			Intraventricular	24	3	12	9	
			Skull base	453	113 (24.9)	153 (33.8)	187 (41.3)	
			Anterior midline	113	30	43	40	
			Sphenoid wing	100	24	11	62	
			Posterior fossa - lateral and posterior	48	22	12	14	
			Posterior fossa - midline	143	18	87	34	
15	888 (43.3)	**Mean diameter, cm (SD)**		2.14 (0.61)	2.11 (0.42)	1.73 (NR)***	2.19 (0.66)	<0.001
10	615 (30.0)	**Calcification, N (%)**	Yes	235	36 (15.3)	NR	199 (84.7)	0.774
			No	380	55 (14.5)	NR	325 (85.5)	
5	298 (14.5)	**Signal intensity, N (%)**	Hyperintense	120	40 (33.3)	NR	80 (66.6)	0.237
			Iso/hypo-intense	178	48 (27.0)	NR	130 (73.0)	
12	1097 (53.5)	**Peritumoral edema, N (%)**	Yes	231	57 (24.7)	19 (8.23)	155 (67.1)	<0.001
			No	866	135 (15.6)	370 (42.7)	361 (41.7)	

*One study which dichotomized location into supratentorial vs infratentorial was excluded [15]

** Available in one study which did not report SD [26]

2.4.6. Treatment outcomes

2.4.6.1. Active monitoring

2.4.6.1.1. Follow-up regimens

Fifteen studies included patients who were subjected to active monitoring, of which only six described their follow-up regimens; endpoint being intervention or death. A maximum follow-up duration for patients who did not experience radiological or clinical progression was not stated. Study-specific follow-up protocols are described in Table 2.5.

Table 2.5. Active monitoring protocols per studies included

Study	Timing of scan following diagnosis
Olivero et al., 1995 (179)	3 months → 9 months →1 to 2 yearly
Nakamura et al., 2003 (182)	6 months → 1 yearly
Sonoda et al., 2004 (183)	3 months → 6 monthly
Jo et al., 2010 (187)	6 months →1 to 2 yearly
Jadid et al., 2014 (9)	1 yearly for a minimum of 10 years
Liu et al., 2015 (191)	3-12 monthly

2.4.6.1.2. Radiological and clinical progression

Clinical and radiological data were available for 1040 patients. Follow-up times were reported for 683 patients, with a mean of 49.5 months (SD=29.3). During follow-up, 235/1040 (22.6%) meningiomas grew, according to each study-specific criterion for growth (outlined in Table 2.6). Time-to-first-evidence-of-radiological-progression was reported for 69 (29.4%) patients at a mean of 28.5 months (SD=7.54). Considering the heterogeneity of growth definitions, a decision was made not to pool data for subsequent comparisons of growing versus non-growing meningiomas.

Table 2.6. Meningioma growth definitions by included studies

Study	Measurement	Definition
Go et al., 1998 (177)	Diameter	≥0.5 cm
Niiro et al., 2000 (180)	Diameter	≥0.5 cm
Yoneoka et al., 2000 (181)	Volume	>1 cm^3/year
Hashiba et al., 2009 (186)	Volume	>15%
Jo et al., 2010 (187)	Volume	>25%
Jadid et al., 2014 (9)	Diameter	>0.2 cm

*Seven studies lacked a definition for growth whilst 2 did not clearly define it

For 432 patients, symptom development (yes/no) was not reported. Out of the remaining 608 patients, 66 (10.9%) patients developed symptoms. These encompassed seizure (n=8), motor deficit (n=6), cognitive deficit (n=3), visual deficit (n=2) and cranial nerve palsy (n=2). The nature of the symptoms was not stated in the remaining 45. Differences in baseline characteristics amongst patients who developed symptoms and those that did not are outlined in Table 2.7.

2.4.6.1.3. Intervention endpoints and timeframe for treatability

Intervention was recommended or carried out in 220 (21.2%) patients. Indications for treatment were radiological progression (n=153), development of symptoms (n=66) and patient preference (n=1). Surgery was performed in 179 whilst SRS was the intervention of choice in the remainder (n=30, 14.2%). Two patients were subject to surgery and adjuvant

SRS. Mean time-to-intervention, available for 175 patients, was 24.8 months (SD=18.2); 94.3% were carried out within five years of diagnosis whilst 5.7% received an intervention after 5 years, latest being performed 88 months following diagnosis. Differences in baseline characteristics amongst patients who had an intervention and those who did not are outlined in Table 2.7.

Table 2.7. Differences in baseline characteristics based on symptom development and intervention

		Symptom development			Intervention		
Factor		Yes	No	P	Yes	No	P
Age (%)	<65 yrs.	37 (13.7)	233 (86.3)	0.032	135 (39.1)	210 (60.9)	<0.001
	≥65 yrs.	23 (8.0)	263 (92.0)		34 (11.4)	264 (88.6)	
Sex (%)	F	39 (9.3)	382 (90.7)	<0.001	166 (21.4)	609 (78.6)	<0.001
	M	27 (21.6)	98 (78.4)		54 (38.0)	88 (62.0)	
Location (%)	Non-skull base	48 (11.3)	376 (88.7)	0.455	146 (31.7)	315 (68.3)	0.059
	Skull base	18 (13.7)	113 (86.3)		42 (24.0)	133 (76.0)	
Diameter (%)	<3.0 cm	51 (9.7)	476 (90.3)	<0.001	164 (27.3)	437 (72.7)	0.564
	≥3.0 cm	15 (42.9)	20 (57.1)		11 (23.4)	36 (76.6)	
Signal intensity (%)	Hyperintense	11 (16.7)	55 (83.3)	0.032	13 (16.9)	64 (83.1)	0.116
	Iso/ hypointense	4 (5.4)	70 (94.6)		10 (9.2)	99 (90.8)	
Calcification (%)	Yes	20 (10.7)	167 (89.3)	0.134	48 (25.3)	142 (74.7)	<0.001
	No	45 (15.5)	245 (84.5)		128 (43.1)	169 (56.9)	
Peri-tumoural oedema (%)	Yes	52 (36.9)	89 (63.1)	<0.001	115 (82.7)	24 (17.3)	<0.001
	No	14 (5.1)	260 (94.9)		55 (17.4)	261 (82.6)	

2.4.6.1.4. Relationship between baseline radiological characteristics, growth dynamics and symptom development

Raw patient data was available for 137, 89 (8.56%) of whom had known symptom status by the end of follow-up; mean duration was 39.7 months (SD=27.7). Seventeen patients developed symptoms while 72 remained asymptomatic. Average follow-up time did not differ between the two groups (41.6 vs. 39.2 respectively, p=0.753). Differences in radiological characteristics are shown in Table 2.8. A binary logistic regression model was used for analysis. Factors that were significantly associated with symptom development were an initial meningioma diameter ≥3.0 cm (OR=37.5 [95% CI=7.57-185.8), p=0.005) and the presence of peritumoural oedema (OR=4.25 [95% CI=1.06-16.9], p=0.21). The absolute growth rate (AGR) of meningiomas measuring ≥3.0 cm was 4.0 cm^3/yr. compared to an AGR of 0.62 cm^3/yr. in meningiomas <3.0 cm (p<0.001).

2.4.6.2. Surgery

Overall, 741/2050 (36.1%) patients had surgery. Five hundred and sixty were operated at initial presentation whilst 181 had a period of active monitoring prior to surgical intervention.

2.4.6.2.1. *Extent of resection*

Extent of resection, as described in each study, was reported for 300/741 (40.5%) patients. GTR was achieved in 285 (95.0%) whereas STR was performed in the remaining 10 (5.0%) patients. Two patients required adjuvant SRS.

Table 2.8. Growth dynamics and symptom development stratified by baseline characteristics

Factor		Mean AGR (cm^3/yr.)	P	Mean RGR (%/yr.)	P	Symptom development, yes/total (%)	BLR P
Location	Non-skull base	2.14	0.942	53.8	0.213	12/64 (18.8)	0.927
	Skull base	1.79		30.5		5/25 (20.0)	
Diameter	<3.0 cm	0.62	<0.001	27.3	0.863	2/62 (3.2)	0.005
	≥3.0 cm	4.00		28.4		15/27 (56.6)	
Signal intensity	Hyperintense	2.04	0.988	53.0	0.262	11/41 (26.8)	0.242
	Iso/ hypointense	2.02		36.1		4/27 (14.8)	
Calcification	Yes	1.35	0.499	60.6	0.093	6/25 (24.0)	0.768
	No	2.42		38.0		10/47 (21.3)	
Peritumoural oedema	Yes	0.34	0.301	55.4	0.727	5/10 (50.0)	0.021
	No	2.32		44.7		12/63 (19.0)	

Abbreviation: AGR=annual growth rate; RGR=relative growth rate; BLR=binary logistic regression

2.4.6.2.2. *Histopathology and recurrence*

Histology reports were available for 316 patients. Three hundred and three (95.9%) had benign WHO grade I meningiomas, 10 (3.16%) had atypical WHO grade II whilst in 3 (0.95%) the pathology revealed anaplastic WHO grade III. Reclassification of these meningiomas according to the 2016 WHO system for brain tumours was not feasible. There was no tumour recurrence observed in 105 patients during a mean follow up time of 20 months (SD=14.2). Recurrence status was not reported for the remaining.

2.4.6.2.3. *Post-operative morbidity and mortality*

From a total of 533/741 (71.9%) patients with available post-operative morbidity data, 88 (15.0%) had complications which were neurological in 47 (53.4%), surgical in 28 (31.8%) and 13 (14.8%) patients had medical complications. Mortality data was not available. Performance status post-surgery was reported in 168 patients. Scales used were Karnofsky performance score (KPS) (n=5) and the Glasgow Outcomes Scale (GOS) (n=163). Four patients assessed by KPS scored 100 whereas 1 patient scored 50. For patients assessed with GOS, 156 (95.7%) patients had a score of 4-5 and four (2.45%) had a score of 1-3. Seven patients were reported to have a score of less than 5.

2.4.6.3. SRS

SRS was the initial treatment of choice in 450 patients. Thirty patients were subjected to active monitoring and subsequently underwent SRS due to clinical or radiological progression.

2.4.6.3.1. SRS treatment parameters

Two studies provided data regarding radiosurgical parameters. Median marginal dose was 14.5 Gy in 1 study and 13.0 Gy in the other. A prescription isodose line of 50% was noted in one study.

2.4.6.3.2. Response rates post SRS

Radiological response was available for 389/480 (81.0%) patients. Three hundred and eighty-two (98.2%) meningiomas remained stable as opposed to 7 (1.80%) which demonstrated progression during follow up. The mean follow-up time was 40.9 months (SD = 14.6). Adjuvant SRS was performed in 2 surgery patients for whom progression was not reported.

2.4.6.3.3. Post SRS complications

No data was available for 91 patients. Of the remaining 389, 304 (78.1%) did not have post-SRS morbidity. Eighty-five (21.9%) patients had the following complications: headache (n=22), epilepsy (n=11), motor deficit (n=6), scalp paraesthesia (n=6), alopecia (n=5), dizziness (n=5), ocular pain (n=4) and tinnitus (n=4). Twenty-two patients suffered from asymptomatic peritumoural oedema.

2.4.7. Meningioma specific mortality

Two patients died as a result of their meningiomas. A 73-year-old male exhibited significant tumour growth at 9 and 12 months following diagnosis and thus surgery was recommended. The patient refused surgery. Consequently, the patient suffered large intracerebral and subdural haemorrhages and died. The post-mortem revealed an angioblastic meningioma, more recently defined as hemangiopericytoma. The second patient was a 74-year-old male who died 88 months following diagnosis. His meningioma grew from 4.5 to 8.2 cm and subsequently was offered surgery however he declined any intervention.

2.4.8. QoL and NCF outcomes

One cross-sectional study examined NCF and QoL in 21 patients with stable radiologically-suspected asymptomatic meningiomas and compared them to a matched healthy population (195). Mean age was 63.4 years. Four were male and 17 were female. Meningioma patients fared worse compared to healthy controls on working memory and motor speed. However, there was no correlation between these findings and radiological characteristics such as tumour location and size. The investigators used the Short Form (36) health survey (SF-36) to assess QoL. The meningioma cohort had lower scores on 2/8 domains namely vitality and general health. A retrospective study comprising of 48 meningioma patients (median age 80 years, 32 females: 16 males), utilising a different battery of NCF measures, found no differences in outcomes compared to a matched population (193). However, when stratified by tumour location, patients with infratentorial meningiomas performed worse on memory and verbal fluency tests. Patients in both studies were treatment-naive. No studies examined the effect of surgery or SRS on NCF and QoL in incidental meningioma.

2.4.9. Quality assessment results

Quality assessment results are summarised in Table 2.8. Ten studies were rated as “good”, eight were “fair” and 2 were deemed to be of “poor” quality. No discrepancies were found between the results of AI & MM. All studies mutually failed to report relevant information needed to answer questions 6, 10 and 12 (see appendix 2).

Table 2.9. Results of the Quality assessment performed for all studies included

Study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Score
Firsching et., 1990 (176)	+	-	NA	+	NA	NR	+	-	+	NR	+	NR	+	-	Fair
Olivero et al., 1995 (179)	+	+	NA	+	NA	NR	+	-	+	NR	-	NR	+	-	Fair
Go et al., 1998 (177)	+	+	NA	-	NA	NR	+	+	-	NR	+	NR	+	-	Fair
Nishizaki et al., 1999 (178)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	-	Fair
Niiro et al., 2000 (180)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	-	Good
Yoneoka et al., 2000 (181)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	+	Good
Nakamura et al., 2003 (182)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	-	Good
Sonoda et al., 2004 (183)	+	+	NA	-	NA	NR	+	-	-	NR	+	NR	+	-	Fair
Yano et al., 2006 (185)	+	+	NA	+	NA	NR	+	+	-	NR	+	NR	+	-	Good
Reinert et al., 2006 (184)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	-	Good
Hashiba et al., 2009 (186)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	+	Good
Jo et al., 2010 (187)	+	+	Na	+	NA	NR	+	-	+	NR	-	NR	+	-	Fair
Rubin et al., 2011 (194)	+	+	NA	+	NA	NR	+	+	-	NR	-	NR	+	-	Fair
Kasuya et al., 2012 (188)	+	-	NA	-	NA	NR	-	-	-	NR	-	NR	+	-	Poor
Van Nieuwenhuizen et al., 2013 (195)	+	+	-	+	NA	NR	+	+	+	NR	+	NR	NA	+	Good
Hoe et al., 2015 (189)	+	-	NA	+	NA	NR	+	+	+	NR	+	NR	+	+	Good
Jadid et al., 2015 (9)	+	+	NA	+	NA	NR	+	+	+	NR	-	NR	+	-	Fair
Liu et al., 2015 (191)	+	+	NA	+	NA	NR	+	-	-	NR	-	NR	+	-	Poor
Zeng et al., 2015 (192)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	+	Good
Butts et al., 2017 (193)	+	+	NA	+	NA	NR	+	+	+	NR	+	NR	+	+	Good

NA=not applicable, NR=not reported
List of 14 questions is available in the appendix

2.5. Discussion

2.5.1. Summary of review aims

This systematic review was conducted with the aim of evaluating the alternate strategies (active monitoring, surgery or SRS) currently in clinical use for the management of incidental meningiomas.

2.5.2. Summary of key findings

Eighteen retrospective studies were identified for quantitative analysis, comprising a final cohort of 2061 patients. At initial presentation around half of these patients (51%) were managed conservatively with active monitoring, 27% of patients underwent surgical resection and 22% of patients were treated with SRS. Eleven patients were discharged without any available clinical or radiological data.

Of patients subjected to active monitoring, 1 in 5 went on to receive either surgical or radiological treatment of their meningioma, with the majority undergoing surgery. The average time from diagnosis to intervention within the active monitoring cohort was two years, with 94% of patients treated within 5 years.

The overall intervention rate within the entire study cohort was 59%. Neurological, surgical and medical complications were encountered by 15% of patients undergoing surgery and 22% of patients receiving SRS. A histological diagnosis of Grade I meningioma was recorded for 96% of operated meningioma patients.

2.5.3. Active monitoring strategies

Active monitoring strategies for the management of incidental meningioma are becoming increasingly more common (152), with recent neuro-oncology guidelines advocating their use in patients demonstrating no clinical symptoms and no accompanying radiological mass effect (69). However, while the guidelines recommend annual clinical and MRI tests after an initial observation period of 6 months, they do not provide advice as to the length of follow up for patients that do not experience clinical or radiological progression. Moreover, while the development of clinical symptoms is a clear indication for treatment, no consensus exists as to what constitutes significant radiological progression and when it may necessitate intervention.

Our results show that of those patients with recorded presence/absence of symptoms, 11% reported subsequent symptomatic development. Predictive factors on univariate analysis were male gender, tumour diameter ≥3.0 cm and the presence of peritumoural oedema. Both radiological factors remained significant on multivariate analysis.

As noted, there is no current agreement on the definition of significant radiological progression. Three different strategies emerged from our results: i) absolute increase in maximum diameter, ii) absolute increase in tumour volume, iii) relative percentage increase in tumour volume. Furthermore, it was evident that the time course over which tumour growth occurred was poorly documented, with only one study assessing annual change (181).

Relative and absolute annual growth rates were analysed for meningiomas with a maximum diameter greater or less than 3 cm. It was apparent that no significant difference was present in the relative growth rate (%/year) between the cohorts. However, absolute growth rates (cm^3/year) were noted to be significantly different. Those meningiomas with a maximum diameter >3 cm demonstrated a higher annual growth rate and were also correlated with a greater incidence of new symptom development. This may suggest the use of absolute growth rate as a more clinically relevant measure of radiological progression. Although only

available for a limited number of patients, the average time to radiological progression was 28.5 months.

A large degree of heterogeneity was similarly observed in the active monitoring regimens. The timing of the first scan ranged from 3 to 12 months with a subsequent frequency of follow-up scans varying from 6 months to 2 years. It is worth considering the impact of this variation in imaging protocols on the recorded time to radiological progression. Only one study commented on the duration of monitoring of patients with no clinical or radiological progression, with a recorded minimum of 10 years or until patient death (9).

2.5.4. Alternative management strategies

At initial presentation, if not undergoing an active monitoring management strategy, patients were treated with either SRS or surgery. Twenty-seven percent of patients underwent surgery at the time of initial diagnosis, with 22% of patients receiving SRS. The overall intervention rate at initial presentation was 49%.

2.5.5. Treatment interventions

Active monitoring endpoints necessitating further intervention were defined as either clinical or radiological progression. Radiological progression was evident in 235 (22.6%) patients within the active monitoring cohort. Of these, 66 patients also reported concurrent symptom development. Two hundred and twenty patients subsequently received or were recommended to receive a therapeutic intervention. The mean time to intervention was two years, with over 9 out of 10 patients receiving their treatment within 5 years of diagnosis of incidental meningioma. Of these patients failing active monitoring strategies, 82% underwent surgical resection of their meningioma.

Of the available histology reports for patients undergoing surgical resection at any time point, 96% received a diagnosis of WHO grade I meningioma. No tumours were reported to be metastatic lesions radiologically misinterpreted as a meningioma, suggesting that an early scan at 3 months is not necessary to rule out metastatic disease.

The post-operative complication rate was reported as 15%, as compared to 22% for patients receiving SRS. This is comparable to the complication rates reported in the literature for operative and radiosurgical treatment of symptomatic meningiomas (143, 196, 197).

2.5.6. Recommendations

2.5.6.1. Clinical implications

We found that only 20% of patients undergoing active monitoring regimes demonstrated radiological or clinical progression requiring a treatment intervention. This confirms the validity of active monitoring strategies and supports the current EANO guidelines. However, it is apparent that within this data set only half of patients were subject to active radiological monitoring. Following the recent publication of these guidelines, we would envisage the proportion of patients undergoing an immediate intervention is likely to reduce.

This data shows that disease progression during active monitoring and subsequent treatment intervention in the vast majority of cases occurs within 5 years of diagnosis. Given the current lack of consensus on the necessary duration of active monitoring, this may suggest that for

those patients not displaying evidence of radiological and/or clinical progression, imaging surveillance beyond a 5-year time point may be less frequently required or unnecessary depending on individual patient demographics including comorbidity and performance status.

The data also suggests that meningiomas measuring more than 3 cm in greatest diameter and those with peritumoural oedema are at a higher risk of symptomatic development. Patients with these features should therefore be more rigorously monitored within the first 5 years of diagnosis.

2.5.6.2. Future research

It is evident from this data that there are a wide variety of measurements of growth reported in the literature. A uniform definition of growth is therefore required for ongoing clinical management and future research.

Furthermore, the current heterogeneity in the frequency of radiological surveillance requires a unified strategy in order to better identify radiological progression, limit radiation exposure and reduce the costs to health care.

For patients at high risk of meningioma growth, it is unclear when the optimal timing for intervention is. A cost-effectiveness analysis comparing early and delayed treatment would help inform this decision.

All studies in this review were retrospective in nature and largely single-centre. There is a clear need for the establishment of a validated core outcome set for data standardisation and its subsequent use in prospective multi-centre studies investigating the management and outcomes of incidental meningiomas.

2.5.7. Comparisons to published review articles

There are only two systematic reviews published assessing the outcomes of incidental meningiomas. One review assessed the risk factors for development of new or worsened symptoms during follow up of untreated symptomatic and asymptomatic meningiomas, concluding that patients with bigger meningiomas are more likely to become symptomatic; a finding which we replicated (150). Low tumour growth was associated with low T2 signal in the other review which attempted to meta analyse the presence or absence of tumour growth during follow-up (10). Our data demonstrated that high T2 signal was associated with symptom development which may have resulted from tumour growth.

2.5.8. Study limitations

This study has several limitations. Firstly, raw data was not available for all studies, which were also of a poor level of evidence base. The heterogeneity of the available data prevented meta-analysis and descriptive analyses performed were not weighted to account for pooling from multiple investigations. The studies included in this review spanned a 27-year time-frame. During this period, significant advances in operative and radiological technology, post-intervention outcomes and management guidelines (including the WHO classification system) occurred, thus introducing confounding variables into our data.

The lack of stratification of complication rates between surgery at the time of initial presentation or on encountering disease progression during active monitoring prevented a detailed analysis of post-treatment outcomes.

2.6. Conclusion

Incidentally-diagnosed asymptomatic meningiomas are common with no clear consensus on optimal management strategies. This review demonstrates a wide variety in current practice of radiological surveillance but suggests that the majority of patients who develop clinical or radiological progression will do so within the first 5 years of diagnosis. Regular monitoring may therefore be less frequently required beyond this time point.

Chapter 3: Incidental Meningioma: Prognostic Analysis Using Patient Comorbidity and MR-Tests (The IMPACT Study)

Acknowledgements: Dr Midhun Mohan (MM), academic foundation doctor at the University of Liverpool, was second observer for assessment of inter-observer variability of radiological factors.

3.1. Introduction

The increased access to various modalities of brain imaging including MR and CT for clinical and research purposes has led to an exponential increase in the number of incidental findings with meningiomas comprising a significant fraction (173, 198-200). International guidelines suggest active radiological and clinical monitoring as the modality of choice for managing these tumours (69, 201), however lack of details surrounding the optimal duration of follow-up and intervals in-between scans highlights the paucity of high-quality studies addressing this issue. Quite a number of investigations have identified prognostic radiological factors which increase the risk of meningioma growth and subsequent clinical symptoms (10, 202). However, the timing of such progression is poorly defined. Moreover, clinical factors such as performance status and patient comorbidity remain unexplored in relation to prognosis of incidental meningiomas.

The understanding of such factors' prognostic implication is essential to risk stratification of incidental meningioma patients. Each stratum could be assigned a management strategy which reduces the health cost burden of these incidental findings and improves the overall clinical practice.

In this study, we used data for individual patients from a retrospective incidental meningioma cohort to develop a prognostic model for the risk of disease progression during active monitoring, and to assess the role of patient demographics and MR characteristics in this prediction. The model was internally validated using a bootstrapping approach enabling assessment of its predictive ability.

3.2. Objectives

3.2.1. Primary objective

Develop a prognostic index to predict the risk of disease progression during active monitoring for incidentally-discovered asymptomatic meningioma.

3.2.2 Secondary objectives

- Establish the most common scenarios that lead to the identification of incidental meningiomas.
- Delineate the histological and pathological characteristics of tumours subjected to surgical intervention.
- Establish growth rates of incidental meningiomas.
- Measure the rate of post-intervention complications and tumour recurrence/growth; both could help inform clinical practice in terms of choosing an intervention.

3.3. Methods

This study was approved by the clinical audit group of the Walton Centre NHS Foundation Trust on 19th April 2017 (appendix 3). Patients who underwent surgery were consented to the Walton Research Tissue Bank (North Wales REC No 11/WNo03/2). All tissue, imaging and clinical information were available for use under that ethics approval.

3.3.1. Study design

A retrospective cohort analysis of asymptomatic meningioma patients identified incidentally.

3.3.2. Study Setting

This retrospective study involved patients seen in the Departments of Neurosurgery and Neurology at a tertiary centre: the Walton Centre NHS Foundation Trust, Liverpool, UK, between 1st January 2007 and 31st December 2015.

3.3.3. Participants

Patients 16 years of age or older with a newly identified incidental meningioma were included. Radiation-induced and NF2-associated meningioma patients were excluded. Eligible patients were identified using the Computerised Radiological Information System (CRIS) search tool. The search terms utilised were “meningioma”, “incidental” and “incidental meningioma”. The two lists of patients obtained from searching "incidental" and "meningioma" were combined and only duplicates (patients that appeared on both lists) were maintained whereas unique records were discarded. One unique record for each patient was subsequently kept. The list acquired from the search using “incidental meningioma” was cross-checked against patients obtained from the first search strategy to ensure they all featured. These steps were performed in Microsoft Excel for Windows version 16.0.

3.3.4. Variables and data sources

- Patients’ demographics. Data source: medical records. Factors recorded included age, sex, WHO PS (Table 3.1) and the age-adjusted Charlson comorbidity index (ACCI) (Table 3.2). History of malignancy, type and status (in-remission /active) were also recorded. Active malignancies included those undergoing treatment, those identified and awaiting treatment, and patients with evidence of clinical or radiological disease progression. In-remission status was assigned to those who had finished their scheduled treatment with no succeeding clinical or radiological evidence of progression, regardless of time.
- Indication for carrying out brain CT/MRI which led to the identification of a meningioma, these reasons had to be unrelated to the tumour itself. Data source: medical records.
- Radiological data. Data source: Carestream Vue picture archiving and communication system (PACS), version 11. Factors recorded included number of meningiomas, calcification status on non-contrast CT (diffuse/partial/absent), MRI field strength, tumour signal intensity compared to the contralateral grey matter on MRI T2/FLAIR (hypo/iso/hyper), peritumoural oedema in relation to tumour volume using the signal change present on MRI T2/FLAIR (0-5%/6-33%/34-66%/67-100%; based on the Visually AcceSAble Rembrandt Images [VASARI] MR features for gliomas(203)), maximum meningioma diameter on gadolinium-enhanced axial MRI T1 (A), diameter perpendicular to A (B), maximum height on coronal/sagittal gadolinium-enhanced MRI T1 (C).

Meningioma volume was calculated using the ABC/2 formula. Meningioma location was classed into non-skull base and skull base and further subcategorised according to the Society for Neuro-oncology International Consortium on Meningioma (ICOM) classification system (unpublished material, appendix 4). Meningiomas in proximity of the major dural venous sinuses (superior sagittal sinus [SSS]/transverse sinus [TS]/sigmoid sinus [SS]/cavernous sinus [CS]/the confluence of sinuses) were categorised as separate, in direct contact or invading. Contact with critical neuro-vascular structures (i.e. ICA, optic apparatus [OA]) was noted. Meningiomas that fulfilled one of the two previous categories were said to be in proximity of critical neurovascular structures. Any other intracranial pathologies were also noted. Fig. 3.1. depicts how certain radiological characteristics were classified.

Table 3.1. WHO performance status classification

Score	Description
0	able to carry out all normal activity without restriction
1	Restricted in strenuous activity but ambulatory and able to carry out light work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.
5	Dead

Table 3.2. Age-adjusted Charlson comorbidity index (204, 205)

Condition		weight
Age (years)	<50	**0**
	50-59	**1**
	60-69	**2**
	70-79	**3**
	≥80	**4**
Myocardial infarction		**1**
Congestive heart failure		**1**
Peripheral vascular disease		**1**
Hemiplegia		**2**
Cerebrovascular disease		**1**
Pulmonary disease		**1**
Diabetes		**1**
	With end organ damage	**2**
Renal disease		**2**
Liver disease	Mild	**1**
	Severe	**3**
Peptic ulcer disease		**1**
Cancer		**2**
	Metastatic	**6**
Dementia		**1**
Connective tissue disease		**1**
AIDS		**6**
Hypertension		**1**
Skin ulcers/cellulitis		**2**
Depression		**1**
On Warfarin		**1**

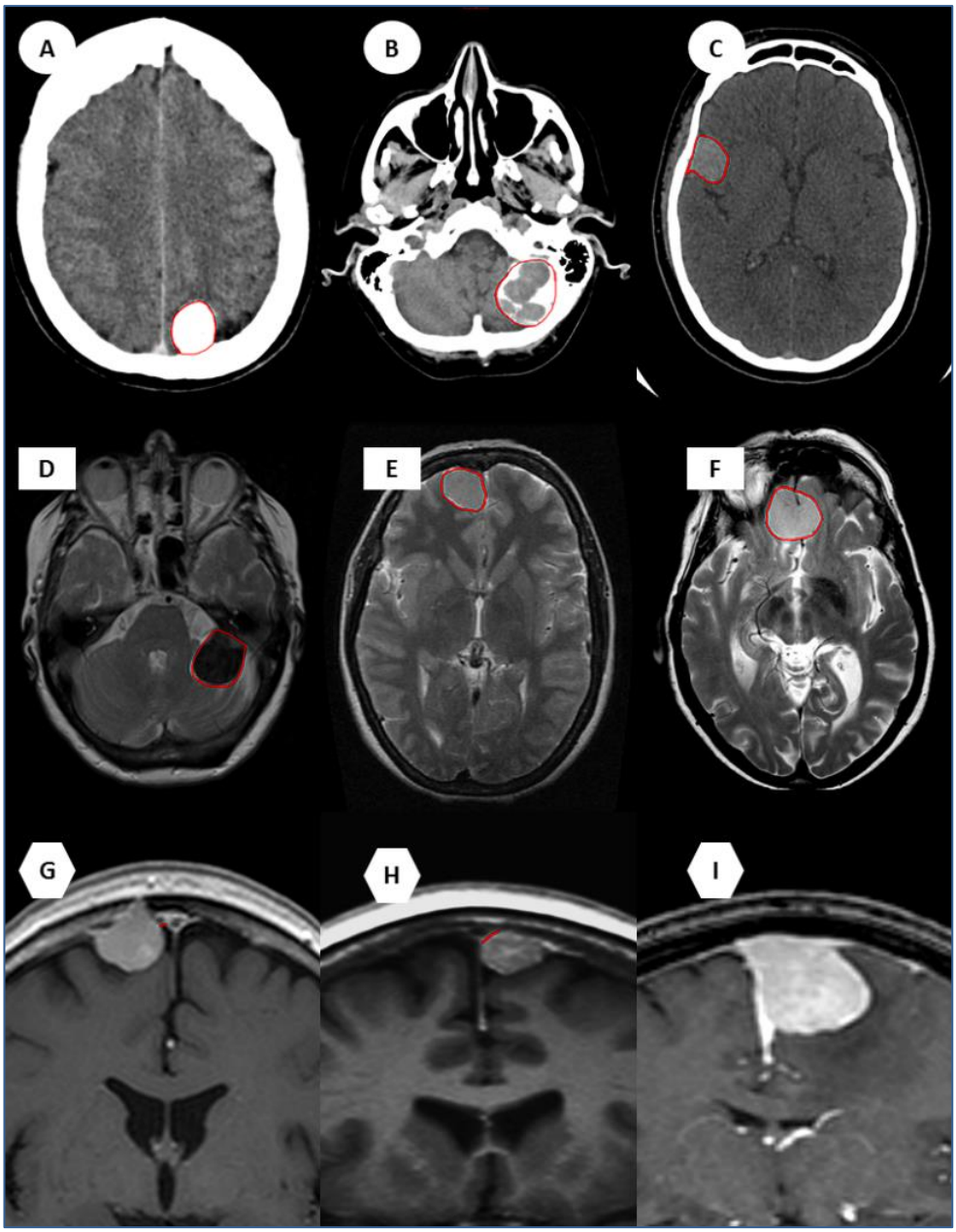


Fig.3.1. (A-C) Non-contrast axial CT scans demonstrating the 3 levels of meningioma calcification (circle). (A) Diffuse calcification. (B) Partial calcification. (C) Absence of calcification. (D-F) T2 MR axial sequences showing the 3 levels of tumour intensity (circle). (D) Hypointense. (E) Isointense. (F) Hyperintense. (G-I) T1-weighted MR with gadolinium (contrast) showing the relationship between the meningioma and the nearby venous sinus (SSS). (G) Separate as there's no clear attachment to the sinus wall. (H) In direct contact with the lateral wall of the sinus. (I) Clear macroscopic distortion and invasion of the sinus.

- Management plan agreed upon following identification of an incidental meningioma (active monitoring/surgery/SRS/FSRT/hospital discharge) and the responsible physician (neurosurgeon/neurologist/clinical oncologist). Data source: medical records.
- Active monitoring defined as regular surveillance imaging and outpatient clinical observation. Data source: medical records and PACS. Recorded factors included: number of scans, and interval between them (months). For each scan the following was noted: imaging modality (CT/MRI and field strength), peritumoural signal intensity, venous sinus involvement, meningioma volume and any new intracranial pathologies. Each scan was examined alongside its corresponding outpatient clinic appointment for any evidence of meningioma-related neurological symptoms

(motor/sensory/language/cognitive/seizure/headache/other). Each appointment's outcome was recorded (resume follow-up/surgery/SRS/FSRT/hospital discharge).

- Intervention details if performed, indication for intervention (radiological/clinical/patient preference) and time-to-intervention. Data source: medical records.
    - Surgery: Simpson score (as recorded by the surgeon in the operative notes), WHO grade (reclassified according to the WHO 2016 system), histological subtype, postoperative medical and surgical complications (Landriel-Ibañez Classification (206)), postoperative WHO PS, postoperative follow-up duration, recurrence during that time (yes/no) and if recurred time-to-recurrence.
    - SRS: dose, early and late (≥3 months) toxicity (assessed by CTCAE [Common Terminology Criteria for Adverse Events] v5.0), duration of follow-up post-radiation and tumour response during that time (progression, regression or stable disease).
    - FSRT: number of fractions, fractionated dose, total dose, early and late toxicity, duration of follow-up post-radiation and tumour response during that time (progression, regression or stable disease).
- Hospital discharge. Data source: medical records. Time-to-discharge was recorded. Data sources were also checked for any readmissions/rescans thought to be attributed to the incidental meningioma within the study time-frame. Outcome following readmissions/rescans was noted.
- Overall outcomes by the end of the study period (hospital discharge/lost to follow-up/dead/under follow-up) and follow-up durations. Data source: medical records.
- Mortality. Any deaths encountered during follow-up were noted. The medical records for patients discharged were also examined for mortality data. Duration between diagnosis and death were noted for deceased patients. Data source: medical records, NHS Spine and CRIS.

Data collection took place between 04/01/2018 and 21/03/2018.

3.3.5. Quantitative analysis

Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA) and R version 3.5.0.

3.3.5.1. Baseline descriptive statistics

Normally distributed continuous variables were expressed as mean (standard deviation (SD)) whereas skewed variables were expressed as median (interquartile range (IQR). Statistical significance for differences in baseline characteristics were assessed using Chi-square test for categorical variables. The Mann-Whitney U test was used for continuous data. Differences were considered to be statistically significant at $P < 0.05$.

3.3.5.2. Active monitoring endpoint definitions

Disease progression during Active monitoring was initially defined as one of: i) new symptom development, ii) venous sinus invasion, iii) peritumoural signal change, iv) meningioma volume exceeding 10 cm^3. The first criterion denotes clinical progression while the latter three are related to loss of treatment options or "window of curability". Venous sinus

invasion precludes from safe maximal resection. Peritumoural signal change and a meningioma volume >10 cm^3 are contraindications to SRS. Time to progression was defined as the time from radiological diagnosis to the first manifestation of these criteria. Disease progression, based on this definition, occurred in 32 (7.94%) patients.

The association between baseline clinical and radiological factors and time to disease progression was assessed using Kaplan-Meier survival analysis. Statistical significance was assessed using the Log-rank test. Patients that did not experience disease progression during active monitoring and remain under continued observation were censored at the last recorded follow-up. Patients discharged from outpatient care, dead during follow-up or lost to follow-up were censored at the last date of follow-up where there was no evidence of clinical or radiological progression. Subsequently, a joint longitudinal and time-to-event model was fitted with the aim of assessing the relationship between the initial meningioma volume, volume change over time and time to disease progression whilst adjusting for baseline covariates with a Log-rank p≤0.10 (Fig.3.2).

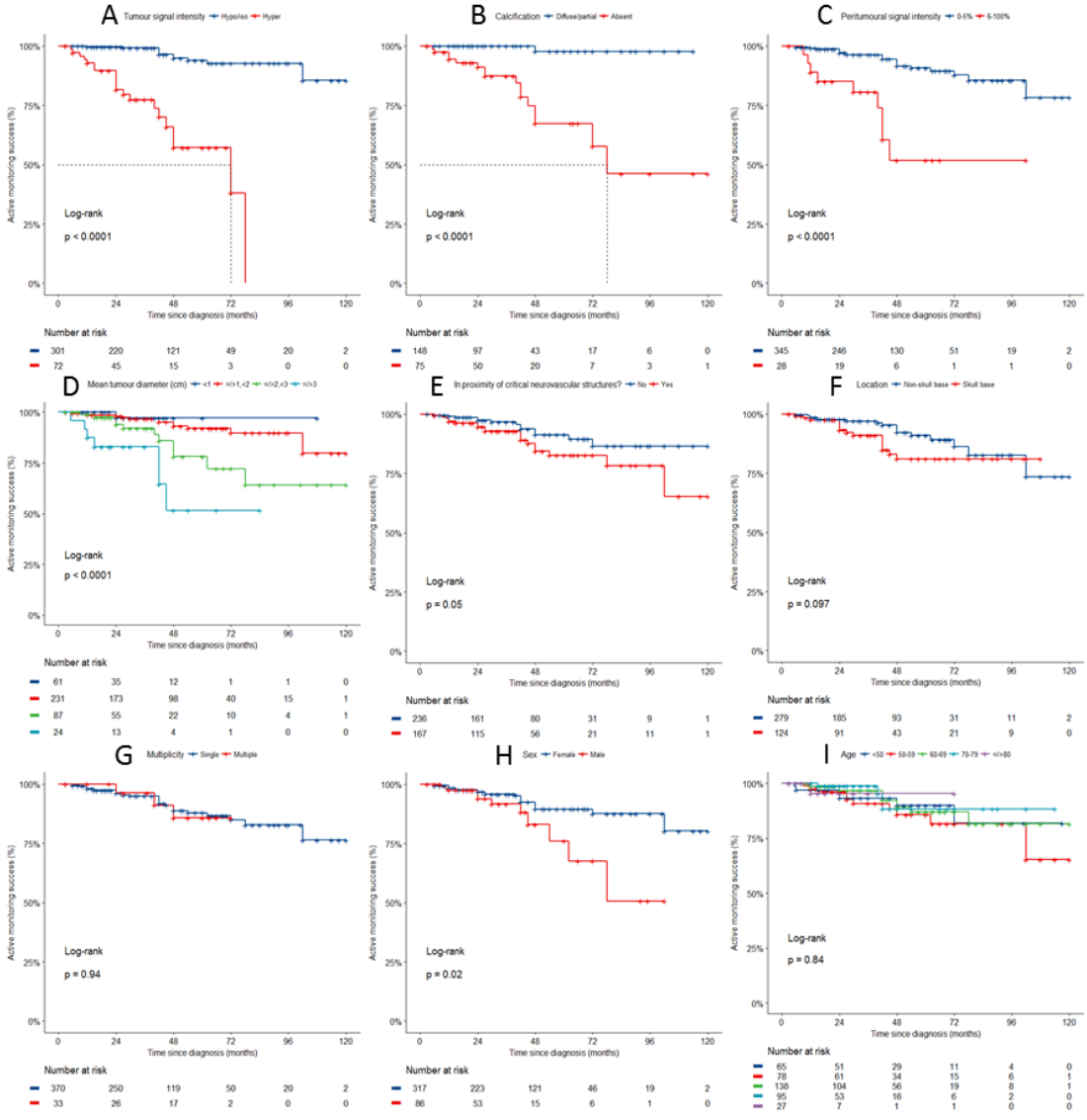


Fig.3.2. Kaplan-Meier survival analyses of (A) Tumour signal intensity. (B) Calcification. (C) Peritumoural signal intensity. (D) Meningioma size. (E) Proximity to neurovascular structures. (F) Location. (G) Multiplicity. (H) Sex. (I) Age. A, B, C, D, E, F and H had a Log-rank p≤0.1

Joint modelling has been developed to explicitly account for the dependence between the longitudinal change of a continuous factor i.e. meningioma volume in this example, and event time data (207). Joint models of this type combine a linear mixed-effects model that describes the longitudinal trajectory of a continuous factor, with a proportional hazards model for the time-to-event. In the former, covariates and random terms (random intercepts and random slopes) are selected using a likelihood-ratio test. In the latter model, the fitted exposure trajectory is related to the hazard for event through a parametric Cox analysis.

To determine how longitudinally changing values of tumour volume relate with the hazard for disease progression, we modelled its natural logarithm within a linear mixed regression framework that includes random intercept and slopes (referred to as the longitudinal sub-model). Time (in months) was included as a random effect. Sex, tumour signal intensity, peritumoural signal intensity, location and proximity to neurovascular structures were included as time-constant covariates with their respective baseline values.

In the survival sub-model, the predicted time-history of meningioma volume (logarithmic transformation) from the linear mixed model was related to the hazard for disease progression through a time-varying parametric Cox. The final model included sex, tumour signal intensity, peritumoural signal intensity, location and proximity to neurovascular structures included as time-constant covariates. The model was developed in 200 bootstrap samples. The results of the joint model are presented in Table 3.3.

Table 3.3. Joint model parameter estimates

Component	Parameter	Parameter estimate (95% CI)	P
Longitudinal	Intercept	0.14 (-0.04-0.31)	0.103
	Time	0.006 (0.005-0.007)	<0.001
	Tumour signal intensity	0.60 (0.23-0.94)	<0.001
	Peritumoural signal intensity	1.45 (1.01-1.94)	<0.001
	Proximity to neurovascular structures	0.37 (0.11-0.60)	0.003
	Location	-0.09 (-0.36-0.14)	0.483
	Sex	0.12 (-0.20-0.39)	0.469
Survival	Tumour signal intensity	2.66 (1.81-3.92)	<0.001
	Peritumoural signal intensity	1.24 (0.16-2.62)	0.041
	Proximity to neurovascular structures	0.65 (-0.25-1.73)	0.161
	Location	0.66 (-0.29-1.63)	0.150
	Sex	0.23 (-0.88-1.32)	0.678
	Meningioma volume	0.93 (0.57-1.52)	<0.001

The definition of significant meningioma growth used in previous studies has shown a great deal of variability. Most definitions are based on a certain extent of growth, such as an increase in the maximal diameter >2 mm or relative increase by 15% in comparison to the preceding volume (9, 186). The time course over which tumour growth occurred was not considered. The main statistical result from the joint data analysis is that tumour volume and time are strongly associated with the four disease progression categories. Moreover, given that tumour growth is likely to precede these endpoints and certain treatment factors such as surgical intervention, in response to growth, might have prevented the observation of these endpoints, it is reasonable that survival analyses incorporate tumour volume change over time (annual rate) as an additional endpoint.

A recent study on outcomes of untreated symptomatic and asymptomatic meningiomas defined significant tumour growth as absolute growth rate (AGR) ≥2 cm^3/year OR AGR ≥1 cm^3/year + relative growth rate (RGR) ≥30%/year (151). AGR and RGR calculations for meningiomas subject to active monitoring in our study are described below. We used a classification and regression tree (CART) analysis to assess the degree of success by which these definitions can set our cohort apart stratified by disease progression (based on the four endpoints). CART analyses are used to develop models that can classify participants into dichotomous splits. Fig. 3.3. outlines the CART analysis.

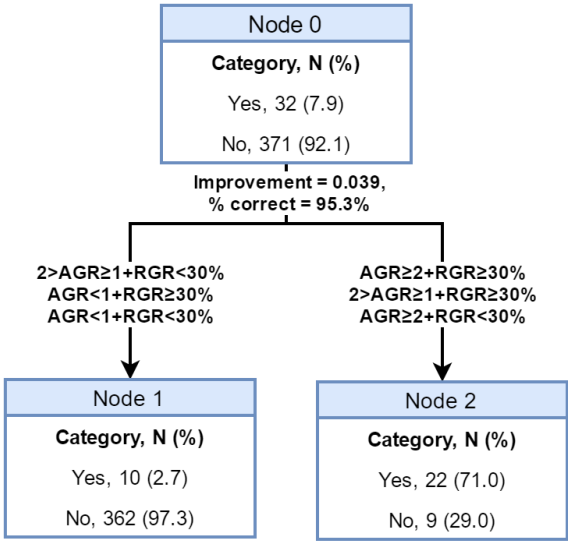


Fig.3.3. CART analysis demonstrating the split in the active monitoring cohort stratified by disease progression and non-progression

The CART analysis demonstrated a misclassification rate of 4.7% and an improvement score of 0.039. These parameters suggest a significant association between the growth definitions used and the four categories of disease progression. The Response Assessment in Neuro-Oncology (RANO) group is working towards standardisation of progression and response assessments (208). In an attempt to standardise the definition of radiological progression for untreated meningioma and in light of this significant association, a decision was made to use these parameters to denote significant tumour growth.

Thus, disease progression in our study was defined as one of:

i. New symptom development.
ii. Significant meningioma growth (AGR ≥2 cm^3/year OR AGR ≥1 cm^3/year + RGR ≥30%/year).
iii. Venous sinus invasion.
iv. Peritumoural signal change.
v. Meningioma volume exceeding 10 cm^3.

Time to disease progression was defined as the time from radiological diagnosis to the first manifestation of these categories. Fig. 3.4. summarises the steps undertaken to reach this definition.

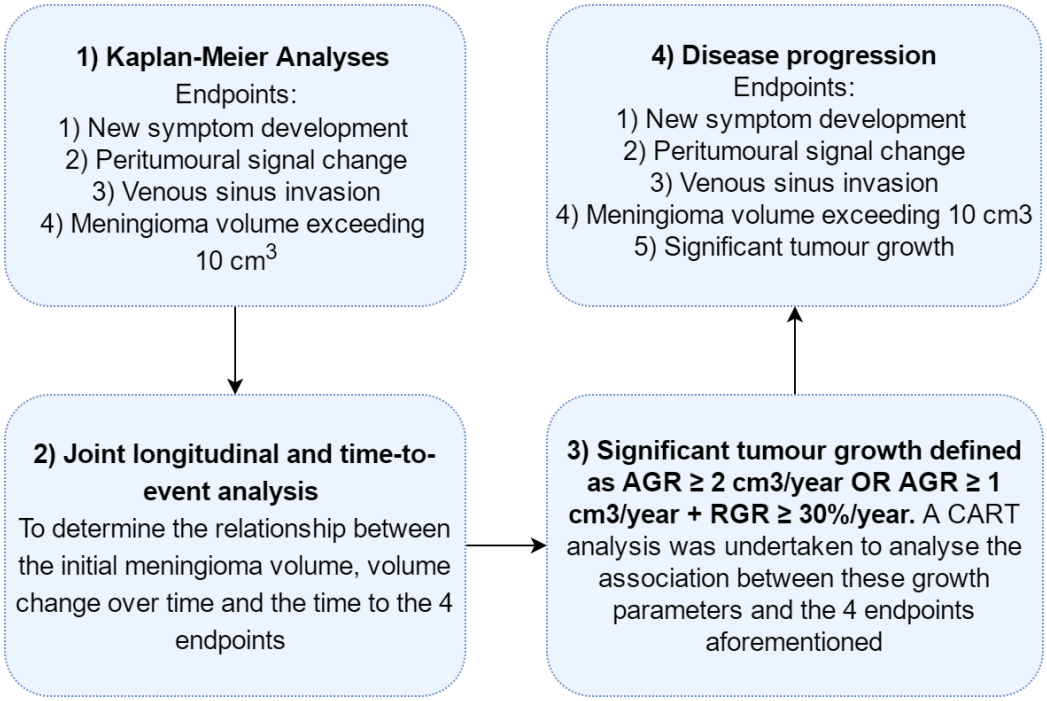


Fig.3.4. Flow chart of statistical analysis steps carried out to reach the final criteria for disease progression

3.3.5.3. Quantification of absolute and relative meningioma growth rates

AGR was defined as the increase in volume (V) per year in cm^3 $\left(\left(\frac{(V2-V1)}{time\ (months)}\right) \times\ 12\right)$ whereas RGR was defined as the percentage increase in volume per year $\left(\left(\frac{\frac{(V2-V1)}{V1}}{time\ (months)}\right) \times\ 12\ \times 100\right)$.

Due the lack of a standardised imaging surveillance protocol in The Walton Centre in terms of timing between scans, imaging modality and duration of follow-up, the growth rate for each meningioma was determined a using a linear mixed model (LMM) with random intercepts and slopes. LMM allows for missing data and does not require regularly spaced time points. A random coefficient model assumes that each meningioma has a different intercept and slope. The sum of the regression coefficients of random and fixed effects for the slope estimated from the linear model best represented the average growth rate for each meningioma.

3.3.5.4. Association between baseline variables and time to disease progression

Distribution of disease progression time was estimated by Kaplan-Meier analysis and stratified for baseline variables. Statistical significance was assessed using the Log-rank test. Patients that did not experience disease progression and remain under continued observation were censored at the last recorded follow-up. Patients discharged from outpatient care, dead during follow-up or lost to follow-up were censored at the last date of follow-up where there was no evidence of clinical or radiological progression. Factors included in the analysis were tumour size, tumour signal intensity, peritumoural signal intensity, calcification status, proximity to neurovascular structures, location, multiplicity, age and sex.

A Cox proportional hazards regression model was subsequently developed. Skewed continuous variables were transformed into their natural logarithms before being inputted into the model. Forward and backward stepwise selection procedures were utilised to determine the model of best fit with factor inclusion at $p \leq 0.05$ and exclusion at $p \geq 0.1$. Certain clinical factors were included in the final model despite being statistically insignificant. Model assumptions were tested by examination of Schoenfeld residuals (proportional hazards). Influential observations were examined using DFBETA panels.

Bootstrapping was performed to assess the internal validity of the model. It involves creating multiple datasets which are drawn from the sample with replacement. In each of these new datasets (n=200), the entire modelling process is repeated and 95% confidence intervals (95% CI) are generated for the factors' hazard ratios (HR).

Model performance was evaluated by determining the calibration and discriminative accuracy. Calibration is the agreement between the observed events of disease progression in the study cohort and the predicted events by the model for several meningioma groups at certain time-points following diagnosis. To evaluate model calibration, the study population was divided into 6 subgroups based on the predicted risk of disease progression. For each, the mean predicted probability and the mean observed rate of disease progression were determined at 2, 5 and 10 years following diagnosis. A calibration plot compares the observed and predicted rates of events for each group. A perfect match (x=y) indicates accurate calibration.

Discriminative accuracy is the model's ability to differentiate between patients who experienced disease progression and those who did not. Discrimination was assessed using Harrell's concordance (C) statistic and Chambless and Diao's time-dependent AUC (area under the receiver operating characteristic curve (ROC)) (209, 210).

3.3.5.5. Development of a prognostic index to predict the risk of disease progression during active monitoring

A prognostic index was developed based on the results of the Cox model. This is calculated for each patient as the sum of the covariate values included in the final model, weighted by the normal logarithmic transformation of the hazard ratios. As an example, an individual with 2/3 factors present, the prognostic index would be as follows: (1 (yes) × lnHR1) + (1 (yes) × lnHR2) + (0 (no) × lnHR3)

Risk group stratification was carried out by visual assessment of a prognostic index histogram. The prognostic index for each patient was plotted along the y-axis whilst the frequencies of observed disease progression and non-progression cases were plotted on the x-axis. Wherever a noticeable increase in the proportion of observed disease progression cases occurred in relation to the frequency of non-progression cases, a cut-off line was drawn. This was carried out twice as to best separate the study cohort into 3 distinct risk groups: low-risk, medium-risk and high-risk. The probabilities of disease progression by 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 years were then calculated for each of these groups. Kaplan-Meier analysis were used to assess the differences across risk groups.

3.3.5.6. Assessment of the impact of age, comorbidity and performance status on timing to hospital discharge and mortality

The effects of patient age, comorbidity and functional status on the distribution of disease progression and intervention times were assessed in a competing risk analysis. Performance status was determined using the WHO scale. This scale is utilised by the neurosurgeons in the Walton Centre and for documentation of performance status in multi-disciplinary team meetings. Patients were split based on PS into two categories: 0-1 and 2-4.

Age and comorbidity were combined to generate for each patient a measure of biologic age. This was done using the age-adjusted Charlson comorbidity index (ACCI). ACCI is among scales validated for use in non-specific site oncology patients and has been shown to predict postoperative outcomes in meningioma patient (211, 212). Furthermore, a systematic review of comorbidity measures in cancer patients showed ACCI to be among the most reliable indices. It also has the advantage of being quick to carry out whilst using routinely collected clinical and administrative data (213). Therefore, considering the lack of a validated comorbidity index in neuro-oncology populations, we decided to use the ACCI. Patients were stratified by ACCI into 3 groups: 0-2, 3-5 and >5. An ACCI score of ≤2 corresponds to patients who are young (<60 years) with few or no comorbidities. An ACCI score of 3–5 corresponds to either an older patient with few comorbidities, or a younger patient with numerous comorbidities, and an ACCI score >5 generally denotes older patient with comorbidities (214, 215).

Two competing risk analyses were performed. One assessing the cumulative incidence rate (CIR) of therapeutic intervention (surgery or radiotherapy) at different time points following diagnosis stratified by PS and ACCI groups. The other evaluated the CIR of disease progression. The competing event for the former was mortality which was either observed during follow-up or after being discharged from outpatient care. Patients that remain under follow-up were censored at the last outpatient clinic appointment. Alive patients discharged from outpatient care were censored at last time they were seen by a health physician i.e. general practitioner.

For the disease progression analysis, mortality after hospital discharge could not be used as a competing event as the time interval between discharge and death could have witnessed radiological changes which meet the disease progression definition. Instead, 4 events were regarded as competing in nature, discharge from outpatient care (HD), loss to follow-up (LTFU), death during follow-up (DDFU) or an intervention before disease progression occurred with the first three grouped together. Censoring was only done for patients who remain under follow-up at the last clinic appointment.

To test the equality across CIR groups, a Fine and Gray test was carried out. Plots of CIRs and 95% CIs were also generated for visual assessment.

3.3.5.7. Intervention outcomes

Intervention details and outcomes are narratively described with no statistical analyses carried out.

3.3.5.8. Data validity

Inter and intra-observer variabilities of MR and CT parameters were assessed on a random sample of 24 patients. Sample size was calculated using the Bland equation $\frac{1.96}{\sqrt{2N(M-1)}} = 0.20$ (216). M is the number of measurements: two by the primary observer to assess intraobserver reliability and one by the secondary observer to assess interobserver reliability (total=3). N is the sample size which has been calculated to be 24, 0.20 is the β-level (1-power) and 1.96 is the standard normal deviate.

Weighted Cohen's Kappa was used to evaluate the inter- and intraobserver variability of categorical variables. Continuous variables were assessed using Bland-Altman plots and the intraclass correlation coefficient (ICC). ICC was set to one-way random for intraobserver variability and two-way mixed for interobserver variability.

3.4. Results

3.4.1. Study population and baseline clinical characteristics

Fig. 3.5. describes the study population selection process. A total of 474 patients met the inclusion criteria; 18.5% (474/2569) of all meningiomas identified and 9.1% (474/5234) of all incidental neurological findings. Thirty-three patients were excluded for lack of corresponding medical records. Of the remaining 441 patients, 78.9% (n=348) were female. Patient demographics and clinical characteristics are summarised in Table 3.4.

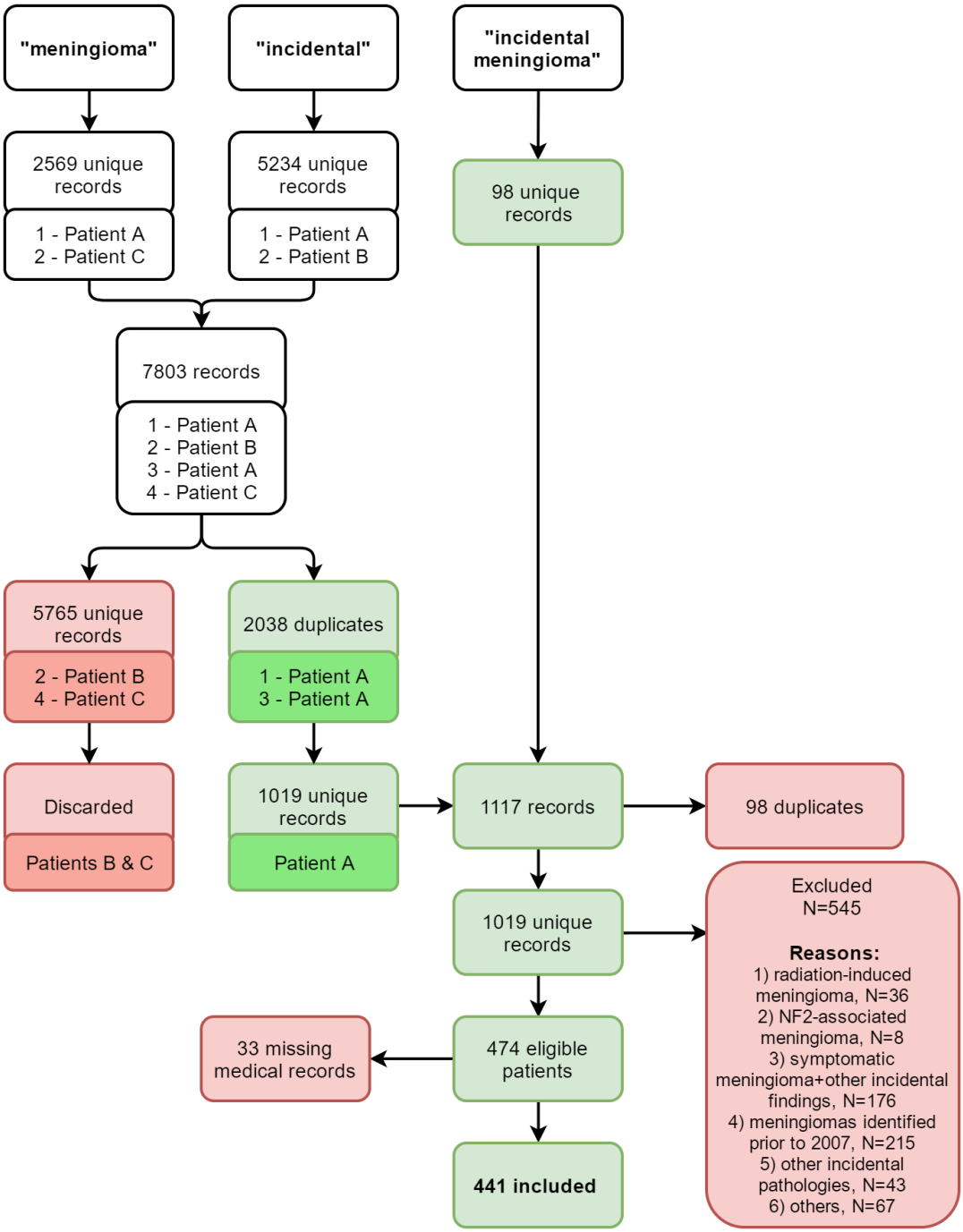


Fig.3.5. Patient selection process

Table 3.4. Patient demographics and clinical characteristics				
Characteristic				**N (%)**
Age	Mean (SD)			63.3 (12.6)
	<50			70 (15.9)
	50-59			83 (18.8)
	60-69			146 (33.1)
	70-79			103 (23.4)
	≥80			39 (8.8)
Gender	Female			348 (78.9)
	Male			93 (21.1)
ACCI	Median (IQR)			4 (3)
	0-2			103 (23.4)
	3-5			212 (48.1)
	>5			126 (28.6)
PS	Median (IQR)			0 (1)
	0-1			387 (87.8)
	2-4			54 (12.2)
History of malignancy	No			377 (85.5)
	Yes	In-remission	Breast	25 (5.7)
			Melanoma	5 (1.1)
			Lung	4 (0.9)
			Colorectal	3 (0.7)
			Others*	11 (2.5)
		Active	Lymphoma	5 (0.7)
			Breast	3 (0.7)
			Lung	3 (0.7)
			Melanoma	1 (2.0)
			Others*	4 (0.9)

Abbreviations: ACCI=Age-adjusted Charlson comorbidity index; PS=performance status
*other malignancies included leukaemia, prostate, cervical, endometrial, head and neck, urinary and skin cancers.

3.4.2. Baseline imaging characteristics

The main indication for imaging was headache (25.9%), cerebrovascular disease (13.8%), audiovestibular symptoms (12.9%), head trauma (7.9%), cognitive deficits (6.1%), visual problems (5.0%), loss of consciousness (4.1%) and miscellaneous (24.3%) including sinusitis, trigeminal neuralgia and lethargy. None of these symptoms were attributed to the meningioma. At initial presentation, 200 patients (45.4%) were examined by MRI and CT, 186 (42.2%) by MRI only and CT was the modality of choice in the remaining 55 (12.5%). MRI scanners had the following strengths: 3 Tesla (T) (30.3%), 1.5T (61.9%), 1T (1.3%) and 0.35T (6.5%). Meningiomas were single in 426 patients and multiple in 15 resulting in an overall meningioma population of 459. Venous sinus involvement was noted for 168 meningiomas. Sinuses involved were: SSS (n=95), CS (n=35), SS (n=21), TS (n=15) and the confluence of sinuses (n=2). Thirty-five meningiomas were in contact with 1 or more critical neurovascular structures and these included: OA (n=17), ICA (n=11), basilar artery (n=7), trigeminal nerve (n=4), middle cerebral artery (n=2) and the vertebral artery (n=2). Detailed imaging characteristics are outlined in Table 3.5.

Table 3.5. Imaging characteristics of the 459 incidental meningiomas included				
Characteristic				**N (%)**
Count	Single			426 (96.6)
	Multiple		2	13 (2.9)
			3	1 (0.2)
			4	1 (0.2)
Meningioma volume, cm^3	Median (IQR)			1.58 (3.39)
Meningioma location	Origin	NSB	Convexity	183 (39.9)
			Parafalcine	77 (16.8)
			Parasagittal	36 (8.2)
			Tentorial	21 (4.6)
			Intraventricular	5 (1.1)
		SB	Sphenoid wing	45 (9.8)
			Post fossa-lateral & posterior	42 (9.2)
			Anterior midline	34 (7.4)
			Post fossa-midline	16 (3.5)
	Relation to brain lobes		Frontal	225 (49.0)
			Parietal	86 (18.7)
			Temporal	52 (11.3)
			Occipital	26 (5.7)
			Cerebellum	51 (11.1)
			Brain stem	19 (4.1)
	Side		Right	228 (49.7)
			Left	214 (46.6)
			Midline	17 (3.7)
Venous sinus involvement	No			291 (63.6)
	Yes		Separate	49 (10.5)
			In direct contact	98 (21.4)
			Invading	21 (4.6)
Neurovascular structures contact	Yes			35 (7.63)
	No			424 (92.4)
Calcification status	Absent			81 (17.6)
	Partial			74 (16.1)
	Diffuse			109 (23.7)
Tumour signal intensity	Hyper			75 (16.3)
	Iso			210 (45.8)
	Hypo			119 (25.9)
Peritumoural signal intensity	0-5%			373 (81.3)
	6-33%			16 (3.5)
	34-66%			13 (2.8)
	67-100%			2 (0.4)
Other intracranial pathologies	No			310 (70.3)
	Yes		Cerebral atrophy	44 (10.0)
			Small vessel ischaemia	39 (8.8)
			Haematoma	14 (3.2)
			Vascular malformation	10 (2.3)
			Periventricular demyelination	6 (1.4)
			High-grade tumour	9 (2.0)
			Low-grade tumour	2 (0.5)
			Cerebral metastases	2 (0.5)
			Others	5 (1.1)

Abbreviations: NSB=non-skull base; SB= skull base

3.4.3. Clinical outcomes

At initial presentation, six patients (1.4%) underwent surgical resection, 50 (11.3%) were discharged whilst the remaining 385 (87.3%) entered active monitoring. Of those 385, 38 eventually required or requested an intervention after a median follow-up period of 24 months (IQR=33.8); surgery (n=32), surgery + SRS (n=1), surgery + FSRT (n=1), SRS (n=2) and FSRT (n=2). Overall outcomes by the end of the study period were: 219 discharged, 12 lost to follow-up, 5 dead during follow-up (unrelated to their meningiomas) and 205 under continued observation. Fifty-two patients died after a median of 18.5 months (IQR=26) of termination of follow-up. Nine had further MRI for unrelated symptoms after a median of 37 months (IQR=36) and one was patient was readmitted for radiological surveillance.

3.4.4. Influence of baseline clinical characteristics on the initial management decision

The differences in clinical characteristics among the three treatment groups are outlined in Table 3.6. The responsible physicians were neurosurgeons (n=392) and neurologists (n=48). One case was managed by a clinical oncologist. Thirty of 50 discharged patients were under the care of a neurologist (p<0.001).

Table 3.6. Differences in clinical characteristics between patients in the 3 management groups

Characteristic		Active monitoring	Discharged	Surgery	P
Age, N (%)	Mean (SD)	62.6 (12.0)	68.5 (15.9)	63.8 (10.5)	0.008
	<50	62 (88.6)	7 (10.0)	1 (1.4)	0.003
	50-59	77 (92.8)	5 (6.0)	1 (1.2)	
	60-69	130 (89.0)	13 (8.9)	3 (2.1)	
	70-79	90 (87.4)	12 (11.7)	1 (1.0)	
	≥80	26 (66.7)	13 (33.3)	0	
Gender, N (%)	Female	301 (86.5)	41 (11.8)	6 (1.7)	0.365
	Male	84 (90.3)	9 (9.7)	0	
ACCI, N (%)	Median (IQR)	4 (3)	6 (4)	3.5 (3)	<0.001
	0-2	94 (91.3)	9 (8.7)	0	0.002
	3-5	193 (91.0)	15 (7.1)	4 (1.9)	
	>5	98 (77.8)	26 (20.6)	2 (1.6)	
PS, N (%)	Median IQR)	0 (1)	1 (2)	0 (1)	<0.001
	0-1	346 (89.4)	35 (9.0)	6 (1.6)	0.001
	2-4	39 (72.7)	15 (27.8)	0	
Malignancy, N (%)	No	330 (87.5)	45 (11.9)	2 (0.5)	0.001
	Yes	55 (85.9)	5 (7.8)	4 (6.3)	

Abbreviations: CCI=Age-adjusted Charlson comorbidity index; PS=performance status

3.4.5. Influence of baseline radiological characteristics on the initial management decision

The differences in radiological characteristics among the 3 management groups are outlined in Table 3.7. Calcification status on CT was available for 255 patients (264 meningiomas), of which 246 had a solitary meningioma. One hundred and nine (41.3%) were diffusely calcified, 74 (28.0%) were partially calcified and the remaining 81 (30.7%) had no evidence of calcification. Of the 109 diffusely calcified meningiomas, 25.7% were discharged as opposed to 5.16% of patients harbouring partially calcified or non-calcified meningiomas (p<0.001). The rates of surgical intervention were 0.9% and 2.58% respectively. Patients discharged were also more likely to have no venous sinus involvement (p=0.043). Median meningioma

volume in patients discharged was 0.65 cm^3 as opposed to 1.70 cm^3 in patients subjected to active monitoring, and 10.6 cm^3 in operated meningioma patients (p<0.001).

Table 3.7. Differences in imaging characteristics between patients in the 3 management groups

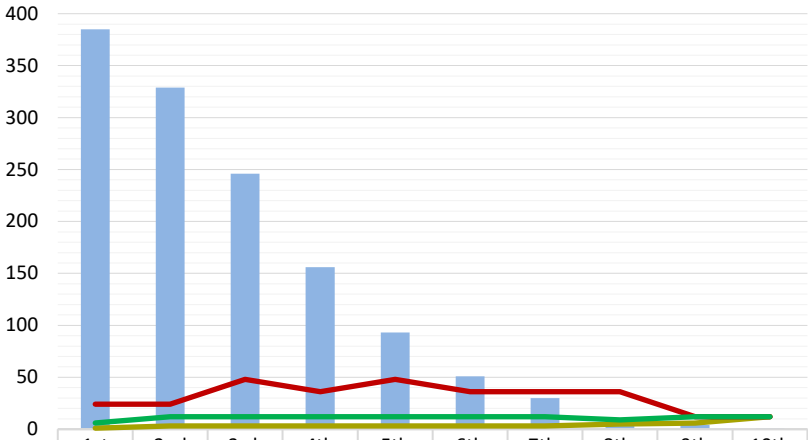
Meningioma characteristic			Active monitoring	Discharged	Surgery	P
Count, N (%)	Single		370 (86.9)	50 (11.7)	6 (1.4)	0.323
	Multiple		15 (100)	0	0	
Volume, cm^3	Median (IQR)		1.70 (3.53)	0.65 (1.10)	10.6 (23.0)	<0.001
Location, N (%)	Origin	NSB	279 (86.6)	38 (11.8)	5 (1.6)	0.478
		SB	124 (90.5)	12 (8.8)	1 (0.7)	
Venous sinus involvement, N (%)	No		246 (84.5)	42 (14.4)	3 (1.0)	0.043
	Yes	Separate	45 (91.8)	3 (6.1)	1 (2.0)	
		Direct contact	92 (93.9)	5 (5.1)	1 (1.0)	
		Invading	20 (95.2)	0	1 (4.8)	
Neurovascular structures contact, N (%)	Yes		33 (94.3)	2 (5.7)	0	0.447
	No		370 (87.3)	48 (11.3)	6 (1.4)	
Calcification, N (%)	Absent		75 (92.6)	4 (4.9)	2 (2.5)	<0.001
	Partial		68 (91.9)	4 (5.4)	2 (2.7)	
	Diffuse		80 (73.4)	28 (25.7)	1 (0.9)	
Tumour signal intensity, N (%)	Hyper		72 (96.0)	2 (2.7)	1 (1.3)	0.052
	Iso		197 (93.8)	9 (4.3)	4 (1.9)	
	Hypo		104 (87.4)	14 (11.8)	1 (0.8)	
Peritumoural signal intensity, N (%)	0-5%		345 (92.5)	25 (6.7)	3 (0.9)	<0.001
	6-33%		16 (100)	0	0	
	34-66%		11 (84.6)	0	2 (15.4)	
	67-100%		1 (50.0)	0	1 (50.0)	

Abbreviations: NSB=non-skull base; SB= skull base

3.4.6. Active monitoring regimens

The total number of scans performed following diagnosis was 1303 with an average of 3.4 (1303/385) scans per patient. Median duration of follow-up was 36.0 months (IQR=41.0). Fig. 3.6. depicts the active monitoring regimens detailing the number of scans and intervals between them. Approximately 90% of scans were performed using MRI (n=1166) whilst the remaining were done in a CT scanner. On three occasions, patients were scanned using both modalities. Most MRI scans were carried out in 0.35T scanners (n=669, 57.2%). Other MRI field strengths included 3T (n=393, 33.6%), 1.5T (n=106, 9.1%) and 1T (n=1, 0.1%). Most patients (n=360, 93.5%) were consistently monitored using the same imaging modality: MRI in 317 patients and CT in 43. The remaining 25 patients were followed-up alternately with CT and MRI studies.

Fig. 3.6. Active monitoring regimens in 385 patients



	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
Number of scans	385	329	246	156	93	51	30	8	4	1
Minimum interval (mos.)	1	3	3	3	3	3	3	5	6	12
Maximum interval (mos.)	24	24	48	36	48	36	36	36	12	12
Median interval (mos.)	6	12	12	12	12	12	12	9	12	12

3.4.7. Disease progression and subsequent intervention

During follow-up, 44 (10.9%) meningiomas experienced disease progression. Endpoints included: significant tumour growth (n=29, 7.20%), new symptom development (n=12, 2.98%), increase in peritumoural signal change (n=10, 2.48%), meningioma volume exceeding 10 cm^3 (9/369 with an initial volume <10 cm^3, 2.44%) and venous sinus invasion (5/137 meningiomas adjacent to but not invading a sinus, 3.65%). Symptoms were: seizure (n=6), motor deficit (n=3), visual deficit (n=2) and ataxia (n=1). Twenty-eight (6.95%) experienced one disease progression endpoint whereas 16 (4.71%) had multiple causes occurring concurrently (12 patients, n=2; 3 patients, n=3; 1 patient, n=4). Median time to disease progression was 33.0 months (IQR=32.0). The 5- and 10-year active monitoring non-progression rates were 83.0% (95% CI=77.1-88.9%) and 70.0% (95% CI=56.3-83.7%) respectively. Differences in growth patterns, clinical outcomes and the cumulative non-progression rate plot are demonstrated in Fig. 3.7.

The longitudinal profiles for meningioma volume against reverse time demonstrate the nature of volume progression. Whilst those that did not progress remained static in size during follow-up, meningiomas that did, exponentially grew prior to reaching an active monitoring endpoint. The time-course over which disease progression occurred is denoted by the black dotted intersection line in Fig. 3.7. It shows that if two equally sized meningiomas were picked up at the same point in time, the meningioma with growth potential will have reached its disease progression endpoint by the 75th month (~6th year) following diagnosis. Mean AGR and RGR were significantly higher in the disease progression group ($p<0.001$). Rates of intervention and its prerequisite recommendation were significantly lower in the non-progression group ($p<0.001$), which comprised six patients that requested surgery after a median follow-up period of 4.5 months (IQR=12.0). As for the disease progression group, an intervention was recommended in 84.1% (37/44) but only carried out in 20 (45.5%) patients. Median time to intervention in the two cohorts was 24.0 months (IQR=33.8).

Patients' primary reason for refusal of treatment was clinical stability as treatment was indicated due to radiological changes (disease progression group, n=11; non-progression group, n=4). Six patients' disease progression additionally involved the development of new symptoms, which patients either elected to control with antiepileptics (seizure, n=5) or were happy to live with due to their minimal effect (visual deficit, n=1). Of 12 patients who progressed and had further radiological surveillance available after doing so, 11 (91.7%) continued to show evidence of significant tumour growth (median follow-up period after initial disease progression=21.0 months (IQR=11.0)). Three epilepsy patients with available follow-up had optimal seizure control at their last recorded appointment, despite continued meningioma growth for two of them (median follow-up period after initial disease progression=18.0 months (IQR=6.)). The antiepileptic used was levetiracetam. The dose was not recorded.

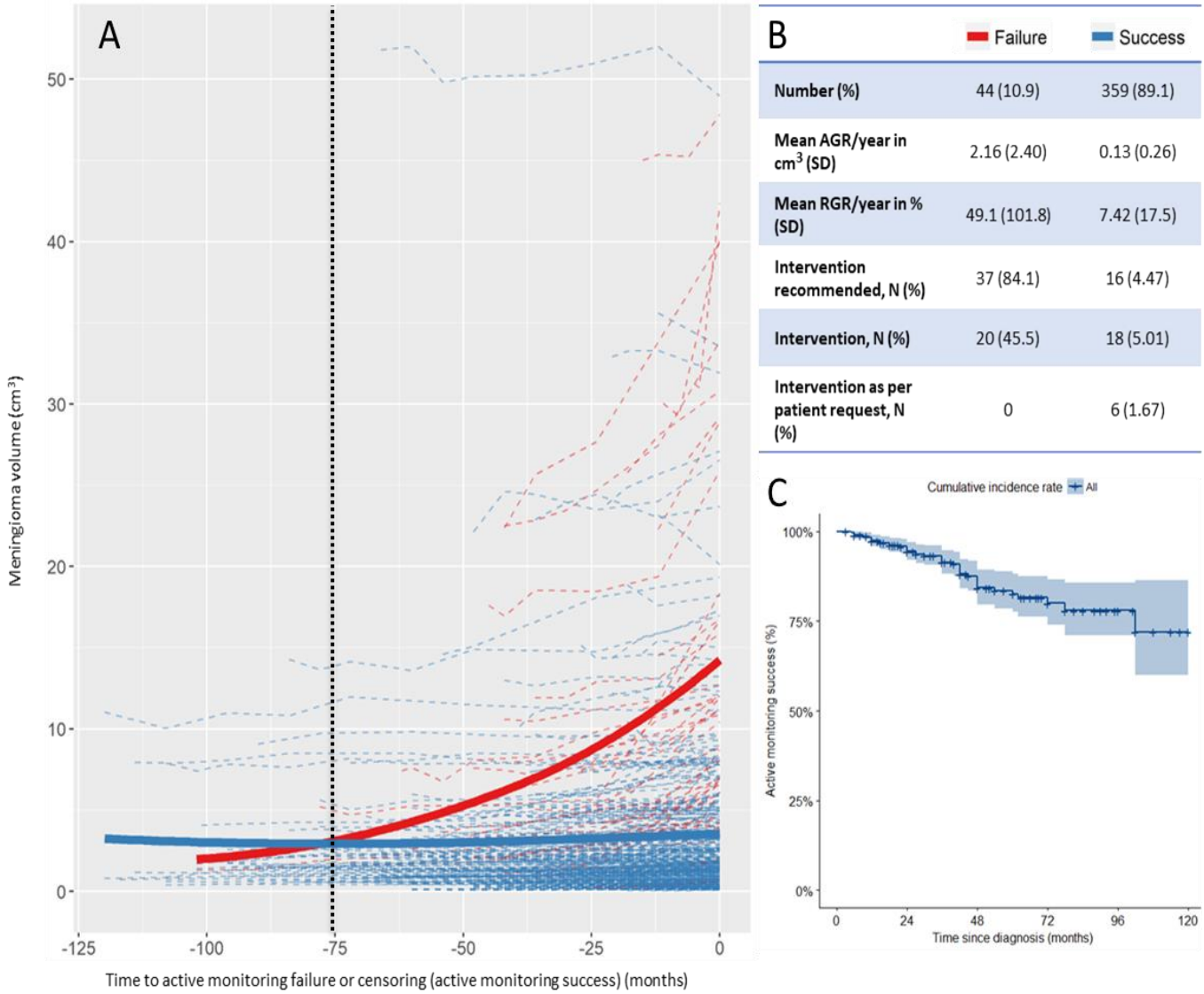


Fig. 3.7. (A) Profile plot for meningioma volume against reverse time stratified by disease progression (red) and non-progression (blue) (the origin of the time axis is the disease progression or censoring time; the bold curves are locally fitted estimated scatterplot smoothing (LOESS) curves. (B) Table showing the differences in AGR, RGR and clinical outcomes between the progression and non-progression groups. (C) Cumulative incidence of non-progression after 10 years of diagnosis. Solid blue line demonstrates the absolute cumulative rate while the shadowing around it is for the 95% CIs.

3.4.8. Clinical and radiological factors related to disease progression

Univariate Kaplan analysis (Fig. 3.8), revealed five factors to be significantly associated with disease progression: male sex (P=0.005), increasing tumour size (p<0.001), absence of calcification (p<0.001), peritumoural signal change (P<0.001) and T2/FLAIR Hyperintense meningioma (p<0.001).

The results of the backward stepwise regression, investigating the set of variables with a significance level of p≤0·10, are presented in Table 3.8 (model 1). Two important prognostic factors were identified: T2/FLAIR hyperintense meningioma, and meningioma volume (natural logarithm). Absence of calcification was not included in the model as hypointensity on T2/FLAIR acts a surrogate for calcification on CT (bivariate correlation, p<0.001). Forward stepwise regression was subsequently performed to examine the prognostic importance of the second set of variables (those with a significance level p>0·10), together with interaction terms of prognostic factors identified in the first model and variables excluded from the first analysis. No additional prognostic factors were identified. Two radiological parameters were however deemed clinically important and were therefore forced into the model: proximity to neurovascular structures and peritumoural signal change (model 2).

Table 3.8. Hazard ratios and 95% CIs of statistically and clinically important factors in multivariate analysis

	Model 1		Model 2	
Factor	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
Tumour volume (natural logarithm)	2.43 (1.82-3.24)	<0.001	2.17 (1.53-3.09)	<0.001
MR FLAIR/T2 hyperintense meningiomas	11.2 (5.72-21.9)	<0.001	10.6 (5.39-21.0)	<0.001
Peritumoural signal change	-	-	1.58 (0.65-3.85)	0.313
Proximity to critical neurovascular structures	-	-	1.38 (0.74-2.56)	0.314

The proportional hazards (PH) assumption of model 2 was checked using statistical tests and graphical diagnostics based on Schoenfeld residuals which are displayed in Fig. 3.9. The statistical tests were not significant for each of the covariates, and the global test was also statistically insignificant. All four plots showed a random pattern against time. Therefore, the proportional hazards assumption was not violated by model 2.

To test influential observations and outliers, DFBETA values were visualised (Fig. 3.10). The DFBETA is a parameter that measures how much impact each observation has on a particular predictor. DFBETA plots showed that none of the observations were terribly influential individually, although some of the DFBETA values for “proximity to neurovascular structures” and “peritumoural signal intensity” were small compared with the others and large for “meningioma volume” and “tumour signal intensity”.

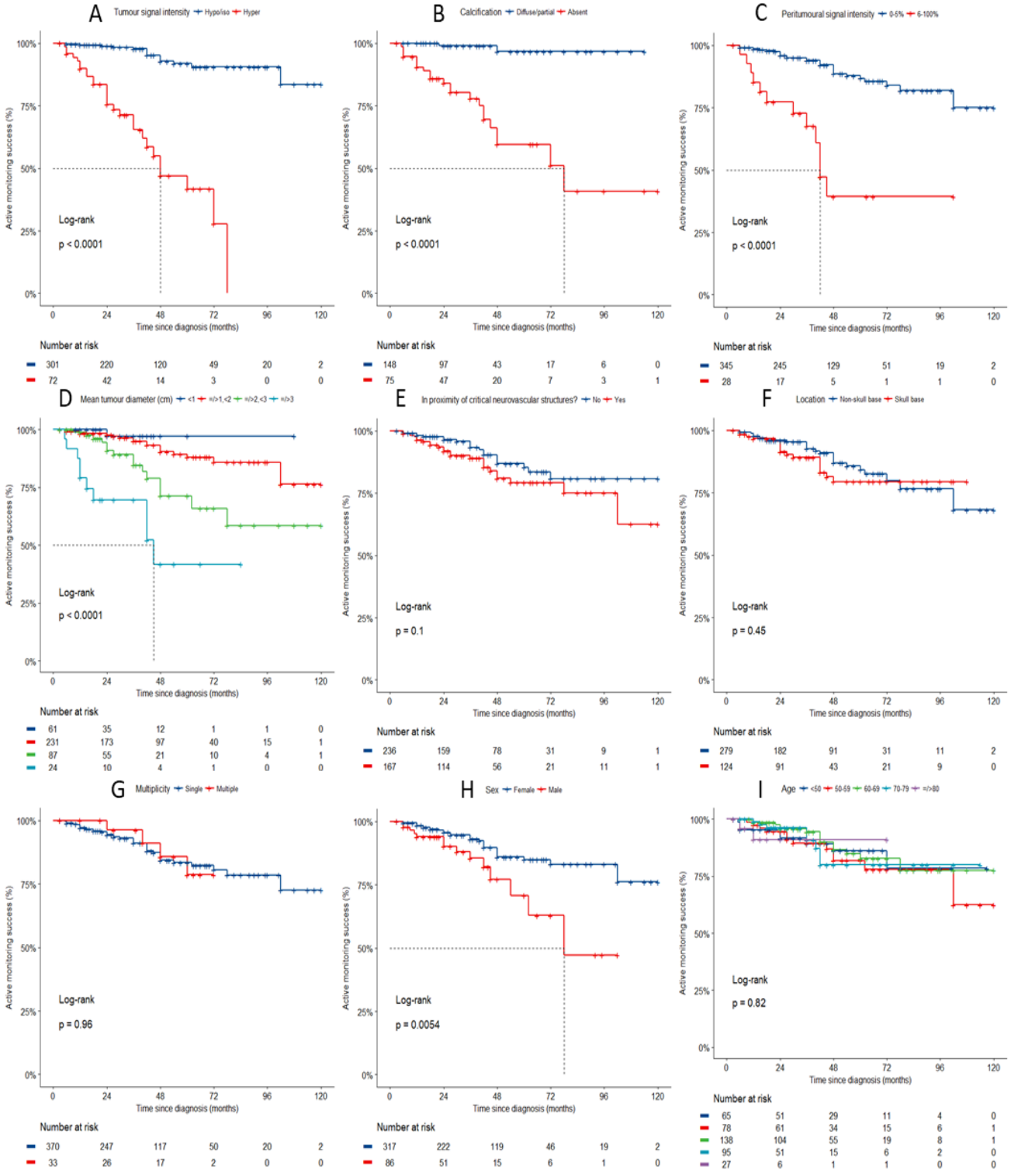


Fig. 3.8. Kaplan-Meier survival analyses of (A) Tumour signal intensity. (B) Calcification. (C) Peritumoural signal intensity. (D) Meningioma size. (E) Proximity to neurovascular structures. (F) Location. (G) Multiplicity. (H) Sex. (I) Age. A, B, C, D, E, F and H had a Log-rank p≤0.1

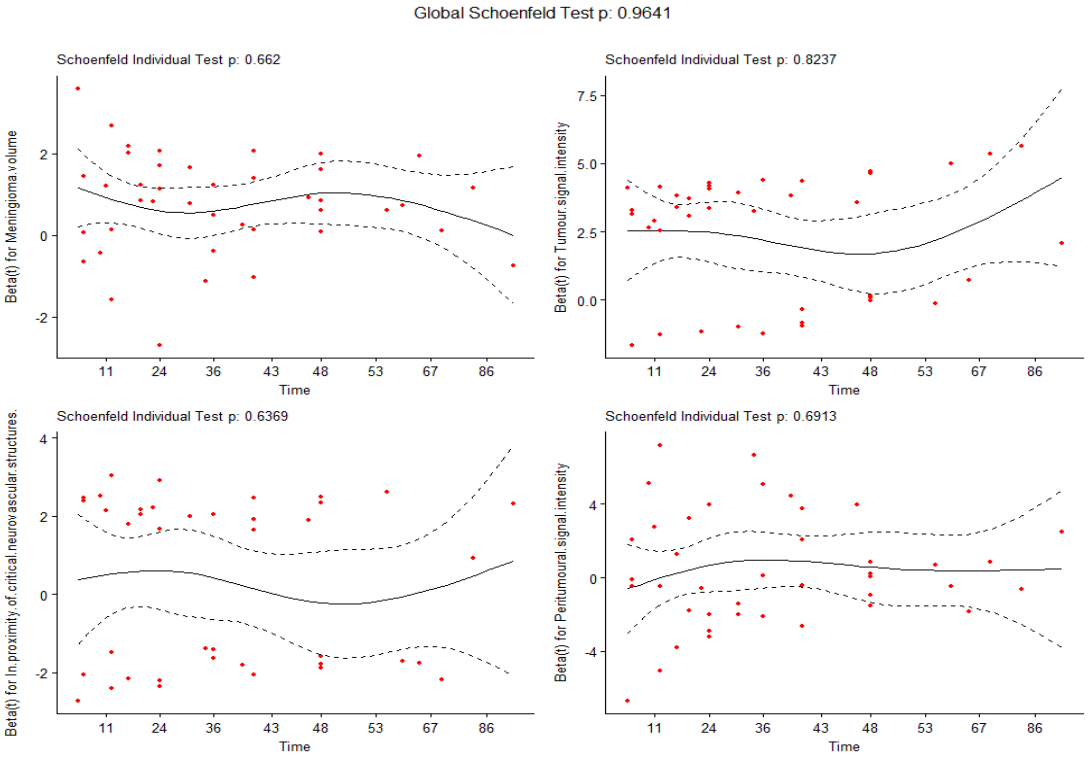


Fig. 3.9. Schoenfeld residual plot for each of the covariates. The solid line is a smoothing spline fit to the plot, with the dashed lines representing a ± 2-standard-error band around the fit. None of the plots demonstrated a regular pattern with time, and tests were all not statistically significant

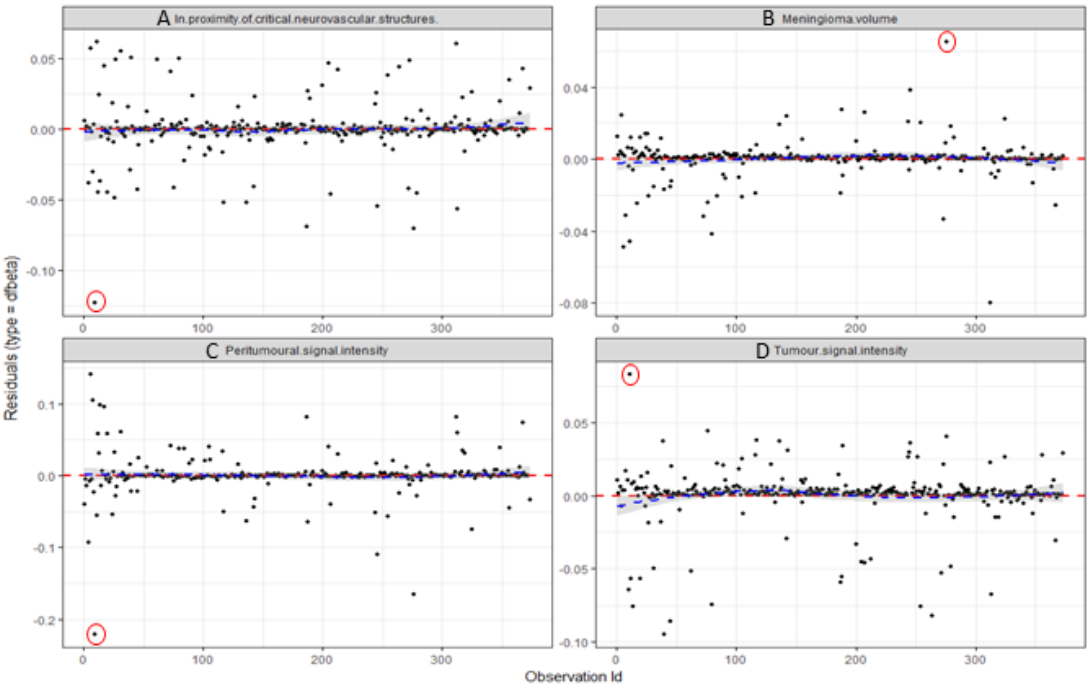
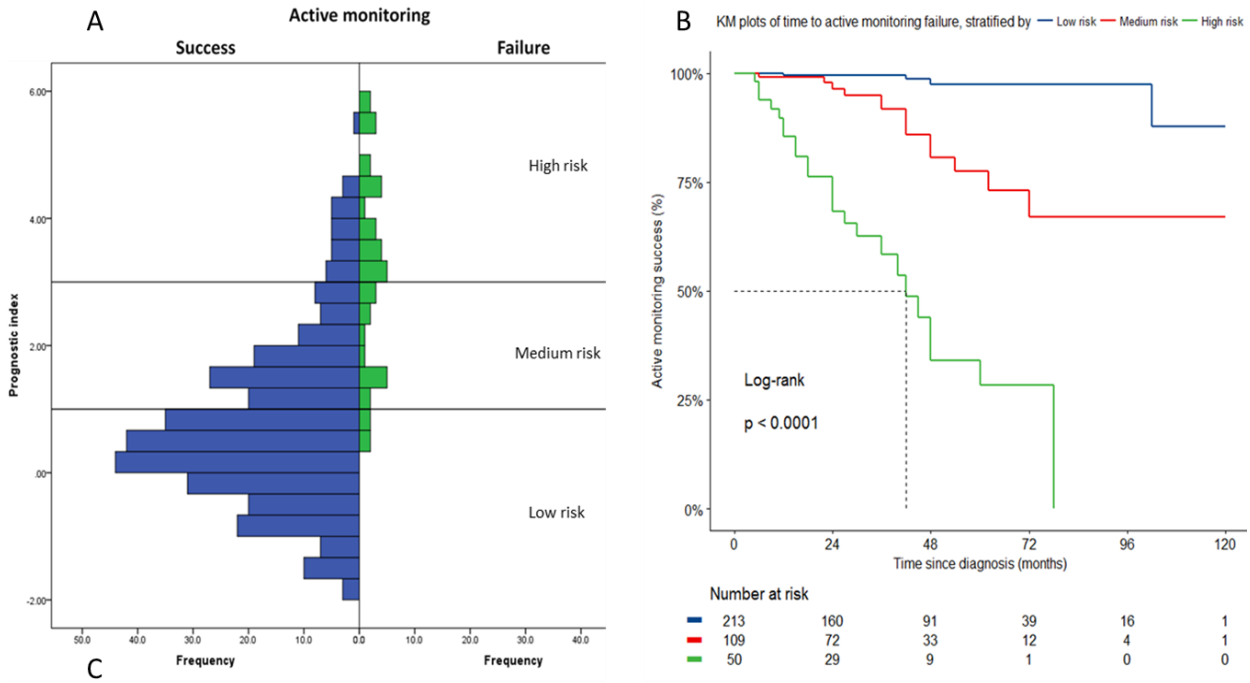


Fig. 3.10. DFBETA plots for each of the covariates. (A) Proximity to neurovascular structures. (B) Meningioma volume. (C) Peritumoural signal intensity. (D) Tumour signal intensity. Red circles denote potential influential observations.

3.4.9. A prognostic index to personalise active monitoring strategies

Based on the results of model 2, a prognostic index was created. For each patient, this could be calculated as the sum of the covariate values included in the final model, weighted by the normal logarithmic transformation of the hazard ratios. As an example, for an individual with a hyperintense meningioma that is 1 cm^3 in volume and which is distant from any critical neurovascular structures unaccompanied by peritumoural signal change, the prognostic index would be: (ln1×ln2.17) + (1×ln10.6) + (0×ln1.58) + (0×ln1·38) = (ln1×0·78) + (1×2.36) + (0×.0.46) + (0×0.32) = (0×0·78) + (1×2.36) = 2.36.

A numeric index based on this formula was then generated for each patient. Aggregates of patients' prognostic indices were subsequently plotted against the observed frequencies of progression and non-progression cases in a histogram (Fig. 3.11). Risk group stratification was performed by visual assessment and appropriate partitioning by cut-off points allowing for the creation of 3 distinct risk groups: low risk (<1), medium risk (<3) and high risk (≥3). Group 1 (low risk) comprises patients with a prognostic index of <1·00, group 2 (medium risk) includes those with a prognostic index of 1.00–2·99, and group 3 (high risk) are individuals with a prognostic index of ≥3·00. Fig. 3.11. shows the disease progression probabilities by 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 years following diagnosis for each risk group and the Kaplan-Meier plot of the three groups. Kaplan-Meier analysis demonstrated a significant difference between the three groups (Log-rank test, p<0.001).



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Risk group	6 mos.	1 yrs.	2 yrs.	3 yrs.	4 yrs.	5 yrs.	6 yrs.	7 yrs.	8 yrs.	9 yrs.	10 yrs.
Low risk (<1)	100%	99 %	99%	99%	97%	97%	97%	97%	89%	89%	89%
Medium risk (<3)	99%	98%	95%	85%	77%	72%	65%	65%	65%	65%	65%
High risk (≥3)	90%	76%	60%	43%	33%	25%	0%	-	-	-	-

Fig. 3.11. (A) Histogram of the disease progression and non-progression cases plotted against the prognostic index demonstrating the two cut-off lines. (B) Kaplan-Meier plot of non-progression stratified by risk group. (C) Table with the non-progressions probabilities at different time points following diagnosis stratified by risk

Discriminative accuracy of the model was assessed by three measures. Harrel's C statistic which was 0.89 (95% CI=0.85-0.93) indicating the prognostic index's excellent discriminative ability, since the confidence interval does not cross zero and the absolute value is very close to one. Time-dependent AUC values at 5 and 10 years were 0.87 and 0.84 (0.80≤AUC≤0.90 = excellent discrimination). Calibration plots demonstrated overall a good level of agreement between the observed and predicted values however some optimism was observed towards the lower probabilities at 2 and 5 years and pessimism was noted towards the larger probabilities at 10 years (Fig. 3.12).

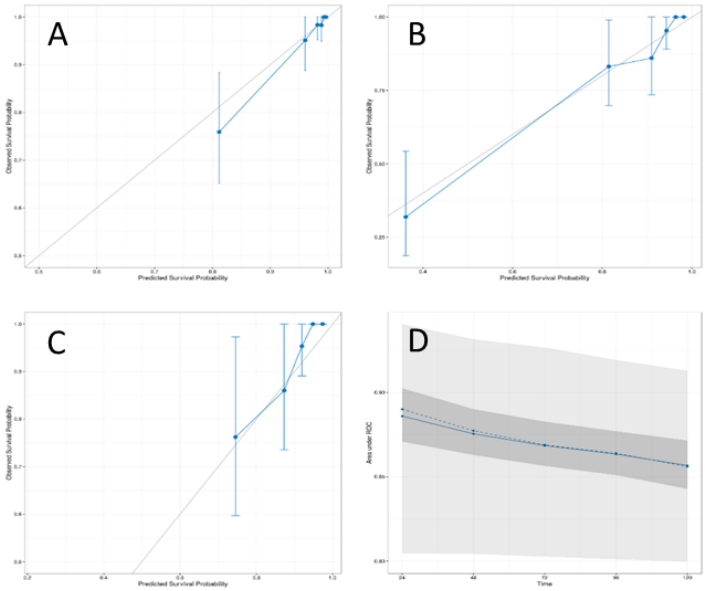


Fig. 3.12. (A-C) Calibration plots at 2, 5 and 10 years respectively. Predicted values are plotted on the x-axis and observed values are plotted on the y-axis. The blue bars represent the 95% CIs. (D) Time-dependent AUC. The solid line represents the mean of the AUC while the dashed line represents the median of the AUC. The darker interval in the plot shows the 25% and 75% quantiles, the lighter interval shows the minimum and maximum. Axes start at 0.80 and end at 1.00

3.4.10. Impact of age-adjusted Charlson comorbidity index and performance status

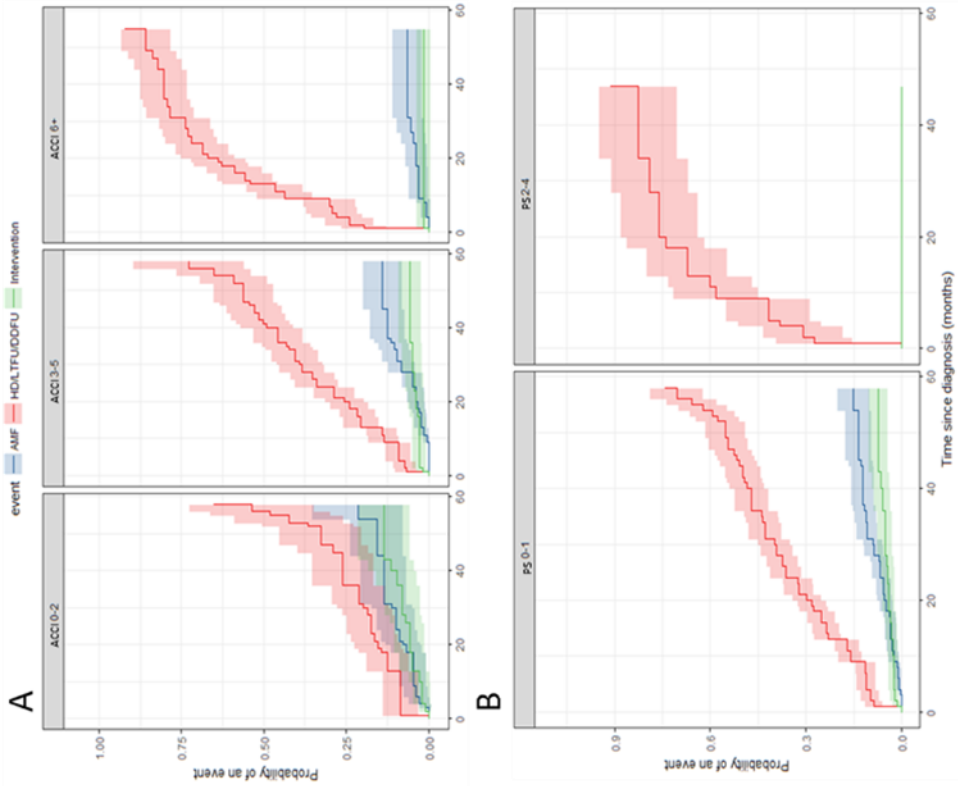
The estimated cumulative incidence rate plots of disease progression, and its competing risks, grouped by ACCI and PS, are shown In Fig. 3.13. On stratification by ACCI, the rates of intervention prior to progression and hospital discharge (HD)/loss to follow-up (LTFU)/death during follow-up (DDFU) were statsitcally different acorss the three groups (p=0.009 & p<0.001 respectively). The rates of disease progression were not statistically diffferent (p=0.09). Differences in incidence rates of disease progression and its competing risk among the PS groups were statistically significant (p<0.001). The CIR of each event at differnet time points are outlined in Fig. 3.13.

Approximatley 80% of patients with an ACCI ≥6 were discharged, deceased or lost to follow-up at 5 years following diagnosis, not having encountered disease progression or an intervention. Patients with an ACCI 0-2 were 3 time more likely to have experienced disease progression at 5 years compared to patients with an ACCI ≥6. No patient with a PS 2-4 had disease progression or inteverntion.

The CIR of intervention, with mortality being the sole competing event was also assessed. The plots, grouped by ACCI and PS, are shown In Fig. 3.14. On stratification by ACCI, the rates of intervention and mortality were statsitcally different acorss the three groups (p<0.001). Differences in incidence rates of intervention and mortality in the two PS groups were

statistically significant (p<0.001 & p=0.011 respectively). The CIR of each event at differnet time points are outlined in Fig. 3.14.

Patients with an ACCI ≥6 were 15-times more likely to die at 5 years of follow-up than to receive an intervention. The rates of intervention and mortaility did not differ in patients with an ACCI 3-5 and a PS 0-1. Patients with an ACCI 0-2 were at lowest risk of death 5 years from diagnosis.



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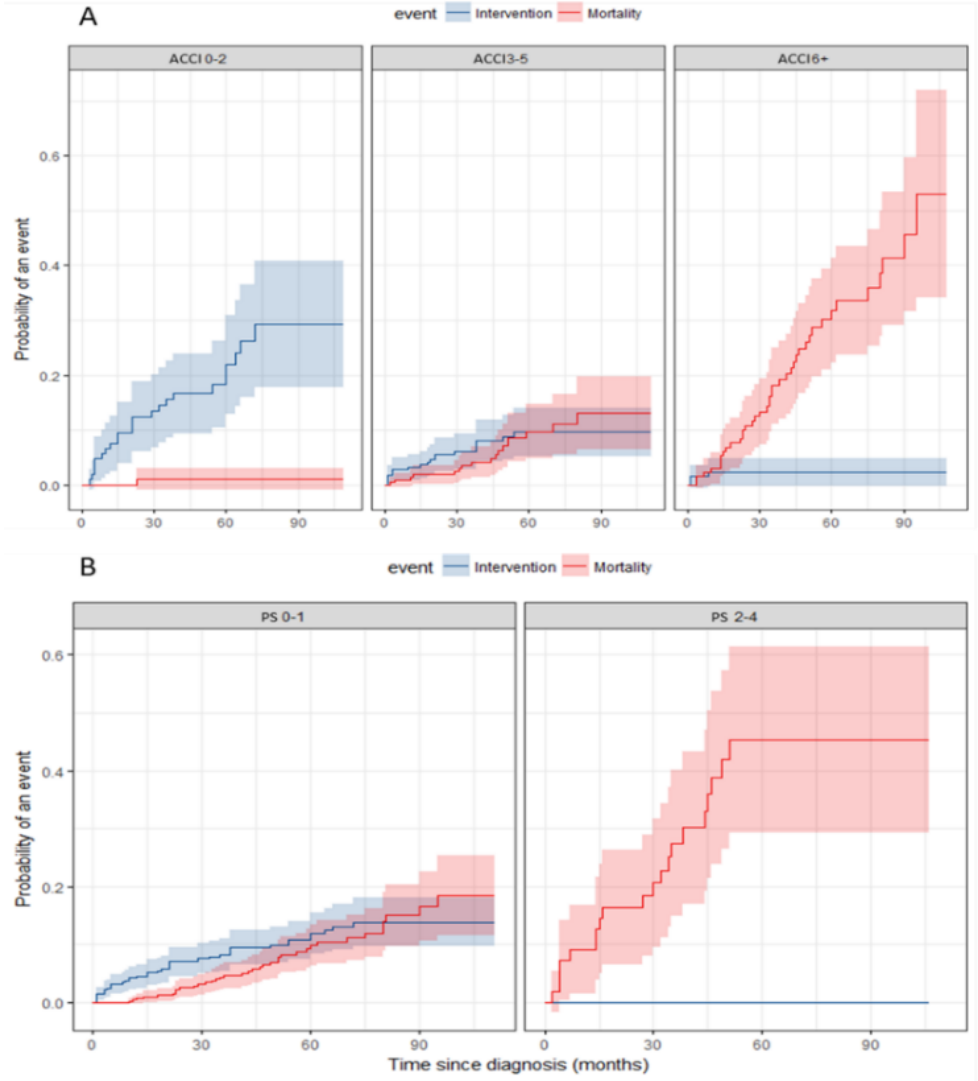
Event	Factor		At diagnosis	5 years
Disease progression	ACCI	0-2	0.00	15.7%
		3-5	0.00	12.4%
		>5	0.00	6.43%
	PS	0-1	0.00	12.8%
		2-4	0.00	0.00
HD/LTFU/DDFU	ACCI	0-2	8.49%	26.0%
		3-5	6.81%	52.8%
		>5	19.5%	82.0%
	PS	0-1	8.66%	51.0%
		2-4	27.3%	82.5%
Intervention	ACCI	0-2	0.00	13.5%
		3-5	1.81%	5.76%
		>5	1.50%	1.50%
	PS	0-1	1.48%	7.27%
		2-4	0.00	0.00

Fig. 3.13. (A-B) Estimated cumulative incidence curves (solid lines) for each event with 95% pointwise confidence intervals (shadowing) stratified by (A) ACCI and (B) PS. (C) Cumulative incidence functions for each event in percentages at diagnosis and after 5 years of diagnosis.



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Event	Factor		At diagnosis	5 years
Intervention	ACCI	0-2	0.00	26.2%
		3-5	1.81%	9.56%
		>5	1.50%	2.26%
	PS	0-1	1.49%	13.9%
		2-4	0.00	0.00
Mortality	ACCI	0-2	0.00	1.02%
		3-5	0.00	9.74%
		>5	0.00	33.6%
	PS	0-1	0.00	10.4%
		2-4	0.00	45.3%

Fig. 3.14. (A-B) Estimated cumulative incidence curves (solid lines) for intervention and mortality with 95% pointwise confidence intervals (shadowing) stratified by (A) ACCI and (B) PS. (C) Cumulative incidence functions for each event in percentages at diagnosis and after 5 years of diagnosis.

3.4.11. Intervention outcomes

By the end of the study period, 40 patients had surgery (6 at diagnosis and 34 after follow-up) and 4 patients had primary radiation treatment (2 SRS and 2 FSRT).

3.4.11.1. Surgical outcomes

Gross total resection (Simspon I-III) was achieved in 92.5% (37/40) of patients. The three subtotal resections (Simpson IV) (7.50%) were for SSS-invading meningiomas, with 2 residuals deemed to require adjuvant radiation treatment. Neurosurgical complications requiring medical therapy or invasive treatment (grades: Ib- IIIb) ocurred in 15.0% (6/40) of patients; 2 persisted beyond 30 days postoperatively. These two serious longstanding complications arose in patients harbouring SSS-invading meningiomas subject to GTR. Five (12.5%) patients experiened grade Ia complications which did not necessitate further medical or surgical intervention. Nine (22.5%) patients experienced postoperative medical complications, 4 of which (grade Ib) required medical treatment. The mean age of patients with postoperative complications was 55.8 years (SD=10.3). The mean age of patients free of complications was 54.1 years (SD=10.5). Median ACCI in the two groups was 2.

Postoperatively all patients were PS 0-1 apart from 3 (7.50%): two patients harbosuring SSS-invading meningiomas which were subject to GTR (PS 3 & 4) and a patient (PS 3) with a posterior fossa meningioma in contact with the tranvserse sinus, which also was subjected to GTR.

Surgery revealed WHO grade I meningiomas in 36 patients (90.0%). The remaining 4 were atypical WHO Grade II (10.0%). WHO grade I meningiomas were of the following histological subtypes: meningiothelial (n=11), psammomatous (n=8), fibrous (n=8), transitional (n=6), angiomatous (n=1), microcytic (n=1) and lymphoplasmacyte-rich (n=1).

During a median follow-up period of 35.5 months (IQR=21.8), only 1 (2.50%) meningioma recurred. An atypical meningioma had an early recurrence 5 months following GTR (Simpson III) which required salvage radiotherapy. The patient was followed-up for 37 months following radiation with no evidence of further recurrence before dying due to hospital-acquired pneumonia unrelated to their meningioma.

3.4.11.2. Radiotherapy outcomes

Radiotherapy treatment details and outcomes are summarised in Table 3.9.

Four patients received primary treatment after a duration of active monitoring, 2 received adjuvant treatment and 1 patient required salvage radiotherapy for recurrence 5 months after surgery. Four patients received FSRT and three had SRS.

All 7 patients exhibited regression or stable disease during a median follow-up period of 31.0 months (IQR=25.0).

Maximum early toxicities were of grade II in 2 (28.6%) patients. Two late grade II toxicities were also observed.

Table 3.9. Radiation treatment details and outcomes

Patient number	Age at treatment, sex	Meningioma location	Meningioma volume (cm^3)	Mode	Modality	Duration of treatment (weeks)	Total Dose	Number of fractions	Fractionated dose	Follow-up (months)	Treatment Response	Early CTCAE toxicity-(0-4)	Late CTCAE toxicity-(0-4)
1	56, F	Anterior convexity	0.50	Primary	SRS	N/A	12.5	1	N/A	70	Regression	Fatigue-1	Neuralgia-1
												Headache-1	
2	49, M	Midline posterior fossa - petro-clival	0.26	Primary	SRS	N/A	12.5	1	N/A	12	Stable	Vomiting-1	Paresthesia-1
3	45, M	Anterior midline - tuberculum sellae	3.20	Primary	FSRT	6	54	30	1.8	33	Stable	Nausea-1	Headache-2
4	67, F	Medial sphenoid wing	0.56	Primary	FSRT	6	54	30	1.8	8	Regression	Nausea-1	TN disorder-2
												Fatigue-2	
5	56, F	Posterior parasagittal	NM	Adjuvant	SRS	N/A	12.5	1	N/A	31	Stable	Fatigue-1	NR
												Paresthesia-1	
6	52, F	Posterior parafalcine	NM	Adjuvant	FSRT	6	54	30	1.8	24	Stable	Nausea-1	NR
												Fatigue-1	
												Alopecia-2	
7	68, M	Anterior convexity	NM	Salvage	FSRT	6	54	30	1.8	37	Stable	Fatigue-1	Phantom pain-1

Abbreviations: N/A=not applicable; NM=not measured; NR=none reported

3.4.12. Data validity

Assessment of inter and intraobserver variability across all tested radiological factors exhibited a great level of agreement. Volume measurements between the primary and secondary raters were consistent (Interobserver, ICC=0.985 (95% CI=0.966-0.999)) and so were the repeated measurements recorded by the primary observer (Intraobserver, ICC=0.997 (95% CI=0.993-0.999)). Bland-Altman plots were also generated to visualise these consistencies (Fig. 3.15).

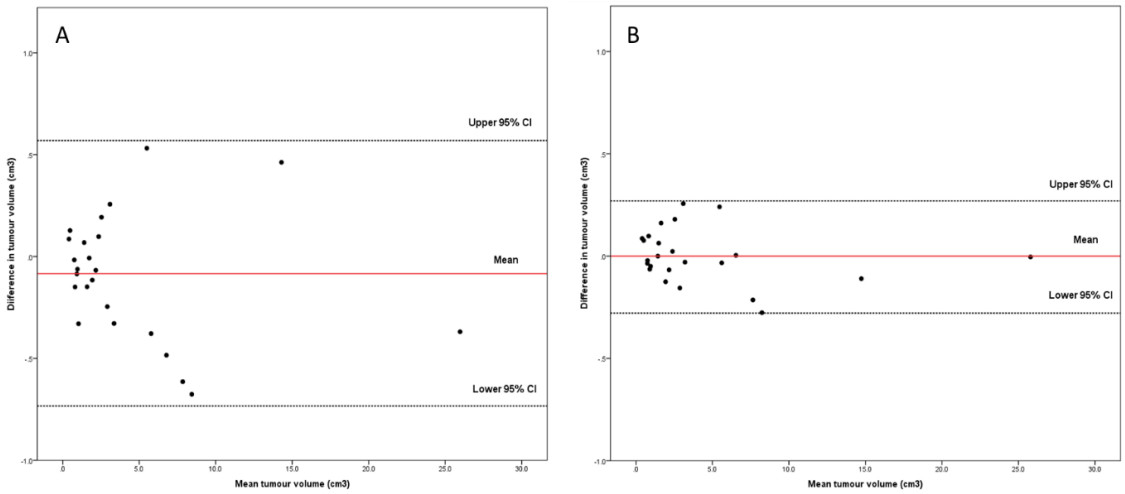

Fig. 3.15. (A) Bland-Altman plot of mean and difference of meningioma volume for the secondary observer with the 95% confidence intervals and the mean shown. All points are within the 95% CI indicating a good level of agreement. (B) Bland-Altman plot for repeat measurements taken by the original observer, indicating again that there is good agreement.

Weighted kappa for agreements between the two raters regarding peritumoural signal intensity and venous sinus invasion were between 0.61 and 0.80 indicating a "good" level of agreement. Weighted kappa values for the remaining parameters were >0.80 indicating a "very good" agreement level.

Table 3.10. Weighted Kappa values assessing the inter- and intraobserver variability among categorical variables

	Weighted Kappa (95% CI)	
Parameter	Inter-observer variability	Intra-observer variability
Calcification	0.82 (0.65-0.99)	0.85 (0.69-1.01)
Tumour signal intensity	0.80 (0.62-0.98)	0.83 (0.66-1.01)
Peritumoural signal intensity	0.79 (0.55-1.02)	1.00 (1.00-1.00)
Venous sinus invasion	0.75 (0.53-0.97)	0.86 (0.67-1.05)

3.5. Discussion

In this study of incidentally-found asymptomatic meningiomas, the prognostic significance of several clinical and radiological factors has been tested. Our results indicate that T2/FLAIR hyperintensity, increasing meningioma volume, proximity to neurovascular structures and peritumoural signal change increase the risk of disease progression within the first 10 years following diagnosis. Based on these factors, patients could be stratified into 3 risk groups with differing management strategies assigned to each. Patients with an ACCI ≥6 and PS 2-4, regardless of risk group allocation, are unlikely to require an intervention for their incidental meningiomas during their estimated life-times and thus do not require continued radiological surveillance. These clinical and radiological factors have been grouped to create the internally-validated prognostic model IMPACT (**I**ncidental **M**eningioma: **P**rognostic **A**nalysis Using Patient **C**omorbidity and MR-**T**ests).

3.5.1. Radiological factors on standard MR and CT sequences

Prognostic radiological factors identified in this study as the most important in relation to disease progression is lent support by previous published work. Hyperintensity has long been recognised as the factor most strongly correlated with progression (180, 185, 202). Peritumoural signal change, indicative of vasogenic oedema, and increasing tumour volume have also been found to be associated with meningioma growth during follow-up (186, 217). Despite the importance of identification of prognostic factors, a vital aspect that's been heavily neglected in previous literature is the timing of such progression during monitoring, which plays a major role in defining the necessary length of radiological and clinical surveillance for incidental meningiomas. Our results indicate that most patients with meningiomas at risk of disease progression will experience progression-related events within the 1st 5 years following diagnosis.

Although statistically insignificant in multivariate analysis, proximity to critical neurovascular structures was the last factor added to IMPACT. The reason being is that we aimed to create a pragmatic model which recognises that meningiomas in eloquent/skull base locations (i.e. medial sphenoid wing compressing the optic chiasm), are at a higher risk of causing significant morbidity compared to convexity meningiomas, which of note constitute the majority of those discovered incidentally. The three MR factors: tumour signal intensity, size and oedema are not always the primary factors in consideration for decision making; tumour location is also a detrimental factor driving recommendations for early intervention (151). Although we do not concur with this concept, particularly for small hypo/isointense meningiomas with no evidence of peritumoural signal change, as surgery or SRS still carries significant risk, we do understand the need to keep a closer eye on these meningiomas and so we have accounted for that in the model.

Calcification status on non-contrast CT was highly correlated with tumour signal intensity on T2/FLAIR. Due to this, it was not included in the model, although having proven to be significantly associated with non-progression during active monitoring. This is supported by the findings of previous papers which note an association between calcification and non-progression (177, 182). Thus, additional characterisation of growth potential using CT Is not warranted for meningiomas identified on MR sequences, given they include T2, FLAIR or

susceptibility weighted sequencing (SWI) which has been shown to reliably delineate meningioma related calcification (218).

3.5.2. Age, comorbidity and performance status

Those three clinical factors are as important as MR characterisation in regard to decision making. An intervention succeeding a duration of follow-up in patients with an ACCI ≥6 was not carried out, although a minority of patients did in fact experience disease progression. Reasons being: i) the high rate of mortality prior to progressing; patients were 15-times more likely to die than to receive an intervention at 5 years following diagnosis and this ratio went up to 24:1 at 10 years. ii) The threshold for intervention being much higher. Older patients with comorbidities should not be subject to surgery or radiation solely due to radiological changes as the risk of morbidity and mortality outweighs treatment (211, 212). For these reasons we recommend that patient with an ACCI ≥6 are either discharged from outpatient care with reassurance that their meningiomas are unlikely to cause them problems during their estimated life-times or that clinical monitoring is initiated. A PS 2-4 draws similar recommendations. For those patients, the mortality rates at 5- and 10-years following diagnosis were much higher and operative or radiation interventions ensue significant morbidity and mortality (219, 220).

3.5.3. Managements strategies based on IMPACT

Our proposed management strategy for incidental meningiomas is demonstrated in Fig. 3.16. Based on the prognostic radiological and clinical factors, incidental meningioma patients could be split into 5 groups. Low and medium risk patients with an ACCI ≥6 or PS 2-4 can be discharged from outpatient care with no subsequent clinical or radiological monitoring. These patients can be counselled about the symptoms that might arise as a result of their meningiomas and which might warrant further clinical and radiological examination. Patients that fall under the remaining 4 categories are to be followed-up. High-risk patients with an ACCI ≥6 or PS 2-4 should be followed clinically with MR or CT scanning offered on clinical progression. Low, medium and high-risk patients with an ACCI <6 and a PS 0-1 are to be followed clinically and radiologically but at different time points corresponding with the rates of disease progression shown in Fig. 3.11. At each appointment, growth rates in concordance with disease progression (AGR ≥2 cm^3/year OR AGR ≥1 cm^3/year + RGR ≥30%/year), peritumoural signal intensity, the relationship with neighbouring neurovascular structures, and the potential to miss out on the opportunity of SRS, should be examined. Based on any observed changes, a recommendation for treatment or a decision to continue follow-up can be made. Worked examples in support of these recommendation can be found in Fig. 3.17.

3.5.4. What to do beyond 10 years?

Prognosis beyond 10 years of follow-up for incidental meningioma remains unclear. One study reported late growth beyond 10 years, however, growth was defined in a time-independent manner of >2 mm progression in any unidimensional diameter (9). The results of the joint model used to define disease progression in this study indicate that the rate of tumour growth is of greater clinical significance and so those results based on extent of growth definitions are unreliable. Assessment of ACCI and PS at this point in time post diagnosis is important. Older patients with comorbidities who remain radiologically and clinically stable can be discharged from outpatient care. Patients with a longer life expectancy

on the other hand pose a dilemma. Based on the observation that radiological changes indicating an intervention are likely to occur early on during follow-up, long-term radiological monitoring might not be necessary and instead infrequent clinical monitoring could be adopted (i.e. 5-yearly).

3.5.5. Use of IMPACT in clinical practice

Although externally invalidated, IMPACT could still be utilised in clinical practice. The number of patients included in this study, despite being based on availability rather than a power calculation, is large and inclusive of a variety of meningioma volumes and locations. Moreover, the demographics of patients included represent the general meningioma population making the model more reliable to predict outcomes. The patient cohort was derived from a large tertiary centre serving a catchment area of 3.5 million people. The parameters associated with internal validation demonstrated adequate accuracy. These elements give us confidence in the clinical utility of the model. Fig 3.18. shows how this model could be used in clinical practice in the form of an online risk calculator. ACCI calculators in different formats are readily available online.

3.5.6. When should IMPACT not be used?

Radiation-induced and NF2 associated meningiomas were excluded from this study and therefore this model could not be applied to those asymptomatic.

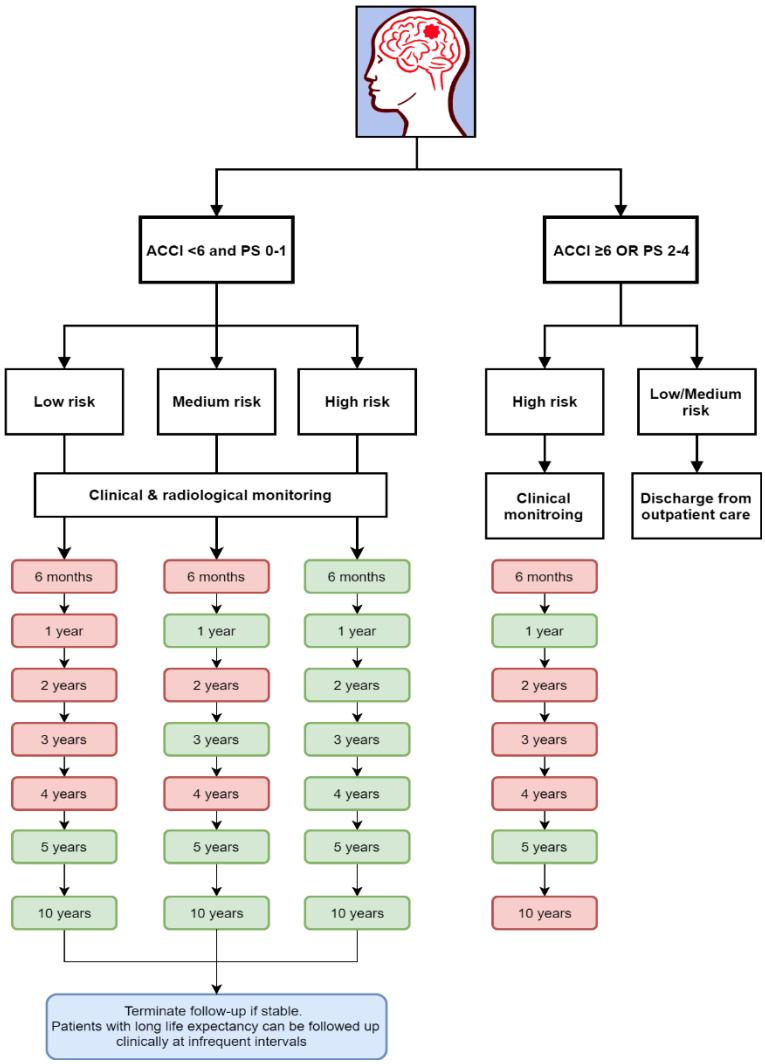

Fig. 3.16. Proposed clinical guidelines for the management of incidentally-found asymptomatic meningiomas. Time intervals in green-shading are our proposed time-points of follow-up.

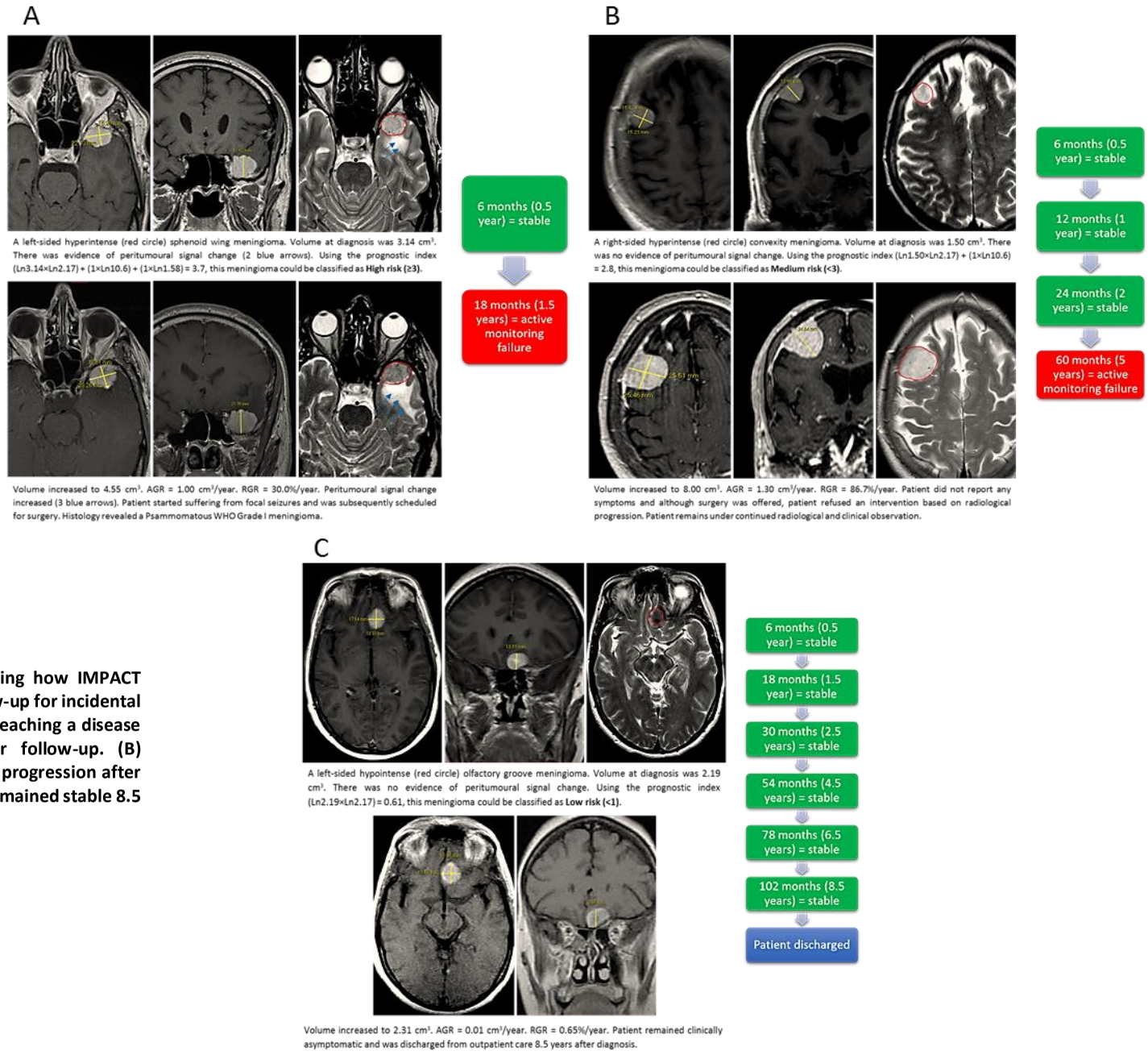

Fig. 3.17. Worked examples demonstrating how IMPACT could be used to guide the timing of follow-up for incidental meningiomas. (A) High-risk meningioma reaching a disease progression endpoint 18 months after follow-up. (B) Medium-risk meningioma demonstrating progression after 5 years. (C) Low-risk meningioma which remained stable 8.5 years after diagnosis

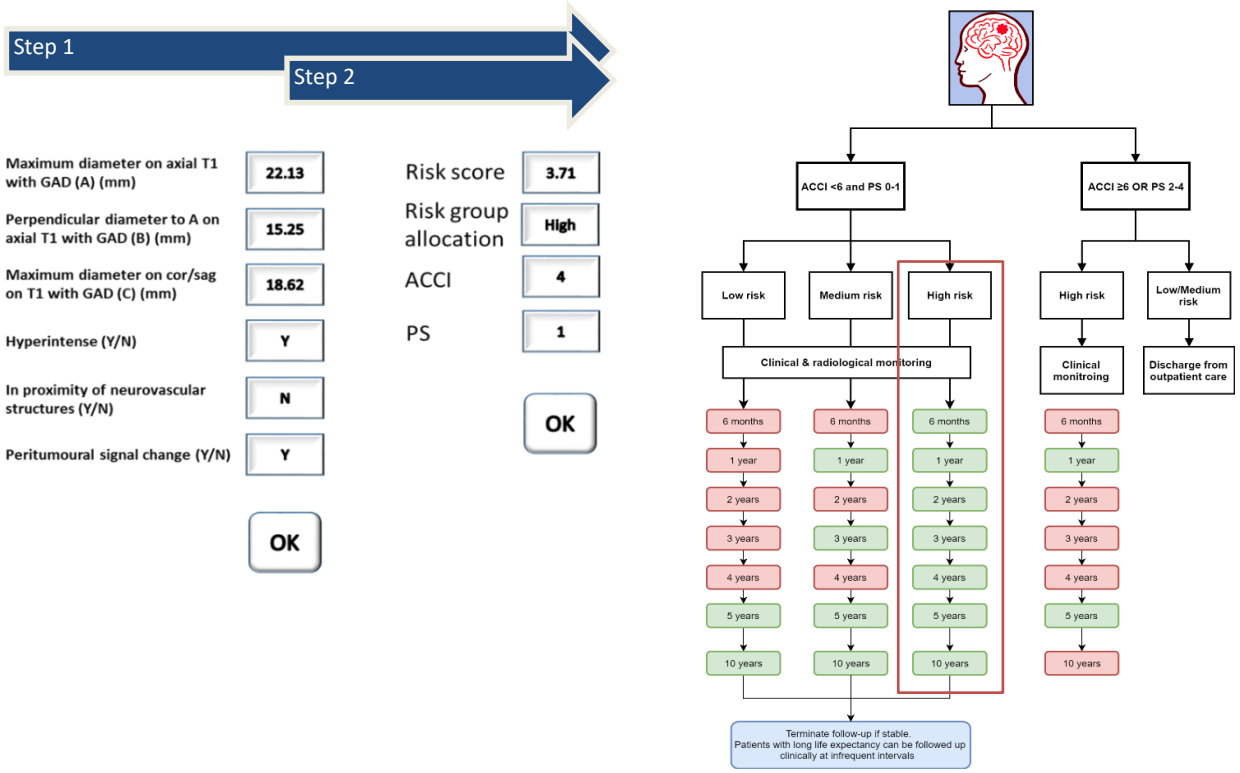

Fig. 3.18. A demonstration of how an online risk calculator based on IMPACT will look like

3.5.7. Which intervention to offer on encountering disease progression

Most patients in this study who progressed went on to undergo surgical resection whilst a minority were subject to radiotherapy. Incidental meningiomas are mostly below 10 cm^3 when need to be treated, and so can be managed using either modality, considering the adequate control rates following both. Ultimately, the decision will be based on the availability of treatment facilities, physician experience, meningioma location and most importantly patient preference. Regardless, patients should be counselled about the rates of post-intervention morbidity accordingly. It seems clear though that for those meningiomas invading a sinus, radical resection should be avoided and instead a combination of STR and adjuvant radiotherapy or active monitoring can be used. The burden of morbidity if subject to GTR or additional treatment if STR underlines the importance of including venous sinus invasion as a radiological criterion of disease progression.

3.5.8. Histopathological findings

The majority of operated meningiomas demonstrated WHO grade I histology. This confirms the safety of active monitoring as an overall strategy for the managament of incidental meningiomas. It also highlights that an early 3-month scan to rule out metastatic disease is unneccesary. A recent study on the utility of DNA methylation for classification of meningiomas demonstrated that certain meningiomas, although benign grade I according to the WHO classficiation, exhibit DNA methylation patterns similar to WHO grade II and III meningiomas (221, 222). It would be interesting to test this in our operated cohort which demonstrated disease progression prior to surgery.

3.5.9. Study limitations and strengths

This study is based on a single-centre retrospective cohort with varying follow-up times. Nevertheless, as aforementioned, the methodology in this study, the number of patients included, and the predictive accuracy parameters give us confidence in the model's performance. Quality of life assessment could not be performed based on clinical notes available. However, the fact that the majority of patients were happy to remain under follow-up indicates that most patients with an incidental meningioma lead normal lives, which is supported by the available QoL studies (193, 195). An area that persists to be unexplored is the effect of surgery or radiotherapy on QoL and NCF in incidental meningioma patients. Although not included in the model, patient anxiety is an important factor that merits consideration (223). Evidently, a minority of patients requested surgery and did so after a very short duration of follow-up. These patients' anxiety might or might not be reduced by the less frequent monitoring and this needs to be further researched.

3.6. Conclusions

IMPACT offers a personalised active monitoring approach with the potential to reduce the cost burden of incidental meningiomas. Radiological factors included in the model are meningioma volume, tumour signal intensity, peritumoural signal change and proximity to critical neurovascular structures. Based on these factors patients could be split into low, medium and high-risk groups with rates of disease progression at 5-years being 3%, 28% and 75% respectively. Further stratification could be performed using patient's age, comorbidity and performance status. External validation of the model should follow but within a multi-centre prospective study where duration of follow-up is uniform and long. Early intervention vs. active monitoring for high-risk meningiomas should be the subject of cost-utility analysis to better determine the optimal management strategy within health systems such as the NHS.

Chapter 4: Final remarks and future research

Incidental discovery of meningioma accounts for about 30% of meningiomas diagnosed and 10% of incidental findings in research and clinical settings. Their management poses a great clinical and economic problem. EANO and NCCN suggest active monitoring for their management. However, details surrounding the duration of monitoring and the time interval between scans lack. The results of the systematic review suggest that clinical or radiological progression occurs primarily within the first 5 years following diagnosis indicating that rigorous follow-up beyond this timepoint might be unnecessary. Risk factors for clinical failure were increasing tumour size and peritumoural signal change. Intervention rates were also higher among hyperintense meningiomas suggesting their propensity to demonstrate growth during follow-up. The results of the IMPACT study come in support of our findings in the systematic review. The risk of disease progression was at its highest during the first 5 years of follow-up and risk factors included in the generated prognostic model were increasing tumour volume, peritumoural signal change and lesion hyperintensity. Stratification of patients was performed based on the model and clinical guidelines for active monitoring were accordingly designed informing the duration of follow-up and time in between scans/appointments. Personalised surveillance has the potential to reduce the cost burden of incidental meningiomas and patient anxiety.

Several aspects to incidental meningiomas warrant further research. All studies performed up to this point are retrospective in nature and of short follow-up duration. High-quality prospective multi-centre studies are needed. These can take one of two forms: i) a one armed study which follows incidental meningioma patients for up to 10-15 years, performing clinical and radiological assessments annually. ii) a two-armed study where patients either get followed-up according to their risk of progression as worked out per our model, systematic review and by consensus or have annual follow-up. The aim of the first study design would be to confirm the prognostic factors identified and risk group stratification and to inform practice accordingly. The 2nd study type would achieve similar outcomes whilst also demonstrating the safety of individualised monitoring and its potential to reduce the costs to health care. A similar approach has been adopted in investigating the utility of individualised screening for diabetic retinopathy with promising preliminary results (224). Needless to say that a trial utilising either design would benefit from a cost-utility analysis, quality of life assessment and serum testing which could be subject to spectroscopy-based identification of molecular biomarker profiles specific to growing and non-growing meningiomas.

For patients at high risk of disease progression, its not clear whether active monitoring supersedes early intervention. A cost-effectiveness study, which we plan to do, will help aid decision making for this group of patients.

The results of the systematic review and the retrospective study suggest that the overall majority of operated incidental meningiomas are WHO grade I. The WHO classification is admittedly not without its problems. It has been heavily critcised for its subjectivity and inadequate delineation of recurrence-prone meningiomas (225). Recent studies demonstrated that a fraction of those meningiomas graded as benign do actually in fact exhibit methylation profiles similar to the more aggressive WHO grade II and III meningiomas

and so it's worth testing whether those that do fail active monitoring by demonstrating rapid growth fit those methylation patterns (221, 222).

In conclusion, this thesis has achieved it primary aims of generating a prognostic index informing guidelines for the management of incidental meningiomas. It also underlines several aspects to incidental meningiomas which warrant further research.

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Appendices

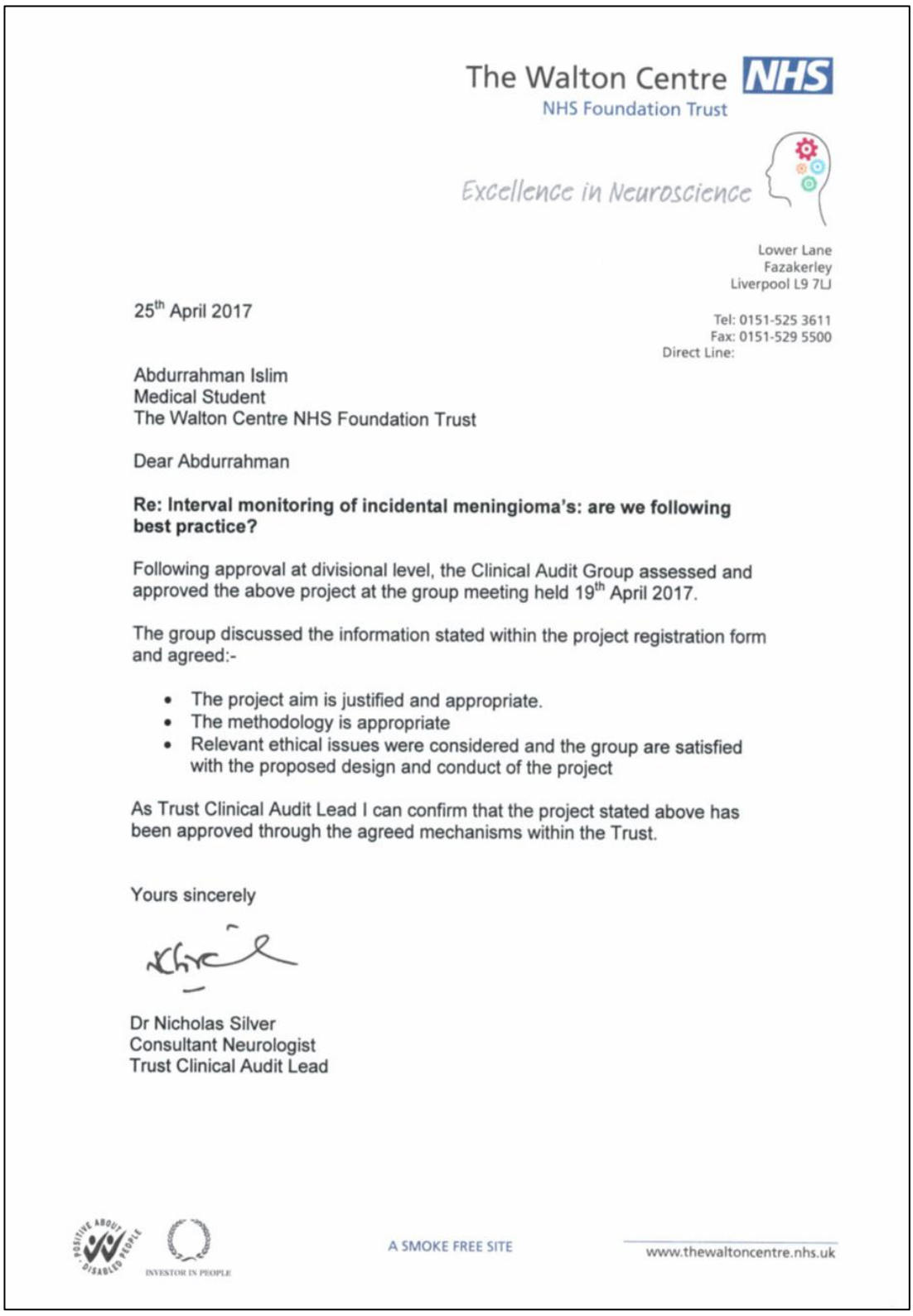
Appendix 1. Pre-piloted proforma used to extract data in the systematic review

Authors:		**Publication date:**
Title:		**Journal:**
Study design:		**Population size:**
Characteristics		
Population demographics	Age	
	Sex	
Clinical demographics at diagnosis	Co-morbidities	
	Functional status (WHO performance score or Karnofsky)	
Radiological data at diagnosis	Location	
	Diameter/volume	
	T2 hyperintensity	
	Calcification Peritumoural oedema	
Scenarios that led to the identification of meningioma		
Intervention		☐ Surgery ☐ SRS ☐ Fractionated radiotherapy ☐ Interval monitoring ☐ Hospital discharge
Outcomes	Neurocognitive function	
	Quality of life	
	Extent of resection (specific to surgery) Post-intervention complications (specific to surgery, SRS and radiotherapy) and if available postoperative PS	
	If operated >> tumour grade	
	Time to tumour recurrence/growth (PFS)	
	Time to intervention (specific to interval monitoring) Meningioma-related readmissions (specific to hospital discharge)	

Appendix 2. List of questions included in the NIH quality assessment of observational studies

Criteria
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Appendix 3. Confirmation letter of approval of the study by The Walton Centre NHS Foundation Trust's clinical audit group.



The Walton Centre NHS
NHS Foundation Trust

Excellence in Neuroscience

Lower Lane
Fazakerley
Liverpool L9 7LJ

Tel: 0151-525 3611
Fax: 0151-529 5500
Direct Line:

25th April 2017

Abdurrahman Islim
Medical Student
The Walton Centre NHS Foundation Trust

Dear Abdurrahman

Re: Interval monitoring of incidental meningioma's: are we following best practice?

Following approval at divisional level, the Clinical Audit Group assessed and approved the above project at the group meeting held 19th April 2017.

The group discussed the information stated within the project registration form and agreed:-

- The project aim is justified and appropriate.
- The methodology is appropriate
- Relevant ethical issues were considered and the group are satisfied with the proposed design and conduct of the project

As Trust Clinical Audit Lead I can confirm that the project stated above has been approved through the agreed mechanisms within the Trust.

Yours sincerely

Dr Nicholas Silver
Consultant Neurologist
Trust Clinical Audit Lead

Appendix 4. ICOM classification of meningioma location

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