Patient-Reported Outcomes and Quality of Life in Intracranial Meningioma: a systematic literature review and cross-sectional study

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

By

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Declaration

This thesis represents original work completed by Sumirat M. Keshwara and the material contained has not been presented either wholly, or in part, for any other degree or qualification.

The research completed for this thesis was conducted at the Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, United Kingdom and The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom.

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Table of Contents

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Abstract

Introduction: Meningiomas are the commonest primary intracranial tumour (1). Meningiomas may be symptomatic and present with a range of clinical features. Alternatively, meningiomas may be asymptomatic and diagnosed incidentally. Symptomatic meningiomas are treated with surgery or radiotherapy. Incidental meningiomas are actively monitored for evidence of progression. The diagnosis and treatment of meningioma can affect a patient's quality of life. There has been little research to evaluate the subjective experiences of meningioma patients following diagnosis and treatment. The aim of this thesis was to investigate the patient-reported and health-related quality of life (HRQoL) outcomes in intracranial meningiomas.

Methods: A systematic review was completed to identify all studies evaluating Patient-Reported Outcomes (PROs) of meningioma. The following databases were searched: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, PsycINFO and AMED. Furthermore, long-term HRQoL outcomes were assessed by the QUALMS study. Patients diagnosed with a meningioma who had been surgically treated or were actively monitored by The Walton Centre hospital were invited to participate. The SF-36, EORTC QLQ-C30, EORTC QLQ-BN20 and study-specific questionnaires were self-administered to participants.

Results: The systematic review identified a total of 7,489 unique articles, of which 33 met the inclusion criteria. The studies evaluated a range of PRO domains: HRQoL (n=25), Health Status (n=2), Patient-Reported Symptoms (n=9), Patient-Reported Functioning (n=8), Patient-Reported Feelings (n=2) and Other PROs (n=2). No meningioma-specific tool was used to evaluate PROs. The results of the systematic review show that the diagnosis and treatment of meningioma has an impact on a variety of PRO domains. Furthermore, there was a shortage of studies evaluating long-term HRQoL, particularly in patients with incidental meningioma. The initial, exploratory analysis of the QUALMS study included 54 patients who responded on average ten years after diagnosis. In comparison to the normative population values, patients had inferior HRQoL scores in the following domains: SF-36 Physical Functioning, Role Physical, General Health and QLQ-C30 Cognitive Functioning. However, QLQ-C30 Diarrhoea scores were higher than normative values. Compared to patients who were only actively monitored for their meningioma, patients that received intervention had HRQoL impairments in the domains of the SF-36 (Role Physical, Energy and Fatigue, Emotional Wellbeing, Social Functioning, Pain), QLQ-C30 (Summary Score, Social Functioning, Fatigue, Cognitive Functioning, Pain) and QLQ-BN20 (Communication Deficit, Drowsiness). The study identified that meningioma patients did not report impairments for several items of QLQ-C30 and QLQ-BN20, raising the question about the content validity of these questionnaires for use in this population.

Conclusion: Patients with meningioma experience a range of issues which persist many years after diagnosis and treatment. Patients with incidental meningiomas and those followed-up with active monitoring alone are more likely to have better HRQoL. Future research should evaluate PROs holistically using meningioma-specific PRO tools.

List of tables

List of figures

List of abbreviations

3D-CRT	3D Conformal Radiotherapy
ACCI	Age-adjusted Charlson Comorbidity Index
ACP	Anterior Clinoid Process
AED	Anti-epileptic drug
ClinRO	Clinician-reported Outcome
CNS	Central Nervous System
CNV	Copy Number Variant
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CpG	Cytosine-Guanine dinucleotide repeats
CT	Computed Tomography
DNMT	DNA methyltransferase
EANO	European Association of Neuro-Oncology
EBRT	External Beam Radiotherapy
ECOG	The Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
GTR	Gross-total resection
HRA	Health Research Authority
HRQoL	Health-related quality of life
HRT	Hormone Replacement Therapy
ICOM	International Consortium of Meningiomas
ICP	Intracranial Pressure
IMRT	Intensity Modulated Radiotherapy
ISOQOL	International Society for Quality of Life research
JBI	Joanna Briggs Institute
LINAC	Linear Accelerator

MeSH	Medical Subject Headings
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NF2	Neurofibromatosis 2
NOS	Newcastle-Ottawa Scale
ObsRO	Observer-reported outcome
PET	Positron Emission Tomography
PICOS	Patient Intervention Comparator Outcome Study type
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient-reported outcome
PTSS	Post-traumatic stress syndrome
QoL	Quality of Life
QUALMS	Quality of Life Outcomes of Incidental and Operated Meningiomas
RANO	Response-Assessment in Neuro-Oncology
RCT	Randomised Controlled Trial
RIM	Radiation-induced Meningiomas
ROAM	Radiation versus Observation following surgical resection of Atypical Meningioma
RT	Radiotherapy
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
SRS	Stereotactic radiosurgery
SRT	Stereotactic radiotherapy
SSR2	Somatostatin receptor 2
STOP 'EM	Surgical Trial of Prophylaxis for Epilepsy in Meningioma
STR	Subtotal resection
VMAT	Volumetric modulated arc therapy
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Introduction

"There is today nothing in the whole realm of surgery more gratifying than the successful removal of a meningioma with subsequent perfect functional recovery, especially should a correct pathological diagnosis have been previously made. The difficulties are admittedly great, sometimes insurmountable, and though the disappointments still are many, another generation of neurological surgeons will unquestionably see them largely overcome."

Harvey Cushing, Professor of Surgery Harvard University, 1922

After nearly one century, neurosurgery has overcome many of the insurmountable challenges that Cushing described. Today, clinicians better understand the natural history and aetiology of meningioma (2, 3). The development of neuroimaging has made it possible to visualise and identify these tumours without operating (4). Surgery is safer than before, and measures exist to excise a tumour while preserving neurological tissue and function (5). Furthermore, techniques of non-surgically treating these tumours continue to emerge (6).

Nevertheless, further questions still exist. What are the molecular mechanisms that underpin the development of meningiomas? How can clinicians personalise management for patients? Is it possible to accurately predict tumour behaviour?

As we learn more about meningioma, the attention is turning to the personal impact they can have on those are afflicted by them. Meningiomas have been long-considered a benign tumour, but increasing reports suggest that patients have long-term and complex health needs. There is an increasing consensus within the neurosurgical community to integrate medical, psychological and social considerations within patient care. Therefore, it is paramount to understand what patients perceive and experience to improve their wellbeing.

The modern-day demands of healthcare give clinicians only limited time with their patients. Follow-up appointments are brief and necessitate a focus on tumour progression and worsening objective deficits. A thorough understanding of patient wellbeing is difficult to ascertain. A patient may never convey their concerns and struggles to a healthcare professional.

Collecting Patient-Reported Outcomes (PROs) is one method to empower patients to express their view. Standardised collection and analysis methods permit quick and objective assessment of a patient's subjective experiences. PROs have the potential to facilitate clinician-patient communication, holistic evaluation of therapies and assessment of healthcare delivery from a patient's perspective. However, routine use of PROs in meningioma care and research is limited.

This thesis explores PROs in the context of meningioma. Firstly, the reader is introduced to the topic of meningioma, PROs and their measurement. Chapter 2 describes a systematic review to identify all PROs and their measurement tools in the meningioma literature. Chapter 3 details the methods and results of the 'QUALMS study' which evaluates health-related quality of life (HRQoL) PROs of meningioma. The results of this thesis will contribute to the aim of the Liverpool Neuro-Oncology Group to routinely collect and utilise PROs to enhance patient care.

1.2 Aims and objectives

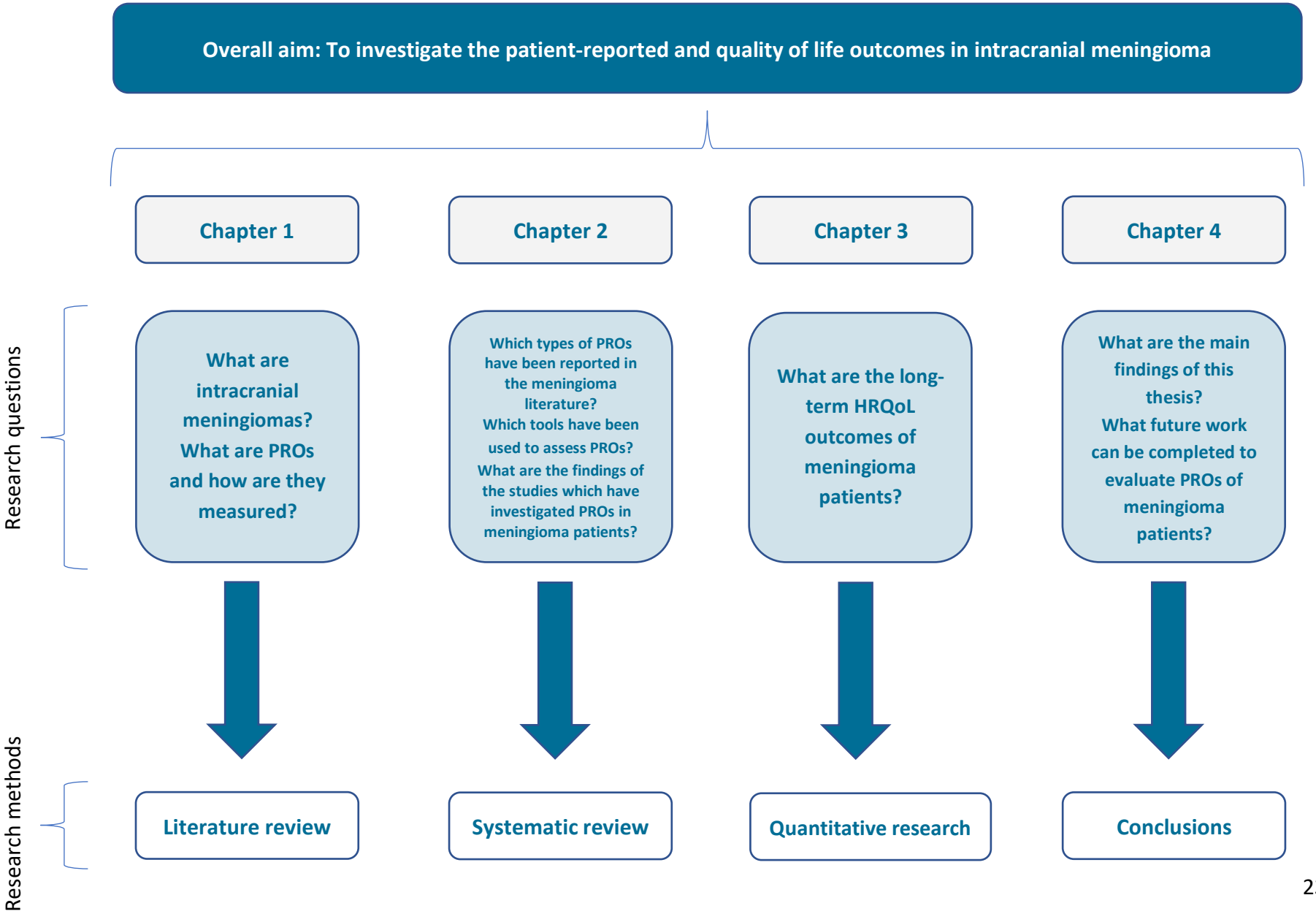
1.2.1 Research question

- What are the patient-reported and quality of life outcomes in intracranial meningioma patients?

1.2.2 Objectives

1. To summarise the current knowledge regarding intracranial meningiomas
2. To describe the concept of patient-reported outcomes (PROs) and their measurement (PROM) tools
3. To systematically identify PROMs currently used in meningioma patients
4. To systematically review the current literature and quality of reporting of PROs in patients with intracranial meningioma
5. To describe the methods and results of a pilot study assessing the HRQoL of patients with either an incidental or operated meningioma.
6. To highlight the applications of the thesis results to future areas for PRO research in meningiomas

Figure 1.1: Thesis overview



1.3 Nomenclature

The earliest description of meningioma comes from the Swiss physician Felix Plater who in 1614 described a '*round fleshy tumor like an acorn … covered with its own membrane and … free of all connection with the matter of the brain*.' (7) These tumours have been known by a variety of names including fungoid tumour, epithelioma and dural sarcoma (8-11).

However, in 1922, Professor Harvey Cushing first proposed the term meningioma (10). This term was chosen because it simplistically summarised that these tumours grew from the meninges which surround the brain. The term meningioma gained favour within the neurosurgical community and has persisted ever since.

1.4 Epidemiology

Meningiomas are the most common primary intracranial tumour. They account for over a third of all central nervous system (CNS) neoplasms and over half of all benign tumours. The incidence rate of meningioma is 8.58 per 100,000 person-years. More than 30,000 patients will be diagnosed with meningioma this year in the USA (1).

The incidence of meningioma increases with age. Meningiomas are rare in children, with an incidence rate of 0.2 per 100,000 between the ages of 0 and 19. The incidence rate increases to 10.2 per 100,000 between the ages of 45 and 54 and 53.4 per 100,000 for those aged 85 and above (1).

Women develop meningiomas with twice the frequency of men (12). Furthermore, the incidence of meningiomas is significantly higher in black patients and those living in urban areas (1).

1.5 Anatomical location of meningiomas

Intracranial meningiomas can originate from skull base and non-skull base locations. Skull base meningiomas arise from the anterior, middle or posterior cranial fossa. The most common skull base locations are the medial sphenoid wing, olfactory groove and the suprasellar region (13). Common non-skull base origins of meningioma are the cerebral convexity, parasagittal and parafalcine regions (13). Rarely, meningiomas can arise from within the ventricular system of the brain and in the pineal region; these locations are deeper within the brain and difficult to access surgically. Meningiomas may be supratentorial or infratentorial, which describes their position in relation to the tentorium cerebelli. Infratentorial meningiomas arise in proximity to the cerebellum or brain stem and can also present surgical challenges. Table 1.1 shows the International Consortium of Meningioma (ICOM) classification of meningiomas by location. Figure 1.2 illustrates the anatomical origins of meningioma.

Table 1.1: ICOM classification of meningiomas by 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
ACP: anterior clinoid process

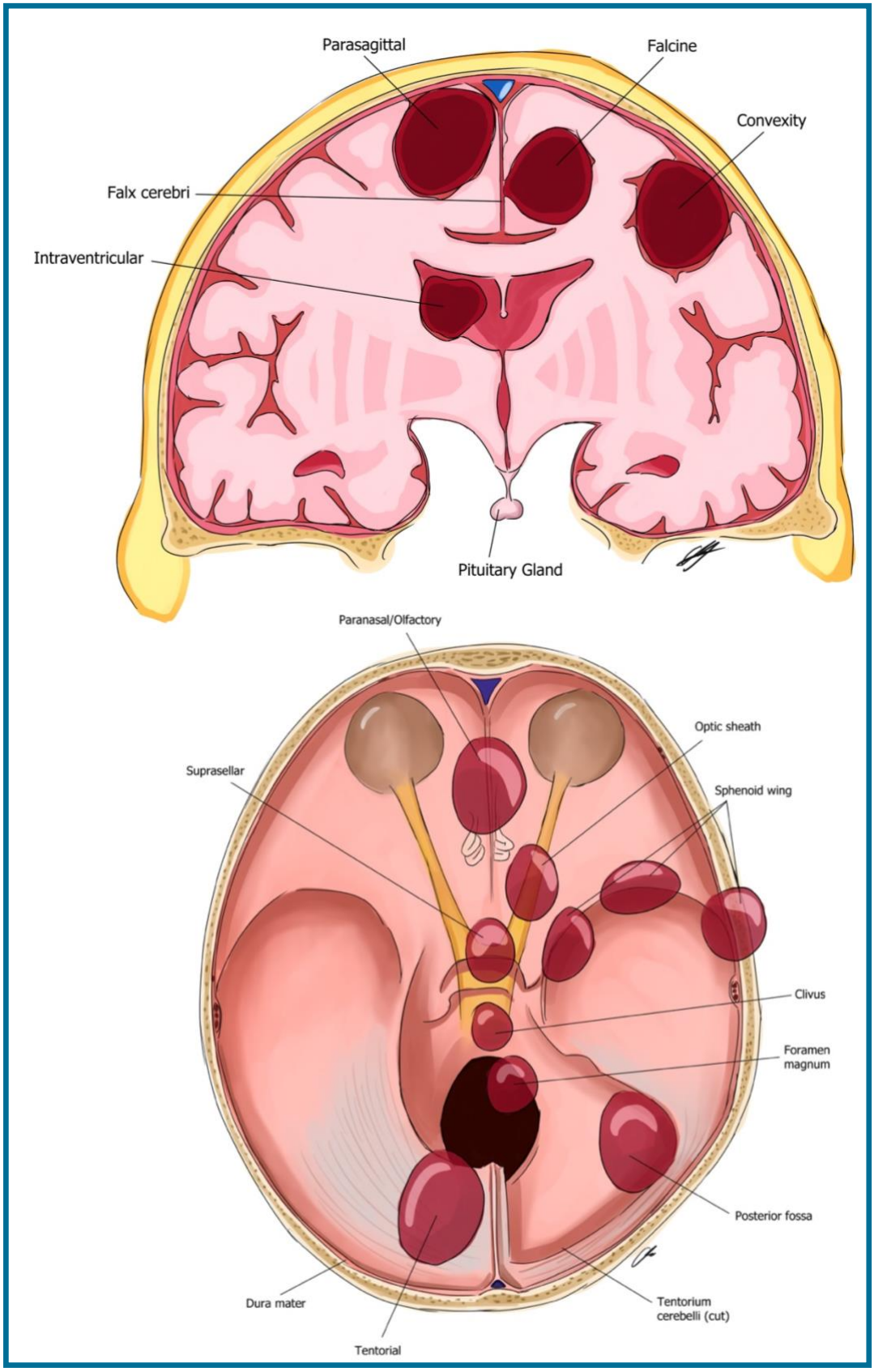


Figure 1.2: Coronal section of the brain and axial view of skull base showing meningioma locations

Illustrations courtesy of Christian Anderson

1.6 Aetiology

Sporadic meningiomas arise in the absence of a specific underlying cause. They are the most common variant of meningioma and the focus of this thesis. Neurofibromatosis type 2-associated meningiomas and radiation-induced meningiomas have a different natural history compared to sporadic meningiomas. For this reason, they are considered different disease entities and addressed separately by the meningioma research community.

1.6.1 Neurofibromatosis type 2

Neurofibromatosis type 2 (NF2) is a rare condition with an incidence of 1 in 30,000 that arises from a mutation of the *NF2* tumour suppressor gene (14). It has an autosomal dominant inheritance pattern; however, up to 50% of NF2 patients have no family history and have acquired de novo mutations. NF2 predisposes patients to develop multiple neoplasias of the nervous system, eyes and skin (15). Development of bilateral vestibular schwannomas is highly sensitive of an NF2 diagnosis (16). As many as half of NF2 patients develop meningiomas in their lives (16). Frequently these are multiple and occur earlier in life compared to patients with sporadic meningioma (17-19). Studies have found that NF2 patients develop clinically aggressive forms of meningioma (20).

1.6.2 Radiation

Over recent decades, research has highlighted an association between radiation and meningioma. Low-dose radiation previously used to treat childhood tinea capitis in the 1950s and 1960s was identified to increase the relative risk of developing meningioma nearly 10-fold (21). Furthermore, those who were within 2km of the 1945 atomic bomb blast in Hiroshima had an increased incidence of meningioma (22). Radiotherapy is an effective treatment modality for childhood malignancies such as acute lymphoblastic leukaemia and CNS tumours. However, childhood cranial irradiation is also associated with the development of meningiomas (23, 24). Meningiomas occurring many years

following cranial radiotherapy are known as radiation-induced meningiomas (RIMs) (25, 26).

In comparison to sporadic meningiomas, RIMs occur equally in both sexes and at a younger age (26). RIMs are more aggressive compared to sporadic meningiomas and demonstrate a substantial proportion of atypical or malignant features (26-29). Following treatment, approximately 20% of RIMs recur (26, 30, 31). Given the strong association between radiation and meningiomas, researchers have questioned whether radiation from telephones or dental x-rays may also increase tumour risk. However, one case-control study showed no increased odds between telephone use and development of meningiomas (32). Furthermore, two meta-analyses have concluded that dental X-rays do not increase the risk of developing meningiomas (33, 34).

1.6.3 Hormonal factors

Meningiomas occur more commonly in females and grow during pregnancy (35-37). This observation has prompted researchers to investigate the association between meningiomas and hormonal factors. Meningiomas express an increased number of progesterone and oestrogen receptors compared to healthy meningeal tissue (38, 39). In vitro studies demonstrate that progesterone agonists can promote the growth of meningioma cell lines. Conversely, progesterone antagonists cause inhibition of meningioma cells in vitro (40, 41). However, clinical studies have failed to show the efficacy of the progesterone receptor antagonist mifepristone in improving patient survival (42, 43).

One recent case-control study found that meningioma patients taking progesterone-only contraception pills have shorter progression-free survival than those taking oestrogen pills with or without progesterone (44). Furthermore, two systematic reviews have identified a significant association between Hormone Replacement Therapy (HRT) use and development of

meningioma (45, 46). Given that large numbers of women use hormonal contraception and HRT, it is vital to demonstrate their safety in women with meningioma. Additionally, a number of case studies have reported an association between intake of anti-androgen and progestin drugs and development of meningioma (47, 48). Some tumours have been reported to regress upon discontinuation of hormonal therapy (49). Further prospective studies are needed to more firmly establish any association.

1.7 Histopathology

The meninges are a protective membrane which envelope the brain and spinal cord. The meninges contain three layers: the dura, arachnoid and pia mater. Meningiomas arise from the arachnoid cap cells found on the outer layer of the arachnoid mater (50, 51). Meningiomas usually have a firm consistency which may become gritty if they are calcified with psammoma bodies (52). Meningiomas have variable vascularity and derive their blood supply from the meningeal vessels (52, 53). Meningiomas can grow in size and compress underlying structures of the brain and spinal cord to cause symptoms. Aggressive meningiomas may invade the brain or metastasise (52, 54). Some meningiomas may release substances which promote osteolysis or hyperostosis of adjacent bone. Cerebral oedema may surround the tumour, which further increases intracranial pressure and risk of symptoms such as seizure (55-57).

The World Health Organisation (WHO) classification of tumours of the central nervous system classifies meningioma as Grade I (benign), II (atypical) and III (anaplastic/ malignant) (54). Increasing WHO Grade denotes increasing aggressiveness of the meningioma and corresponds with worsening prognosis (58). Over 80% of meningiomas are WHO grade I (1). Within each WHO grade, a variety of histological subtypes exist. WHO Grade is determined by either identification of specific histological features or subtypes. Table 1.2 illustrates the histological criteria used to determine the WHO Grade of meningiomas.

Brain invasion is a histological criterion which has been controversial within meningioma research. WHO defines brain invasion as an invasion of the brain by a meningioma without an intervening layer of leptomeninges (58). Studies have found that the presence of brain invasion conveys a similar recurrence rate to atypical meningiomas (59). Accordingly, WHO recently made the presence of brain invasion a standalone feature which can define a tumour as a WHO grade II meningioma (54). However, one systematic review identified that various definitions of brain invasion exist in the literature, and there is a weak correlation with prognosis (60). The classification change is significant as WHO Grade II meningiomas will be increasingly diagnosed (61). Since WHO grading guides management decisions, the diagnosis of a WHO Grade II meningioma may prompt adjuvant treatment and more frequent MRI follow-up, which may necessarily be required.

Table 1.2: Prevalence and diagnostic criteria of WHO Grade I, II and III meningiomas. Modified from Bi et al. 2016 (62)			
	WHO Grade I	**WHO Grade II**	**WHO Grade III**
Prevalence (%) (1)	80.5	17.7	1.7
Diagnostic criteria (54)	Low mitotic rate, <4 per 10 HPF **AND** Absence of brain invasion	4 - 19 mitotic figures/10 HPF **OR** Brain invasion **OR** 3/5 of these histologic features: I. Increased cellularity II. High nuclear/cytoplasmic ratio III. Large and prominent nucleoli IV. Architectural sheeting V. Foci of "spontaneous" or geographic necrosis **OR** Clear/ Chordoid subtype	Either 20 or more mitotic figures/10 HPF **OR** Display frank anaplastic **OR** Rhabdoid/Papillary histology
Histological subtypes (54)	Meningothelial Fibrous (fibroblastic) Transitional (mixed) Psammomatous Angiomatous Microcystic Secretory Lymphoplasmocyte-rich Metaplastic	Atypical by criteria Clear cell subtype Chordoid subtype	Anaplastic by criteria Rhabdoid subtype Papillary subtype

1.8 Molecular biology of meningiomas

As biomedical technology and techniques continue to improve, research is providing a better understanding of the molecular changes occurring within tumour cells. Routine neuro-oncology clinical practice now applies this knowledge: molecular features currently contribute to the classification of glioma and medulloblastoma (54). Nevertheless, meningioma classification remains entirely based on histopathology. The investigation into the molecular landscape of meningioma is rapidly expanding, and changes to clinical practice are likely to soon reflect this.

1.8.1 Copy number variations

Copy number variations (CNVs) are losses, gains or duplications of sections of chromosomes (63). While CNVs are present in healthy individuals, some CNVs are implicated in disease. Pathological CNVs alter the function of genes involved in regulating cell proliferation (64). Loss of the long arm of chromosome 22 is a prevalent CNV in meningioma (65, 66). This CNV occurs early in meningioma development and increases in prevalence with WHO Grade (66, 67). WHO Grade II meningiomas have an increased frequency of CNVs on chromosome 1p and 14q (66, 67). Grade III tumours frequently demonstrate CNVs on chromosome 4p, 6q, 7p, 10q, 11p and 18q (66). Frequency of CNVs is associated with meningioma aggressiveness. WHO Grade I, II and III tumours show a median chromosomal arm loss per tumour of 1.0, 3.0 and 9.5, respectively (66).

1.8.2 Genetic mutations

The *NF2* gene is located on the long arm of chromosome 22 and codes for the protein neurofibromin 2 (also known as merlin). This cell-membrane bound protein interacts with the cytoskeleton and is responsible for contact-dependent regulation of cellular proliferation (68). Germline or de novo *NF2* mutations lead to neurofibromatosis type 2 (NF2), which is known to increase the risk of meningioma (69). However, as many as 50% of sporadic meningioma cells also have an *NF2* mutation (70-72). Specific mutations correspond to WHO Grade and clinical phenotypes. For example, *TRAF7*, *AKT1* and *KLF4* mutations are more frequent in WHO grade I meningioma (73). Mutations of the *SMO* gene are exclusively associated with WHO grade I meningiomas (73-75). However, mutations of the proto-oncogene *TERT* and tumour suppressor gene *BAP1* are associated with aggressive meningiomas (2).

1.8.3 Methylation

Imbalances of DNA methylation patterns are involved in meningioma development (76). In healthy cells, DNA methylation of CpG islands (cytosine-guanine dinucleotide repeats) regulates gene expression. The promoter regions of genes contain CpG islands, and their function is to regulate gene transcription (77). When unmethylated, CpG islands allow transcription of genes (77). However, DNA methyltransferase (DNMTs) enzymes can methylate the CpG islands and cause downstream gene silencing (78). Pathological hypermethylation of CpG islands near tumour suppressor genes such as *THBS1*, *MGMT*, *TIMP-3*, $p16^{INK4a}$, $p14^{ARF}$ and *p73* causes gene silencing and contributes to tumorigenesis (76).

Conversely, widespread hypomethylation may increase transcription of genes involved in carcinogenesis, tumour invasion and metastasis (79). Genome-wide hypomethylation is associated with atypical and malignant meningiomas (80).

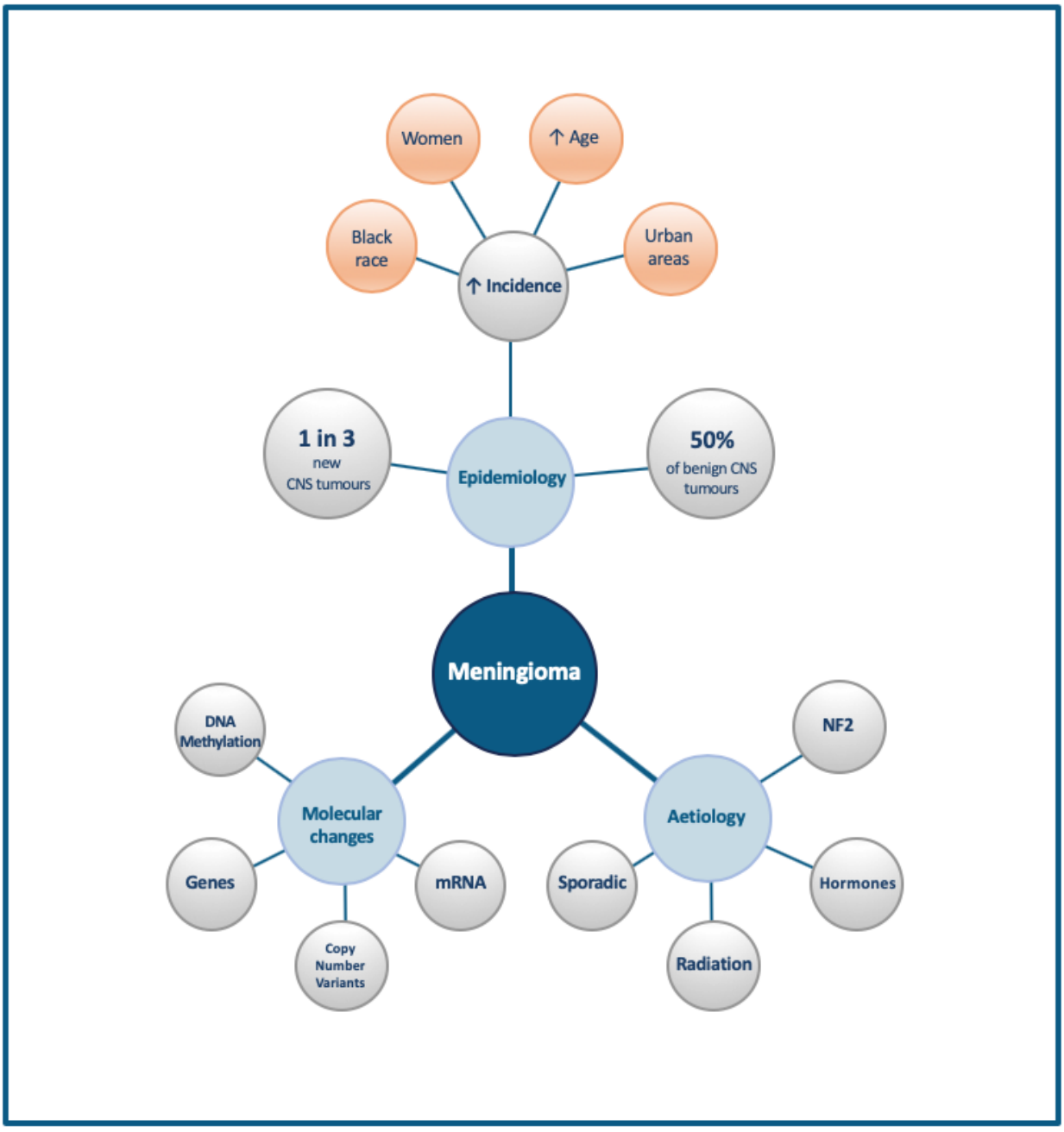


Figure 1.3: An infographic to summarise epidemiological, aetiological and molecular aspects of meningioma.

1.9 Clinical features

Meningiomas give rise to both generic and location-specific symptoms; many are slow-growing, and symptom onset can be insidious (81). Moreover, meningiomas may be asymptomatic and identified by neuroimaging completed for unrelated reasons.

1.9.1 General features

One of the earliest features of a meningioma may be the onset of epilepsy (82). Approximately 25% of meningioma patients will experience seizures, particularly those with supratentorial tumours (56, 57, 83). The aetiology of tumour-induced epilepsy is unclear. Hypotheses suggest a role of biochemical abnormalities, dysfunctional NMDA receptors and altered immunological activity (82). Several studies purport an association between peritumoral oedema and seizures (56, 83). Generalised seizures involve the whole brain and patients may present with tonic-clonic seizures. Alternatively, focal seizures may present with auras such as a 'rising epigastric' sensation or the déjà vu phenomenon.

Headache is considered by many as the archetypal symptom of a brain tumour. However, as an isolated symptom, it has a low positive predictive value for brain tumours in adult patients (84). No headache type or syndrome is pathognomic for meningioma. However, a change in a pre-existing headache phenotype or a headache associated with red flags (such as abnormal neurological examination or a headache which causes awakening from sleep) may prompt clinicians to further investigate for the presence of a brain tumour (85). The main factors thought to induce headaches from brain tumours are related to distortion and displacement of pain-sensitive structures within the blood vessels, cranial nerves, dura mater and periosteum (85, 86).

Other clinical features include the development of cognitive impairment such as deficits of memory, attention and executive function (87). Meningiomas that increase intracranial pressure (ICP) can present with reduced consciousness or papilledema (88). Occasionally, symptoms mimicking a mental health disorder may be the only presenting feature of meningioma (89). Frontal lobe meningiomas can cause psychosis, delirium, depression, apathy, mania and change in personality (90).

1.9.2 Focal features

Patients may present with a variety of focal symptoms arising as local neuronal structures are distorted and compressed. Left hemisphere meningiomas in the perisylvian region may cause an expressive, receptive or mixed dysphasia. A paresis or apraxia can arise from meningioma overlying the motor cortices. Involvement of the parietal lobe may lead to somatosensory disturbances. Occipital lobe meningiomas can result in visual field defects or agnosia. Skull base meningiomas frequently compress the cranial nerves (91, 92). Olfactory groove meningiomas distorting cranial nerve I may lead to a loss of smell and anterior skull base lesions may compress the optic nerve or chiasm leading to a visual deficit. Cavernous sinus meningiomas can involve cranial nerves III, IV, V and VI manifesting as visual loss, diplopia and facial numbness. Cerebellopontine angle meningiomas affecting cranial nerve VII or VIII can produce facial pain, sensory disturbance, sensorineural hearing loss and vertigo. Meningiomas of the clivus and foramen magnum can manifest as a complex syndrome of both lower cranial nerve and spinal signs.

1.10 Incidental meningiomas

Small, asymptomatic meningiomas are common and may occur in up to 1% of the population (93). These clinically indolent meningiomas may go unnoticed through an individual's life or get identified by chance through neuroimaging performed for unrelated reasons. The diagnosis of these so-called 'incidental meningiomas' is increasing due to the widespread use of neuroimaging in clinical practice and research (94). Over 90% of these meningiomas are WHO Grade I (95). Consensus guidelines suggest that incidental meningiomas should be managed by observation, although variation exists in practice (96, 97).

Three critical questions concerning incidental meningiomas include:

1. Is long-term follow-up necessary to monitor the growth of incidental meningiomas?
2. Do patients with incidental meningiomas experience neurocognitive deficits?
3. Does a diagnosis and follow-up of incidental meningioma affect a patient's quality of life?

Approximately 10% of incidental meningioma patients develop symptoms during follow-up, and 20% demonstrate radiological progression (95). The majority of patients who have clinical or radiological progression do so within five years of diagnosis (95). Larger size and peri-tumoural oedema are variables associated with progression of incidental meningiomas (95). These radiological factors can be combined with clinical information to develop personalised incidental meningioma monitoring regimes (98).

There is a paucity of research regarding neurocognitive outcomes of patients with an incidental meningioma. One study has identified that patients with incidental meningioma have similar neurocognition to matched controls (99). However, another has found that patients have lower psychomotor speed and working memory (100). Regarding the quality of life outcomes, patients report

lower vitality and self-perceived general health (100). A diagnosis of a brain tumour and follow-up may lead to anxiety for patients. Quality of life outcomes in incidental meningioma patients is reviewed further in Chapter 2.

1.11 Investigation

The confirmation of a meningioma diagnosis is by histological analysis of tissue obtained during surgery. However, neuroimaging is accurate in predicting meningioma in the majority of cases. Consensus guidelines recommend a Magnetic Resonance Imaging (MRI) scan as the initial investigation for diagnosis (96). However, complex meningiomas may require the use of additional diagnostic modalities.

1.11.1 MRI

Magnetic Resonance Imaging (MRI) scans of meningioma typically reveal a well-circumscribed and extra-axial lesion (81). Meningiomas are isointense or hypointense to adjacent grey matter on T1-weighted MRI sequences. They are isointense or hyperintense on T2-weighted sequences. Following injection of gadolinium contrast, a meningioma demonstrates homogenous enhancement. MRI may identify a dural tail which represents thickening of dura extending peripherally from the meningioma. MRI may also reveal the CSF cleft sign, which refers to a high signal intensity between the meningioma and the brain parenchyma. Oedema can surround a meningioma, and this is best visible on T2 and T2 FLAIR sequences (81). Magnetic Resonance Spectroscopy (MRS) utilises magnetic fields to identify metabolic activity in tissues (101). MRS of meningioma shows increased choline and alanine peaks and decreased peaks of N-acetyl aspartate and creatinine when compared to healthy brain tissue (102).

1.11.2 CT

Computed Tomography (CT) scans are regularly requested for assessment of headaches, head injury and suspected stroke (103). Therefore, CT frequently identifies incidental meningiomas. Similar to MRI, CT reveals an extra-axial, hyperdense and well-circumscribed lesions (104). CT is ideally suited to identifying calcification and bony changes such as osteolysis and hyperostosis (81, 104). CT may also be beneficial for patients in whom MRI is unsuitable or contraindicated.

1.11.3 Angiography

Angiography involves injecting contrast into arteries and taking radiographs. Meningiomas may be highly vascularised by meningeal arteries. Therefore, angiography demonstrates a 'tumour blush' and delayed 'washout' as the contrast is taken up and leaves the meningioma (104-106). Angiography is not required for diagnosing meningioma but may be used to understand the arterial supply of complex tumours (96).

1.11.4 Somatostatin analogue

Meningiomas show increased expression of somatostatin receptor 2 (SSR2) (107). DOTATE and DOTATOC are ligands which bind with high affinity to meningioma SSR2 (108). These ligands are marked with radioisotopes such as Gallium-68 which allows their detection using Positron Emission Tomography (PET) scans. This PET tracing discriminates between tumour and healthy tissue, makes their use valuable for diagnosis and treatment planning of complex meningiomas (109-111).

1.11.5 Differential diagnosis

No further investigation or biopsy is necessary for tumours which show typical imaging characteristics of meningioma. However, clinicians should be aware of potential mimics of meningioma (96). Primary lesions that may mimic meningioma include solitary fibrous tumours, hemangiopericytomas and schwannomas (112-114). Dural metastases, usually originating from breast or lung carcinomas, are an important differential diagnosis to exclude with further investigations such as CT Thorax Abdomen Pelvis (115-117).

1.12 Management

1.12.1 Surgery

Surgery represents a safe and effective method to reduce tumour burden for a majority of patients. Surgery may be curative in WHO Grade I meningiomas and can reduce tumour burden. It is an established first-line therapy for symptomatic or growing meningiomas. However, not all patients may be suitable for surgery. Factors which influence the decision to operate include patient's general health, functional status and presence of comorbidities. Some tumours, such as petroclival or foramen magnum meningiomas, are surgically challenging to access and preclude resection.

The goal of surgery is maximal safe resection of the meningioma to obtain a diagnosis, reduce ICP and relieve symptoms. Intra-operatively, surgeons can estimate the extent of resection using the Simpson grading system (118). This is confirmed by MRI postoperatively. Modern interpretation favours that Simpson Grade 1-3 denotes gross total resection (GTR) and grades 4 and 5 are a subtotal resection (STR). The extent of resection is considered a prognostic indicator and influences decisions about further management such as whether to offer adjuvant therapy. The surgical gold-standard is to achieve a Simpson Grade 1 resection which is complete resection of the tumour, dural attachment and abnormal bone (118).

Table 1.3: Simpson classification of the extent of resection for meningioma	
Simpson Grade *(118)*	**Description**
Grade 1	Macroscopic complete removal of the tumour and excision of its dural attachment and any abnormal bones. If a tumour arises from the wall of a dural venous sinus, a Grade I resection involves excision of the sinus.
Grade 2	Macroscopic complete removal of the tumour and its visible extensions, with endothermy coagulation (to the point of charring) of dural attachment.
Grade 3	Macroscopic complete removal of the intradural tumour without resection or coagulation of its dural attachment or extradural extensions, e.g. invaded sinus or hyperostotic bone.
Grade 4	Partial removal of the tumour, leaving intradural tumour *in situ*.
Grade 5	Decompression of tumour with or without biopsy.

However, surgical resection of meningioma is not without risk of long-term complications. Convexity meningioma resection can lead to hemiparesis, hemisensory loss and dysphasia. Skull-base surgery may cause CSF leak or meningitis. Cranial nerve damage can occur, causing loss of sensation (smell, vision, hearing and taste) and motor control (facial paresis, mastication, speech and swallowing). Previously seizure-naïve patients can develop epilepsy postoperatively (56). Cognitive decline may follow, leading to difficulty with concentration and memory (87). In this regard, surgery can sometimes induce the deficits it attempts to relieve.

1.12.2 Radiation therapy

A variety of techniques exist to deliver radiation to meningiomas, such as external beam radiotherapy (EBRT) and stereotactic radiosurgery. EBRT is the name given to conventional external radiation delivery techniques. EBRT is favourable for larger tumours or those adjacent to critical neurovascular structures. Examples of EBRT include 3D conformal radiotherapy (3D-CRT), Intensity-modulated radiotherapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and Proton beam therapy (119-121). Stereotactic radiosurgery (SRS) and fractionated stereotactic radiotherapy (SRT) both use steep dose gradients to spare radiation toxicity to healthy tissue (122). Examples of SRS include Linear

Accelerator (LINAC) and Gamma Knife techniques. SRS is useful for controlling the growth of small or incompletely resected meningiomas (123).

Radiotherapy is a largely safe and effective treatment option which can be used as primary or adjuvant therapy. Radiation therapy can be used to treat residual or recurring meningiomas. Complication rates from EBRT are low but can include radiation necrosis, visual deficit and osteomyelitis (124). SRS is a day-case procedure and usually well tolerated by patients (6). However, complications of treatment include new cranial nerve dysfunction, visual loss and worsening headache (125). SRT has shown reduced symptom burden in comparison to SRS, particularly from symptomatic radiation-induced oedema (126-128).

Other radiation-based treatments may have value for high-grade or recurring meningiomas where alternative treatment options are exhausted or unsuitable. Brachytherapy involves surgically placing a radioactive source in close proximity to meningioma tissue (129). Radionuclide therapy involves administering analogues which bind to meningioma-specific SSR2 receptors and deliver radiation to meningioma cells (130). Further prospective studies are required to evaluate the efficacy of these treatments for managing meningiomas.

1.12.3 Systemic therapy

A variety of chemotherapy, hormone receptor antagonist and SSR2 receptor analogue therapies have been assessed for efficacy in clinical studies and shown sub-optimal treatment benefits (6, 131). However, studies investigating the efficacy of systemic therapies are currently on-going. Immunotherapy using pembrolizumab and nivolumab is currently being investigated for patients with high-grade meningioma (NCT03279692, NCT02648997). Furthermore, molecular therapies targeting the NF2, AKT and Hedgehog pathways are being developed (6, 96). Medical management of meningioma is an evolving area of

research and currently remains reserved for when surgical and radiotherapy options have been exhausted.

1.12.4 Active monitoring

Active monitoring through neuroimaging assists clinicians in deciding when to treat a patient and also to assess the objective response from treatment. Consensus guidelines recommend that both incidental and symptomatic WHO Grade I meningiomas are followed-up with a yearly MRI scan. Patients with WHO Grade II and III meningiomas have an increased risk of recurrence and should have an MRI biannually or quarterly (96). Active monitoring can identify tumour recurrence in patients who have had a complete resection of their meningioma. Furthermore, active monitoring may reveal tumour progression in patients with incompletely resected or incidental meningiomas.

1.13 Guidelines for the management of meningiomas

1.13.1 WHO Grade I

For symptomatic meningiomas or those causing mass-effect, the primary treatment option is surgical resection. Incompletely resected meningiomas may undergo active surveillance or be treated with adjuvant stereotactic radiosurgery or fractionated radiotherapy (96). Some skull base meningiomas are intentionally incompletely resected to spare damage to critical neurovascular structures such as the cranial nerves. The residual tumour is treated with adjuvant stereotactic radiosurgery (96). For patients who are not fit for surgery, stereotactic or fractionated radiotherapy techniques can be used as primary treatment (96).

1.13.2 WHO Grade II

Completely resected WHO Grade II meningiomas can be treated with either upfront adjuvant radiotherapy or observation using MRI scans (96). At present, there is a paucity of high-quality, prospective studies showing the superiority of either approach following surgery. This clinical equipoise forms the basis for the on-going ROAM/EORTC 1308 (ISRCTN71502099) clinical trial (132). For incompletely resected WHO Grade II meningiomas, adjuvant radiotherapy is given to improve tumour control and reduce the risk of recurrence (96). Consensus guidelines recommend fractionated radiotherapy over SRS in these cases (96).

1.13.3 WHO Grade III

Anaplastic meningiomas should be treated with surgery and adjuvant fractionated radiotherapy (96). In the event of tumour recurrence and exhaustion of surgical and radiation treatment options, experimental pharmacotherapy may be offered (96).

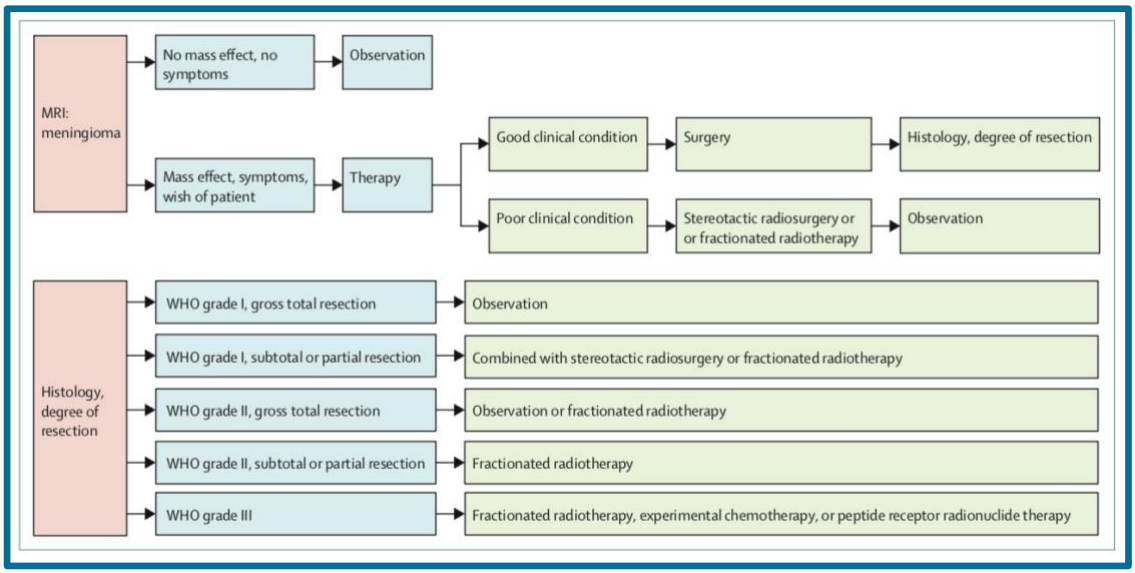


Figure 1.4: EANO recommendations for the treatment of WHO Grade I, II and III meningiomas (96)

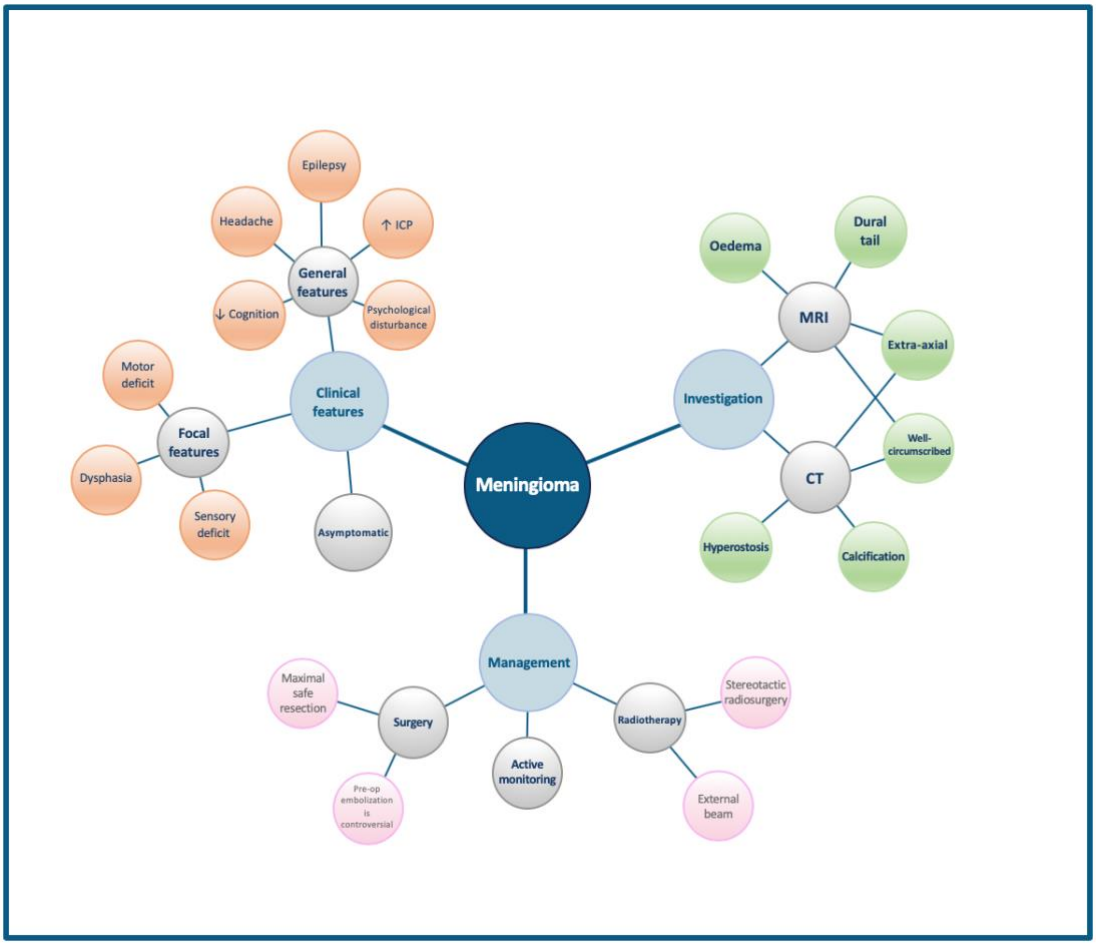


Figure 1.5: An infographic to summarise the clinical features, investigations and management of intracranial meningioma

1.14 Prognosis

A comprehensive discussion of the prognostic factors influencing meningioma outcome is beyond the scope of this thesis. Combining clinical, histopathological and molecular factors is necessary to improve classification and prognostication (133). An integrated clinical model can help to develop personalised meningioma management algorithms.

The life expectancy of meningioma patients remains lower than the general population (134, 135). Overall survival of meningioma decreases with increasing WHO Grade. The overall 5-year and 10-year UK survival rates for WHO Grade I meningioma is 90% and 81%, for WHO Grade II it is 80% and 63% and for WHO Grade III it is 30% and 15% (136).

WHO grading also determines the risk of meningioma recurrence. The risk of recurrence for WHO Grade I, II and III meningiomas is 7-25%, 29-52% and 50-94%, respectively (58). Histological parameters that are associated with an increased risk of recurrence include an increasing number of mitotic figures and the presence of focal necrosis (137). Furthermore, the risk of recurrence increases with Simpson grades of meningioma resection. In Simpson's original study, the meningioma recurrence rate was 9%, 19%, 29%, 44% and 100% for Simpson grades 1–5, respectively (118). Similar recurrence trends are evident in modern series (138-141) and Simpson grades 4 and 5 are also associated with decreased overall survival (141).

The value of molecular markers for prognostication of meningioma is increasing. One study has suggested that 'TRAKLS' (*TRAF7*, *AKT1* and *KLF4*) mutations generally confer a better prognosis genotype (73, 142). Moreover, mutations of the transcription factor FOXM1 are a marker for aggressive meningioma and poor clinical outcomes (143). More recently, methylation data has been combined with clinical factors to develop a nomogram which accurately predicts meningioma recurrence (144, 145).

Survival and recurrence represent one aspect of meningioma prognosis. Morbidity is also high, and patients experience a variety of physical, cognitive and emotional difficulties which impair quality of life (87, 146). Chapter 2 of this thesis will highlight this in further detail.

1.15 Patient-Reported Outcomes

The World Health Organisation defines health as 'a state of complete physical, mental, and social wellbeing not merely the absence of disease or infirmity' (147). Therefore, an evaluation of a person's health must include a holistic review of wellbeing in addition to an investigation of the morbidity from disease. Traditionally, researchers have assessed health by using objective measures of morbidity and mortality and patient wellbeing was considered of secondary importance. However, in the last two decades, healthcare and research have appropriately become patient-centred with increasing importance given to the subjective experiences of patients.

Healthcare in economically developed countries is increasingly focussing on long-term management of chronic diseases. The goal of clinicians is often to reduce symptom burden and disability from disease and treatment. Modern healthcare places emphasis on increasing the functioning and participation of a patient in activities of daily living. Thorough measurement of these outcomes requires an assessment of a patient's own perspective (148).

Patient-Reported Outcomes (PROs) are a patient's expression of their subjective perceptions and experiences. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) define a PRO as an outcome directly from a patient about the status of their health condition or perception of a disease and its treatment (149, 150). A PRO must be without amendment or interpretation of the patient's response by anyone else (150). PRO is an umbrella term encompassing measurement of quality of life, health

status, symptom burden, adherence to and satisfaction with treatment (149, 151).

1.15.1 Quality of Life

Quality of life (QoL) is a specific type of PRO that concerns a person's state of wellbeing. In many ways, it is an abstract term that carries a different meaning to each person. Campbell et al. described Quality of Life as a '*vague and ethereal entity, something that many people talk about, but which nobody knows very clearly what to do about*.' (152)

However, some aspects of QoL are generally agreed. Firstly, QoL is subjective and understood only from an individual's perspective. Secondly, QoL is multidimensional and influenced by a variety of factors. Subjectivity and multidimensionality form the foundations of understanding QoL (153). WHO defines QoL as 'an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.' (154)

Health-related quality of life (HRQoL) refers to 'the extent to which one's usual or expected physical, emotional, and social wellbeing are affected by a medical condition or its treatment.' (155) This definition highlights that HRQoL is not merely a measure of wellbeing, but how this aligns with a patient's subjective expectations (156).

1.16 Application of PROs

1.16.1 Clinical research

Within clinical research, PROs allow assessment of net clinical benefit of a treatment. Integration of PRO data with traditional endpoints within clinical trials and studies provides a holistic overview of disease burden and efficacy of an intervention (157, 158). The US FDA states that Clinical Outcome Assessment

(COA) of drug development should encompass both objective clinical evidence of benefit and subjective experiences reported by patients (150).

In clinical trials, PROs may be a primary outcome used to differentiate therapies in non-inferiority studies. For example, a patient's subjective experiences can be a primary outcome used to compare two palliative therapies (159). Alternatively, clinical trials may use PROs as a secondary outcome. Traditional endpoints such as survival describe only the physical benefit of treatment; PROs add a patient perspective which contributes to a holistic assessment (148, 151). For example, the ROAM clinical trial is assessing the clinical benefit of radiation treatment compared to observation alone for atypical meningiomas (132). The primary outcome of the trial is progression-free survival, and HRQoL is a secondary outcome. The trial may identify that radiotherapy confers a modest survival advantage but at the expense of decreasing HRQoL. In this case, the PROs would provide an additional lens to assess the value of radiotherapy against observation. Such information would be necessary for future patients and clinicians when making management decisions.

The increasing use of PROs in clinical effectiveness research is reflected by the PRO extensions to the CONSORT and SPIRIT checklists for reporting clinical trials and their protocols (160, 161). The Response Assessment in Neuro-Oncology (RANO) working group is currently producing guidelines for the use of PROs in neuro-oncology (162).

However, there are some challenges to using PROs in clinical research. Firstly, the PRO instrument must be appropriate (valid) for use within the population being assessed. This is a particular issue for meningioma research; one review found that only three of thirteen quality of life tools used in meningioma research were validated for use (146). Using unvalidated tools may cast doubt on the study findings. Furthermore, systematic reviews have found shortcomings in reporting of PRO results which may hamper the interpretation of results (163, 164). Common issues include not reporting method of collecting

PROs or not detailing the extent of missing data. Such reporting omissions reduce the confidence of stakeholders in using the PRO data to make clinical decisions (165).

1.16.2 Clinical practice

PROs can maximise the clinician-patient interaction by providing items for discussion. Sometimes, patient issues are not acknowledged or addressed by clinicians in a consultation (166-169). In clinic appointments (where there is often limited time), discussion about the objective measures of meningioma may predominate, and issues that are distressing to the patient may not be offered for discussion by the patient or asked about by the clinician. One solution to this is for patients to complete a PRO assessment before the clinic appointment, and the results are made available for the patient and clinician to discuss. PROs quantify the experiences of patients across a range of domains. In this way, domains that are low-scoring can be used as discussion points to enhance clinician-patient communication (170). PRO alerts, which are 'concerning levels of psychological distress or physical symptoms that may require an immediate response' (171), can be used to notify clinicians to issues that the patient may not volunteer during the clinic consultation. Additionally, serial measurements during long-term follow-up may identify trends in PROs that the patient has not noticed. Healthcare professionals can address the identified issues during clinic appointments. In this way, PROs can be used as an objective measurement of wellbeing and as an adjunct in monitoring a patient's condition.

1.16.3 Healthcare delivery

Healthcare delivery can be assessed using PROs. In Sweden, National Quality Registers collect PRO data alongside information about medical interventions and outcomes (172). This amalgamation of clinical and PRO data allows policymakers to make comparisons of outcomes from different hospitals. Swedish quality registers are publicly available, and patients can use this

information to choose where they would like to receive elective treatment (173). Furthermore, the quality registries allow for population-based data which can be used for research and quality improvement of existing services (172, 174).

Since 2009, NHS England has collected PRO data from patients undergoing two elective surgical procedures (175). All patients undergoing hip or knee repair are invited to complete a generic and disease-specific PROM preoperatively and three months postoperatively. The data assesses health gains and cost-effectiveness of treatment. Like the Swedish National Quality Registries, the PRO data can allow for comparisons of the performance and variability of NHS funded care providers (176).

1.17 Patient-Reported Outcome Measures

A Patient-Reported Outcome Measure (PROM) is an instrument or tool used to measure a PRO (150, 151). PROMs are typically paper-based or electronic questionnaires that ask a variety of questions (items) to record a patient's subjective perceptions and experiences. PROMs typically capture PRO data through rating scales or counts of events rather than free-text responses (150).

PROMs may be generic or disease-specific (148). Generic PROMs measure aspects which are common to a variety of conditions. These PROMS allow for comparisons between different medical conditions (151). Generic PROMs such as the EQ-5D tool also allow for cost-utility analysis to assess the cost of an intervention and the benefit it confers. However, generic PROMs may not cover essential issues which are experienced by patients with specific medical conditions.

Disease-specific PROMs concern aspects of a particular medical condition and their impact on patient's wellbeing (151). Examples of disease-specific PROMs are the EORTC QLQ-C30 and FACT-G for cancer. Disease-specific PROMs include items which are more relevant to patients than generic PROMs and

therefore have greater face validity (151). However, it is not typically possible to use disease-specific PROMs to make comparisons between medical conditions (151).

1.17.1 Method of PROM administration

PRO data collection can yield varying results depending on the mode of administration (177). Some studies have found that patients report higher HRQoL scores when completing a PROM through telephone interview compared with mailed responses (178, 179). PROM scores may be higher because patients are more reluctant to express their quality of life difficulties to an interviewer.

Additionally, the mode of administration may influence the response rate. One study found that PROM response rates were higher when by mail (88%) or telephone (79%) compared to e-mail (33%) (180). Telephone administration has the advantages of reduced missing data and cost when compared to administering postal questionnaires (181, 182).

Response-rate is important, and studies with a high response rate have greater power and precision. A low response rate may increase the risk of bias if non-responses are associated with health status. Previous studies mailing questionnaires to surgical patients postoperatively or surveying hospitalised in-patients have found an association between non-responses and poorer health, social deprivation, substance abuse, cognitive limitations and sight deficiency; all of which may reduce a patient's perceived health outcome (183, 184). Furthermore, non-response may be associated with demographic variables such as age, gender and ethnicity, which may hamper generalisability of the findings (184, 185).

A variety of strategies can improve PRO questionnaire response rates (186). If the PROM is to be completed in the clinic, then the research staff can explain

the purpose of the PROM and clarify how to answer the questions (187). PROMs should contain straightforward instructions for use (188), postal PROMs should provide, a pre-paid, self-addressed return envelopes (189) and electronic or telephone reminders may be sent (190, 191). Where possible, the research team should minimise the number of PROMs each person is asked to complete and the time required of the person (192). Statistical methods may be used to account for lower response rates (193).

1.17.2 Patient, Clinician and Observer Responses

It is important to consider who should make assessments about a patient's subjective experiences and perceptions. Studies have found only moderate concordance between the outcomes reported by patients and clinicians (194-197). Similarly, HRQoL reports completed by observers such as carers vary from the patients (198-201). Clinicians and observers cannot predict a patient's views with certainty; thus, outcome assessment should always include patients. However, clinician reports do remain of value, particularly when evaluating more easily observable patient outcomes such as toxicity (202, 203). Likewise, observer reports such as from carers can be of value when patients are not able to express themselves. Observer reports are particularly relevant for the paediatric population and those who may be cognitively impaired. Outcome reporting from the perspective of the patient (PRO), observer (ObsRO) and clinician (ClinRO) are essential in the holistic evaluation of a patient's health status (150).

1.17.3 PROM theoretical background

A PROM will contain several items (questions) which assess a patient's subjective experience or perception. One example of an item in the EORTC QLQ-C30 questionnaire is 'have you vomited?'. The response for this item can be graded on a 4-point scale (not at all - very much) (204). This single-item provides valuable information about an aspect of vomiting. However, this single

item does not capture the severity or duration of vomiting, which may be items of interest. Therefore, multiple items can be added together to produce a multi-item vomiting scale. PROMs typically contain both single and multi-item scales. Both single and multi-item scales can be scored to quantify the response. (205)

Multi-item scales are used to measure factors (also known as latent traits). Examples of factors include physical functioning, emotional functioning and social functioning. Multiple items (such as pain, fatigue and nausea) may be combined to represent a factor (physical functioning) (205).

One or more factors can represent an overarching construct (also known as latent variables). Constructs are unobservable and theoretical concepts and can only be measured by theorising their relationship with factors. For example, HRQoL is a theoretical construct which is believed to be related to measurable factors such as physical functioning, emotional functioning and social functioning. HRQoL is multidimensional since it is a construct with multiple underlying factors. Unidimensional constructs have only one underlying factor. (205)

1.18 Quality assessment of PROM

1.18.1 Reliability

PROMs must be reliable and measure in a consistent, repeatable and reproducible manner. If a patient's HRQoL remains stable, a repeated PROM administration over time should obtain a similar score. However, each patient may display variability in their responses to individual items. Multi-item scales account for inter-respondent variation by averaging the score of multiple items within a scale (205).

Since there will be variability between respondents, there is a margin for error in responses. Reliable instruments are able to distinguish between respondents despite the presence of error (206).

Furthermore, reliable multi-item scales of PROMs should demonstrate high internal consistency. Internal consistency refers to the extent to which individual items correlate in their measurement of a factor (207). For example, patients who indicate that they strongly agree with the item 'I always feel tired' should strongly disagree with the item 'I never feel tired'. The internal consistency of a multi-item scale can be statistically measured using Cronbach's coefficient alpha (α). Cronbach's α between 0.70 and 0.95 are considered to represent satisfactory internal consistency of multi-item scales (208).

Precision is an aspect of PROM reliability and indicates the reliability of a scale to discriminate between responders. A single-item scale which asks a patient to rate their subjective importance of vomiting on a 5-point scale (not at all important, slightly important, moderately important, very important, extremely important) can discriminate between respondents better than a 2-point scale (not important and important). However, increasing response categories can sometimes lead to difficulty interpreting the difference between adjacent options. For example, it is easier for a patient to score their pain on an 11-point scale (0 - 10) than a 101-point scale (0 - 100). The difference between pain score of 9 and 10 is easier to understand than between 90 and 91. (205)

1.18.2 Validity

The validity of a PROM refers to whether it can measure what it intends to, and there are several types. Content validity refers to whether patients and clinicians consider the content (items) of a PROM to be relevant to the condition (206). A PROM designed to assess anxiety which includes items related to concentration, restlessness and irritability will show higher content validity

than a PROM which includes items related to vomiting. The former items are of greater relevance to a patient with anxiety. Face validity is a type of content validity referring to the extent to which patients and clinicians perceive that a scale is measuring what it intends to (209). Construct validity refers to how well a PROM measures the underlying construct it intends to (209). For example, a PROM designed to measure the construct anxiety will have a high construct validity if the scores obtained from it correlate with other anxiety PROMs.

1.19 Conclusion

Meningioma is a common intracranial tumour which can present with a variety of clinical features. Surgery and radiotherapy form the mainstay of therapy for symptomatic meningiomas, and both can cause morbidity for patients. For incidental meningiomas, long-term follow-up with MRI may cause anxiety for patients. The long-term survival of meningioma patients is good. Therefore, it is important to consider how meningiomas and their management affect patient-reported outcomes and quality of life. The next chapter details a systematic review performed to identify PROs and PROMs included in meningioma research to date.

Chapter 2: A systematic review of Patient-Reported Outcomes in intracranial meningiomas

2.1 Chapter overview

Patient-Reported Outcomes (PROs) and their measurement tools (PROMs) are recognised as an important asset to clinical effectiveness research, healthcare organisation and individual patient care. Over the last decade, there has been an increase in the number of studies examining the PROs of meningioma.

A majority of studies assessing PROs investigate Health-Related Quality of Life (HRQoL). However, meningioma and its treatment may have effects on domains that are not captured by HRQoL. Furthermore, HRQoL assessments cover a breadth of issues and may not evaluate particular domains (such as symptom burden, fatigue or employment) in depth. As meningioma-specific HRQoL tools are still being validated (210), current HRQoL studies may omit matters which are relevant to patients. A holistic evaluation of all PROs of meningioma is required.

This systematic review identifies all studies of meningioma patients which report PROs. The PROs of meningioma studies are summarised qualitatively. The quality of reporting and risk of bias of each study is evaluated. This chapter concludes by providing recommendations for future PRO research. To date, no study has summarised all research reporting the PROs of meningioma.

2.2 Scoping search

An umbrella review was conducted to identify all systematic reviews of meningioma. This identified two systematic reviews of HRQoL in meningioma patients published between 2015 and 2017 (146, 211). Tanti et al. reviewed four studies and concluded that epilepsy in meningioma patients has an adverse effect on quality of life (211). Zamanipoor et al. reviewed 19 studies and concluded that patients with meningioma have impaired HRQoL (146). The results of that review were used by Zamanipoor et al. to interview meningioma patients and the healthcare professionals (HCPs) involved in their care (212). The interviewers first asked the patients and HCPs to identify issues that meningioma patients experience, and then asked patients and HCPs to assess the relevance of the issues identified from both the HRQoL tools and the interview. This study concluded that the 14 included HRQoL tools contain a number of issues which are not relevant to meningioma patients, and there are additional issues which are not captured by existing tools (212). Both systematic reviews focused on HRQoL, and none examined PROs of meningioma patients in their entirety.

A scoping search on MEDLINE (Ovid) was undertaken to identify additional HRQoL studies of meningioma which were not included in previous systematic reviews. Additionally, systematic reviews examining reporting standards of PROs within neuro-oncology and other surgical specialities were identified (164, 213-215). No studies qualitatively summarising PROs were found, and this therefore justified undertaking the systematic review of the PROs of meningioma.

2.3 Research question and objectives

2.3.1 Research question

- What are the PROs reported in primary studies of adult patients with an intracranial meningioma examined before or after intervention (such as surgery, fractionated radiotherapy or stereotactic radiosurgery) or active monitoring.

2.3.2 Aims

- To identify all published studies with PROs in meningioma
- To identify the PROMs used to assess PROs
- To qualitatively summarise the current literature of PROs in meningioma
- To assess the quality of reporting and risk of bias of the identified studies
- To identify areas for future research

2.4 Methods

The review protocol was registered on PROSPERO (CRD42020191947). The systematic review has been reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (216).

2.4.1 Inclusion and exclusion criteria

Table 2.1 details the inclusion and exclusion criteria of this systematic review. The focus of this systematic review is the PROs of adults with sporadic, intracranial meningioma. Studies including spinal meningiomas were excluded as they are anatomically distinct to intracranial meningioma and have different presenting features, surgical outcomes and morbidity. Studies of neurofibromatosis type 2 (NF2)-associated meningioma and radiation-induced meningioma (RIM) were excluded as they are considered a different biological

entity to sporadic meningioma and patients often have other associated comorbidities and history of previous medical treatment. Finally, studies including other brain tumours such as glioma were excluded as the study authors wanted to identify PROM tools used specifically in the cohort of meningioma patients.

Table 2.1: A PICOS table of inclusion and exclusion criteria

	Include	Exclude
Population	• Patients aged 18 years and above	• Patients aged below 18 years • Animal studies
Intervention	• Perioperative care • Surgery • Radiotherapy • Radiosurgery • Medical therapy • Active monitoring • Combinations of the above	• N/A
Condition	• Intracranial meningioma: WHO Grade I, II or III	• Spinal meningioma • NF2-associated meningioma • RIM • Studies with mixed pathology (i.e. meningioma and other tumours)
Comparator	None	
Outcome	• PRO such as HRQoL as a primary or secondary outcome	
Study design	• Primary research • Retrospective, cross-sectional or prospective study • English language • Full text available • Studies including ten or more patients • Any year of publication	• Reviews, systematic review and meta-analysis • Studies not making clear reference within abstract to obtaining a PRO • Studies including only one PRO item (question), e.g. subjective pain rating scale • Conference abstracts

2.4.2 Article identification

2.4.2.1 Electronic database searches

Electronic databases were searched using a search string based on terms identified from two previous systematic reviews of PROs (164, 213). The search string was adapted for meningiomas, and a number of modifications were made to increase the sensitivity of the search. The final search string included a combination of free text and MeSH terms related to meningiomas, outcome assessment, PRO, quality of life, symptoms and PROM tools. The search string was adapted to the syntax requirements of each electronic database. The EMBASE search string is included in appendix 1.

Electronic databases searches were conducted between 29th April and 1st May 2020. No restriction was placed on the date of publication. However, only publications in the English language were eligible for inclusion. The following electronic databases were searched:

- PubMed
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL) via The Cochrane Library
- Cochrane Database of Systematic Reviews (CDSR) via The Cochrane Library
- CINAHL via EBSCO
- PsycInfo via EBSCO
- Allied and Complementary Medicine Database (AMED) via EBSCO

2.4.2.2 Removal of duplicates

Articles from online databases were imported into Endnote X9.3.3 and de-duplicated. De-duplicated articles were transferred onto the online systematic review management platform Rayyan (217).

2.4.2.3 Article screening

Two reviewers (SMK and CPM[1]) used Rayyan to independently screen the title and abstract of articles in accordance with the pre-determined inclusion criteria[2].

2.4.3 Full-text analysis

Full texts were obtained for articles included at the end of the screening process. These full-texts were read and evaluated against the inclusion criteria. Reasons for exclusion of articles were recorded.

2.4.4 Additional methods of study identification

The reference lists of all included articles were searched for further relevant studies. The two systematic reviews identified from the umbrella review were also screened to identify studies not identified by the search (146, 211).

2.4.5 Data extraction

Each article was read by one of three authors (SMK, CPM or AII[3]) and data were extracted and independently entered into a spreadsheet in Microsoft Excel (v16.34, Microsoft, Washington DC, USA). Table 2.2 lists the extracted data fields. The spreadsheet was not pre-piloted before data extraction started.

---

[1] Mr Christopher P. Millward
[2] See study limitations for description of an error during study screening process
[3] Dr Abdurrahman Islim

Table 2.2: A PICOS table of extracted study data	
Field	**Description**
Study details	Author, title, year of publication, study location, study type, study objective, inclusion and exclusion criteria
Population	Number of meningioma participants, participation rate, number of controls, age of meningioma participants, sex, WHO Grade, tumour location, tumour laterality, functional status, previous treatment
Intervention	Type of intervention, extent of surgical resection, dose of radiation treatment
Outcome	Name of PROM, PROM used in entirety or part, method of administration, time point of measurement, description of article PRO findings

2.4.6 Qualitative synthesis

Each included study was categorised according to the domain of PRO it reported: 'HRQoL', 'Patient-Reported Symptoms', 'Patient-Reported Functioning', 'Patient-Reported Feelings' or 'Other PROs'. These categories were chosen on the basis of previous publications categorising the domains of PRO (218-220). Since HRQoL tools incorporate Symptoms and Functioning assessment, a study was only categorised as encompassing Symptoms or Functioning if these were measured or reported separately to the HRQoL assessment. For example, a study may measure HRQoL using the SF-36 tool and Anxiety and Depression using the HADS tool. This study would be categorised as measuring both HRQoL and Symptoms. The Patient-Reported Outcome Measure (PROM) tools used in the studies were summarised. The descriptions of PROs were qualitatively summarised.

2.4.7 Quality of reporting assessment

Each article was assessed for quality of reporting according to the International Society for Quality of Life Research (ISOQOL) reporting standards (221). These standards are recommendations for high-quality PRO reporting of RCTs and were developed following a process of systematic review and consensus discussions. The ISOQOL standards have informed the development of the Consolidated Standards of Reporting Trials (CONSORT) PRO extension (222, 223). Whilst originally designed for use in randomised controlled trials (RCTs),

the ISOQOL standards have been implemented in systematic reviews which include a variety of study types (146, 224). The original ISOQOL standards contain 17 recommendations for any study which reports PROs. A further 11 recommendations are provided for studies where PRO is a primary outcome. Dirven et al. applied these standards to neuro-oncology RCTs and added four new items and split one item (164).

Therefore, the final standards used in this study contained 22 recommendations for all PRO studies and 11 additional recommendations where PRO is a primary outcome.

Each study was evaluated against the ISOQOL recommendations. As these recommendations were developed for RCTs, not all recommendations were applicable to other study types. Appendix 2 shows the ISOQOL recommendations with the modifications made by the review authors. To judge the reporting quality of studies, a total reporting score was calculated as the percentage of applicable and original ISOQOL recommendations met by the study. In line with previous systematic reviews, studies meeting 66% of recommendations were deemed as having satisfactory reporting quality (225).

2.4.8 Quality assessment

Methodological quality assessment was completed last so that the review authors would not be biased during the data extraction stage or reporting quality assessment stages. Quality assessment was completed at the study level of included articles. Quality assessment did not influence the data synthesis presented in this chapter. Since both cross-sectional and prospective cohort studies were included within this review, two different tools were used to assess the risk of bias according to study type (appendices 3 & 4). The Joanna Briggs Institute (JBI) checklist for analytical cross-sectional studies assesses the methodological quality and extent of bias (226). The JBI critical appraisal tool has been developed following an extensive peer-review process. The Newcastle-

Ottawa Scale (NOS) for cohort studies uses a 'star system' to assess the methodological quality of non-randomised studies (227). The NOS tool was created by the University of Newcastle, Australia and the University of Ottawa, Canada and is a widely used tool for measuring the risk of bias.

2.4.9 Meta-analyses

No meta-analyses were completed due to heterogeneity of the included studies. Studies varied in patient characteristics, type of intervention, PROM tool used and time point of assessment.

2.5 Results

2.5.1 Study identification

Figure 2.1 summarises the study identification process. A total of 9,898 articles were identified from searching the electronic databases. One additional article was identified from hand-searching included studies. After removing duplicates, 7,489 articles were screened, and 54 full-texts were then examined for eligibility. Thirty-three articles met the inclusion criteria for this systematic review.

2.5.2 Study and patient characteristics

Table 2.3 details the study and patient characteristics. The majority of studies were completed in European hospitals (n=23), although studies from America (n=5), Canada (2), Australia (n=2) and Brazil (1) were also identified. The number of meningioma patients included per study ranged from 14 to 1722. Six studies included a control group of participants; in the remaining studies, PRO results were compared to the normative general population, brain tumour patient data or not compared at all. The participation rate of studies ranged from 13% to 100%. The average age of meningioma patients was between 50 and 60 years for most studies (median of means= 57.2, range of means= 52.0 - 67.3).

All studies had a high proportion of female participants (median of proportion female= 76.5, range= 59.0 – 100.0).

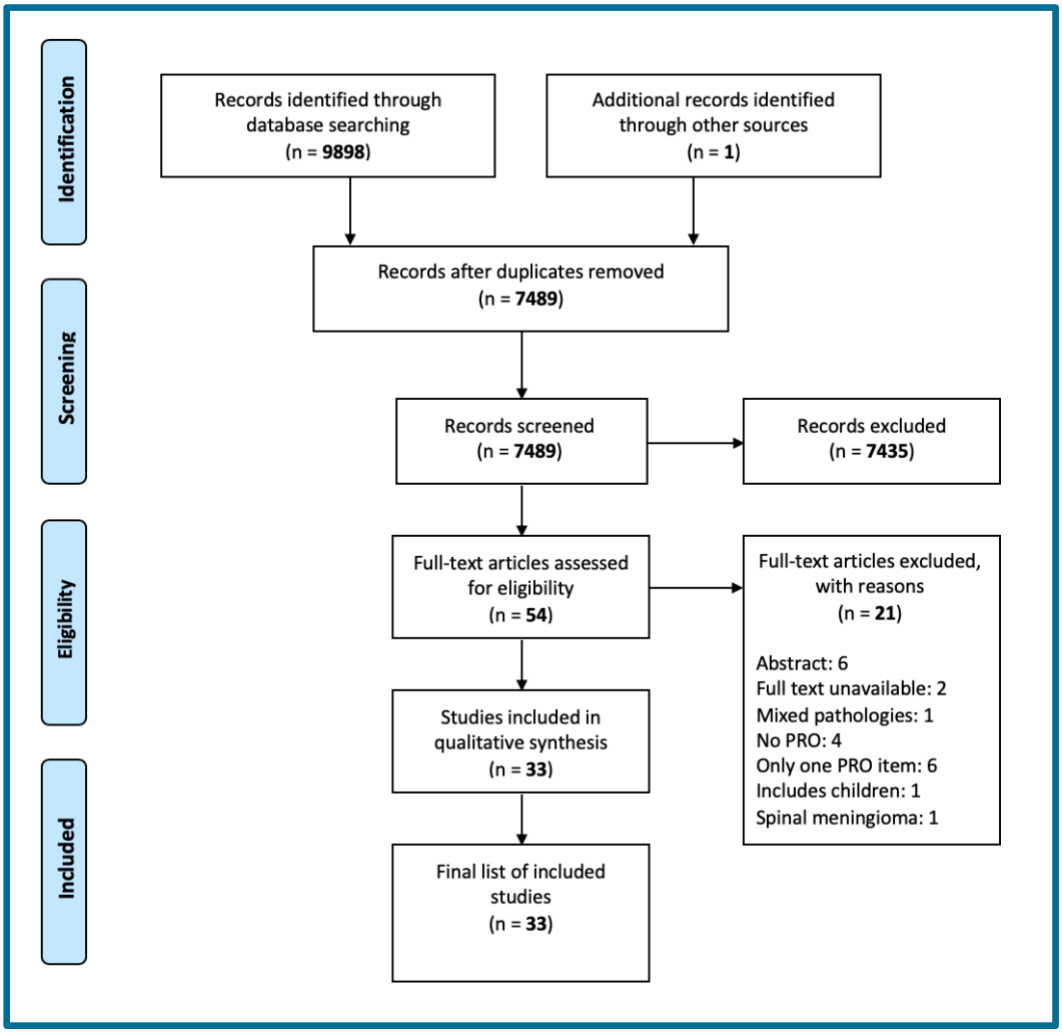


Figure 2.1: PRISMA flow diagram [4]

[4] See limitations for description of incomplete systematic review screening process

Table 2.3: Study and patient characteristics							
Author (year)	**Location**	**Patients and controls**	**Participation rate**	**Age of meningioma participants at assessment (years)**	**Sex (% female)**	**WHO Grade**	**Primary intervention**
Kangas (2012) (228)	Australia	Meningioma: 70	Unspecified	Mean: 57.2 Range 36-87.5	77	I: 100	Radiotherapy
Tanti (2017) (229)	United Kingdom	• Meningioma alone: 109 • Meningioma & epilepsy: 56 • Epilepsy without meningioma: 64	33	Mean: 59.9	81	I: 100	Surgery
Krupp (2009)(230)	Germany	Meningioma: 91	77	Mean: 56 Range: 31-75	66	I: 100	Surgery
van Nieuwenhuizen (2019)(231)	The Netherlands	Meningioma: 21 Controls: 21	75	Mean: 55.3 Range: 35-72	66	I: 100	Surgery
Kangas (2011) (232)	Australia	Meningioma: 70	85	Mean: 57.2 Range: 38-87	77	Benign meningioma: 100%	Radiotherapy
Owens (2015) (233)	United States of America	Meningioma 121	Not applicable	Median: 44 years	100	*Low grade: 60 Intermediate grade: 7 Unsure: 34	Surgery
van der Vossen (2014) (234)	The Netherlands	Meningioma: 136	76	Mean: 59.1	78	I: 86 II: 12 III: 2	Surgery

Table 2.3: Study and patient characteristics (continued)							
Author (year)	**Location**	**Patients and controls**	**Participation rate**	**Age of meningioma participants at assessment (years)**	**Sex (% female)**	**WHO Grade**	**Primary intervention**
Makarenko (2016)(235)	Canada	Meningioma: 37	70	Unspecified	74	Unspecified	Surgery
van Nieuwenhuizen (2007) (236)	The Netherlands	Meningioma: 36 Controls: 18	40	Mean: RT -ve: 63 RT +ve: 63	RT -ve: 88 RT +ve: 89	I: 100	Surgery Radiotherapy
Mathiesen (2007)(237)	Sweden	Meningioma: 16	80	Mean: 53.5 Range: 27-74	69	Unspecified	Surgery
Pintea (2018)(238)	Germany	Meningioma: 54	69	Mean: 57 Range: 31-82	78	Unspecified	Surgery
Jones (2016)(239)	United States of America	Meningioma: 34	100	Unspecified	79	Unspecified	Surgery
Jakola (2012)(240)	Norway	Meningioma: 54	Unspecified	Unspecified	67	I: 83 II: 9	Surgery
Waagemans (2011)(241)	The Netherlands	Meningioma: 89 Controls: 89	72	Mean: 58.4	74	I: 100	Surgery Radiotherapy
Timmer (2019)(242)	Germany	Meningioma: 133	52	Mean: 67.3 Range: 55-84	62	I: 82 II: 16.5 III: 1.5	Surgery
Van Nieuwenhuizen (2013)(100)	The Netherlands	Meningioma: 21 Controls: 21	75	Mean: 63.4	81	I: 100	Active monitoring
Lang (1999)(243)	United Kingdom	Meningioma: 17	100	Range: 29-63	77	Unspecified	Surgery Radiotherapy
Neil-Dwyer (2000)(244) *Related to publication by Lang et al. (above).*	United Kingdom	Meningioma: 19	100	Range: 29-63	88	Unspecified	Surgery Radiotherapy

Table 2.3: Study and patient characteristics (continued)							
Author (year)	**Location**	**Patients and controls**	**Participation rate**	**Age of meningioma participants at assessment (years)**	**Sex (% female)**	**WHO Grade**	**Primary intervention**
Konglund (2012) (245)	Norway	Meningioma: 47	87	Unspecified	Unspecified	Unspecified	Surgery SRS
Schepers (2018) (246)	The Netherlands	Meningioma: 136	76	Mean: 59.1	78	I: 86 II: 12 III: 2	Surgery Radiotherapy
Van der Linden (2020) (247)	The Netherlands	Meningioma: • Pre-op: 65 • Post-op: 53	Not applicable	Mean • Pre-op: 56.2 • Post-op: 54.8	Pre-op: 74 Post-op: 76	I: 100	Surgery
Zweckberger (2017) (248)	Germany	Meningioma: 58	100	Mean: 56.6 Range: 29-75	81	I: 100	Surgery Radiotherapy
Henzel (2013) (249)	Germany	Meningioma: 52	67	Median: 57 Range: 40-81	75	I: 78.6 II: 16.6 III: 4.8	Stereotactic radiotherapy
Benz (2017)(250)	United States of America	Meningioma: 1722 Controls: 1622	67	Mean: 57.6 Range: 20-79	72	Unspecified	Surgery Radiotherapy
Kalkanis (2000)(251)	United States of America	Meningioma: 155	95	Mean: 59.3	67	Unspecified	Surgery SRS Radiotherapy
Wagner (2019)(252)	Germany	Meningioma • Pre-op: 78 • Post-op: 71	13	Median: 60	76	I: 93 II: 6 III: 1	Surgery
Combs (2013)(253)	Germany	283	58	Unspecified	Unspecified	Unspecified	SRT Radiotherapy
Wirsching (2020)(254)	Switzerland	249	61	Unspecified	74	I: 88 II/III: 12	Surgery

Table 2.3: Study and patient characteristics (continued)							
Author (year)	**Location**	**Patients and controls**	**Participation rate**	**Age of meningioma participants at assessment (years)**	**Sex (% female)**	**WHO Grade**	**Primary intervention**
Honeybul (2001)(255)	United Kingdom	14	93	Mean: 52 Range: 32-70	80	Unspecified	Surgery
van Lonkhuizen (2019)(256)	The Netherlands	Meningioma: 242	Not applicable	Mean: 57.2 Range: 23-82	69	I: 91 II: 9	Surgery
Akagami (2002)(257)	United States of America	225	88	Unspecified	Unspecified	Unspecified	Unspecified
dos Santos (2011)(258)	Brazil	29	Not applicable	Unspecified	59	I: 100	Surgery
Nassiri (2019) (259)	Canada	291	100	Mean age: • Cohort 1: 60 • Cohort 2: 59 • Cohort 3: 59 • Cohort 4: 55	79	I: 100	Surgery

2.5.3 PRO characteristics of studies

Table 2.4 summarises the PRO assessment characteristics of the included studies. There were 24 cross-sectional and eight prospective cohort studies. HRQoL was evaluated by 25 studies. The Patient-Reported Symptom and Functioning outcomes were reported by nine and eight studies, respectively. Health Status, Patient-Reported Feelings and Other PROs were each reported by two studies. Most studies used self-administered PROMs (n=21), though some studies administered PROMs by telephone (n=6) or interview (n=4). There was heterogeneity in reporting of the time point of PRO assessments; studies provided time since surgery (n=21), others since diagnosis (n=3) and some did not specify a time point (n=10).

Table 2.4: PRO characteristics of studies					
Author (year)	**PRO domains reported**	**PRO collection tool/ interview**	**Method of PROM administration**	**Study type regarding PRO collection**	**Timepoint of assessment (meningioma patients)**
Kangas (2012) (228)	*HRQoL* *Symptoms* *Other*	• Semi-structured interview • IES-R • FACT-G • FACT-BR • POMS	Unclear	Cross-sectional	Since diagnosis: Mean: 53.4 months
Tanti (2017) (229)	*HRQoL*	• SF-36 • FACT-G • FACT-BR • LAEP	Self-administered	Cross-sectional	Postoperative: Median: 3.9 years Range: 0.8-11.5 years
Krupp (2009) (230)	*HRQoL* *Functioning*	• Structured interview • FKV • Questions on life satisfaction survey	Interview-administered	Cross-sectional	Postoperative: Mean: 15 months
van Nieuwenhuizen (2019) (231)	*HRQoL*	• SF-36	Unclear	Cross-sectional	Since histological diagnosis Mean: 1.3 years
Kangas (2011) (232)	*Symptoms* *Feelings*	• BFS • POMS • IES-R • MSPSS	Self-administered	Cross-sectional	Since diagnosis (mean) • Early group: 11.3 months • Late group: 79.9 months
Owens (2015) (233)	*Feelings*	• Study-specific survey	Self-administered	Cross-sectional	Unspecified

Table 2.4: PRO characteristics of studies (continued)					
Author (year)	**PRO domains reported**	**PRO collection tool/ interview**	**Method of PROM administration**	**Study type regarding PRO collection**	**Timepoint of assessment (meningioma patients)**
van der Vossen (2014) (234)	*Symptoms* *Functioning*	• CFQ • HADS	Self-administered	Cross-sectional	Postoperative: Mean: 32.6 months
Makarenko (2016) (235)	*HRQoL*	• SF-36	Unclear	Prospective cohort	Pre- and postoperative assessment (time-point unspecified)
van Nieuwenhuizen (2007) (236)	*HRQoL*	• SF-36 • BCM-20	Self-administered	Cross-sectional	Mean time since diagnosis • RT -ve group: 3.0 years • RT +ve group: 7.6 years
Mathiesen (2007) (237)	*HRQoL*	• SF-36	Unclear	Cross-sectional	Postoperative assessment (time-point unspecified)
Pintea (2018) (238)	*HRQoL*	• SF-36	Self-administered	Cross-sectional	Follow-up 59 months
Jones (2016) (239)	*HRQoL*	• ASBQ • SNOT-22	Self-administered	Cross-sectional & Prospective cohort for a subsample	Postoperative: Median: 2 years Range: 0.5-10 years
Jakola (2012) (240)	*Health Status*	• EQ-5D	• Preoperative: self-administered • Postoperative: telephone-administered	Prospective cohort	• Preoperative: 1-3 days before surgery • Early assessment: median 47 days postoperatively • Late assessment: median 33 months postoperatively

Table 2.4: PRO characteristics of studies (continued)					
Author (year)	**PRO domains reported**	**PRO collection tool/ interview**	**Method of PROM administration**	**Study type regarding PRO collection**	**Timepoint of assessment (meningioma patients)**
Waagemans (2011) (241)	*HRQoL*	• SF-36	Self-administered	Cross-sectional	Mean • From diagnosis: 4.2 years • From last-treatment: 3.4 years
Timmer (2019) (242)	*HRQoL* *Functioning*	• SF-36 • IADL	Telephone administered	Cross-sectional	Postoperative: Mean: 3.8 years
Van Nieuwenhuizen (2013) (100)	*HRQoL*	• SF-36	Self-administered	Cross-sectional	Unspecified
Lang (1999)(243)	*HRQoL*	• SF-36	Self-administered	Cross-sectional	One year postoperatively
Neil-Dwyer (2000)(244) *Related to publication by Lang et al. (above).*	*HRQoL*	• SF-36	Self-administered	Cross-sectional	Postoperatively (time-point unspecified)
Konglund (2012) (245)	*HRQoL* *Symptoms*	• EORTC QLQ-C30 • EORTC BN20 • HADS	Unclear	Cross-sectional	Six months postoperatively
Schepers (2018) (246)	*Functioning*	• USER-P • CFQ • HADS	Self-administered	Cross-sectional	Postoperative: Mean: 32.6 months
Van der Linden (2020) (247)	*Symptoms*	• MFI • HADS • CFQ	Interview-administered	Prospective cohort	• One day preoperatively • One year postoperatively

Table 2.4: PRO characteristics of studies (continued)					
Author (year)	**PRO domains reported**	**PRO collection tool/ interview**	**Method of PROM administration**	**Study type regarding PRO collection**	**Timepoint of assessment (meningioma patients)**
Zweckberger (2017) (248)	*HRQoL* *Symptoms*	• EORTC QLQ-C30 • HADS	Self-administered	Prospective cohort	• One day preoperatively • 3-5 months postoperatively • 9-12 months postoperatively
Henzel (2013) (249)	*HRQoL*	• SF-36	Self-administered	Prospective cohort	• Before initiation of SRT • At the last day of SRT • 6, 12, 18 and 24 months post-treatment
Benz (2017) (250)	*HRQoL*	• SF-36	Telephone-administered	Cross-sectional	Postoperative: Median: 0.53 years
Kalkanis (2000) (251)	*HRQoL* *Functioning*	• FACT-BR	Telephone-administered	Cross-sectional	Postoperative: Mean: 4.26 years
Wagner (2019) (252)	*HRQoL* *Health Status* *Symptoms*	• ADS • STAI-T & STAI-S • PTSS-10 • ASI-3 5 • EQ-5L • SF-36	Self-administered Telephone-administered	Prospective cohort	• Preoperatively • 3 & 12 months postoperatively
Combs (2013) (253)	*HRQoL*	• Study-specific questionnaire	Self-administered	Cross-sectional	Unspecified

Table 2.4: PRO characteristics of studies (continued)					
Author (year)	**PRO domains reported**	**PRO collection tool/ interview**	**Method of PROM administration**	**Study type regarding PRO collection**	**Timepoint of assessment (meningioma patients)**
Wirsching (2020) (254)	*HRQoL* *Functioning* *Symptoms* *Other*	• EPICES • EORTC QLQ-C30 • EORTC BN20 • MDASI-BT	Self-administered	Cross-sectional	Unspecified
Honeybul (2001) (255)	*HRQoL*	• SF-36	Self-administered	Cross-sectional	Unspecified
van Lonkhuizen (2019) (256)	*Functioning*	• CFQ • HADS	Self-administered	Prospective cohort	• One day preoperatively • Three months postoperatively • 12 months postoperatively
Akagami (2002) (257)	*Functioning* *Symptoms* *Other*	• Study-specific questionnaire	Self-administered Telephone administered	Cross-sectional	Postoperatively (time point unspecified)
dos Santos (2011) (258)	*HRQoL*	• NHP • IHD-NS	Interview-administered	Prospective cohort	• Preoperatively • Three months postoperatively • Six months postoperatively 12 months postoperatively
Nassiri (2019) (259)	*HRQoL*	• EORTC QLQ-C30	Interview-administered	Cross-sectional	Postoperatively (multiple time points)

2.5.4 Patient-Reported Outcome Measures

Table 2.5 describes all PROMs identified in meningioma studies (n=27) (excluding measures developed by the study authors themselves, e.g. the PROM used by Owens et al. (233)). In total, ten generic or disease-specific HRQoL PROMs were found to have been used across the studies. The SF-36 was most commonly used HRQoL PROM (n=15). Two brain cancer-specific HRQoL tools (EORTC BCM20/BN20 and FACT-BR) were used in three studies each. An additional brain cancer and location-specific questionnaire (ASBQ) was used in one study. No meningioma-specific tool has been used in any study to date.

Ten Symptom PROMs were identified, of which seven assessed emotional symptoms. HADS was the most frequently used Symptom PROM (n=6). Three tools were Functioning PROMs, of which the CFQ was most used (n=4). The only Health Status PROM identified was EQ-5D. BFS was the only Feelings PROM. Three tools (Freiburg Questionnaire on Coping with Illness, MSPSS, EPICES) could not be categorised as HRQoL, Symptom, Function, Health Status or Feeling PROMs and were identified as Other.

Table 2.5: Summary of PRO tools used in meningioma studies			
PROM	**PRO domain and subdomain**	**Description**	**# studies using this PROM (n)**
Medical Outcomes Study Short Form Health Survey-36 (MOS SF-36) (260)	*HRQoL* • Generic	Subscales: 8 • *Physical Activities, Social Activities, Role- Physical*, *Role-Emotional, Bodily Pain, Vitality* (energy and fatigue), *General Health* perceptions, *General Mental Health* • Subscales added to form *Physical Component Score (PCS)* and *Mental Component Score (MCS)* Items: 36	15
Nottingham Health Profile (NHP) (261)	*HRQoL* • Generic	Domains: 6 • Part I: Pain, Physical Mobility, Emotional Reactions, Energy, Social Isolation, Sleep. • Part II: additional questions related to daily living Items: 45 (Part 1 [38] & 2 [7])	1
Questions on life satisfaction survey/ Fragebogen zur Lebenszufriedenheit (FLZ)	*HRQoL* • Generic	Domains: • *Health*, *Income/ Financial Security*, *Leisure Time/Hobbies*, *Physical Condition/Fitness*, *Sexuality*, *Friends/Acquaintances*, *Housing/Living Conditions*, *Occupation/*Work, *Marriage*, *Family Life/Children* Items: 70	1
The Functional Assessment of Cancer Therapy Scale-General version (FACT-G) (262)	*HRQoL* • Cancer-specific	Subscales: 4 • *Physical*, *Functional*, *Social*, and *Emotional wellbeing* Other: Satisfaction with treatment Items: 27	2 (without FACT-BR)
EORTC Quality of Life Questionnaire Cancer 30 (QLQ C30) (204, 263)	*HRQoL* • Cancer-specific	Subscales: 10 • Function (*Physical*, *Role*, *Cognitive*, *Emotional* and *Social*), Symptom (*Fatigue*, *Pain*, *Nausea and Vomiting*), *Global Health*, *Quality of Life* Additional single items Items: 30	4

Table 2.5: Summary of PRO tools used in meningioma studies (continued)			
PROM	**PRO domain and subdomain**	**Description**	**# studies using this PROM (n)**
The Functional Assessment of Cancer Therapy Scale- brain subscale (FACT-BR) (264)	*HRQoL* • Brain cancer-specific	Subscale: 1 • Subscale is specific for patients with a brain tumour. When combined with FACT-G, it is known as FACT-BR. Items: 23	3
EORTC Brain Cancer Module (BCM20/BN20) (265)	*HRQoL* • Brain cancer-specific	Subscales: 4 • *Future Uncertainty*, *Visual Disorder*, *Motor Dysfunction*, *Communication Deficit* Additional single items: 7 Items: 20	3
Anterior Skull Base Questionnaire (ASBQ) (266)	*HRQoL* • Cancer-specific • Location-specific	Domains: • *Performance*, *Physical Function*, *Vitality*, *Pain*, *Influence on Emotions*, *Specific Symptoms* Items: 35	1
Sinonasal Outcome Test 22 (SNOT-22) (267, 268)	*HRQoL* • Disease-specific: Chronic Rhinosinusitis	Domains: • *Physical Problems*, *Functional Limitations*, *Emotional Consequences* Items: 22	1
Innsbruck Health Dimensions Questionnaire for Neurosurgical Patients (IHD-NS)(269)	*HRQoL* • Neurosurgery-specific	Domains • *Communication*, *Physical Condition*, *Autonomic Function*, *Independence*, *Psychological Condition*, *Social Isolation* Items: 38	1
EuroQoL 5 Dimensions (EQ-5D) (270)	*Health status* • Generic	Versions: • EQ-5D-3L: previous version: 3 Levels of severity assessment • EQ-5D-5L: new version: 5 Levels of severity assessment Domains: 5 • *Mobility*, *Self-Care*, *Usual Activities*, *Pain/Discomfort*, *Anxiety/Depression* • *Visual Analogue Scale* Items: EQ-5D-3L (15), EQ-5D-5L (25)	2

Table 2.5: Summary of PRO tools used in meningioma studies (continued)			
PROM	**PRO domain and subdomain**	**Description**	**# studies using this PROM (n)**
Hospital Anxiety and Depression Scale (HADS) (271)	*Symptoms* • Emotions	Subscales: 2 • *Anxiety*, *Depression* Items: 14	6
Impact of Event Scale-Revised (IES-R) (272)	*Symptoms* • Emotions	Subscales: 3 • *Intrusions* (repeated thought about traumatic experience), *Avoidance* (avoiding situations which remind the individual of traumatic experience), *Hyperarousal* Items: 22 (273)	2
Profile of Mood States (POMS) (274)	*Symptoms* • Emotions	Subscales: 6 • *Tension-Anxiety*, *Depression-Dejection*, *Anger-Hostility, Vigor, Fatigue, Confusion-Bewilderment* Items: 65 (228)	2
General Depression Scale/ Allgemeine Depressions Skala (ADS) (275)	*Symptoms* • Emotions	This is a modified version of the Centre for Epidemiological Studies - Depression (CES-D) Scale Items: 20	1
The State-Trait Anxiety Inventory (STAI)	*Symptoms* • Emotions	Subscales: • Trait Anxiety (STAI-T), State Anxiety (STAI-S) Items: 40 (20 items in STAI-T and STAI-S each)	1
Post-Traumatic Stress Syndrome 10-Questions Inventory (PTSS-10)	*Symptoms* • Emotions	Assesses: Post-Traumatic Stress Syndrome Items: 10	1
Anxiety Sensitivity Index 3 (ASI-3) (276)	*Symptoms* • Emotions	Domains: • Physical, Cognitive, Social Concerns Items: 18	1

Table 2.5: Summary of PRO tools used in meningioma studies (continued)			
PROM	**PRO domain and subdomain**	**Description**	**# studies using this PROM (n)**
M.D. Anderson Symptom Inventory- Brain Tumor Module (MDASI-BT) (277)	*Symptoms* Symptom burden	This brain tumour module is combined with core items from MDASI tool to make then MDASI-BT Domains: • *Generalized Neurologic Symptoms*, *Focal Neurologic Symptoms*, *Treatment-related Symptoms.* Items: 13 core items, 18 additional brain-tumor specific items	1
Multi-dimensional Fatigue Inventory (MFI) (278)	*Symptoms* • Fatigue	Subscales: 5 • *General Fatigue*, *Physical Fatigue*, *Mental Fatigue*, *Reduced Motivation, Reduced Activity* Items: 20	1
The Liverpool Adverse Events Profile (LAEP) (279)	*Symptoms* • Toxicity from AEDs	Subscale: 1 • Symptom checklist common side-effects of anti-epileptic drugs Items: 19	1
Cognitive Failures Questionnaire (CFQ) (280)	*Functioning* • Subjective Cognitive Functioning	Domains: • *Perception*, *Memory*, *Motor Functioning* Items: 25	4
Instrumental of Activities of Daily Living (IADL) (281)	*Functioning* • Activities of Daily Living	Domains: 8 • *Telephoning*, *Shopping*, *Food Preparation*, *Housekeeping*, *Laundering*, *Use of Transportation*, *Use of Medicine*, *Financial Behaviour* Items: 8	1
Utrecht Scale Evaluation Rehabilitation-Participation (USER-P) (282)	*Functioning* • Participation	Subscales: 3 • *Frequency*, *Restrictions*, *Satisfaction* Items: 31	1

Table 2.5: Summary of PRO tools used in meningioma studies (continued)			
PROM	**PRO domain and subdomain**	**Description**	**# studies using this PROM (n)**
Benefit Finding Scale (BFS) (283, 284)	*Feelings* • Benefit finding	Domains: • *accepting life circumstances*, awa*reness of the role of others in life*, *developing a sense of purpose* Items: 17	1
Freiburg Questionnaire on Coping with Illness (FKV)	*Other* • Coping	Subscales: 5 • Depressive Coping, Active Problem-Oriented Coping, Distractions, Spirituality, Minimizing Importance Items: 35	1
The Multidimensional Scale of Perceived Social Support (MSPSS) (285)	*Other* • Support	Domains: • Support from *Significant Other*, *Friends*, *Family* Items: 12	1
Evaluation of Deprivation and Inequalities in Health Examination Centres (EPICES) (286)	*Other* • Deprivation	Domains • Marital Status, Health Insurance Status, Economic Status, Family Support, Leisure Activity Items: 11	1

2.5.5 HRQoL

2.5.5.1 Surgery: prospective assessment

Four studies provided a longitudinal assessment of HRQoL in patients with surgically treated meningioma (235, 248, 252, 258). All four studies reported some improvement in HRQoL postoperatively. This improvement was identified by studies using the EORTC QLQ-C30 (total score), SF-36 (Mental Component Score - MCS) and NHP (pain, emotional reaction, sleepiness, physical abilities) and IHD-NS (communication, physical condition, independence, psychological). However, one study found increased SF-36 MCS scores but decreased SF-36 Physical Component Score (PCS) upon follow-up of 71 patients (252). Furthermore, in a study comparing outcomes of 37 patients with 'simple' or 'complex' skull base tumours, patients with complex skull base tumours had reduced SF-36 total scores postoperatively but the 'simple' tumour group improved (235). One study included an analysis of a subset of patients who had completed both preoperative and postoperative HRQoL assessments following endoscopic endonasal resection and found that ASBQ scores remained stable (239).

2.5.5.2 Early postoperative HRQoL outcomes

Five cross-sectional studies assessed HRQoL in meningioma patients on average within two years of surgery (median of mean= 1.125 years, range of mean= 0.5 - 1.3 years) (230, 231, 243, 245, 250). One study evaluated HRQoL six months postoperatively using the EORTC QLQ-C30 (245). Meningioma patients reported significantly lower Functional domain scores compared to normative values, yet *Symptom* domain scores were not different. Another study assessed HRQoL one year postoperatively using SF-36; meningioma patients reported significantly lower SF-36 scores in all domains except Body Pain in comparison to healthy controls (250). Patients had clinically significant lower scores in the domains of Vitality, Physical Functioning, Social

Functioning, Role Emotional and Role Physical. Furthermore, a different study assessed HRQOL one year after histological diagnosis in 21 patients with WHO Grade I meningioma and found no significant differences between scores of meningioma patients and healthy controls (231).

2.5.5.3 Late postoperative HRQoL outcomes

Eight studies assessed HRQoL in meningioma patients on average two years or more after surgery (median of mean= 4.2 years, range of mean= 3.8 – 4.3 years)(229, 236, 238-242, 251). One study of 165 patients used SF-36, FACT-G and FACT-BR at a median time of 3.9 years postoperatively (229). Meningioma patients had worse SF-36 MCS summary scores compared to normative values. In another study using SF-36 at a mean time of 3.4 years since last treatment meningioma patients scored similar to healthy controls in all domains but reported worse scores in the domain of Role Physical (241). In a study of skull base meningiomas (petroclival and posterior petrous) using SF-36; patients had significantly reduced values of Physical Functioning, Role Physical, General Health, Vitality and Social Functioning scores in comparison to normative values (238). In a large study of 291 patients assessed cross-sectionally with EORTC QLQ-C30 at different timepoints, overall HRQoL was impaired at 12, 48, 108, and 120 months postoperatively compared to normative values (259). By contrast, in a study of 133 patient 3.8 years postoperatively, similar scores were identified between patients and the normative values of SF-36, with improved patient scores reported in domains of Physical Role Functioning and Bodily Pain (242).

2.5.5.4 Postoperative variables associated with HRQoL

One study reported that age had no association with HRQoL scores (248). However, another study assessing HRQoL following endonasal endoscopic resection of skull base meningiomas found that younger patients reported better ASBQ and SNOT-22 scores (239). In a study specifically assessing HRQoL

in elderly patients, younger patients generally reported higher SF-36 scores which decreased with age (242). By contrast, a study which assessed HRQoL by qualitative interview found that younger patients were more likely to report lower self-esteem, inability to accept disease, and dissatisfaction with life (230). Another study reported that younger patients were more likely to give a negative response to the question '*are you content with quality of life right now?*' (251).

Meningioma patients with epilepsy report worse HRQoL outcomes (229). Two studies report that patients taking anti-epileptic drugs (AEDs) have inferior HRQoL irrespective of seizure frequency (229, 241). Unemployment, lower subjective work ability, impaired cognitive functioning and elevated depression and PTSS scores are also associated with inferior HRQoL outcome (228, 229, 241, 254). No association has been identified between HRQoL and tumour size, preoperative tumour volume or preoperative presence of peri-tumoural oedema (231, 248).

2.5.5.5 Stereotactic radiotherapy (SRT)

Three studies reported HRQoL outcomes in patients who received stereotactic radiotherapy (SRT) (249, 251, 253). Two of these studies give outcomes of SRT and radiotherapy combined (251, 253). One study prospectively evaluated HRQoL using SF-36 in 52 patients undergoing SRT (249). Pre-treatment HRQoL scores were lower in all eight domains of SF-36 compared to normative values. At the end of SRT, HRQoL scores decreased further in six domains, most prominently in the domains Role Physical, Role Emotional, and Pain. At six months post-treatment HRQoL scores improved, and at 12 months post-treatment HRQoL began to return to initial values. Patients who had prior surgery had significantly improved MCS scores compared to patients with primary SRT.

2.5.5.6 Fractionated radiotherapy

Five studies provided HRQoL outcomes in patients who received fractionated radiotherapy (228, 236, 250, 251, 253). In a study of 1722 patients assessed by SF-36 0.53 years postoperatively, HRQoL scores were lower in the domains of Vitality, Role Physical and Social Functioning for patients who received radiotherapy compared to patients who had surgery only (250). However, in a study assessing late HRQoL outcomes in 36 patients, no significant differences were identified between SF-36 and EORTC BCM20 scores in patients treated with adjuvant radiotherapy compared with surgery only (236).

2.5.5.7 Incidental meningiomas

One study investigated HRQoL outcomes of incidental meningioma (100). The 21 included patients reported significantly lower scores on the SF-36 domains of General Health and Vitality compared to healthy controls.

2.5.6 Health status

Two studies report Health Status of patients; both were prospective and used the EQ-5D tool (240, 252). In a study evaluating health status changes from preoperatively to one year postoperatively, the EQ-5D-5L remained stable (252). Anxiety, depression and PTSS scores negatively correlated with EQ-5D-5L values. Anxiety, depression and PTSS scores negatively correlated with EQ-5D-5L values. In a study of 54 patients, clinically meaningful improvement occurred in 49% and worsening in 20% of patients at late assessment. The domains of EQ-5D which improved were pain/discomfort, anxiety/depression, usual activity.

2.5.7 Symptoms

2.5.7.1 Symptom burden

Symptom burden was reported specifically as an outcome by two studies (254, 257). One study used MDASI-BT to compare symptom burden preoperatively and one year postoperatively of 249 patients (254). Improvement was identified in the domains of Total Symptom Severity, General Symptoms, Focal Neurological Symptoms, GI Symptoms, Affective Symptoms, Symptom Interference with Mood, Symptom Interference with Activity and Symptom Interference with Daily Function. However, no MDASI-BT subdomain showed clinically meaningful improvement. There was postoperative worsening of the Cognitive Symptom domain, but this was not significant. Akagami et al. assessed symptom severity postoperatively in patients with skull base meningioma and found the prevalence of no, minor, some and severe symptoms to be 32, 34, 30 and 4% respectively (257).

2.5.7.2 Emotional symptoms

Emotional symptoms were specifically reported by six studies (228, 232, 234, 245, 248, 252). In a study assessing psychological wellbeing of 78 meningioma patients, 68% of patients had abnormal anxiety scores preoperatively. Abnormal anxiety decreased to 57% at three months and 39% at 12 months postoperatively (252). Another study showed that six months postoperatively anxiety and depression scores were not significantly different from normative values (245). Two studies identified that anxiety is significantly higher early after surgery compared to late (228, 252). However, one study showed that anxiety scores remain stable (248).

Patient-reported depression scores are similar to normative values at six months postoperatively (245). Two cohort studies report that depression scores remain stable upon follow-up (248, 252). One study reported depression scores

were higher early after surgery compared to late, but this difference was not significant (232). Variables associated with higher depression scores include unemployment due to health problems, presence of epilepsy and lower Karnofsky Performance Status (KPS) scores (234, 245).

Three studies reported on emotional symptoms other than anxiety and depression (228, 232, 252). One study identified that post-traumatic stress syndrome (PTSS) scores significantly decreases between preoperative and postoperative assessment (252). However, meningioma associated PTSS is still reported by 16% of patients on longer-term follow-up (228). This group of patients were increasingly likely to seek support services due to feeling of distress or fear of tumour progression and recurrence. Furthermore, meningioma patients reported significantly higher anger/hostility scores on early assessment compared to late postoperatively (232).

2.5.7.3 Fatigue

One study specifically assessed patient's fatigue using MFI preoperatively and one year postoperatively (247). High fatigue scores in one or more subscales were reported by 68% preoperatively and 57% postoperatively. Compared to normative values, meningioma patients reported significantly higher fatigue scores in all domains (General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Activity, Reduced Motivation) both preoperatively and postoperatively. One year postoperatively, General Fatigue, Physical Fatigue and Mental Fatigue scores remained unchanged, but improvements occurred in the domains of Reduced Activity and Reduced Motivation. Fatigue was significantly associated with self-reported anxiety, depression and subjective cognitive complaints.

2.5.7.4 Toxicity from AEDs

One study assessed symptoms of AED toxicity using LAEP (229). Meningioma patient's with epilepsy had higher toxicity from AEDs and the presence of 'shaky hands'.

2.5.8 Functioning

2.5.8.1 Subjective cognitive functioning

Subjective cognitive functioning (SCF) was reported by three studies (230, 234, 256). In a study of 136 patients assessing using CFQ at a mean time of 32.6 months postoperatively, 23% reported subjective cognitive complaints (234). However, SCF was identified as similar or marginally better in meningioma patients compared to normative values. Similarly, in a study of 242 patients assessed prospectively, SCF was significantly higher preoperatively and three months postoperatively compared to normative values (256). However, SCF significantly decreased one year postoperatively and became similar to the normative group.

Factors influencing SCF include country of birth, anxiety and depression or burn out in medical history (234, 256). SCF was not associated with objective cognitive functioning assessment scores, sociodemographic or clinical characteristics (256).

Another study assessed patient perceptions of cognition using qualitative interview (230). This study identified that older meningioma patients considered cognitive deficit a general problem of ageing. However, younger patients were more doubtful of their cognitive functioning than older patients. These doubts caused patients to feel mentally disabled and socially isolated; some reported that they had retreated from their social life.

2.5.8.2 Employment

Five studies discuss the employment outcomes of patients with meningioma (230, 246, 251, 254, 257). In a cross-sectional study of 136 patients, 32.9% of those in work preoperatively did not resume paid employment postoperatively (246). Similarly, in a study specifically assessing socioeconomic outcomes of 249 patients, 20% of participants did not resume work one year postoperatively; 10% had retired due to age, 5% were unemployed and 5% were disabled (254). Significantly fewer patients were employed full-time postoperatively compared to preoperatively. Three other studies report postoperative impaired work ability affecting 17-19% of participants (230, 251, 257).

2.5.8.3 Participation

Five studies comment on participation in activities by patients with meningioma (230, 242, 246, 251, 257), with up to 51% of patients reporting participation restrictions (246). Restrictions were most frequently reported in the items 'household duties' (41.5%), 'paid work, unpaid work and education' (41.1%) and 'sports or other physical exercise' (40.4%). Dissatisfaction with participation was most frequently reported in the items 'sports or other physical exercise' (43.4%), 'going out' (41.0%) and 'day trips and other outdoor activities' (36.8%). Anxiety or depression were related to inferior participation scores on all three scales.

By contrast, another study reported that 87% of patients consider themselves 'quite a bit' or 'very much' independent (251). Furthermore, a study of 225 skull base meningioma patients found that 83% of patients can complete activities either 'normally' or 'with effort' (257). In a study of 133 patients, 85% scored 7 or 8 on the self-reported IADLs scale (242).

2.5.9 Feelings

2.5.9.1 Benefit finding

Benefit finding (BF) was assessed in a cross-sectional study of 70 patients with benign meningioma (232). BF was defined as 'positive changes that result from a trauma experience'. Moderate BF (total BFS score >2) was reported by 63% of participants. The items 'having had a meningioma (brain tumor) has taught me how to adjust to things I cannot change' and '… helped me to take things as they come' were scored as 'quite a bit' or 'extremely' by 61% of patients. Elevated depression scores were significantly associated with greater benefit finding in patients diagnosed with meningioma for two years or less.

2.5.9.2 Birth desires

One study reported on birth desires of female meningioma patients living in America (233). Patients in the age group 25-44 were significantly more likely to indicate that they would like to have a baby compared to normative values of women. Factors which influenced birth desires in patients aged 25-44 include 'risk of meningioma returning & need for more treatment' (62%), 'risk of lasting symptoms or impairments' (44%), 'fear of dying' (34%), 'medical advice against getting pregnant' (31%).

2.5.10 Other PROs

2.5.10.1 Support

Patient-reported support requirements are described by three studies (228, 254, 257). In one study, support services were sought by 67% of patients following the diagnosis of meningioma (228). Another study found that 10% more patients required professional care following surgery (254). In a study of skull base meningioma patients, occasional assistance was required by 20% of patients and considerable assistance or specialist care by 5% (257).

2.5.10.2 Deprivation

One study retrospectively assessed deprivation before surgery and at one year postoperatively by using the EPICES tool (254). Social deprivation was not found to change significantly from preoperatively to one year postoperatively.

2.5.11 PRO reporting across studies

2.5.11.1 ISOQOL core recommendations

Table 2.6 describes adherence to ISOQOL core recommendations across all of the included studies (n=33). All studies identified PRO within the abstract (n= 33, 100%). Most specified the mode of PROM administration (n=26, 79%), identified PRO as a primary or secondary outcome (n=29, 88%) and provided baseline participant characteristics and PROs (n=31, 94%). The majority of studies did not provide a rationale for the choice of PRO instrument (n= 21, 64%) or report the clinical significance of PRO findings (n= 24, 73%).

2.5.11.2 ISOQOL additional recommendations

Table 2.7 describes adherence to ISOQOL additional recommendations across all of the studies in which PRO was a primary outcome (n=27). Most studies summarised the PRO research relevant to the study (n= 26, 96%) and provided results for all domains of PROM (n= 26, 96%). The majority of studies did not make clear reference to PRO in the study title (n= 25, 93%) or specify and justify windows for valid PRO responses (n= 19, 70%).

2.5.11.3 Total score

In studies where PRO was a primary outcome (n=27), the mean ISOQOL reporting score was 73% (range 28-89%). The number of studies with satisfactory reporting quality (total ISOQOL score >66%) was 24 (89%).

In studies where PRO was a secondary outcome (n=6), the mean ISOQOL reporting score was 54% (range 36%-80%). The number of studies with satisfactory reporting quality was 2 (33%).

Table 2.6: The level of Patient-Reported Outcome (PRO) reporting in included studies		
ISOQOL core recommendations for all studies reporting PRO	**Option**	**Total: 33 n (%)**
Title and abstract		
1. The PRO should be identified as an outcome in the abstract	Yes	33 (100)
	No	0 (0)
Introduction, background and objectives		
2. The PRO hypothesis should be stated and should specify the relevant PRO domain(s) if applicable	Yes	6 (18)
	No	0 (0)
	N/A	27 (82)
Methods		
3. The mode of administration of the PRO tool and the methods of collecting data (e.g., telephone, other) should be described	Yes	26 (79)
	No	7 (21)
4. Electronic modes of distribution? [a]	Yes	1 (3)
	No	32 (97)
5. The rationale for choice of the PRO instrument used should be provided	Yes	11 (33)
	No	21 (64)
	N/A	1 (3)
6. Evidence of PRO instrument validity and reliability should be provided or cited	Yes	21 (64)
	No	10 (30)
	N/A	2 (6)
7. The intended HRQL data collection schedule should be provided	Yes	9 (27)
	No	2 (6)
	N/A	22 (67)
8. PROs should be identified in the trial protocol; post hoc analyses should be identified	Yes	9 (27)
	No	0 (0)
	N/A	24 (73)
9. The status of PRO as either a primary or secondary outcome should be stated [c]	Yes	29 (88)
	No	4 (12)
10. There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested	Yes	8 (24)
	No	0 (0)
	N/A	25 (76)
11. Extent of missing data should be stated [b, c]	Yes	25 (76)
	No	8 (24)
12. Statistical approaches for dealing with missing data should be explicitly stated [b]	Yes	3 (9)
	N/A	30 (91)
Results		
13. A flow diagram or a description of the allocation of participants and those lost to follow-up should be provided for PROs specifically	Yes	5 (15)
	No	3 (9)
	N/A	25 (76)
14. The reasons for missing data should be explained	Yes	20 (61)
	No	6 (18)
	N/A	7 (21)
15. The study patients' characteristics should be described, including baseline PRO scores.	Yes	31 (94)
	No	2 (6)
16. Are PRO outcomes also reported in a graphical format? [a]	Yes	12 (36)
	No	21 (64)
17. The limitations of the PRO components of the trial should be explicitly discussed	Yes	26 (79)
	No	7 (21)

18. Generalizability issues uniquely related to the PRO results should be discussed, if applicable	Yes	16 (49)
	No	9 (27)
	N/A	8 (24)
19. Are PRO interpreted? (not only restated) [a]	Yes	31 (94)
	No	2 (6)

Table 2.6: The level of Patient-Reported Outcome (PRO) reporting in included studies (continued)		
ISOQOL core recommendations for all studies reporting PRO	**Option**	**Total: 33 n (%)**
Discussion		
20. The clinical significance of the PRO findings should be discussed [d]	Yes	8 (24)
	No	24 (73)
	N/A	1 (3)
21. Methodology used to assess clinical significance (in case this was addressed) [a]	Distribution	7 (21)
	Anchor	1 (3)
	N/A	25 (76)
22. The PRO results should be discussed in the context of the other clinical trial (study) outcomes	Yes	13 (39)
	No	0 (0)
	N/A	20 (61)

[a] These items are not part of original ISOQOL recommended standards (221) but were added by Dirven et al. (164) to provide a wider outlook on the level of reporting. These do not form part of the final reporting score. [b] These items were originally combined in the ISOQOL recommended standards (221) but were split by Dirven et al. (164) to better investigate possible discrepancies between documentation of PRO missing data. [c] These items have been misapplied in the ISOQOL assessment of studies – please see limitations. [d] Any description of clinical significance (statistically calculated or qualitatively summarised) was considered acceptable.

Table 2.6: The level of Patient-Reported Outcome (PRO) reporting in included studies		
ISOQOL additional recommendations for all studies where PRO is primary outcome	**Option**	**Total: 27 n (%)**
Title and abstract		
1. The title of the paper should be explicit as to the RCT including a PRO	Yes	2 (7)
	No	25 (93)
Introduction, background and objectives		
2. The introduction should contain a summary of PRO research that is relevant to the RCT	Yes	26 (96)
	No	1 (4)
3. Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment	Yes	6 (22)
	N/A	21 (78)
Methods		
4. A citation for the original development of the PRO instrument should be provided	Yes	15 (56)
	No	10 (37)
	N/A	2 (7)
5. Windows for valid PRO responses should be specified and justified as being appropriate for the clinical context	Yes	8 (30)
	No	19 (70)
6. There should be a power/sample size calculation relevant to the PRO based on a clinical rationale (e.g., anticipated effect size)	N/A	27 (100)
7. The manner in which multiple comparisons have been addressed should be provided	Yes	5 (19)
	N/A	22 (81)
Results		
8. The analysis of PRO data should account for survival differences between treatment groups if relevant	N/A	27 (100)

Table 2.7: The level of Patient-Reported Outcome (PRO) reporting in included studies (continued)		
ISOQOL additional recommendations for all studies where PRO is primary outcome	**Option**	**Total: 27 n (%)**
Results (continued)		
9. Results should be reported for all PRO domains (if multi-dimensional) and items identified by the reference instrument (i.e., not just those that are statistically significant)	Yes	26 (96)
	No	1 (4)
10. The proportion of patients achieving pre- defined responder definitions should be provided where relevant	N/A	27 (100)
11. A copy of the instrument should be included if it has not been published previously	Yes	3 (11)
	N/A	24 (89)

2.5.12 Quality assessment of studies

Table 2.8 and 2.9 summarise the results of the quality assessment of the included cross-sectional studies and prospective cohort studies, respectively. One cross-sectional study provided a prospective analysis on a subgroup of participants and so was assessed by both the JBI and NOS appraisal tools (239).

From the JBI tool, question 3 (*was the exposure measured in a valid and reliable way?*) was omitted because the exposure was often the condition and therefore assessed in question 4 (*were objective, standard criteria used for measurement of the condition?*). Question 7 (*were the outcomes measured in a valid and reliable way?*) was also omitted. This is because valid PRO measurement requires that PROM tools are validated for use in patients with the disease. A majority of PROMs are not validated for use in meningioma patients, so this question could not discriminate reporting quality between studies. However, the analysis of the validity of PROMs constitutes a separate piece of work and is not included within this review.

From the NOS tool, question 1 of the Outcome section (*Assessment of outcome-independent blind assessment, record linkage, self-report, no description*) was omitted. This is because PROs by definition are self-reported and so no study could not receive a star for this question.

Table 2.8: Risk of bias in cross-sectional studies

	Joanna Briggs Institute Critical Appraisal Checklist					
Author (year)	**Q1**	**Q2**	**Q4**	**Q5**	**Q6**	**Q8**
Kangas (2012)(228)	YES	YES	YES	YES	YES	YES
Tanti (2017)(229)	YES	YES	YES	YES	UNCLEAR	YES
Krupp (2009)(230)	YES	YES	YES	N/A	N/A	YES
van Nieuwenhuizen (2019)(231)	YES	YES	YES	YES	YES	YES
Kangas (2011)(232)	YES	YES	UNCLEAR	YES	N/A	YES
Owens (2015)(233)	YES	YES	NO	YES	YES	YES
van der Vossen (2014)(234)	YES	YES	YES	YES	YES	YES
van Nieuwenhuizen (2007)(236)	YES	YES	YES	YES	YES	YES
Mathiesen (2007)(237)	YES	YES	YES	YES	NO	YES
Pintea (2018)(238)	YES	YES	YES	YES	NO	YES
Jones (2016)(239)	YES	YES	YES	NO	N/A	YES
Waagemans (2011)(241)	YES	YES	YES	YES	YES	YES
Timmer (2019)(242)	YES	YES	YES	UNCLEAR	UNCLEAR	YES
Van Nieuwenhuizen (2013)(100)	YES	YES	YES	YES	YES	YES
Lang (1999)(243)	YES	UNCLEAR	YES	NO	N/A	NO
Neil-Dwyer (2000)(244)	YES	UNCLEAR	YES	NO	NO	NO
Konglund (2012)(245)	YES	UNCLEAR	YES	UNCLEAR	UNCLEAR	YES
Schepers (2018)(246)	YES	YES	YES	YES	N/A	YES
Benz (2017)(250)	YES	YES	YES	YES	YES	YES
Kalkanis (2000)(251)	YES	YES	YES	YES	NO	YES
Combs (2013)(253)	YES	NO	YES	NO	NO	YES
Wirsching (2020)(254)	YES	YES	YES	YES	NO	YES
Honeybul (2001)(255)	NO	NO	YES	NO	N/A	N/A
Akagami (2002)(257)	YES	NO	UNCLEAR	NO	N/A	YES
Nassiri (2019)(145)	YES	YES	YES	YES	UNCLEAR	YES

Table 2.9: Risk of bias in prospective cohort studies

	Newcastle-Ottawa Scale for Cohort Studies						
	Selection				Comparability	Outcome	
Author (year)	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**
Makarenko (2016)(235)	1 star	N/A	1 Star	1 Star	2 Stars	1 Star	0 Star
Jones (2016)(239)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star
Jakola (2012)(240)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star
Van der Linden (2020)(247)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	0 Star
Zweckberger (2017)(248)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star
Henzel (2013)(249)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star
Wagner (2019)(252)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star
van Lonkhuizen (2019)(256)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star
dos Santos (2011)(258)	1 Star	N/A	1 Star	1 Star	N/A	1 Star	1 Star

2.6 Discussion

The aim of this review was to identify all studies which assessed PROs of meningioma patients. In total, 33 studies were identified. They measured a range of PRO domains including HRQoL, Health Status, Symptoms, Functioning and Feelings. Of the 27 PROMs used, only nine were HRQoL tools. This highlights that PROs extend beyond the HRQoL.

The most frequently used PROM was SF-36. Whilst it is a popular generic HRQoL instrument, this tool remains unvalidated for use in intracranial meningioma, and it is uncertain whether the issues covered in the SF-36 are relevant to these patients. Patients may have unique issues arising from their meningioma which affect HRQoL and that are not assessed within the SF-36. To date, the only meningioma-specific PROM that has been developed is the FACT-MNG (210). However, this tool has not been validated in an independent meningioma patient cohort and has not used in a published clinical study to date. Given the importance of PROs in clinical effectiveness research, there is an urgent requirement for the validation of existing tools for the meningioma population.

HRQoL covers attitudes towards one's quality of life alongside an assessment of the impact of symptoms and functional limitations. Therefore, one advantage of HRQoL PROMs is that they have a breadth of coverage and can highlight issues which can be explored further. However, HRQoL tools do not assess all issues in depth; for example, the FACT-G only includes one item related to fatigue ('*I have a lack of energy*'). Symptom and Functioning-specific PROMs are necessary to evaluate specific issues in detail; for example, the MFI explores fatigue using 20 items encompassing five different domains. Alongside using validated HRQoL PROMs to capture a breadth of issues, it is important to have validated Symptom and Functioning PROMs which investigate specific issues in depth. However, the majority of current studies focus on HRQoL.

Moreover, this review identified PROs which are not typically assessed within the scope of existing HRQoL studies, for instance, in studies reporting feelings of benefit finding and the birth desires of women. This highlights that the diagnosis of meningioma and its treatment has effects on aspects of life beyond *HRQoL*, *Symptoms* and *Functioning*. Research into other domains of PRO research such as *Feelings* is welcomed in order to better understand patient's perspectives and experiences.

2.6.1 Summary of clinical outcomes

Most studies assessed PROs through self-administered reports, but ten studies used telephone or interview-based reporting. Telephone and interview methods of data collection have advantages such as reduced missing data, but patients may report better outcomes using these methods than through self-assessments (178, 179, 181, 182). Future studies should consider this when collecting data, particularly when comparing outcomes collected by mixed methods as some meningioma studies did. Additionally, there was heterogeneity in the reporting of timepoint of data collection as some studies reported measurements from the time of surgery and others from the point of diagnosis. As a result of the lack of standardisation in the timing of assessing PROs, it is not possible to conduct a meta-analysis. Future studies should measure PROs at defined time points, for example, at initial diagnosis, postoperatively, post-radiotherapy (if given), at recurrence (if it occurs) and longer-term (e.g. five years).

Prospective studies reported overall improvement of HRQoL scores postoperatively. This suggests that surgery does have a beneficial effect on patient wellbeing. However, studies reporting early outcomes within one year of surgery suggest that HRQoL remains impaired in comparison to normative patient values and healthy controls. In studies assessing late HRQoL outcomes postoperatively, most report at least one impaired domain of HRQoL. However, there are conflicting results regarding this, and further studies are required to verify late HRQoL of patients. Furthermore, studies suggest that HRQoL is low

in the months following radiotherapy treatment, but not different from that of those treated with surgery alone in the longer-term. There are very few studies investigating HRQoL after stereotactic radiotherapy and in patients diagnosed with incidental meningiomas.

Patients with meningioma-associated epilepsy and those using anti-epileptic drugs (AEDs) after being diagnosed with a meningioma reported worse HRQoL outcomes and the studies in this review indicate that HRQoL is lower in patients taking AEDs irrespective of seizure frequency (229, 241). In the absence of objective clinical benefit and in light of inferior HRQoL outcomes, the routine use of AEDs in meningioma patients is questionable. Globally, seizure prophylaxis with AEDs is common practice. However, there is a paucity of evidence supporting their routine use (287, 288). Clinical trials such as Surgical Trial Of Prophylaxis for Epilepsy in Meningioma (STOP 'EM) are planned to provide high-quality, prospectively-collected evidence of their objective clinical benefit for patients (289).

The symptom burden of meningioma patients appears to reduce following surgery; psychological symptoms, anxiety and PTSS scores are high before surgery and decrease postoperatively. This is likely to be due to patients adjusting to their diagnosis and treatment. However, one study highlighted that in the long-term, nearly a sixth of patients reported abnormal PTSS scores. Clinicians should be aware of the long-term psychological impact patients may experience and screen for emotional wellbeing as part of routine clinical follow-up.

After surgery, nearly 20% of patients report impaired work ability. The reason for this and the specific challenges patients face requires exploring in further detail. Employment is important for financial wellbeing but also because it can cultivate a sense of purpose and facilitate reintegration into society (220, 290). Unemployment is associated with higher anxiety and depression scores, and

further qualitative research investigating patient perceptions of work restrictions and challenges in resuming employment would be beneficial.

2.6.2 Quality of studies

Overall, studies in which PRO was a primary outcome had a high quality of reporting. For studies in which PRO was a secondary outcome, the quality of reporting was low. For studies which report PROs, the review authors would encourage reporting study results according to the ISOQOL recommendations; this would improve the clarity of research findings.

Studies which report a PRO as a primary outcome should make specific reference within the title as to outcomes being patient-reported as this is not always implied. Whilst it is commonly accepted that domains such health-related quality of life are patient-reported, studies do exist which assess HRQoL by means of clinician reports. Furthermore, this review identified that most studies did not justify their use of particular PROMs. This is particularly important in meningioma as no meningioma-specific PROM is validated and a range of tools are available for use.

2.6.3 Comparison to previous reviews

Previous systematic reviews of meningioma have only assessed outcomes and quality of reporting of HRQoL studies (146, 211).

2.6.4 Recommendations for future research

1. The most commonly used PROMs in meningioma research should be validated. This includes generic HRQoL (SF-36), cancer-specific HRQoL (EORTC-BN20), meningioma-specific HRQoL (FACT-MNG) tools, HADS and CFQ.

2. HRQoL studies of meningioma should focus on outcomes following stereotactic radiosurgery and the diagnosis of incidental meningioma. Validated tools should be used for assessment.
3. Future studies should provide in-depth outcomes of specific symptoms (anxiety, depression, fatigue) and functional limitations (subjective cognitive functioning and employment) of meningioma patients.
4. Researchers and healthcare professionals should collaborate to produce large-scale, multicentre PRO research. This will improve the generalisability of PRO results. Furthermore, this will increase the confidence of policymakers to translate the results of PRO research into interventions to improve patient care.
5. PRO results should be reported in accordance with ISOQOL criteria to improve the clarity of study findings.

2.6.5 Strengths and limitations

One of the strengths of this study is that an extensive search strategy was used. The search was based on searches used in previous systematic reviews, and modifications were made to further increase the sensitivity of the search. Accordingly, 7,489 unique articles were identified. However, it was not feasible to search the full manuscript of all studies to be screened. Therefore, the review authors screened abstracts for reference to a PRO. It is possible that some studies have assessed PROs (e.g. as a secondary outcome) and not described this in the abstract. These studies would not have been identified as part of the screening process; however, we assume that the PRO component of these study were likely to be limited and/or of low quality.

Furthermore, only English language articles were screened, which may be a reason as to why most identified articles are from Europe and North America. Additionally, the grey literature (e.g. conference abstracts) was not included

because the review authors wanted to assess PRO reporting quality which required full manuscripts.

Screening of unique articles, data extraction and quality assessment was performed by only one reviewer. This raises the potential for error and introduction of rater bias. This limitation may affect how studies were categorised, e.g. as 'HRQoL', 'Health Status', 'Symptoms', 'Functioning' or 'Other'. The systematic review manuscript for publication will utilise an alternative method of classification (Dodd et al. (291)) to reduce the potential for ambiguity in classifying outcomes.

The screening process was initially incomplete and not robust at the time of writing this chapter. The PRISMA diagram included in this chapter is not reflective of the complete article identification process. At least 11 additional articles of relevance were identified from the search after this chapter was written. These articles are included in Appendix 9. These additional articles identify PROs of relevance to meningioma patients, and further highlight the heterogeneity of PRO assessment. Therefore, the additional articles are not considered to significantly change the conclusions of this chapter. However, the newly identified articles will be incorporated into the systematic review manuscript for publication. A second reviewer will screen a proportion of unique articles prior to submission of the manuscript for publication. The second reviewer will re-read all included articles and confirm data extraction and ISOQOL and study quality assessment decisions. This will reduce the likelihood of a similar error in the published manuscript.

In the ISOQOL assessment of studies assessing PRO, items 9 (*PRO as primary or secondary outcome*) and 11 (*extent of missing data*) were misapplied. Readers should be aware of this when interpreting the results. The final manuscript for publication will rectify this error.

Finally, we did not assess whether the PROs included in this study are valid for use in meningioma patients. This constitutes an additional piece of work to assess the methodological quality of PROMs and develop of a holistic PROM reporting tool and is described in further detail in Chapter 4.

2.7 Conclusion

This systematic review is the first to identify and summarise studies reporting PROs of patients with intracranial, sporadic meningioma. PRO studies can be categorised as assessing 'HRQoL', 'Health Status', 'Symptoms', 'Functioning', 'Feelings' or 'Other PROs'. HRQoL is the most frequently reported PRO domain, and SF-36 is the most commonly used PRO tool. The diagnosis of meningioma has an impact on each of the PRO domains. Studies suggest HRQoL is impaired in meningioma patients, but there is a shortage of studies investigating outcomes following SRT and in incidental meningiomas. The reporting quality of studies is good for studies in which PRO is a primary outcome. Future work should reflect all domains of PRO to comprehensively evaluate outcomes from a patient's perspective.

Chapter 3: Patient-Reported Health-Related Quality of Life outcomes of patients with meningioma

3.1 Introduction

The care for patients with meningiomas has steadily improved over the past three decades due to a combination of a better understanding of the natural history and disease biology of meningioma, advances in surgical frameworks and increasing adjuvant and salvage therapy options. Survival rates and neurological outcomes have consequently improved (292, 293). Traditionally, neurosurgical outcomes have been reported in terms of morbidity, mortality and disability. However, these standard metrics are by themselves insufficient, and the metrics for measuring treatment outcomes are appropriately shifting to become increasingly patient-centred.

As identified in Chapter 2, Patient-Reported Outcomes (PROs) can focus on 'Health-Related Quality of Life' (HRQoL), 'Patient-Reported Health Status', 'Patient-Reported Symptoms', 'Patient-Reported Functioning', 'Patient-Reported Feelings' or 'Other PROs'. Most studies investigating PROs of patients with meningiomas focus on HRQoL. However, few studies have assessed the long-term HRQoL of patients. Furthermore, only one study has reported HRQoL outcomes of radiologically suspected meningiomas, and no studies have specifically evaluated long-term HRQoL in patients with incidental meningiomas (100).

This chapter describes an exploratory analysis of initial findings from 'the QUALMS study' (Quality of Life outcomes in patients with Incidental and Operated Meningiomas). The chapter compares the HRQoL outcomes of the cohort to normative population values. Furthermore, patients are stratified into distinct, clinically relevant groups and their HRQoL outcomes compared.

3.1.1 Study reporting

This study has been reported in accordance with ISOQOL standards for reporting Patient-Reported Outcomes (221, 294).

3.2 Aims and objectives

3.2.1 Research question

- In patients with incidental and/or operated intracranial meningioma, what are the physical, cognitive and psychosocial quality of life outcomes?

3.2.2 Primary objective

- To determine the prevalence of physical, cognitive and psychosocial problems in patients with either incidental meningioma and/or operated meningioma

3.2.3 Secondary objectives

- Determine the difference in the HRQoL between patients with incidental and non-incidental meningioma
- Determine the difference in the HRQoL between patients with meningioma receiving intervention compared to active monitoring alone
- Determine the difference in the HRQoL between patients with meningioma stratified tumour locations of skull base versus non-skull base
- Determine the difference in HRQoL of patients with meningioma who completed assessments during the Coronavirus disease 2019 (COVID-19) lockdown compared to before the lockdown.

As this is an exploratory analysis, there is no hypothesis as to whether HRQoL will be affected in patients. Patient-reported HRQoL was the primary outcome of this study.

3.3 Methods

3.3.1 Research team

Professor Michael D Jenkinson was the Chief Investigator for the study. Sumirat M Keshwara was the Primary Investigator.

3.3.2 Study sponsorship and ethical approval

The QUALMS study protocol is included in appendix 5. The University of Liverpool was the study sponsor. The QUALMS study received Health Research Authority (HRA) approval and was accepted onto the National Institute for Health Research (NIHR) Clinical Research Network portfolio in December 2019.

3.3.3 Study design

3.3.3.1 Design and setting

A cross-sectional study was completed at The Walton Centre NHS Foundation Trust (The Walton Centre), Liverpool, England between December 2019 and July 2020.

3.3.3.2 Participant inclusion and exclusion criteria

Table 3.1 lists the participant inclusion and exclusion criteria. The focus of the QUALMS study was to identify long-term HRQoL outcomes of adult patients with meningioma. Incidental meningiomas were diagnosed on the basis of radiological features. Patients with operated meningiomas had a diagnosis

confirmed by histology. In the QUALMS study, patients followed-up for a minimum of 5 years were eligible to participate.

Table 3.1: The QUALMS study inclusion and exclusion criteria

	Inclusion	Exclusion
General	• Age ≥16 years at the time of diagnosis of meningioma • Communicate effectively using the English language	• Aged <16 years at the time of diagnosis of meningioma • Lacks capacity to consent • Identified as having suffered a cerebral neurological insult (e.g. trauma, meningitis, stroke) prior to presenting with meningioma • Diagnosed with any congenital or neurological disease prior to a diagnosis of meningioma (e.g. cerebral palsy) • Radiation-induced meningioma • Neurofibromatosis type II-associated meningioma • Diagnosed with any condition which leads to cognitive decline (e.g. dementia, Parkinson's disease or intellectual disabilities), either before or after the diagnosis of meningioma.
Incidental meningioma cohort	• Patients with radiological diagnosis of meningioma and have been followed-up for a minimum of 5 years	• Patients with radiological diagnosis of meningioma and have been followed-up for less than 5 years • Diagnosis of meningioma considered not to be an incidental finding
Operated meningioma cohort	• Patients who have had surgery for their meningioma and have a minimum of 5 years follow-up	• Patients who have had surgical resection of their meningioma and have less than 5 years follow-up

3.3.4 HRQoL assessment tools

Three HRQoL Patient-Reported Outcome Measures (PROMs) were chosen for use in this study. In order to assess HRQoL holistically, one general, one cancer-specific and one brain-tumour specific tool were selected. Although a meningioma-specific HRQoL tool exists, this was not chosen as it has not been used in a clinical study to date and its validity has not been assessed (210). In

addition to the three HRQoL PROMs, patients were asked to complete one study-specific questionnaire which asked patients to provide demographic (e.g. employment status) and clinical (e.g. current medications) data.

3.3.4.1 SF-36

The RAND 36-item Short Form Health Survey version 1.0 (SF-36) was chosen as the general HRQoL tool (260, 295). This tool is identical to the MOS SF-36 but differs in its scoring. The SF-36 contains 36 items and assesses eight HRQoL domains: Physical Functioning, Bodily Pain, role limitations due to Physical ealth problems (Role Physical), role limitations due to personal or emotional problems (Role Emotional), Emotional Wellbeing, Social Functioning, Energy/ Fatigue, and General Health perceptions. It includes one item asking patients to rate their current health compared to one year previously. Many of the items assess HRQoL in the last four weeks. All items are statistically transformed so that a higher score represents a more favourable health state. The SF-36 is a validated PROM with Cronbach's α reported to be greater than 0.85 (296).

3.3.4.2 EORTC QLQ-C30

The EORTC Core Quality of Life Questionnaire (EORTC QLQ-C30) was chosen as the cancer-specific HRQoL tool (204). The QLQ-C30 contains 30 items and assesses five functional scales (Physical, Role, Cognitive, Emotional and Social) and three symptom scales (Fatigue, Pain, Nausea and Vomiting) and one Global Health Status/ QoL scale. Six single items evaluate specific symptoms (Dyspnoea, Insomnia, Appetite Loss, Constipation, Diarrhoea and Financial Difficulties). Many of the items assess HRQoL in the last one week.

A higher functional scale score and Global Health Status score represent higher level of functioning and health status, respectively. However, a higher symptom scale or item score represents higher symptom burden. It is possible to combine the scores of each scale and single items (excluding Global Health Status and

Financial Difficulties) to produce a summary score. A higher summary score represents a higher overall HRQoL. The QLQ-C30 is a validated PROM with Cronbach's $\alpha \geq 0.7$ in all scales except role functioning (204).

3.3.4.3 EORTC QLQ-BN20

The EORTC Quality of Life Questionnaire Brain Cancer Module (EORTC QLQ-BN20) was chosen as a brain tumour-specific HRQoL tool (265). The QLQ-BN20 contains 20 items and assesses four symptom scales (Future Uncertainty, Visual Disorder, Motor Dysfunction and Communication Deficit). Seven single items evaluate specific symptoms (Headaches, Seizures, Drowsiness, Hair Loss, Itchy Skin, Weakness of Legs and Bladder Control). All of the items evaluate HRQoL over the last one week. All scales and items are statistically transformed so that a higher score represents a higher level of symptom burden. The QLQ-BN20 has been internationally validated, and Cronbach's α reported as ≥ 0.7 in all scales (297).

3.3.5 Rationale for assessment schedule

Assessment of HRQoL five or more years after diagnosis (incidental cohort) or surgery (operated cohort) was chosen to represent long-term HRQoL outcomes. This is because if an incidental meningioma is to progress, it will usually do so within five years of diagnosis. Patients with incidental meningiomas diagnosed five or more years ago can expect clinical stability (98). For operated meningiomas, 5-year survival rates for WHO Grade I and II meningiomas are 90% and 80% respectively (136). As a majority of patients are alive and clinically stable five years postoperatively, this seemed an appropriate time-point to assess long-term HRQoL of patients.

3.3.6 Study size

A total of 699 patients were eligible to participate and were contacted by post. No sample-size calculation was necessary as the QUALMS study is exploratory and therefore does not need to be powered to assess a specific hypothesis. Eligible patients attending routine clinic appointments were also identified and invited to participate.

3.3.7 Invitation to participation

Eligible patients were identified from three existing databases of meningioma patients held at The Walton Centre. Eligible patients included patients currently under active follow-up and those who have previously received care for their meningioma at The Walton Centre but were subsequently discharged. The three databases were combined to form The Walton Meningioma database, and deceased patients were removed. Patient contact details were identified using the NHS Spine. Date of the patient's next clinic appointment at The Walton Centre was recorded.

Eligible patients were approached in one of two ways: either when they attended routine clinic appointments or by post. Eligible patients that attended routine clinic appointments at The Walton Centre between December 2019 and March 2020 were approached by the Primary Investigator and invited to participate. Patients were informed of the study purpose, given the study invitation letter and the Patient Information Sheet (appendices 6, 7 and 8) and offered an opportunity to ask questions. Patients who were willing to participate signed the study consent form (appendix 8) and completed the study questionnaires individually or with the person that they attended the clinic appointment with.

In March 2020, all eligible patients identified through The Walton Meningioma database were contacted by post. Patients were sent a cover letter explaining

the study purpose, the Patient Information Sheet and a study consent form. A pre-paid return envelope was provided for patients to return the study consent form. Patients who returned the consent form were mailed the study questionnaires alongside another pre-paid return envelope. After four weeks, the patients who had not responded to the initial invitation to participate letter were re-sent the cover letter, Patient Information Sheet, consent form and a pre-paid return envelope.

3.3.8 Mode of PROM administration

The study questionnaires were self-administered whether the patient was invited to participate by post or during clinic appointments.

3.3.9 Study data

HRQoL outcomes and responses from the study-specific questionnaire were entered into The Walton Meningioma database. Patient demographic, diagnosis and treatment data were extracted from digital case-notes and from the study-specific questionnaire. The digital case notes only provide data after 2007. Therefore, some data recorded before 2007 were not available to access. A manual case-note review was not possible to complete at the time of writing this chapter. Table 3.2 shows the information extracted from the case-notes and the study-specific questionnaire.

Table 3.2: Study data obtained from case-note review or from the study-specific questionnaire

Variables	Description
Patient	Age at the completion of questionnaire*†, time since diagnosis*†, sex†, highest education level*, employment status*, driving status*
Clinical	Presenting features†, preoperative performance status (ECOG)†, medical conditions*† (to calculate Age-adjusted Charlson Comorbidity Index - ACCI), number of medications*, number of AEDs*
Tumour	WHO Grade†, tumour location†, tumour laterality†
Intervention	Initial management†, subsequent management†, the extent of surgical resection†
Outcome	Progression since diagnosis (defined as either regrowth or recurrence)†

ECOG*: Eastern Cooperative Oncology Group*. AEDs*: Anti-epileptic drugs*

* Obtained or calculated from the study-specific questionnaire. † Obtained or calculated from case-note review.

3.3.10 Quantitative variables

HRQoL scores obtained from patient questionnaires were transformed into the scale and single item scores as per their scoring manuals (295, 298). No scoring manual is available for the QLQ-BN20. Therefore, the QLQ-BN20 scales were constructed using information about the domains and their corresponding items that can be obtained from the development and validation studies (265, 297). The QLQ-BN20 scales were computed and transformed using the QLQ-C30 manual (298), which is the same methodology as was used in the QLQ-BN20 development study (265). Table 3.3 shows all variables assessed in this exploratory analysis.

Table 3.3: Variables used in the QUALMS study analysis

Variable type	Variable name
Continuous	Age at the completion of questionnaires, time since the initial diagnosis, number of medications, number of AEDs, HRQoL outcomes (quasi-continuous)
Ordinal	Performance status (ECOG) at diagnosis, ACCI, highest education level
Nominal	Tumour location, tumour laterality, employment status, presenting features
Dichotomous	Sex, WHO Grade, skull-base tumour, multiple meningioma, incidental meningioma, initial management, intervention, subsequent surgery, subsequent SRS, subsequent FRT, extent of resection, progression since diagnosis, current driving status, currently taking AEDs, response during COVID-19 lockdown

SRS*: stereotactic radiosurgery,* FRT*: fractionated radiotherapy*

3.3.11 Statistical analysis

Statistical analysis was completed using IBM SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). The exception to this is the comparison of the HRQoL scores of the total meningioma cohort to normative populations values, which was completed using the two-sample test on a statistical calculator website (www.select-statistics.co.uk)(299). Continuous variables with normal distributions were

described with means and standard deviations. Continuous variables which were not normally distributed were described with medians. Ordinal, nominal and dichotomous data were described by counts and percentages.

For all significance testing, a statistically significant result was defined as $p<0.05$. The independent samples t-test was used to compare means between HRQoL and normative population data. This test assumes normality of data, absence of outliers and equality of variances. Where these assumptions were not met, between-groups comparisons of continuous outcomes were completed using Mann-Whitney-U (Wilcoxon rank-sum test) and reported with the Mann-Whitney-U (U) statistic, the standard test statistic (Z) and significance values (p). Medians could be directly compared when HRQoL scores were considered equally distributed (as assessed by visual inspection). Mean ranks are additionally reported where HRQoL scores were not considered equally distributed.

Between groups comparisons of dichotomous or multinomial dependent variables was completed using the chi-square test (test of two proportions). This test assumes independence of observations, random sampling of two populations and expected frequency values of 5 or more. Where an expected frequency was identified as being less than 5, Fisher's exact test was used. Between groups comparisons of ordinal data were completed using the Mann-Whitney-U test.

Internal consistency of questionnaires was calculated using Cronbach's α (300). This test is used to measure how much individual items measure within a scale measure the same dimension. A satisfactory internal consistency was pre-defined as an alpha value between 0.700-0.950 (301).

A multivariate linear regression model was not performed due to limited sample size, presence of outliers and no linear relationship between dependent and independent variables. As this is an exploratory analysis, the p values were not

adjusted to account for multiple comparisons. This was to reduce the risk of making a type 2 error and obtaining a false negative result (302).

3.3.11.1 HRQoL missing data analysis

The RAND SF-36 manual states that missing responses to items within a scale did not preclude a patient from inclusion in the study. The items that have been answered can be used to compute an average score for the scale (295). If no items of the scale are answered it is not possible to produce a scale score. For the EORTC QLQ-C30 and QLQ-BN20, if 50% or more of items that form a scale are answered, those responses can be used to compute a scale score. If less than 50% of items for a scale are answered, a scale score should not be computed (298). Little's test was used to assess whether missingness occurred completely at random.

3.4 Results

3.4.1 Sample characteristics

Table 3.4 describes the patient demographic, clinical and treatment characteristics. A total of 699 patients were contacted by post, of which 31 patients had responded and subsequently had their responses recorded at the point that this analysis was undertaken. The postal response rate was therefore 4.4%. An additional 23 patients were identified at outpatient clinic appointments, and their questionnaire responses were also analysed. Therefore, a total of 54 patients were included in this initial exploratory analysis.

The mean age of participants was 66.2, and 80% were female. Of those with histological diagnosis, 89% of patients had WHO Grade I meningiomas. Patient's meningiomas were equally distributed between right (41%) and left (43%) hemispheres, and 16% were located in the midline. Approximately half (48%) of patients had skull base meningiomas. Cerebral convexity (33%),

anterior midline (22%) and sphenoid wing (16%) were the commonest tumour locations. Incidental meningiomas were diagnosed in 41% of the cohort. Twenty nine patients (54%) had an operation to remove their meningioma as initial management. The mode highest education level was GCSE (41%), and a majority of participants were retired (59%). Ten patients (19%) reported they were taking anti-epileptic drugs. Thirty-one patients (57%) in this analysis completed the questionnaires during COVID-19 lockdown.

Table 3.4: QUALMS study responder characteristics

Characteristic	Value
Sample size	54 (100)
Mean age (years) at completion of questionnaires (standard deviation)	66.2 (11.6)
Mean years since diagnosis (standard deviation)	10.3 (4.1)
Sex	
Female	43 (80)
Male	11 (20)
WHO Grade (where histology available) *	
I	31 (89)
II	4 (11)
III	0 (0)
Tumour location (ICOM) †	
Convexity	17 (33)
Anterior midline	11 (22)
Sphenoid wing	8 (16)
Parasagittal	5 (10)
Posterior fossa- lateral and posterior	4 (8)
Parafalcine	3 (6)
Posterior fossa- midline	1 (2)
Pineal	1 (2)
Tentorial	1 (2)
Skull base tumour ‡	25 (48)
Tumour laterality §	
Right	21 (41)
Left	22 (43)
Midline	8 (16)

Table 3.4: QUALMS study responder characteristics (continued)

Characteristic	Value
Performance Status at diagnosis (ECOG) ¶	
0	17 (34)
1	22 (44)
2	10 (20)
3	1 (2)
ACCI	
0	2 (4)
1	5 (9)
2	12 (22)
3	14 (26)
4	9 (17)
5	4 (7)
6	5 (9)
7	3 (6)
Intervention (surgery, SRS, FRT)	37 (69)
Initial management	
Active Monitoring	25 (46)
Surgery	29 (54)
Further management	
Surgery	9 (17)
Fractionated Radiotherapy	7 (13)
SRS	2 (4)
Extent of resection (if operated) #	
GTR	22 (61)
STR	14 (39)
Progression since diagnosis	9 (17)

Table 3.5: QUALMS study responder characteristics (continued)	
Characteristic	**Value**
Multiple meningioma	4 (7)
Presenting features	
Seizure	8 (15)
Headache	7 (13)
Nausea	1 (2)
Vomiting	0 (0)
Motor weakness	6 (11)
Sensory deficit	10 (19)
Language deficit	2 (4)
Cognitive deficit	5 (9)
Psychiatric manifestations	2 (4)
Altered GCS score	0 (0)
Incidental finding	22 (41)
Mean number of medications (standard deviation)	3.3 (2.7)
Currently taking AEDs	10 (19)

* The meningioma WHO Grade of two patients is unknown.
† Three patients have multiple meningiomas in different cerebral locations. Therefore, these patients have been omitted from analyses of ICOM location and are not presented here.
‡ Two patients have multiple meningiomas in skull base and non-skull base locations. They have been omitted from analyses of skull base and are not presented here.
§ Three patients have multiple meningiomas in both right and left hemispheres. Therefore, these patients have been omitted from analyses of tumour laterality and are not presented here.

All results in Table 3.4 are reported as frequency and percentages: n (%) unless stated otherwise.

Table 3.6: QUALMS study responder characteristics (continued)	
Characteristic	**Value**
Highest education level	
No education	9 (17)
GCSE	22 (41)
A Levels	13 (24)
Undergraduate	5 (9)
Master's degrees	5 (9)
Employment status	
Retired	32 (59)
Part-time employment	7 (13)
Full-time employment	6 (11)
Self-employed	4 (7)
Unable to work due to health	4 (7)
Homemaker	1 (2)
Current driving status	31 (57)
COVID-19 response	31 (57)

¶ Performance status of four patients is unknown
# The Extent of Resection of one patient is unknown.

3.4.2 Missing data

Table 3.5 shows the items with missing responses from patient questionnaires. Of the cohort, 13 patients (24%) had missing data in their returned questionnaires. Eight of these patients (62%) had only one missing item. Eleven patients (85%) had missing data from SF-36. Little's MCAR (Missing Completely at Random) test revealed p=0.000, suggesting missingness was not completely random across the three questionnaires.

Table 3.6 shows a description of items which were missing in more than one patient. Notably, SF-36 Item 23 (*did you feel full of pep?*) was missing in five patients. Additionally, SF-36 Item 32 (*physical health interference in social activities*) was missing in four patients, and SF-36 Item 3 (*limitations in vigorous activities*) was missing in three patients.

No multiple imputation method was necessary for the analysis of HRQoL data.

Table 3.7: Missing items from responses

Patient number	Method of contact	Missing items		
		SF-36	QLQ-C30	QLQ-BN20
1	Postal	32	-	-
2	Postal	23	-	-
17	Postal	3, 4, 32	-	-
18	Postal	32	-	-
22	Postal	3, 33, 34, 36	-	-
32	Postal	3, 7, 10, 11	-	-
38	Clinic	-	12	-
40	Clinic	23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36	-	-
45	Clinic	6	-	-
58	Clinic	23	-	-
60	Clinic	13, 14, 15, 16, 17, 18, 19, 23, 25, 26, 28, 30	10	-
62	Clinic	23	-	-
64	Clinic	-	-	42

Table 3.8: Frequency and description of missing items				
Questionnaire name	**Item number**	**Verbatim item summarised**	**Domain**	**Frequency missing**
SF-36	3	*'Does your health now limit you in… vigorous activities, such as running, lifting heavy objects, participating in strenuous sports'*	Physical functioning	3
SF-36	23	*'Did you feel full of pep?'*	Energy/ Fatigue	5
SF-36	25	*'Have you felt so down in the dumps that nothing could cheer you up?'*	Emotional wellbeing	2
SF-36	26	*'Have you felt calm and peaceful?'*	Emotional wellbeing	2
SF-36	28	*'Have you felt downhearted and blue?'*	Emotional wellbeing	2
SF-36	30	*'Have you been a happy person?'*	Emotional wellbeing	2
SF-36	32	*'How much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?'*	Social functioning	4
SF-36	33	*'I seem to get sick a little easier than other people'*	General health	2
SF-36	34	*'I am as healthy as anybody I know'*	General health	2
SF-36	36	*'My health is excellent'*	General health	2

3.4.3 Internal consistency

Table 3.7 shows the internal consistency of individual scales. Across all scales, alpha ranged between 0.518 and 0.950. Of the 21 individual scales, 19 scales (90%) scored above the pre-defined satisfactory score of 0.700. The QLQ-C30 Nausea and Vomiting and QLQ-BN20 Motor Dysfunction scale scored 0.646 and 0.518, respectively.

Table 3.9: Internal consistency of the HRQoL tools

Questionnaire	Scale	Items	Cronbach's α
SF-36	Physical functioning	3 4 5 6 7 8 9 10 11 12	0.946
SF-36	Role limitations due to physical health	13 14 15 16	0.908
SF-36	Role limitations due to emotional problems	17 18 19	0.950
SF-36	Energy/ Fatigue	23 27 29 31	0.919
SF-36	Emotional well-being	24 25 26 28 30	0.812
SF-36	Social functioning	20 32	0.827
SF-36	Pain	21 22	0.908
SF-36	General health	1 33 34 35 36	0.870
QLQ-C30	Global health status/ QoL	29, 30	0.950
QLQ-C30	Physical functioning	1, 2, 3, 4, 5	0.844
QLQ-C30	Role functioning	6, 7	0.896
QLQ-C30	Emotional functioning	21, 22, 23, 24	0.934
QLQ-C30	Cognitive functioning	20, 25	0.819
QLQ-C30	Social functioning	26, 27	0.871
QLQ-C30	Fatigue	10, 12, 18	0.836
QLQ-C30	Nausea and Vomiting	14, 15	0.646
QLQ-C30	Pain	9, 19	0.912
QLQ-BN20	Future Uncertainty	31, 32, 33, 35	0.858
QLQ-BN20	Visual Disorder	36, 37, 38	0.852
QLQ-BN20	Motor Dysfunction	40, 45, 49	0.518
QLQ-BN20	Communication Deficit	41, 42, 43	0.772

3.4.4 HRQoL of the entire cohort

3.4.4.1 Normative values

Table 3.8 shows the HRQoL scores of the 54 participants and compares their scores to normative population values (303, 304). The SF-36 normative values were obtained from surveying the general population of Wales [5]. The QLQ-C30 normative values were obtained from surveying patients across Europe. Normative general population values for the QLQ-BN20 were unavailable.

3.4.4.2 Justification for comparison

HRQoL scores were not normally distributed as assessed by with Shapiro-Wilk test (p values <0.05). QLQ-BN20 scores and QLQ-C30 symptom scores were generally positively skewed, QLQ-C30 functional scale and SF-36 scores were negatively skewed. This is similar to previously reported studies (303, 305). Some domains contained outliers as assessed by inspection of box plots, but these were considered to be true patient values and not data collection or data entry errors. There was no justification for removing outliers from the analysis. As previous studies have compared means of sample data to normative population values by independent samples t-test, it seemed appropriate to do this for this exploratory analysis. This was justified as the independent samples t-test is considered stable against assumptions of non-normality. It was not possible to test homogeneity of variances or use the non-parametric Mann-Whitney-U test as raw normative population values were not available (306). The purpose of this analysis was to identify domains reported as impaired in meningioma patients compared to the general population.

[5] See limitations section

Table 3.10: HRQoL scores for the entire cohort and comparison with normative population values								
Domain	**Sample**					**Normative**		**Sig**
	median	**IQR**	**mean**	**SD**	**95% CI**	**mean**	**SD**	***p***
SF-36 Physical Functioning	85.0	53.8	68.6	30.4	60.2-77.1	77.8	30.0	**0.031**
SF-36 Role Physical	100.0	75.0	63.5	42.4	51.6-75.3	78.3	32.3	**0.014**
SF-36 Role Emotional	100.0	58.3	76.3	40.9	64.9-87.7	87.0	26.0	0.063
SF-36 Energy/ Fatigue	60.0	45.0	57.1	26.8	49.6-64.5	57.2	22.3	0.978
SF-36 Emotional Wellbeing	80.0	27.0	75.1	19.3	69.7-80.5	74.0	18.9	0.680
SF-36 Social Functioning	93.8	46.9	75.7	31.4	67.0-84.5	80.2	28.1	0.298
SF-36 Pain	68.8	45.0	66.2	28.0	58.4-74.0	70.1	28.9	0.312
SF-36 General Health	57.5	37.5	58.8	24.1	52.1-65.6	66.2	24.0	**0.028**
QLQ-C30 Summary Score	88.3	20.0	81.8	16.8	77.1-86.5	-	-	-
QLQ-C30 Physical Functioning	86.7	40.0	79.2	22.3	73.0-85.4	85.1	18.9	0.058
QLQ-C30 Role Functioning	100.0	33.3	81.1	28.8	73.1-89.1	84.3	24.6	0.419
QLQ-C30 Emotional Functioning	83.3	33.3	76.9	25.0	70.0-83.9	74.2	24.7	0.432
QLQ-C30 Cognitive Functioning	83.3	50.0	72.1	27.2	64.6-79.7	84.8	21.3	**0.001**
QLQ-C30 Social Functioning	100.0	33.3	79.8	29.2	71.7-87.9	86.2	24.1	0.114
QLQ-C30 Fatigue	22.2	38.9	27.0	26.2	19.8-34.3	29.5	25.5	0.487
QLQ-C30 Nausea & Vomiting	0.0	0.0	4.8	12.1	1.5-8.2	5.9	16.0	0.509
QLQ-C30 Pain	16.7	45.8	28.2	30.5	19.7-36.7	23.5	27.1	0.263
QLQ-C30 Dyspnoea	0.0	0.0	9.6	23.2	3.2-16.1	15.9	24.6	0.052
QLQ-C30 Insomnia	33.3	58.3	32.7	34.6	23.1-42.3	26.6	30.3	0.202
QLQ-C30 Appetite Loss	0.0	0.0	10.3	23.4	3.7-16.8	10.0	21.6	0.925
QLQ-C30 Constipation	0.0	25.0	9.0	16.3	4.4-13.5	12.5	23.3	0.122
QLQ-C30 Diarrhoea	0.0	0.0	3.8	12.6	0.3-7.4	9.5	20.9	**0.002**
QLQ-C30 Financial Difficulties	0.0	0.0	5.8	18.3	0.7-10.9	10.6	23.6	0.060
QLQ-C30 Global Health Status/QoL	75.0	22.9	70.8	22.6	64.5-77.1	66.1	21.7	**0.133**

Table 3.8: HRQoL scores for the entire cohort and comparison with normative population values (continued)								
Domain	**Sample**					**Normative**		**Sig**
	median	**IQR**	**mean**	**SD**	**95% CI**	**mean**	**SD**	***p***
QLQ-BN20 Future Uncertainty	16.7	41.7	22.4	22.8	16.1-28.8	-	-	-
QLQ-BN20 Visual Disorder	0.0	22.2	14.5	23.3	8.0-21.0	-	-	-
QLQ-BN20 Motor Dysfunction	11.1	22.2	13.9	17.4	9.0-18.7	-	-	-
QLQ-BN20 Communication Deficit	0.0	22.2	11.5	16.8	6.9-16.2	-	-	-
QLQ-BN20 Headaches	0.0	33.3	22.4	30.8	13.9-31.0	-	-	-
QLQ-BN20 Seizures	0.0	0.0	1.3	6.5	0.0-3.1	-	-	-
QLQ-BN20 Drowsiness	0.0	33.3	23.7	29.8	15.4-32.0	-	-	-
QLQ-BN20 Hair Loss	0.0	0.0	6.4	18.7	1.2-11.6	-	-	-
QLQ-BN20 Itchy Skin	0.0	0.0	8.3	20.7	2.6-14.1	-	-	-
QLQ-BN20 Weakness of Legs	0.0	0.0	9.6	21.2	3.7-15.5	-	-	-
QLQ-BN20 Bladder Control	0.0	33.3	14.7	27.5	7.1-22.4	-	-	-

3.4.4.3 HRQoL

Three domains of the SF-36 were significantly impaired in meningioma patients compared to normative population values. Physical Functioning (*mean 68.6 vs 77.8, p=0.031*), Role Physical (*mean 63.5 vs 78.3, p=0.014*) and General Health scores (*58.8 vs 66.2, p=0.028*) were significantly lower. Role Emotional scores were also lower (*mean 76.3 vs 87.0*), but this was not statistically significant (*p=0.063*).

In the QLQ-C30, Cognitive Functioning scores were lower in the meningioma patients compared to the general population (*mean 72.1 vs 84.8, p=0.001*). Meningioma patients reported better HRQoL scores for Diarrhoea (*3.8 vs 9.5, p=0.002*), Dyspnoea (*mean 9.6 vs 15.9, p=0.052*) and Financial Difficulties (*mean 5.8 vs 10.6, p=0.060*).

3.4.5 Incidental meningioma

HRQoL scores were compared between patients whose meningioma was diagnosed incidentally compared with non-incidentally. HRQoL scores in the groups were not normally distributed as assessed by the Shapiro-Wilk test (p values < 0.05). Individual group sizes were small. A number of domains had outliers. The most appropriate test for comparing the HRQoL scores of the groups was the non-parametric Mann-Whitney-U test.

3.4.5.1 Group characteristics

Table 3.9 shows the group characteristics of patients with incidental and non-incidental meningioma. The two groups differed in their site of tumour location (*p=0.020*), and patients with incidental meningioma had significantly lower baseline ECOG performance status (*p=0.004*)[6]. Patients with incidental meningioma were significantly less likely to receive treatment interventions (*23% vs 100%, p=0.000*) or to experience progression of their tumour (*0% vs 28%, p=0.007*).

[6] A lower ECOG performance status score indicates a better level of functioning

Table 3.11: Comparison of demographic, clinical and treatment variables between patients diagnosed with an incidental and non-incidental meningioma			
Variable	**Incidental**	**Non-incidental**	**p**
Sample size (n=54)	22	32	n/a
Median age at completion of questionnaires	67.8 (27.9*)	67.9 (27.2*)	0.874
Median years since diagnosis	7.7 (21.9*)	10.4 (26.7*)	0.238
Female	19 (86)	24 (75)	0.493†
WHO Grade	I: 5 (100) II: 0 (0)	I: 26 (87) II: 4 (13)	1.000†
Tumour location	Convexity: 10 (48) Anterior midline: 6 (29) Sphenoid wing: 1 (5) Parasagittal: 0 (0) Posterior fossa- lateral and posterior: 1 (5) Parafalcine: 3 (14) Posterior fossa- midline: 0 (0) Pineal: 0 (0) Tentorial: 0 (0)	Convexity: 7 (23) Anterior midline: 5 (17) Sphenoid wing: 7 (23) Parasagittal: 5 (17) Posterior fossa- lateral and posterior: 3 (10) Parafalcine: 0 (0) Posterior fossa- midline: 1 (3) Pineal: 1 (3) Tentorial: 1 (3)	**0.020**†
Skull base tumour	8 (38)	17 (55)	0.236
Tumour laterality	Right: 8 (40) Left: 10 (50) Midline: 2 (10)	Right: 13 (42) Left: 12 (39) Midline: 6 (19)	0.641†
Multiple meningiomas	2 (9)	2 (6)	1.00†
Median number of medications	3.0 (27.6*)	2.5 (27.4*)	0.965
Median number of AEDs	0.0	0.0	0.124
Baseline Performance Status (ECOG)	0: 12 (55) 1: 8 (36) 2: 2 (9) 3: 0 (0)	0: 5 (18) 1: 14 (50) 2: 8 (29) 3: 1 (4)	**0.004**
ACCI	0: 0 (0) 1: 2 (9) 2: 5 (23) 3: 7 (32) 4: 2 (9) 5: 3 (14) 6: 2 (9) 7: 1 (5)	0: 2 (6) 1: 3 (9) 2: 7 (22) 3: 7 (22) 4: 7 (22) 5: 1 (3) 6: 3 (9) 7: 2 (6)	0.740
Initial management	Active monitoring: 21 (95) Surgery: 1 (5)	Active monitoring: 4 (12.5) Surgery: 28 (87.5)	**0.000**

Table 3.9: Comparison of demographic, clinical and treatment variables between patients diagnosed with an incidental and non-incidental meningioma (continued)			
Variable	**Incidental**	**Non-incidental**	**p**
Intervention	5 (23)	32 (100)	**0.000**
If operated, GTR	5 (100)	17 (55)	0.134†
Progression since diagnosis	0 (0)	9 (28)	**0.007**†
Highest education level	No education: 1 (5) GCSE: 10 (45) A-Levels: 6 (27) Undergraduate: 3 (14) Master's degrees: 2 (9)	No education: 8 (25) GCSE: 12 (38) A-Levels: 7 (22) Undergraduate: 2 (6) Master's degrees: 3 (9)	0.151
Employment status	Retired: 15 (68) Part-time employment: 4 (18) Full-time employment: 2 (9) Self-employed: 1 (5) Unable to work due to health: 0 (0) Homemaker: 0 (0)	Retired: 17 (53) Part-time employment: 3 (9) Full-time employment: 4 (13) Self-employed: 3 (9) Unable to work due to health: 4 (13) Homemaker: 1 (3)	0.446†
Current driving status	14 (64)	17 (53)	0.443
COVID-19 response	15 (68)	16 (50)	0.184

* Mean rank
† Fisher's Exact Test
All results in Table 3.9 are reported as frequency and percentages: n (%) unless stated otherwise.

3.4.5.2 HRQoL

Table 3.10 shows the comparison of HRQoL scores between patients with incidental and non-incidental meningiomas. HRQoL scores were similar between patients with incidental and non-incidental meningioma. The only statistically significant finding was lower QLQ-BN20 Communication Deficit scores, indicating less communication deficit, in patients with incidental meningioma (*0.0 vs 11.1, U= 465.0 Z= 2.17 p=0.030*). QLQ-C30 summary scores were higher, implying higher overall HRQoL, in patients with incidental meningioma compared to non-incidental meningioma (*mean rank 32.5 vs 24.1, U= 243.0 Z= -1.91 p=0.055*). QLQ-C30 Cognitive Functioning scores were higher in patients with incidental meningioma (*91.7 vs 75.0, U= 256.5 Z= -1.72 p=0.085*). Finally, QLQ-C30 Fatigue scores were lower in the incidental meningioma cohort (*16.7 vs 27.8, U= 455.5 Z=1.85 p=0.065*).

Table 3.12: Comparison of HRQoL scores between incidental and treated meningioma					
Domains	**Incidental (median) n = 22**	**Non-incidental (median) n = 32**	***U***	***Z***	***p***
SF-36 Physical Functioning	85.0	85.0	348.5	-0.62	0.950
SF-36 Role Physical	100.0	50.0	281.0	-1.18	0.238
SF-36 Role Emotional	100.0	100.0	294.5	-1.09	0.276
SF-36 Energy/ Fatigue	70.0	60.0	255.0	-1.56	0.119
SF-36 Emotional Wellbeing	84.0	76.0	269.0	-1.30	0.192
SF-36 Social Functioning	100.0	81.3	296.0	-1.06	0.291
SF-36 Pain	77.5	67.5	312.5	-0.70	0.483
SF-36 General Health	57.5 (26.1*)	52.5 (28.5*)	383.0	0.55	0.584
QLQ-C30 Summary Score	91.9 (32.5*)	81.6 (24.1*)	243.0	-1.91	0.055
QLQ-C30 Physical Functioning	93.3	86.7	303.5	-0.87	0.385
QLQ-C30 Role Functioning	100.0	100.0	322.5	-0.58	0.563
QLQ-C30 Emotional Functioning	91.7	75.0	276.5	-1.35	0.177
QLQ-C30 Cognitive Functioning	91.7	75.0	256.5	-1.72	0.085
QLQ-C30 Social Functioning	100.0	91.7	297.5	-1.07	0.286
QLQ-C30 Fatigue	16.7	27.8	455.5	1.85	0.065
QLQ-C30 Nausea & Vomiting	0.0	0.0	294.0	-1.51	0.131
QLQ-C30 Pain	8.3	25.0	423.5	1.30	0.194
QLQ-C30 Dyspnoea	0.0	0.0	354.5	0.07	0.948
QLQ-C30 Insomnia	16.7	33.3	409.0	1.06	0.288
QLQ-C30 Appetite Loss	0.0	0.0	379.5	0.715	0.474
QLQ-C30 Constipation	0.0	0.0	340.0	-0.28	0.781
QLQ-C30 Diarrhoea	0.0	0.0	378.0	0.91	0.362
QLQ-C30 Financial Difficulties	0.0	0.0	348.5	-0.106	0.916
QLQ-C30 Global Health Status	66.7	79.2	377.5	0.46	0.647
BN20 Future Uncertainty	12.5	16.7	390.0	0.68	0.497
BN20 Visual Disorder	0.0	0.0	338.0	-0.274	0.784
BN20 Motor Dysfunction	0.0 (24.2*)	11.1 (29.8*)	424.0	1.35	0.179
BN20 Communication Deficit	0.0	11.1	465.0	2.17	**0.030**
BN20 Headaches	0.0	0.0	334.0	-0.354	0.723
BN20 Seizures	0.0	0.0	385.0	1.46	0.143
BN20 Drowsiness	0.0	33.3	418.0	1.27	0.205
BN20 Hair Loss	0.0	0.0	373.0	0.63	0.526
BN20 Itchy Skin	0.0	0.0	377.0	0.65	0.515
BN20 Weakness of Legs	0.0	0.0	404.5	1.27	0.203
BN20 Bladder Control	0.0	0.0	393.0	0.90	0.369

* Mean rank

3.4.6 Intervention versus Active monitoring

HRQoL scores of patients who have had an intervention for their meningioma (surgery, fractionated radiotherapy, SRS) were compared with patients who have been followed-up with active monitoring only. HRQoL scores in the groups were not normally distributed as assessed by the Shapiro-Wilk test (p values < 0.05). Individual group sizes were small. A number of domains had outliers. The most appropriate test for comparing the HRQoL scores of the groups was by using the non-parametric Mann-Whitney-U test.

3.4.6.1 Group demographics

Table 3.11 shows the characteristics of patients treated with an intervention compared to active monitoring alone. Patients treated with intervention had a longer median follow-up time (*10.6 years vs 7.5 years, mean rank 27.7 vs 18.7, p=0.032*) and were more likely to have a higher baseline ECOG performance status (*p=0.042*)[7]. Patients treated with an intervention were more likely to have experienced progression than the group managed with active monitoring (*24% vs 0%, p=0.044*).

[7] A higher ECOG performance status score indicates a lower level of functioning

Table 3.13: Comparison of demographic, clinical and treatment variables between patients treated with an intervention compared to followed with active monitoring alone			
Variable	**Intervention**	**Active monitoring**	**p**
Sample size (n=54)	37	17	n/a
Median age at completion of questionnaires	66.58 (26.1*)	68.34 (30.7*)	0.319
Median years since diagnosis	10.6 (27.7*)	7.5 (18.7*)	**0.032**
Female	28 (76)	15 (88)	0.470†
WHO Grade	I: 31 (89) II: 4 (11)	I: n/a II: n/a	n/a
Tumour location	Convexity: 11 (31) Anterior midline: 6 (17) Sphenoid wing: 7 (20) Parasagittal: 5 (14) Posterior fossa- lateral and posterior: 3 (9) Parafalcine: 0 (0) Posterior fossa- midline: 1 (3) Pineal: 1 (3) Tentorial: 1 (3)	Convexity: 6 (38) Anterior midline: 5 (31) Sphenoid wing: 1 (6) Parasagittal: 0 (0) Posterior fossa- lateral and posterior: 1 (6) Parafalcine: 3 (19) Posterior fossa- midline: 0 (0) Pineal: 0 (0) Tentorial: 0 (0)	0.109†
Skull base tumour	18 (50)	7 (44)	0.677
Tumour laterality	Right: 15 (42) Left: 15 (42) Midline: 6 (17)	Right: 6 (40) Left: 7 (47) Midline: 2 (13)	1.000†
Multiple meningiomas	2 (5)	2 (12)	0.582†
Incidental meningioma	5 (14)	17 (100)	**0.000**
Number of medications (median)	3.0 (27.6*)	3.0 (27.3*)	0.955
Current AEDs (median)	0.0 (29.1*)	0.0 (24.0*)	0.101
Baseline Performance Status (ECOG)	0: 8 (24) 1: 16 (48) 2: 8 (24) 3: 1 (3)	0: 9 (53) 1: 6 (35) 2: 2 (12) 3: 0 (0)	**0.042**
ACCI	0: 2 (5) 1: 4 (11) 2: 9 (24) 3: 8 (22) 4: 8 (22) 5: 1 (3) 6: 3 (8) 7: 2 (5)	0: 0 (0) 1: 1 (6) 2: 3 (18) 3: 6 (35) 4: 1 (6) 5: 3 (18) 6: 2 (12) 7: 1 (6)	0.259
Initial management	Active monitoring: 8 (22) Surgery: 29 (78)	Active monitoring: 17 (100) Surgery: 0 (0)	**0.000**

Table 3.11: Comparison of demographic, clinical and treatment variables between patients treated with an intervention compared to followed with active monitoring alone (continued)			
Variable	**Intervention**	**Active monitoring**	**p**
Progression since diagnosis	9 (24)	0 (0)	**0.044**†
Highest education level	No education: 8 (22) GCSE: 13 (35) A-Levels: 10 (27) Undergraduate: 2 (5) Master's degrees: 4 (11)	No education: 1 (6) GCSE: 9 (53) A-Levels: 3 (18) Undergraduate: 3 (18) Master's degrees: 1 (6)	0.572
Employment status	Retired: 19 (51) Part-time employment: 5 (14) Full-time employment: 4 (11) Self-employed: 4 (11) Unable to work due to health: 4 (11) Homemaker: 1 (3)	Retired: 13 (76) Part-time employment: 2 (12) Full-time employment: 2 (12) Self-employed: 0 (0) Unable to work due to health: 0 (0) Homemaker: 0 (0)	0.482†
Current driving status	22 (59)	9 (53)	0.653
COVID-19 response	20 (54)	11 (65)	0.462

* Mean rank
† Fisher's Exact Test
All results in Table 3.11 are reported as frequency and percentages: n (%) unless stated otherwise.

3.4.6.2 HRQoL

Table 3.12 shows the comparison of HRQoL scores between meningioma patients treated with intervention or followed-up with active monitoring alone. A number of domains across SF-36, QLQ-C30 and QLQ-BN20 were impaired in patients treated with intervention. Patients receiving intervention scored lower, indicating impairment, in the following SF-36 domains: Role Physical (*mean rank 23.6 vs 34.3, U=429.5 Z= 2.57 p=0.010*), Energy and Fatigue (*mean rank 23.4 vs 34.6, U=435.0 Z=2.47 p=0.014*), Emotional Wellbeing, (*mean rank 24.5 vs 32.3, U=396.5 Z=1.73 p=0.083*), Social Functioning (*75.0 vs 100.0, U=418.0 Z=2.06 p=0.039*) and Pain (*mean rank 24.6 vs 33.8, U=422.0 Z=2.02 p=0.043*).

Patients receiving intervention had impaired scores compared to those followed with active monitoring alone in the following QLQ-C30 domains: Summary Score (*80.7 vs 92.1, U=436.0 Z=2.26 p=0.024*), Social Functioning (*83.3 vs 100.0,*

U=411.0 Z= 2.00 p=0.045), Fatigue (*33.3 vs 11.1, U=199.5 Z=-2.173 p=0.030*), Cognitive Functioning (*mean rank 25.0 vs 33.0, U= 407.5 Z= 1.78 p=0.076*) and Pain (*mean rank 30.5 vs 20.9, U=203.0 Z=-2.15 p=0.032*). In the QLQ-BN20, impairments were identified in the domains of Communication Deficit (11.1 vs 0.0, *U=212.0 Z=-2.09 p=0.037*) and Drowsiness (*mean rank 30.6 vs 20.8, U= 200.5.0 Z=-2.32 p=0.020*).

Table 3.14: Comparison of HRQoL scores between patients receiving an intervention or active monitoring alone

Domains	Intervention (median) n = 37	Active monitoring (median) n = 17	*U*	*Z*	*p*
SF-36 Physical Functioning	85.0	85.0	331.5	0.32	0.750
SF-36 Role Physical	50.0 (23.6*)	100.0 (34.3*)	429.5	2.57	**0.010**
SF-36 Role Emotional	100.0	100.0	368.0	1.53	0.126
SF-36 Energy/ Fatigue	52.5 (23.4*)	70.0 (34.6*)	435.0	2.47	**0.014**
SF-36 Emotional Wellbeing	76.0 (24.5*)	84.0 (32.3*)	396.5	1.73	0.083
SF-36 Social Functioning	75.0	100.0	418.0	2.06	**0.039**
SF-36 Pain	67.5 (24.6*)	80.0 (33.8*)	422.0	2.02	**0.043**
SF-36 General Health	50.0	65.0	358.5	0.82	0.411
QLQ-C30 Summary Score	80.7	92.1	436.0	2.26	**0.024**
QLQ-C30 Physical Functioning	86.7	93.3	359.5	0.85	0.393
QLQ-C30 Role Functioning	100.0	100.0	363.0	1.01	0.314
QLQ-C30 Emotional Functioning	75.0	91.7	400.5	1.63	0.103
QLQ-C30 Cognitive Functioning	66.7 (25.0*)	100.0 (33.0*)	407.5	1.78	0.076
QLQ-C30 Social Functioning	83.3	100.0	411.0	2.00	**0.045**
QLQ-C30 Fatigue	33.3	11.1	199.5	-2.17	**0.030**
QLQ-C30 Nausea & Vomiting	0.0	0.0	372.0	1.58	0.113
QLQ-C30 Pain	33.0 (30.5*)	0.0 (20.9*)	203.0	-2.15	**0.032**
QLQ-C30 Dyspnoea	0.0	0.0	337.0	0.62	0.535
QLQ-C30 Insomnia	33.3 (29.5*)	0.0 (23.1*)	240.0	-1.47	0.142
QLQ-C30 Appetite Loss	0.0 (28.2*)	0.0 (25.9*)	287.5	-0.74	0.457
QLQ-C30 Constipation	0.0 (26.2*)	0.0 (30.3*)	361.5	1.15	0.250
QLQ-C30 Diarrhoea	0.0 (27.9*)	0.0 (26.7*)	301.0	-0.50	0.617
QLQ-C30 Financial Difficulties	0.0	0.0	280.5	-1.09	0.278
QLQ-C30 Global Health Status	75.0	66.7	342.0	0.52	0.602

Table 3.15: Comparison of HRQoL scores between patients receiving an intervention or active monitoring alone (continued)					
Domains	**Intervention (median) n = 37**	**Active monitoring (median) n = 17**	***U***	***Z***	***p***
BN20 Future Uncertainty	25.0	8.3	232.5	-1.55	0.121
BN20 Visual Disorder	0.0	0.0	320.5	0.12	0.901
BN20 Motor Dysfunction	11.1	0.0	255.0	-1.18	0.240
BN20 Communication Deficit	11.1	0.0	212.0	-2.09	**0.037**
BN20 Headaches	33.3	0.0	249.5	-1.35	0.176
BN20 Seizures	0.0 (28.2*)	0.0 (26.0*)	289.0	-1.20	0.232
BN20 Drowsiness	33.3 (30.6*)	0.0 (20.8*)	200.5	-2.32	**0.020**
BN20 Hair Loss	0.0	0.0	311.0	-0.11	0.911
BN20 Itchy Skin	0.0	0.0	260.5	-1.49	0.137
BN20 Weakness of Legs	0.0	0.0	292.0	-0.58	0.564
BN20 Bladder Control	0.0	0.0	283.5	-0.72	0.472

* Mean rank. Statistically significant (p<0.05) results highlighted in bold.

3.4.7 Skull base meningiomas

HRQoL scores of patients who have skull base meningiomas were compared to patients who have non-skull base meningiomas. HRQoL scores in the groups were not normally distributed as assessed by the Shapiro-Wilk test (p values < 0.05). Individual group sizes were small. A number of domains had outliers. The most appropriate test for comparing the HRQoL scores of the groups was by using the non-parametric Mann-Whitney-U test.

3.4.7.1 Group demographics

Table 3.13 shows the characteristics of patients with skull base compared to non-skull base meningiomas. The two groups had similar characteristics. However, the two groups differed in the proportion of WHO Grade I and II meningiomas (p=0.039). Skull base meningiomas were less likely to have been completely resected (47% vs 78%, p=0.060).

Table 3.16: Comparison of demographic, clinical and treatment variables between patients with skull base and non-skull base meningioma			
Variable	**Skull base**	**Non-skull base**	**p**
Sample size* (n=52)	25	27	n/a
Median age at completion of questionnaires	67.6 (24.9*)	68.3 (28.0*)	0.469
Median years since diagnosis	9.9 (24.0*)	9.3 (23.1*)	0.826
Female	18 (72)	23 (85)	0.245
WHO Grade	I: 18 (100) II: 0 (0)	I: 12 (75) II: 4 (25)	**0.039**†
Tumour location	Convexity: 0 (0) Anterior midline: 11 (46) Sphenoid wing: 8 (33) Parasagittal: 0 (0) Posterior fossa- lateral and posterior: 4 (17) Parafalcine: 0 (0) Posterior fossa- midline: 1 (4) Pineal: 0 (0) Tentorial: 0 (0)	Convexity: 17 (63) Anterior midline: 0 (0) Sphenoid wing: 0 (0) Parasagittal: 5 (19) Posterior fossa- lateral and posterior: 0 (0) Parafalcine: 3 (11) Posterior fossa- midline: 0 (0) Pineal: 1 (4) Tentorial: 1 (4)	**0.000**†
Tumour laterality	Right: 8 (32) Left: 10 (40) Midline: 7 (28)	Right: 13 (50) Left: 12 (46) Midline: 1 (4)	0.057†
Multiple meningiomas	1 (4)	1 (4)	1.000†
Incidental meningioma	8 (32)	13 (48)	0.236
Number of medications	2.0 (27.8*)	3.0 (25.3*)	0.535
Current AEDs	0.0 (29.2*)	0.0 (24.0*)	0.058
Baseline Performance Status (ECOG)	0: 9 (39) 1: 10 (43) 2: 4 (17) 3: 0 (0)	0: 7 (28) 1: 12 (48) 2: 5 (20) 3: 1 (4)	0.374
ACCI	0: 1 (4) 1: 3 (12) 2: 5 (20) 3: 7 (28) 4: 4 (16) 5: 1 (4) 6: 3 (12) 7: 1 (4)	0: 0 (0) 1: 2 (7) 2: 6 (22) 3: 7 (26) 4: 5 (19) 5: 3 (11) 6: 2 (7) 7: 2 (7)	0.461
Initial management	Active monitoring: 11 (44) Surgery: 14 (56)	Active monitoring: 13 (48) Surgery: 14 (52)	0.764
Intervention	18 (72)	18 (67)	0.677
If operated, GTR	8 (47)	14 (78)	**0.060**

Table 3.13: Comparison of demographic, clinical and treatment variables between patients with skull base and non-skull base meningioma (continued)			
Variable	**Skull base**	**Non-skull base**	**p**
Progression since diagnosis	4 (16)	4 (15)	1.000†
Highest education level	No education: 1 (4) GCSE: 13 (52) A-Levels: 7 (28) Undergraduate: 2 (8) Master's degrees: 2 (8)	No education: 8 (30) GCSE: 8 (30) A-Levels: 6 (22) Undergraduate: 2 (7) Master's degrees: 3 (11)	0.314
Employment status	Retired: 16 (64) Part-time employment: 3 (12) Full-time employment: 3 (12) Self-employed: 1 (4) Unable to work due to health: 2 (8) Homemaker: 0 (0)	Retired: 16 (59) Part-time employment: 3 (11) Full-time employment: 3 (11) Self-employed: 2 (7) Unable to work due to health: 2 (7) Homemaker: 1 (4)	1.000†
Current driving status	15 (60)	14 (52)	0.554
COVID-19 response	14 (56)	16 (59)	0.812

* Mean rank

† Fisher's Exact Test

All results in Table 3.13 are reported as frequency and percentages: n (%) unless stated otherwise.

3.4.7.2 HRQoL

Table 3.14 shows the comparison of HRQoL scores between patients with skull base and non-skull base meningiomas. HRQoL scores between patients with skull base and non-skull base meningiomas were similar. However, patients with skull base meningiomas were found to have higher SF-36 Role Physical scores (*mean rank 30.1 vs 22.3, U=225.0 Z=-2.04 p=0.041*) and Social Functioning scores (*100.0 vs 75.0, U=234.5 Z=-2.02 p=0.043*). However, patients with skull base meningiomas had impaired QLQ-BN20 Visual Disorder domain scores (*mean rank 31.2 vs 22.2, U=220.5 Z=-2.36 p=0.018*).

Table 3.17: Comparison of HRQoL scores between patients with skull base and non-skull base meningiomas					
Domains	**Skull-base (median) n = 25**	**Non-skull-base (median) n = 27**	***U***	***Z***	***p***
SF-36 Physical Functioning	85.0	75.0	250.0	-1.62	0.106
SF-36 Role Physical	100.0 (30.1*)	50.0 (22.3*)	225.0	-2.04	**0.041**
SF-36 Role Emotional	100.0	100.0	257.5	-1.61	0.108
SF-36 Energy/ Fatigue	63.3 (27.4*)	55.0 (24.7)	290.0	-0.64	0.520
SF-36 Emotional Wellbeing	80.0	80.0	300.0	-0.45	0.650
SF-36 Social Functioning	100.0	75.0	234.5	-2.02	**0.043**
SF-36 Pain	77.5 (29.2*)	57.5 (24.0*)	269.5	-1.26	0.209
SF-36 General Health	55.0 (28.4*)	55.0 (24.8*)	291.0	-0.86	0.393
QLQ-C30 Summary Score	89.7 (28.4*)	84.3 (24.8*)	290.5	-0.86	0.389
QLQ-C30 Physical Functioning	93.3 (29.5*)	86.7 (23.7*)	262.5	-1.40	0.162
QLQ-C30 Role Functioning	100.0	100.0	279.5	-1.19	0.236
QLQ-C30 Emotional Functioning	83.3	83.3	336.0	-0.03	0.978
QLQ-C30 Cognitive Functioning	83.3 (25.6*)	83.3 (27.4*)	361.0	0.44	0.659
QLQ-C30 Social Functioning	100.0	100.0	318.5	-0.39	0.698
QLQ-C30 Fatigue	22.2 (25.4*)	22.2 (27.5*)	364.0	0.49	0.623
QLQ-C30 Nausea & Vomiting	0.0	0.0	334.0	-0.09	0.926
QLQ-C30 Pain	16.7 (25.2*)	33.3 (27.7*)	370.0	0.61	0.539
QLQ-C30 Dyspnoea	0.0	0.0	383.5	1.23	0.219
QLQ-C30 Insomnia	33.3 (26.7*)	33.3 (26.4*)	333.5	-0.08	0.938
QLQ-C30 Appetite Loss	0.0	0.0	352.5	0.40	0.689
QLQ-C30 Constipation	0.0	0.0	359.5	0.52	0.601
QLQ-C30 Diarrhoea	0.0	0.0	346.5	0.32	0.747
QLQ-C30 Financial Difficulties	0.0	0.0	320.5	-0.53	0.599
QLQ-C30 Global Health Status	83.3	66.7	271.0	-1.24	0.215

Table 3.18: Comparison of HRQoL scores between patients with skull base and non-skull base meningiomas					
Domains	**Skull-base (median) n = 25**	**Non-skull-base (median) n = 27**	***U***	***Z***	***p***
BN20 Future Uncertainty	16.7	25.0.7	373.0	0.66	0.509
BN20 Visual Disorder	11.1 (31.2*)	0.0 (22.2*)	220.5	-2.36	**0.018**
BN20 Motor Dysfunction	11.1	11.1	332.0	-0.11	0.915
BN20 Communication Deficit	11.1 (27.5*)	0.0 (25.6*)	313.5	-0.48	0.634
BN20 Headaches	0.0	0.0	376.5	0.80	0.424
BN20 Seizures	0.0	0.0	322.5	-0.68	0.497
BN20 Drowsiness	0.0	0.0	332.0	-0.11	0.912
BN20 Hair Loss	0.0	0.0	334.0	-0.12	0.908
BN20 Itchy Skin	0.0	0.0	282.5	-1.47	0.142
BN20 Weakness of Legs	0.0	0.0	275.5	-1.54	0.123
BN20 Bladder Control	0.0	0.0	343.5	0.14	0.890

* Mean rank. Statistically significant ($p<0.05$) results highlighted in bold.

3.4.8 COVID-19

A post-hoc analysis was completed to assess the association of COVID-19 with HRQoL in patients with meningioma. HRQoL scores of patients who responded during the COVID-19 lockdown period were compared to patients had responded prior (at clinic appointments). HRQoL scores in the groups were not normally distributed as assessed by the Shapiro-Wilk test (p values < 0.05). Individual group sizes were small. A number of domains had outliers. The most appropriate test for comparing the HRQoL scores of the groups was by using the non-parametric Mann-Whitney-U test.

3.4.8.1 Group demographics

Table 3.15 shows the characteristics of patients responding during COVID-19 compared to before COVID-19. Patients responding during COVID-19 lockdown were older (median age *72.3 vs 61.4, mean rank 32.9 vs 20.2, p=0.003*) and had a higher age-adjusted Charlson Comorbidity Index (ACCI) (*p=0.005*)[8]. The two groups differed in their tumour laterality (*p = 0.031*) and their initial management (*p=0.044*). COVID-19 respondents were less likely to have experienced progression since diagnosis (*6% vs 30%, p=0.028*). The two groups differed in their employment (*p=0.015*) and current driving status (*p =0.035*).

[8] A higher ACCI indicates a higher number of comorbid conditions

Table 3.19: Comparison of demographic, clinical and treatment variables between patients responding during and before COVID-19 lockdown			
Variable	**COVID-19 lockdown**	**Pre-COVID-19 lockdown**	**p**
Sample size (n=54)	31	23	n/a
Median age at completion of questionnaires	72.3 (32.9*)	61.4 (20.2*)	**0.003**
Median years since diagnosis	9.8 (25.0*)	10.0 (23.7*)	0.760
Female	27 (87)	16 (70)	0.173†
WHO Grade	I: 19 (95) II: 1 (5)	I: 12 (80) II: 3 (20)	0.292†
Tumour location	Convexity: 11 (37) Anterior midline: 8 (27) Sphenoid wing: 5 (17) Parasagittal: 3 (10) Posterior fossa- lateral and posterior: 1 (3) Parafalcine: 1 (3) Posterior fossa- midline: 0 (0) Pineal: 1 (3) Tentorial: 0 (0)	Convexity: 6 (29) Anterior midline: 3 (14) Sphenoid wing: 3 (14) Parasagittal: 2 (10) Posterior fossa- lateral and posterior: 3 (14) Parafalcine: 2 (10) Posterior fossa- midline: 1 (5) Pineal: 0 (0) Tentorial: 1 (5)	0.550†
Skull base tumour	14 (47)	11 (50)	0.812
Tumour laterality	Right: 16 (55) Left: 8 (28) Midline: 5 (17)	Right: 5 (23) Left: 14 (64) Midline: 3 (14)	**0.031**†
Multiple meningioma	2 (6)	2 (9)	1.000†
Incidental meningioma	15 (48)	7 (30)	0.184
Number of medications	3.0 (28.2*)	2.0 (26.5*)	0.684
Number of AEDs	0.0 (25.8*)	0.0 (29.8*)	0.170
Baseline Performance Status (ECOG)	0: 12 (39) 1: 12 (39) 2: 6 (19) 3: 1 (3)	0: 5 (26) 1: 10 (53) 2: 4 (21) 3: 0 (0)	0.614
ACCI	0: 1 (3) 1: 1 (3) 2: 5 (16) 3: 8 (26) 4: 5 (16) 5: 4 (13) 6: 4 (13) 7: 3 (10)	0: 1 (4) 1: 4 (17) 2: 7 (30) 3: 6 (26) 4: 4 (17) 5: 0 (0) 6: 1 (4) 7: 0 (0)	**0.005**
Initial management	Active monitoring: 18 (58) Surgery: 13 (42)	Active monitoring: 7 (30) Surgery: 16 (70)	**0.044**
Intervention	20 (65)	17 (74)	0.462
If operated, GTR	15 (75)	7 (44)	0.056

Table 3.15: Comparison of demographic, clinical and treatment variables between patients responding during and before COVID-19 lockdown (continued)			
Variable	**COVID-19 lockdown**	**Pre-COVID-19 lockdown**	**p**
Progression since diagnosis	2 (6)	7 (30)	**0.028**†
Highest education level	No education: 6 (19) GCSE: 13 (42) A-Levels: 6 (19) Undergraduate: 3 (10) Master's degrees: 3 (10)	No education: 3 (13) GCSE: 9 (39) A-Levels: 7 (30) Undergraduate: 2 (9) Master's degrees: 2 (9)	0.570
Employment status	Retired: 22 (71) Part-time employment: 5 (16) Full-time employment: 1 (3) Self-employed: 0 (0) Unable to work due to health: 2 (6) Homemaker: 1 (3)	Retired: 10 (43) Part-time employment: 2 (9) Full-time employment: 5 (22) Self-employed: 4 (17) Unable to work due to health: 2 (9) Homemaker: 0 (0)	**0.015**†
Current driving status	14 (45)	17 (74)	**0.035**

* Mean rank
† Fisher's Exact Test
All results in Table 3.15 are reported as frequency and percentages: n (%) unless stated otherwise.

3.4.8.2 HRQoL

SF-36 Physical Functioning scores were significantly lower in patients responding during COVID-19 lockdown (*mean rank 23.8 vs 32.5, U= 471.0 Z= 2.02 p=0.044*). A similar finding was also observed in the QLQ-C30 Physical Functioning scale (*86.7 vs 93.3, U=514.5 Z=2.81 p=0.005*). All other HRQoL domain scores were similar.

Table 3.20: Comparison of HRQoL scores between patients who responded during or before the COVID-19 lockdown					
Domains	**COVID-19 (median) n = 31**	**Pre-COVID-19 (median) n = 23**	***U***	***Z***	***p***
SF-36 Physical Functioning	75.0 (23.8*)	85.0 (32.5*)	471.0	2.02	**0.044**
SF-36 Role Physical	75.0 (25.3*)	100.0 (29.4*)	394.0	1.04	0.297
SF-36 Role Emotional	100.0 (24.6*)	100.0 (30.4*)	416.0	1.76	0.079
SF-36 Energy/ Fatigue	60.0 (28.0*)	57.5 (25.6*)	309.0	-0.58	0.562
SF-36 Emotional Wellbeing	80.0 (27.0*)	78.0 (27.1*)	342.0	0.02	0.986
SF-36 Social Functioning	100.0	87.5	381.5	0.47	0.640
SF-36 Pain	67.5	77.5	402.0	0.80	0.422
SF-36 General Health	55.0	55.0	373.0	0.29	0.772
QLQ-C30 Summary Score	85.7	88.7	392.5	0.63	0.529
QLQ-C30 Physical Functioning	86.7	93.3	514.5	2.81	**0.005**
QLQ-C30 Role Functioning	100.0	100.0	423.5	1.31	0.192
QLQ-C30 Emotional Functioning	83.3 (27.1*)	75.0 (28.1*)	369.5	0.231	0.817
QLQ-C30 Cognitive Functioning	83.3 (29.3*)	66.7 (25.1*)	300.5	-1.01	0.315
QLQ-C30 Social Functioning	100.0	100.0	372.5	0.31	0.755
QLQ-C30 Fatigue	22.2	22.2	309.5	-0.83	0.404
QLQ-C30 Nausea & Vomiting	0.0	0.0	378.0	0.56	0.578
QLQ-C30 Pain	33.3 (30.2*)	16.7 (23.9*)	272.5	-1.52	0.129
QLQ-C30 Dyspnoea	0.0	0.0	292.5	-1.66	0.098
QLQ-C30 Insomnia	33.3 (27.7*)	33.3 (27.2*)	349.0	-0.14	0.890
QLQ-C30 Appetite Loss	0.0	0.0	353.0	-0.09	0.928
QLQ-C30 Constipation	0.0	0.0	361.5	0.12	0.909
QLQ-C30 Diarrhoea	0.0	0.0	352.0	-0.16	0.876
QLQ-C30 Financial Difficulties	0.0	0.0	388.5	0.96	0.337
QLQ-C30 Global Health Status	66.7	83.3	428.0	1.28	0.202
BN20 Future Uncertainty	16.7	16.7	341.0	-0.28	0.783
BN20 Visual Disorder	0.0	0.0	341.0	-0.30	0.763
BN20 Motor Dysfunction	11.1	0.0	304.0	-0.97	0.330
BN20 Communication Deficit	0.0	0.0	381.0	0.47	0.639
BN20 Headaches	0.0	33.3	437.5	1.58	0.114
BN20 Seizures	0.0	0.0	376.5	0.88	0.378
BN20 Drowsiness	0.0	33.3	405.5	0.94	0.349
BN20 Hair Loss	0.0	0.0	409.0	1.58	0.115
BN20 Itchy Skin	0.0	0.0	351.5	-0.13	0.897
BN20 Weakness of Legs	0.0	0.0	298.0	-1.41	0.159
BN20 Bladder Control	0.0	0.0	286.5	-1.53	0.127

* Mean rank. Statistically significant ($p<0.05$) results highlighted in bold.

3.5 Discussion

The aim of the QUALMS study was to identify the physical, cognitive and psychosocial quality of life outcomes of patients with meningioma. This study identified long-term HRQoL outcomes an average of ten years after diagnosis. The QUALMS study is the first to specifically assess HRQoL in patients with incidental meningioma and compare patients managed with intervention to active monitoring alone. A total of 54 patients were included in this exploratory analysis.

In comparison to normative population values, meningioma patients reported impairments in the domains of Physical Functioning, Role Physical, General Health and Cognitive Functioning. Similarly, impairments of Physical Functioning, Role Physical and General Health have been reported in two previous studies assessing HRQoL of meningioma patients with SF-36 on average 3.4 and 4.9 years after treatment (238, 241).

This study highlights that patients have do have long-term HRQoL issues persisting many years after initial diagnosis. Issues relating to physical health problems are most evident. However, this study showed that many other domains encompassing self-reported emotional wellbeing and social functioning were comparable to normative values. Previous studies have highlighted that impairments within these domains are prevalent early after diagnosis and treatment (245, 250). However, this study found that these issues are less reported as the time since diagnosis increases. A potential reason for this is the phenomenon of 'response shift' which is defined as a change in the meaning of one's self-evaluation of the target construct QOL (307). Initially, after diagnosis and treatment, a number of limitations may affect one's quality of life, but over time patients may re-evaluate what they consider normal. Therefore, issues which were initially considered problematic become less so over time.

Overall, patients diagnosed with incidental meningioma reported better HRQoL scores in the domains of Communication Deficit, Cognitive Functioning and Fatigue compared to patients with a non-incidental meningioma. Furthermore, the QLQ-C30 summary scores were higher, indicating better HRQoL in patients with incidental meningioma. Patients in the incidental meningioma cohort had overall a lower baseline ECOG performance status and were less likely to have had an intervention and or experienced tumour progression. Previous studies have shown that patients treated with surgery experience cognitive deficits and have a high prevalence of fatigue (87, 247). Therefore, it may be hypothesised that patients with incidental meningioma, who tend to follow a course of active monitoring alone, may have better HRQoL scores because they are less likely experience the morbidity associated with the treatment of meningioma.

In a comparison of patients treated with intervention and those followed by active monitoring alone, the intervention cohort reported impaired HRQoL scores. The intervention cohort reported inferior scores in Role Physical, Energy and Fatigue, Emotional Wellbeing, Social Functioning, Pain, Cognitive Functioning, Communication Deficit and Drowsiness. Specifically, the domains relating to Fatigue, Social Functioning and Pain were found to be impaired across multiple questionnaires. The QLQ-C30 summary score was lower in patients receiving an intervention. These results suggest that patients managed with intervention experience lower long-term HRQoL.

However, a causal relationship between intervention and HRQoL scores cannot be inferred from this study. Patients receiving intervention are more likely to have a health burden which would lower their quality of life. For example, the patients in this study who received an intervention were more likely to have a higher baseline ECOG performance status, which may have predisposed them to inferior long-term HRQoL outcomes. Future analyses could statistically adjust for this potential confounding.

A post-hoc analysis was completed to investigate the impact of COVID-19 on HRQoL in patients with meningioma. Patients responding during COVID-19 lockdown had similar HRQoL outcomes to those who had responded before the COVID-19 lockdown. Lower Physical Functioning scores were reported by patients responding during COVID-19 lockdown; however, these patients were older and had a higher ACCI. Notably, COVID-19 lockdown was not associated with poorer Social Functioning, Emotional Wellbeing of Future Uncertainty scale scores. It may be hypothesised that since COVID-19 lockdown placed limitations on travel and interaction with others, patients may have felt isolated or had increased anxiety. However, early results from the QUALMS study seems to indicate that this was not the case, and patients had similar HRQoL during COVID-19 compared to before.

3.5.1 Choice of HRQoL tools

SF-36 was chosen as it is the most popular HRQoL tool used in the meningioma literature, which allows for the comparison of this study's results to previous studies. Suitable alternatives to SF-36 include the EuroQoL 5-Dimensions 5-Levels (EQ-5D-5L) survey, Nottingham Health Profile (NHP) and Questions on Life Satisfaction Survey. The QLQ-C30 was chosen because it assesses a range of domains and items which are relevant to patients diagnosed and treated for cancer. A suitable alternative is the FACT-G; however, the QLQ-C30 was chosen because, by comparison, it covers a wider range of issues. Luckett et al. have published a decision algorithm to help researchers to decide whether to use QLQ-C30 or FACT-G (308). The Anterior Skull Base Questionnaire (ABSQ) is another cancer-specific tool but was not chosen as it assesses issues arising from anterior skull base tumours only. The QLQ-BN20 was chosen as it assesses issues relevant to patients with a brain tumour. The FACT-BR is a suitable alternative, however the QLQ-BN20 was considered more appropriate as the scales and items are an extension of the QLQ-C30.

However, the results of the preliminary analysis of the meningioma cohort (Table 3.8) show limited impairments across a number of symptom items (e.g. dyspnoea, appetite loss, constipation, hair loss, itchy skin) on the QLQ-C30 and BN20. Indeed, items such as these are more relevant to patients with cancer, whose disease and treatment may lead to the onset of systemic symptoms. It is not expected that many meningioma patients would suffer these particular symptoms as a result of their condition or treatment. Therefore, the content validity of these particular questionnaires to meningioma patients is uncertain. In retrospect, this study could have utilised (and perhaps validated) the FACT-MNG, therefore presenting items of potentially greater relevance to meningioma patients.

3.5.2 Strengths and Limitations

This is the first study to specifically investigate the long-term HRQoL outcomes of patients with incidental meningiomas, and to compare outcomes of patients who received an intervention with those managed with active monitoring alone. A combination of general, cancer-specific and brain tumour-specific tools was used to identify issues affecting the lives of patients with meningioma (see Discussion – Choice of HRQoL tools). The inclusion criteria were broad; patients with incidental and/or operated meningiomas of any WHO Grade were eligible to participate.

However, a meningioma-specific tool was not used to assess patients. This is because none have been clinically validated for use. No pre-treatment or baseline HRQoL scores are available, and so it is not possible to determine causality between variables and HRQoL scores. No healthy controls were sampled in this study, and so comparisons to the general population were made using normative population values. However, these values are not matched for age, sex, geography or education level when making comparisons to patient responses in the QUALMS study. It was identified after the completion of this chapter that there is a British and American version of the SF-36 questionnaire.

The QUALMS study used the American version of the questionnaire, but compared results to the Welsh normative population data, which seem to have been assessed using the British version of the questionnaire (303). Future analyses will attempt to rectify this issue.

As this study is from a single centre in the North-West of England, it is not possible to confidently generalise the study findings to all meningioma patients in different countries. There is a risk of responder bias, as the participants who responded may be more cognitively able and have a higher HRQoL; those who are the most unwell are unlikely to participate.

Moreover, patients contacted by post and those attending clinic would be able to discuss their responses with friends and family. Therefore, there is a risk that some proxy-reported outcomes may have been provided. This is the case for up to three patients that completed the questionnaires at clinic appointments. However, this is an unavoidable limitation of the sampling strategy. Finally, this exploratory analysis contained a small sample size and data was not normally distributed. Therefore, it was not possible to adjust for confounders using regression analyses and to isolate variables with the greatest effect on HRQoL.

This chapter details a preliminary analysis of the responses to the QUALMS study. At the point of analysis, the postal response rate was only 4%. Therefore the generalisability of the results to the wider meningioma population is questionable. The final analysis of QUALMS responses will incorporate a larger number of postal responses, and the response rate is anticipated to be in the region of 25-35%. There is also a potential bias in that the patients who were approached at clinic appointments may have been more likely to have on-going issues relating to their care, which may impact on their HRQoL responses. To address this concern, the final analysis of QUALMS will include a comparison of clinical and demographic details of the responders and non-responders. This will allow readers to make an assessment of the representativeness of the responder cohort and therefore the generalisability of the QUALMS study

results. If confounders are identified, the final analysis will attempt to adjust for these.

A proportion of participants who returned the completed questionnaires during COVID-19 interpreted and answered some questions (e.g. related to social functioning) in different ways. For example, some patients wrote on their questionnaires about how their social functioning was normal usually, but currently limited due to the COVID-19 lockdown. Other patients chose to answer these questions not considering the impact of COVID-19. Therefore, there were differences of interpretation of selected questions due to the effect of the COVID-19 lockdown.

Finally, the pre-COVID-19 responder cohort are patients who responded at clinic appointments, and the COVID-19 responder cohort are patients who responded by post. Therefore, it is to be noted that the methods of collecting the HRQoL results for these two cohorts were different. The difference in the response collection may impact the HRQoL results. This is a limitation of the study. However, the questionnaires were self-administered in both methods of collection. Furthermore, the two groups differed in their responder characteristics.

3.6 Conclusion

The results of this exploratory analysis suggest that patients with meningioma experience long-term HRQoL issues many years after diagnosis. However, patients with incidental meningiomas and patients who are managed with active monitoring alone are more likely to have better HRQoL outcomes. Patients are still being recruited to the study, and future analyses will aim to further characterise the nature and magnitude of HRQoL impairments in patients with meningioma.

Chapter 4: Conclusion

Meningiomas are a common intracranial tumour, and their management constitutes a large proportion of neuro-oncology clinical practice. The majority of sporadic meningiomas are diagnosed in women, and their incidence increases with age. Incidental meningiomas are usually managed with active monitoring using MRI scans, and symptomatic meningiomas are typically treated with surgery or radiotherapy. Patients have good five- and ten-year survival outcomes. Patient-Reported Outcomes (PROs) allow the burden of disease and treatment to be evaluated through a patient's perspective. PROs can be categorised into assessments of health-related quality of life (HRQoL), 'Patient-Reported Health Status', 'Patient-Reported Symptoms', 'Patient-Reported Functioning', 'Patient-Reported Feelings' or 'Other PROs'. Over the last three decades, little research has been completed to investigate PROs of meningioma.

A systematic review was conducted to identify studies assessing PROs of meningiomas. In total, thirty-three studies were identified. HRQoL was evaluated by 25 studies, which highlighted that patients have impairments across a number of physical and psychological domains. Symptoms and functioning were specifically assessed by nine and eight studies, respectively. Patients have elevated anxiety scores following diagnosis and treatment; however, these tend to improve over time. In a subset of patients, long-term anxiety and post-traumatic stress may remain. Meningioma patients were found to have reduced participation in activities, and employment levels decreased postoperatively. Patient-reported feelings were assessed by two studies, which showed that meningioma patients have increased benefit finding following their experiences. For young, female patients, the diagnosis of meningioma can impact birth desires.

The systematic review shows that PROs extend beyond HRQoL, which has been the focus of meningioma PRO research in recent decades. Furthermore, the

diagnosis and treatment of meningiomas impact a range of PRO domains other than HRQoL. At present, no meningioma-specific tool has been validated for use in patients. The FACT-MNG tool is meningioma-specific but focusses only on HRQoL tool, and is currently unvalidated (210). Given the results of the systematic review, the Liverpool Neuro-Oncology Group will consider developing a meningioma-specific, holistic PRO assessment tool. The next step in developing this tool is to assess the methodological quality of the 27 PROMs identified in this study and to extract individual items for further evaluation.

Furthermore, the systematic review highlights that long-term HRQoL of patients has not been evaluated thoroughly. Moreover, there is a lack of studies assessing the HRQoL of patients with incidental meningiomas or those treated with active monitoring alone. A cross-sectional research study (the QUALMS study) assessed HRQoL of patients with incidental and/or operated meningiomas. An initial exploratory analysis was completed of 54 patients who provided HRQoL outcomes on average ten years after diagnosis. Compared to normative population values, meningioma patients reported impaired HRQoL scores in the domains of Physical Functioning, Role Physical, General Health and Cognitive Functioning. The domains related to emotional and social functioning were similar to normative values. Patients with incidental meningiomas and those followed-up with active monitoring alone reported better scores than patients with non-incidental meningioma or those who received treatment, respectively. However, the QUALMS study design precludes assessment of causality. The QUALMS study is currently recruiting patients, and a larger sample size will allow for adjustment of confounders to better evaluate associations. The Liverpool Neuro-Oncology Group is considering a national multicentre study to assess long-term, patient-reported outcomes further.

In conclusion, this thesis has investigated the patient-reported and quality of life outcomes in intracranial meningioma. Future research is being planned to

evaluate PROs further and to develop a meningioma-specific, holistic measurement tool for use in clinical practice.

References

1. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. Neuro-Oncology. 2019;21(Supplement_5):v1-v100.
2. Suppiah S, Nassiri F, Bi WL, Dunn IF, Hanemann CO, Horbinski CM, et al. Molecular and translational advances in meningiomas. Neuro-Oncology. 2019;21(Supplement_1):i4-i17.
3. Preusser M, Brastianos PK, Mawrin C. Advances in meningioma genetics: novel therapeutic opportunities. Nat Rev Neurol. 2018;14(2):106-15.
4. Villanueva-Meyer JE, Mabray MC, Cha S. Current Clinical Brain Tumor Imaging. Neurosurgery. 2017;81(3):397-415.
5. Badie B, Brooks N, Souweidane MM. Endoscopic and Minimally Invasive Microsurgical Approaches for Treating Brain Tumor Patients. Journal of Neuro-Oncology. 2004;69(1):209-19.
6. Brastianos PK, Galanis E, Butowski N, Chan JW, Dunn IF, Goldbrunner R, et al. Advances in multidisciplinary therapy for meningiomas. Neuro Oncol. 2019;21(Suppl 1):i18-i31.
7. Plater F. Observationum in hominis affectibus plerisque, corpori et animo, functionum laesione, dolore, aliave, molestia et vitio incommodantibus, libri tres. Ludovici Konig. 1614.
8. Bright R. Reports of medical cases, symptoms and morbid anatomy: Longman; 1831.
9. Meyer L. Die Epithelsgranulationen der Arachnoidea. Virchows Arch. 1859;17:209–27.
10. Cushing H. THE MENINGIOMAS (DURAL ENDOTHELIOMAS): THEIR SOURCE, AND FAVOURED SEATS OF ORIGIN1. Brain. 1922;45(2):282-316.
11. Okonkwo DO, Laws ER. Meningiomas: Historical Perspective. In: Lee JH, editor. Meningiomas. London: Springer London; 2009. p. 3-10.
12. Wiemels J, Wrensch M, Claus EB. Epidemiology and etiology of meningioma. Journal of neuro-oncology. 2010;99(3):307-14.
13. Meling TR, Da Broi M, Scheie D, Helseth E. Meningiomas: skull base versus non-skull base. Neurosurg Rev. 2019;42(1):163-73.
14. Evans DG, Huson SM, Donnai D, Neary W, Blair V, Teare D, et al. A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. J Med Genet. 1992;29(12):841-6.
15. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z, et al. Neurofibromatosis type 2. Lancet. 2009;373(9679):1974-86.
16. Parry DM, Eldridge R, Kaiser-Kupfer MI, Bouzas EA, Pikus A, Patronas N. Neurofibromatosis 2 (NF2): clinical characteristics of 63 affected individuals and clinical evidence for heterogeneity. Am J Med Genet. 1994;52(4):450-61.
17. Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, et al. The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery. 1996;38(5):880-5; discussion 5-6.

18. Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. Arch Dis Child. 1999;81(6):496-9.
19. Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. J Child Neurol. 2003;18(10):718-24.
20. Antinheimo J, Haapasalo H, Haltia M, Tatagiba M, Thomas S, Brandis A, et al. Proliferation potential and histological features in neurofibromatosis 2-associated and sporadic meningiomas. J Neurosurg. 1997;87(4):610-4.
21. Ron E, Modan B, Boice JD, Jr., Alfandary E, Stovall M, Chetrit A, et al. Tumors of the brain and nervous system after radiotherapy in childhood. N Engl J Med. 1988;319(16):1033-9.
22. Shintani T, Hayakawa N, Hoshi M, Sumida M, Kurisu K, Oki S, et al. High incidence of meningioma among Hiroshima atomic bomb survivors. J Radiat Res. 1999;40(1):49-57.
23. Bowers DC, Nathan PC, Constine L, Woodman C, Bhatia S, Keller K, et al. Subsequent neoplasms of the CNS among survivors of childhood cancer: a systematic review. Lancet Oncol. 2013;14(8):e321-8.
24. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2010;102(14):1083-95.
25. Cahan WG, Woodard HQ, et al. Sarcoma arising in irradiated bone; report of 11 cases. Cancer. 1948;1(1):3-29.
26. Yamanaka R, Hayano A, Kanayama T. Radiation-Induced Meningiomas: An Exhaustive Review of the Literature. World Neurosurg. 2017;97:635-44.e8.
27. Al-Mefty O, Topsakal C, Pravdenkova S, Sawyer JR, Harrison MJ. Radiation-induced meningiomas: clinical, pathological, cytokinetic, and cytogenetic characteristics. J Neurosurg. 2004;100(6):1002-13.
28. Morgenstern PF, Shah K, Dunkel IJ, Reiner AS, Khakoo Y, Rosenblum MK, et al. Meningioma after radiotherapy for malignancy. J Clin Neurosci. 2016;30:93-7.
29. Galloway TJ, Indelicato DJ, Amdur RJ, Swanson EL, Morris CG, Marcus RB. Favorable outcomes of pediatric patients treated with radiotherapy to the central nervous system who develop radiation-induced meningiomas. Int J Radiat Oncol Biol Phys. 2011;79(1):117-20.
30. Sadetzki S, Flint-Richter P, Ben-Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. J Neurosurg. 2002;97(5):1078-82.
31. Soffer D, Pittaluga S, Feiner M, Beller AJ. Intracranial meningiomas following low-dose irradiation to the head. J Neurosurg. 1983;59(6):1048-53.
32. Group IS. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol. 2010;39(3):675-94.
33. Mupparapu M, Baddam VRR, Lingamaneni KP, Singer SR. Dental x-ray exposure is not associated with risk of meningioma: a 2019 meta-analysis. Quintessence Int. 2019;50(10):822-9.
34. Xu P, Luo H, Huang GL, Yin XH, Luo SY, Song JK. Exposure to ionizing radiation during dental X-rays is not associated with risk of developing meningioma: a meta-analysis based on seven case-control studies. PLoS One. 2015;10(2):e0113210.

35. Bickerstaff ER, Small JM, Guest IA. The relapsing course of certain meningiomas in relation to pregnancy and menstruation. J Neurol Neurosurg Psychiatry. 1958;21(2):89-91.
36. Kerschbaumer J, Freyschlag CF, Stockhammer G, Taucher S, Maier H, Thomé C, et al. Hormone-dependent shrinkage of a sphenoid wing meningioma after pregnancy: case report. J Neurosurg. 2016;124(1):137-40.
37. Michelsen JJ, New PF. Brain tumour and pregnancy. J Neurol Neurosurg Psychiatry. 1969;32(4):305-7.
38. Cahill DW, Bashirelahi N, Solomon LW, Dalton T, Salcman M, Ducker TB. Estrogen and progesterone receptors in meningiomas. J Neurosurg. 1984;60(5):985-93.
39. Carroll RS, Glowacka D, Dashner K, Black PM. Progesterone receptor expression in meningiomas. Cancer Res. 1993;53(6):1312-6.
40. Olson JJ, Beck DW, Schlechte J, Loh PM. Hormonal manipulation of meningiomas in vitro. J Neurosurg. 1986;65(1):99-107.
41. Matsuda Y, Kawamoto K, Kiya K, Kurisu K, Sugiyama K, Uozumi T. Antitumor effects of antiprogesterones on human meningioma cells in vitro and in vivo. J Neurosurg. 1994;80(3):527-34.
42. Ji Y, Rankin C, Grunberg S, Sherrod AE, Ahmadi J, Townsend JJ, et al. Double-Blind Phase III Randomized Trial of the Antiprogestin Agent Mifepristone in the Treatment of Unresectable Meningioma: SWOG S9005. J Clin Oncol. 2015;33(34):4093-8.
43. Sharma R, Garg K, Katiyar V, Tandon V, Agarwal D, Singh M, et al. The role of mifepristone in the management of meningiomas: A systematic review of literature. Neurol India. 2019;67(3):698-705.
44. Harland TA, Freeman JL, Davern M, McCracken DJ, Celano EC, Lillehei K, et al. Progesterone-only contraception is associated with a shorter progression-free survival in premenopausal women with WHO Grade I meningioma. J Neurooncol. 2018;136(2):327-33.
45. Qi ZY, Shao C, Huang YL, Hui GZ, Zhou YX, Wang Z. Reproductive and exogenous hormone factors in relation to risk of meningioma in women: a meta-analysis. PLoS One. 2013;8(12):e83261.
46. Fan ZX, Shen J, Wu YY, Yu H, Zhu Y, Zhan RY. Hormone replacement therapy and risk of meningioma in women: a meta-analysis. Cancer Causes Control. 2013;24(8):1517-25.
47. Raj R, Korja M, Koroknay-Pál P, Niemelä M. Multiple meningiomas in two male-to-female transsexual patients with hormone replacement therapy: A report of two cases and a brief literature review. Surg Neurol Int. 2018;9:109.
48. Mancini I, Rotilio A, Coati I, Seracchioli R, Martelli V, Meriggiola MC. Presentation of a meningioma in a transwoman after nine years of cyproterone acetate and estradiol intake: case report and literature review. Gynecol Endocrinol. 2018;34(6):456-9.
49. Gonçalves AM, Page P, Domigo V, Méder JF, Oppenheim C. Abrupt regression of a meningioma after discontinuation of cyproterone treatment. AJNR Am J Neuroradiol. 2010;31(8):1504-5.
50. Perry A, Gutmann DH, Reifenberger G. Molecular pathogenesis of meningiomas. J Neurooncol. 2004;70(2):183-202.

51. Bailey P, Bucy PC. The Origin and Nature of Meningeal Tumors. The American Journal of Cancer. 1931;15(1):15.
52. Alahmadi H, Croul SE. Pathology and genetics of meningiomas. Semin Diagn Pathol. 2011;28(4):314-24.
53. Lamszus K. Meningioma pathology, genetics, and biology. J Neuropathol Exp Neurol. 2004;63(4):275-86.
54. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol. 2016;131(6):803-20.
55. Berhouma M, Jacquesson T, Jouanneau E, Cotton F. Pathogenesis of peri-tumoral edema in intracranial meningiomas. Neurosurg Rev. 2019;42(1):59-71.
56. Englot DJ, Magill ST, Han SJ, Chang EF, Berger MS, McDermott MW. Seizures in supratentorial meningioma: a systematic review and meta-analysis. J Neurosurg. 2016;124(6):1552-61.
57. Baumgarten P, Sarlak M, Baumgarten G, Marquardt G, Seifert V, Strzelczyk A, et al. Focused review on seizures caused by meningiomas. Epilepsy Behav. 2018;88:146-51.
58. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol. 2007;114(2):97-109.
59. Perry A, Stafford SL, Scheithauer BW, Suman VJ, Lohse CM. Meningioma grading: an analysis of histologic parameters. Am J Surg Pathol. 1997;21(12):1455-65.
60. Brokinkel B, Hess K, Mawrin C. Brain invasion in meningiomas-clinical considerations and impact of neuropathological evaluation: a systematic review. Neuro Oncol. 2017;19(10):1298-307.
61. Sokratous G, Burford C, Loh D, Ashkan K, Bhangoo R, Vergani F. Meningiomas: Brain invasion as a marker for classification. Neuro-Oncology. 2018;20(suppl_1):i12-i3.
62. Bi WL, Zhang M, Wu WW, Mei Y, Dunn IF. Meningioma Genomics: Diagnostic, Prognostic, and Therapeutic Applications. Front Surg. 2016;3:40.
63. Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, et al. Global variation in copy number in the human genome. Nature. 2006;444(7118):444-54.
64. Zhang F, Gu W, Hurles ME, Lupski JR. Copy number variation in human health, disease, and evolution. Annu Rev Genomics Hum Genet. 2009;10:451-81.
65. Seizinger BR, de la Monte S, Atkins L, Gusella JF, Martuza RL. Molecular genetic approach to human meningioma: loss of genes on chromosome 22. Proc Natl Acad Sci U S A. 1987;84(15):5419-23.
66. Lee Y, Liu J, Patel S, Cloughesy T, Lai A, Farooqi H, et al. Genomic landscape of meningiomas. Brain Pathol. 2010;20(4):751-62.
67. Lee JYK, Finkelstein S, Hamilton RL, Rekha R, King JT, Jr., Omalu B. Loss of Heterozygosity Analysis of Benign, Atypical, and Anaplastic Meningiomas. Neurosurgery. 2004;55(5):1163-73.
68. Michael K, Mohammed AA, Hussam A-A-S, Jian G, Ilyas E, Randy LJ, et al. Clinical potential of meningioma genomic insights: a practical review for neurosurgeons. Neurosurgical Focus FOC. 2018;44(6):E10.

69. Petrilli AM, Fernández-Valle C. Role of Merlin/NF2 inactivation in tumor biology. Oncogene. 2016;35(5):537-48.
70. Brastianos PK, Horowitz PM, Santagata S, Jones RT, McKenna A, Getz G, et al. Genomic sequencing of meningiomas identifies oncogenic SMO and AKT1 mutations. Nat Genet. 2013;45(3):285-9.
71. De Vitis LR, Tedde A, Vitelli F, Ammannati F, Mennonna P, Bigozzi U, et al. Screening for mutations in the neurofibromatosis type 2 (NF2) gene in sporadic meningiomas. Hum Genet. 1996;97(5):632-7.
72. Ruttledge MH, Sarrazin J, Rangaratnam S, Phelan CM, Twist E, Merel P, et al. Evidence for the complete inactivation of the NF2 gene in the majority of sporadic meningiomas. Nat Genet. 1994;6(2):180-4.
73. Yuzawa S, Nishihara H, Tanaka S. Genetic landscape of meningioma. Brain Tumor Pathol. 2016;33(4):237-47.
74. Clark VE, Erson-Omay EZ, Serin A, Yin J, Cotney J, Ozduman K, et al. Genomic analysis of non-NF2 meningiomas reveals mutations in TRAF7, KLF4, AKT1, and SMO. Science. 2013;339(6123):1077-80.
75. Carballo GB, Honorato JR, de Lopes GPF, Spohr TCLdSe. A highlight on Sonic hedgehog pathway. Cell Communication and Signaling. 2018;16(1):11.
76. Bello MJ, Amiñoso C, Lopez-Marin I, Arjona D, Gonzalez-Gomez P, Alonso ME, et al. DNA methylation of multiple promoter-associated CpG islands in meningiomas: relationship with the allelic status at 1p and 22q. Acta Neuropathologica. 2004;108(5):413-21.
77. Antequera F. Structure, function and evolution of CpG island promoters. Cellular and Molecular Life Sciences CMLS. 2003;60(8):1647-58.
78. Baylin SB, Herman JG, Graff JR, Vertino PM, Issa JP. Alterations in DNA methylation: a fundamental aspect of neoplasia. Adv Cancer Res. 1998;72:141-96.
79. Ehrlich M. DNA hypomethylation in cancer cells. Epigenomics. 2009;1(2):239-59.
80. Gao F, Shi L, Russin J, Zeng L, Chang X, He S, et al. DNA methylation in the malignant transformation of meningiomas. PLoS One. 2013;8(1):e54114-e.
81. Buerki RA, Horbinski CM, Kruser T, Horowitz PM, James CD, Lukas RV. An overview of meningiomas. Future Oncol. 2018;14(21):2161-77.
82. Beaumont A, Whittle IR. The pathogenesis of tumour associated epilepsy. Acta Neurochir (Wien). 2000;142(1):1-15.
83. Lieu AS, Howng SL. Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. Epilepsy Res. 2000;38(1):45-52.
84. Schmidt-Hansen M, Berendse S, Hamilton W. Symptomatic diagnosis of cancer of the brain and central nervous system in primary care: a systematic review. Fam Pract. 2015;32(6):618-23.
85. Kahn K, Finkel A. It IS a tumor -- current review of headache and brain tumor. Curr Pain Headache Rep. 2014;18(6):421.
86. Boiardi A, Salmaggi A, Eoli M, Lamperti E, Silvani A. Headache in brain tumours: a symptom to reappraise critically. Neurol Sci. 2004;25 Suppl 3:S143-7.
87. Meskal I, Gehring K, Rutten GJ, Sitskoorn MM. Cognitive functioning in meningioma patients: a systematic review. J Neurooncol. 2016;128(2):195-205.
88. Freeman WD. Management of Intracranial Pressure. Continuum (Minneap Minn). 2015;21(5 Neurocritical Care):1299-323.

89. Madhusoodanan S, Ting MB, Farah T, Ugur U. Psychiatric aspects of brain tumors: A review. World J Psychiatry. 2015;5(3):273-85.
90. Gyawali S, Sharma P, Mahapatra A. Meningioma and psychiatric symptoms: An individual patient data analysis. Asian J Psychiatr. 2019;42:94-103.
91. Kumar K, Ahmed R, Bajantri B, Singh A, Abbas H, Dejesus E, et al. Tumors Presenting as Multiple Cranial Nerve Palsies. Case Rep Neurol. 2017;9(1):54-61.
92. Wu A, Garcia MA, Magill ST, Chen W, Vasudevan HN, Perry A, et al. Presenting Symptoms and Prognostic Factors for Symptomatic Outcomes Following Resection of Meningioma. World Neurosurg. 2018;111:e149-e59.
93. Rausing A, Ybo W, Stenflo J. Intracranial meningioma--a population study of ten years. Acta Neurol Scand. 1970;46(1):102-10.
94. Miller KL, Alfaro-Almagro F, Bangerter NK, Thomas DL, Yacoub E, Xu J, et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. Nat Neurosci. 2016;19(11):1523-36.
95. Islim AI, Mohan M, Moon RDC, Srikandarajah N, Mills SJ, Brodbelt AR, et al. Incidental intracranial meningiomas: a systematic review and meta-analysis of prognostic factors and outcomes. J Neurooncol. 2019;142(2):211-21.
96. Goldbrunner R, Minniti G, Preusser M, Jenkinson MD, Sallabanda K, Houdart E, et al. EANO guidelines for the diagnosis and treatment of meningiomas. Lancet Oncol. 2016;17(9):e383-91.
97. Mohammad MH, Chavredakis E, Zakaria R, Brodbelt A, Jenkinson MD. A national survey of the management of patients with incidental meningioma in the United Kingdom. Br J Neurosurg. 2017;31(4):459-63.
98. Islim AI, Kolamunnage-Dona R, Mohan M, Moon RDC, Crofton A, Haylock BJ, et al. A prognostic model to personalize monitoring regimes for patients with incidental asymptomatic meningiomas. Neuro Oncol. 2020;22(2):278-89.
99. Butts AM, Weigand S, Brown PD, Petersen RC, Jack CR, Jr., Machulda MM, et al. Neurocognition in individuals with incidentally-identified meningioma. J Neurooncol. 2017;134(1):125-32.
100. van Nieuwenhuizen D, Ambachtsheer N, Heimans JJ, Reijneveld JC, Peerdeman SM, Klein M. Neurocognitive functioning and health-related quality of life in patients with radiologically suspected meningiomas. J Neurooncol. 2013;113(3):433-40.
101. Tognarelli JM, Dawood M, Shariff MIF, Grover VPB, Crossey MME, Cox IJ, et al. Magnetic Resonance Spectroscopy: Principles and Techniques: Lessons for Clinicians. J Clin Exp Hepatol. 2015;5(4):320-8.
102. Harting I, Hartmann M, Bonsanto MM, Sommer C, Sartor K. Characterization of necrotic meningioma using diffusion MRI, perfusion MRI, and MR spectroscopy: case report and review of the literature. Neuroradiology. 2004;46(3):189-93.
103. (NICE) NIfHaCE. Head injury: assessment and early management clinical guideline 2014 [Available from: https://www.nice.org.uk/guidance/cg176/resources/head-injury-assessment-and-early-management-pdf-35109755595493.
104. O'Leary S, Adams WM, Parrish RW, Mukonoweshuro W. Atypical imaging appearances of intracranial meningiomas. Clin Radiol. 2007;62(1):10-7.
105. Buetow MP, Buetow PC, Smirniotopoulos JG. Typical, atypical, and misleading features in meningioma. Radiographics. 1991;11(6):1087-106.

106. Dowd CF, Halbach VV, Higashida RT. Meningiomas: the role of preoperative angiography and embolization. Neurosurg Focus. 2003;15(1):E10.
107. Dutour A, Kumar U, Panetta R, Ouafik L, Fina F, Sasi R, et al. Expression of somatostatin receptor subtypes in human brain tumors. Int J Cancer. 1998;76(5):620-7.
108. Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. 2000;27(3):273-82.
109. Rachinger W, Stoecklein VM, Terpolilli NA, Haug AR, Ertl L, Pöschl J, et al. Increased 68Ga-DOTATATE uptake in PET imaging discriminates meningioma and tumor-free tissue. J Nucl Med. 2015;56(3):347-53.
110. Gehler B, Paulsen F, Oksüz MO, Hauser TK, Eschmann SM, Bares R, et al. [68Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning. Radiat Oncol. 2009;4:56.
111. Laudicella R, Albano D, Annunziata S, Calabrò D, Argiroffi G, Abenavoli E, et al. Theragnostic Use of Radiolabelled Dota-Peptides in Meningioma: From Clinical Demand to Future Applications. Cancers (Basel). 2019;11(10).
112. Starr CJ, Cha S. Meningioma mimics: five key imaging features to differentiate them from meningiomas. Clin Radiol. 2017;72(9):722-8.
113. Kanesen D, Kandasamy R, Idris Z. Occipital Falcine Anaplastic Hemangiopericytoma Mimicking Meningioma. J Neurosci Rural Pract. 2016;7(Suppl 1):S95-s8.
114. Ribeiro da Cunha P, Alves JL, Rocha A. Supra and infratentorial ectopic schwannoma mimicking a meningioma. BMJ Case Rep. 2017;2017.
115. Johnson MD, Powell SZ, Boyer PJ, Weil RJ, Moots PL. Dural lesions mimicking meningiomas. Hum Pathol. 2002;33(12):1211-26.
116. Backhouse O, Simmons I, Frank A, Cassels-Brown A. Optic nerve breast metastasis mimicking meningioma. Aust N Z J Ophthalmol. 1998;26(3):247-9.
117. Ohba S, Kurokawa R, Yoshida K, Kawase T. Metastatic adenocarcinoma of the dura mimicking petroclival meningioma--case report. Neurol Med Chir (Tokyo). 2004;44(6):317-20.
118. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry. 1957;20(1):22-39.
119. Cho B. Intensity-modulated radiation therapy: a review with a physics perspective. Radiat Oncol J. 2018;36(1):1-10.
120. Teoh M, Clark CH, Wood K, Whitaker S, Nisbet A. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol. 2011;84(1007):967-96.
121. Scaringi C, Agolli L, Minniti G. Technical Advances in Radiation Therapy for Brain Tumors. Anticancer Res. 2018;38(11):6041-5.
122. Biau J, Khalil T, Verrelle P, Lemaire JJ. Fractionated radiotherapy and radiosurgery of intracranial meningiomas. Neurochirurgie. 2018;64(1):29-36.
123. Elia AE, Shih HA, Loeffler JS. Stereotactic radiation treatment for benign meningiomas. Neurosurg Focus. 2007;23(4):E5.

124. Tanzler E, Morris CG, Kirwan JM, Amdur RJ, Mendenhall WM. Outcomes of WHO Grade I meningiomas receiving definitive or postoperative radiotherapy. Int J Radiat Oncol Biol Phys. 2011;79(2):508-13.
125. Colombo F, Casentini L, Cavedon C, Scalchi P, Cora S, Francescon P. Cyberknife radiosurgery for benign meningiomas: short-term results in 199 patients. Neurosurgery. 2009;64(2 Suppl):A7-13.
126. Unger KR, Lominska CE, Chanyasulkit J, Randolph-Jackson P, White RL, Aulisi E, et al. Risk factors for posttreatment edema in patients treated with stereotactic radiosurgery for meningiomas. Neurosurgery. 2012;70(3):639-45.
127. Mahadevan A, Floyd S, Wong E, Chen C, Kasper E. Clinical outcome after hypofractionated stereotactic radiotherapy (HSRT) for benign skull base tumors. Comput Aided Surg. 2011;16(3):112-20.
128. Girvigian MR, Chen JC, Rahimian J, Miller MJ, Tome M. Comparison of early complications for patients with convexity and parasagittal meningiomas treated with either stereotactic radiosurgery or fractionated stereotactic radiotherapy. Neurosurgery. 2008;62(5 Suppl):A19-27; discussion A-8.
129. Magill ST, Lau D, Raleigh DR, Sneed PK, Fogh SE, McDermott MW. Surgical Resection and Interstitial Iodine-125 Brachytherapy for High-Grade Meningiomas: A 25-Year Series. Neurosurgery. 2017;80(3):409-16.
130. Seystahl K, Stoecklein V, Schüller U, Rushing E, Nicolas G, Schäfer N, et al. Somatostatin receptor-targeted radionuclide therapy for progressive meningioma: benefit linked to 68Ga-DOTATATE/-TOC uptake. Neuro-oncology. 2016;18(11):1538-47.
131. Kaley T, Barani I, Chamberlain M, McDermott M, Panageas K, Raizer J, et al. Historical benchmarks for medical therapy trials in surgery- and radiation-refractory meningioma: a RANO review. Neuro Oncol. 2014;16(6):829-40.
132. Jenkinson MD, Javadpour M, Haylock BJ, Young B, Gillard H, Vinten J, et al. The ROAM/EORTC-1308 trial: Radiation versus Observation following surgical resection of Atypical Meningioma: study protocol for a randomised controlled trial. Trials. 2015;16:519.
133. Jenkinson MD. 'Meningiomics'-an integration of data on the patient, tumour, extent of resection and molecular pathology to optimise the management and follow-up for meningiomas. Acta Neurochir (Wien). 2019;161(12):2551-2.
134. van Alkemade H, de Leau M, Dieleman EM, Kardaun JW, van Os R, Vandertop WP, et al. Impaired survival and long-term neurological problems in benign meningioma. Neuro Oncol. 2012;14(5):658-66.
135. Woehrer A, Hackl M, Waldhör T, Weis S, Pichler J, Olschowski A, et al. Relative survival of patients with non-malignant central nervous system tumours: a descriptive study by the Austrian Brain Tumour Registry. Br J Cancer. 2014;110(2):286-96.
136. Brodbelt AR, Barclay ME, Greenberg D, Williams M, Jenkinson MD, Karabatsou K. The outcome of patients with surgically treated meningioma in England: 1999–2013. A cancer registry data analysis. British Journal of Neurosurgery. 2019;33(6):641-7.
137. Böker DK, Meurer H, Gullotta F. Recurring intracranial meningiomas. Evaluation of some factors predisposing for tumor recurrence. J Neurosurg Sci. 1985;29(1):11-7.

138. Gallagher MJ, Jenkinson MD, Brodbelt AR, Mills SJ, Chavredakis E. WHO grade 1 meningioma recurrence: Are location and Simpson grade still relevant? Clin Neurol Neurosurg. 2016;141:117-21.
139. Nanda A, Bir SC, Maiti TK, Konar SK, Missios S, Guthikonda B. Relevance of Simpson grading system and recurrence-free survival after surgery for World Health Organization Grade I meningioma. J Neurosurg. 2017;126(1):201-11.
140. Gousias K, Schramm J, Simon M. The Simpson grading revisited: aggressive surgery and its place in modern meningioma management. J Neurosurg. 2016;125(3):551-60.
141. Hasseleid BF, Meling TR, Rønning P, Scheie D, Helseth E. Surgery for convexity meningioma: Simpson Grade I resection as the goal: clinical article. J Neurosurg. 2012;117(6):999-1006.
142. Yuzawa S, Nishihara H, Yamaguchi S, Mohri H, Wang L, Kimura T, et al. Clinical impact of targeted amplicon sequencing for meningioma as a practical clinical-sequencing system. Mod Pathol. 2016;29(7):708-16.
143. Vasudevan HN, Braunstein SE, Phillips JJ, Pekmezci M, Tomlin BA, Wu A, et al. Comprehensive Molecular Profiling Identifies FOXM1 as a Key Transcription Factor for Meningioma Proliferation. Cell Reports. 2018;22(13):3672-83.
144. Sahm F, Schrimpf D, Stichel D, Jones DTW, Hielscher T, Schefzyk S, et al. DNA methylation-based classification and grading system for meningioma: a multicentre, retrospective analysis. Lancet Oncol. 2017;18(5):682-94.
145. Nassiri F, Mamatjan Y, Suppiah S, Badhiwala JH, Mansouri S, Karimi S, et al. DNA methylation profiling to predict recurrence risk in meningioma: development and validation of a nomogram to optimize clinical management. Neuro Oncol. 2019;21(7):901-10.
146. Zamanipoor Najafabadi AH, Peeters MCM, Dirven L, Lobatto DJ, Groen JL, Broekman MLD, et al. Impaired health-related quality of life in meningioma patients-a systematic review. Neuro Oncol. 2017;19(7):897-907.
147. Organisation WH. Constitution [Available from: https://www.who.int/about/who-we-are/constitution.
148. Black N. Patient reported outcome measures could help transform healthcare. Bmj. 2013;346:f167.
149. (CHMP) EMACfMPfHU. Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man
The use of patient-reported outcome (PRO) measures in oncology studies 2016 [Available from: https://www.ema.europa.eu/en/documents/other/appendix-2-guideline-evaluation-anticancer-medicinal-products-man_en.pdf.
150. Group. F-NBW. BEST (Biomarkers, EndpointS, and other Tools) Resource: Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016-. 2016 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK326791/.
151. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). Health Serv Insights. 2013;6:61-8.
152. Angus Campbell PEC, Willard L. Rodgers. The Quality of American Life: Perceptions, Evaluations, and Satisfactions. United States of America: Russell Sage Foundation; 1976. 597 p.

153. Cella DF. Quality of life: concepts and definition. J Pain Symptom Manage. 1994;9(3):186-92.
154. Organisation WH. WHOQOL: Measuring Quality of Life [Available from: https://www.who.int/healthinfo/survey/whoqol-qualityoflife/en/.
155. Cella DF. Measuring quality of life in palliative care. Semin Oncol. 1995;22(2 Suppl 3):73-81.
156. Cella DF. Measuring Quality of Life: 1995 Update 1995 [Available from: https://www.cancernetwork.com/view/measuring-quality-life-1995-update.
157. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. Patient Relat Outcome Meas. 2018;9:353-67.
158. Health USDo, Human Services FDACfDE, Research, Health USDo, Human Services FDACfBE, Research, et al. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes. 2006;4:79.
159. Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. J Clin Oncol. 1996;14(6):1756-64.
160. Calvert M, Brundage M, Jacobsen PB, Schünemann HJ, Efficace F. The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. Health Qual Life Outcomes. 2013;11:184.
161. Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. Jama. 2018;319(5):483-94.
162. Dirven L, Armstrong TS, Blakeley JO, Brown PD, Grant R, Jalali R, et al. Working plan for the use of patient-reported outcome measures in adults with brain tumours: a Response Assessment in Neuro-Oncology (RANO) initiative. Lancet Oncol. 2018;19(3):e173-e80.
163. Efficace F, Fayers P, Pusic A, Cemal Y, Yanagawa J, Jacobs M, et al. Quality of patient-reported outcome reporting across cancer randomized controlled trials according to the CONSORT patient-reported outcome extension: A pooled analysis of 557 trials. Cancer. 2015;121(18):3335-42.
164. Dirven L, Taphoorn MJ, Reijneveld JC, Blazeby J, Jacobs M, Pusic A, et al. The level of patient-reported outcome reporting in randomised controlled trials of brain tumour patients: a systematic review. Eur J Cancer. 2014;50(14):2432-48.
165. Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis. Health Qual Life Outcomes. 2019;17(1):156.
166. Basch E. The missing voice of patients in drug-safety reporting. N Engl J Med. 2010;362(10):865-9.
167. Pakhomov SV, Jacobsen SJ, Chute CG, Roger VL. Agreement between patient-reported symptoms and their documentation in the medical record. Am J Manag Care. 2008;14(8):530-9.
168. Weingart SN, Gandhi TK, Seger AC, Seger DL, Borus J, Burdick E, et al. Patient-reported medication symptoms in primary care. Arch Intern Med. 2005;165(2):234-40.

169. Hanmer J, Hays RD, Fryback DG. Mode of administration is important in US national estimates of health-related quality of life. Med Care. 2007;45(12):1171-9.
170. Dobrozsi S, Panepinto J. Patient-reported outcomes in clinical practice. Hematology. 2015;2015(1):501-6.
171. Kyte D, Draper H, Calvert M. Patient-Reported Outcome Alerts: Ethical and Logistical Considerations in Clinical Trials. JAMA. 2013;310(12):1229-30.
172. Nilsson E, Orwelius L, Kristenson M. Patient-reported outcomes in the Swedish National Quality Registers. J Intern Med. 2016;279(2):141-53.
173. Kvalitetsregister N. Swedish National Quality Registries 2019 [Available from: http://kvalitetsregister.se/englishpages.2040.html.
174. Adami HO, Hernán MA. Learning how to improve healthcare delivery: the Swedish Quality Registers. J Intern Med. 2015;277(1):87-9.
175. England N. Patient Reported Outcome Measures (PROMs) [Available from: https://www.england.nhs.uk/statistics/statistical-work-areas/proms/.
176. England N. THE NATIONAL PATIENT REPORTED OUTCOME MEASURES (PROMS) PROGRAMME 2018 [Available from: https://www.england.nhs.uk/wp-content/uploads/2018/08/proms-guide-aug-18-v3.pdf.
177. Weinberger M, Nagle B, Hanlon JT, Samsa GP, Schmader K, Landsman PB, et al. Assessing health-related quality of life in elderly outpatients: telephone versus face-to-face administration. J Am Geriatr Soc. 1994;42(12):1295-9.
178. Hays RD, Kim S, Spritzer KL, Kaplan RM, Tally S, Feeny D, et al. Effects of mode and order of administration on generic health-related quality of life scores. Value Health. 2009;12(6):1035-9.
179. Miller DR, Clark JA, Rogers WH, Skinner KM, Spiro A, 3rd, Lee A, et al. The influence of place of administration on health-related quality-of-life assessments: findings from the Veterans Health Study. J Ambul Care Manage. 2005;28(2):111-24.
180. Palmen LN, Schrier JCM, Scholten R, Jansen JHW, Koëter S. Is it too early to move to full electronic PROM data collection?: A randomized controlled trial comparing PROM's after hallux valgus captured by e-mail, traditional mail and telephone. Foot and Ankle Surgery. 2016;22(1):46-9.
181. Harris LE, Weinberger M, Tierney WM. Assessing inner-city patients' hospital experiences. A controlled trial of telephone interviews versus mailed surveys. Med Care. 1997;35(1):70-6.
182. Schwartzenberger J, Presson A, Lyle A, O'Farrell A, Tyser AR. Remote Collection of Patient-Reported Outcomes Following Outpatient Hand Surgery: A Randomized Trial of Telephone, Mail, and E-Mail. J Hand Surg Am. 2017;42(9):693-9.
183. Gayet-Ageron A, Agoritsas T, Schiesari L, Kolly V, Perneger TV. Barriers to participation in a patient satisfaction survey: who are we missing? PLoS One. 2011;6(10):e26852.
184. Hutchings A, Neuburger J, Grosse Frie K, Black N, van der Meulen J. Factors associated with non-response in routine use of patient reported outcome measures after elective surgery in England. Health Qual Life Outcomes. 2012;10:34.
185. Emberton M, Black N. Impact of non-response and of late-response by patients in a multi-centre surgical outcome audit. Int J Qual Health Care. 1995;7(1):47-55.

186. Mercieca-Bebber R, Palmer MJ, Brundage M, Calvert M, Stockler MR, King MT. Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: a systematic review. BMJ Open. 2016;6(6):e010938.
187. Calvert MJ, Freemantle N. Use of health-related quality of life in prescribing research. Part 2: methodological considerations for the assessment of health-related quality of life in clinical trials. J Clin Pharm Ther. 2004;29(1):85-94.
188. Bernhard J, Peterson HF, Coates AS, Gusset H, Isley M, Hinkle R, et al. Quality of life assessment in International Breast Cancer Study Group (IBCSG) trials: practical issues and factors associated with missing data. Stat Med. 1998;17(5-7):587-601.
189. Kleinpell-Nowell R. Strategies for assessing outcomes in the elderly in acute care. AACN Clin Issues. 2000;11(3):442-52.
190. Nielsen LK, King M, Möller S, Jarden M, Andersen CL, Frederiksen H, et al. Strategies to improve patient-reported outcome completion rates in longitudinal studies. Qual Life Res. 2020;29(2):335-46.
191. Weston D, Parsons V, Ntani G, Rushton L, Madan I. Mixed contact methods to improve response to a postal questionnaire. Occupational Medicine. 2017;67(4):305-7.
192. Basch E, Abernethy AP, Mullins CD, Reeve BB, Smith ML, Coons SJ, et al. Recommendations for incorporating patient-reported outcomes into clinical comparative effectiveness research in adult oncology. J Clin Oncol. 2012;30(34):4249-55.
193. Bell ML, Fairclough DL. Practical and statistical issues in missing data for longitudinal patient-reported outcomes. Stat Methods Med Res. 2014;23(5):440-59.
194. Atkinson TM, Li Y, Coffey CW, Sit L, Shaw M, Lavene D, et al. Reliability of adverse symptom event reporting by clinicians. Qual Life Res. 2012;21(7):1159-64.
195. Quinten C, Maringwa J, Gotay CC, Martinelli F, Coens C, Reeve BB, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. J Natl Cancer Inst. 2011;103(24):1851-8.
196. Di Maio M, Gallo C, Leighl NB, Piccirillo MC, Daniele G, Nuzzo F, et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol. 2015;33(8):910-5.
197. Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: a review. J Clin Epidemiol. 1992;45(7):743-60.
198. Low G, Gutman G. Couples' ratings of chronic obstructive pulmonary disease patients' quality of life. Clin Nurs Res. 2003;12(1):28-48.
199. Tamim H, McCusker J, Dendukuri N. Proxy reporting of quality of life using the EQ-5D. Med Care. 2002;40(12):1186-95.
200. Roydhouse JK, Gutman R, Keating NL, Mor V, Wilson IB. Proxy and patient reports of health-related quality of life in a national cancer survey. Health and Quality of Life Outcomes. 2018;16(1):6.

201. Wennman-Larsen A, Tishelman C Fau - Wengström Y, Wengström Y Fau - Gustavsson P, Gustavsson P. Factors influencing agreement in symptom ratings by lung cancer patients and their significant others. (0885-3924 (Print)).
202. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101(23):1624-32.
203. Gotay C. Patient Symptoms and Clinician Toxicity Ratings: Both Have a Role in Cancer Care. JNCI: Journal of the National Cancer Institute. 2009;101(23):1602-3.
204. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
205. Peter M. Fayers DM. Quality of Life: The Assessment, Analysis and Reporting of Patient-Reported Outcomes. Chapter 2: Principles of measurement scales. 3 ed. Chichester, [England]: Wiley Blackwell; 2016. 651 p.
206. Johnston BC PD, Devji T, Maxwell LJ, Bingham III CO, Beaton D, Boers M, Briel M, Busse JW, Carrasco-Labra A, Christensen R, da Costa BR, El Dib R, Lyddiatt A, Ostelo RW, Shea B, Singh J, Terwee CB, Williamson PR, Gagnier JJ, Tugwell P, Guyatt GH. Chapter 18: Patient-reported outcomes. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane; 2019.
207. Alrubaiy L, Hutchings HA, Williams JG. Assessing patient reported outcome measures: A practical guide for gastroenterologists. United European Gastroenterol J. 2014;2(6):463-70.
208. Terwee CB, Bot SD, de Boer MR, van der Windt DA, Knol DL, Dekker J, et al. Quality criteria were proposed for measurement properties of health status questionnaires. J Clin Epidemiol. 2007;60(1):34-42.
209. Frost MH, Reeve BB, Liepa AM, Stauffer JW, Hays RD. What is sufficient evidence for the reliability and validity of patient-reported outcome measures? Value Health. 2007;10 Suppl 2:S94-s105.
210. Zlotnick D, Kalkanis SN, Quinones-Hinojosa A, Chung K, Linskey ME, Jensen RL, et al. FACT-MNG: tumor site specific web-based outcome instrument for meningioma patients. J Neurooncol. 2010;99(3):423-31.
211. Tanti MJ, Marson AG, Chavredakis E, Jenkinson MD. The impact of epilepsy on the quality of life of patients with meningioma: A systematic review. Br J Neurosurg. 2016;30(1):23-8.
212. Zamanipoor Najafabadi AH, Peeters MCM, Lobatto DJ, Broekman MLD, Smith TR, Biermasz NR, et al. Health-related quality of life of cranial WHO grade I meningioma patients: are current questionnaires relevant? Acta Neurochir (Wien). 2017;159(11):2149-59.
213. Coulman KD, Abdelrahman T, Owen-Smith A, Andrews RC, Welbourn R, Blazeby JM. Patient-reported outcomes in bariatric surgery: a systematic review of standards of reporting. Obes Rev. 2013;14(9):707-20.
214. McNair AG, Whistance RN, Forsythe RO, Rees J, Jones JE, Pullyblank AM, et al. Synthesis and summary of patient-reported outcome measures to inform the

development of a core outcome set in colorectal cancer surgery. Colorectal Dis. 2015;17(11):O217-29.
215. Macefield RC, Jacobs M, Korfage IJ, Nicklin J, Whistance RN, Brookes ST, et al. Developing core outcomes sets: methods for identifying and including patient-reported outcomes (PROs). Trials. 2014;15:49.
216. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009;339:b2535.
217. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
218. Johnston BC PD, Devji T, Maxwell LJ, Bingham III CO, Beaton D, Boers M, Briel M, Busse JW, Carrasco-Labra A, Christensen R, da Costa BR, El Dib R, Lyddiatt A, Ostelo RW, Shea B, Singh J, Terwee CB, Williamson PR, Gagnier JJ, Tugwell P, Guyatt GH. Chapter 18: Patient-reported outcomes. : Cochrane; 2019 [Available from: www.training.cochrane.org/handbook.
219. Cella D HE, Jensen SE et al. Patient-Reported Outcomes in Performance Measurement: RTI Press; 2015.
220. McKenna SP. Measuring patient-reported outcomes: moving beyond misplaced common sense to hard science. BMC Med. 2011;9(1741-7015 (Electronic)):86.
221. Reeve BB, Wyrwich KW, Wu AW, Velikova G, Terwee CB, Snyder CF, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. Qual Life Res. 2013;22(8):1889-905.
222. Calvert M, Blazeby J, Altman DG, Revicki DA, Moher D, Brundage MD. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. Jama. 2013;309(8):814-22.
223. Brundage M, Blazeby J, Revicki D, Bass B, de Vet H, Duffy H, et al. Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. Qual Life Res. 2013;22(6):1161-75.
224. Fountain DM, Allen D, Joannides AJ, Nandi D, Santarius T, Chari A. Reporting of patient-reported health-related quality of life in adults with diffuse low-grade glioma: a systematic review. Neuro Oncol. 2016;18(11):1475-86.
225. Efficace F, Feuerstein M, Fayers P, Cafaro V, Eastham J, Pusic A, et al. Patient-reported outcomes in randomised controlled trials of prostate cancer: methodological quality and impact on clinical decision making. Eur Urol. 2014;66(3):416-27.
226. Institute TJB. Checklist for Analytical Cross Sectional Studies 2017 [Available from: www.joannabriggs.org.
227. Wells GA SB, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
228. Kangas M, Williams JR, Smee RI. The Association Between Post-traumatic Stress and Health-Related Quality of Life in Adults Treated for a Benign Meningioma. Applied Research in Quality of Life. 2012;7(2):163-82.

229. Tanti MJ, Marson AG, Jenkinson MD. Epilepsy and adverse quality of life in surgically resected meningioma. Acta Neurol Scand. 2017;136(3):246-53.
230. Krupp W, Klein C, Koschny R, Holland H, Seifert V, Meixensberger J. Assessment of neuropsychological parameters and quality of life to evaluate outcome in patients with surgically treated supratentorial meningiomas. Neurosurgery. 2009;64(1):40-7; discussion 7.
231. van Nieuwenhuizen D, Slot KM, Klein M, Verbaan D, Aliaga ES, Heimans JJ, et al. The association between preoperative edema and postoperative cognitive functioning and health-related quality of life in WHO grade I meningioma patients. Acta Neurochir (Wien). 2019;161(3):579-88.
232. Kangas M, Williams JR, Smee RI. Benefit Finding in Adults Treated for Benign Meningioma Brain Tumours: Relations with Psychosocial Wellbeing. Brain Impairment. 2011;12(2):105-16.
233. Owens MA, Craig BM, Egan KM, Reed DR. Birth desires and intentions of women diagnosed with a meningioma. J Neurosurg. 2015;122(5):1151-6.
234. van der Vossen S, Schepers VP, Berkelbach van der Sprenkel JW, Visser-Meily JM, Post MW. Cognitive and emotional problems in patients after cerebral meningioma surgery. J Rehabil Med. 2014;46(5):430-7.
235. Makarenko S, Carreras EM, Akagami R. Craniotomy for perisellar meningiomas: comparison of simple (appropriate for endoscopic approach) versus complex anatomy and surgical outcomes. J Neurosurg. 2017;126(4):1191-200.
236. van Nieuwenhuizen D, Klein M, Stalpers LJ, Leenstra S, Heimans JJ, Reijneveld JC. Differential effect of surgery and radiotherapy on neurocognitive functioning and health-related quality of life in WHO grade I meningioma patients. J Neurooncol. 2007;84(3):271-8.
237. Mathiesen T, Gerlich A, Kihlström L, Svensson M, Bagger-Sjöbäck D. Effects of using combined transpetrosal surgical approaches to treat petroclival meningiomas. Neurosurgery. 2007;60(6):982-91; discussion 91-2.
238. Pintea B, Kandenwein JA, Lorenzen H, Boström JP, Daher F, Velazquez V, et al. Factors of influence upon the SF-36-based health related quality of life of patients following surgery for petroclival and lateral posterior surface of pyramid meningiomas. Clin Neurol Neurosurg. 2018;166:36-43.
239. Jones SH, Iannone AF, Patel KS, Anchouche K, Raza SM, Anand VK, et al. The Impact of Age on Long-Term Quality of Life After Endonasal Endoscopic Resection of Skull Base Meningiomas. Neurosurgery. 2016;79(5):736-45.
240. Jakola AS, Gulati M, Gulati S, Solheim O. The influence of surgery on quality of life in patients with intracranial meningiomas: a prospective study. J Neurooncol. 2012;110(1):137-44.
241. Waagemans ML, van Nieuwenhuizen D, Dijkstra M, Wumkes M, Dirven CM, Leenstra S, et al. Long-term impact of cognitive deficits and epilepsy on quality of life in patients with low-grade meningiomas. Neurosurgery. 2011;69(1):72-8; discussion 8-9.
242. Timmer M, Seibl-Leven M, Wittenstein K, Grau S, Stavrinou P, Röhn G, et al. Long-Term Outcome and Health-Related Quality of Life of Elderly Patients After Meningioma Surgery. World Neurosurg. 2019;125:e697-e710.
243. Lang DA, Neil-Dwyer G, Garfield J. Outcome after complex neurosurgery: the caregiver's burden is forgotten. J Neurosurg. 1999;91(3):359-63.

244. Neil-Dwyer G, Lang DA, Davis A. Outcome from complex neurosurgery: an evidence based approach. Acta Neurochir (Wien). 2000;142(4):367-71.
245. Konglund A, Rogne SG, Lund-Johansen M, Scheie D, Helseth E, Meling TR. Outcome following surgery for intracranial meningiomas in the aging. Acta Neurol Scand. 2013;127(3):161-9.
246. Schepers VPM, van der Vossen S, Berkelbach van der Sprenkel JW, Visser-Meily JMA, Post MWM. Participation restrictions in patients after surgery for cerebral meningioma. J Rehabil Med. 2018;50(10):879-85.
247. van der Linden SD, Gehring K, Rutten GM, Kop WJ, Sitskoorn MM. Prevalence and correlates of fatigue in patients with meningioma before and after surgery. Neurooncol Pract. 2020;7(1):77-85.
248. Zweckberger K, Hallek E, Vogt L, Giese H, Schick U, Unterberg AW. Prospective analysis of neuropsychological deficits following resection of benign skull base meningiomas. J Neurosurg. 2017;127(6):1242-8.
249. Henzel M, Fokas E, Sitter H, Wittig A, Engenhart-Cabillic R. Quality of life after stereotactic radiotherapy for meningioma: a prospective non-randomized study. J Neurooncol. 2013;113(1):135-41.
250. Benz LS, Wrensch MR, Schildkraut JM, Bondy ML, Warren JL, Wiemels JL, et al. Quality of life after surgery for intracranial meningioma. Cancer. 2018;124(1):161-6.
251. Kalkanis SN, Quiñones-Hinojosa A, Buzney E, Ribaudo HJ, Black PM. Quality of life following surgery for intracranial meningiomas at Brigham and Women's Hospital: a study of 164 patients using a modification of the functional assessment of cancer therapy-brain questionnaire. J Neurooncol. 2000;48(3):233-41.
252. Wagner A, Shiban Y, Lange N, Joerger AK, Hoffmann U, Meyer B, et al. The relevant psychological burden of having a benign brain tumor: a prospective study of patients undergoing surgical treatment of cranial meningiomas. J Neurosurg. 2019;131(6):1840-7.
253. Combs SE, Adeberg S, Dittmar JO, Welzel T, Rieken S, Habermehl D, et al. Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). Radiother Oncol. 2013;106(2):186-91.
254. Wirsching HG, Morel C, Roth P, Weller M. Socioeconomic burden and quality of life in meningioma patients. Qual Life Res. 2020;29(7):1801-8.
255. Honeybul S, Neil-Dwyer G, Lang DA, Evans BT, Ellison DW. Sphenoid wing meningioma en plaque: a clinical review. Acta Neurochir (Wien). 2001;143(8):749-57; discussion 58.
256. van Lonkhuizen PJC, Rijnen SJM, van der Linden SD, Rutten GM, Gehring K, Sitskoorn MM. Subjective cognitive functioning in patients with a meningioma: Its course and association with objective cognitive functioning and psychological symptoms. Psychooncology. 2019;28(8):1654-62.
257. Akagami R, Napolitano M, Sekhar LN. Patient-evaluated outcome after surgery for basal meningiomas. Neurosurgery. 2002;50(5):941-8; discussion 8-9.
258. dos Santos Camila Batista dSMFG, Aguiar Paulo Henrique. Meningiomas: Quality of life before and after surgery. Journal of Neuroscience and Behavioural Health. 2011;3(1):8-15.

259. Nassiri F, Price B, Shehab A, Au K, Cusimano MD, Jenkinson MD, et al. Life after surgical resection of a meningioma: a prospective cross-sectional study evaluating health-related quality of life. Neuro Oncol. 2019;21(Suppl 1):i32-i43.
260. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
261. Hunt SM, McEwen J. The development of a subjective health indicator. Sociol Health Illn. 1980;2(3):231-46.
262. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 1993;11(3):570-9.
263. Aaronson NK, Bullinger M, Ahmedzai S. A modular approach to quality-of-life assessment in cancer clinical trials. Recent Results Cancer Res. 1988;111:231-49.
264. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. Cancer. 1995;75(5):1151-61.
265. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. Qual Life Res. 1996;5(1):139-50.
266. Gil Z, Abergel A, Spektor S, Shabtai E, Khafif A, Fliss DM. Development of a cancer-specific anterior skull base quality-of-life questionnaire. J Neurosurg. 2004;100(5):813-9.
267. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447-54.
268. Piccirillo JF, Merritt MG, Jr., Richards ML. Psychometric and clinimetric validity of the 20-Item Sino-Nasal Outcome Test (SNOT-20). Otolaryngol Head Neck Surg. 2002;126(1):41-7.
269. Mohsenipour I, Deusch E, Gabl M, Hofer M, Twerdy K. Quality of life in patients after meningioma resection. Acta Neurochir (Wien). 2001;143(6):547-53.
270. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.
271. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-70.
272. Weiss DS, Marmar CR, Wilson JP, Keane TM. Assessing psychological trauma and PTSD. The Impact of Events Scale—Revised. 1997;19:399-411.
273. Beck JG, Grant DM, Read JP, Clapp JD, Coffey SF, Miller LM, et al. The impact of event scale-revised: psychometric properties in a sample of motor vehicle accident survivors. J Anxiety Disord. 2008;22(2):187-98.
274. Biehl B, Landauer A. Das profile of mood states (POMS). Unpublished manuscript, University of Mannheim, Germany. 1975.
275. Meyer TD, Hautzinger M. Allgemeine Depressions-Skala (ADS). Diagnostica. 2001;47(4):208-15.
276. Taylor S, Zvolensky MJ, Cox BJ, Deacon B, Heimberg RG, Ledley DR, et al. Robust dimensions of anxiety sensitivity: development and initial validation of the Anxiety Sensitivity Index-3. Psychol Assess. 2007;19(2):176-88.

277. Armstrong TS, Cohen MZ, Eriksen L, Cleeland C. Content validity of self-report measurement instruments: an illustration from the development of the Brain Tumor Module of the M.D. Anderson Symptom Inventory. Oncol Nurs Forum. 2005;32(3):669-76.
278. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995;39(3):315-25.
279. Baker G. Development of a patient-based symptom check list to quantify adverse effects in persons receiving antiepileptic drugs. Epilepsia. 1993;34:18.
280. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology. 1982;21(1):1-16.
281. Lawton MP, Brody EM. Assessment of Older People: Self-Maintaining and Instrumental Activities of Daily Living1. The Gerontologist. 1969;9(3_Part_1):179-86.
282. Post MW, van der Zee CH, Hennink J, Schafrat CG, Visser-Meily JM, van Berlekom SB. Validity of the utrecht scale for evaluation of rehabilitation-participation. Disabil Rehabil. 2012;34(6):478-85.
283. Antoni MH, Lehman JM, Kilbourn KM, Boyers AE, Culver JL, Alferi SM, et al. Cognitive-behavioral stress management intervention decreases the prevalence of depression and enhances benefit finding among women under treatment for early-stage breast cancer. Health Psychol. 2001;20(1):20-32.
284. Tomich PL, Helgeson VS. Is finding something good in the bad always good? Benefit finding among women with breast cancer. Health Psychol. 2004;23(1):16-23.
285. Zimet GD, Dahlem NW, Zimet SG, Farley GK. The Multidimensional Scale of Perceived Social Support. Journal of Personality Assessment. 1988;52(1):30-41.
286. Sass C MJ, Gueguen R, Abric L, Dauphinot V, Dupre C, Giordanella JP, Girard F, Guenot C, Labbe E, La Rosa E, Magnier P, Martin E, Royer B, Rubirola M, Gerbaud L. Le score EPICES: un score individuel de précarité. Construction et évaluation du score dans une population de 197389 personnes. Bulletin Epidémiologique Hebdomadaire. 2006:93-6.
287. Islim AI, Ali A, Bagchi A, Ahmad MU, Mills SJ, Chavredakis E, et al. Postoperative seizures in meningioma patients: improving patient selection for antiepileptic drug therapy. J Neurooncol. 2018;140(1):123-34.
288. Islim AI, McKeever S, Kusu-Orkar TE, Jenkinson MD. The role of prophylactic antiepileptic drugs for seizure prophylaxis in meningioma surgery: A systematic review. J Clin Neurosci. 2017;43:47-53.
289. Jenkinson MD, Ali A, Islim AI, Helmy A, Grant R. Letter to the Editor. Establishing the role of prophylactic antiepileptic drugs in glioma and meningioma surgery. J Neurosurg. 2019;131(3):985-7.
290. Dunn EC, Wewiorski NJ, Rogers ES. The meaning and importance of employment to people in recovery from serious mental illness: results of a qualitative study. Psychiatr Rehabil J. 2008;32(1):59-62.
291. Dodd S, Clarke M, Becker L, Mavergames C, Fish R, Williamson PR. A taxonomy has been developed for outcomes in medical research to help improve knowledge discovery. J Clin Epidemiol. 2018;96:84-92.

292. Bekelis K, Bakhoum SF, Desai A, Mackenzie TA, Roberts DW. Outcome prediction in intracranial tumor surgery: the National Surgical Quality Improvement Program 2005-2010. J Neurooncol. 2013;113(1):57-64.
293. Chen ZY, Zheng CH, Tang L, Su XY, Lu GH, Zhang CY, et al. Intracranial meningioma surgery in the elderly (over 65 years): prognostic factors and outcome. Acta Neurochir (Wien). 2015;157(9):1549-57; discussion 57.
294. Cuschieri S. The STROBE guidelines. Saudi J Anaesth. 2019;13(Suppl 1):S31-s4.
295. Care RH. 36-Item Short Form Survey (SF-36) Scoring Instructions [Available from: https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/scoring.html.
296. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. Bmj. 1992;305(6846):160-4.
297. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer. 2010;46(6):1033-40.
298. Fayers PM AN, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001.
299. Select Statistical Services Ltd. Two-Sample t-test [Available from: https://select-statistics.co.uk/calculators/two-sample-t-test-calculator/.
300. Cronbach LJ. Coefficient alpha and the internal structure of tests. Psychometrika. 1951;16(3):297-334.
301. Tavakol M, Dennick R. Making sense of Cronbach's alpha. Int J Med Educ. 2011;2:53-5.
302. Bender R, Lange S. Adjusting for multiple testing--when and how? J Clin Epidemiol. 2001;54(4):343-9.
303. Burholt V, Nash P. Short Form 36 (SF-36) Health Survey Questionnaire: normative data for Wales. Journal of Public Health. 2011;33(4):587-603.
304. Nolte S, Liegl G, Petersen MA, Aaronson NK, Costantini A, Fayers PM, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer. 2019;107:153-63.
305. Bowling A, Bond M, Jenkinson C, Lamping DL. Short Form 36 (SF-36) Health Survey questionnaire: which normative data should be used? Comparisons between the norms provided by the Omnibus Survey in Britain, the Health Survey for England and the Oxford Healthy Life Survey. J Public Health Med. 1999;21(3):255-70.
306. Kim TK. T test as a parametric statistic. Korean J Anesthesiol. 2015;68(6):540-6.
307. Schwartz CE, Andresen EM, Nosek MA, Krahn GL. Response shift theory: important implications for measuring quality of life in people with disability. Arch Phys Med Rehabil. 2007;88(4):529-36.
308. Luckett T, King MT, Butow PN, Oguchi M, Rankin N, Price MA, et al. Choosing between the EORTC QLQ-C30 and FACT-G for measuring health-related quality of

life in cancer clinical research: issues, evidence and recommendations. Ann Oncol. 2011;22(10):2179-90.
309. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro Oncol. 2018;20(suppl_4):iv1-iv86.
310. Cea-Soriano L, Wallander MA, García Rodríguez LA. Epidemiology of meningioma in the United Kingdom. Neuroepidemiology. 2012;39(1):27-34.
311. Chamoun R, Krisht KM, Couldwell WT. Incidental meningiomas. Neurosurg Focus. 2011;31(6):E19.
312. Marciscano AE, Stemmer-Rachamimov AO, Niemierko A, Larvie M, Curry WT, Barker FG, 2nd, et al. Benign meningiomas (WHO Grade I) with atypical histological features: correlation of histopathological features with clinical outcomes. J Neurosurg. 2016;124(1):106-14.
313. Tucha O, Smely C, Preier M, Becker G, Paul GM, Lange KW. Preoperative and postoperative cognitive functioning in patients with frontal meningiomas. J Neurosurg. 2003;98(1):21-31.
314. Nakamura M, Roser F, Michel J, Jacobs C, Samii M. The natural history of incidental meningiomas. Neurosurgery. 2003;53(1):62-70; discussion -1.
315. Yano S, Kuratsu J. Indications for surgery in patients with asymptomatic meningiomas based on an extensive experience. J Neurosurg. 2006;105(4):538-43.
316. Miao Y, Lu X, Qiu Y, Jiang J, Lin Y. A multivariate analysis of prognostic factors for health-related quality of life in patients with surgically managed meningioma. J Clin Neurosci. 2010;17(4):446-9.
317. Dijkstra M, van Nieuwenhuizen D, Stalpers LJ, Wumkes M, Waagemans M, Vandertop WP, et al. Late neurocognitive sequelae in patients with WHO grade I meningioma. J Neurol Neurosurg Psychiatry. 2009;80(8):910-5.
318. Collins C, Gehrke A, Feuerstein M. Cognitive tasks challenging brain tumor survivors at work. J Occup Environ Med. 2013;55(12):1426-30.
319. Wong J, Mendelsohn D, Nyhof-Young J, Bernstein M. A qualitative assessment of the supportive care and resource needs of patients undergoing craniotomy for benign brain tumours. Support Care Cancer. 2011;19(11):1841-8.

Appendices

Appendix 1: Systematic review search strategy- EMBASE

Database: EMBASE	
Date: 29.04	
Number	**Term**
1	'Meningioma*':ti,ab
2	'Meningioma'/de
3	#1 OR #2
4	'outcome assessment'/de
5	'patient-reported outcome'/de
6	'self concept'/exp
7	'health status'/exp
8	'patient satisfaction'/de
9	('patient outcome' OR 'patient outcomes'):ti,ab
10	('patient reported' OR 'patient rated' OR 'patient assessed' OR 'patient evaluated' OR 'self reported' OR 'self rated' OR 'self assessed' OR 'self evaluated' OR 'person reported' OR 'person rated' OR 'person assessed' OR 'person evaluated'):ti,ab
11	('PRO' OR 'PROs'):ti,ab
12	('PROM' OR 'PROMs'):ti,ab
13	('health outcome' OR 'health outcomes'):ti,ab
14	'health status':ti,ab
15	('health profile' OR 'health profiles'):ti,ab
16	('well being' OR 'wellbeing'):ti,ab
17	'satisfaction':ti,ab
18	('expectation' OR 'expectations'):ti,ab
19	'quality of life'/de
20	'quality of life':ti,ab
21	'QOL':ti,ab
22	'HRQOL':ti,ab
23	'HRQL':ti,ab
24	'Lifestyle':ti,ab
25	'emotion'/exp
26	'behavior'/exp
27	'fatigue'/de
28	'pain'/de
29	'anxiety':ti,ab
30	'depression':ti,ab
31	'fatigue':ti,ab
32	'pain':ti,ab
33	'stress':ti,ab
34	'emotion*':ti,ab

Number	Term
35	'cogniti*':ti,ab
36	'social':ti,ab
37	'psychosocial':ti,ab
38	'psychological':ti,ab
39	'sexual':ti,ab
40	('financ*' OR 'economic*' OR 'employment'):ti,ab
41	'distress':ti,ab
42	'burden':ti,ab
43	'disabilit*':ti,ab
44	('cope' OR 'coping'):ti,ab
45	'symptom assessment':ti,ab
46	('functional status' OR 'functional outcome' OR 'functional outcomes'):ti,ab
47	'functioning':ti,ab
48	'questionnaire'/exp
49	('survey' OR 'surveys'):ti,ab
50	('questionnaire' OR 'questionnaires'):ti,ab
51	('scale' OR 'scales'):ti,ab
52	('ASK NASAL 12' OR 'EORTC' OR 'EuroQoL' OR 'EQ5D' OR 'EQ 5D' OR 'FACT' OR 'IHDNS' OR 'MDASI' OR 'NHP' OR 'PCMIS' OR 'SF36' OR 'SF 36' OR 'SNAS' OR 'VAS' OR 'WHOQOL'):ti,ab
53	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
54	#3 AND #53
55	**#3 AND #53 AND [english]/lim**

Appendix 2: Modified ISOQOL criteria

Appendix 2: Modified ISOQOL criteria		
Number	**Core Recommendation**	**Options**
1	The PRO should be identified as an outcome in the abstract	YES NO
2	The PRO hypothesis should be stated and should specify the relevant PRO domain(s) if applicable	YES NO NA (if explorative)
3	The mode of administration of the PRO tool and the methods of collecting data (e.g., telephone, other) should be described	YES NO
4 [a]	Electronic modes of distribution?	YES NO
	Note to reviewer: this does not account for reporting quality and should not be incorporated in final score.	
5	The rationale for choice of the PRO instrument used should be provided	YES NO
	Note to reviewer: question requires a specific explanation as to why a tool was chosen over another	
6	Evidence of PRO instrument validity and reliability should be provided or cited	YES NO (if all PROMs used are unvalidated) N/A (if new tool)
	Note to reviewer: validation and reliability in population the tool was designed for, not necessarily meningioma patients.	
7	The intended HRQL data collection schedule should be provided	YES NO N/A *(if not prospective)*
8	PROs should be identified in the trial protocol; post hoc analyses should be identified	YES NO N/A *(if protocol unavailable AND no post-hoc analyses)*
	Note to reviewer: not all studies will have a trial protocol	
9	The status of PRO as either a primary or secondary outcome should be stated	YES NO
	Note to reviewer: Mark as YES if PRO is the only outcome of the study	
10	There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested	YES NO NA (if hypothesis not stated)
11 [b]	Extent of missing data should be stated	YES NO
	Note to reviewer: missing data defined as either whole questionnaires not completed because patients did not participate or items missing from individual questionnaires. If there is a 100% response rate- this question requires the study authors to comment that there is no missing data within the questionnaires. I.e. requires a clear comment as to the extent of missing data.	

Appendix 2: Modified ISOQOL criteria (continued)		
Number	**Core Recommendation**	**Options**
12 [b]	Statistical approaches for dealing with missing data should be explicitly stated	YES NO N/A *(if no to Q11 or no statistical methods used/needed I.e. acknowledged missing data but didn't input statistically-created data)*
13	A flow diagram or a description of the allocation of participants and those lost to follow-up should be provided for PROs specifically *Note to reviewer: For prospective studies assessing PROs (where allocation of participants to treatment isn't a feature of the study); to score this mark it is sufficient if the study explains if and how many patients were lost to follow-up on prospective data collection*	YES NO N/A (if not prospective)
14	The reasons for missing data should be explained *Note to reviewer: Mark as YES if study provides a response rate and a summary of non-responder characteristics.*	YES NO N/A (if no missing data)
15	The study patients' characteristics should be described, including baseline PRO scores. *Note to reviewer: Baseline PROs may not be applicable e.g. to cross-sectional studies. Patient characteristics of respondents required.*	YES NO
16 [a]	Are PRO outcomes also reported in a graphical format? *Note to reviewer: this does not account for reporting quality and should not be incorporated in final score.*	YES NO
17	The limitations of the PRO components of the trial should be explicitly discussed	YES NO
18	Generalizability issues uniquely related to the PRO results should be discussed, if applicable *Note to reviewer: A description of selection/responder bias as a limitation OR discussion of the cohort not completely representing the community of meningioma patients is satisfactory*	YES NO N/A
19 [a]	Are PRO interpreted? (not only restated) *Note to reviewer: this does not account for reporting quality and should not be incorporated in final score.*	YES NO
20	The clinical significance of the PRO findings should be discussed.	YES NO N/A
21 [a]	Methodology used to assess clinical significance (in case this was addressed) *Note to reviewer: this does not account for reporting quality and should not be incorporated in final score.*	*Anchor based, Distribution based* N/A (if no to Q20)
22	The PRO results should be discussed in the context of the other clinical trial *(study)* outcomes	YES NO N/A *(if no other study outcomes)*

Appendix 2: Modified ISOQOL criteria (continued)		
Number	**Additional Recommendation if PRO is primary outcome of study**	**Options**
1	The title of the paper should be explicit as to the RCT including a PRO	YES NO
2	The introduction should contain a summary of PRO research that is relevant to the RCT	YES NO
3	Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment *Note to reviewer: time points is not relevant to cross-sectional studies*	YES NO N/A *(if no hypothesis provided)*
4	A citation for the original development of the PRO instrument should be provided	YES NO N/A (if new tool)
5	Windows for valid PRO responses should be specified and justified as being appropriate for the clinical context	YES NO N/A
6	There should be a power/sample size calculation relevant to the PRO based on a clinical rationale (e.g., anticipated effect size) *Note to reviewer: this question may not be applicable to all studies*	YES NO N/A
7	The manner in which multiple comparisons have been addressed should be provided *Note to reviewer: this question may not be relevant for exploratory studies.*	YES NO
8	The analysis of PRO data should account for survival differences between treatment groups if relevant	YES NO N/A
9	Results should be reported for all PRO domains (if multi-dimensional) and items identified by the reference instrument (i.e., not just those that are statistically significant)	YES NO
10	The proportion of patients achieving pre- defined responder definitions should be provided where relevant	YES NO
11	A copy of the instrument should be included if it has not been published previously	YES NO N/A

Modifications in *italics*

[a] = new items added by Dirven et al. (164) do not form part of ISOQOL reporting score.
[b] = included in the original ISOQOL checklist (221) as one item but were split by Dirven et al. (164).

Appendix 3: The Joanna Briggs Institute (JBI) checklist for analytical cross-sectional studies

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

Appendix 4: The Newcastle-Ottawa Scale (NOS) for cohort studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection

1) Representativeness of the exposed cohort
   a) truly representative of the average _____ (describe) in the community ✱
   b) somewhat representative of the average _____ in the community ✱
   c) selected group of users eg nurses, volunteers
   d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
   a) drawn from the same community as the exposed cohort ✱
   b) drawn from a different source
   c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
   a) secure record (eg surgical records) ✱
   b) structured interview ✱
   c) written self report
   d) no description

4) Demonstration that outcome of interest was not present at start of study
   a) yes ✱
   b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor) ✱
   b) study controls for any additional factor ✱ (This criteria could be modified to indicate specific control for a second important factor.)

Outcome

1) Assessment of outcome
   a) independent blind assessment ✱
   b) record linkage ✱
   c) self report
   d) no description

2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest) ✱
   b) no

3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for ✱
   b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost) ✱
   c) follow up rate < ____% (select an adequate %) and no description of those lost
   d) no statement

Appendix 5: The QUALMS study Protocol

QUALMS

Quality of Life outcomes in patients with Incidental and Operated Meningiomas: a cross-sectional study

(The QUALMS study)

Protocol

Version: 3.0

20/09/2019

University of Liverpool Ref: 5130

IRAS Project ID: 269742

Quality of life in patients with incidental and operated meningiomas: a cross-sectional study

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QUALITY OF LIFE OUTCOMES IN PATIENTS WITH INCIDENTAL AND OPERATED MENIGIOMAS: A CROSS-SECTIONAL STUDY

ABSTRACT

Aim:

The aim of this study is to investigate the quality of life (QoL) outcomes in patients with incidental or operated meningioma. This will be completed using retrospective case note review and cross-sectional surveys of patients, who, between 2007 and 2014 were either diagnosed with an incidental meningioma or underwent surgical resection of their meningioma.

Patients with meningiomas generally have a good prognosis with long-term survival and tumour control. Therefore it is important to understand the long-term effects that patients experience whilst living with incidental meningiomas or following surgical resection. At present, little research has been completed to investigate the long-term effects in both of these patient groups.

Methods:

Patients will be identified from hospital records and existing audit databases. Data collection will comprise (i) case note review and (ii) patient self-reported outcomes and quality of life assessments. Results of previous outcome audits and quality of life studies[(229)] completed at The Walton Centre NHS Foundation Trust suggest that approximately 392 patients will take part in this study. The retrospective case note review will identify patient diagnosis, the age of diagnosis, clinical presentation, documented comorbidities and long-term problems, documented details of choice of management and length of follow-up. In the operated meningioma cohort, case note review will identify operative details, postoperative complications, date of discharge following surgery and tumour recurrence (where applicable). Patient self-reported outcomes and quality of life assessments will be completed by sending questionnaires by post or handing to patients at routine follow-up appointments. The SF-36, EORTC-BN20 and EORTC QLQ-C30 questionnaires will be used. Quality of life outcomes will be treated as continuous data and analysed accordingly. A multivariate analysis of factors related to quality of life will be performed.

RESEARCH PROTOCOL

Background

Meningioma is the most common primary brain tumour and originates from the linings of the brain. With an estimated annual incidence of 8.33 per 100,000 person-years, it accounts for approximately 40% of all intracranial neoplasms[309]. The incidence increases with age and peaks between the ages of 40 and 60[310]. The World Health Organisation classifies these tumours into three groups: benign (grade I), atypical (grade II) and anaplastic (grade III)[54]. Approximately 80% of these tumours are WHO grade I tumours[309].

The care for patients with meningioma has steadily improved over the past three decades due to a combination of better understanding of the natural history and disease biology of meningioma, advances in surgical frameworks and increasing adjuvant and salvage therapy options. Survival rates and neurological outcomes have consequently improved[292, 293]. Traditional neurosurgical outcomes have been reported in terms of morbidity, mortality and disability. However, these standard metrics are out-dated and the metrics for measuring treatment outcomes are appropriately shifting to become increasingly patient-centred. The assessment of the quality of life (QoL) of patients has become increasingly recognised as an important outcome measure in brain tumour research and the correlation between the two needs to be further explored. Health-related QoL is a broad, multi-dimensional and self-assessed concept encompassing physical, mental, emotional and social functioning related to illness and its management.

The rapid advancement in neuroimaging modalities and their increased availability mean more of these tumours are being discovered whilst in a clinically dormant state. These are referred to as incidental meningiomas[311]. In contrast, some meningiomas go unnoticed until they clinically manifest with headaches[92], seizures[56] or focal neurological deficit (e.g. motor, sensory or language disturbance). These are labelled as symptomatic meningiomas. The primary treatment for symptomatic meningiomas is surgical resection, which, in the majority of cases is curative[139, 312]. Studies suggest that patients experience long-lasting effects following surgery, particularly as life expectancy is long with the 20-year survival rate exceeding 50%[134]. In operated

meningiomas, a single prospective study (n=54), reported improvements in neurocognitive function (NCF) after surgery, although QoL was not assessed[313]. Detailed studies assessing QoL and long-term functional, social and cognitive outcomes in this patient cohort are lacking.

The management of incidental meningioma is controversial, with opinions varying between active monitoring, surgical resection and stereotactic radiosurgery. However, international consensus guidelines suggest that active monitoring with MRI is the most appropriate management strategy in the first instance[96], with most patients remaining clinically[314, 315] and radiologically stable[95]. Quality of life studies which show the superiority of any one management option are lacking. There is only one underpowered cross-sectional study (n=21) showing that patients have impaired QoL[100], and there are no studies examining the effect of stereotactic radiosurgery on QoL in patients with incidental meningioma.

A recent systematic review by Meskal et al. concluded that patients with meningioma suffer from dysfunction in several cognitive domains along their treatment journeys which impacts on short and long-term QoL[87]. Other retrospective studies have shown that although there are improvements in the physical domains of QoL, executive function is frequently impaired[316, 317]. Such impairments in domains of NCF could prove problematic for patients at work and in their social lives[230, 318].

QoL questionnaires such as EORTC-BN20 and QLQ-C30 have been validated for use in brain tumour patients, however, none of them are specific to meningiomas[297]. A recent qualitative study reported that the experiences of meningioma patients are different to existing models of cancer survivorship, but that the supportive care and resource needs are similar in both groups at the time of surgery[319]. The COMET (Core Outcome Measures in Effectiveness Trials) initiative facilitates and supports the development of agreed standardised core outcome sets in trials for any disease and has a key focus on patient involvement. Any prospective meningioma studies performed should take this into consideration in an attempt to define meningioma-specific patient-reported outcomes.

Justification for research

Patients with incidental and operated meningioma are followed-up long-term in clinic to monitor their clinical condition and for tumour recurrence that may need further treatment. Whilst objective neurological deficits (e.g. hemiparesis) or symptoms (e.g. seizures) can be readily identified, the limited time frame in the outpatient clinic precludes the routine assessment of quality of life and the impact of meningioma and treatment.

QoL is an important outcome measure of patient wellbeing. Studying how the QoL of patients is affected would help healthcare professionals and patients to better understand the course of meningioma and its effects over time. Completing this research would allow for the identification of subtle or subclinical deficits that are difficult to identify in the outpatient setting. Furthermore, understanding which domains of QoL are affected in patients would assist healthcare professionals in providing relevant and holistic patient-centred care.

Aims and objectives

Research question: 'In patients with incidental or operated intracranial meningioma, what are the physical, cognitive and psychosocial quality of life outcomes?'

Primary objective

- To determine the prevalence of physical, cognitive and psychosocial problems in patients with either incidental meningioma or operated meningioma

Secondary objectives

- Determine the difference in the QoL between patients with incidental and operated meningioma
- Determine the difference in the QoL between patients with operated meningioma stratified by anatomical location (skull base versus non-skull base)
- Determine the difference in the QoL between patients with operated meningioma stratified by epilepsy status
- Determine the difference in the QoL between patients with operated meningioma stratified by whether they received adjuvant radiotherapy

Study design

A cross-sectional study will be conducted at the Walton Centre NHS Foundation Trust. This will involve:

- Retrospective review of patient case notes and pre-existing databases in order to establish patient demographics, details of diagnosis and treatment data
- Analysis of patient self-reported QoL assessments. These will be completed as questionnaires sent through the post or given to patients whilst attending for routine clinic appointments.

Patient cohort

Patient identification

Patients who received a radiological diagnosis of incidental meningioma or patients who underwent surgery for their meningioma between 2007 and 2014 (inclusive) will be identified from pre-existing surgical logs, MDT records and case records held at The Walton Centre NHS Foundation Trust. This includes inviting patients who attend routine clinic appointments following their meningioma surgery. Furthermore, patients who were discharged and are not currently under active follow-up with regards to their meningioma care at The Walton Centre will be invited for participation in this study.

A list of medical record numbers of potential study participants will be produced. These notes will be anonymised and a paper conversion table containing the patient's hospital number and study number will be produced. Each patient's individual case notes will be reviewed and compared against the inclusion and exclusion criteria to determine eligibility for participation in this study. A screening and enrolment log will be completed. Patients will only be identified by their study number within the log.
Previous audit data from The Walton Centre NHS Foundation Trust between 2007-2015 identified 440 patients with incidental meningioma (approximately 55 new diagnoses per year). Audit data from 2010-2015 identified 283 patients with operated meningioma (approximately 57 surgeries per year). In total each year there are approximately 112 patients with either a newly diagnosed incidental meningioma or a

surgically resected meningioma. We estimate that approximately 784 patients will meet our inclusion criteria for the period of 2007 to 2014. In a previous QoL study[229] investigating patients with meningioma and epilepsy at The Walton Centre NHS Foundation Trust, after applying exclusion criteria and taking into account non-responders and study dropouts, the final response rate was 50%. Assuming a similar response rate, we estimate our final study cohort will be approximately 392 patients.

Inclusion criteria

- Patients aged ≥16 years at the time of diagnosis of meningioma
- Able to communicate effectively using the English language
- To be included in the incidental meningioma cohort:
    - Patients who received a radiological diagnosis of meningioma and have been followed-up for a minimum of 5 years
- To be included in the operated meningioma cohort:
    - Patients who have had surgery for their meningioma and have a minimum of 5 years follow-up

Exclusion criteria

- Patients aged <16 years at the time of diagnosis of meningioma
- Patients considered to lack capacity in order to consent to participate in this study (e.g. due to a significant neurological deficit)
- In the incidental meningioma cohort:
    - Patients who received a radiological diagnosis of meningioma and have been followed-up for less than 5 years
    - Diagnosis of meningioma considered not to be an incidental finding (e.g. meningioma is responsible for the patient's presenting complaint) by clinician responsible for patient's care
- In the operated meningioma arm:
    - Patients who have had surgical resection of their meningioma and have less than 5 years follow-up
- Patients identified as having suffered a cerebral neurological insult (e.g. trauma, meningitis, stroke) prior to presenting with meningioma

- Patients diagnosed with any congenital or neurological disease prior to diagnosis of meningioma (e.g. cerebral palsy)
- Patients diagnosed with radiation-induced meningioma or neurofibromatosis type II-associated meningioma
- Patients with a diagnosis of any condition which leads to cognitive decline (e.g. Dementias, Parkinson's disease or intellectual disabilities), either before or after the diagnosis of meningioma.

Patient recruitment

Invitation to participate and consent

Recruitment of patients to this study will be led by the Chief Investigator and Primary Investigator of the research team. Using pre-existing surgical logs, MDT records and case records, patients who are suitable for participation in the study will be identified. Following confirmation of eligibility criteria, the patient cohort will be contacted and invited to participate by post.

Each eligible patient will receive three documents by post:

1. Cover letter summarising the study and the purpose of contacting the patient by post
2. A detailed patient information sheet containing information about the study in non-scientific terms
3. Consent form

The cover letter sent to the patients will be signed by members of the research team.

In order to ensure informed consent for participation in the study, patients will receive sufficient information about the study and be given sufficient time to consider whether they would like to participate in this study. The study information sheet will include a description of the study, the purpose of the study, methods, risks of the study, advantages and disadvantages of the study, confidentiality, voluntary participation,

right to withdraw, dissemination of results and details of investigators conducting the study.

In order to ensure the best understanding for patients, the cover letter, patient information sheet and consent form will all be written in plain English. Both cover letters, patient information sheet and consent form have been reviewed by two lay people to ensure the language used is understandable.

This study will assume that all eligible patients have the capacity to consent to participate in the study unless proven otherwise, which is in accordance with the Mental Health Act 2005. A thorough examination of the patient's hospital records will allow for the study investigators to highlight any factors which may affect a patient's capacity to consent for participation in the study.

The patient information sheet will include the contact details of the research team and the Patient Experience Team. Participants can contact these departments in order to gain any further information with regards to the study or their participation.

By consenting to participate in this study, patients will consent to complete the research study questionnaires. Patients will also be giving consent to the study investigators to analyse the answers given in the study questionnaires and complete a retrospective review of the patient's case notes.

Patients will have four weeks to read the cover letter and patient information sheet and return the consent form should they wish to participate in the study. A pre-paid envelope will be provided for the patient to return their consent form to The Walton Centre NHS Foundation Trust. If no consent form has been returned from a patient, they will be sent a second cover letter inviting them for participation in the study, alongside another patient information sheet and consent form. If there is no response from the patient after this, then it will be assumed that the patient does not wish to participate in the study and will not be contacted regarding this study any further.
For patients who do not wish to participate in the study, no explanation will be requested. However, if a patient gives a voluntary explanation regarding why they do not wish to be included in the study then a record of this will be kept.

Patients who attend routine clinical follow-up appointments at The Walton Centre NHS Foundation Trust will also be approached during the recruitment period and invited to participate. The patient will be given the opportunity to complete the quality of life questionnaires at the hospital or to return them by post to the research team.

Data collection

After receiving the signed consent forms from all patients who would like to participate in this study, the research team will ask these patients to complete the study questionnaires. Patients will receive the questionnaires through the post along with a pre-paid envelope which would allow the patients to send their completed questionnaires back to the research team free of charge. For those patients who have long-term follow-up at The Walton Centre NHS Foundation Trust and their next clinic appointment is due to take place during the time of the data collection stages, questionnaires will be provided at the next clinic appointment.

Data from completed questionnaires will be recorded onto a database designed for case-report forms, alongside baseline data identified during case note review. All patients will be anonymised and assigned a sequential study number, and all information gathered from completed questionnaires and case note review will be recorded under this study number. Data that is obtained will be collated to be used for statistical analysis.

Study data

Data fields

1. Baseline data to be obtained from case note review:

- Diagnosis and tumour grade (according to WHO classification)
- Age of patient at diagnosis
- Patient gender
- Clinical presentation
- Anatomical location of meningioma (using the International Consortium on Meningioma classification system)
- Documented comorbidities
- Documented neurological problems
- Past surgical history including any previous neurosurgical operations
- Documented details of choice of management for meningioma (e.g. active monitoring, surgical resection or adjuvant radiotherapy)
- Operated meningioma arm:
    - Operative details (including date of surgery, type of surgery, the extent of surgical resection: Simpson grade 1-5)
    - Immediate postoperative complications
    - Date of discharge following surgery
- Tumour recurrence and date of recurrence (recurrence-free survival)
- Treatment for recurrence (e.g. active monitoring, surgery, radiotherapy)
- Adjuvant radiotherapy after the first operation
- Length of follow-up

2. All patients will receive a study-specific questionnaire identifying:
    - Active medical problems
    - Current medications (and indications)

3. All patients participating in the study will complete:
    - General QoL questionnaire
        - Short Form 36 (SF-36)
    - Brain tumour-specific questionnaire

    - The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire- Brain Neoplasm (EORTC-BN20)
- Cancer patient QoL questionnaire
    - The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30)

Research ethics

Ethical approval for research

The University of Liverpool will be the sponsor for the study.

The study protocol, invitation to participate letter and patient information sheet will be submitted for local research ethics approval. IRAS ethical application will also be submitted for HRA approval.

Data

The SF-36, EORTC-BN20 and EORTC QLQ-C30 QoL questionnaires have been fully validated for use, with permission for academic reproduction for the purposes of this study granted by authors where appropriate. All questionnaires and validation studies will be referenced in any publication to ensure compliance with licence and trademark agreements.

All electronic records will be stored on University or NHS computers which are password-protected. Electronic records will be encrypted, and no patient identifiable data will be stored digitally on any computers or other electronic devices.

All data will be anonymised by the use of a study number, except a paper conversion table detailing patient name, hospital number, address and allocated patient study number. All study documentation will include this study number.

All paper-based records (including conversion table) will be stored safely in a lockable filing cabinet in a university office on NHS property (locked whilst unattended). Medical notes and paper-based patient records that are in use will be tracked to and held within a lockable filing cabinet within the Chief Investigator's office at The Walton Centre NHS Foundation Trust. Use of this information will comply with all information governance policies at The Walton Centre NHS Foundation Trust. Medical notes and paper-based patient records will be returned back to the Health Records Library when they are no longer required.

All data will be stored for 10 years following the completion of this study as per University of Liverpool protocol. Following this, all data will be archived with the permission of the Chief Investigator, who is the custodian, as per University of Liverpool Data Management Policy.

The Chief Investigator will act as the data custodian and will lead the research team in ensuring appropriate security of all patient and study information. The Chief Investigator will ensure full compliance of The Walton Centre NHS Foundation Trust's and The University of Liverpool's data security and information governance policies. Access to patient identifiable information will be on a strict need-to-know basis between investigators and all patient personally-identifiable information will be kept strictly confidential. No confidential patient data or study information will be transferred outside of The Walton Centre NHS Foundation Trust or University of Liverpool.

For those patients who are not included in the study (e.g. patients that would not like to participate in the study, patients not meeting inclusion/exclusion criteria or those removed due to non-response) the research team will destroy all stored data pertaining to the patient (deleting electronic data or shredding paper records). Any requested medical notes or paper-based patient records relating to these patients will be returned back to the Health Records Library.

There is a small risk of the invitation to participate letter, patient information sheet, consent form and the study questionnaires being sent to a household where the patient no longer resides. This is particularly the case with patients that have been discharged

from long-term follow-up at The Walton Centre NHS Foundation Trust. The research team will make every effort to ensure that up-to-date patient contact information is used. For those patients who have been discharged from having long-term follow-up, up-to-date patient contact details and postal address will be obtained from hospital case notes and NHS summary care records which are accessible through the NHS spine.

Patients will be able to consent to the use and storage of their data, with the exception of this first contact. This is an unavoidable situation, but as described above, any risks will be minimised during this process.

Risks and benefits to participants

Participation in this study provides no risk to the patients in terms of pain, discomfort, change in lifestyle or risk from physical intervention. Participating or choosing not to participate in this study will in no way alter the ongoing or future medical care that the patient receives.

There is a risk that participating in this study and completing the study questionnaires may generate strong emotions for some participants regarding their medical condition. The study information literature will include the details of the research team and The Patient Experience Team (an independent advisory service), and participants would be able to contact these departments for further support. At the discretion of the Chief Investigator, if it is felt necessary and the participant consents, there may be a referral made to psychological services for support as per the current standard of care.

If patients that are discharged from ongoing care complete this study and experience any further issues, then they would be able to contact the research team who would be able to book an appointment at The Walton Centre. From this appointment, patients can be directed to the appropriate supporting services if required. For patients who are under long-term follow-up at The Walton Centre NHS Foundation Trust that require additional clinical support, the Chief Investigator may book a follow-up appointment with the clinician responsible for the patient's care. This will only be done if deemed

appropriate and necessary by the Chief Investigator and the patient has given permission for the Chief Investigator to do so.

Completing the study questionnaires will take approximately 30 minutes to 1 hour and may be an inconvenience for some participants. Pre-paid envelopes will be included with the questionnaires to reduce any costs to the participant.

The patient study information literature and consent forms will detail all of the above points clearly so that patients are fully informed of what participation in this study will involve for them. It will explain that patients have a right to withdraw from the study completely at any point. This study has selected the most appropriate questionnaires so that any intrusion to patients is minimised.

There are no potential risks to the members of the research team as a result of conducting this study.

Research team

The Chief Investigator of this study (Mr Michael Jenkinson) is an honorary consultant neurosurgeon and is part of the neuro-oncology team at The Walton Centre NHS Foundation Trust. He is also a Reader within the Institute of Translational Medicine at The University of Liverpool. The Primary Investigator of this study (Sumirat Keshwara) is currently a fourth year student doctor (medical student) at The University of Liverpool. He will conduct this research study as part of his intercalated MPhil course between August 2019 and August 2020.

Analysis

Descriptive statistical analysis will be undertaken. For the quality of life questionnaire data, an analysis will be undertaken and values compared to reference values from validation studies. Each questionnaire will be scored according to the scoring systems that were published by the original authors.

The study results will be analysed and reported using the 'Strengthening the Reporting of Observational studies in Epidemiology' STROBE checklist for cohort studies. QoL outcomes will be treated as continuous data and analysed accordingly. A multivariate analysis of factors related to QoL will be performed.

Dissemination of findings

This study will form the basis of the Primary Investigator's MPhil thesis and will be submitted to the University of Liverpool for assessment. The research team will disseminate findings of this study at local, national, international scientific and clinical meetings. The research team will publish the study results in peer-reviewed journals. The results will be shared with charitable organisations such as The Brain Tumour Charity and brainstrust.

Patients who have participated in this study will also be given the opportunity to receive a break-down of the results and explanation of the findings at the end of the study. On the consent form, patients will be given the choice of whether they want to be made aware of the study results or not. Any patients who have consented to receive this information will receive a newsletter at the end of the study.

Project timeline

The planned study start date is 01/08/19. Recruitment will be open for 6 months until 31/01/20. Data analysis and interpretation will take 6 months until 31/07/20. The study will close after analysis and data filing on 31/10/20.

Funding

Funding for this quality of life study has been received by the Chief Investigator (Michael Jenkinson) as part of a larger programme grant from The Brain Tumour Charity ('Deciphering the genetic and epigenetic landscape of clinically aggressive meningioma' Objective 1: Establishing quality of life and symptoms in patients with meningioma. The overall principle investigator for the Brain Tumour Charity grant is

Dr Gelareh Zadeh, University of Toronto). The principle investigator for the QUALMS study is Michael Jenkinson, University of Liverpool.

Declaration of interest

The authors declare no conflict of interest with regards to completing this study.

Appendix 6: Incidental meningioma cohort cover letter

UNIVERSITY OF LIVERPOOL

The Walton Centre NHS
NHS Foundation Trust

The Walton Centre NHS Foundation Trust
Lower Lane
Liverpool
L9 7LJ

Re: Quality of life outcomes in patients with incidental and operated meningiomas (The QUALMS study)

Dear Sir/ Madam,

We are a group of doctors based at The Walton Centre NHS Foundation Trust. We are conducting a study into the long-term quality of life in patients with an incidental meningioma.

We are writing to invite you to participate since you have previously been diagnosed with an incidental meningioma. We want to assess the impact of having an incidental meningioma on your quality of life, and we would be very grateful for your response.

With the increasing use of brain scans (such as CT scans or MRI scans), more and more incidental meningiomas are being found. These are benign meningiomas that are found by chance and usually do not need any treatment. Sometimes, incidental meningiomas cause anxiety and uncertainty for patients and we would like to know the impact of this on quality of life. This will help doctors to understand the problems patients face and will help future patients.

Our study will ask you to complete 4 questionnaires, sent to you by post or given to you during your next clinic appointment at The Walton Centre if you are currently under follow-up. The enclosed information letter explains this in more detail. The questionnaires will ask about your current quality of life. We would also like to review your hospital notes. This will help us to understand more about your incidental meningioma. We will only do this with your consent.

If you would like to take part in our study, please read the enclosed information letter. If you are happy then please complete and return the enclosed consent form. You will then be sent the study questionnaires. The questionnaires will take between 30 minutes to 1 hour to complete. We will supply pre-paid return envelopes so there will be no direct costs to taking part.

If you have any further questions that are not answered in the information letter, please contact the study team. Their contact details are in the information letter.

Thank you for your time in considering this study.

Yours faithfully,

Michael Jenkinson

Sumirat Keshwara

IRAS Project ID: 269742 QUALMS Research Study Invitation Letter Version 3.0 13th August 2019

Appendix 7: Operated meningioma cohort cover letter

UNIVERSITY OF LIVERPOOL

The Walton Centre NHS Foundation Trust

The Walton Centre NHS Foundation Trust
Lower Lane
Liverpool
L9 7LJ

Re: Quality of life outcomes in patients with incidental and operated meningiomas (The QUALMS study)

Dear Sir/ Madam,

We are a group of doctors based at The Walton Centre NHS Foundation Trust. We are conducting a study into the long-term quality of life in patients who have had an operation to remove a meningioma.

We are writing to invite you to participate since you have previously had an operation to remove a meningioma. We want to assess your quality of life after having surgery, and we would be very grateful for your response.

The long-term outcome for patients after an operation to remove a meningioma is good. This makes it important for doctors to study the long-term effects that patients experience after having surgery. We want to see if any long-term effects after surgery are affecting your quality of life. This will help doctors to understand the problems patients face and will help future patients.

Our study will ask you to complete 4 questionnaires, sent to you by post or given to you during your next clinic appointment at The Walton Centre if you are currently under follow-up. The enclosed information letter explains this in more detail. The questionnaires will ask about your current quality of life. We would also like to review your hospital notes. This will help us to understand more about your operated meningioma. We will only do this with your consent.

If you would like to take part in our study, please read the enclosed information letter. If you are happy then please complete and return the enclosed consent form. You will then be sent the study questionnaires. The questionnaires will take between 30 minutes to 1 hour to complete. We will supply pre-paid return envelopes so there will be no direct costs to taking part.

If you have any further questions that are not answered in the information letter, please contact the study team. Their contact details are in the information letter.

Thank you for your time in considering this study.

Yours faithfully,

Michael Jenkinson

Sumirat Keshwara

IRAS Project ID: 269742 QUALMS Research Study Invitation Letter Version 3.0 13th August 2019

Appendix 8: Patient Information Sheet and Consent Form

Quality of Life outcomes in Incidental and Operated Meningiomas (The QUALMS study)

Patient information sheet and consent form

Version 4

The Walton Centre NHS Foundation Trust

The Walton Centre NHS Foundation Trust

Lower Lane

Liverpool

L9 7LJ

Contents

You are invited to take part in our study

- This study is investigating the impact on quality of life by having an incidental meningioma or having surgery to remove a meningioma.
- You have been asked to take part because you been told you have an incidental meningioma, or you have had surgery to remove a meningioma.
- This leaflet will explain why the study is being done and what it will involve for you.
- Please read for more information. You may discuss it with others if you wish, such as your family and friends.
- Taking part is voluntary. If you do not wish to take part, you do not need to tell us why.
- Please ask a member of the clinical team if anything is not clear or if you require further information. Their contact details are below.
- Thank you for taking the time to read this information letter, we appreciate your support.

What is this letter?

This letter provides information on the study that we are asking you to take part in. It explains the aims of the study, what it will involve for you and any benefits or risks to you.

What is the study?

A meningioma is a brain tumour arising from the protective linings of the brain. Meningiomas that are found by chance on brain scans (such as CT scan or MRI scan) are called incidental meningiomas. An operated meningioma is one that was removed by surgery.

The aim of this study is to investigate the impact on quality of life of patients who have an incidental meningioma or had surgery to remove a meningioma. We would like to understand the long-term effects of the meningioma or any treatment that you may have received.

Why is this study needed?

Quality of life describes a patient's general well-being. It encompasses multiple aspects of life, including both physical and emotional. We know that disease and medical treatments can affect your quality of life.

Patients with incidental meningioma often don't need treatment. However, having an incidental meningioma may cause some anxiety for patients. This makes it important for doctors to understand the quality of life for patients with an incidental meningioma.

The outcome for operated meningioma is good, however, treatment may affect a patient's quality of life. Not much is known about how surgery to remove a meningioma affects a patient's quality of life. This makes it more important to examine the long-term effects of surgery. Understanding this would help doctors to better support patients in the future.

How will the study achieve its aim?

An effective way to look at quality of life and what influences it is to complete questionnaires during day-to-day life.

We will ask you to fill out 4 questionnaires. These will focus on both general aspects of quality of life, and also those more specifically related to brain tumours.

We can establish whether specific aspects of daily life are impacted by collecting the responses from a large group of participants.

The study will also review hospital notes with your consent. This is to identify whether any particular factors (e.g. location or size of meningioma) impact on quality of life.

Why have I been asked to take part?

We are asking you to take part in this study because you have either (i) been informed that you have an incidental meningioma or (ii) had an operation to remove a meningioma. We would like to understand more about your quality of life and any long-term effects that you may be experiencing. We would, therefore, value your personal responses.

What will happen during the study?

If you decide to take part in this study, we will ask you to complete 4 questionnaires. These will either be posted to you or given to you at your next clinic appointment at The Walton Centre NHS Foundation Trust. We will supply pre-paid return envelopes to prevent any cost to yourself. The study questionnaires will take between 30 minutes and 1 hour to complete.

The names of the study questionnaires are:

7. SF-36
8. Study-specific questionnaire (asking about current medical conditions and medications)
9. EORTC QLQ-C30
10. EORTC-BN20

We will also review your hospital notes. This is to help us understand which other factors may be influencing your quality of life. We will only look at your hospital notes with your consent.

If you are happy to take part in this study, we ask that you complete and return the attached consent form in the pre-paid envelope provided. Please do this within 4 weeks of receiving this letter.

Once we have received your completed consent form, we will then send you the study questionnaires. Please return these in the pre-paid envelope as soon as possible, or, if you are still under follow-up at The Walton Centre NHS Foundation Trust, you can choose to complete the questionnaires at your next clinic appointment and hand them in to your doctor.

What are the risks/disadvantages of taking part?

There is no direct risk to you from taking part in this project. The study poses no risk to you in terms of pain, discomfort or change in lifestyle.

The only inconvenience from the study will be the time taken to complete the questionnaires. We want to limit any inconvenience to you, so the questionnaires will take less than 1 hour to complete in total. All postage will be pre-paid.

There is a very small risk from the use of your personally identifiable information (e.g. name and address). To limit this, all of your details will be stored securely. Access to your data will be strictly limited to members of the research team with your consent.

Some questionnaires ask about work, your emotions, and relationships with other people. While it is unlikely, some people may find these questions upsetting. If this is a problem for you, you may stop answering these questions and withdraw yourself from the study.

We would like to support you if you are upset by the questionnaires. If you would like further support, then please contact either the research team or the Patient Experience Team (see details below). If it is felt necessary, you may be offered an appointment at The Walton Centre to discuss which services would be able to best support you. You may choose to contact the doctor responsible for your care for further information if you are still under follow-up at The Walton Centre.

This study, and your decision to take part or not, will not impact on any on-going medical care that you are receiving.

What are the benefits of taking part?

There is no direct benefit to you from taking part in this study. However, you may be interested to learn about the influences on your quality of life. By taking part in this study you will be able to help doctors to better understand the effects of meningioma. This would help doctors to treat future patients more effectively.

Will my taking part be kept confidential?

Your involvement in this study will be kept confidential at all times, and maintaining confidentiality is a priority for the research team. Only the researchers involved in this study will have access to the data, including your completed questionnaires and hospital notes. All data will be collected, stored and destroyed in keeping with The Data Protection Act 2018. Only the minimum personal data necessary will be collected. We will hold personally identifiable data for 18 months.

We will anonymise all of your study data, including the questionnaire results. All electronic data will be stored on password-protected and encrypted computers. We will not store any of your personally identifiable data digitally. The data which we will record for analysis will not contain any personally identifiable data. It will not be possible to identify you from the recorded datasets.

Once the study has been completed, we will archive study data and identifiable information according to NHS protocols. This is to allow future use of the data in scientific articles and conferences and to comply with local research policies.

If necessary and relevant to the study, selected individuals from the University of Liverpool (study sponsor) and/or regulatory authorities may review your medical and research records.

Please see General Data Protection Regulation Statement (page 6) for more details.

Do I have to take part, and what if I change my mind?

You do not have to take part in this study. Your decision to take part is completely voluntary. You are able to change your mind and withdraw yourself from the project at any stage. You can do so without giving a reason. The decision to participate or not to participate in this study will not affect any medical care you receive from The Walton Centre currently or in the future.

What will happen to the results of this study?

We will report the findings of this study through national and international conferences and scientific journals. We will also share the results with charitable organisations such as The Brain Tumour Charity and brainstrust. We will not use any identifiable information when presenting the study results.

If you would like to know the results of this study and have the findings explained to you, please tick and initial the relevant box on the consent form. We will send you a newsletter once the study is complete.

Who is conducting this study?

This study is taking place at The Walton Centre NHS Foundation Trust. This is the location where the study team will collect and process data. The Chief Investigator for this study is Mr Michael Jenkinson. Mr Jenkinson is a Consultant Neurosurgeon at The Walton Centre and Reader at The University of Liverpool.

The Primary Investigator is Sumirat Keshwara, who is a student doctor (medical student) at The University of Liverpool. Sumirat is conducting this study as part of his MPhil course.

The University of Liverpool is the study sponsor. The study sponsor is responsible for how the study is completed. The research team at The Walton Centre NHS Foundation Trust will be under the instruction of The University of Liverpool.

This study has received ethical approval and Health Research Authority (HRA) approval.

Contact details

If you would like to speak to the research team, please do not hesitate to contact us via the following:

- Telephone:
  - Chief investigator: Michael Jenkinson
    - 0151 529 5683
  - Primary investigator: Sumirat Keshwara
    - 0151 529 5945
- Email:
  - Chief Investigator: Michael Jenkinson (secretary):
    - joan.leary@thewaltoncentre.nhs.uk
- Post:

  The QUALMS Study Research Team
  c/o Mr Michael Jenkinson
  Department of Neurosurgery
  The Walton Centre NHS Foundation Trust
  Lower Lane
  Liverpool
  L9 7LJ

If you wish to discuss the study with someone independent of the study team, please consider contacting the Patient Experience Team at the Walton Centre NHS Foundation Trust. This service offers further support, confidential advice and information. You can contact them by calling 0151 556 3090 or by sending an email to them on PatientExperienceTeam@thewaltoncentre.nhs.uk.

What are the next steps?

If you understand what this study involves and would like to participate in it, please complete the enclosed consent form within 4 weeks of receiving this letter. You can return the consent form back to us using the pre-paid return envelope that has been provided.

We are thankful to you for your time in considering this study. If you have any further questions, then please do not hesitate to contact us.

General Data Protection Regulation statement

As a University and as a NHS Trust we use personally-identifiable information to conduct research to improve health, care and services. As publicly-funded organisations, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

The University of Liverpool and The Walton Centre NHS Foundation Trust take great care to abide by our legal and moral obligations when handling your personal and healthcare data. Due to changes introduced in the EU General Data Protection Regulation (GDPR), we are providing you with information on the lawful basis on which we are processing your data. The lawful basis for the processing of your personal data for the research study which you have participated in is a task in the public interest.

The data you provide for the '*quality of life outcomes in incidental and operated meningiomas'* study will be stored for 10 years as per protocol. You are free to withdraw your consent for your data to be collected, processed, or stored at any time. However, if the data has already been anonymised it will not be possible to withdraw your data.

We will not share your data unless you have provided explicit consent for us to do so. This study will not share your personally-identifiable data with any external organisations.

The data controller for this study is the University of Liverpool (study sponsor) (tel. 0151 794 8739) and the University Data Protection Officer, Mrs Victoria Heath, can be contacted on 0151 794 2148.

The University and NHS Trust strive to maintain the highest standards of rigour in the processing of your data. However, if you have any concerns about the way in which the University processes your personal data, it is important that you are aware of your right to lodge a complaint with the Information Commissioner's Office by calling 0303 123 1113.

Quality of Life outcomes in Incidental and Operated Meningiomas (The QUALMS study)

The Walton Centre NHS
NHS Foundation Trust

Return address

The QUALMS study c/o MDJ, Department of Neurosurgery

The Walton Centre NHS Foundation Trust

Lower Lane, Liverpool, L9 7LJ

Adult Consent Form (page 1)

To be completed by the patient:

Once you have read, understood, and agreed to each statement please put a tick in the box and initial.

	Tick	Initial
1. I confirm that I have read and understood the information sheet (version 4) for the study, and have had the opportunity to ask questions if I so wish.	☐	☐
2. I understand that my participation is entirely voluntary and that I am free to withdraw from the study at any stage, without giving a reason.	☐	☐
3. I understand that my decision to participate or not, or to withdraw from this study will have no impact on any current or future medical care I receive.	☐	☐
4. I give my permission for the study team, the University of Liverpool (study sponsor) and the Walton Centre NHS Foundation Trust (host NHS site) to have access to my medical records for study purposes.	☐	☐
5. I give my permission for the study team, the University of Liverpool (study sponsor) and the Walton Centre NHS Foundation Trust (host NHS site) to collect and analyse data that is relevant to the study.	☐	☐
6. I understand that any information about me will be treated in confidence and in conjunction with data protection laws, and that I will not be named in any written work.	☐	☐

Consent form continued on page 2, please turn over.

Quality of Life outcomes in Incidental and Operated Meningiomas (The QUALMS study)

The Walton Centre NHS
NHS Foundation Trust

Return address

The QUALMS study c/o MDJ, Department of Neurosurgery

The Walton Centre NHS Foundation Trust

Lower Lane, Liverpool, L9 7LJ

Adult Consent Form (page 2)

Consent form continued

7. I agree to my data being anonymised and used in scientific publications resulting from this research. ☐ ☐

8. I agree to my data being shared with the University of Liverpool (study sponsor) and regulatory authorities where it is relevant to my taking part in this research. ☐ ☐

9. I agree to the University of Liverpool (study sponsor) having access to the study data for monitoring and auditing purposes. ☐ ☐

10. I agree to take part in the study. ☐ ☐

Optional question:

11. I would like to be kept informed of the results of this study ☐ ☐

To be completed by the patient:

Patient name (print): Signature: Date:

To be completed by the researcher taking consent:

Researcher name (print): Signature: Date:

Appendix 9: Additional systematic review articles

The articles named below meet the inclusion criteria for the systematic review but were not initially identified from the screening process as it was incomplete at the time of writing the chapter. Therefore, the following articles are not represented in the PRISMA diagram, results or discussion of Chapter 2.

1. Williams T, Brechin D, Muncer S, Mukerji N, Evans S, Anderson N. Meningioma and mood: exploring the potential for meningioma to affect psychological distress before and after surgical removal. Br J Neurosurg. 2019
2. Kondziolka D, Levy EI, Niranjan A, Flickinger JC, Lunsford LD. Long-term outcomes after meningioma radiosurgery: physician and patient perspectives. J Neurosurg. 1999
3. Steinvorth S, Welzel G, Fuss M, Debus J, Wildermuth S, Wannenmacher M, Wenz F. Neuropsychological outcome after fractionated stereotactic radiotherapy (FSRT) for base of skull meningiomas: a prospective 1-year follow-up. Radiother Oncol. 2003
4. Guenther F, Swozil F, Heber S, Buchfelder M, Messlinger K, Fischer MJ. Pre- and postoperative headache in patients with meningioma. Cephalalgia. 2019
5. Karsy M, Jensen MR, Guan J, Ravindra VM, Bisson EF, Couldwell WT. EQ-5D Quality-of-Life Analysis and Cost-Effectiveness After Skull Base Meningioma Resection. Neurosurgery. 2019
6. Ozbayir T, Malak AT, Bektas M, Ilce AO, Celik GO. Information needs of patients with meningiomas. Asian Pac J Cancer Prev. 2011
7. Sachsenheimer W, Bimmler T. Assessment of quality of survival in patients with surgically treated meningioma. Neurochirurgia (Stuttg). 1992
8. Natarajan SK, Sekhar LN, Schessel D, Morita A. Petroclival meningiomas: multimodality treatment and outcomes at long-term follow-up. Neurosurgery. 2007
9. Neil-Dwyer G, Lang D, Garfield J. The realities of postoperative disability and the carer's burden. Ann R Coll Surg Engl. 2001
10. Heufelder MJ, Sterker I, Trantakis C, Schneider JP, Meixensberger J, Hemprich A, Frerich B. Reconstructive and ophthalmologic outcomes following resection of spheno-orbital meningiomas. Ophthalmic Plast Reconstr Surg. 2009
11. Westerlund U, Linderoth B, Mathiesen T. Trigeminal complications arising after surgery of cranial base meningiomas. Neurosurg Rev. 2012

Additional articles for further consideration for inclusion in the systematic review

- Gande A, Kano H, Bowden G, Mousavi SH, Niranjan A, Flickinger JC, Lunsford LD. Gamma Knife radiosurgery of olfactory groove meningiomas provides a method to preserve subjective olfactory function. J Neurooncol. 2014

- Kessel KA, Fischer H, Oechnser M, Zimmer C, Meyer B, Combs SE. High-precision radiotherapy for meningiomas : Long-term results and patient-reported outcome (PRO). Strahlenther Onkol. 2017
- Faramand A, Kano H, Niranjan A, Park KJ, Flickinger JC, Lunsford LD. Tumor Control and Cranial Nerve Outcomes After Adjuvant Radiosurgery for Low-Grade Skull Base Meningiomas. World Neurosurg. 2019