Treating Meningioma: does the patient benefit? A paradigm shift from tumor to patient

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PhD-thesis, Leiden University and Leiden University Medical Center, Leiden, the Netherlands

ISBN: 978-94-6361-623-2
Cover Design: Anna Zamanipoor Najafabadi
Lay-out and Printing: Optima Grafische Communicatie, Rotterdam, the Netherlands
Publication of this thesis was kindly supported by ChipSoft and Stöpler Medical B.V.

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Proefschrift

ter verkrijging van
de graad van doctor aan de Universiteit Leiden,
op gezag van rector magnificus prof.dr.ir. H. Bijl,
volgens besluit van het college voor promoties
te verdedigen op donderdag 13 januari 2022
klokke 16:15 uur

door

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geboren te Karaj (Iran)
in 1994

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When nothing is sure, everything is possible.

Chapter 1

General introduction and outline of this thesis

MENINGIOMA

Epidemiology and diagnosis

Meningiomas develop from the arachnoid cap cells of the arachnoid membrane[1]. The arachnoid membrane is part of the meninges, covering the central nervous system[1,2]. Hence these tumors grow within the cranium and spinal canal, although predominantly (> 95% of cases) intracranially.[1,2] With the aging population and the increasing use of neuro-imaging, the number of meningioma diagnoses, especially asymptomatic meningioma (i.e., incidental findings), is rising[3–6]. Currently, these tumors are the most frequently diagnosed primary intracranial tumors, accounting for 38.3% of all intracranial tumors[6]. As these tumors grow from the meninges, they show a dural tail on magnetic resonance imaging (MRI). While tumors at the convexity often present as sharply delineated circumferential tumors, skull base meningioma can grow "en-plaque", like thin carpet-like structures over the skull base bones. These tumors can also be associated with hyperostosis of the adjacent cranial bones. The patients recruited for the studies described in this thesis were all patients with intracranial meningioma.

Presentation

Patients with symptomatic intracranial meningioma can present with a wide variety of symptoms, depending on tumor location[7]. Patients with convexity meningioma often present with deficits correlated to direct compression of the cortex, such as unilateral or bilateral motor and sensory deficits, homonymous hemianopia, frontal lobe syndrome, and seizures[8]. Patients with skull base meningioma often present with symptoms of cranial nerve deficits[9–12]. Visual deficits are often observed with anterior skull base tumors[10,13,14]. A specific type of meningioma is the spheno-orbital meningioma, which grows like thin carpet-like structures on the medial edge of the sphenoid wing, and causes extensive hyperostosis of the sphenoid and surrounding bones. Patients with this type of meningioma often present with both visual deficits and exophthalmos of the eye[10]. Symptoms and signs of raised intracranial pressure, such as headache, can also be observed due to tumor mass, associated vasogenic edema in meningioma, or obstructive hydrocephalus in posterior fossa meningioma specifically[1].

Histological classification

Meningiomas are classified according to the World Health Organisation (WHO) classification of tumors of the central nervous system into 16 subtypes, which can be divided into three WHO grades: grade I benign (approximately 80% of patients), grade II atypical (<20%), and grade III malignant (<1%)[15]. Patients with grade I and II tumors have a near-normal survival, while patients with grade III tumors have a 5-year survival chance of 64% (95%CI: 61-67%)[3]. Benign WHO grade I meningiomas tend to grow slowly over time. WHO grade II meningioma can show invasion in brain parenchyma, and grade III tumors have the ability to metastasize within and outside the central nervous system[1,15]. Nevertheless, in clinical practice, the current

WHO classification does not always correlate with the observed tumor behavior. In recent landmark studies, it was indeed shown that more sophisticated molecular information (i.e., methylation profiles) results in more homogenous pathology groups with stronger predictive power of tumor behavior and recurrence[16,17]. The patients recruited in the studies described in this thesis were all diagnosed with a WHO grade I or II meningioma.

THE ROAD TO CURRENT TREATMENT STRATEGIES

Wait-and-scan

Multiple treatment options exist for meningioma[1]. A recent guideline of the European Association of Neuro-Oncology (EANO) advises a wait-and-scan approach for asymptomatic meningioma patients to evaluate proximity of the tumor to critical neurovascular structures and follow-up of tumor growth over time[18]. In the Netherlands, the frequency of MRI imaging for asymptomatic patients depends on growth rate, tumor characteristics on MRI (e.g., edema and signs of calcification), and age[19]. Regular follow-up is recommended up to the age of 80 years, as studies regarding the natural history of meningioma have shown that tumor growth after the age of 80 seldom results in symptomatic lesions, while interventions in this group of patients are associated with a substantial risk of severe complications. More recently, evidence-based follow-up schemes were developed, providing more tailored follow-up schedules based on tumor characteristics on imaging, patient functioning, age, and comorbidities[20]. These follow-up schemes are currently being validated internationally, which is needed before implementation in clinical practice.

Meningioma surgery

Surgery is often the first-line treatment for patients with symptomatic or growing meningioma[18,21]. Advantages of surgical resection are actual removal of the tumor mass with consequently rapid improvement of neurological symptoms and deficits in the majority of patients. An additional benefit is that tumor tissue is collected for histological diagnosis and grading, and in recent years for molecular profiling, which provides relevant information for possible post-surgical treatment (i.e., the need for radiotherapy) and follow-up schemes[18,21]. Surgeons aim at maximum safe resection, while preserving neurological and neurocognitive function. Already in 1957, Simpson described that the degree of resection, as observed intraoperatively, predicts tumor recurrence, also known as the Simpson Grade[22]. Sixty years later, we still use the same classification system to describe the degree of tumor removal[22,23].

In the last two centuries, meningioma surgery has been subject to great developments, not only improving meningioma resection, but also contributing to the development of modern neurosurgical techniques[24,25]. The first successful meningioma resection, or as described by the

surgeon Zanobi Pecchioli "fungus of the dura mater", was performed in Siena in 1835[26]. In his notes, he describes that the patient had no major morbidities in at least the first 30 months after surgery[26]. The first successful resection of a skull base meningioma can be credited to Francesco Durante, an Italian surgeon who operated on a 35-year old patient with an "apple-sized" olfactory groove meningioma in 1885, who survived, as he describes in his 1887 Lancet publications, in good health up to 20 years after the surgery[27,28]. It was Harvey Cushing, who introduced the name "meningioma" in 1922 during the famous Cavendish lecture[29]. He was also the first to adopt electrocautery to control tumor vessels in meningioma surgery, which led to a major decrease in hemorrhage and mortality[29]. Development of a surgical plane and preservation of venous sinuses were other developments facilitating successful and safe resection of meningioma.

In the second half of the twentieth century, meningioma surgery has undergone major developments too. Improved neuroimaging facilitates appreciation of tumor extension and venous anatomy preoperatively, and intraoperative neuro-imaging techniques have been developed to anatomically guide the surgeon during surgery[30]. The diffuse growth patterns and close anatomical location to critical neurovascular structures has stimulated the development of extensive skull base approaches and reconstruction techniques, development of microsurgical techniques, and multidisciplinary surgery with head and neck surgeons, plastics surgeons, orbital surgeons, and other specialties[11,31–35].

Radiotherapy

Fractioned radiotherapy or radiosurgery is reserved for patients with anatomically complex tumors, prohibiting surgical resection. It is also indicated for patients with a tumor remnant or recurrent tumor, and patients with severe comorbidities in whom surgery is associated with high complication risks[18,21]. Recently, adjuvant postoperative radiotherapy for patients with fully resected WHO grade II and grade III meningioma has been advocated, which is currently being compared with a postoperative wait-and-scan follow-up in two phase III trials[21,36]. Previously used radiation techniques were 3-dimensional conformal irradiation (3D-CRT), in which the radiation field of multiple beams project to the target volume. Current standards are intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), which improve dose distribution and consequently decrease irradiation of surrounding (healthy) tissue.

While conventional radiotherapy techniques use photons to irradiate the tumor, there has been a rise in particles-based irradiation techniques, such as proton beam therapy, with the opening of proton beam therapy centers in the Netherlands. The greatest advantage of proton beam therapy lies in the Bragg peak phenomena, resulting in lower scatter doses beyond the target, i.e., the tumor. Consequently, it is expected that patients will suffer less from long-term

radiation toxicity, such as neurocognitive deficits, which is now being evaluated in prospective longitudinal feasibility Phase II studies with adequate long-term follow-up[21].

Systemic therapy

Historically, systemic therapies have shown no added benefit in outcomes such as tumor progression or tumor regression in meningioma. Currently, multiple trials are evaluating the efficacy of targeted molecular agents for patients with tumors harboring specific mutations (e.g., *SMO*, *AKT1* and *NF2*)[21]. While these therapies are especially needed in patients with WHO grade II and III tumors, these mutations are primarily observed in patients with low grade WHO I tumors[37]. In the latter group, systematic therapy might be of added value in poor surgical candidates due to tumor location, or patients with rapid regrowth of tumor remnants.

MEASURING OUTCOMES ALONG THE ROAD

History of outcome measurement in surgical specialties and neurosurgery

In the early 20th century, the high morbidity and mortality rates were an incentive for a small number of surgeons to start measuring their patients' outcomes. One of them, dr. Ernest Codman, is regarded as one of the pioneers of monitoring surgical outcomes. Fascinated by precise record-keeping, he followed-up his patients up to one year after surgery, measuring the degree of surgical resection, surgical complications, and physician-reported patient functioning, as he believed that this was essential to evaluate and improve surgical care[38]. His opinion was that patients should be provided with information on the surgical results of previous patients to make an informed decision about their own treatment. Inspired by his classmate, Harvey Cushing pioneered outcome measurement in neurosurgery[39]. Not only did he systemically measure the outcomes of patients he operated on, similar to dr. Codman, he also tried to associate his successes and failures to his surgical judgment, operative technique, and used surgical equipment, paving the way for clinical neurosurgical outcomes studies. Although these efforts were considered unconventional and unnecessary by his colleagues, he made his outcomes publicly available. His efforts were not fruitless, as brain surgery mortality declined from 50% to 13% during his career in the early 20th century[40].

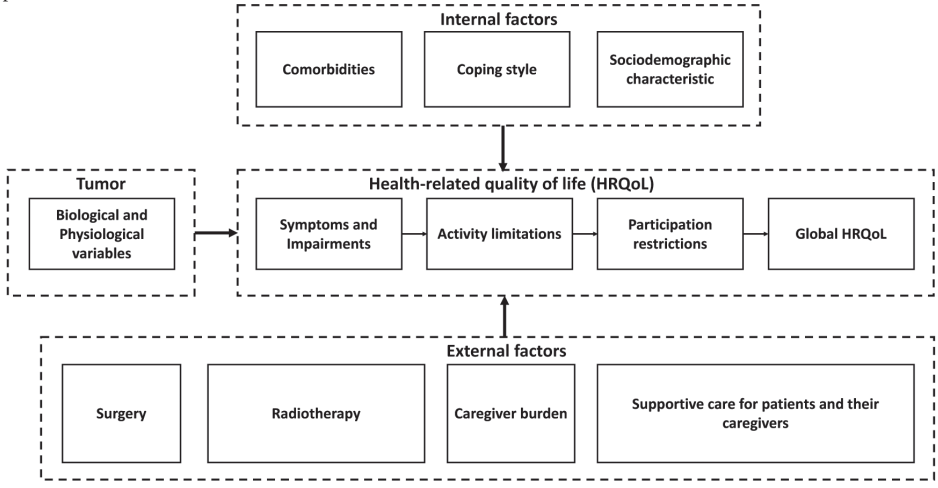
Despite Cushing's efforts, it is still not the standard to measure surgical outcomes and publish the results in the public domain. In recent years there have been great national and international efforts to measure outcomes in neurosurgery structurally[41,42]. In the Netherlands, the Dutch Society of Neurosurgery has implemented a Quality NeuroSurgery Registry (QRNS) to compare outcomes between centers, with the aim to define quality criteria for surgical care and to improve outcomes for patients throughout the Netherlands[43]. While the act of measuring

outcomes should already be applauded, it is equally important to measure outcomes in a standardized way to facilitate comparability between surgeons and centers, and to evaluate not only conventional outcomes such as done by dr. Codman and Cushing, but also patient-centered outcomes (e.g., patient-reported functioning). As this is not yet the standard in most current registries, one can question how informed our patients actually are if they consent for surgery.

World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF)

For this thesis, we aimed to design studies measuring outcomes that matter to the patient. Multiple frameworks exist to describe patient functioning. In this thesis we have adapted the World Health Organization International Classification of Functioning, Disability and Health (WHO-ICF) framework to describe health-related quality of life (HRQoL) of meningioma patients, which measures functioning at three distinct levels (Figure 1). The WHO ICF model not only conceptualizes 1) symptoms and impairments (e.g., visual field deficit), but also 2) activity limitations (e.g., unable to walk due to a visual field deficit) and 3) participation restrictions (e.g., unable to work). Although not described by the WHO ICF model, all three levels eventually impact patients' global health status. Both internal factors (patient-related) and external factors (treatment, caregiver, and environment) may impact patient functioning.

Figure 1. Framework for Health-related quality of life (HRQoL) in WHO grade I/II intracranial meningioma patients.



Clinical Outcome Assessment

Conventional outcomes to evaluate the effects of both the tumor and its treatment are clinician-reported outcomes such as the degree of tumor resection and neurological functioning. Equally important are patient-centered outcomes. The US Food and Drug Administration denominates

patient-centered outcomes as Clinical Outcome Assessments (COA), which can be measured as clinician-reported outcomes, observer-reported outcomes, performance measures, and patient-reported outcomes[44]. The combination of these outcomes provides a comprehensive view of patient functioning. Importantly, as physician-reported outcomes do not necessarily correlate with patient-reported outcomes, it is advocated to measure patient-reported outcomes (PROs) to capture the disease burden as experienced by patients[45–47].

Patient-reported outcome measures (PROM) and Health-related quality of life (HRQoL)

Patient-reported outcome measures (PROMs) are used to evaluate the patient's perspective on the impact of disease and treatment on their functioning and well-being. One commonly evaluated concept is HRQoL, which encompasses physical, emotional, psychological, and social domains, among other domains. Typically, PROMs focusing on HRQOL measure aspects on all three WHO ICF levels. Other PROMs may address one WHO ICF level. For example, the Hospital Anxiety and Depression Scale (HADS) is used as a symptom-specific PROM, i.e., measuring anxiety and depression only[48,49]. An example of a PROM focusing on participation restrictions, in particular work productivity, is the Short form – Health and Labour Questionnaire (SF-HLQ)[50]. Activity limitations and global health status are typically measured with PROMs that cover multiple WHO ICF levels (e.g., SF-36 and EORTC QLQ-BN20) [51–55].

PROMs can be used in both clinical practice and clinical research. In clinical care, the results obtained with PROMs create a dialogue between patients and physicians on patient-relevant topics, which results in improved communication, continuity of care, and eventually, patient well-being[46,56–60]. In clinical research, PROMs can be used as a primary or secondary outcome measure to evaluate treatment effects[61,62]. Distinction can be made between disease-specific (e.g., EORTC QLQ-BN20) and generic (e.g. SF-36) instruments. Disease-specific instruments are often developed and validated in a specific patient group, tailored to the experienced symptoms and dysfunction related to the disease and treatment. A disadvantage of these disease-specific PROMs is that one cannot easily compare the results with other patient groups or (healthy) controls. Generic instruments enable comparison with other groups, but often lack relevant items for specific patient groups. Hence, it may be warranted to use both generic and disease-specific PROMs. Importantly, there are currently no meningioma-specific PROMs[46].

In addition to PROMs filled out by patients, there are also self-reported instruments filled out by informal caregivers. In this thesis, the Caregiver Burden Scale (CBS) was used for caregivers to rate their experienced caregiver burden[63]. Such an instrument should not be confused with an observer-reported outcome, as the CBS is not used to rate patient functioning and well-being by their informal caregivers, but to assess the burden as experienced by caregivers themselves.

Performance outcomes

Performance outcomes are objectively measured outcomes, based on a standardized and repeatable task performed by a patient with instructions from a healthcare worker, such as neuropsychological tests, eye charts to evaluate the best-corrected visual acuity, and static perimetry to evaluate patient's visual fields. In the described studies in this thesis, neurocognitive functioning was measured objectively with a comprehensive test battery consisting of the following tests: the Concept Shifting Test, Auditory Verbal Learning Test, Categoric Word Fluency Test, Memory Comparison Test, Digit-Symbol Substitution Test, and the Stroop Colour-Word Test[64]. Based on these tests, scores for the following neurocognitive domains were calculated: verbal memory, executive functioning, psychomotor functioning, working memory, information processing speed, and attention[65]. The importance of using objective tests is emphasized by the poor correlation between objectively measured cognitive functioning and self-reported cognitive symptoms that has been observed in patients with brain tumors, underlining that different concepts are measured[66,67]. Moreover, patients with frontal lobe syndrome, severe cognitive deficits, or patients who suffer from these deficits for a longer period of time might not be aware of their deficits and hence report fewer deficits on self-report instruments. Conversely, patients with psychiatric symptoms such as anxiety and depression might overreport their cognitive symptoms[66]. Hence we chose to measure neurocognitive functioning with a standardized test battery, including frequently used neuropsychological tests that are considered relevant to brain tumor patients.

Clinician-reported outcomes

While in recent years we have seen an increase in the use of patient-reported and performance outcomes, clinician-reported outcomes still deserve an important role in clinical outcome assessment in meningioma. Clinician-reported outcomes are observations from trained healthcare professionals of a patient's health condition. These outcomes regard a clinical interpretation of observable signs, symptoms, and behaviors related to the disease or condition, such as the Karnofsky Performance Status (KPS), postoperative complications, and evaluation of patient's neurological functioning.

Observer-reported outcomes

Observer-reported outcomes reflect observations by someone other than a patient or healthcare provider, such as caregivers or parents who observe the patient in daily life. These outcomes are particularly useful in cases where the patient cannot report their level of functioning and well-being themselves, for instance a patient with severe cognitive impairments. An example is the evaluation of the patient's instrumental activities of daily living by the caregiver.

PARADIGM SHIFTS

Historically, the primary aim of surgery was to fully resect meningioma, which, especially for skull base meningioma, required extensive approaches associated with complications and severe comorbidity[68]. However, in the nineties, a strongly needed paradigm shift slowly occurred with renowned and respectful surgeons urging that a full tumor resection should not be the primary aim[31,69,70]. They questioned the added value of complete resection, which may result in devastating complications, leading to impaired patient functioning. Instead, they advised that patient well-being and functioning should direct surgery[31]. However, necessary information to guide such treatment decisions was, and is still largely missing, including outcome assessment with PROMs[71]. With the primary aim shifting from complete resection to optimal functional outcomes, less invasive surgical techniques were developed and adapted for skull base meningioma, such as adaptation of the endoscopic endonasal technique, which originally was used for pituitary tumors[9,72]. In the last century, improvement of meningioma surgery has resulted in a near-normal survival of patients[73]. Hence the long-term disease burden, including survivorship issues, has become more relevant for this patient group[74]. To fully understand the long-term disease burden, it is important not to forget about informal caregivers[70]. They are often the patient's partner or close friend or relative, who provides the majority of emotional and physical support. Previous work in brain tumor patients has shown that patient disease burden and caregiver burden are strongly interlinked[75,76]. Therefore, measurement of multiple outcomes is required to capture the complete picture of the long-term sequelae caused by meningioma and its treatment.

A shift in roads from tumor to patient

WHO grade I meningioma is historically perceived as a completely benign disease, curable by total resection of the tumor (i.e., Simpson Grade I resection)[7]. Furthermore, the degree of tumor resection (i.e., the Simpson grade) is by many surgeons perceived as an important predictor of tumor recurrence. A Simpson grade 0 resection, including resection of healthy surrounding dura, has even been advocated for convexity meningioma[77]. However, a complete tumor resection sometimes comes at the cost of devastating and permanent complications, with a negative value for the patient, which may even outweigh the positive value of complete resection[68]. Recently multiple groups, including our own group, have described that while surgical cure of WHO grade I tumors may sometimes be achieved, patients might still suffer from long-lasting neurological, psychological, and functional sequelae, even without regrowth of possible tumor remnants[78,79]. Hence, even in patients with a fully resected tumor, meningioma can be perceived as a chronic disease[71,79]. Based on these observations, we advocate for a paradigm shift from tumor to patient. The aim of surgery should not just be to resect as much tumor as possible, but surgery should aim to improve, or preserve, patient's functioning and well-being. This could also be achieved by repeated surgery or two-staged surgery. For patients,

the degree of tumor resection is perhaps less important if this means that their level of functioning and ability to participate in society is compromised. Thus, as clinicians it is our opinion that there is a trade-off between the amount of tumor resection and the patients' functioning and well-being, in which functioning should be rated higher than radical resection.

While we advocate for a paradigm shift from tumor to patient with respect to meningioma resection, the tumor itself could provide useful information in the subsequent care of patients. Information on molecular markers and methylation profiles of meningioma has shown to be more accurate predictors of tumor regrowth and recurrence than the Simpson grade[16,80]. In the future, information on these molecular tumor markers could aid in the initiation of postoperative interventions, such as radiotherapy and reoperation, in those patients that may benefit. Thus, integrating detailed tumor information in clinical practice can aid improving patient care and patient outcomes.

The road doesn't stop after intervention: a shift from short-term to survivorship issues.

As most meningioma patients have a near-normal life-expectancy, survivorship issues become relevant in the long-term for this patient group. Different definitions for cancer survivors are described in the literature, varying from patients who survived the initial tumor and treatment phase, to patients who survived the tumor for a certain period of time[81–84]. Importantly, most definitions for survivor also include informal caregivers, as the long-term consequences are not only experienced by patients, but also by their family, friends and relatives who provide the needed physical and emotional support[83]. In our survivorship study, we used an arbitrary cut-off of 5 years after diagnosis and/or treatment to capture the chronic care setting with possible permanent sequelae. Notably, some problems only become apparent in the long-term, such as radiotherapy induces neurocognitive deficits and regrowth of tumor remnants[46,65,74,82,85,86]. In contrast, some complications of tumor and treatment are transient or eventually resolve over the years and, therefore, might minimally impact long-term outcomes. Patients also tend to adapt to the situation and change their coping strategies over time[46,87]. Hence, outcomes evaluating tumor and treatment impact are not readily translatable to the long-term chronic care setting, warranting studies on the long-term effects and survivorship issues.

From describing the road to understanding and predicting the road

Routine evaluation of COAs in both research and clinical practice builds on an important body of knowledge, allowing to better inform patients on the outcomes of interventions. However, a better understanding of the determinants and predictors of COAs is needed to guide treatment decisions and facilitate allocation of scarce supportive care services to those most likely to benefit. This is especially the case for meningioma, which is a very heterogeneous disease, and consequently, outcomes might differ tremendously between patients. As these tumors originate

from the meninges, tumors can develop at different anatomical locations intracranially, causing distinct symptoms and impairments. Moreover, it is described that internal factors influence outcomes, such as comorbidities, coping styles, and sociodemographic characteristics. External variables might influence these outcomes too, such as surgery, radiotherapy, and caregiver support (Figure 1). Hence it is important to not only describe the meningioma disease burden, but also to better understand determinants for this disease burden on group level, and predictors of this disease burden on the individual patient level.

Determinants are variables that are causally associated with the outcome, independent of confounders that can affect the association between the determinant and outcome. Determinants should not be confused with predictors. Predictors are often used altogether with other predictors within prediction models to predict an individual patient's risk to develop a certain outcome at a specific time point in the future. Hence predictors are not determinants per se, but can also be a proxy of a determinant or just be associated with the outcome without assumptions of causality. For example, eating ice cream is associated with drowning. However, this is not a causal relationship, as people eat more ice cream and swim more often in open water in warm weather.

Recently, there has been much attention to improve the methods and reporting of prediction research. Faulty developed and validated models are not useful in clinical practice, and poorly reported methods hamper implementation in daily care. International efforts have resulted in the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement, including an explanation and elaboration document explaining best current practices.[88]

The road from above or below for anterior skull base meningioma

Conventionally, anterior skull base meningiomas are resected using a transcranial approach (e.g., pterional or subfrontal) through a craniotomy. To reach the tumor, an incision is made in the skin. Skin and, if needed, muscle is reflected from the location where the bone flap will be created. Using a drill, one or two burr holes are made. The craniotome is then used to create a bone flap, after which the dura is opened to reach the meningioma. Throughout the process, hemostasis is reached by coagulation and the use of bone wax.

In the last three decades, less invasive surgical techniques have been developed and adapted for skull base lesions. One of these techniques is the endoscopic endonasal approach for pituitary tumors, which has been adapted for anterior and middle cranial fossa meningioma[9,72]. Using an endoscope through the nose, surgeons drill away bone from the skull base to reach the tumor from below. In patients with a certain tumor configuration, this technique provides better visualization of, and direct access to, the tumor, while important neurovascular structures are less

imposed and manipulated[36]. Therefore, the endoscopic technique might provide better visual outcomes than the transcranial approach, especially in patients whose meningioma pushes the visual apparatus cranially[18]. A major disadvantage of these extended approaches is the chance of large dural defects with an increased risk of cerebrospinal fluid (CSF) leak[18]. Most centers use multilayer closure techniques with autologous and synthetic materials and lumbar drain in selected cases to prevent CSF leak[37,38]. Landmark developments were the pedicled Haddad-Bassagasteguy flap, its modification to a "rescue flap", and more recently, the gasket seal closure technique[39-41]. The endoscopic endonasal technique might become a more favored approach to resect certain anterior and middle skull base meningioma, if we can reduce the risk of CSF leak. Meta-analytic approaches are especially useful to evaluate the effectiveness and safety of this technique, as these extended approaches are still relatively new and used for uncommon pathologies, resulting in small single-center case series[42,43]. Meta-analyses enable pooling the published results of different centers providing a more accurate estimate of the effect of the treatment. Of note, these analyses summarize the average results of different centers. Individual patients are not re-analyzed together in conventional meta-analytic methods.

Beyond the patient: the caregiver road

There is increasing attention for the impact of the tumor and its treatment beyond the patient. Informal caregivers provide the needed support and actively assist in home medical treatment, coordination of care, and outpatient clinic appointments. Studies in caregivers of primary malignant brain tumor patients have shown high caregiver burden due to the often sudden, but chronic, neuropsychological, and physical symptoms of the patient.[89] Moreover, previous work in patients with primary brain tumors has shown that patient disease burden and caregiver burden is strongly interlinked[75,76]. Hence supportive care interventions, such as self-management programs and guidance by case-manager, might not only improve the patient disease burden, but also reduce the caregiver burden of informal caregivers[90]. Vice versa, interventions aimed at the caregiver burden might also improve the patient's disease burden. A holistic approach, including not only patients but also their caregivers, is therefore warranted.

Organizing the road: Value-Based Healthcare

In the last decade, meningioma care trajectories were not yet aligned with the patient's or partner's needs, especially regarding supportive care in the chronic care setting. Although an increasing number of studies provided evidence of long-lasting daily life problems in meningioma patients, they received little attention in the current care trajectories[57,91]. This was confirmed by data from a patient survey in meningioma patients conducted by the Dutch Comprehensive Cancer Organization (DCCO), which showed that patients experience various problems and unmet needs during their care trajectories, such as a lack of information on treatment and patient-centered outcomes. Thus, from different sources, we concluded that there is a strong

need to restructure meningioma care in a patient-centered fashion, starting with collecting outcomes in clinical practice that matter to the patient.

A framework for outcome measurement in clinical practice is Porter's and Teisberg's Value-Based Healthcare (VBHC) framework. Within this framework, patient value is defined as patient outcomes and experiences against the costs of care. Hence, value can be created by improving outcomes and/or reducing costs. Outcomes are measured in a three-tiered fashion: 1) health status achieved or retained, 2) process of recovery, 3) sustainability of health, including long-term outcomes and survivorship issues. Measuring outcomes using these three tiers helps to comprehensively collect patient-centered outcomes, and strengthen the patient voice in evaluating the care they receive. Ideally, this is done within multidisciplinary teams who work together to provide the best possible care for the patient. In the Leiden University Medical Center we have multidisciplinary VBHC teams that strengthen the collaboration between physicians and between departments, enabling high-quality care for specific meningioma groups. These teams involve neurosurgeons, neurologists, radiation oncologists, radiologists, endocrinologists, ENT-surgeons, facial reconstructive surgeons, plastic surgeons, ophthalmologists, pathologists, physiatrists, psychologists, case managers, nurse specialists, and others involved in the care of the patient.

OUTLINE OF THIS THESIS

The general aim of this thesis was to establish a paradigm shift from tumor to patient. To this end part 1 aimed to evaluate the disease burden and quality of care of meningioma patients and their caregivers through a systematic review, a multicenter cross-sectional study, focus groups, and semi-structured interviews. The aim of part 2 was to better understand and predict outcomes of meningioma patients, including their disease burden. Special attention is provided to anterior skull base meningioma, and more specifically spheno-orbital meningioma.

Part 1: The patient road: disease burden and quality of care of meningioma patients and their caregivers

As stated earlier, we observed in clinical practice that patients might suffer from sequelae of tumor and treatment, resulting in impairments in their level of functioning even in the long-term. To provide evidence for this observation, we started with a systematic review on HRQoL in meningioma patients **(Chapter 2)**. In this review we evaluated published results on the impact of the tumor and its treatment on HRQoL in meningioma patients. Moreover, we assessed the quality of reporting of the PROs in these studies following the International Society of Quality of Life Research (ISOQOL) criteria for PROs. Finally, we assessed the methodological quality of the used PROMs using the criteria of the Consensus-based Standards for the

selection of health Measurement Instruments (COSMIN). To evaluate the long-term disease burden and survivorship issues of meningioma patients, and its association with the received treatment, we conducted a large cross-sectional study in both meningioma patients and their informal caregivers at least 5 years after the last received treatment. In **Chapter 3,** we report on the long-term HRQoL outcomes, neurocognitive functioning, anxiety and depression, as well as patients' work productivity. Moreover, we report on the impact of different treatment strategies on these outcomes. Next, in **Chapter 4**, we evaluated the long-term caregiver burden of meningioma informal caregivers, the impact of the caregiver burden on caregiver well-being, and both patient and caregiver determinants for this burden. As part of work done to improve the meningioma care trajectory according to the principles of VBHC, we describe in **Chapter 5** current issues in meningioma care trajectories and possible solutions for these issues based on a mixed-method study using data from the Dutch Comprehensive Cancer Organization and focus groups with patients, their caregivers, and healthcare providers. Moreover, in **Chapter 6** we evaluated currently used PROMs in meningioma research, focusing on their relevance and comprehensiveness by means of semi-structured interviews with patients and healthcare professionals.

Part 2: Understanding and predicting outcomes of meningioma patients

In the medical field, there has been a great increase in prediction research. However, multiple reviews concluded that the methods and results of these studies are often poorly reported. In reaction to these reviews and to improve the reporting of the methods and results of such studies, the TRIPOD statement was published. In **Chapter 7**, we compared prediction articles published before and after the TRIPOD statement in high-impact general medicine journals on their quality of reporting and used methods, regardless of the topic and patient population of the presented prediction model. In **Chapter 8**, we identified determinants and developed prediction models for the long-term disease burden of meningioma patients to better understand the impact of patient, tumor, and treatment characteristics on long-term HRQoL outcomes and neurocognitive functioning, and to estimate the risk for an individual patient to suffer from long-term impairments in these outcomes. **In Chapter 9**, we specifically evaluated visual outcomes in spheno-orbital meningioma, a challenging tumor for surgical resection. For this patient group, we also evaluated the association between patient and tumor characteristics and postoperative visual outcomes to formulate recommendations for this challenging surgery. Finally, **in Chapter 10**, we performed a meta-analysis on the outcomes of the extended endoscopic endonasal approach for anterior skull base meningioma over the last 20 years, reporting on outcomes such as CSF leak, resection grade, visual outcomes, and complications. This approach is relatively new and is reported to be associated with a higher chance of CSF leak than the conventional transcranial approach. We evaluated outcomes over the years, as we

believed that recent improvement in surgical reconstruction techniques might have lowered this complication.

This thesis' results are summarized and placed into the context of published literature in the summary **(Chapter 11)**, where we also provide directions for future research, and guidance for changes in clinical practice that are based on the results obtained in this thesis.

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Part 1

The patient road: disease burden and quality of care of meningioma patients and their caregivers

Chapter 2

Impaired health-related quality of life in meningioma patients – a systematic review

Neuro-Oncology, 2017;19(7):897–907.

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ABSTRACT

While surgical and radiotherapeutic improvements increased life expectancy of meningioma patients, little is known about these patients health-related quality of life (HRQoL). Therefore, the objectives of this systematic review were to assess HRQoL in meningioma patients, the methodological quality of the used questionnaires (COSMIN criteria) and the reporting-level of patient-reported outcomes (PRO) in the included studies (ISOQOL criteria). Nineteen articles met our inclusion criteria. HRQoL was measured with 13 different questionnaires, three validated in meningioma patients. According to our predefined cut-off, HRQoL data was reported sufficiently in 5/19 studies. Both findings hamper interpretation of the PRO results. In general, meningioma patients reported clinically worse HRQoL than healthy controls. Although meningioma patients had better HRQoL than glioma patients, this difference was not clinically relevant. Radiotherapy seemed to improve some domains of HRQoL on the short-term, while HRQoL decreased to pre-radiotherapy levels on the long-term. Tumor resection increased HRQoL, but long-term follow-up showed persistent reduced HRQoL compared to healthy controls. These results suggest an impaired HRQoL in meningioma patients, even years after anti-tumor treatment. Results of this systematic review warrant high quality prospective studies, better instruments to assess HRQoL and improved level of reporting for this group of patients.

Key words: Meningioma; Health-related Quality of Life; Patient-reported outcome; Questionnaires; Reporting level

INTRODUCTION

Meningiomas are the most prevalent tumors of the central nervous system (36.4%), originating from the arachnoid cap cells[1], with an incidence rate of 7.86 per 100,000 population[2]. About 90% of meningiomas are benign (WHO grade I)[3]. Depending on the location of the mass, patients may suffer from a wide variety of somatic and psychological symptoms, such as epileptic seizures, visual loss, cognitive symptoms, psychiatric symptoms and neuropathies.[3] In addition, the majority of patients suffer from more general symptoms, such as tiredness, sleep problems and psychosocial problems. Both the disease-specific and more general symptoms may cause limitations of daily activities and consequently participation restrictions, which is reflected in a deterioration of patients' health-related quality of life (HRQoL).

During the last two decades, new radiation and surgical techniques have improved the treatment of meningioma patients (MP). In modern case series, meningioma patients have a near normal 5 and 10 years life expectancy (5 year survival 92%, expected survival 94%; 10 year survival 81%, expected survival 86%), but often suffer from moderate to severe neurological deficits, even 5 years after surgery (67%)[4]. Parallel to these improvements in therapy and life expectancy, a shift is occurring in treatment objectives; from survival and radical tumor removal to patient performance and HRQoL.[5] Indeed, one should now start to measure the net clinical benefit of meningioma therapy.[6]

HRQoL is a multidimensional concept covering generally valued aspects of life (defined as health or health-related), such as in the physical, social and psychological domains, as well as disease-specific signs and symptoms caused by the disease and its treatment.[7] HRQoL should be patient-reported since doctor-reported and patient-reported HRQoL results differ significantly and patients are thought to be the best source of information on their own HRQoL.[8] HRQoL can be measured using generic (e.g. SF-36, EQ-5D, FACT-G, EORTC QLQ-C30, MDASI)[9–14] or disease-specific questionnaires (e.g. FACT-BR, EORTC QLQ-BN20, MDASI-BT).[14–16] However, neither in clinical practice, nor in research this is done frequently in meningioma patients.

The main objective of this systematic review was to assess HRQoL in meningioma patients. In addition, we assessed the methodological quality of the used HRQoL questionnaires as well as the level of reporting of the patient-reported outcomes (PROs) in the included studies.

MATERIALS AND METHODS

Search Strategy and paper selection

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[17].

Search Strategy

A literature search was conducted in the following electronical databases: Embase, MEDLINE, Web of Science, CINAHL, PsychInfo, Academic Search Premier, COCHRANE and ScienceDirect up to October 2015. Search terms used were "meningioma", "quality of life" and terms formulated to exclude case reports and studies with animals only (see supplementary Table 1 for the search strategy in MEDLINE). The search strategy was adapted for the other electronical databases. Reference lists of included articles were scanned for additional studies.

Paper selection

Inclusion criteria were the following: original peer-reviewed articles measuring patient-reported HRQoL in meningioma patients (whole population or reported separately as a subpopulation) using a questionnaire. Both observational and interventional studies, either retrospective or prospective, were included. Exclusion criteria were as follows: articles not in English, case reports (up to five patients), reviews, studies with only animals and studies including a main population of patients younger than 18 years old. Two independent reviewers (AHZN and MCMP) screened all titles and abstracts for eligibility. Disagreement was resolved with discussion and consensus and when discussion failed to lead to consensus, a third researcher mediated (LD).

Data extraction

Information was extracted per included article by two independent researchers (AHZN and MCMP) on study design, main inclusion criteria and subject characteristics: mean age at time of intervention, percentage women, percentage WHO grade I, II or III tumors, location of tumor and functional status. In addition, when applicable, type of intervention and Simpson Grade were noted. Regarding study outcomes, the timing of HRQoL assessments, the used questionnaire and the HRQoL outcomes (mean and when reported the standard deviation) itself were extracted. Data are presented for all studies separately. No meta-analysis was performed due to the small number of studies and heterogeneity of the studies in population (different tumor grades, tumor location), intervention (surgery, radiotherapy, wait-and-scan) and outcomes (different HRQoL questionnaires used). Assessment of reporting level of included articles and quality assessment of used questionnaires

Assessment of reporting level of PROs in the included articles

The level of reporting of the PRO data in the included articles was assessed by two researchers independently (AHZN and MCMP) following the criteria for patient-reported outcomes of the International Society of Quality Of Life Research (ISOQOL)[18]. The criteria were adapted for non-randomised studies and are presented in Supplementary Table 2. A maximum of 16 points could be scored and the predefined cut-off for sufficient reporting was 11/16 points, which is in line with previous work.[19]

Quality assessment of used questionnaires

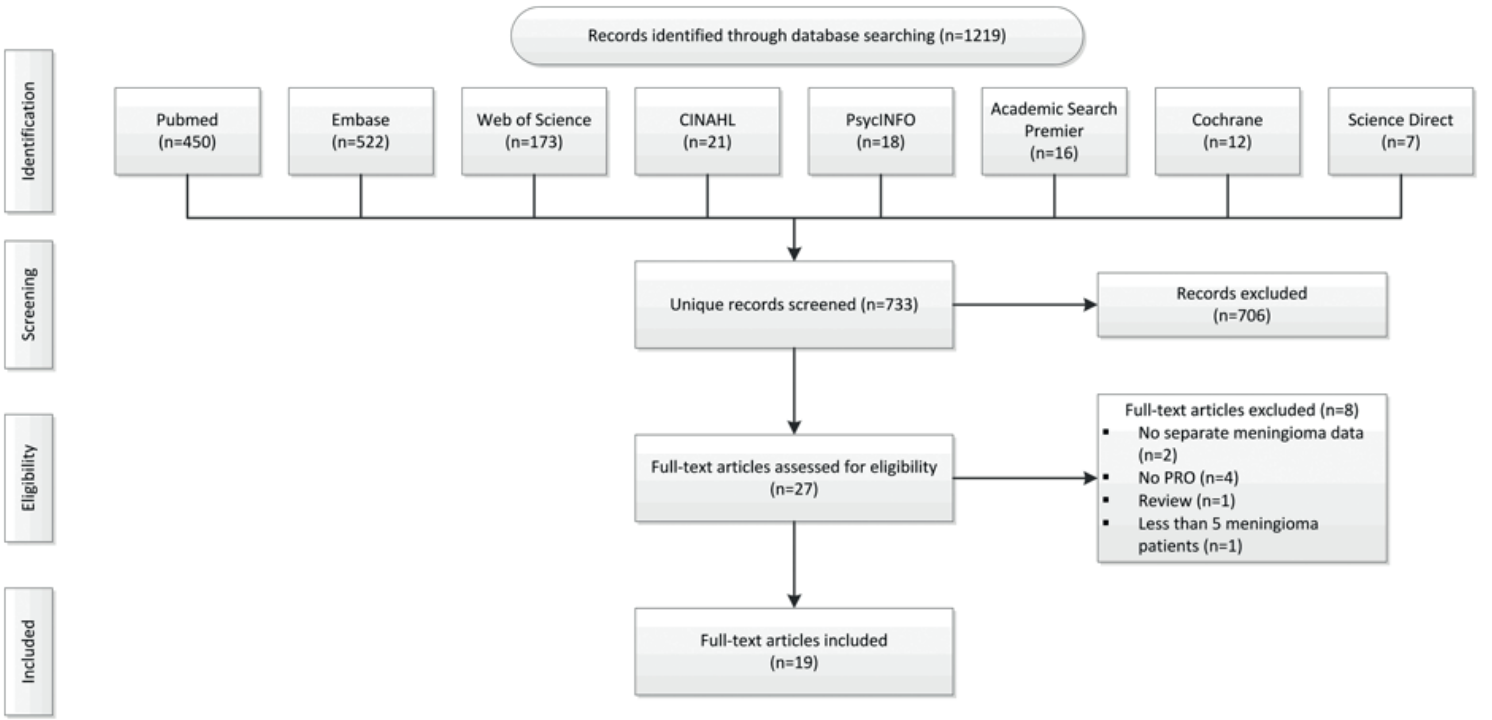
Quality of the used questionnaires was assessed by two researchers independently (MCMP and LD) using the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) criteria[20]. In short, the following aspects were evaluated for meningioma patients or patients with other acquired brain injuries: content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects and interpretability.

RESULTS

Study characteristics

Titles and abstracts of 733 unique articles were screened, resulting in 27 eligible articles. These articles were read full-text and 19 met our inclusion criteria[21–40]. Flow diagram of record analysis and article inclusion is depicted in Figure 1. Study characteristics are presented in Table 1. Of the 19 included articles, four studies used a longitudinal[21,22,29,38] and 15 a cross-sectional study design[23–28,30–34,36,37,39,40]. Six studies included only patients with WHO grade I meningioma[23,30–32,36,38], four studies also included patients with WHO grade II or III meningioma[21,22,25,29] and nine studies did not report the WHO grade[24,26–28,33,34,37,39,40]. Study population size ranged between 16 and 155 meningioma patients (median 47 patients). Seven studies compared the results of meningioma patients with normative data of healthy controls (HC)[21,23,29–32,34], one study compared results of meningioma patients with normative data of healthy controls and (brain) cancer patients[25], one study compared meningioma patients with glioma patients[33] and eight studies presented only results for meningioma patients[22,24,26–28,36–40]. Surgery was the primary intervention in 13 studies[21–28,33,34,36–40], of which two compared HRQoL results before and after surgery[21,22]. Radiotherapy was the primary intervention in three studies[29–31], of which one compared HRQoL results before and after radiotherapy.[29] A wait-and-scan approach was the primary treatment modality in one study.[32]

Fig. 1 Flow diagram of record analysis and article inclusion.



Data extraction

Data of the included studies is depicted in Supplementary Table 4, significant and/or clinically relevant results as described in the original articles are presented here.

Meningioma vs. normative data healthy controls

In general, meningioma patients reported worse HRQoL compared to healthy controls before surgery. Overall health status was lower (study specific questionnaire (SSQ): MP 74±2, HC 91±2, $p<.0001$; SF-36: MP 53±25, HC 66±21, $p=.030$)[21,32] and also the following subdomains: physical health (SSQ: MP 27±1, HC 37±3, $p<.0001$)[21], patient satisfaction with medical care (SSQ: MP 5±2, HC 7±2, $p<.001$)[21], self-care (SSQ: MP 14±2, HC 20±1, $p<.0001$)[21] and vitality (SF-36: MP 56±19, HC 66±23, $p=.043$)[32]. Postoperatively, studies reported both worse and better HRQoL scores in meningioma patients compared to healthy controls. About 3.4 years after surgery meningioma patients had more role limitations caused by physical problems (SF-36: MP 50, HC 65, $p<.05$)[23], while they had less role limitations 6 months after surgery (SF-36: MP 77, $p=.01$)[25]. Compared to healthy controls, meningioma patients still scored worse 6 months after tumor removal on cognitive functioning (EORTC QLQ-C30: MP 79, $p=.02$), yet better on physical functioning (EORTC QLQ-C30: MP 80, $p=.01$) and social functioning (EORTC QLQ-C30: MP 84, $p<.01$).[25] Data for healthy controls was not described in this article by Konglund et al.[25]

Meningioma vs. glioma patients and normative data of cancer and brain cancer patients

HRQoL of meningioma patients and glioma or (brain) cancer patients was compared using the EORTC QLQ-C30 and QLQ-BN20 questionnaires. Compared to glioma patients (GP), meningioma patients scored better on cognitive functioning (MP 73±25, GP 64±28, $p=.008$), social functioning (MP 81±26, GP 64±34, $p<.001$), physical functioning (MP 75±20, GP 66±29, $p=.02$), future uncertainty (MP 28±21, GP 39±24, $p=.003$), motor dysfunction (MP 24±23, GP 34±33, $p=.02$) and communication deficits (MP 16±23, GP 30±31, $p<.001$).[33] Compared to brain cancer patients (all grades), meningioma patients scored also better on cognitive functioning (MP 79, $p=.02$) and emotional functioning (MP 82, $p=.04$), but meningioma patients had more insomnia (MP 28, $p=.01$).[25] Compared to the general cancer population, meningioma patients scored better on the following domains of the EORTC QLQ-C30 and QLQ-BN20: physical functioning (MP 80, $p=.01$), role functioning (MP 77, $p=.02$), emotional functioning (MP 82, $p=.04$) and social functioning (MP 84, $p=.03$) but worse on cognitive functioning (MP 79, $p=.02$). Data for healthy controls was not described in this article by Konglund et al.[25]

Table 1 – Study characteristics of included studies

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Miao (2010)[21]	Prospective	Meningioma patients histologically confirmed and operated	Meningioma patients: 147 Controls: 96, age-matched	Meningioma patients median age: 43 (5-77) Controls Median age: 42 (range N/A)	Meningioma patients: 59% Controls: 67%	I: 80% II: 7% III: 6%	Parasagittal: 3% Falcine: 16% Convexity: 39% Olfactory groove: 9% Sphenoid ridge: 13% Clivus: 5% Intraventricular: 6% Cerebellum: 4% Other: 4%	0: 8% I: 18% II: 20% III: 27% IV: 27% V: -	N/A	Surgery	Before and after surgery, not further specified
Jakola (2012)[22]	Prospective	Meningioma patients, histologically confirmed, aged ≥ 18 years	Meningioma patients: 46	Meningioma patients mean age: 55±13	Meningioma Patients: 67%	I: 83% II: 17%	Convexity: 24% Parasagittal or falcine: 33% Supratentorial skull base: 35% Infratentorial: 8%	I-II: 66% III: 17% IV-V: 17%	KPS: 85±11	Surgery	Before surgery: 1-3 days Short term after surgery: 6 weeks Long term after surgery: 10-58 months

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Waagemans (2010)[23]	Cross-sectional	Meningioma patients: histologically confirmed WHO grade I, without signs of tumor recurrence for at least 1 year after last intervention	Meningioma patients: 89 Controls: 89, age-, sex-, educational level-matched	Meningioma patients mean age: 58±13 Controls mean age: 58±13	Meningioma patients: 74% Controls: 74%	I: 100%	Convexity: 51% Skull base: 45% Tentorium/falx: 20% Orbital: 7% Olfactory tract: 3%	I: 23% II: 34% III: 13% IV: 24% V: 3% Unknown: 3%	N/A	Surgery	After surgery: at least 1 year after last intervention (mean 3.4 years)
Mathiesen (2007)[34]	Cross-sectional	Meningioma patients: petroclival tumors, larger than 30mm.	Meningioma patients: 16	Meningioma patients mean age: 54 (SD N/A)	Patients: 69%	MIB+ <2%: 94% 6%>: 6%	Petroclival tumors	I: 4% II: 38% III: 7% IV:52% V: -	N/A	Surgery	Postoperative, at least 1 year after surgery (mean 66 months)
Neil-Dwyer (2000)[24] Neil-Dwyer (2001)*[40] Lang (1999)*[39] (same study population and results)	Cross-sectional	Meningioma patients: petroclival tumors arising medial to the 5th cranial nerve	Meningioma patients: 19 (*17)	Meningioma patients age range: 29-63	Meningioma patients: 79%	N/A	Petroclival tumors	N/A	N/A	Surgery	Postoperative, at least 1 year after surgery

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Konglund (2012)[25]	Cross-sectional	Meningioma patients, ≥60 years, elective surgery	Meningioma patients: 47	Meningioma patients median age: 70 (60-84)	Meningioma patients: 65%	I: 94% II: 4% Missing: 2%	Convexity: 44% Skull base: 33% Parasagittal: 11% Tentorial: 9% Intraventricular: 2%	I: 35% II: 39% III: 13% IV: 13%	KPS <50: 2% 50-70: 9% >70: 89%	Surgery	Postoperative, 6 months after surgery
Shin (2013)[33]	Cross-sectional	Patients ≥18 years, histologically diagnosed brain tumor: meningioma, glioma and other tumors	Meningioma patients: 107	All patients: mean age 48 (18-81)	All patients: 57%	N/A	N/A	N/A	All patients: KPS ≤70: 11% >70: 89%	Surgery	Postoperative, not further specified
Mohsenipour (2001)[26]	Cross-sectional	Meningioma patients, neurosurgical treatment	Meningioma patients: 82	Meningioma patients: mean age 61±15	Meningioma patients: 65%	N/A	Convexity: 72% Petrosal: 12% Cerebropontine: 4% Multiple: 4% Spinal: 9%	N/A	N/A	Surgery	Postoperative, not further specified
Kalkanis (2000)[27]	Cross-sectional	Meningioma patients, undergone craniotomy	Meningioma patients: 155	Meningioma patients: mean age 59±14	Meningioma patients: 66%	N/A	N/A	N/A	N/A	Surgery	Postoperative, mean time after surgery 33 months (0-165)

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Salo (2002)[28]	Cross-sectional	Brain tumor patients, ≥16 years, diagnosed by imaging	Meningioma patients: 31	All patients: 49 (20-82)	Meningioma patients: 61%	N/A	Intracranial Left: 46% Right: 35% Bilateral: 14% Undefined: 4%	N/A	N/A	Surgery	Preoperative
Henzel (2013)[29]	Prospective	Meningioma patients, ≥18 years, ECOG performance status ≥2, KPS≥70%, life expectancy>2 years.	Meningioma patients: 52	Meningioma patients median age: 57 (40-81)	Meningioma patients: 75%	Known of previous operated 42/52 I: 79% II: 17% III: 5%	Medial wing sphenoid: 56% Petroclival: 15% Tentorial: 6% Petroclival up to sphenoid bone: 12% Falx cerebi: 8% Optic nerve sheath: 2% Olfactory: 2%	N/A	N/A	SRT (42/52 previous surgery)	Before SRT, last day of SRT, thereafter biannually
Kangas (2012)[30]	Cross-sectional	Meningioma patients, WHO grade I, treated with radiotherapy	Meningioma patients: 70	Meningioma patients: 57±12	Meningioma patients: 77%	I: 100%	N/A	N/A	N/A	Radiotherapy	After RT, mean 1.7 years

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Van Nieuwenhuizen (2007)[31]	Cross-sectional	Meningioma patients, WHO grade I	Meningioma patients only surgery: 18 Meningioma patients: surgery and radiotherapy: 18 Healthy controls: 18, age- and sex-matched	Meningioma patients surgery only: 63±12 Meningioma patients surgery and radiotherapy: 63±11	Meningioma patients surgery only: 84% Meningioma patients surgery and radiotherapy: 89%	I: 100%	N/A	N/A	KPS Surgery only: 83±20 Surgery and radiotherapy: 71±18 Barthel Surgery: 17±1 Surgery and radiotherapy: 17±2	Surgery with or without RT	Postoperative, at least 1 year after surgery Surgery only: mean 3.3±2.0 years after surgery Surgery and RT: mean 3.3±1.9 years after surgery
Van Nieuwenhuizen (2013)[32]	Cross-sectional	Meningioma patients: radiologically suspected WHO grade I, who have not received surgery or radiotherapy	Meningioma patients: 21 Controls: 21	Meningioma patients: 63±14 Controls: 62±14	Meningioma patients: 81% Controls: 76%	I: 100%	Convexity: 38% Tentorium/Falx: 24% Skull base: 38%:	N/A	KPS 80 (40-100)	No intervention	Pre-operative
Bunevicius (2014)[37]	Cross-sectional	Adult patients admitted for brain tumor surgery	Meningioma patients: 77	All patients: 56±15	All patients: 69%	N/A	N/A	N/A	N/A	Before surgery	Pre-operative

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Krupp (2009)[36]	Cross-sectional	Meningioma patients, supratentorial, WHO grade I, surgically treated	Meningioma patients: 91	Meningioma patients: 56±10	Meningioma patients: 66%	I: 100%	Convexity: 46% Sphenoid ridge: 21% Parasagittal, falx: 20% Frontal cranial base: 13%	N/A	N/A	Surgery	Postoperative (mean 15 months, range 10-19 months)
Curey (2012)[38]	Prospective	Tuberculum sellae meningioma, surgically treated with the superior interhemispheric approach	Meningioma patients: 20	Meningioma patients: 59±11	Meningioma patients: 85%	I: 100%	Tuberculum sellae meningioma	I or II: 95%	N/A	Surgery	Pre-operative and postoperative at 6 months

Percentages do not add up to 100% due to rounding
KPS: Karnofsky Performance Score
N/A: not assessed or not reported
(S)RT: (stereotactic) radiotherapy

HRQoL in meningioma patients before and after intervention

Long-term (10-58 months postoperative) general HRQoL improved significantly after surgery (EQ-5D: mean improvement 0.09, p=.040; SSQ: preoperative 74±2, postoperative 85±2, p<.0001)[22] and also on the following domains: physical health (SSQ: preoperative 27±1, postoperative 36±2, p<.0001)[21], patient satisfaction with medical care (SSQ: preoperative 5±2, postoperative 7±1, p=.01)[21], self-care (SSQ: preoperative 14±2, postoperative 16±3, p=.04)[21] and olfactory function (impact of surgery on VAS score for olfactory function +5.7±2.2).[38] Patients who had undergone surgery before radiotherapy (OP+RT) had significantly better mental health (SF-36) compared to patients who only received radiotherapy (RT), both before radiotherapy (OP+RT 43, RT 32, p=.04), at the end of radiotherapy (OP+RT 42, RT 29, p=.014) and at 6/12/18/24 months follow up (6 months: OP+RT 45, RT 36; 12 months: OP+RT 43, RT 33; 18 months: OP+RT 44, RT 31; 24 months: OP+RT 42, RT 34, all p=.004)[29]. Moreover, the addition of RT to surgery resulted in worse scores on the following domains: physical functioning (OP+RT 55±55, RT 73±33, p=.05), role limitations caused by physical functioning (OP+RT 34±39, RT 61±43, p=.03) and on the physical component score (OP+RT 33±11, RT 52±12, p=.007).[31] However, these differences could be explained by the longer disease length for patients treated with OP+RT compared to those treated with OP only (7.6 versus 3.0 years after diagnoses, respectively).[31]

Factors negatively influencing HRQoL in meningioma patients

A larger tumor size (p=.037), higher histological grade (p=.011) and tumor recurrence (p=.018) were all associated with lower overall HRQoL.[21] In addition, larger tumor size was associated with more physical mobility impairment.[21,26] The presence of a meningioma was associated with emotional well-being in a univariable analysis (r=-0.14, p=.048); however this association was not confirmed in the multivariable analysis.[37] Waagemans et al. found that meningioma patients who used anti-epileptic drugs had lower scores on physical health (p<.01), social functioning (p<.05), mental health (p<.05), vitality (p<.01) and overall health status (p<.05) when compared to healthy controls.[23] They also found significant associations between impaired HRQoL and problems in neurocognitive functioning (executive functioning, information processing, verbal memory, psychomotor speed).[23] Furthermore, shorter time since diagnosis (p=.013), more posttraumatic stress (p=.005), confusion (p=.000) and tumor location in the left hemisphere (p=.009) were negatively associated with HRQoL in meningioma patients.[30]

Factors positively influencing HRQoL in meningioma patients

A longer follow-up was associated with better HRQoL outcomes (SF-36); meningioma patients scoring on more than 4 subscales below the 25th percentile of normative data of healthy controls had a mean follow-up period of 2.9 years, whereas patients scoring less than 4 subscales below the 25th percentile had a mean follow-up period of 5.4 years (p<.05).[34] Furthermore, less emotional impairment was associated with longer follow-up time after surgery (IHD-NS).[26]

Table 2 – Assessment of PRO-reporting level of included studies

			Methods (6pnt)		Results (3pnt)			Discussion (4pnt)				
Author (year)	**Title and abstract (1pnt)**	**Introduction Background and Objectives (1pnt)**	**Outcomes (4pnt)**	**Statistical methods (2pnt)**	**Participant flow / missing data (1pnt)**	**Baseline data (1pnt)**	**Outcomes and estimation (1pnt)**	**Limitations (1pnt)**	**Generalizability (1pnt)**	**Interpretation (2pnt)**	**Protocol / copy of instrument (1pnt)**	**Total points (Max 16 points)**
Miao (2010)[21]	1	1	2	1	1	0	0	0	1	0	1	8
Jakola (2012)*[22]	1	0	3	2	1	1	1	1	1	2	1	14
Waagemans (2010)*[23]	1	1	3	1	1	1	1	1	1	1	1	13
Mathiesen (2007)[34]	1	0	1	0	1	0	0	0	1	1	1	6
Neil-Dwyer (2000)[24]	1	0	2	0	0	0	1	0	1	0	1	6
Neil-Dwyer (2001)[40]	1	0	1	0	0	0	1	1	0	1	1	6
Lang (1999)[39]	1	0	3	0	0	0	1	1	0	1	1	8
Konglund (2012)[25]	1	0	1	1	0	0	1	0	1	1	1	7
Shin (2013)[33]	1	1	2	1	0	0	1	1	0	1	1	9
Mohsenipour (2001)[26]	1	0	2	1	0	0	1	0	1	0	1	7
Kalkanis (2000)[27]	1	0	3	1	1	0	1	0	0	0	1	8
Salo (2002)[28]	1	1	0	1	0	0	1	0	0	1	1	6
Henzel (2013)[29]	1	0	1	1	1	1	1	0	0	1	1	8
Kangas (2012)*[30]	1	1	3	1	0	1	1	0	1	1	1	11
Van Nieuwenhuizen[31] (2007)*	1	1	3	1	1	1	1	0	1	1	1	12
Van Nieuwenhuizen (2013)*[32]	1	0	3	1	1	1	1	0	1	1	1	11
Bunevicius (2014)[37]	1	0	2	1	1	0	0	0	1	1	1	8
Krupp (2009)[36]	1	0	3	1	1	1	1	0	0	1	1	10
Curey (2012)[33]	1	0	2	0	0	1	1	0	0	1	1	7
Percentage of studies scoring maximum score per criterium	100%	32%	0%	5%	53%	42%	84%	26%	58%	5%	100%	Mean 8 points

* Articles with sufficient reporting level (predefined cut-off ≥ 11 points)

Assessment of reporting level of PRO data in the included articles

Reporting level of PRO data in the included studies is depicted in Table 2. Median reporting level score was 8 points (range: 6-14 points) and in five articles PRO data could be classified as sufficiently reported (≥11 points).[22,23,30–32] All articles described the PRO in the title or abstract and included or cited the used questionnaire. However, most articles did not report the PRO methods (none), used statistical methods (for missing data, 5%)[22] or how the results should

be interpreted (e.g. presenting the number of patients with a minimal important change or describing the cut-off for normal scores for the used scale, 5%).[22] On all other criteria, 26% to 84% of the articles scored the highest possible score.

Quality assessment of used questionnaires

Of the 13 used questionnaires three questionnaires were validated in meningioma patients, the FACT-G/FACT-BR[14] and a study-specific QOL questionnaire (SSQ)[41]. In addition, five questionnaires were (partially) validated for other types of acquired brain injury or brain cancer: EQ-5D[42,43], SF-36[44], EORTC QLQ-C30 and QLQ-BN20[15,45] and the IHD(NS)[46]. Validity and reliability varied among all questionnaires and none of the questionnaires met all requirements as specified in the COSMIN criteria. Data are presented in Supplementary Table 3.

DISCUSSION

Although HRQoL is an important outcome for meningioma patients, this systematic literature review showed that only a few studies are published describing HRQoL in this patient group. Of those published, unfortunately, the level of PRO reporting of most articles was of low quality; only three HRQoL questionnaires have been validated in meningioma patients and only one study has reported minimal important changes of the PRO results, all hampering interpretation of HRQoL results. Nevertheless, based on the available results we can conclude that in general meningioma patients had a clinically relevant worse HRQoL than healthy controls. Tumor resection improved HRQoL, but long-term follow-up still showed reduced HRQoL compared to healthy controls. In addition, meningioma patients seemed to have a better HRQoL than (brain) cancer patients after surgery, although, this difference was not clinically relevant. These results suggest an impaired HRQoL in some meningioma patients even years after tumor resection.

In general, meningioma patients reported worse HRQoL than healthy controls both before and after surgery. However, because of the few available studies, the use of different questionnaires and low PRO reporting level, PRO results could not be pooled and results could not be compared for patients with different tumor location (e.g. convexity vs. skull base). When comparing results of the EORTC QLQ-C30 of postoperative meningioma patients[25,33] with normative data of healthy controls[47], meningioma patients had a clinically relevant lower score on the following domains: physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning and insomnia. In different studies meningioma patients scored both better and worse on overall health status and fatigue. Likewise, when comparing preoperative results of the SF-36 for meningioma patients with matched controls (age, sex and education) in a small study, meningioma patients had clinically significant more

role limitations caused by physical and emotional problems, worse general health and less vitality.[32] However, these clinically relevant differences between meningioma patients and healthy controls disappeared after surgery[23,31], except for the role limitations caused by physical problems[23]. These seemingly confounding findings may be the result of psychological mechanisms of coping with surgery and illness, which may lead to a positive mental change, also called posttraumatic growth, a known phenomenon generally found in long-term follow-up of patients with different types of cancer or acquired brain injury[48–50]. In addition, a mental change often causes a "response shift", i.e. a change in patient's internal standards, values and consequently perception of HRQoL.[47]

Results of the included studies further showed that, compared to glioma patients, meningioma patients generally had a statistically significant better HRQoL. One study however, showed that meningioma patients had more insomnia than glioma patients.[33] When comparing scores of newly diagnosed glioblastoma patients with scores of meningioma patients on the EORTC QLQ-C30 and QLQ-BN20 questionnaires[25,33], these scores were surprisingly similar between both patient groups.[52] Although differences in 11 HRQoL domains were statistically significant, these results were not clinically relevant. Moreover, meningioma patients experienced more pain and visual problems than other brain cancer patients.[52] Compared with a meta-analysis on SF-36 data in rheumatoid arthritis patients, the study of Waagemans et al. showed that meningioma patients scored similar on the mental and physical component score five years after tumor removal.[53] This implies that five years after tumor removal HRQoL scores of meningioma patients are similar to that of a chronic disease and substantially lower than HRQoL scores of healthy controls.[53]

Results on the impact of different therapies on both the survival and HRQoL/cognition may be used to determine the net clinical benefit of specific therapies.[6] This information is important for clinical decision-making and patient-tailored therapy. Although two studies showed a statistically significant improvement in HRQoL after surgery, this improvement was not clinically relevant in one study and not interpretable in the other study as characteristics of the used questionnaire were not presented.[21,22] Patients who underwent radiotherapy perceived a clinically relevant reduction in role limitations caused by physical problems immediately after radiotherapy and a clinically relevant reduction in role limitations caused by emotional problems 6 months after radiotherapy. However, both of these differences disappeared after 2 years of follow-up[29], suggesting that HRQoL returns to pre-radiotherapy levels on the long-term. However, studies in low grade glioma patients give strong evidence that radiotherapy causes long-term (after 6 years) cognitive problems and a decline in HRQoL[54–56]. These results, while not in all respects comparable with meningioma patients due to different radiation fields and/or techniques, suggest that meningioma patients who receive radiotherapy might also experience a decline in HRQoL and cognitive performance on the long-term. As the results of the

impact of surgery and radiotherapy are not conclusive and potentially suffer from confounding by indication, prospective studies are needed to investigate the impact of treatment on both HRQoL and cognition on the long-term.

PRO reporting of the included articles was on average of low quality. While the used study design, data acquisition methods, and analysis of the results may be correctly performed, it was not adequately described by the authors. As patient and tumor characteristics (e.g. WHO grade, tumor location) were often not fully reported, and HRQoL data not stratified for these characteristics, generalizability of the results is hampered.

Studies comparing HRQoL results after radiotherapy and surgery may suffer from confounding by indication, as patients who are only treated with radiotherapy may have a worse prognosis due to unfavourable tumor location (close to critical structures) and/or higher WHO grade (WHO grade II and III). Moreover, most studies did not report whether to have included consecutive patients in a predefined time period and did not describe characteristics of non-responders. Since reasons for patients not to participate in a study are frequently poor health status and age[57], this could result in an overestimation of HRQoL of meningioma patients in the included studies. Another major limitation of the included studies is that no article clearly reported the PRO data registration and intended collection schedule, while both can influence results[58]. Self-report tools suffer more from patients' cognitive deficits than interviews, while both may be hampered by aphasia.[6] Interpretation of HRQoL results depends on the intended moment of measurement, short-term or long-term, which may lead to different outcomes and interpretations. Indeed Jakola and colleagues showed that compared with preoperative HRQoL, the mean improvement of patients HRQoL was not significantly improved 6 weeks after surgery, while it was improved 10-58 months after surgery.[22]

There is great variety of available HRQoL questionnaires and a lack of argumentation for choosing a particular questionnaire, prohibiting comparison of results between studies. The most commonly used questionnaires were the SF-36[9,10], the FACT-G and FACT-BR[14] and the EORTC QLQ-C30[12] and QLQ-BN20[15] questionnaires. Of these questionnaires the FACT-G and FACT-BR were also validated in meningioma patients. In addition, the minimal important change is determined for the SF-36, FACT and EORTC questionnaires, which is necessary for critical appraisal of found differences. Currently, the SF-36, FACT and EORTC questionnaires seem most suitable for measuring HRQoL in meningioma patients.

In conclusion, this systematic review describes 19 studies reporting on HRQoL in meningioma patients. Most questionnaires that were used to assess HRQoL were not validated in meningioma patients and the reporting quality of the PRO data in the included studies was on average of low quality, both hampering interpretation of the results. In contrast to the current

impression of patients and physicians, data are still insufficient and not conclusive on the effect of interventions on HRQoL in meningioma patients. To improve clinical-decision making, more high-quality evidence is needed on the effect of meningioma and its different treatment modalities on HRQoL. Therefore, new prospective studies, validated meningioma-specific instruments to assess HRQoL in meningioma patients and improved level of reporting seem warranted. Current data suggests that, even though tumor removal through surgery may be beneficial, some meningioma patients have long term clinically significant impaired HRQoL.

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SUPPLEMENTS

Supplementary Table 1 – Search strategy for MEDLINE

Search terms: Meningioma, quality of life and terms to exclude studies with only animals and case reports
(((“Meningioma”[MesH] OR “Meningioma”[Tw] OR “Meningiomas”[Tw] OR “Meningiomatosis”[Tw] OR “Meningiomatoses”[Tw] OR “Meningeal Neoplasms”[MeSH] OR “Meningeal Neoplasms”[Tw] OR “Meningeal Neoplasm”[Tw]) AND (“Quality of Life”[mesh] OR “Health Surveys”[mesh] OR “Questionnaires”[Mesh] OR “Self Report”[mesh] OR “Patient Outcome Assessment”[mesh] OR “Health Status Indicators”[mesh] OR “Quality of Life”[tw] OR “QoL”[tw] OR “HRQL”[tw] OR “HRQOL”[tw] OR “PQoL”[tw] OR “AQoL”[tw] OR “subjective wellbeing”[tw] OR “subjective well-being”[tw] OR “Patient Reported Outcome”[tw] OR “Patient Reported Outcomes”[tw] OR “patient reported”[tw] OR “PRO”[tw] OR “PROs”[tw] OR “PROM”[tw] OR “PROMs”[tw] OR “health survey”[tw] OR “health surveys”[tw] OR “Questionnaires”[tw] OR “questionnaire”[tw] OR “Self reports”[tw] OR “Self report”[tw] OR “Self-reported”[tw] OR “Patient Outcome Assessments”[tw] OR “Patient Outcome Assessment”[tw] OR “health status indicator”[tw] OR “health status indicators”[tw] OR health status indicat*[tw] OR “outcome instrument”[tw] OR “outcome instruments”[tw] OR “health score”[tw] OR “health scores”[tw] OR health scor*[tw])) **NOT** (“Animals”[mesh] NOT “Humans”[mesh]) NOT (“Case Reports”[pt] NOT “Clinical Trial”[pt]))

The search strategy was adapted for the following electronical databases: Embase, Web of Science, CINAHL, PsychInfo, Academic Search Premier, COCHRANE and ScienceDirect.

Supplementary Table 2 – adapted ISOQOL-recommended PRO reporting standards for non-randomised clinical studies

Title and abstract	The PRO should be identified as an outcome in the abstract	1 point
Introduction, background and objectives	The PRO hypothesis should be stated and should specify the relevant PRO domain(s) if applicable	1 point
Methods		
Outcomes registration	The mode of administration of the PRO tool and the methods of collecting data (e.g., telephone, other) should be described	1 point
	The rationale for choice of the PRO instrument used should be provided	1 point
	Evidence of PRO instrument validity and reliability should be provided or cited	1 point
	The intended HRQL data collection schedule should be provided	1 point
Statistical methods	There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested	1 point
	Statistical approaches for missing data should be explicitly stated, and the extent of missing data should be stated	1 point
Results		
Participant flow (a diagram is strongly recommended)	The reasons for missing data on PRO scores should be explained	1 point
Baseline data	The study patients' characteristics should be described	1 point
Outcomes and estimation	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)	1 point
Discussion		
Limitations	The limitations of the PRO components of the study should be explicitly discussed	1 point
Generalizability	Generalizability issues uniquely related to the PRO results should be discussed, if applicable	1 point
Interpretation	The clinical significance of the PRO findings should be discussed	1 point
	The PRO results should be discussed in the context of the other clinical studies	1 point
Other information		
Protocol	A copy of the instrument should be included if it has not been published previously*	1 point
		Maximum: 16 points

* When the used instrument has previously been published, 1 point is given.

Supplementary Table 3 – Quality assessment of used questionnaires

Questionnaire	Articles	Domains	Population validated in	Content validity	Internal consistency	Criterion validity	Construct Validity	Agreement	Reliability	Responsive-ness	Floor and ceiling effects	Interpre-tability
EQ-5D	Jakola (2012)[22]	N/A	Glioma* / stroke	-	0	-	+	-*	0	-*	-*	?
SF-36	Bunevicius (2014)[37] Waagemans (2010)[23] Mathiesen (2007)[34] Neil-Dwyer (2000)[24] Henzel (2013)[29] van Nieuwenhuizen (2007 & 2013)[31,32]	PF, RP, BP, GH, VT, SF, RE, MH	Stroke patients	-	-	?	-	0	0	0	-	?
FACT-G	Kangas (2012)[30]	PWB, SWB, EWB, FWB	Brain tumor Meningioma	-	+	-	?	0	-	0	0	?
FACT-Br	Kalkanis (2000)[27] Kangas (2012)[30]	N/A	Brain tumor Meningioma	+	+	-	?	0	+	0	0	?
SSQ	Miao (2009)[21]	PH, PS, PSMC, SC	Brain tumor Meningioma	+	?	0	0	0	0	?	0	0
EORTC QLQ-C30	Konglund (2012)[25] Shin (2013)[33]	QOL, PF, RF, EF, CF, SF, FA, NV, PA, DY, SL, AP, CO, DI, FI	Brain cancer	+	0	0	0	0	0	+	0	0
EORTC QLQ-BN20	Konglund (2012)[25] Shin (2013)[33] Van Nieuwenhuizen (2007)[31]	FU, VD, MD, CD, BHA, BSE, BDR, BHL, BIS, BWL, BBC	Brain cancer	+	+	-	-	0	0	+	-	?
Freiburg questionnaire on coping with illness	Krupp (2009)[36]	N/A	Not described	0	0	0	0	0	0	0	0	0
Questions on life satisfaction survey	Krupp (2009)[36]	N/A	Cancer patients	0	0	0	0	0	0	0	0	0
VAS score for olfaction	Curey (2012)[33]	N/A	Chronic rhinosinusitis	0	0	0	0	0	0	0	0	0
NHP	Mohsenipour (2001)[26] Salo (2002)[28]	N/A	Chronic diseases	0	0	0	0	0	0	0	0	0
IHD	Mohsenipour (2001)[26]	N/A	Brain tumor	?	?	-	0	0	-	0	0	0
Sintenon's 15D	Salo (2002)[28]	N/A	Hospitalized patients, not further specified	0	0	0	0	0	0	0	0	0

Supplementary Table 3 – Quality assessment of used questionnaires

SF 36 domains and subscales: physical functioning (PF), role limitation caused by physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation caused by emotional problems (RE), mental health (MH), physical component scale (PSC), mental component scale (MSC)

FACT-G domains: Physical well-being (PWB), Social well-being (SWB), Emotional well-being (EWB), Functional well-being (FWB)

SSQ domains: Physiological (PH), Psychological (PS), Patient satisfaction with medical care (PSMC), Self-care (SC)

EORTC QLQ-C30 subscales and symptoms: general health status (QOL), physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF), fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), financial difficulties (FI)

EORTC QLQ-BN20 subscales and symptoms: future uncertainty (FU), visual disorder (VD), motor dysfunction (MD), communication deficit (CD), headaches (HA), seizures (SE), drowsiness (DR), hair loss (HL), itchy skin (IS), weakness of legs (WL), bladder control (BC)

NHP domains: emotional reactions (EM), energy (EN), pain (P), physical mobility (PM), social isolation (SO), sleep (SL)

+ Rating: criteria met and adequate analysis for content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects, interpretability.

? Rating: doubtful design or method was used or description of analysis was lacking.

- Rating: criteria not met, despite adequate design and method.

0 Rating: no information presented on patients with meningioma, acquired brain injury or other brain tumors

Supplementary Table 4 – Patient-reported outcomes per study

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Surgery						
Miao (2010)[21]	Before and after surgery, not further specified	SSQ Physiological (PH) Psychological (PS) Patient satisfaction with medical care (PSMC) Self-care (SC)	Meningioma patients Total: 74±2 PH: 27±1 PS: N/A PSMC: 5±2 SC: 14±2	Meningioma patients Total: 85±2 PH: MNG 36±2 PS: N/A PSMC: 7±1 SC: 16±3	Healthy controls Total: 91±2 PH 37±3 PS: N/A PSMC: 7±2 SC: 20±1	Follow-up vs. baseline: Meningioma patients scored higher on all domains during follow-up: Total and PH (p=.0001), SC (p=.004), PSMC (p=.01) At baseline meningioma patients score worse than controls: Total, PH and SC (p=.0001), PSMC (p=.001)
Jakola (2012)[22]	Before surgery: 1-3 days Short term after surgery: 6 weeks Long term after surgery, 10-58 months	EQ-5D Change in index value defined as clinical significant > 0.10	Meningioma patients mean scores: All patients: 0.7±0.3 Skull base: 0.6 (SD N/A) Other location: 0.8 (SD N/A) Patients experiencing improvement or unchanged HRQoL at follow-up: 0.6 Patients experiencing deterioration at follow-up: 0.8	Meningioma patients: Short-term: Mean improvement: 0.06 (95% CI, -0.03–0.16) Clinical improvement: 44% Clinically unchanged: 37%, Clinically deteriorated: 19% Long-term: Mean improvement: 0.09 (95% CI, 0.00–0.17) Clinical improvement: 49% Clinically unchanged: 31% Clinically deteriorated: 20%	N/A	Long term vs. baseline: Mean long term improvement in all patients (95% CI 0.00-0.17, p=.040) Preoperative scores were higher for patients experiencing deterioration of HRQOL vs. patients with a unchanged or improved HRQL (p=.049)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Waagemans[23] (2010)	After surgery: at least 1 year after last intervention (mean 3.4 years)	SF-36:	Meningioma patients: PF: 71 RP: 50 BP: 67 GH: 57 VT: 56 SF: 70 RE: 72 MH: 69	N/A	Normative data of Dutch healthy controls PF: 74 RP: 65 BP: 67 GH: 63 VT: 61 SF: 77 RE: 79 MH: 73	Meningioma vs. control postoperative: meningioma patients have more role limitations caused by physical health problems (p<.05)
Mathiesen[34] (2007)	Postoperative, at least 1 year after surgery (mean 66 months)	SF-36	Meningioma patients: PSC: 39 MSC: 45 Below mean of normative data: PF 50%, RP 50%, BP 68%, GH 74%, VT62%, SF 56%, RE 25%, MH 50% Below 25th percentile: PF 50%, RP 44%, BP 30%, GH 18%, VT 30%, SF 61%, RE 25%, MH 25%	N/A	Normative data of normal aged and sex-adjusted Swedish population	Meningioma vs. control Mean time between surgery and SF-36 examination was 2.9 years for patients reporting more than 4 subscale items below the 25th percentile and 5.4 years for patients reporting less than 4 subscale items (p<.05)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Neil-Dwyer (2000)[24] Neil-Dwyer (2001)[40] Lang (1999)[39] Same study study population and results	Postoperative, at least 1 year after surgery	SF-36	Meningioma patients: Individual scores below accepted norms: PF: 56% RP: 61% BP: 39% GH: 56% VT: 72% SF: 61% RE: 56% MH: 44%	N/A	N/A	N/A

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Konglund (2012)[25]	Postoperative, 6 months after surgery	EORTC QLQ-C30 EORTC QLQ-BN20	Meningioma patients EORTC QLQ-C30: QoL: 74 (95% CI, 68-82) PF: 80 (95% CI, 74-88) RF: 77 (95% CI, 69-89) EF: 82 (95% CI, 75-89) CF: 79 (95% CI, 74-87) SF: 84 (95% CI, 79-92) FA: 22 (95% CI, 16-28) NV: 2 PA: 14 (95% CI, 6-23) DY: 10 (95% CI, 3-12) SL: 28 (95% CI, 18-40) AP: 5 (95% CI, 1-9) CO: 14 (95% CI, 4-21) DI: 8 (95% CI, 1-15) FI: 4 QLQ-BN20: mean score 26.7	N/A	Normative data of the Norwegian population for cancer patients, brain cancer patients, and healthy controls	Meningioma vs. cancer patients Meningioma patients scored better than cancer patients on PF (p=.01), RF (p=.02), EF (p=.04), SF (p=.03) and worse than cancer patients on CO (p=.01). Meningioma vs. brain cancer Meningioma patients scored better than brain cancer patients on CO (p=.02), EF (p=.04) and worse on SL (p=.01) Meningioma vs. healthy controls Meningioma patients scored better than healthy controls on PF (p=.01), RF (p=.01), SF (p<.01), yet poorer CF (p=.02)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients		Results: follow-up results	Results: healthy controls	Significant differences
Shin (2013)[33]	Postoperative, not further specified	EORTC QLQ-C30 EORTC QLQ-BN20	Meningioma EORTC QLQ-C30 PF:75±20 RF:75±25 EF:74±21 CF:73±25 SF: 81±26 QOL: 58±24 FA:34±20 NV:9±14 PA:24±24 EORTC QLQ-BN20 FU:28±21 VD:31±27 MD:24±23 CD:16±23	Glioma EORTC QLQ-C30 PF:66±29 RF:65±36 EF:68±25 CF:64±28 SF:64±34 QOL:51±26 FA:40±26 NV:14±19 PA:26±30 EORTC QLQ-BN20 FU:39±24 VD:22±26 MD:34±33 CD:30±31	N/A	N/A	Meningioma vs. glioma EORTC QLQ-C30 Meningioma patients scored significantly better than glioma patients on PF (p=.02), SF (p<.001), CF (p=.008). EORTC QLQ-BN20 Meningioma patients scored significantly better than glioma patients on FU (p=.003), MD (p=.02) and CD (p<.001)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients		Results: follow-up results	Results: healthy controls	Significant differences
Mohsenipour (2001)[26]	Postoperative, not further specified	IHD(NS) Score: None QoL impairment (no): 0 Mild (mi): 1-8 Moderate (mod): 9-16 Severe (sev): 17-38 NHP	Meningioma NHP Energy Pain Emotional Sleep Social isolation Physical mobility NHP total IHD Communication Physical condition Autonomic funct. Independence Psych. Funct. Social isolation IHD total	Percentages No/mi/mod/sev 52/11/15/22 65/11/15/10 42/34/12/12 40/21/32/7 79/12/4/5 50/15/17/18 21/40/27/12 No/mi/mod/sev 32/55/10/4 34/21/23/22 49/28/22/1 9/54/26/1 0/57/31/12 40/48/9/4 1/59/24/16	N/A	N/A	Meningioma patients Emotional impairment decreased significantly with increasing time after the date of operation. Physical mobility impairment increased significantly with age. Size of tumor correlated significantly with impairment in physical mobility.
Kalkanis (2000)[27]	Postoperative, mean time after surgery 33 months (0-165)	Adapted FACT-BR (26 out of 53 questions)	Descriptive data of 26 questions: percentage of subjects answering each question with 'not at all', 'a little bit', 'somewhat','quite a bit', 'very much'.		N/A	N/A	N/A

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Salo (2002)[28]	Preoperative	Sintenon's 15D NHP	Meningioma patients Sintenon's 15D: 0.86 (n=32) NHP median values Energy: 0 Pain: 8.8 Emotional: 6.2 Sleep: 27 Social isolation.: 0 Mobility: 0	N/A	N/A	N/A
Bunevicius (2014)[37]	Pre-opreative	SF-36	Meningioma In a univariable analysis having a meningioma was correlated with the emotional well-being subscale (-0.14, p=0.048). However this association was not found in the multivariable analysis.	N/A	N/A	Meningioma There is a significant negative correlation between meningioma and emotional well-being (p=.048). However this association was not found in the multivariable analysis.

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Krupp (2009)[36]	Postoperative (mean 15 months, rang 10-19)	Freiburg Questionnaire on Coping with Illness Questions on Life Satisfaction Survey Both in German	Meningioma: Coping strategies: Single and female meningioma patients suffer report more often a depressive coping stile (p<.05) than those who are married or have a partner or are who are men. Female patients report more concerning spirituality (p<.05) Satisfaction with life: Meningioma patients living as a single report less satisfaction with life than those who are marries (p<.05), with single men reporting lower satisfaction than single women (p<.05). Elderly report more satisfaction with disease-related health ((p<.05) and less satisfaction with sexuality (p<.001)	N/A	N/A	Coping strategies: Marital status and gender influence coping strategies. Satisfaction with life: Marital status, gender and age influence satisfaction with life
Curey (2012)[33]	Preoperative and postoperative at 6 months	VAS score for olfaction	Meningioma: Normal olfaction: 85% Hyposmia: 10% Anosmia: 5%	Meningioma long-term: Preserved olfactory function: 50% Hyposmia; 3/20 Anosmia: 7/20 VAS score: 5.7±2.2 (95% CI 4.1-7.3)	N/A	Meningioma patients: long term olfactory function is significantly worse than preoperative olfactory function (95% CI, 4.1-7.3)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results		Results: healthy controls	Significant differences
Radiotherapy							
Henzel (2013)[29]	Before SRT, last day of SRT, thereafter biannually	SF-36	Meningioma PF: 63 RP:42 BP:64 GH:53 VT:45 SF:71 RE:46 MH:57	Domain PF RP BP: GH: VT: SF: RE: MH:	After/6/12/18/24 months 61/72/67/66/64 31/51/57/46/42 59/67/61/57/59 56/55/54/53/50 43/48/45/47/44 67/72/67/69/65 40/60/55/47/50 59/61/57/58/56	German normal population PF: 86 PR: 84 BP:79 GH:68 VIT:63 SF:89 RE:90 MH:74	Meningioma At baseline (p=.004) the end of RT (p=.014) and in each follow-up (p=.004) the values for MCS were better in patients who received previous surgery
Kangas (2012)[30]	After RT, mean 1.7 years	FACT-G FACT-BR	Meningioma: PWB: 23±5 SWB: 21±6 EWB: 19±5 FWB: 21±5 FACT-G: 83±15 FACT-BR: 57±12 FACT-G/FACT-BR: 140±24	N/A		Percentile norms US cancer sample 50%/25% PWB: 23/18 SWB: 23/19 EWB: 20/16 FWB: 20/14 FACT-G: 83/70	Meningioma Patients with tumors of the left hemisphere scored significantly lower (19.3±5.7) than patients with a tumor of the right hemisphere (22.5±3.9) on the FACT-FWB (p=.009)

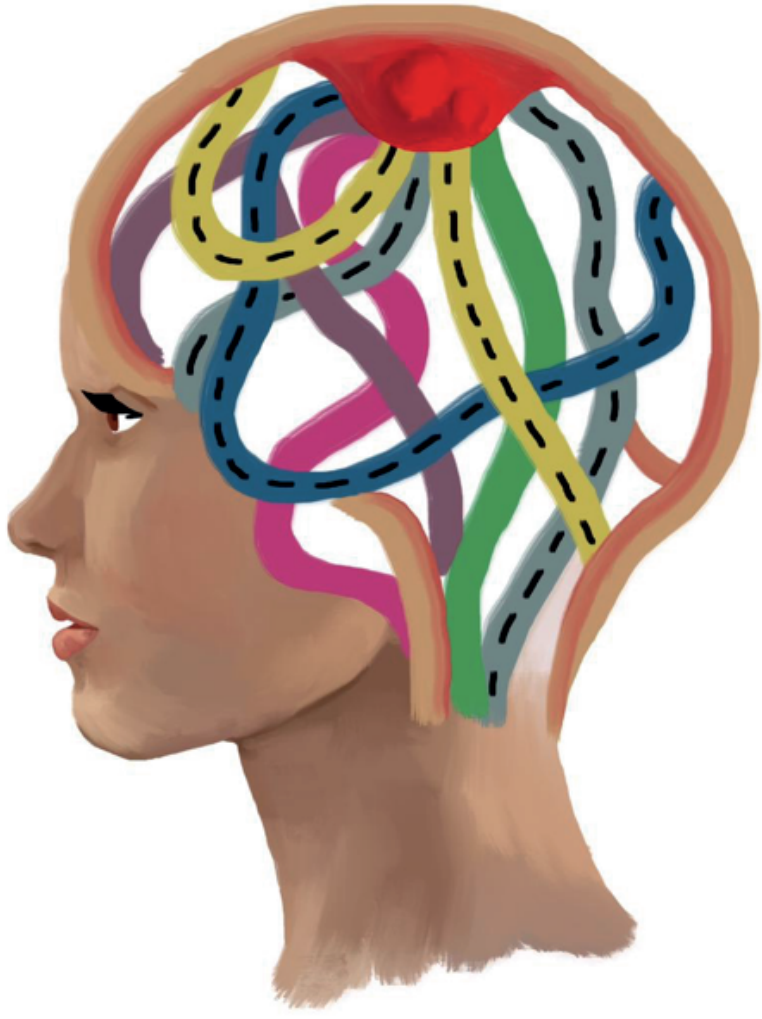
Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients		Results: follow-up results	Results: healthy controls	Significant differences
Van Nieuwenhuizen (2007)[31]	Postoperative, at least 1 year after surgery Surgery only: mean 3.3±2.0 years after surgery Surgery and RT: mean 3.3±1.9 years after surgery	SF-36 EORTC QLQ-BN20	Meningioma: Surgery only SF36 PF: 73±33 RP: 61±43 BP: 67±40 GH: 61±25 VT: 61±31 SF: 70±34 RE: 78±41 MH: 72±24 PCS: 45±13 MCS: 52±12 EORTC QLQ-BN20 FU: 23±26 VD: 15±22 MD: 17±26 CD: 21 ±30 HD: 24±23 SZ: 6±18 DR: 22±31 HL: 6±13 IS: 24±35 WL: 12±23 CB: 14±24	Surgery and Radio therapy SF36 PF: 55±55 RP: 34±39 BP: 56±24 GH: 45±27 VT: 44±21 SF: 67±24 RE: 73±43 MH: 71±23 PCS: 33±11 MCS: 51±13 EORTC QLQ-BN20 FU: 29±26 VD: 28±28 MD: 27±25 CD: 19±21 HD: 41±42 SZ: 13±28 DR: 33±32 HL: 15±26 IS: 24±38 WL: 24±34 CB: 19±33	N/A	Normative data for healthy controls SF36 PF: 74±25 RP: 63±34 BP: 62±25 GH: 65±18 VT: 62±18 SF: 71±26 RE: 75±36 MH: 70±19 PCS: 45±12 MCS: 49±12	Surgery vs. surgery and radio therapy Meningioma patients treated with surgery and with radiotherapy scored lower than patients treated with surgery alone on PF (p=.05), RP (p=.03), PCS (p=.007). This difference disappeared when corrected for duration of disease.

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Wait-and-scan						
Van Nieuwenhuizen (2013)[32]	Pre-operative	SF-36	Meningioma PF: 68±26 RP: 52±42 BP: 59±27 GH: 53±25 VT: 56±19 SF: 75±24 RE: 78±40 MH: 74±23	N/A	Normative data for healthy controls PF: 70±31 RP: 69±45 BP: 65±29 GH: 66±21 VT: 66±23 SF: 80±23 RE: 89±30 MH: 78±21	Meningioma vs. Healthy controls Meningioma patients scored lower than healthy controls on GH (p=.030) and VT (p=.043)

SF 36 domains and subscales: physical functioning (PF), role limitation caused by physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation caused by emotional problems (RE), mental health (MH), physical component scale (PSC), mental component scale (MSC)
FACT-G: Physical well-being (PWB), Social well-being (SWB), Emotional well-being (EWB), Functional well-being (FWB)
SSQ: Physiological (PH), Psychological (PS), Patient satisfaction with medical care (PSMC), Self-care (SC)
EORTC QLQ-C30 subscales and symptoms: general health status (QOL), physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF), fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), financial difficulties (FI)
EORTC QLQ-BN20 subscales and symptoms: future uncertainty (FU), visual disorder (VD), motor dysfunction (MD), communication deficit (CD), headaches (BHA), seizures (BSE), drowsiness (BDR), hair loss (BHL), itchy skin (BIS), weakness of legs (BWL), bladder control (BBC)
N/A: not assessed or not report



Chapter 3

Long-Term Disease Burden and Survivorship Issues After Surgery and Radiotherapy of Intracranial Meningioma Patients

Neurosurgery, 2021;88(1):155–164.

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ABSTRACT

Background

Many intracranial meningioma patients have an impaired health-related quality of life (HRQoL) and neurocognitive functioning up to 4 years after intervention.

Objective

We assessed the long-term (≥5 years) disease burden of meningioma patients.

Methods

In this multicenter cross-sectional study, patients ≥5 years after intervention (including active MRI surveillance) were included and assessed for HRQoL (SF-36), neurocognitive functioning (neuropsychological assessment), anxiety and depression (HADS), and work productivity (SF-HLQ). Multivariable and propensity score regression analyses were used to compare patients and controls, and different treatment strategies corrected for possible confounders. Clinically relevant differences were reported.

Results

At a median of 9 years follow-up after intervention, meningioma patients (n=190) reported more limitations due to physical (difference 12.5 points, p=0.008) and emotional (13.3 points, p=0.002) functioning compared with controls. Patients also had an increased risk to suffer from anxiety (OR: 2.6, 95%CI: 1.2-5.7) and depression (OR: 3.7, 95%CI: 1.3-10.5). Neurocognitive deficits were found in 43% of patients. While postoperative complications, radiotherapy and reresection were associated with worse verbal memory, attention and executive functioning when compared to patients resected once, the only clinically relevant association was between reresection and worse attention (-2.11, 95%CI: -3.52-0.07). Patients of working age less often had a paid job (48%) compared with the working-age Dutch population (72%) and reported more obstacles at work compared with controls.

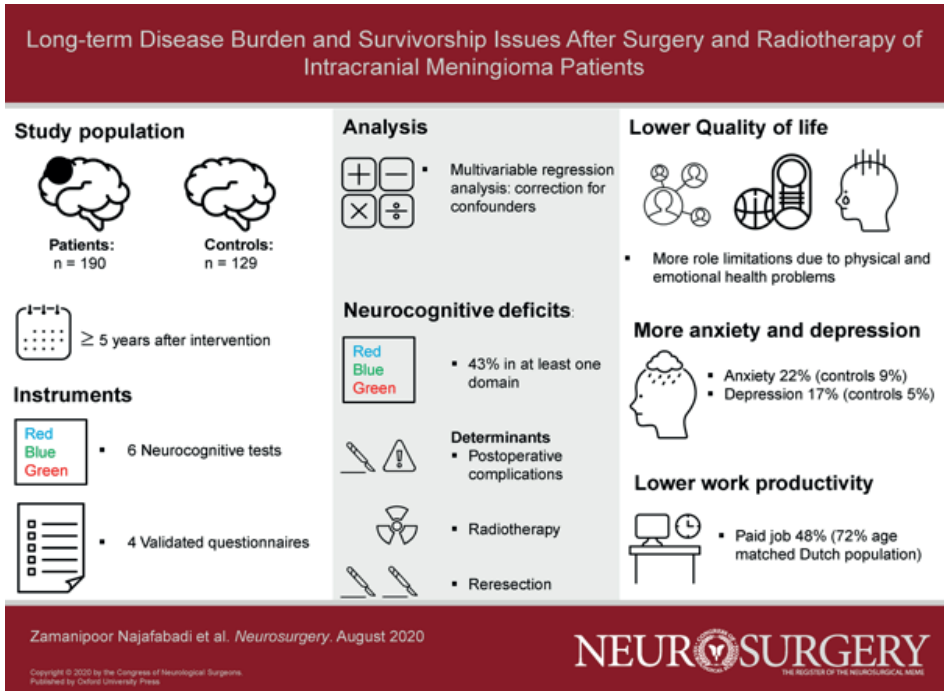
Conclusion

On the long-term, a large proportion of meningioma patients have impaired HRQoL, neurocognitive deficits, and high levels of anxiety or depression. Patients treated with one resection have the best neurocognitive functioning.

Keywords

Meningioma; Quality of Life; Cognitive function; Anxiety; Depression

VISUAL ABSTRACT



INTRODUCTION

Meningioma accounts for 37% of all primary brain tumors.[1,2,3] Morbidity of intracranial meningiomas is primarily due to compression of brain tissue and cranial nerves, or treatment-related complications (e.g. hemorrhage).[3] Primary treatment for these tumors consists of surgery, with in selected cases first-line or adjuvant radiotherapy, resulting in a 10-year relative survival of 82% for WHO grade I meningioma.[2,4,5]

One might expect that after decompression of central nervous tissue, symptoms are resolved and functioning returns to normal eventually. Historically, long-term meningioma survivors (≥5 years after intervention) who lived through the diagnosis and treatment of a meningioma, were often considered 'cured'.[3,6,7] However, it is known from cancer populations that the experience of living beyond tumor and treatment entails considerable life-long physical, cognitive and psychological issues (e.g. neurocognitive impairments and disrupted social roles), which often differ from the acute complications patients experience during diagnosis and treatment (e.g. impaired physical function due to paresis).[8,9]

While it is known that surgery and radiotherapy might improve health-related quality of life (HRQoL) and cognitive function in the first year, recent studies have shown that up to a median of 4 years after intervention, meningioma patients may still suffer from impaired HRQoL and neurocognitive functioning, and increased anxiety and depression.[7,10,11] While data on long-term effects of meningioma and its treatment on these outcomes are lacking, studies in low-grade glioma suggest that some impairments and deficits only manifest 5 years beyond treatment.[12] Moreover, the impact on societal participation in terms of work productivity is currently unknown.[7]

Thus, we aimed to assess the long-term (≥5 years after their intervention, i.e. last anti-tumor treatment or initiation of active MRI surveillance) disease burden of meningioma patients in terms of HRQoL, anxiety and depression, neurocognitive functioning, and work productivity. We also assessed if these outcomes were affected by the type of treatment received. Better knowledge of long-term survivorship issues in meningioma patients will help to manage patient's expectations, and design long-term meningioma care plans, tailored to patient's physical, psychological and social needs.

METHODS

Participants

In this multicenter cross-sectional study, consecutive meningioma patients were included if the end of the primary anti-tumor treatment was at least 5 years prior to recruitment, or in case of active MRI surveillance, at least five years after diagnosis. Eligible patients had to be 18 years or older; with a histologically confirmed WHO grade I or grade II meningioma in case of surgery and an MRI-based clinically suspected meningioma in case of radiotherapy or active MRI surveillance. Consecutive patients were recruited from the neurosurgery, neurology and radiation oncology outpatient clinics of two academic hospitals and one large non-academic teaching hospital between July 2016 and April 2019. All eligible patients were approached for this study via a letter signed by a member of their treatment team. Patients were excluded if they had a history of whole brain radiotherapy, were diagnosed with neurofibromatosis type II or any neurodegenerative disease, or had insufficient mastery of the Dutch language.

Informal caregivers of participating meningioma patients were included for comparison of HRQoL, anxiety and depression and work productivity, and were eligible for participation if they were a spouse, family member or close friend to the patient, 18 years or older, and provided the majority of emotional or physical support to the patient as reported by the patient. It was not possible to include an informal caregiver for every patient, as some patients were not able to identify an informal caregiver motivated to participate in the study.

Procedures

This study was approved by the medical ethical committees of all participating centers, and participants provided informed consent before study procedures. Both questionnaires and neurocognitive assessment were administered once on the same day, at least 5 years after their last meningioma treatment. Hence, there is variation in the follow-up length between patient's last meningioma treatment and moment of study participation. Clinical information on tumor and treatment was obtained from the medical records, while sociodemographic information about patients and controls was obtained through a structured interview at the beginning of the assessments.

Questionnaires

Patients completed questionnaires measuring HRQoL consisting of the Short-Form Health Survey (SF-36) and European Organization for Research and Treatment of Cancer quality of life questionnaire, brain specific module (EORTC QLQ-BN20). In addition, patients completed the Hospital Anxiety and Depression Scale (HADS), and Short Form-Health and Labour Questionnaire (SF-HLQ) measuring work productivity. Informal caregivers completed the same questionnaires, except for the EORTC QLQ-BN20 (Supplemental Digital Content 1).

Neuropsychological assessment

A comprehensive battery of neuropsychological tests was administered by trained research nurses or research assistants and consisted of the Auditory Verbal Learning Test (AVLT), Concept Shifting Test (CST), Memory Comparison Test (MCT), Categoric Word Fluency Test (CWFT), Digit-Symbol Substitution Test (DSTT) and the Stroop Colour-Word Test (SCWT). Based on these tests, scores for the following neurocognitive domains were calculated: executive functioning, verbal memory, working memory, psychomotor functioning, information processing speed, and attention (Supplemental Digital Content 1).

Statistical Analysis

A description of the sample size calculation is provided in Supplemental Digital Content 2. SF-36 and EORTC QLQ-BN20 scores were presented for each domain or scale/item, respectively, ranging from 0-100, with higher scores representing better HRQoL (SF-36), or more symptomatology (QLQ-BN20). Total scores for both anxiety and depression as measured with the HADS range from 0 to 21 and were classified into no (scores: 0-7), borderline (scores: 8-10), and severe anxiety or depression (scores: 11-21).[13] Work productivity was measured as having a paid job or not and experienced difficulties at work on six items.[14] Unadjusted crude scores on the SF-36, EORTC QLQ-BN20, and HADS for both patients and controls (i.e. informal caregivers) are presented in bar graphs.

Data on HRQoL (SF-36 only), anxiety and depression, and work productivity were compared between meningioma patients and informal caregivers, corrected for known confounders (i.e. age, gender, education level and comorbidity) using multivariable regression analysis.[10,12] As a sensitivity analysis, data on HRQoL as measured with the SF-36 was also compared between meningioma patients and published normative data using an one-sample t-test. For the EORTC QLQ-BN20 data we performed a one-sample t-test to compare meningioma data with baseline data (i.e. after surgery but before further anti-tumor treatment) of glioblastoma patients from the AVAglio trial.[15] This comparison with the most common primary malignant brain tumor was done to put disease-specific HRQoL into context. As minimal clinically important differences (MCIDs) were not known for the used instruments in brain tumor patients specifically, we used MCIDs previously established for other patient groups. MCIDs was set on 10 points for scales/items of the EORTC QLQ-BN20.[16] Similarly, we set the MCID for the SF-36 domains also at 10 points, as the majority of reported MCID's for the different domains were <10 points.[17] For the SF-36 mental and physical component scales (MCS and PCS), MCIDs were set at 4.6 points and 3.0 points, resepectively.[18] Furthermore, for calculation of Z-scores for each neurocognitive domain, means and standard deviations from a reference sample from the Maastricht Aging Study (MAAS; large longitudinal study on the psychological and biological determinants of cognitive aging) were used, matched on group-level for age, gender and educational level.[19] Per domain, differences in z-scores greater than -1.5 were considered

clinically relevant.[20] In addition, meningioma patients of working-age were compared with net average working-age Dutch population (source: Statistics Netherlands) for comparison of the percentage patients with a paid job.[21]

The effects of surgery and radiotherapy were compared for those SF-36 HRQoL and neurocognitive functioning domains on which patients scored clinically relevant lower compared with controls, limiting the number of statistical tests performed. Propensity score regression analysis was used (see Supplemental Digital Content 2 for details) to adjust for potentially relevant confounders (e.g. age, tumor size, tumor location, and Simpson grade).[7,22]

A non-responders analysis was performed comparing important clinical and sociodemographic characteristics between participating meningioma patients and patients who chose not to participate.

For all statistical tests, SPSS 23 (SPSS Inc, Chicago, IL) was used, and P less than .05 was considered statistically significant.

RESULTS

Demographics

A total of 190 patients (female: n=149, 78%) were included with a median follow-up since intervention of 9 years (IQR: 7-12 years) (Table 1, Figure 1). Patients were on average 63 (SD: 12) years old. Tumors were located on the skull base in 92 patients (48%), the cerebral convexity in 93 patients (49%) and the optic nerve sheets or intraventricularly in 5 patients (3%). The majority of surgically treated meningioma was classified as WHO grade I (88%). Surgery was the primary choice of treatment in 168 (88%) patients of which 63 suffered from any postoperative complication, such as cranial nerve deficits (n=8) or cerebrospinal fluid leak (n=8). A total of 26 (14%) were treated with adjuvant radiotherapy and 13 (7%) with reresection. Primary radiotherapy was limited to 10 (5%) patients with anatomically complicated skull base tumors. A total of 12 patients (6%) was solely followed with active MRI surveillance without any anti-tumor treatment. Patient- and tumor-related characteristics in each treatment group are presented in Supplemental Digital Content 3. A total of 129 informal caregivers of participating meningioma patients were included and data from 151 participants of the MAAS study. Non-responder analysis showed that participating and not participating meningioma patients were similar on important sociodemographic and clinical characteristics, except for age, as not participating patients were slightly older (Supplemental Digital Content 4).

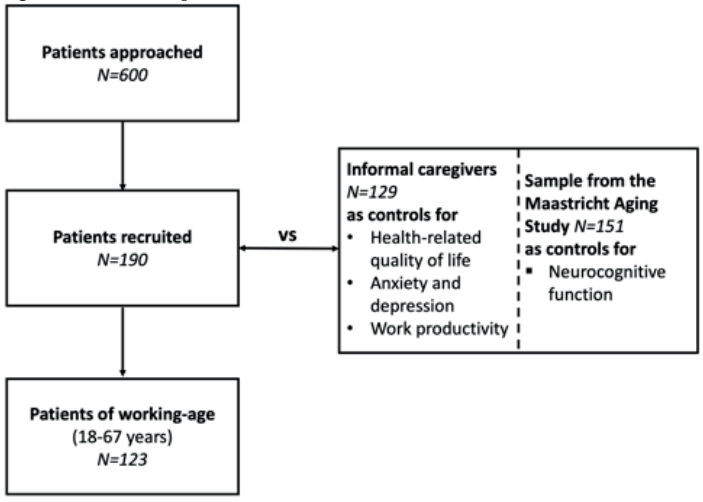
Table 1: Sociodemographic and clinical characteristics of meningioma patients and controls (i.e. informal caregivers and controls from the MAAS study)

	Meningioma Patients n=190	Informal caregivers (n=129)	MAAS controls (n=151)
Age, years	63 (SD 12)	61 (13)	60 (13)
Female	149 (78%)	47 (36%)	109 (72%)
Academic hospital	142 (75%)		
Meningioma Location			
Skull base	92 (48%)		
Convexity	93 (49%)		
Other	5 (3%)		
Symptoms of presentation (multiple options possible per patient)			
Epilepsy	31 (16%)		
Motor deficit	28 (15%)		
Sensory deficit	24 (13%)		
Visual deficit	51 (27%)		
Cognitive impairment	14 (7%)		
Headache	32 (17%)		
Incidental finding	17 (9%)		
Other	48 (26%)		
Time since first symptoms, years	11 (9-14)		
Time since diagnosis, years	10 (8-12)		
Tumor size before intervention, mm	38 (26-50)		
Tumor size before study, mm	0 (0-16)		
Tumor growth on last MRI before study	10 (5%)		
Number of meningiomas			
≥2	26 (14%)		
Active MRI surveillance	12 (6%)		
Surgery as initial treatment	168 (88%)		
Complication first surgery (operated patients: n=168)	63 (38%)		
Second surgery	13 (7%)		
Third surgery	2 (1%)		
Time since first surgery, years	9 (7-12)		
Simpson Grade (operated patients: n=168)			
Grade I-III	109 (65%)		
Grade IV-V	40 (24%)		
Unknown	19 (11%)		
WHO grade (operated patients: n=168)			
Grade I	148 (88%)		
Grade II	12 (7%)		
Unknown	8 (5%)		
Radiotherapy	36 (19%)		
Radiotherapy as initial treatment	10 (5%)		

Table 1: Sociodemographic and clinical characteristics of meningioma patients and controls (i.e. informal caregivers and controls from the MAAS study) (continued)

	Meningioma Patients n=190	Informal caregivers (n=129)	MAAS controls (n=151)
Adjuvant radiotherapy	26 (14%)		
Time since radiotherapy, years	8 (6-9)		
Complications of radiotherapy (radiotherapy treatment: n=36)	3 (8%)		
Karnofsky Performance Status at time of study	100 (90-100)		
Self-reported cognitive deficit at time of study	94 (49%)		
Self-reported motor deficit at time of study	55 (29%)		
Seizures in the last three months before study	8 (4%)		
Antiepileptic drug use at any moment during the care trajectory	90 (47%)		
Dexamethasone use for symptoms at any moment during the care trajectory	22 (12%)		
Physical rehabilitation	37 (19%)		
Cognitive rehabilitation	8 (4%)		
Psychological support	21 (11%)		
Other supportive care	10 (5%)		
Education level			
Primary/Secondary	40 (21%)	14 (11%)	58 (38%)
Tertiary: technical/vocational	85 (45%)	55 (43%)	49 (32%)
Academic	59 (31%)	57 (44%)	45 (30%)
Not provided	6 (3%)	3 (2%)	
Charlson Comorbidity Index			
0	127 (67%)	88 (68%)	
1≥	63 (23%)	41 (32%)	
Right-handed	147 (77%)	92 (71%)	

Figure 1. Flow chart of patients and controls



Health-related quality of life (HRQoL)

After correction for confounders, patients had clinically relevant lower HRQoL scores than controls on 2 of the 8 SF-36 domains: role limitations due to physical functioning (corrected difference 12.5 points, p=0.008), and role limitations due to emotional problems (13.3, p=0.002). In addition, they scored statistically significantly, but not clinically relevant, lower on 2 additional domains and 1 component score: social functioning (7.4, p=0.008), vitality (7.1, p=0.016), and the mental component score (3.8, p=0.005). No differences were found for the other 4 domains and physical component score (Figure 2). In the sensitivity analysis comparing meningioma patients with normative data without correction for confounders, patients had clinically relevant lower scores on 1 domain and 1 component score: role limitations due to physical problems (uncorrected difference 12.2, p<0.001), and the physical component score (5.0, p<0.001). They scored statistically significant, but not clinically relevant, lower on 3 additional domains: physical functioning (5.4, p=0.004), general health (7.2, p<0.001), and social functioning (5.6, p=0.005) (Supplemental Digital Content 5). Comparing meningioma patients with glioblastoma patients after surgery but naïve to chemotherapy and radiotherapy, we found that meningioma patients had statistically similar scores on 4/11 EORTC QLQ-BN20 scales/items, showing impaired HRQoL: visual disorder (difference: 2.5, p=0.078), communication deficit (-1.8, p=0.291), headache (2.8, p=0.296), and hair loss (2.3, p=0.101). The differences were not clinically relevant for these scales/items, or any of the other scales/items, except future uncertainty, for which glioblastoma patients reported more uncertainty (Figure 3).

Figure 2. SF-36 health-related quality of life domain and component scores for both meningioma patients and controls, presented as bar charts and absolute scores.

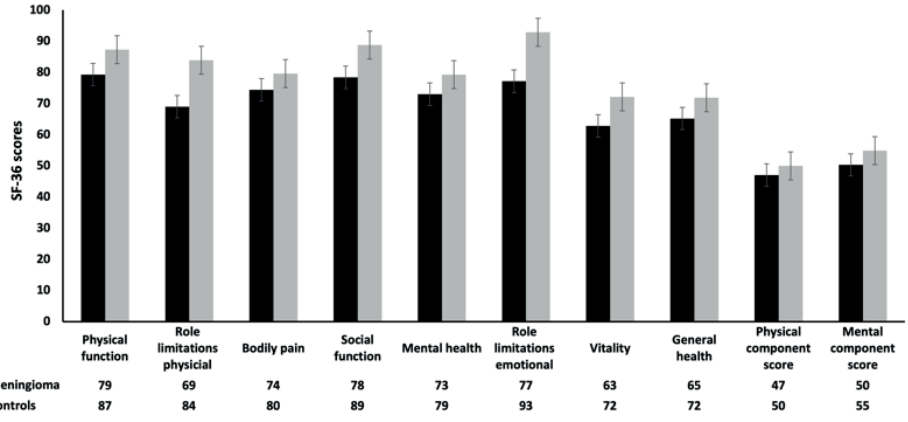
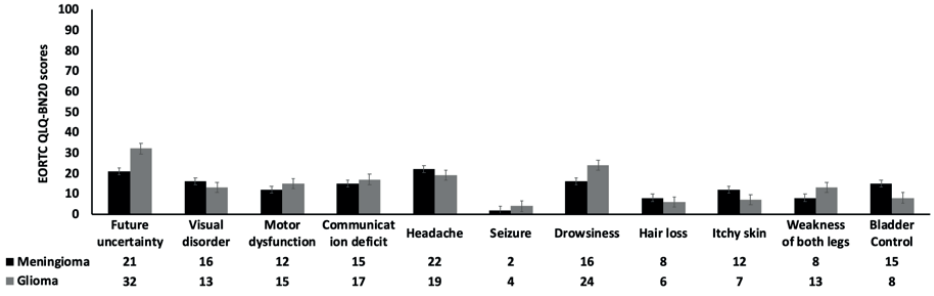


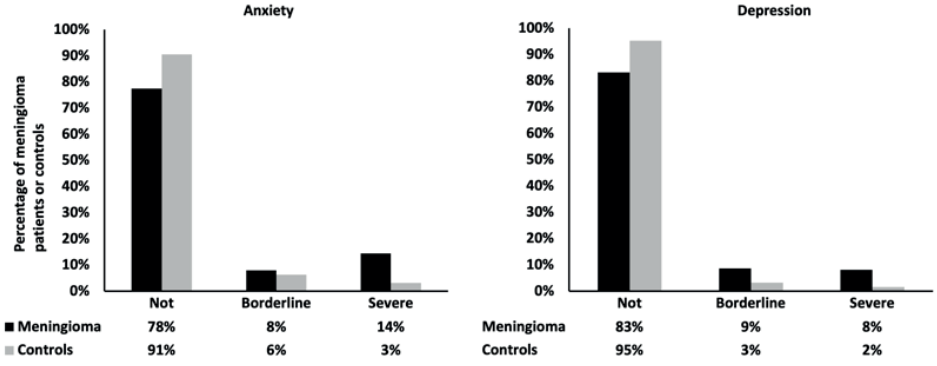
Figure 3. EORTC QLQ-BN20 scores for meningioma patients (median 9 years after treatment) and for glioblastoma patients participating in the AVAglio study at baseline (i.e. comparison group for this analysis), presented as bar charts and absolute scores.



Anxiety and depression

Patients suffered more frequently from borderline (8%, n=15) and severe (14%, n=27) anxiety, compared with controls (borderline: 6%, n=8; severe: 3%, n=4; overall p=0.047, Figure 4). Patients also suffered more frequently from borderline (9%, n=16) and severe (8%, n=15) depression, compared with controls (borderline: 3%, n=4; severe: 2%, n=2; overall p=0.099, Figure 4). Compared to controls, patients had an increased risk to develop borderline or severe anxiety (OR: 2.6, 95%CI: 1.2-5.7) and borderline or severe depression (OR: 3.7, 95%CI: 1.3-10.5) after correction for confounders.

Figure 4. Percentage of patients and controls with borderline or severe anxiety and depression as measured with the Hospital Anxiety and Depression Scale.

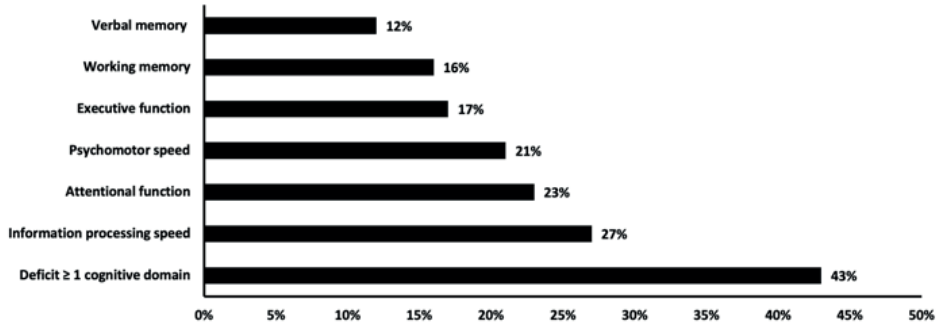


Neurocognitive functioning

A total of 43% (n=82) of patients suffered from a clinically relevant neurocognitive deficit in at least one of the six measured domains, most often in the domains information processing speed (n=51, 27%) and attention (n=44, 23%) (see Figure 5 for all domains). Furthermore, 47 (25%) patients suffered from a clinically relevant impairment in at least two domains, 32

(17%) patients in three domains, 22 (12%) patients in four domains, 20 (11%) patients in four domains, and 7 (4%) patients in all six domains.

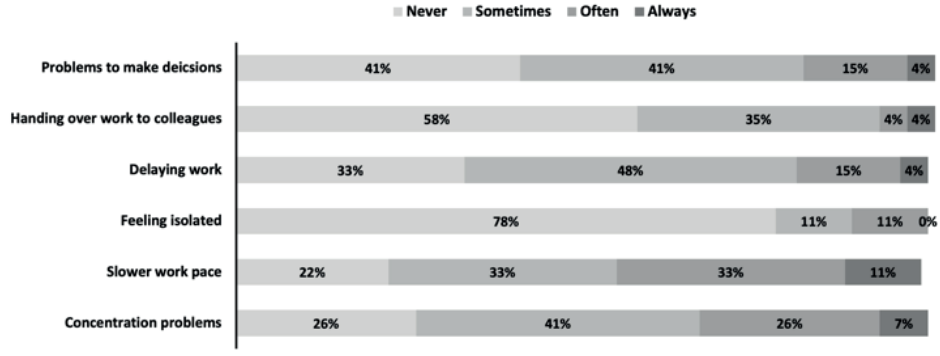
Figure 5. Percentage of patients with a clinically relevant neurocognitive deficit, (difference in z-score greater than -1.5 compared to the mean of controls), separately for each domain and in at least 1 domain.



Work productivity

Out of 190 meningioma patients, 123 (65%) were aged between 18 and 67 years and considered being of working-age. At the time of assessment, 50% (62/123) of meningioma patients had a paid job, compared with 72% of the net average working-age Dutch population (p<0.001). Reported reasons to not have a paid job were being a homemaker (female patients 15%, male patients 0%) or poor health condition (both male and female patients: 24%). More patients reported obstacles at work (46%) than controls (17%, p=0.005). The following problems at work were reported to occur sometimes to always (Figure 6): impaired concentration (74%), slower work pace (78%), feeling isolated (22%) delaying work (67%), the need for someone to take over their work (42%), and problems to make decisions (59%).

Figure 6. Percentage of meningioma patients reporting difficulties with specific aspects of work.



Impact of surgery and radiotherapy on HRQoL and neurocognition

Patients primarily treated with surgery or radiotherapy did not score significantly different on HRQoL or neurocognitive functioning compared to patients followed with active MRI surveillance (Supplemental Digital Contents 6-11). However, comparing surgery with radiotherapy as first-line treatment showed that patients treated with radiotherapy scored significantly worse on verbal memory (-0.99, 95%CI -1.78 to -0.20). Similarly, patients receiving additional radiotherapy after surgery scored worse on verbal memory (-0.45, 95%CI -0.86 to -0.03) compared with patients solely treated by surgery. Patients who suffered from a complication of their first surgery scored worse on attention (-0.78, 95%CI -1.42 to -0.14) compared with those without complications. Especially the need for a second resection for residual tumor or recurrence resulted in worse scores in executive functioning (-0.92, 95%CI -1.78 to -0.07), verbal memory (-0.66, 95%CI -1.25 to -0.08,) and attention (-2.11, 95%CI -3.52 to -0.71) compared with patients who only needed a single resection. Except for attention in those patients needing a second resection, differences were not clinically relevant.

DISCUSSION

Key results

Although most meningioma patients have a benign WHO grade I tumor with an associated near-normal life expectancy, and are often considered cured after intervention, our results show firm evidence that patients still suffer from a significant disease burden even after a median follow-up of 9 years. Many patients suffer from clinically relevant impaired HRQoL and neurocognitive functioning, higher levels of anxiety and depression, and lower levels of work productivity. The type of treatment also impacted outcomes; patients who received one single resection had better neurocognitive functioning compared with patients who experienced surgical complications or were treated with (additional) radiotherapy or who needed a reresection.

Limitations

Due to the observational cross-sectional design of this study, no conclusions can be drawn on possible improvement or deterioration after treatment and the results might suffer from confounding and bias. Especially for the comparison between patients treated with surgery or radiotherapy as first-line treatment, selection bias might have affected the results, as radiotherapy is often reserved for patients who are older, suffer from comorbidities, or with a complicated anatomical location. To reduce the impact of confounding on our results, particularly when analyzing the cohort, we corrected our analyses for multiple confounders using multivariable and propensity scores regression analysis. Furthermore, we included a limited number of patients with active MRI surveillance or radiotherapy as only treatment. Although radiotherapy is expected to have a negative impact on outcomes on the long-term,

the number of patients included with radiotherapy was too small to detect small meaningful differences. In addition, we might miss meningioma-specific HRQoL issues as we used the widely implemented SF-36, which enabled comparisons with other patient groups. There is no validated meningioma-specific HRQoL instrument that we could have used.[23] Moreover, as brain tumor-specific MCIDs are not available for the questionnaires used, we used more conservative MCIDs based on other patient populations. Hence the presented results might be on the more conservative side. Lastly, we used both informal caregivers and normative data as controls for HRQoL. As informal caregivers are indirectly affected by the disease course of their loved ones, but not suffer directly from the same physical and neurological consequences, we were able to more accurately assess the impact of the tumor and its treatment. Results of both comparisons were fairly similar showing that compared with informal caregivers or normative data, patients scored clinically relevant lower on several domains/component scores of the SF-36.

Interpretation

Existing frameworks for survivorship issues describe that while in the acute phase of diagnosis and treatment bodily impairments can be expected, on the longer term patients primarily experience disruptions of their social roles.[7,9] Indeed, we found that patients on the longer term reported clinically relevant more role limitations due to physical and emotional functioning, whereas previous studies reported impairments in cognitive and physical functioning at a median of 6 month and 4 years after surgery[7,24] Remarkably, we found that patients with a benign meningioma after long-term follow-up had similar HRQoL scores compared with chemotherapy and radiotherapy naive glioblastoma patients. Although the two groups are not comparable in terms of follow-up length after treatment initiation, glioblastoma patients are often considered having HRQoL impairments. [25] To put the results in context of major surgery in non-CNS related conditions, which may also have a huge long-term impact on the patients' functioning and well-being, meningioma patients reported lower physical and mental HRQoL than similarly aged patients who received coronary artery bypass graft (CABG) surgery[26], and lower mental but better physical HRQol compared with patients who received a total hip replacement[27]. No neuropsychological impairments in meningioma patients have been reported up to a median of 3 years after intervention.[10,28] In low-grade glioma patients these deficits might only become apparent after more than 10 years of follow-up.[12] Indeed, we found that neurocognitive deficits were present in over 40% of meningioma patients. The limited published data on anxiety and depression describes that approximately 10%-15% of meningioma patients suffer from severe depression or anxiety respectively, both before and 6 months after surgery.[11,29] It seems this percentage does not reduce over time, as we found a percentage of patients at risk for severe depression or anxiety of 8% and 14%, respectively. Furthermore, we found that patients less often have a paid job than the age-matched Dutch population, because they were identified as a homemaker (female patients 15%, male patients

0%) or due to poor health condition (both male and female patients: 24%). Compared with patients with prolactinoma, another benign intracranial lesion primarily affecting women, meningioma patients of working-age had less often a paid job (meningioma patients: 50%; prolactinoma patients: 80%).[27] Comparably, female breast cancer patients do not have a paid job due to their health issues and less often because they were homemakers.[28,29] Although not measured over time, we found that patients who were treated by single surgery reported better HRQoL and neurocognitive functioning compared with patients treated primarily with radiotherapy or additional radiotherapy or reresection. Previous longitudinal studies in meningioma patients reported improved, but not normalized neurocognitive functioning and HRQoL after surgery.[28,30] Patients treated with radiotherapy showed improvement in HRQoL in the first 6 months after irradiation, with deterioration to pre-radiotherapy levels after two years.[31] Only one (n=18) study has compared the effects of postoperative radiotherapy in meningioma patents, reporting no differences in HRQoL.[32] However, the limited follow-up of 1 year hampered assessment of possible long-term neurotoxicity of radiotherapy.

Generalizability

We believe that our results are generalizable, as the amount of missing data was very limited (all assessments were performed on a single day), patients were recruited from both academic and non-academic hospitals in the Netherlands, and because our non-responder analysis showed that our study population was representative of the general meningioma population. Generalizability to other countries might be hampered, due to differences in health care settings and the impact of cultural differences on outcomes such as HRQoL.

Conclusions

Although the continued improvement in surgical and radiotherapeutic techniques for meningioma treatment has resulted in an increase in long-term survivors, little was known about the survivorship issues of these patients. The results of this study show that the longer-term disease burden is considerable. This information is of importance to properly inform healthcare providers and patients on the long-term sequelae of tumor and treatment. This is relevant for proper expectation management, as well as to develop care plans for long-term survivors, focusing on the identified longer-term impairments. Lastly, the results of this study can be used as a benchmark for comparison of multiple patient-centered outcomes on the long-term when evaluating new treatment modalities.[33] Possible determinants for the long-term disease burden is an important topic, and should be explored in more detail in future studies.

Acknowledgements:

We would like to acknowledge the research nurses of the LUMC/HMC Neurosurgery department for their help with the data collection.

Funding:

AHZN was supported by a personal MD/PhD grant of the Leiden University Medical Center.

No specific funding was received for this project.

Conflicts of interest:

None of the authors declares a conflict of interest

Prior presentations:

Parts of the results described in this manuscript were presented at the 2018 Society for Neuro-Oncology (SNO) conference in New-Orleans (Louisiana, USA) as an oral presentation on 17 November 2018. In addition, parts of the results were presented at the 2018 European Association of Neuro-Oncology (EANO) conference in Stockholm (Sweden) as an oral presentation on 13 October 2018.

Ethics committee approval:

This cross-sectional study was approved by the medical ethical committees of all participating centers (NL54866.029.15), and participants provided informed consent before study procedures.

Contributorship:

LD, FWB, and SMP designed the study. Data collection was primarily performed by AHZN and PBvdM. AHZN performed data analysis with input from LD. AHZN wrote the first and successive versions of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the drafts of the paper, and approved the final version. AHZN had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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SUPPLEMENTS

Supplemental Digital Content 1. Outcome measures: questionnaires and neuropsychological test.

	Explanation	Patients	Controls
Health-related quality of life questionnaires			
Medical Outcomes Study (MOS) Short-Form Health Survey (SF-36)[1–3]	The SF-36 is a self-report questionnaire and is composed of 36 items, organized into eight multi-item scales assessing physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-36 also yields two higher order component scores, one for Physical Health (PCS) and one for Mental Health (MCS). Higher scores represent better HRQoL.	yes	yes
European Organisation for Research and Treatment of Cancer quality of life questionnaire, brain specific submodule (EORTC QLQ-BN20)[4,5]	This questionnaire comprises four multi-item scales (future uncertainty, visual disorders, motor dysfunction and communication deficit) and seven single items covering other symptoms. Higher scores represent lower HRQoL.	yes	no
Anxiety and Depression			
Hospital Anxiety and Depression Scale (HADS)[6,7]	This patient-reported outcome measure comprises 14 items; seven of the items are related to anxiety and seven items to depression. Total scores for both anxiety and depression range from 0 to 21 and are classified into no (scores: 0-7), borderline (scores: 8-10) and severe anxiety or depression (scores: 11-21).	yes	yes
Work productivity			
Short form – Health and Labour Questionnaire (SF-HLQ)[8]	This patient-reported questionnaire, comprising 11 questions, was used to assess whether participants had a paid job and whether they experienced problems at work.	yes	yes
Neurocognitive Tests[9–11]	**Neurocognitive Domains**		**Controls**
Auditory Verbal Learning Test (AVLT)	Verbal memory	yes	yes
Concept Shifting Test (CST)	Executive functioning and psychomotor functioning	yes	yes
Memory Comparison Test (MCT)	Working memory	yes	yes
Categoric Word Fluency Test (CWFT)	Executive functioning	yes	yes
Digit-Symbol Substitution Test (DSTT)	Information processing speed	yes	yes
Stroop Colour-Word Test (SCWT)	Attention	yes	yes

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Supplemental Digital Content 2. Sample size calculation and Rationale propensity score regression analysis.

Sample size calculation

A sample size of 200 meningioma patients was calculated to have 90% power to detect a minimal clinically important difference (MCID) of at least 4.6 points on the Mental health Component Scale (MCS) of the SF-36 questionnaire with a 0.05 two-sided significance level, assuming that healthy controls have a mean score of 50, with a standard deviation of 10 (also assumed for patients), based on normative data of 2393 Americans of the general population.[12] From all the published MCIDs of the domains and component scores of the included questionnaires, the SF-36 MCS was used for the sample size calculation, as it encompasses psychological and cognitive issues relevant for this patient group, is a frequently used MCID and one of the smaller MCIDs, requiring a bigger sample size, sufficient for the majority of other measured outcomes.[13]

Although we were not able to recruit the calculated 200 patients, which was needed to ensure 90% power to able to detect the predefined MCID, we were able to include 190 patients. This is more than the 150 patients required to reach 80% power, an often-used percentage for sample size calculations for clinical studies.

Rationale propensity score regression analysis

Instead of regular multivariable analysis, propensity score analysis was used to increase the power with the limited number of patients receiving radiotherapy as primary or adjuvant treatment.[14] Relevant confounders were identified and included in the propensity score models using the DAG (Directed Acyclic Graph) representation, defined as being associated with both the determinant and the outcome based on prior knowledge, but not laying in the causal path.[15] The following variables were included om the propensity score analysis: age, comorbidities (CCI), tumor location (skull base vs convexity), tumor size, and Simpson grade (in case of reresection or adjuvant radiotherapy).

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Supplemental Digital Content 3. Sociodemographic and clinical characteristics of meningioma patients stratified per treatment strategy.

	Active MRI surveillance (n=12)	Surgery (n=142)	Radiotherapy (n=10)	Surgery + radiotherapy (n=26)
Age, years (SD)	74 (11)	63 (10)	61 (15)	59 (15)
Female	10 (83%)	112 (79%)	8 (80%)	19 (73%)
CCI				
0	6 (50%)	95 (67%)	7 (70%)	19 (73%)
1≥	6 (50%)	47 (33%)	3 (30%)	7 (27%)
Tumor location				
Skull base	4 (33%)	62 (44%)	6 (60%)	20 (77%)
Convexity	8 (67%)	78 (55%)	1 (10%)	6 (23%)
Other	0 (0%)	2 (1%)	3 (30%)	0 (0%)
Tumor diameter, mm (SD)	20 (21)	41 (17)	25 (16)	40 (13)
Simpson				
I-III	-	98 (79%)	-	11 (42%)
IV-V	-	26 (18%)	-	13 (50%)
Unknown	-	18 (13%)	-	2 (8%)

Supplemental Digital Content 4. Non-responder analysis: comparing participating patients with patients who declined to participate in this study.

	Participants (n=190)	Declined (n=410)	p-value
Age, years	63 (SD 12)	67 (SD 15)	0.003
Female	149 (78%)	312 (76%)	0.513
Treatment location			0.000
Academic hospital I	97 (51%)	147 (36%)	
Academic hospital II	44 (23%)	119 (29%)	
Non-academic hospital	49 (26%)	144 (35%)	
Time since first surgery, years	9 (7-12)	10 (8-14)	0.410
Meningioma location			0.617
Skull base	92 (48%)	187 (46%)	
Convexity	93 (49%)	208 (51%)	
Other	5 (3%)	14 (3%)	
Tumor size at diagnosis, mm	38 (26-50)	37 (28-53)	0.406
Surgery, yes	168 (89%)	338 (82%)	0.129
Simpson (surgery, yes: 168 and 338)			0.302
Grade I-III	109 (65%)	235 (70%)	
Grade IV-V	40 (24%)	68 (20%)	
Unkown	19 (11%)	35 (10%)	
Radiotherapy, yes	36 (19%)	90 (22%)	0.579

Supplemental Digital Content 5. Raw SF-36 score and EORTS QLQ-BN20 scores

Domain/component score	Meningioma patients		Informal caregivers		Normative data		Avaglio glioblastoma patients	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
SF-36								
Physical function	79	24,8	87	16.5	85	23	-	-
Role limitations physical	69	40,5	84	30.6	81	34	-	-
Bodily pain	74	25,6	80	23.9	75	24	-	-
Social function	78	24,9	89	16.6	84	23	-	-
Mental health	73	29,8	79	26.9	75	18	-	-
Role limitations emotional	77	37,3	93	22.6	81	33	-	-
Vitality	63	25,3	72	18.4	61	21	-	-
General health	65	24	72	18.7	72	20	-	-
Physical component score	47	10.9	50	8.8	50	10	-	-
Mental component score	50	11.8	55	7.4	50	10	-	-
EORTC QLQ-BN20								
Future uncertainty	21	22	-	-	-	-	32	-
Visual disorder	16	19	-	-	-	-	13	-
Motor dysfunction	12	17	-	-	-	-	16	-
Communication deficit	15	21	-	-	-	-	17	-
Headache	22	38	-	-	-	-	19	-
Seizure	2	12	-	-	-	-	4	-
Drowsiness	16	27	-	-	-	-	24	-
Hair loss	8	19	-	-	-	-	6.0	-
Itchy skin	12	25	-	-	-	-	7.2	-
Weakness of both legs	8	21	-	-	-	-	13.4	-
Bladder Control	15	24	-	-	-	-	7.9	-

Supplemental Digital Content 6. Propensity score adjusted differences between meningioma patients and controls for the SF-36 domains role limitations due to physical functioning and social functioning

	Role limitations due to physical functioning			Social functioning		
	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value
Surgery (ref. active MRI surveillance)	-12.4	(-59.7 to 35.0)	0.61	-14.5	(-44.4 to 15.5)	0.34
Radiotherapy (ref. active MRI surveillance)	-37.4	(-131.8 to 57.0)	0.38	-6.7	(-54.4 to 41.0)	0.75
Radiotherapy (ref. surgery)	-26.7	(-63.6 to 10.2)	0.16	-9.6	(-33.2 to 13.9)	0.42
Surgery + radiotherapy (ref. surgery)	-8.1	(-27.8 to -11.7)	0.42	-7.2	(-19.5 to 5.1)	0.25
Second surgery (ref. single surgery)	-0.1	(-28.5 to 28.3)	0.99	7.78	(-10.0 to 25.6)	0.39
Surgical complication (ref. no complication)	-13.4	(-27.3 to 0.6)	0.06	-3.2	(-11.5 to 5.4)	0.47

Supplemental Digital Content 7. Propensity score adjusted differences between meningioma patients and controls for the SF-36 domains role limitations due to emotional functioning, vitality and the mental component score

	Role limitations due to emotional functioning			Vitality			Mental component score		
	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value
Surgery (ref. active MRI surveillance)	6.3	(-37.4 to 49.9)	0.78	-0.2	(-24.8 to 24.4)	0.99	3.3	(-11.1 to 17.7)	0.65
Radiotherapy (ref. active MRI surveillance)	-10.4	(-92.6 to 71.8)	0.77	-5.9	(-29.3 to 17.5)	0.57	-0.5	(-14.1 to 13.0)	0.93
Radiotherapy (ref. surgery)	-16.6	(-50.6 to 17.4)	0.34	-18.3	(-37.2 to 0.7)	0.06	-4.9	(-16.1 to 6.2)	0.38
Surgery + radiotherapy (ref. surgery)	-8.6	(-26.4 to 9.2)	0.34	-2.2	(-15.1 to 10.6)	0.74	-3.6	(-9.5 to 2.2)	0.22
Second surgery (ref. single surgery)	-1.0	(-26.5 to 24.5)	0.94	-3.0	(-21.7 to 15.7)	0.75	0.1	(-8.3 to 8.6)	0.98
Surgical complication (ref. no complication)	-0.8	(-13.7 to 12.2)	0.91	0.6	(-8.2 to 9.5)	0.89	-0.3	(-4.4 to 3.8)	0.90

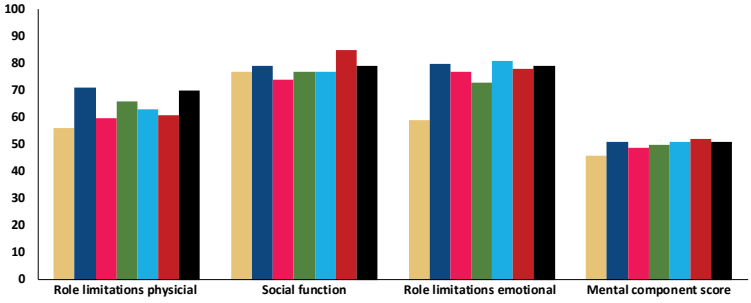
Supplemental Digital Content 8. Propensity score adjusted differences between meningioma patients and controls for the cognitive domains executive functioning, verbal memory and working memory.

	Executive functioning			Verbal Memory			Working Memory		
	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value
Radiotherapy (ref. active MRI surveillance)	-0.60	(-2.10 to 0.87)	0.42	0.08	(-0.92 to 1.09)	0.87	-0.01	(-1.59 to 1.58)	0.99
Radiotherapy (ref. active MRI surveillance)	-0.47	(-2.77 to 1.84)	0.64	-0.62	(-2.87 to 1.64)	0.54	-0.44	(-2.80 to 2.00)	0.69
Radiotherapy (ref. surgery)	-0.07	(-1.21 to 1.08)	0.91	-0.99	(-1.78 to -0.20)	0.01	-0.45	(-1.70 to 0.79)	0.47
Surgery + radiotherapy (ref. surgery)	-0.53	(-1.14 to 0.07)	0.08	-0.45	(-0.86 to -0.03)	0.03	-0.44	(-1.08 to 0.21)	0.18
Second surgery (ref. single surgery)	-0.92	(-1.78 to -0.07)	0.04	-0.66	(-1.25 to -0.08)	0.03	-0.65	(-1.59 to 0.29)	0.18
Surgical complication (ref. no complication)	-0.40	(-0.81 to 0.02)	0.06	-0.24	(-0.55 to 0.07)	0.13	-0.14	(-0.67 to 0.38)	0.59

Supplemental Digital Content 9. Propensity score adjusted differences between meningioma patients and controls for the cognitive domains attention, information processing speed and psychomotor functioning.

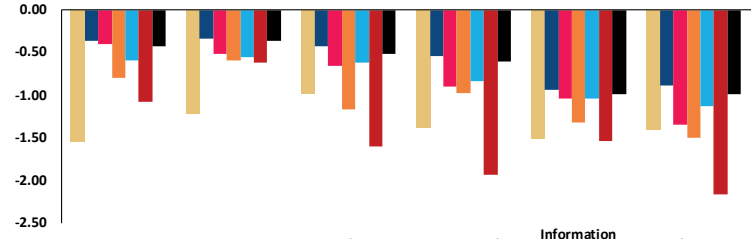
	Attention			Information processing speed			Psychomotor functioning		
	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value
Radiotherapy (ref. active MRI surveillance)	-2.04	(-4.45 to 0.36)	0.01	-0.05	(-1.08 to 0.98)	0.92	-0.21	(-1.65 to 1.24)	0.78
Radiotherapy (ref. active MRI surveillance)	-1.85	(-4.04 to 0.34)	0.09	-0.74	(-2.51 to 1.03)	0.36	-0.63	(-2.04 to 0.78)	0.33
Radiotherapy (ref. surgery)	-0.71	(-2.60 to 1.19)	0.46	-0.61	(-1.40 to 0.19)	0.13	-0.50	(-1.62 to 0.62)	0.38
Surgery + radiotherapy (ref. surgery)	-0.79	(-1.89 to 0.11)	0.08	-0.40	(-0.85 to 0.05)	0.08	-0.41	(-0.99 to 0.17)	0.16
Second surgery (ref. single surgery)	-2.11	(-3.52 to -0.71)	0.00	-0.46	(-1.12 to 0.20)	0.17	-0.34	(-1.20 to 0.52)	0.44
Surgical complication (ref. no complication)	-0.78	(-1.42 to -0.14)	0.02	-0.04	(-0.35 to 0.28)	0.83	-0.25	(-0.76 to 0.26)	0.33

Supplemental Digital Content 10. Health-related quality of life scores for different treatment strategies.



	Role limitations physicial	Social function	Role limitations emotional	Mental component score
Wait-and-scan	56	77	59	46
Primary surgery	71	79	80	51
Primary radiotherapy	60	74	77	49
Surgery plus adjuvant radiotherapy	66	77	73	50
Complication first surgery	63	77	81	51
Reresection	61	85	78	52
All patients	70	79	79	51

Supplemental Digital Content 11. Neurocognitive functioning scores for different treatment strategies.



	Executive function	Verbal memory	Working memory	Attentional function	Information processing speed	Psychomotor speed
Wait-and-scan	-1.54	-1.21	-0.98	-1.38	-1.51	-1.40
Primary surgery	-0.36	-0.33	-0.42	-0.54	-0.93	-0.88
Primary radiotherapy	-0.40	-0.52	-0.66	-0.90	-1.03	-1.34
Surgery plus adjuvant radiotherapy	-0.80	-0.59	-1.16	-0.97	-1.32	-1.50
Complication first surgery	-0.59	-0.55	-0.61	-0.83	-1.04	-1.12
Reresection	-1.08	-0.61	-1.60	-1.93	-1.53	-2.16
All patients	-0.42	-0.36	-0.52	-0.60	-0.99	-0.98

Chapter 4

The long-term caregiver burden in WHO grade I and II meningioma: it is not just the patient

Neuro-Oncology Advances, 2021;3(1):1-9

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ABSTRACT

Background

Little is known about long-term caregiver burden in meningioma patients. We assessed meningioma caregiver burden, its association with informal caregiver's well-being and possible determinants.

Methods

In this multicenter cross-sectional study, informal caregivers completed the Caregiver Burden Scale (five domains and total score). Patients completed a disease-specific health-related quality of life (HRQoL) questionnaire focusing on symptoms (EORTC QLQ-BN20) and underwent neurocognitive assessment. Both groups completed a generic HRQoL questionnaire (SF-36) and the Hospital Anxiety and Depression Scale. We assessed the association between caregiver burden and their HRQoL, anxiety and depression. Furthermore, we assessed determinants for the caregiver burden. Multivariable regression analysis was used to correct for confounders.

Results

129 informal caregivers were included (median 10 years after patients' treatment). Caregivers reported burden in ≥1 domain (35%) or total burden score (15%). A one-point increase in total caregiver burden score was associated with a clinically relevant decrease in caregiver's HRQoL (SF-36) in 5/8 domains (score range: -10.4 to -14.7) and 2/2 component scores (-3.5 to -5.9), and with more anxiety (-3.8) and depression (-3.0). Patients' lower HRQoL, increased symptom burden, and increased anxiety and depression were determinants for higher caregiver burden, but not patients' or caregivers' sociodemographic characteristics, patients' neurocognitive functioning, or tumor- and treatment-related characteristics.

Conclusions

Ten years after initial treatment, up to 35% of informal caregivers reported a clinically relevant burden, which was linked with worse HRQoL, and more anxiety and depression in both patients and caregivers, emphasizing the strong interdependent relationship. Support for meningioma caregivers is therefore warranted.

Key words

Meningioma; caregiver burden; anxiety; depression; health-related quality of life

Key Points

- 35% of meningioma informal caregivers report a clinically relevant caregiver burden
- Caregiver burden was associated with lower HRQoL and more anxiety and depression
- Caregiver support could not only benefit caregivers themselves, but also patients

Importance of the study

Previous studies have described a significant caregiver burden in caregivers of patients with neurological and oncological conditions. However, no studies have been performed to evaluate the caregiver burden in meningioma. We describe that up to 35% of informal caregivers of meningioma patients reported a clinically relevant caregiver burden, in a sample assessed at least 5 years after diagnosis and treatment. This burden was associated with significantly lower levels of HRQoL and higher levels of anxiety and depression in caregivers. Interestingly, the caregiver burden was related to the patient's HRQoL, but not determined by the patient's neurocognitive functioning, nor their sociodemographic, tumor- or treatment-related characteristics. Our results emphasize that the caregiver burden is inherently part of the chronic nature of meningioma and support for caregivers of meningioma patients is therefore needed. Further studies should be performed to identify resources to support informal caregivers. As our results show that caregiver and patient wellbeing are strongly interlinked, caregiver support could not only benefit caregivers themselves, but also patients.

INTRODUCTION

Meningioma comprises the majority of primary intracranial tumors (37%) and are classified as World Health Organization (WHO) grade I and II tumors in more than 95% of cases.[1] There has been a paucity of research on the possible long-term negative effects of tumor and treatment.[2] Recent studies, however, have reported a significant disease burden in terms of diminished health-related quality of life (HRQoL) and neurocognitive impairment after treatment.[3,4] Although no studies are published on the caregiver burden in the meningioma context, one might expect that patients' functioning and well-being may also have a noteworthy impact on informal caregivers.

Informal caregivers are often relatives or friends of patients, who deliver a substantial amount of emotional, physical and/or psychological support. While this role can be rewarding, it often also results in caregiver burden.[5] Compared with other cancer groups (e.g., lung, breast, prostate), caregivers of patients with brain tumors – particularly glioblastoma – report more severe caregiver burden and poorer HRQoL.[6,7] Previously a conceptual model of caregiver burden in primary malignant brain tumor patients, and an updated version for oncology caregiving, has been described by Sherwood et al.[5,8] According to this model the patient disease characteristics (including tumor, treatment, functional, cognitive and neuropsychiatric status) alongside caregiver personal characteristics (e.g., personal or social attributes) impact on caregiver psychological and behavioral responses, including caregiver burden. These may trigger biologic responses and affect caregivers' overall health and wellbeing (e.g. HRQoL).[5,8]

A multitude of determinants of caregiver burden have been reported, which vary considerably between different patient groups (e.g., malignant brain tumors, stroke), but comprise both patient and informal caregiver characteristics, including age, sex and comorbidities.[7,9] However, the severity of the caregiver burden as well as the determinants of burden may be different in caregivers of meningioma patients, who generally have a better life-expectancy and fewer neurological deficits compared with patients with malignant brain tumors (e.g. glioblastoma) or stroke. In addition, treatment regimens differ significantly between groups, and therefore not only the disease but also the long-term effects of its treatment might differently affect caregivers[1,10]

The primary aim of this study was to assess the long-term caregiver burden of informal caregivers. Furthermore, we investigated the association between caregiver burden and caregivers' HRQoL, and levels of anxiety and depression. We also assessed determinants for caregiver burden in terms of caregiver's and patients' sociodemographic characteristics, patients' clinical characteristics, tumor- and treatment-related characteristics, HRQoL, anxiety and depression scores, and level of neurocognitive functioning. Better knowledge of caregiver burden and its

determinants can be used in clinical practice to guide caregivers, to relieve their burden and to support them in caring for the patient, which might improve outcomes of not only informal caregivers, but also patients.

METHODS

Participants

Patients and caregivers were invited to participate in a multicenter quantitative cross-sectional study on the long-term disease burden of meningioma patients and caregiver burden of their informal caregivers.[11] Patients and informal caregivers who were 18 years or older with sufficient mastery of Dutch were recruited between July 2016 and April 2019. Patients were recruited at least five years after their last anti-tumor treatment, or in case of a wait-and-scan follow-up at least five years after meningioma diagnosis. Patients were excluded if diagnosed with neurodegenerative disease, neurofibromatosis type II, or who had a history of whole brain radiotherapy. Informal caregivers were eligible for participation if they were a spouse, family member or close friend to the patient, and provided the majority of physical, emotional and/or social support to the patient. Detailed study procedures are described in the main report.[11]

Procedures

Questionnaires

On the same day, neurocognitive tests were administered in person by a research assistant, structured interviews conducted, and questionnaires were completed on paper. Informal caregivers completed the Caregiver Burden Scale (CBS), which is a 22-item questionnaire measuring caregiver burden in five domains: stress, social isolation, feeling of disappointment, emotional problems and problems due to environmental factors.[12,13] Each of the 22 items is scored on a 4-point Likert scale (ranging from 1=never to 4=nearly always) and items within a domain are averaged to obtain the domain score. The average of the domain scores reflects the total caregiver burden score.[12,13] For dichotomous analysis, CBS domain and total scores were classified into low burden (scores: 1 - 1.9) and medium/high burden (scores ≥2). Both patients and informal caregivers completed a generic HRQoL instrument, the Short-Form Health Survey (SF-36), ranging from 0 to 100 with higher scores indicating better HRQoL.[14,15] The SF-36 is the most frequently used HRQoL instrument in meningioma patients.[2] Patients additionally completed the European Organisation for Research and Treatment of Cancer quality of life questionnaire, brain neoplasm (EORTC QLQ-BN20) module to specifically measures brain tumor-specific symptoms as part of HRQoL measurement, ranging from 0 to 100 with higher scores indicating worse HRQoL.[16,17] Both groups also completed the Hospital Anxiety and Depression Scale (HADS), for which clinically relevant cut-offs exist for individual patients: mild (0-7), moderate (8-10) and severe (11-21) anxiety or depression.[18,19] All

questionnaires are validated in Dutch and further details, including references, are presented in Supplemental Table 1.

Neuropsychological assessment of meningioma patients

A frequently used comprehensive battery of neuropsychological tests was administered to patients by trained research assistants and consisted of the Concept Shifting Test, Auditory Verbal Learning Test, Categoric Word Fluency Test, Memory Comparison Test, Digit-Symbol Substitution Test, and the Stroop Colour-Word Test.[20] Based on these tests, scores for the following neurocognitive domains, which are relevant for meningioma patients, were calculated: verbal memory, executive functioning, psychomotor functioning, working memory, information processing speed, and attention (Supplemental Table 1).[21]

Clinically relevant cut-offs

We used clinically relevant cut-offs, based on established minimal clinically important differences (MCID) as reported in the literature. For the CBS this was set on 1 point, based on the previously published cut-offs (low burden: 1-1.9, medium burden 2-2.9, high burden: 3.0-4.0).[13] Cut-off for the SF-36 domains was set at 10 points, as the majority of published studies reported MCID's for the different domains lower than 10 points.[22] For the SF-36 mental and physical component scored, cut-offs were set at 4.6 points and 3.0 points, respectively.[23] The cut-off for the HADS anxiety and depression scale were set at 2.0 points, as most studies report MCIDs lower than 2.0.[24,25] For calculation of Z-scores of patient's neurocognitive domains, means and standard deviations from a reference sample from the Dutch Maastricht Aging Study (MAAS) were used, matched on group-level for age, sex and educational level.[26] Per domain, differences in z-scores greater than

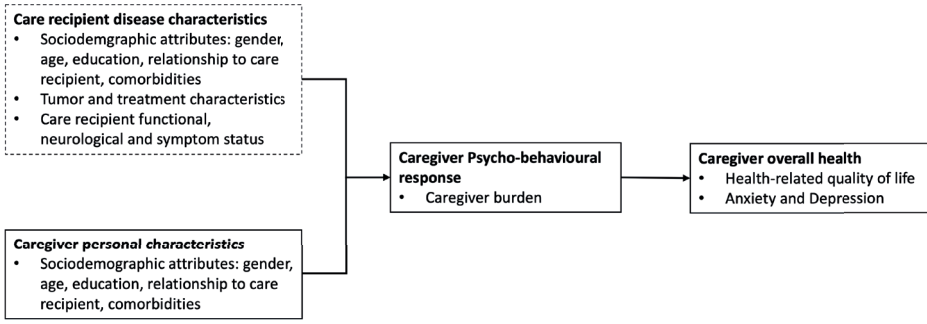
-1.5 were considered clinically relevant.[27] MAAS is a large longitudinal study among the general Dutch population on the psychological and biological determinants of cognitive aging with reference data for all used tests.

Statistical analysis

Conceptual model

Based on our previous focus groups with meningioma patients and caregivers, we adapted Sherwood's conceptual model of caregiver burden in primary malignant brain tumors and used it to guide the evaluated associations (Figure 1)[5,8]. Although originally developed for patients with malignant brain tumors, this conceptual model is with small adaptations an excellent fit for the meningioma patient-caregiver population[5].

Figure 1: Adapted conceptual model for meningioma caregiving, based on Sherwood et al.



Association between the caregiver burden and caregiver well-being

Separate multivariable regression analyses were performed to assess the association between total Caregiver Burden Scale score (independent variable) and informal caregiver's HRQoL (SF-36), and levels of anxiety and depression as measured with the HADS (dependent variables). For these analyses, clinically relevant cut-offs as described above were used to interpret the impact of the total caregiver burden score on the outcomes (i.e. SF-36 and HADS).

Associations between determinants and the caregiver burden

Next, separate multivariable regression analyses were performed to assess the association between each potential patient determinant (independent variables) and the total Caregiver Burden Scale score (dependent variable). Based on the literature and Sherwood's conceptual model for caregiver burden in neuro-oncology, we hypothesized the following variables to be possible determinants: caregiver demographic characteristics (sex, age, Charlson Comorbidity Index, education level, relationship) patient demographic and clinical characteristics (sex, age, Charlson Comorbidity Index, education level, KPS), tumor and treatment characteristics (tumor location (convexity/skull base), tumor size before intervention (largest diameter), baseline tumor size (largest diameter), surgery (yes/no), surgical complications (yes/no), Simpson grade (I-V), WHO Grade (I-II), radiotherapy (yes/no)), time since diagnosis in years, patients' HRQoL as expressed with the mental and physical component scores (SF-36), level of anxiety and depression (HADS), neurocognitive impairment (clinically relevant impairment in any of the 6 domains), and the number of experienced brain-tumor related HRQoL symptoms (scales dichotomized: not at all vs. a little, quite a bit, or very much problems) as measured with the EORTC QLQ-BN20.[5,9,28,29]

To assess how the independent variables contribute to the total caregiver burden score, the explained variance (R^2) from univariable analysis was used, describing the percentage that each variable explains the total caregiver burden score. For analysis modeling multiple variables

simultaneously, the adjusted R^2 was used, correcting for overprediction due to the presence of multiple variables within the same analysis.

Correction for confounding

All multivariable analyses were corrected for confounders, which means that in addition to the independent variable, we included in each model variables defined as confounders specific for the assessed association to approximate the causal association between the dependent and independent variable.[30–32] Confounders were identified using the Directed Acyclic Graph representation (see Supplemental Figure 1 for examples), defined as being associated with both the determinant and the outcome, but not in the causal path of the association, based on prior clinical knowledge.[30–32]

Ethics committee approval

This cross-sectional study was approved by the medical ethical committees of all participating centers (NL54866.029.15), and participants provided informed consent before study procedures.

RESULTS

A total of 190 meningioma patients were recruited to the original study, of whom 61 indicated to not have an informal caregiver willing to participate in the study. Therefore 129 informal caregivers with a mean age of 61.3 years (SD 13.5), and 129 meningioma patients with a mean age 62.7 (SD 11.7) were included in the described analyses. Median follow-up length since patient diagnosis was 10 years (IQR: 8-12) (Table 1 and Supplemental Table 2). Most informal caregivers were male (n=82, 63%), while most patients were female (n=98, 76%). The majority of informal caregivers were patients' partners (n=105, 81%). Most patients were operated for their meningioma (n=113, 87%) of whom 104 (92%) patients were diagnosed with a WHO grade I meningioma. Primary radiotherapy was limited to 6 (5%) patients and 18 (14%) received adjuvant radiotherapy (Supplemental Table 2).

Caregiver burden

Informal caregivers reported medium/high caregiver burden in at least one domain of the Caregiver Burden Scale in 44 (34%) cases, and on the total score in 19 (15%) cases. More specifically, 26 (20%) caregivers suffered from stress, 16 (12%) from social isolation, 17 (13%) from feelings of disappointment, 25 (19%) from emotional problems, and 16 (12%) from environmental factors complicating the care for the patient. Caregiver Burden Scale scores were similar comparing partners (mean 1.5, SD 0.4) with other relatives (1.4, SD 0.4; (p=0.274), and different types of caregivers were therefore combined in all further analyses. Uncorrected and untransformed outcome measures are presented in Supplemental Table 3 and 4.

Table 1: Sociodemographic and clinical characteristics of informal caregivers and meningioma patients

	Informal caregivers (n=129)	Meningioma Patients (n=129)
Age, years	62.7 (SD 11.7)	61.3 (SD 13.5)
Female	47 (36.4%)	98 (76%)
Relationship with the patient		
Partner	105 (81%)	
Child	11 (9%)	
Friend	6 (5%)	
Sibling	5 (4%)	
Parent	2 (2%)	
Education level		
Primary/Secondary	14 (11%)	25 (19%)
Tertiary: technical/vocational	55 (43%)	60 (47%)
Academic	54 (42%)	40 (31%)
Missing	6 (5%)	4 (3%)
Charlson Comorbidity Index		
1≥	36 (28%)	44 (34%)

N=number, SD=standard deviation

Association between caregiver burden and caregiver HRQoL, anxiety and depression

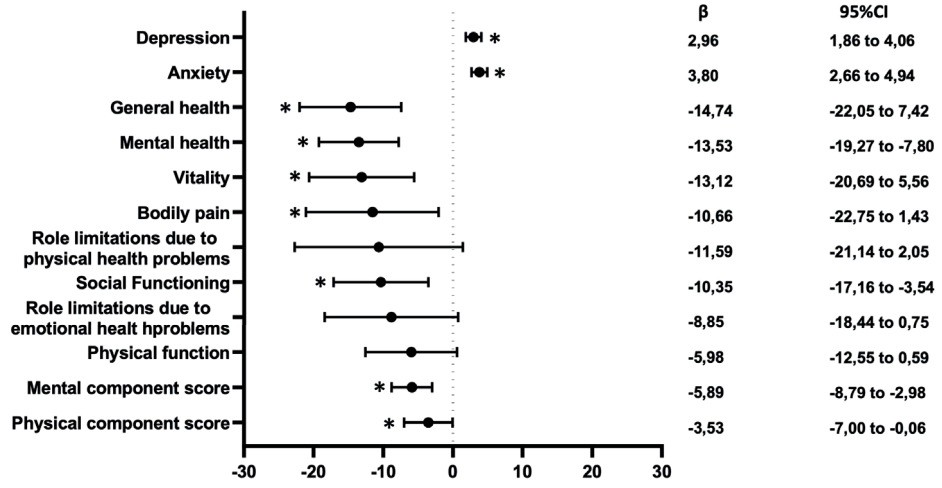
A one point increase in the total caregiver burden score (range 1-4) was significantly associated with clinically relevant worse HRQoL (SF-36) on 5/8 scales and 2/2 component scores, Figure 2: bodily pain (β=-12.1, 95%CI: -22.8 to -1.4), social function (β=-10.4, 95%CI: -17.2 to -3.5), mental health (β=-13.5, 95%CI: -19.3 to -7.8), vitality (β=-13.1, 95%CI: -20.7 to -5.6), general health (β=-14.7, 95%CI: -22.1 to -7.4), physical component score (β=-3.5, 95%CI: -7.0 to -0.1), and mental component score (β=-5.9, 95%CI: -8.8 to -3.0). Furthermore, a one-point increase in the total caregiver burden score was significantly associated with clinically relevant higher anxiety (β=3.8, 95%CI: 2.7 to 4.9) and depression levels (β=3.0, 95%CI: 1.9 to 4.1), as measured with the HADS.

Determinants for caregiver burden

Patients' HRQoL (SF-36) was significantly associated with the total caregiver burden scale score for both the physical component score (β: -0.015, 95%CI -0.025 to -0.005, R^2=9.1%) and mental component score (β: -0.017, 95%CI -0.090 to 0.000, R^2=20.4%). The number of symptoms (EORTC QLQ-BN20) patients experience was also significantly associated with the total caregiver burden scale score (β: 0.081, 95%CI 0.014 to 0.149, R^2=7.3%). The symptom most often reported by patients was future uncertainty (71% of patients, Supplemental Table 4). Furthermore, both patient anxiety (β: 0.042, 95%CI 0.020 to 0.065) and depression (HADS,

β: 0.051, 95%CI 0.031 to 0.072) were significantly associated with and contributed greatly to the total caregiver burden score, respectively 27.8% and 14.3%. Patients' neurocognitive function, sociodemographic or clinical characteristics, and tumor and treatment characteristics were not associated with caregiver burden (Supplemental Table 5). Indeed, patient's sociodemographic and clinical characteristics (age, sex, KPS, education level, Charlson Comorbidity Index) only contributed between 0.3% and 6.0% to the caregiver burden score, and tumor and treatment characteristics (i.e., tumor location, length of follow-up, received anti-tumor treatment, tumor size, WHO grade, and Simpson grade in case of surgery) between 0.1% and 2.2% to the total caregiver burden score (Supplemental Table 5). Aspects as measured with the self-report questionnaires (SF-36, EORTC QLQ-BN20, HADS) contributed 43.8% of caregiver burden, which raised to 65.4% with the addition of patient's sociodemographic and clinical characteristics, and tumor and treatment characteristics (Table 2). Caregiver sociodemographic characteristics were poorly associated with the caregiver burden.

Figure 2. The relation between caregiver burden and caregiver's level of depression, anxiety and health-related quality of life.



A higher caregiver burden was related to more depression and anxiety (represented with positive values) and lower health-related quality of life (represented with negative values). For each outcome a separate multivariable regression analysis was performed to estimate a regression coefficient corrected for confounders (age, sex, education level, comorbidities) and presented with the 95% confidence intervals. Associations are significant when not crossing the dotted line, and are depicted with *. R^2 represent the explained variance regarding the total burden by each variable in univariable analysis.

DISCUSSION

This is the first, and therefore explorative study to assess caregiver burden specifically in meningioma, a population of patients and caregivers in a chronic setting who often have to deal with permanent sequalae and impairments.[11] A median of 10 years after the last meningioma intervention, up to 35% of caregivers reported caregiver burden in any domain and

Table 2: Explained variance of the total Caregiver Burden Scale score by patient variables

Variable(s)	R^2 adjusted (explained variance)
Patient sociodemographic characteristics	3.8%
Caregiver sociodemographic characteristics	2.3%
Tumor and treatment characteristics	1.1%
Neurocognitive functioning	3.3%
Anxiety and depression (HADS)	28.0%
General HRQoL (SF-36)	34.5%
Brain tumor specific symptoms (EORTC QLQ-BN20)	27.7%
Anxiety and Depression + General HRQoL + Brain tumor-specific symptoms	43.8%
Neurocognitive functioning + Anxiety and Depression + General HRQoL + Brain tumor-specific symptoms	47.4%
Patient characteristics + Neurocognitive functioning + Anxiety and Depression + General HRQoL + Brain tumor-specific symptoms	50.7%
Tumor and treatment characteristics + Neurocognitive functioning + Anxiety and Depression + General HRQoL + Brain tumor-specific symptoms	53.8%
Patient characteristics + Tumor and treatment characteristics + Neurocognitive functioning + Anxiety and Depression + General HRQoL + Brain tumor-specific symptoms	65.4%

15% reported overall caregiver burden. Higher caregiver burden was associated with lower HRQoL, and higher levels of anxiety and depression in informal caregivers. Determinants for caregiver burden were patients' generic HRQoL and disease-specific HRQoL focusing on brain tumor symptoms, and levels of anxiety and depression, but not patients' or caregivers' sociodemographic characteristics, patients' level of neurocognitive functioning, or tumor- and treatment-related characteristics.

Clinical implications: caregiver burden

Compared with other patient groups (Table 3), the average total meningioma Caregiver Burden Scale score at a median of 10 years post-diagnosis tends to be higher than caregiver burden in patients with traumatic brain injury, epilepsy, Parkinson's disease, multiple sclerosis, and lung cancer, but lower than the caregiver burden in stroke, dementia, and dialysis, most likely related to the severity of the disease of the patient.[12,13,33–39] Although some of these scores were fairly similar and therefore differences between scores not always clinically relevant. Higher caregiver burden was found to be strongly associated with a lower HRQoL and more anxiety and depression in meningioma informal caregivers. In contrast to studies in glioma patients and patients with stroke, we did not find that sociodemographic characteristics of patients were related to caregiver burden.[7,9] Also surprisingly, tumor- and treatment-related characteristics, such as the need for additional radiotherapy and reoperation, were not related to caregiver burden in this study. The differences between our results and the reported results in the literature

in other patient groups might be explained by the fact that meningioma patients tend to have fewer complications of disease and treatment.[2] Furthermore, differences in follow-up length might affect both the disease burden of patients as well as the associated caregiver burden.[11] In the short-term, patients primarily suffer from physical impairments, while in the long-term role limitations become more prominent.[2,3,11] Informal caregivers might also adapt to their role as caregiver or might face new challenges in taking care of their loved ones, as shown in a study with informal caregivers of stroke patients 5 years after stoke.[40] Our results suggest that the current well-being of the patient is most strongly related to caregiver burden, emphasizing the strong interdependent relationship between caregiver and patient wellbeing. Similar relationships were previously demonstrated in high-grade glioma patient-caregiver dyads and described in Sherwood's conceptual model of caregiver burden in primary malignant brain tumors and the updated version for oncology caregiving. [75,8] Furthermore, other studies suggest that worse neurocognitive status of glioma patients or elderly is related to higher caregiver burden.[41,42]

Table 3: Caregiver Burden in meningioma and other diseases

Author year	Patient group	Caregiver burden, mean	Follow-up length, mean or median
Current study	Meningioma	1.4	10 years
Elmståhl (1996)[12]	Stroke	1.7-2.0	3 years
Belasco (2006) [35]	Dialysis	2.1	2-4 years
Andrén (2007)[13]	Dementia	2.1	Not reported
Martinez-Martin (2007)[36]	Parkinson's disease	1.2*	Not reported
Rivera-Navarro (2009)[37]	Multiple Sclerosis	1.0*	9 years
Pagnini (2010)[38]	Amyotrophic lateral sclerosis	0.9*	2 years
Manskow (2015)[33]	Traumatic Brain Injury	1.0	1 year
Karakis (2014)[39]	Epilepsy	0.9*	16 years
Tan (2018)[34]	Lung Cancer	1.1	Not repoted

* Original values as reported by the authors were transformed to the scale used in the current study, as different versions and scales exist of the Caregiver Burden Scale.

Clinical implications: providing support for informal caregivers

Apart from supportive care for patients, which may help to decrease caregiver burden, informal caregivers' needs should also be addressed by healthcare providers, as it enables them to provide the needed care for their loved ones.[43] A recent Cochrane systematic review summarizing eight intervention studies (e.g., support based on cognitive behavioural therapy; psychoeducation; cognitive rehabilitation) aimed at improving caregiver wellbeing in those taking care of a patient with a brain or spinal cord tumor, showed some evidence for positive effects of caregiver support on caregiver distress, mastery, and HRQoL, but no effect on caregiver burden.[44] However, in other patient groups psychoeducation programs have proven to decrease caregiver burden and depression, and improve caregiver general well-being.[45,46] Importantly, none of

the trials included were focused on caregivers of meningioma patients, highlighting that much work is still needed in this area. This was confirmed in recent focus group studies by our groups and another group with meningioma patients and their informal caregivers, which, showed that current care trajectories have minimal focus on the needs of caregivers and most caregivers received no caregiver support.[47,48]

Limitations

A limitation of this study is the cross-sectional study design, hampering assessment of causal relationships and the direct, possibly transient effects, of tumor and treatment on the outcomes. Similarly, we cannot exclude that the reported results might be affected by reverse causation, however most published studies in the literature as well as Sherwood's conceptual framework report the impact of the caregiver burden on their well-being and HRQoL, and not vice versa.[7,39] Another limitation of this study might be some degree of selection bias, in that informal caregivers with a high burden might be too distressed to participate in these studies or might actually participate in these studies as they have a strong relationship with the patient. Furthermore, our sample size could be considered relatively small, especially regarding certain statistical analyses, such as on determinants for the caregiver burden. Also, by using an existing instrument, it is possible that we have failed to measure aspects of caregiver burden that may be relevant in the meningioma setting, which are not covered by this instrument. Similarly, the SF-36 and EORTC QLQ-BN20 are not developed for meningioma patients, and hence might miss items relevant for this patient group. Nevertheless, we chose these instruments as they are often used in meningioma research to measure generic and disease-specific HRQoL[2,49] Finally, there is no clear consensus on the exact MCIDs used for some of the used PROMs. A MCID can be estimated through different distribution and anchor based methods, which might results in different MCIDs.[50] For this study we preferred the use of clinically relevant cut-offs based on MCIDs calculated using anchor based methods, as these MCIDs ensure clinical relevance.[50] Furthermore, if multiple MCIDs were reported in the literature, preference was given to more conservative cut-offs to prevent reporting of marginally clinically relevant outcomes.

Conclusions

Even 5 years after the last intervention, one out of three informal caregivers still experienced a caregiver burden that also decreased their own HRQoL and increased their feelings of anxiety and depression, emphasizing that caregiver burden is inherently a part of the chronic nature of meningioma. Findings of this study warrant especially attention for those caregivers who take care of patients who experience a lower HRQoL, and more anxiety and depression. Further high-quality studies should be performed to identify supportive care resources for patients and caregivers and the impact of these resources on patient and caregiver HRQoL, as well as caregiver burden. Ideally these studies involve both patients and their informal caregivers, as we showed that the disease burden is strongly interlinked with the caregiver burden in the chronic

care setting. Information on the effectiveness of supportive care resources helps to increase structural funding for these resources and is even needed in some countries for reimbursement by health care insurances. Indeed, previous qualitative studies showed a large unmet need regarding supportive care in the chronic care setting.[47,48]

Funding:

No funding was received for this study.

Conflict of interest:

The authors report no conflict of interest

Authorship:

LD, FWB, and SMP designed the study. Data collection was performed by AHZN and PBvdM. AHZN performed data analysis with input from LD. AHZN wrote the first and successive versions of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the drafts of the paper, and approved the final version. AHZN had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Prior presentations:

Parts of the results described in this manuscript were presented at the 2018 Society for Neuro-Oncology (SNO) conference in New-Orleans (Louisiana, USA) as an oral presentation on 17 November 2018. In addition, parts of the results were presented at the 2018 European Association of Neuro-Oncology (EANO) conference in Stockholm (Sweden) as an oral presentation on 13 October 2018.

Acknowledgements:

We would like to acknowledge the research nurses of the LUMC/HMC Neurosurgery department for their help with the data collection.

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SUPPLEMENTS

Supplemental Table 1: Outcome measures used in this study: questionnaires and neuropsychological test

	Explanation	Patients	Caregivers
Caregiver Burden			
Caregiver Burden Scale Score(1,2)	Informal caregivers completed the self-report version of the Caregiver Burden Scale (CBS), which is a 22-item questionnaire measuring caregiver burden in five domains: stress, social isolation, feeling of disappointment, emotional problems and problems due to environmental factors. (14) Each of the 22 items is scored on a 4-point Likert scale (ranging from 1=never to 4=nearly always) and items within a domain are averaged to obtain the domain score. The average of the domain scores reflects the total caregiver burden score.	No	yes
Health-related quality of life questionnaires			
Medical Outcomes Study (MOS) Short-Form Health Survey (SF-36)(3–5)	The SF-36 is a self-report questionnaire and is composed of 36 items, organized into eight multi-item scales assessing physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. The SF-36 also yields two higher order component scores, one for Physical Health (PCS) and one for Mental Health (MCS). Higher scores represent better HRQoL.	yes	yes
European Organisation for Research and Treatment of Cancer quality of life questionnaire, brain specific submodule (EORTC QLQ-BN20)(6,7)	This questionnaire comprises four multi-item scales (future uncertainty, visual disorders, motor dysfunction and communication deficit) and seven single items covering other symptoms. Higher scores represent lower HRQoL.	yes	no
Anxiety and Depression			
Hospital Anxiety and Depression Scale (HADS)(8,9)	This patient-reported outcome measure comprises 14 items; seven of the items are related to anxiety and seven items to depression. Total scores for both anxiety and depression range from 0 to 21 and are classified into no (scores: 0-7), borderline (scores: 8-10) and severe anxiety or depression (scores: 11-21).	yes	yes
Neurocognitive Tests(10–12)	**Neurocognitive Domains**		**Controls**
Auditory Verbal Learning Test (AVLT)	Verbal memory	yes	yes
Concept Shifting Test (CST)	Executive functioning and psychomotor functioning	yes	yes
Memory Comparison Test (MCT)	Working memory	yes	yes
Categoric Word Fluency Test (CWFT)	Executive functioning	yes	yes

Supplemental Table 1: Outcome measures used in this study: questionnaires and neuropsychological test (continued)

	Explanation	Patients	Caregivers
Digit-Symbol Substitution Test (DSTT)	Information processing speed	yes	yes
Stroop Colour-Word Test (SCWT)	Attention	yes	yes

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Supplemental Table 2: Sociodemographic and clinical characteristics of the included meningioma patients

	Meningioma patients (n=129)
Age, years	61.3 (SD 13.5)
Female	98 (76%)
Meningioma Location	
Skull base	66 (51%)
Convexity	60 (47%)
Optic nerve sheath meningioma	3 (2%)
Time since first symptoms, years	10.7 (IQR 8.1 – 14.7)
Time since diagnosis, years	9.6 (IQR 7.6 – 12.4)
Tumor size before intervention, mm	38.2 (SD 17.4)
Tumor size before study, mm	9.3 (SD 13.1)
Tumor growth on last MRI before study	7 (5%)
Number of meningiomas	
≥2	16 (12%)
Active MRI surveillance	11 (9%
Surgery as initial treatment	113 (87%)
Complication first surgery (operated patients: n=113)	42 (37%)
Second surgery	9 (7%)
Third surgery	1 (1%)
Time since first surgery, years	8.9 (IQR 7.0-12.0)
Simpson Grade (operated patients: n=113)	
Grade I-III	70 (62%)
Grade IV-V	30 (27%)
Unknown	13 (10%)
WHO grade (operated patients: n=113)	
Grade I	104 (92%)
Grade II	7 (7%)
Unknown	2 (2%)
Radiotherapy	
Radiotherapy as initial treatment	6 (5%)
Adjuvant radiotherapy	18 (14%)
Time since radiotherapy, years	6.8 (IQR: 5.6 – 8.5)
Complications of radiotherapy (radiotherapy treatment: n=24)	2 (8%)
Karnofsky Performance Status at time of study	100 (90-100)
Self-reported cognitive deficit at time of study	63 (49%)
Self-reported motor deficit at time of study	35 (27%)
Seizures in the last three months before study	7 (5%)
Antiepileptic drug use at any moment during the care trajectory	56 (43%)
Dexamethasone use for symptoms at any moment during the care trajectory	14 (11%)
Physical rehabilitation	25 (19%)

Supplemental Table 2: Sociodemographic and clinical characteristics of the included meningioma patients (continued)

	Meningioma patients (n=129)
Cognitive rehabilitation	5 (4%)
Psychological support	14 (11%)
Other supportive care	7 (5%)
Education level	
Primary/Secondary	25 (19%)
Tertiary: technical/vocational	60 (47%)
Academic	40 (31%)
Not provided	4 (3%)
Charlson Comorbidity Index	
1≥	44 (34%)

Supplemental Table 3: raw scores of the Caregiver Burden Scale, SF-36, EORTC QLQ-BN20 and HADS

Domain/component score	Meningioma patients	Informal caregivers
	Mean (SD)	Mean (SD)
Caregiver Burden Scale scores (range: 0-4)		
Stress	-	1.55 (0.56)
Social isolation	-	1.33 (0.56)
Feelings from disappointment	-	1.33 (0.48)
Emotional problems	-	1.41 (0.58)
Environmental factors complications care for the patients	-	1.31 (0.46)
Total score	-	1.42 (0.43)
SF-36 (range: 0-100)		
Physical function	82 (23)	87 (17)
Role limitations due to physical health problems	74 (37)	80 (24)
Bodily pain	78 (24)	89 (17)
Social function	83 (22)	79 (27)
Mental health	74 (28)	93 (23)
Role limitations due to emotional health problems	81 (34)	72 (18)
Vitality	65 (26)	72 (19)
General health	67 (23)	50 (9)
Physical component score	48 (10)	55 (7)
Mental component score	52 (11)	55 (7)
EORTC QLQ-BN20 (range: 0-100)		
Future uncertainty	18 (20)	-
Visual disorder	14 (19)	-
Motor dysfunction	11 (16)	-
Communication deficit	13 (19)	-
Headache	16 (26)	-
Seizure	3 (13)	-
Drowsiness	14 (24)	-
Hair loss	6 (17)	-
Itchy skin	16 (25)	-
Weakness of both legs	7 (21)	-
Bladder Control	15 (23)	-
HADS (range: 0-21)		
Anxiety, mean (SD)	4.4 (3.8)	3.1 (3.2)
Depression, mean (SD)	3.1 (3.8)	1.9 (2.8)

Supplemental Table 4: categorized outcomes of the Caregiver Burden Scale, EORTC QLQ-BN20, HADS, and neuropsychological tests

Domain/component score	Meningioma patients (N=129)	Informal caregivers (N=129)
	N (%)	N (%)
Caregiver Burden Scale scores (range: 0-4)		
Stress	-	26 (20%)
Social isolation	-	16 (12%)
Feelings from disappointment	-	17 (13%)
Emotional problems	-	25 (19%)
Environmental factors complications care for the patients	-	16 (12%)
Total score	-	19 (15%)
EORTC QLQ-BN20 (range: 0-100)		
Future uncertainty	92 (71%)	-
Visual disorder	68 (53%)	-
Motor dysfunction	59 (46%)	-
Communication deficit	63 (49%)	-
Headache	44 (34%)	-
Seizure	7 (5%)	-
Drowsiness	39 (30%)	-
Hair loss	18 (14%)	-
Itchy skin	44 (34%)	-
Weakness of both legs	15 (12%)	-
Bladder Control	44 (34%)	-
HADS (range: 0-21)		
Anxiety		
Mild (0-7)	103 (80%)	114 (89%)
Moderate (8-10)	12 (9%)	8 (6%)
Severe (11-21)	12 (9%)	4 (3%)
Missing	2 (2%)	3 (2%)
Depression		
Mild (0-7)	107 (83%)	119 (92%)
Moderate (8-10)	9 (7%)	4 (3%)
Severe (11-21)	8 (6%)	2 (2%)
Missing	5 (4%)	4 (3%)
Neurocognitive domains		
Verbal memory	12 (9%)	
Working memory	16 (12%)	
Executive function	19 (15%)	
Psychomotor speed	21 (16%)	
Attentional function	26 (19%)	
Information processing speed	30 (23%)	
Deficits in at least one domain	46 (36%)	

Supplemental Table 5: Association between patient and caregiver determinants and caregiver burden, corrected for possible confounders

	Beta	Lower bound 95%CI	Upper bound 95%CI	p-value	R^2	Confounders included in multivariable analysis
Caregiver sociodemographic characteristics						
Sex, female (ref: male)	0.102	-0.068	0.272	0.237	1.1%	age
Age	0.001	-0.005	0.007	0.772	0%	gender
CCI	0.001	-0.063	0.065	0.976	0%	age, gender, education
Education	-0.064	-0.181	0.053	0.284	1.0%	age, gender
Relationship, other (ref: partner)	0.083	-0.164	0.331	0.507	0.9%	age, gender
Patient sociodemographic characteristics						
Sex, female (ref: male)	-0,055	-0,238	0,127	0,550	0.3%	age
Age	0,002	-0,005	0,009	0,561	0.2%	gender
CCI	0,013	-0,056	0,082	0,708	0.2%	age, gender, education
Education	0,016	-0,096	0,129	0,775	0.1%	age, gender
KPS	-0,018	-0,030	-0,005	0,005	6.0%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy
Tumor and treatment characteristics						
Skull base (ref: convexity)*	0,064	-0,102	0,230	0,446	0.3%	age, gender
Tumor size before intervention	0,001	-0,004	0,006	0,727	0.1%	age, gender
Tumor size before study	0,005	-0,006	0,017	0,373	2.2%	age, gender, simpson grade, radiotherapy
Surgery yes	-0,020	-0,398	0,385	0,917	0.3%	age, convexity/skull base, tumor size before intervention, cci
Surgical complications	-0,020	-0,209	0,169	0,834	0.4%	age, convexity/skull base, tumor size before intervention, cci
Simpson grade first resection	-0,175	-0,518	0,169	0,315	0.2%	age, convexity/skull base, simpson grade, cci
WHO_Grade	0,126	-0,193	0,445	0,435	0.7%	age, convexity/skull base, tumor size before intervention
Radiotherapy	0,016	-0,228	0,259	0.898	0.1%	age, convexity/skull base, simpson grade, cci
Time since diagnosis, years	-0,016	-0,037	0,006	0,154	1.7%	None
Neurocognitive functioning (z-scores)						

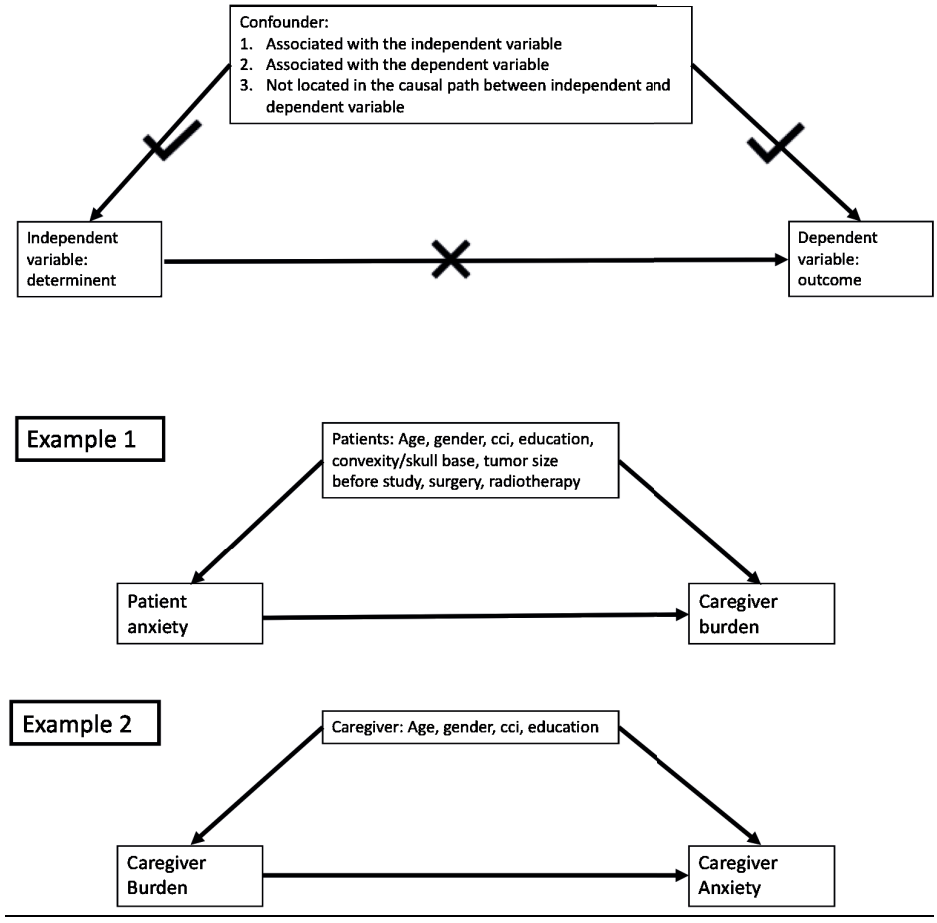
Supplemental Table 5: Association between patient and caregiver determinants and caregiver burden, corrected for possible confounders (continued)

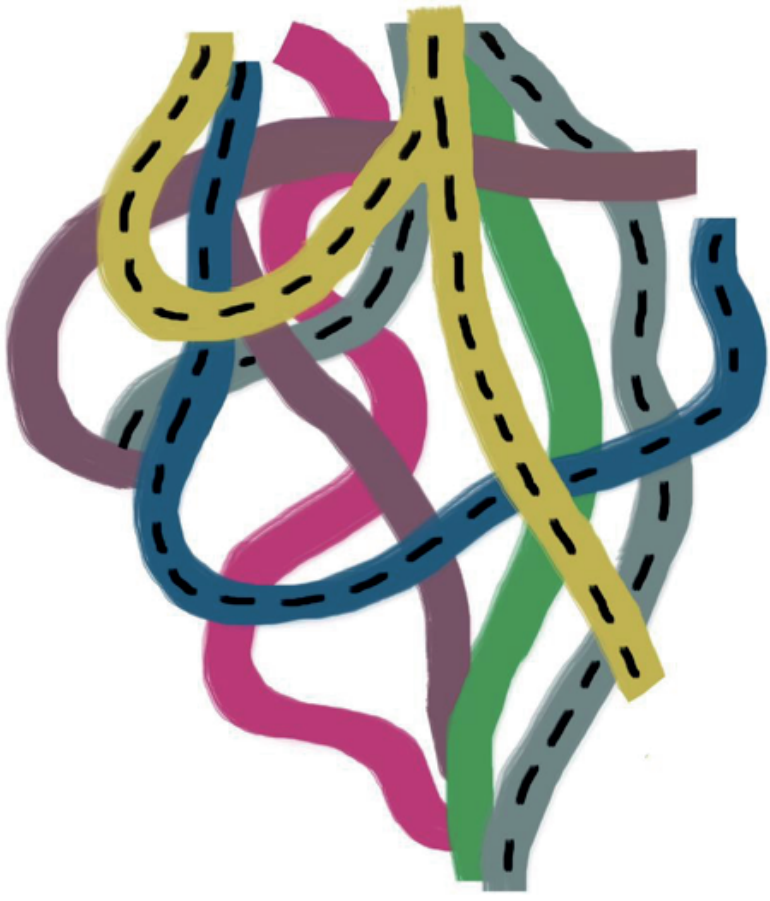
	Beta	Lower bound 95%CI	Upper bound 95%CI	p-value	R^2	Confounders included in multivariable analysis
Neurocognitive impairment in any domain	0.126	-0.077	.328	0.220	3.0%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy
Anxiety and depression						
Anxiety	0,042	0,020	0,065	0,000	14.3%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy
Depression	0,051	0,031	0,072	0,000	27.8%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy, KPS
SF-36						
Physical component score	-0,015	-0,025	-0,005	0,003	9.1%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy
Mental component score	-0,017	-0,025	-0,090	0,000	20.4%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy
EORTC QLQ-BN20						
Number of symptoms	0.081	0.014	0.149	0.019	7.3%	age, gender, cci, education, convexity/skull base, tumor size before study, surgery, radiotherapy

CCI=Charlson Comorbidity Index, KPS=Karnofsky Performance Score

*For the analyses on the association between tumor location and caregiver burden, we only compared patients with convexity and skull base meningioma, excluding patients with optic nerve sheath meningioma.

Supplemental Figure 1: Visual representation of Directed Acyclic Graphs for theoretical identification of confounders, including two examples





Chapter 5

Unmet needs and recommendations to improve meningioma care through patient, partner, and health care provider input: a mixed-method study

Neuro-Oncology Practice, 2020; 7(2): 239-248

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ABSTRACT

Background

It has been suggested that lack of ongoing registration of patient-centred outcomes resulted in existing care trajectories that have not been optimized for sequelae experienced by meningioma patients. This study aimed to evaluate the structure of current meningioma care and identify issues and potential high impact improvement initiatives.

Methods

Using the grounded theory approach, a thematic framework was constructed based on the Dutch Comprehensive Cancer Organisation survey about issues in meningioma care trajectories. This framework was used during three semi-structured interviews and two focus groups with patient-partner dyads (n=16 participants), and two focus groups with healthcare providers (n=11 participants), to assess issues in current meningioma care trajectories and possible solutions, including barriers and facilitators for implementation.

Results

Identified issues (n=18 issues) were categorized into three themes: availability and provision of information, care and support, and screening for (neurocognitive) rehabilitation. A lack of information about the intervention and possible outcomes/complications, lack of support after treatment focusing on bodily and psychological functions, and reintegration into society were considered most important. Sixteen solutions were suggested, such as appointment of case managers (solution for 11/18 issues, 61%), assessment and treatment by physiatrists (22%), and routine use of patient-reported outcome measures for patient monitoring (17%). Barriers for these solutions were lack of budget, capacity, technology infrastructure, and qualified personnel with knowledge about issues experienced by meningioma patients.

Conclusions

This study identified issues in current multidisciplinary meningioma care, which are considered unmet needs by patients, partners and healthcare providers and could guide innovation of care.

Key words

Case manager, Meningioma, Patient Reported Outcome Measures (PROMs), Value-Based Healthcare

INTRODUCTION

Meningiomas are tumours developing from the leptomeninges, accounting for 36.4% of primary intracranial tumours.[1,2,3] More than 80% of meningiomas are benign (WHO grade I) and patients have a near-normal life expectancy.[2,5] Morbidity is due to compression of the central nervous system and/or cranial nerves and vessels.[5,6] Recent European and Dutch guidelines advise a wait-and-scan policy in patients with asymptomatic meningiomas, and surgery or stereotactic radiotherapy in case of symptoms or established tumour growth.[4] Even though their life expectancy is near-normal, the limited data currently available suggests that patients suffer from long-term neurological sequelae and that their health-related quality of life (HRQoL) is impaired on all domains compared to the general population, both before and after interventions.[7]

Meningioma literature and guidelines traditionally focus on the extent of tumour resection, recurrence and neurological outcomes.[4] While these outcomes are highly relevant, they fail to reflect the continuing impact of the tumour and treatment on a patient's daily life.[8] Due to the lack of HRQoL data and other patient-reported outcomes, the few existing current care trajectories have not been optimized for these long-term sequelae.[4,7] This is supported by recent results from a patient survey in meningioma patients performed by the Dutch Comprehensive Cancer Organisation (DCCO), which showed that patients experience various problems and unmet needs during their care trajectory, such as a lack of information on the treatment and outcomes and lack of meningioma-specific care, e.g. meningioma-specific rehabilitation after intervention.[9] Although the results of the DCCO survey provided insight into the magnitude of the problem on a national level, the survey lacked detailed information on the actual experienced issues and possible solutions needed to improve current care trajectories.

As we are in the process of reorganizing meningioma care, we investigated in detail the current state of meningioma care trajectories, particularly focusing on issues that were perceived as problematic. We also studied possible solutions for the identified issues, as perceived by patient-partner dyads and healthcare providers. In addition, we aimed to assess barriers and facilitators for the implementation of proposed solutions that might have a high impact on the outcomes of meningioma care trajectories, as perceived by healthcare providers.

MATERIALS AND METHODS

Sampling of patients, partners and healthcare providers from meningioma care trajectories

In the Netherlands, meningioma care is primarily organised in academic and a few large teaching hospitals. Asymptomatic patients are followed by a neurologist and in case of symptom development or evident tumour growth, patients are referred through a tumour board to a neurosurgeon or radiation oncologist. After intervention, most patients are again followed by a neurologist or in select cases an endocrinologist. Before and after an intervention some patients are seen by an ophthalmologist, endocrinologist or healthcare providers from another specialty (e.g. physiatrist) depending on tumour localization and symptoms.

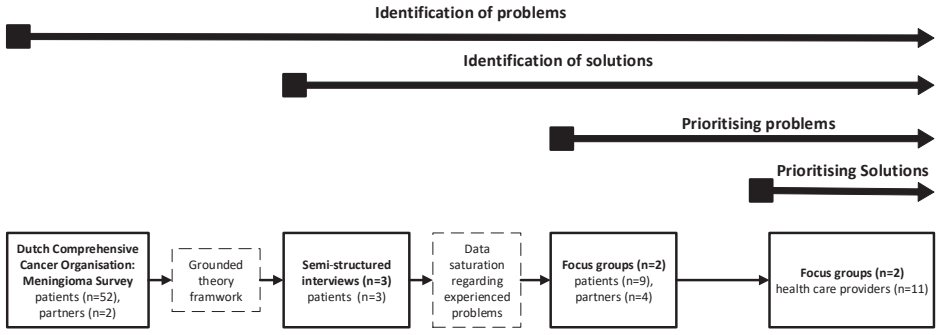
Patients with a clinical suspicion or histopathological confirmation of a WHO grade I or II meningioma, during wait-and-scan follow-up or after surgery or radiotherapy followed at the Leiden University Medical Center (LUMC) or Haaglanden Medical Center (HMC) between November 2017 and April 2018, were invited to participate in this study. Purposive sampling was used to ensure patients were included from all possible care trajectories, i.e. based on intervention (surgery, radiotherapy or wait-and-scan), and follow-up by neurologist or endocrinologist. In addition, they were included based on their sociodemographic and clinical characteristics, i.e. age, gender and tumour location (convexity versus skull base), to ensure generalizability of the study sample towards the general meningioma population.[10] Only patients with at least four months of follow-up after receiving their last treatment (surgery, radiotherapy) or after initiation of a wait-and-scan follow-up were selected to ensure that patients had experienced a large part of a meningioma post-diagnostic care trajectory. Additional inclusion criteria were 18 years of age or higher, and adequate Dutch language skills. Partners were eligible if they had accompanied the patient to their appointments on a regular basis. Informed consent was obtained on paper before study participation.

Eligible healthcare professionals were neurosurgeons, neurologists, ophthalmologists, radiation oncologists, psychologists, endocrinologists, and physiatrists, who treated a minimum of five new meningioma patients per year and worked at or were affiliated to a Dutch meningioma intervention centre.

Study design and concept

This study consisted of four consecutive steps, including data analysis from the DCCO survey (step 1) and semi-structured interviews and focus groups (step 2-4), and was approved by the medical ethics committees of both LUMC & HMC Institutions. Details on the study concept and design are presented in Figure 1. General procedures for all four steps are described in Supplementary Text 1.

Figure 1 – Study concept and design



Step 1: Dutch Comprehensive Cancer Organisation (DCCO) survey

Two researchers independently identified issues from data of the DCCO survey, which were used to construct a thematic framework of issues for each part of the Dutch meningioma care trajectory as identified by meningioma patients (Supplementary Table 1).[9] The thematic framework was constructed following the principles of the grounded theory approach, which is an inductive method through which theoretical insights are generated from collected data, rather than being restricted by existing theoretical frameworks.[11] Detailed information on the patient population cannot be provided, as the DCCO survey collected data anonymously. During both the semi-structured interviews and focus groups, the whole meningioma care trajectory was discussed and for each part of the care trajectory the relevant themes as described in the thematic framework were discussed (Supplementary Table 1).

Step 2: Semi-structured interviews with patients

Separate semi-structured interviews were conducted with three patients. Using the thematic framework from step 1, participants were asked to identify issues regarding their meningioma care trajectory, as well as possible solutions for these issues. This was done until data saturation was reached, which was defined as the point at which no new issues were brought up.[10,11]

Step 3: Focus groups with patient-partner dyads

Two focus group sessions (n=6 and n=7 participants) were organised with patients and their partners in an effort to generate possible solutions for issues reported during the semi-structured interviews, and to evaluate previously reported solutions. The issues were prioritised based on importance at the end of each session.

Step 4: Focus groups with healthcare providers

Two focus groups sessions (n=5 and n=6 participants) were organised with healthcare providers, aiming at identifying potential solutions for issues reported by patient-partner dyads from a healthcare providers' perspective, as well as more details on the raised issues and possible solu-

tions. Through an elaborate process, solutions were prioritised using an adapted Eisenhower matrix, according to the perceived importance and degree of effort (both: high versus low) at the end of each session. In addition, participants were asked to identify barriers and facilitators for high importance, high effort solutions.

Qualitative analysis of semi-structured interviews and focus groups

Results of the semi-structured interviews and focus group sessions were transcribed verbatim and anonymously analysed by two researchers (AHZN & JPMvdM) independently in a three-step approach, as described in previous studies.[12] In step 1, meaningful units were identified, which were allocated to subconcepts in step 2 and grouped into comprehensive concepts in step 3 (an example is given in Supplementary Figure 1). Discrepancies between the two researchers were discussed after each step and when no consensus was reached, a third researcher (LD) mediated the discussion. Issues reported as important in at least two focus groups or semi-structured interviews are reported.

Barriers and facilitators were categorised into six categories, using the well-established framework of Grol and Wensing, which consists of the following categories: innovation, individual professional, patient, social context, organizational context, and external environment (political and economic factors).[13]

Reporting was done according to the COnsolidated criteria for REporting Qualitative research (COREQ).[14]

Quantitative analysis

Baseline sociodemographic and clinical characteristics are reported for patients, partners and healthcare providers separately. Continuous data are reported as medians with an interquartile range (IQR), due to the small number of participants and the skewed distribution of variables. Nominal data are reported as proportions. All statistics were performed using IBM SPSS Statistics for Windows version 23.0 (Armonk, NY, USA).

RESULTS

In total, 52 patients and 2 partners completed the DCCO survey after a median of 66 months (range: 6-348). In addition, 12 patients, 4 partners and 11 healthcare providers participated in the semi-structured interviews and focus groups. Demographic information on the participants of the semi-structured interviews and focus groups are presented in table 1. Most of these patients were surgically treated (n=11, 92%) and 4 (25%) patients had also received radiotherapy. Median lengths of follow-up after the last intervention was 24 months (range:

4-148). Postoperative complications occurred in 2 patients, namely ischaemic stroke of the temporal lobe with transient aphasia and transient deterioration of visual acuity.

Table 1: Baseline sociodemographic and clinical characteristics of patients, partners and healthcare providers included in the focus groups and semi-structured interviews

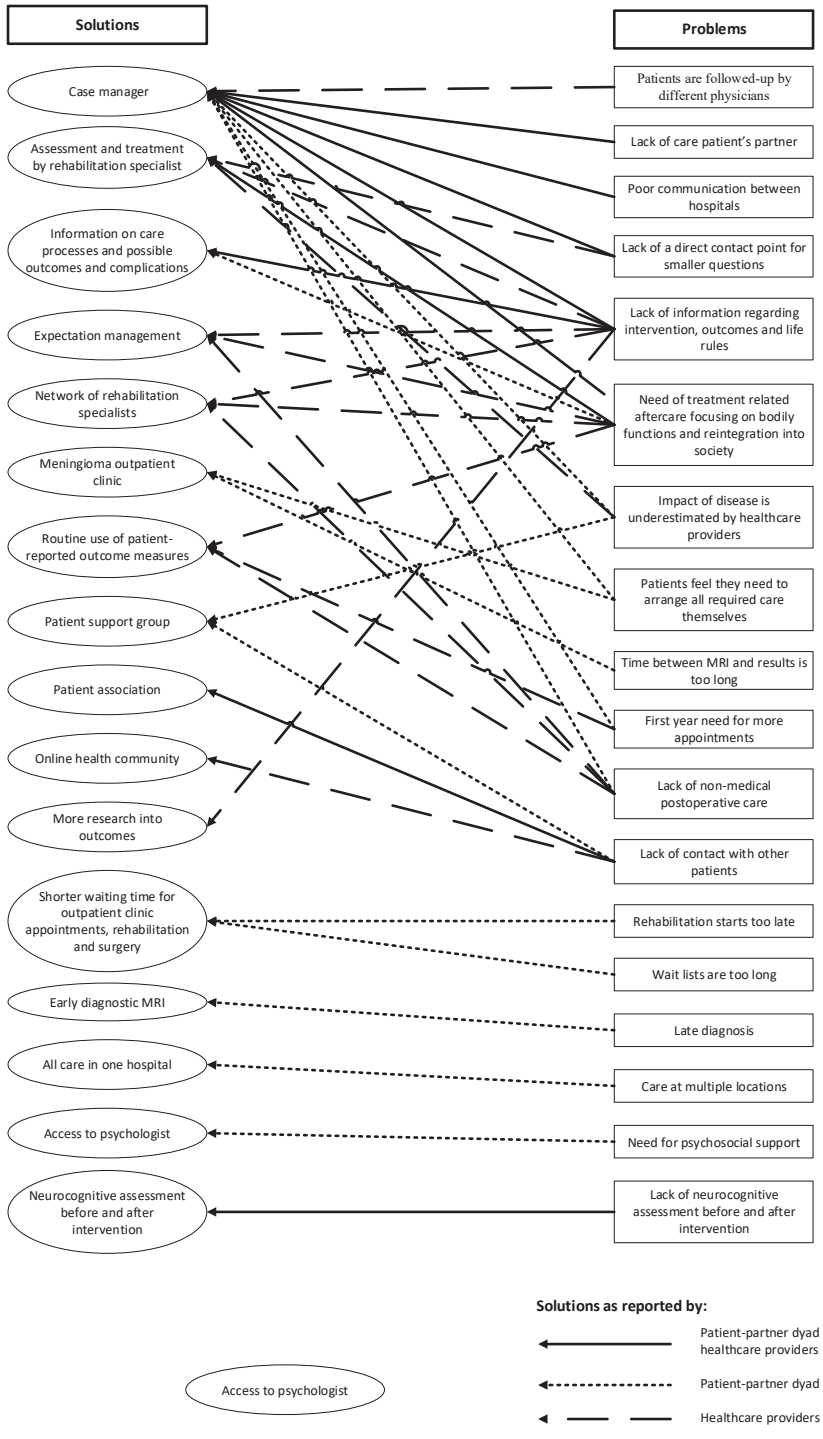
	Patients (n=12)	Partners (n=4)	Healthcare providers (n=11)
Age in years at interview, median (range)	52 (39-70)	56 (47-65)	42 (39-53)
Sex, n (%) female	10 (83%)	0 (0%)	6 (55%)
Highest obtained educational degree, n (%)			
Primary/Secondary	0 (0%)	0 (0%)	-
Vocational/technical	5 (42%)	1 (25%)	-
Academic/University	7 (58%)	3 (75%)	-
Paid job, n (%)	9 (75%)	3 (75%)	-
Tumour location, n (%)			
Convexity	4 (25%)	-	-
Skull base	8 (75%)	-	-
Karnofsky Performance Status, median (range)	100 (50-100)	100 (100-100)	-
Charlson Comorbidity Index, median (range)	1 (0-7)	1 (0-1)	-
Surgery, n (%)	11 (92%)	-	-
Radiotherapy, n (%)	4 (25%)	-	-
Months since last intervention, median (range)	24 (4-148)		
Neurological deficits, n (%)	1 (8%)	-	-
Visual deficits, n (%)	1 (8%)	-	-
Academic hospital, n (%)	8 (68%)	2 (50%)	9 (82%)
Years' experience, median (range)	-	-	9 (8-20)
Average number of new meningioma patients seen each year, median (range)	-	-	20 (10-25)

n=number

Issues and solutions

Following the principles of the grounded theory approach, issues were eventually categorized into a thematic framework consisting of the following three themes: (1) availability and provision of information, (2) care and support, and (3) screening for (neurocognitive) rehabilitation. A complete overview of all issues and possible solutions is presented in figure 2 and supplementary Table 2. Data saturation on the identified issues was reached after the semi-structured interviews, so the focus groups primarily focused on evaluating these issues into more detail and on identifying possible solutions for these problems (Figure 1). Examples of quotes from participants in the semi-structured interviews and focus groups are presented in Supplementary Text 2.

Figure 2 – Issues and solutions in meningioma care trajectories



Availability and provision of information

Both patient-partner dyads and healthcare providers reported the following issues as important: 1) not receiving sufficient information about the logistics of care during the period prior to the intervention (surgery or radiotherapy), 2) a lack of information about the intervention itself and what to expect afterwards, including information on complications and symptoms, and 3) what they are allowed to do after the intervention (Patient quote: "How will I feel after the surgery? And how long will it take to have a somewhat normal life again?").

A potential solution for these unmet needs was the availability and provision of information (e.g., flyer/website) on the care trajectories, treatment options, short- and long-term outcomes and potential complications, as suggested by both patient-partner dyads and healthcare providers. Patient-partner dyads who had positive experiences with guidance from case managers for their comorbidities, suggested that a specialized nurse / case manager could potentially provide this information. Healthcare providers confirmed the necessity, however, also indicated that more outcome research is necessary to provide evidence-based information on outcomes.

Care and support

Both patient-partner dyads and healthcare providers reported that patients experience a lack of support, especially on the long-term, by healthcare providers after being diagnosed and treated for a meningioma. Specifically, information was lacking information on 1) bodily functions, 2) reintegration into society, 3) psychosocial aftercare, and 4) care for the partner of the patient (Patient quote: "If I only had someone during the process whom to call to ask questions, such as whether it's normal to be so tired the entire day, […] or whether I was allowed to cycle […] I had no idea of what I was capable of doing."). Patient-partner dyads reported the need for a contact person to ensure continuity of care and for minor everyday questions. They furthermore reported they missed a patient support group and believed that the overall impact of the disease is often underestimated by healthcare providers. Both patient-partner dyads and healthcare providers reported that a specialized nurse or case manager could be of assistance to inform and guide patients and their partners after an intervention. Psychological aftercare provided by a specialised healthcare provider focusing on cognitive revalidation, self-management strategies, and mood disorders such as anxiety and depression is also currently missing according to patient-partner dyads. In addition, patient-partner dyads expressed the wish for shorter waiting lists for scans, outpatient clinic appointments and intervention.

Screening for (neurocognitive) rehabilitation

Patient-partner dyads reported the need for a neurocognitive assessment and health-care providers the use of PRO measures (PROMs) both before and after the treatment to provide patients with information about the impact of treatment and the possible need for (neurocognitive) rehabilitation. Healthcare providers and patient-partner dyads reported the need to

have the possibility to refer more patients to a physiatrist to determine whether rehabilitative treatment should be initiated focusing on neurological, and physical functions (Patient quote: "Fair enough, I received some exercises in the hospital the first two weeks, but after that, there was nothing. I did not know what I had to do at all.").

Prioritisation and implementation of solutions

A total of 16 solutions were identified during all the focus groups. Potential solutions for most of the problems could be the appointment of a case manager in current care trajectories (solution for 11/18 problems, 61%), assessment and treatment by a physiatrist (22%), routine use of PROMs (17%) and providing expectation management (17%). Most solutions (56%) were categorised by at least one participant as highly important, low effort solutions, which should readily be implemented, e.g. access to a (neuro)psychologist and the availability and provision of information on interventions and outcomes of treatments (Figure 3).

Figure 3 – Eisenhower matrix categorising solutions based on their importance/effort ratio.

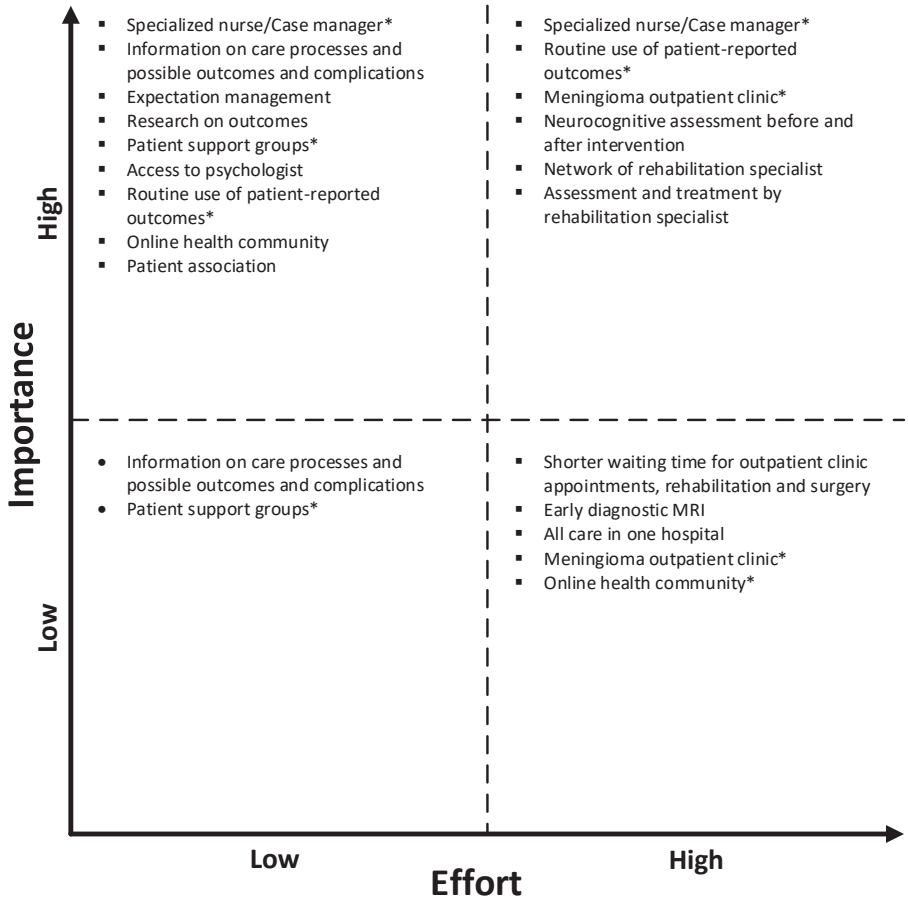


Table 2: Barriers and facilitators for high effort high importance solutions

Solution	Barrier (category)	Facilitator (category)
Case manager	• Lack of qualified personnel (Organisation context) • Multidisciplinary meningioma care (Organisation context) • Lack of capacity (Organisation context) • Lack of budget (Economic and political context) • Training of nurses (Individual professional)	• Qualified personnel (Organisation context) • Interdisciplinary consultation by case manager (Organisation context) • Budget (Economic and political context) • Use examples from other diseases (Innovation) • Saves time of doctors (Innovation) • Results in improvement quality of care (Innovation) • Priority hospital / board of directors (Social context)
Routine use of patient-reported outcomes	• Lack of time (Organisation context) • Lack of link with electronic patient record (Organisation context) • Lack of ICT infrastructure (Organisation context) • Implementation problems (Organisation context) • Lack of budget (Economic and political context) • Non-validated PROMs (Innovation) • Unmotivated patients to complete PROMs (Patient)	• Qualified ICT team (Organisation context) • Link with electronic patient record (Organisation context) • Use examples from other diseases (Innovation) • Use of tablets (Innovation) • Well-developed and validated PROMs (Innovation) • Motivated patients to complete PROMs (Patient)
Meningioma outpatient clinic	• Lack of capacity (Organisation context) • Lack of space and equipment (Organisation context) • Lack of budget (Economic and political context) • Heterogeneity disease (Patient)	• Budget (Economic and political context) • Results in publicity for hospital (Innovation) • Results in higher patient numbers (Innovation) • Results in improvement quality of care (Innovation) • Patient association voicing the need (Patient) • Priority hospital / board of directors (Social context)
Neurocognitive assessment	• Lack of qualified personnel (Organisation context) • Lack of capacity neuropsychologist (Organisation context) • Lack of budget (Economic and political context)	• Incorporation reimbursement system (Organisation context) • Link with electronic patient record (Organisation context) • Budget (from board of directors) (Economic and political context) • Simultaneous use of data for research (Innovation) • Inform patients on usability neurocognitive assessment (Patient)
Physiatrist network	• Lack of budget (Economic and political context) • Unfamiliarity other disciplines with rehabilitation possibilities (Individual professional) • Lack of know-how (Individual professional) • Lack of interest by other disciplines (Individual professional)	• Physiatrist part of multidisciplinary team (Organisation context) • Budget (Economic and political context) • Results in improvement quality of care (Innovation) • Priority hospital / board of directors (Social context)
Physiatrist screening	• Lack of capacity (Organisation context) • Lack of budget (Economic and political context) • Choice of screening instrument (Innovation)	• Budget (Economic and political context) • Results in improvement quality of care (Innovation) • Patient self-screening (Patient) • Priority hospital / board of directors (Social context)

Barriers and facilitators are categorised following the framework of Grol and Wensing into six categories: (1) innovation, (2) individual professional, (3) patient, (4) social context, (5) organizational context, and (6) external environment (political and economic factors).[14]

High importance/high effort solutions (38%) were: incorporation of a case manager in current care trajectories, creating a meningioma-specific outpatient clinic, performing neurocognitive assessments before and after an intervention, routine use of PROMs, and routine assessment of the need for rehabilitative therapy by a physiatrist, preferably in a network of physiatrists. The most important barriers for implementing these solutions were a lack of budget, capacity, ICT infrastructure, qualified personnel with knowledge about the management of meningioma patients and treatment issues focusing on HRQoL (Table 2). The most important identified facilitators were: using examples from other diseases and hospitals, and prioritisation by the hospital board. Most barriers and facilitators could be classified according to the Grol and Wensing criteria as factors associated with organizational aspects or the innovation (solution) itself.

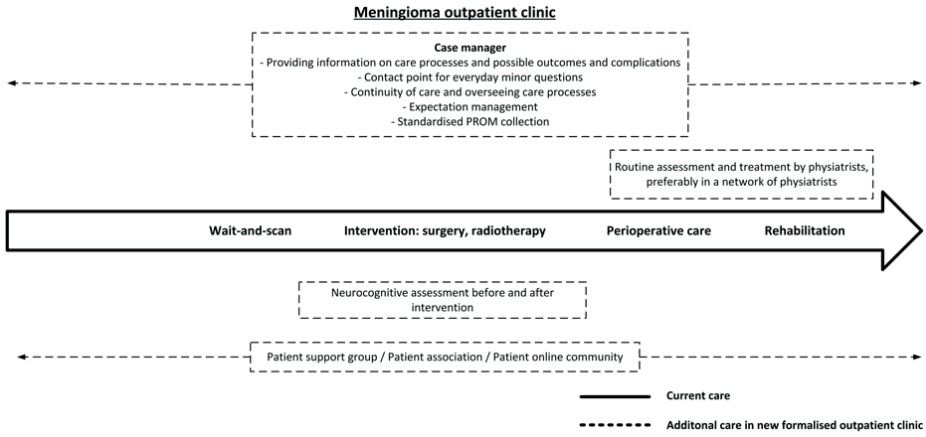
DISCUSSION

This study identified issues in current multidisciplinary meningioma care, which are considered unmet needs by patients, partners and healthcare providers that potentially contribute to delivering suboptimal care. This is the first study systemically evaluating these needs, including the identification of potential high impact solutions to improve care.

Transition of care

In our tertiary referral centre, multiple initiatives have been introduced in the last years to improve the care for patients with skull base and intracranial lesions. For those developing endocrine dysfunction or ophthalmological deficits, a formalised care trajectory was developed, including appointment of dedicated nurse case managers, standardised outcome measurements with PROMs, and implementation of self-management interventions, which all generally showed improvement of care outcomes.[15–18] Results of our study strongly support the need of a similar transformation of care and support system for meningioma patients, as depicted in Figure 4. Particularly, patients and healthcare providers reported the need for availability and provision of information about the intervention and its possible outcomes and complications, (continuity) of aftercare for patients and their partners including PROM use, focusing on bodily and psychological functions and reintegration into society, a point of contact for smaller (non-) medical questions, and patient support groups. Addressing these issues may possibly contribute to increased quality of care, as well as clinical outcomes. While physicians may be able to provide this needed extra guidance and aftercare, a nurse case manager seems more time- and cost-effective, thereby facilitating value based meningioma healthcare.[19] Furthermore, to ensure high quality care on a national level, quality criteria for meningioma centres should be defined regarding the structure of care, minimum number of operations and routine collection of outcomes. These criteria already exist for other intracranial pathology such as glioma and pituitary tumours, and has even resulted in the appointment of centres of excellence.[20,21]

Figure 4 – Transformation of meningioma care



Evidence for suggested solutions

Multiple studies in meningioma and other patient groups have found that the use of nurse case managers, (cognitive) rehabilitation programmes and routine assessment with PROMS in care trajectories led to better outcomes,[22–28] and that patients and physicians reported high satisfaction with provided care and perceived improvement in quality of care after appointment of a case manager.[30] While in general the effects were perceived as beneficial, large efforts needed to be made in the beginning to ensure proper implementation of these initiatives. Multiple effective meningioma or intracranial tumour rehabilitation programs exist focusing on bodily functions, cognitive rehabilitation and self-management.[15,25,27] Additionally, there are currently ongoing efforts to develop meningioma-specific PROMS and outcome sets.[7,8,30] While routine assessment with PROMs might be perceived as a burden in effort and time, it is beneficial for patient-doctor communication, adequate monitoring of treatment response (e.g. from a patient's home), reduction of the number of outpatient visits, detection of unrecognised symptoms by physicians, and consequently changes in the treatment and care of patients.[31] In general, future studies are needed to assess the actual effect of the suggested solutions on patient's HRQoL and the additional costs for the care trajectories.

Strengths and limitations of this study

A strength of this study is the combination of quantitative and qualitative data, as new issues were identified during the semi-structured interviews and focus groups, which were not mentioned in the DCCO survey data. Another strength is the inclusion of not only patients, but also partners and healthcare providers to cover all relevant themes in current meningioma care trajectories. The absence of nurses during the semi-structured interviews and focus-groups

is a limitation, as they could have identified different issues and solutions. Through purposive sampling, an adequate representation of meningioma patients was ensured, and healthcare providers represented almost all specialties involved in meningioma care trajectories. Obviously, like in comparable studies, we could not completely exclude some selection bias, since it is likely that only patients, and possibly also healthcare providers with an interest in this disease and topic, were more likely to participate. Data saturation was reached early in the study process, likely due to the availability of the quantitative results of the DCCO survey. Furthermore, even though we included patients from both an academic and a non-academic hospital, we were only able to include patients from a specific region in The Netherlands for the semi-structured interviews and focus groups, potentially limiting generalisability. However, we were able to include healthcare providers working in different regions of The Netherlands, which is a strength of the study. Although not all results may be generalised to countries other than The Netherlands, evidence for many of the reported issues and solutions are supported by international literature.[22–24,27,28,32–36] A difficulty with qualitative studies is that commonly only issues are identified, and not possible solutions, hampering actual change of care. Therefore, we asked healthcare providers to prioritise the identified solutions based on their perceived importance/effort ratio and to identify barriers and facilitators for implementation of these solutions, which is another strength of this study. Patients were not asked to identify barriers and facilitators for the identified solutions, as we felt that thorough understanding of Dutch hospitals and the Dutch healthcare system was needed for this purpose. Finally, as the median follow-up of patients was 5.5 years for the DCCO survey and 2 years for the semi-structured interviews and focus-groups, our results cover both the period around diagnosis and intervention as well as the longer-term sequelae.

Recommendations and future directions

In conclusion, the most important issues, as identified through patient-partner dyads, were a lack of information about the intervention and its possible outcomes and complications, and a lack of support after treatment focusing on bodily and psychological functions, and reintegration into society. To improve most of these unmet needs of patients, partners and healthcare providers, it is advisable to appoint a case manager, routinely use PROMs, and to incorporate a (neurocognitive) rehabilitation screening programme into current meningioma care trajectories. These solutions might subsequently result in lower costs and better outcomes, which is in line with the principles of value-based healthcare. Information on the identified barriers and facilitators should be used to successfully implement these initiatives. Ideally, these initiatives should be evaluated within integrated practice units (i.e. IPU), which involve the entire multidisciplinary team around the patient group of interest, to ensure broad support.[37] As it is difficult to reach sustainable change in existing care trajectories, iterative evaluation of implemented initiatives is required. For instance, the PDSA-cycle could be used, which requires initiatives to be redirected based on evaluated outcomes.[38,39] Within our IPU, we are

currently training case managers and developing a core outcome set together with and for meningioma patients as a first step to reorganise our care following the VBHC principles.

Acknowledgements:

We would like to acknowledge prof. Thea P.M. Vliet Vlieland for her input in the study design and prof. Saskia M. Peerdeman for her involvement in the data collection of the Dutch Comprehensive Cancer Organisation survey.

Funding:

AHZN was supported by the Leiden University Medical Center MD/PhD Scholarship and a personal grant by Bewustzijnsproject Nederland.

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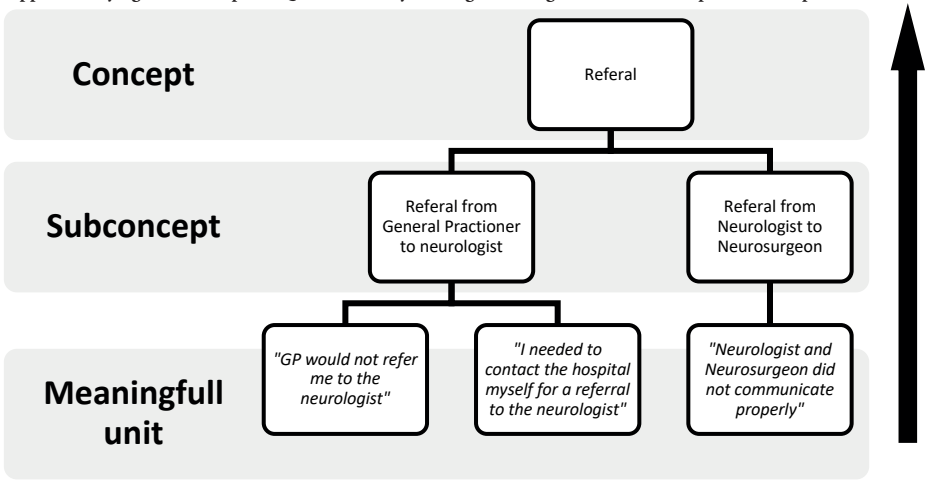
SUPPLEMENTS

Supplementary Table 1: Thematic framework used for the focus group sessions, based on the results of the DCCO survey.

Parts of meningioma care trajectory	Signs and symptoms	Referral	Diagnostics	Support and guidance	Efficiency	Empathy physician	Accessibility care	Quality of care	Information
Before appointment general practitioner							x	x	
Appointment general practitioner	x	x	x		x	x	x	x	x
Before appointment neurologist	x	x	x	x	x		x	x	x
Appointment neurologist	x	x	x		x	x	x	x	x
Before MRI	x		x	x	x		x		x
Before appointment neurosurgeon	x			x			x	x	x
Appointment neurosurgeon	x				x	x	x	x	x
Wait-and-scan	x		x	x	x		x	x	x
Operation	x							x	
Hospitalisation	x			x		x		x	
Postoperative care	x			x	x	x	x	x	x
Before radiation	x			x			x	x	x
Radiation	x				x	x		x	
After radiation	x			x			x	x	
Rehabilitation period	x			x		x	x	x	

Supplementary figure 1: Example of Qualitative analysis trough meaningful units, subconcepts and concepts.



Supplementary text 1: General procedures of semi-structured interviews and focus groups

All semi-structured interviews and focus groups were conducted by AHZN, who moderated the focus group, and JPMvdM, who took notes and managed time. Both researchers had prior experience with, and were trained for, conducting semi-structured interviews and focus groups. No relationship was established between the researchers and patients before this study. The grounded thematic framework based on data of the DCCO survey was used during all sessions (see Supplementary Table 1 for an overview of the aspects in this framework). Non-suggestive open-ended probing questions were initially asked, but when participants were not able to answer the questions, additional examples as identified in the DCCO survey results were provided. Interviews and focus groups were scheduled for 90 to 120 minutes. Interviews were organised in a quiet and comfortable room in the hospital or patient's home, as preferred by the patient and partner. Focus groups were organised in the Leiden University Medical Center. All sessions were audiotaped and transcribed verbatim.

Supplementary Table 2 – Identified issues during focus groups with patient-partner dyads and healthcare providers

Issues	Patient-partner dyads	Healthcare providers	DCCO survey
Lack of information regarding (the period before) surgery or radiotherapy	x	x	11
Lack of information on outcomes, complications, and life rules after intervention	x	x	4
Lack of support after intervention focusing on neurological and physical functions	x	x	4
Lack of support after intervention focusing on reintegration	x	x	2
Lack of support after intervention focusing on psychosocial aftercare (e.g. mood disorders such as anxiety and depression)	x	x	5
Lack of support after intervention focusing on the patient's partner	x	x	
Lack of a direct contact person for smaller questions	x	x	
Lack of a person with a 'helicopter-view' responsible for the care process	x	x	
Patients are not referred to rehabilitation specialist	x	x	
Rehabilitation is initiated too late	x		
Diagnostic MRI should be made earlier in the care trajectory	x		1
Time between MRI and (outpatient appointment) communication of the results is too long	x		1
Long waiting time between the first outpatient clinic visit and intervention	x		
Lack of a patient support group	x		15
Impact of disease is underestimated by healthcare providers	x		9
Patient's symptoms are not always taken seriously by physicians	x		
Need for higher amount of follow-up appointments during the first year after the intervention	x		
Patients feel that they need to arrange all required care themselves	x		
Patients have questions that remain unanswered after visiting specialists	x		6
Patients are followed-up by different physicians	x		6
Care takes place at different hospitals	x		
Poor communication between physicians in different hospitals	x		
Lack of information on the implications of an incidentally found meningioma		x	
Lack of clarity on who is responsible for the patient in the hospital		x	

Supplementary text 2: Examples of quotes from semi-structured interview and focus groups

Availability and provision of information

Quote 1

"I did not know whether they would cut the mastication muscles, but I would have liked to know that beforehand."

Quote 2

"Actually, I also want the neurosurgeon to explain exactly what is going to happen. About the period before the operation, about the stickers on the head, that the skull is being lifted, what the risks are […]"

Quote 3

"They told me about a patient who started working again after six weeks. I thought that is way too soon, […] Indeed, during those six weeks I was wheelchair bound and I was unable to do anything, I was so tired and I did not have any endurance, I couldn't do a thing."

Quote 4

"What can you expect during the period before surgery?... I would have liked to receive flyers with information about how the day of the surgery will look like."

Quote 6

"*So somebody should have accompanied me to the appointment, because of the MRI results and all the fuss around it…. You are not allowed to drive, nobody ever told me that. I had to find out about those things myself."*

Quote 7

"[…] what really struck us was that you do not receive any life rules, for instance when you can start exercising. When are you able to take a walk again?"

Quote 9

"*A lot of simple questions, such as 'how will they perform the surgery', 'how do they close the skull afterwards'? Those are very simple questions, but we had to ask for them ourselves."*

Quote 10

"*The information provision after discharge should focus on two things; follow-up at the outpatient clinic, and what you can expect afterwards. … I have three solutions; an approachable specialised nurse, an information leaflet about the treatment and care after surgery, and, if it was up to me, an earlier start of a rehabilitation trajectory, which can help to get insight in your current problems."*

Care and support

Quote 1

"These things [the symptoms and impact on daily life] are also the case, I think, with patients suffering from other brain tumours, they do not necessarily have to do with meningiomas. … there is more attention for somebody with a malignant tumour, while everyone thinks: 'right, but it is only a meningioma, you can become old with a meningioma'."

Quote 2

"… my husband suffered from a weak heart and I experienced that entire clinical pathway, and the aftercare is absolutely amazing. Both the patient and the partner can attend information evenings, receive help with their diet and other things, that is absolutely amazing. I therefore said to my husband: 'they should do something like that also for people with a brain tumour."

Quote 3

"Well, my mother had a nurse practitioner, I believe, who she could always call. … That is something I wish I had too."

Quote 4

"Actually, what is lacking in the whole care pathway is a medical doctor who is in charge of the whole care process."

Quote 5

"Someone you can talk to and who listens to you"…someone that speaks out of experience" "Just someone you can go to with questions, somebody who listens to you."

Quote 6

"Yes, I have been three times to the national brain tumour association meeting. That helped me quite a lot". "How did it help you?". "Speaking to people who also suffered from brain tumours" … recognition, that you are not alone."

Quote 7

"Actually it is about the aftercare, and the aftercare is not only medical. It is very much focused, at least in this hospital, on medical care, but everything that has been discussed in this focus group has nothing to do with the medical care."

Quote 8

"The symptoms are vague, such as headaches or concentration problems. These symptoms can also be interpreted as purely psychological, but, in fact, are a result physical problems. You don't get any support for these symptoms."

Quote 9

"There should be recognition for the fact that it is not just tumour surgery, but that you will suffer from many problems in daily life. So there should also be better support, for instance in the form of a case-manager. And indeed, we should also create patient support groups."

Quote 10

"Just somebody you can call who has some knowledge about meningiomas and can advise me about what I should do, who can comfort me with all those weird symptoms I still have."

Quote 11

"Also support and comfort after the surgery. I missed that a lot. There should be a case manager, a nurse practitioner, a specialised nurse, who you can call, who fills the existing gap."

Quote 12

"Why don't they make an MRI earlier in the care trajectory?" "If they would make it earlier, they would not need all those extra steps in the meantime that cost money" "All these steps may actually be more expensive than the MRI."

Quote 13

"And the neurologist did not even know that an MRI was performed. … Afterwards, it turned out that the ophthalmologist sent me to the neurologist for the neurological tests, and that the ophthalmologist had ordered the MRI, so he would receive the MRI results. I understand that the one who orders the scan, will receive the results of that test."

Quote 14

"The first year after surgery I would get an MRI-scan, well, that was hard to get actually, because I had to call them and arrange everything myself."

Quote 15

"There has only been one appointment before surgery. You hear your diagnosis and you receive very limited information. There should be at least another appointment with the surgeon before the surgery is performed. You only see him the day before surgery, and that's it."

Quote 16

"Actually, I think, the first year after surgery you should have more regular appointments."

Quote 17

"They plan the surgeries one week ahead. … In the end, it took eight weeks until it was my turn."

Screening for (neurocognitive) rehabilitation

Quote 1

"I applied for rehabilitation in the rehabilitation clinic. Well, everybody thought that was a smart idea. … A week after the surgery I still had not heard from them, so I called them and they said: "oh, but that is only after two months after surgery", and I thought 'two months? I will surely not lie in bed for two months, right? I just want some guidance, what is allowed and what is not?' It would have been very helpful for me if I could have attended the rehabilitation clinic earlier."

Quote 2

"I will undergo a neuropsychological test in a week and I would have liked to have a baseline measurement of such a test, because I honestly do not know how to interpret the results if I do not know how I scored before surgery."

Chapter 6

Health-related quality of life of cranial WHO grade I meningioma patients: are current questionnaires relevant?

Acta Neurochirurgica, 2017;159(11):2149-2159.

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ABSTRACT

Background

The clinical relevance of Health-Related Quality of Life (HRQoL) in meningioma patients is increasingly acknowledged in recent years. Various questionnaires have been used. However, almost none of these questionnaires is particularly developed for and/or validated in this patient group. Therefore, the aim of this study was to assess the relevance and comprehensiveness of existing HRQoL questionnaires used in meningioma research and to assess the agreement between patients and health care professionals (HCPs) on the most relevant and important HRQoL issues.

Methods

A systematic literature search, following the PRISMA statement, was conducted to identify all HRQoL questionnaires used in meningioma research. Semi-structured interviews were organised with patients and HCPs to 1) assess the relevance of all issues covered by the questionnaires (score 0-3: not relevant – highly relevant), 2) assess the 10 most important issues, 3) identify new relevant HRQoL issues.

Results

Fourteen different questionnaires were found in the literature, comprising 140 unique issues. Interviews were conducted with 20 patients (median age 57, 71% female) and 10 HCPs (4 neurosurgeons, 2 neurologists, 2 radiotherapists, 1 rehabilitation specialist, 1 neuropsychologist; median experience 13 years). Meningioma patients rated 17-80% of the issues in each of the questionnaires as relevant; HCPs 90-100%. Patients and HCPs agreed on the relevance of only 49 issues (35%, Cohen's kappa: .027). Both patients and HCPs considered lack of energy the most important issue. Patients and HCPs suggested 5 additional relevant issues, not covered by current HRQoL questionnaires.

Conclusions

Existing HRQoL questionnaires currently used in meningioma patients do not fully cover all relevant issues to these patients. Agreement between patients and HCPs on the relevance of issues was poor. Both findings support the need to develop and validate a meningioma-specific HRQoL questionnaire.

Key words

Meningioma, Health-Related Quality of Life, Questionnaires, content validity

INTRODUCTION

Meningioma is the most prevalent (53.4%) type of benign central nervous system tumor with an incidence of 7.86 per 100.000 person years.[1] As these tumors originate from the arachnoid cap cells, the majority of tumors are supratentorial (90%)[2]. In general, patients have a near normal life-expectancy after surgery and/or radiotherapy.[1,3] However, based on the location of the tumor, patients may suffer from a wide variety of signs and symptoms and problems in the physical, psychological and social domains, even on the long-term after intervention.[2,4]

Patient function can be categorized into three distinct levels, as described by the World Health Organisation International Classification of Functioning, Disability and Health (ICF, 2001) criteria: impairment (e.g. visual problems), activity limitations (e.g. not able to drive due to physical problems) and participation restrictions (e.g. not able to work). A Health-Related Quality of Life (HRQoL) instrument is a multidimensional outcome measure, including domains on physical, psychological and social functioning as well as symptoms induced by the disease and its treatment, thereby covering function on all three ICF levels.[5]

HRQoL data can be physician-, proxy- or patient-reported, but the use of patient-reported outcome measures (PROM), reflecting the patient's perspective, is increasing in the last decade.[4,6] Indeed, patients are thought to be the best source to rate their own health status.[5] HRQoL can be measured using more generic (e.g. SF-36, EQ-5D, MDASI)[7–9], cancer specific (e.g. FACT-G, EORTC QLQ-C30)[10,11] or disease-specific questionnaires (e.g. FACT-BR, EORTC QLQ-BN20, MDASI-BT)[10,12,13] and can be used both in clinical research and in daily practice. In clinical research, HRQoL questionnaires can be used as primary or secondary outcome measure, which in combination with survival rates can be used to measure the net clinical benefit of different treatment modalities.[14] Treatment either improves or worsens the duration and quality of (progression-free) survival, but the effect on both is not necessarily the same. When duration and quality of life are affected in opposite directions, a trade-off discussion arises.[15] In clinical practice, HRQoL questionnaires can be used as a facilitating tool for patient-doctor communication, for monitoring patients' problems and functioning during the disease trajectory and as quality indicator of healthcare.[16]

While the number of meningioma studies using HRQoL questionnaires as primary or secondary outcome measure has increased in the last decade, it is remarkable to note that almost all existing HRQoL questionnaires used in meningioma research are not developed and/or validated in earlier series with this condition.[7,8,11,12] It may therefore be questioned whether the issues addressed in these questionnaires are relevant for meningioma patients and whether these questionnaires cover the entire spectrum of issues and symptoms of this patient group. Validation of these questionnaires in meningioma patients is therefore needed to assess

whether all items are applicable to meningioma patients, but also to assess the performance (i.e. measurement properties) of the PROM in the target population. At the moment, multiple questionnaires may be needed to comprehensively cover all issues relevant for meningioma patients.

The aim of this study was to assess whether existing HRQoL questionnaires used in cranial meningioma research indeed cover issues that are relevant for meningioma patients and whether relevant problems/issues are missing (i.e. content validity). In addition, we aimed to assess the agreement between patients and physicians with respect to the most relevant and important issues for meningioma patients.

METHODS AND MATERIALS

A literature search was conducted to identify all HRQoL questionnaires used in clinical research with meningioma patients. Issues covered by these questionnaires were categorized into different HRQoL domains, which were subsequently used in semi-structured interviews with both patients and health care professionals (HCPs). The aim of these semi-structured interviews was to assess the content validity (i.e. the degree to which the content of existing questionnaires is an adequate reflection of the HRQoL of meningioma patients) and consisted of three parts: (1) to identify all relevant HRQoL issues (the interviews continued until no new issues arose), (2) to determine the relevance of all issues identified in the literature search, including those in the existing HRQoL questionnaires and (3) to determine the ten most important HRQoL issues.

Literature study

A literature search was conducted in the following electronical databases: Embase, MEDLINE, Web of Science, CINAHL, PsychInfo, Academic Search Premier, COCHRANE and ScienceDirect up to October 2015, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17] Search terms used were "meningioma", "quality of life" and terms formulated to exclude case reports and studies with animals only (see supplementary Table 1 for the formal search strategy). Reference lists of included articles were scanned for additional studies. Inclusion criteria were the following: original peer-reviewed articles including HRQoL questionnaires as outcome measure in adult meningioma patients. Exclusion criteria were as follows: articles not in English and studies with animals. Two independent reviewers (AHZN and MCMP) screened all titles and abstracts for HRQoL questionnaires. HRQoL domains and issues covered by these questionnaires were categorized by one researcher (AHZN) and verified independently by two other researchers (LD, WRvF). Disagreement was resolved with discussion and consensus.

Semi-structured interviews with patients and healthcare professionals

Subject selection

A convenient number of patients, randomly selected, were eligible for inclusion if clinically diagnosed (symptoms and imaging) with a benign intracranial meningioma (WHO grade I) for which they visited the neurosurgery outpatient clinic in the Leiden University Medical Center (LUMC) between 2011 and 2015. Patients were older than 18 years and fluent in Dutch. Both patients with a convexity meningioma and a skull base meningioma, irrespective of previous anti-tumor therapy (surgery and/or radiotherapy), were included to reflect the heterogeneity of this patient group. Similarly, patients before treatment, short-term after treatment (up to two years after surgery) and long-term after treatment (at least two years after surgery) were included. Patients were interviewed only once. Patients were excluded when histopathological diagnosis revealed that the tumor was not a benign meningioma (all patients had been surgically treated prior to analysis), diagnosed with neurofibromatosis type 2, or when they had a history of tumors of the central nervous system other than benign meningioma. HCPs were neurosurgeons, neurologists, radiotherapist, rehabilitation specialists and clinical psychologists who treated meningioma patients in their daily practice.

Semi-structured interviews

Semi-structured interviews were conducted by AHZN with both patients and HCPs, consisting of 4 steps: step 1) patients had to answer the open question "*What are your meningioma-related problems/issues at this moment?*" and HCPs had to answer the question "*Which problems/issues are relevant for meningioma patients?*", step 2) HRQoL domains identified in the questionnaires were discussed to identify all relevant HRQoL issues for meningioma patients, step 3) patients and HCPs scored the relevance of each found issue on a 4-point Likert scale (0=not relevant at all, 1=of little relevance, 2=quite relevant, 3=highly relevant) and in step 4) patients and HCPs had to indicate which ten problems/issues they deemed most important. Relevance and importance was assessed by patients for themselves based on their experiences of the last month and by HCPs for meningioma patients in general.

Data analysis

In step 1 and 2 of the interviews, issues and problems not covered by existing HRQoL questionnaires used in meningioma research, were identified. In step 3, all HRQoL problems/issues covered by existing questionnaires were assessed for relevance: issues were considered relevant when ≥30% of the patients or ≥30% of the HCPs scored the issue as relevant (score 1-3) on the 4-point Likert scale. A cut-off of ≥30% was chosen because of the heterogeneity of the disease (e.g. based on tumor characteristics patients are likely to assesses different issues as relevant) and variability due to the small number of participants. Agreement between patients and HCPs was assessed using Cohen's kappa (degree of agreement: moderate 0.41-0.60, substantial 0.61-0.80, excellent 0.81-0.99).[18] In addition, specific positive and negative agreement were assessed

which describes the probability of the described groups finding the same issue relevant or not relevant.[19] In step 4, HRQoL issues were considered important when at least 30% of patients or HCPs reported the issue as important. Results were compared between patients and HCPs, but also between patients with skull base and convexity meningiomas, and between patients before surgery, up to two years after surgery and patients followed for at least two years after surgery. Baseline characteristics and relevance and importance of HRQoL questionnaires and items were described using descriptive statistics. Descriptive statistics are presented, as median and interquartile range (IQR) as data were skewed. To determine significant differences in baseline characteristics, Pearson's chi-square and Fisher Exact test were used for dichotomous outcomes and the Mann-Whitney U Test or Kruskal–Wallis test for continuous outcomes. All statistics were performed using IBM SPSS Statistics for Windows version 23.0 (Armonk, NY, USA.) and *p*-values <0.05 were considered statistically significant.

Ethics statement

This study was conducted after approval of our institutional review board. Informed consent was obtained before participation.

RESULTS

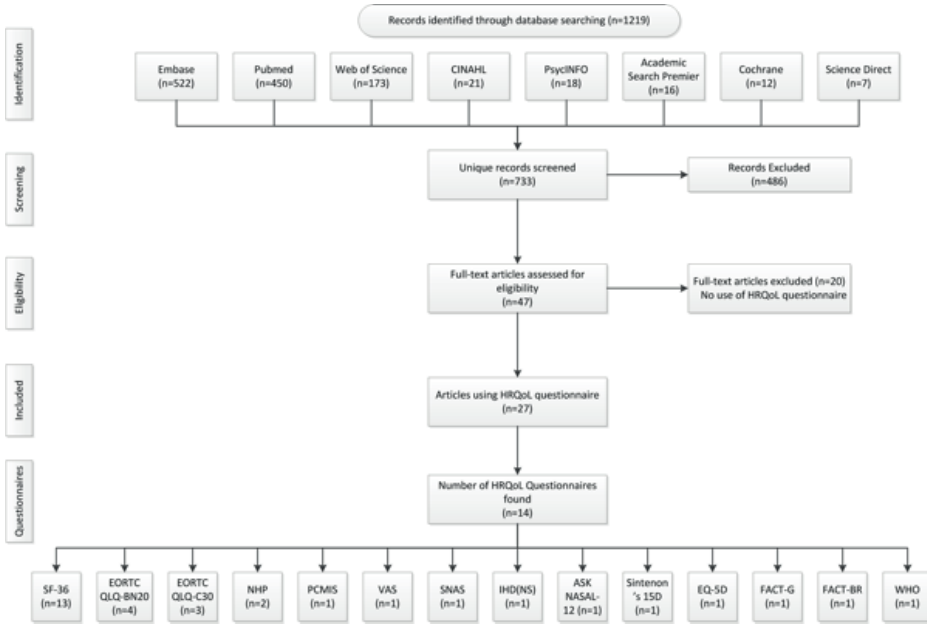
Literature study

A total of 733 unique records were found, including 27 articles using HRQoL questionnaires in meningioma patients (Figure 1). The following questionnaires were used: five generic HRQoL questionnaires (SF-36: n=13; NHP: n=2; Sintenon's 15D: n=1; EQ-5D: n=1; WHOQOL: n=1)[7,20–23], two disease-specific questionnaires for cancer patients (EORTC QLQ-C30: n=3; FACT-G: n=1)[11,24], two disease-specific questionnaires for brain tumor patients (EORTC QLQ-BN20: n=2; FACT-BR: n=1)[10,25], one disease-specific questionnaire for patients with advanced breast cancer (VAS: n=1)[26], one disease-specific questionnaire for petroclival meningiomas (PCMIS: n=1)[27], one disease-specific questionnaire for neurosurgically treated patients with central nervous system tumors (IHDNS: n=1)[28], one disease-specific questionnaire for neuro-oncology tumors (SNAS: n=1)[29] and one disease-specific questionnaire for patients with anterior skull base pathology (ASK Nasal-12: n=1)[30]. Only the FACT-G and FACT-BR questionnaires have been validated in meningioma patients.[10,24] Out of the 439 items covered by the questionnaires, a total of 140 unique HRQoL issues were identified (i.e. many questionnaires covered the same issues or multiple items covered one issue in the same questionnaire).

Subject characteristics

Subject characteristics are presented in table 1. A total of 20 meningioma patients (75% females) were interviewed, with a median age of 57 years (IQR: 48-67): skull base (n=10),

Figure 1: Flow chart of literature search and questionnaire selection



convexity/cerebral falx (n=10), before surgery (n=5), up to two years after surgery (n=9) and patients followed for at least two years after surgery (n=6). Two patients received postsurgical radiotherapy. Baseline characteristics of subgroups are presented in supplementary table 2 and 3. In addition, 10 HCPs (4 neurosurgeons, 2 neurologists, 1 rehabilitation specialist and 1 neuropsychologist; 30% female) were interviewed, with a median age of 50 years (IQR: 40-54). HCPs had a median experience of 13 years (IQR: 8-23), consulting a median of 25 (IQR: 10-40) new meningioma patients each year.

Semi-structured interviews

Relevance of existing HRQoL questionnaires

Meningioma patients assessed 45/140 (32%) issues as relevant, whereas HCPs assessed 136/140 (97%) issues as relevant. Meningioma patients and HCPs agreed on the relevance of 49 out of 140 issues (35%, Cohen's kappa: 0.027). Specific positive agreement was 0.247, which means that the probability that patients and HCPs assess the same issues as relevant is 24.7%. The specific negative agreement, the probability that patients and HCPs assess the same issue as non-relevant was 0.040 (4%), which is driven by the observation that physicians found almost all items relevant. When analysing the results per questionnaire, meningioma patients rated 17-80% of the issues in the questionnaires as relevant with the ASK NASAL-12 as least relevant (17%) and the EQ-5D as most relevant (80%). HCPs on the other hand rated 90-100% of the issues as relevant with the EORTC QLQ-C30 as least relevant (90%) and the

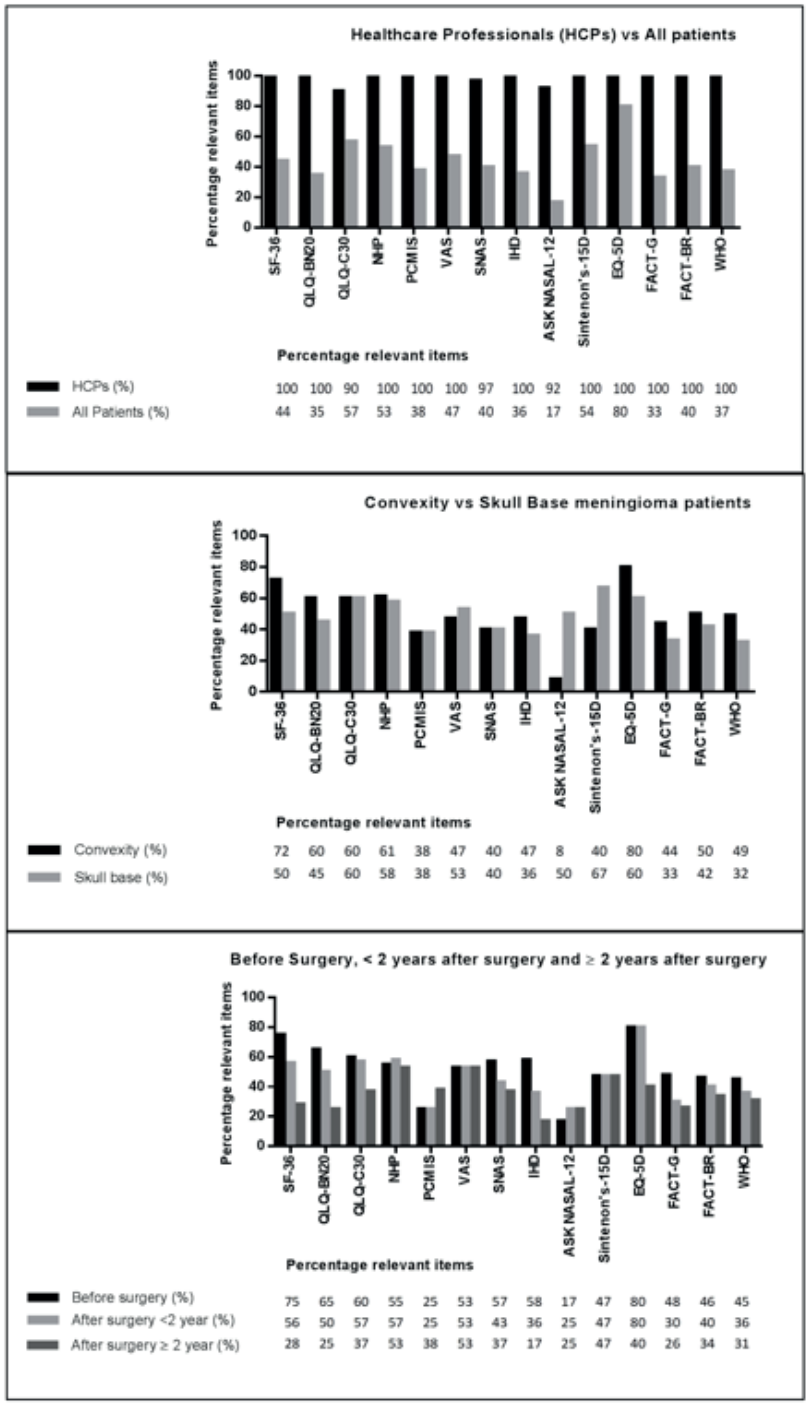
EORTC QLQ-BN20, SF-36, PCMIS, VAS, IHD(NS), NHP, Sintenon's 15D, WHOQOL, EQ-5D, FACT-G and FACT-BR as most relevant (all 100%). Convexity meningioma patients rated 8-80% of the issues in the questionnaires as relevant (least relevant: ASK NASAL-12, 8%; most relevant: EQ-5D, 80%), while skull base meningioma patients rated 32-67% of the issues as relevant (least relevant: WHOQOL, 32%; most relevant: Sintenon's 15D, 67%). Patients interviewed before surgery rated 17-80% of the issues in the questionnaires as relevant (least relevant: ASK NASAL-12, 17%; most relevant: EQ-5D, 80%), while patients interviewed <2 years after surgery rated 25-80% of the issues as relevant (least relevant: PCMIS and ASK NASAL-12, 25%; most relevant: EQ-5D, 80%) and patients interviewed ≥2 years after surgery rated 17-53% of the issues as relevant (least relevant: IHDNS, 17%; most relevant: NHP and VAS, 53%). See Figure 2 for the percentage of relevant issues per questionnaire, presented for patients and HCPs, and stratified for tumor location (convexity vs skull base) and different treatment phases (before intervention, up to two years after intervention and at least 2 years after intervention).

Table 1 – Patient characteristics

	All patients (n=20)
Age in years at interview, median (IQR)	57 (48-67)
Sex, n (% female)	15 (75%)
Time since clinical diagnosis in months, median (IQR)	23 (5-51)
Karnofsky Performance Status, median (IQR)	95 (80-100)
Charlson Comorbidity Index, n (%)	
0	15 (75%)
1-2	4 (20%)
>2	1 (5%)
Midline shift present, n (%)	4 (20%)
Edema present, n (%)	16 (80%)
Corticosteroid use, n (%)	3 (15%)
Antiepileptic drug use, n (%)	3 (15%)
Tumor Location	
Convexity meningioma	10 (50%)
Skull base meningioma	10 (50%)
Moment of interview, n (%)	
Before surgery	5 (25%)
After surgery < 2 year	9 (45%)
After surgery ≥ 2 years	6 (30%)
Surgical resection, n (%)	15 (75%)
Simpson grade I-III	13 (86%)
Simpson grade IV-V	2 (13%)
Postsurgical radiotherapy, n (%)	2 (10%)

n: number. IQR: interquartile range

Figure 2: Relevance of Health-related quality of life items in questionnaires used in meningioma research: percentages describe the proportion of items assessed as relevant per questionnaire



Issue Importance

The most frequently reported HRQoL issue that was considered 'important' was lack of energy. This issue was reported by all patient groups and HCPs, except for patients interviewed before surgery (all patients: 42%; skull base patients: 44%; convexity patients: 40%; patients interviewed up to two years after surgery: 38%; patients interviewed at least two years after surgery: 67%; and HCPs: 90%). Patients interviewed before surgery only reported issues in the physical domain as important (i.e. walking: 60% and coordination 40%). Issues in the cognitive domain and behaviour and mood domain were only reported by patients with skull base meningiomas (concentration: 44%; memory: 33%; worries 33%), patients interviewed at least 2 years after surgery (concentration: 50%; memory: 33%; crying: 33%; nervousness: 33%) and by HCPs (memory: 60% and personality changes: 30%). Activity of daily living (ADL) issues were primarily reported to be important by convexity meningioma patients (transport, daily functioning and driving, all 30%) and patients up to two years after surgery (transport and daily functioning, both 38%), less frequent by skull base patients (hobbies: 33%), and not by the other (sub)groups. Further details are presented in Table 2.

New relevant issues

During the semi-structured interviews with meningioma patients and HCPs, 3 new issues were generated by patients (loss of sensation around surgery scar: 15%; difficulty handling stress: 10%, non-visibility of the disease and its symptoms: 10%), 1 issue by HCPs (symptoms related to pituitary dysfunction: 30%) and 1 new issue by both patients and HCPs (symptoms related to executive functioning, such as multitasking: patients 25%; HCPs 20%).

DISCUSSION

The increase in use of PROMs in the last decade to measure HRQoL in meningioma patients reflects the importance of HRQoL assessment in this patient group. However, both generic and disease-specific HRQoL questionnaires used in meningioma research cover a significant array of issues that are not relevant for meningioma patients and frequently overlook relevant issues for this patient group. Moreover, patients and HCPs considered different HRQoL issues as relevant and most important. These findings support the need of a meningioma-specific PROM, measuring the construct HRQoL.

Health-Related Quality of Life of meningioma patients

While there is an increase in use of PROMs to measure HRQoL in meningioma patients, the number of studies describing HRQoL data of meningioma patients is limited.[4] It is known that meningioma patient's HRQoL before intervention is worse than healthy controls and depending on the HRQoL domain better or similar compared with glioma patients

Table 2 – Most important issues as assessed by patients and health care professionals (HCPs): percentages describe the proportion of subjects in each group assessing an issue as important

Patients			
Results stratified for different treatment phase			
Before Surgery (N=5)	**After Surgery < 2 years (N=8)***	**After surgery ≥ 2 years (N=6)**	**Total (N=19)***
Walking: 60% Coordination: 40%	Energy: 38% Walking: 38% Instability while standing: 38% Dependence: 38% Daily functioning: 38% Transport: 38%	Energy: 67% Recurrence: 50% Concentration: 50% Pain: 33% Hearing: 33% Memory: 33% Crying: 33% Nervousness: 33%	Energy: n=8 (42%)
Results stratified for different tumor locations			
Skull base (N=9)*	**Convexity (N=10)**		
Energy: 44% Concentration: 44% Headache: 33% Memory: 33% Hobbies: 33% Worries: 33%	Energy: 40% Uncertainty future: 40% Dependence: 40% Walking: 30% Coordination: 30% Transport: 30% Daily functioning: 30% Driving: 30%		
Health care professionals			
HCPs (n=10)			
Energy: 90% Quality of life: 50% Memory: 60% Epilepsy: 30% Visual acuity: 30% Personality changes: 30%			

Issues are reported for each subgroup if at least 30% of subjects assessed the issue as important
[a]One skull base meningioma patient, interviewed short-term after surgery, did not assess the 10 most important issues.

(all grades).[4] HRQoL is only measured longitudinally in two studies. While about 50% of meningioma patients have an improved HRQoL after surgery both on the short (6 weeks) and long-term (10-58 months), about 20% of patients have a worse HRQoL.[31] Meningioma patients receiving radiotherapy have an improved HRQoL 6 months after radiotherapy, but after two years of follow-up their HRQoL decreases to pre-radiotherapy levels.[32] These studies show that measuring HRQoL, in addition to conventional outcomes like complications, resection grade, neurological complications and progression free survival, helps to assess the effectiveness of different treatment strategies.[15] However, it is important to measure HRQoL using a questionnaire covering all aspects of HRQoL relevant to the target group. This study shows that current questionnaires, as they are not developed for meningioma patients, just

partially cover relevant items for meningioma patients This could be due to the fact that many general HRQoL PROMs (e.g. SF-36, EQ-5D) do not cover disease-specific issues, and many cancer-related PROMs (e.g. EORTC QLQ-C30, FACT-G) cover issues related to side-effects of systemic therapy and radiotherapy while most meningioma patients are primarily treated by surgery. Our findings therefore suggest that multiple existing questionnaires would be needed to comprehensively measure HRQoL in this patient group.

Disagreement between patients and health care professionals

Patients and HCPs considered different HRQoL problems/issues relevant. While HCPs assessed almost all issues of all questionnaires as relevant, meningioma patients assessed a high number of issues as non-relevant. This can be explained by the fact that HCPs have a broader knowledge of potential issues in meningioma patients, while patients only have their own situation as a reference. Another possible explanation could be that mainly HCPs, and not a sufficient number of patients, were involved in the development of some of these questionnaires. Nowadays patients are more frequently involved in the development of new questionnaires.[33] A previous study has shown that agreement between physician-reported and patient-reported issues is indeed poor and that HRQoL should be patient-reported.[5] Furthermore, a disease-specific PROM, measuring the construct HRQoL, could facilitate patient-doctor communication and consequently align patient and doctor on patients' issues and problems in clinical practice.[16]

Heterogeneity in relevance and importance of issues

Meningioma is a heterogeneous disease, as these tumors can occur at a variety of intracranial locations, possibly leading to different problems and issues. In addition, timing of assessment in studies assessing HRQoL may be important, as it is known that patients find different issues important at different treatment phases[17]. In order to get a comprehensive image of issues relevant and important for meningioma patients, a heterogeneous group of patients was included in this study. Indeed, we found differences in relevance and importance of issues in different subgroups based on tumor location and treatment phase. Compared with skull base meningioma patients, convexity meningioma patients rated more issues of the generic HRQoL questionnaires as relevant. Issues in the cognitive domain (e.g. concentration problems) were rated as important by skull base meningioma patients, but not by convexity meningioma patients. This is in line with previous studies which showed that skull base meningioma patients had significantly more problems than patients with a convexity meningioma in the cognitive domain (memory, verbal memory, information processing and psychomotor speed).[34,35] This could possibly be explained by the anatomical proximity of these tumors to the temporal lobe, which is known to support memory function.[36] In contrast, convexity meningioma patients assessed issues in the ADL domain (e.g. bathing, and driving) as important, while skull base meningioma patients did not. This may be due to the fact that convexity meningioma patients had more motor deficits (70%) than patients with a skull base meningioma (40%).

Relevance of individual HRQoL questionnaires was higher for patients interviewed before surgery than for postoperative patients, especially for those patients at least 2 years after tumor resection. Patients interviewed before surgery only reported issues in the physical domain (e.g. walking and coordination) as most important, while up to two years after surgery particularly problems in the ADL-domain (e.g. dependence and daily functioning) were reported. Remarkably, these problems were not reported by patients interviewed after a minimum of 2 years of post-surgical follow-up, suggesting a different coping style of patients on the long-term and/or psychological adjustments to chronic issues and problems.[37] Particularly issues in the cognitive domain (e.g. concentration and memory), and mood and behaviour (e.g. crying and nervousness) domain were reported as "most important" by patients after a minimum of two years of follow-up. The long-term consequences of surgery on cognitive functioning and issues in the behaviour and mood domain is unknown.[38]

Most important issue: lack of energy

The most important issue assessed by HCPs and almost all patients, except patients interviewed before surgery, was to our surprise "lack of energy" (fatigue). To our knowledge, literature on fatigue as a tumor-related symptom in meningioma patients is lacking. It is known from trials in newly diagnosed glioma patients that fatigue is a tumor-related symptom.[39] Possible underlying mechanisms of brain tumor related fatigue in patients with primary brain tumors include activation of inflammatory pathways and disturbances of the hypothalamic and corticotropic axis.[40] Moreover in skull base meningioma patients (all grades) receiving radiotherapy, fatigue was the most frequently reported acute and chronic symptom.[41] Studies in glioma patients have reported that 13% to 79% of patients suffer from a somnolence syndrome after radiotherapy with a peak in severity after 6 weeks.[42] In our study only a few patients were included who received radiotherapy, so the effect of radiotherapy could not be reliably assessed. However, patients interviewed after surgery, (both <2 years and ≥2 years after surgery) rated the issue "lack of energy" as most important issue, suggesting a possible surgical or anaesthesia effect on patients' energy levels both on the short- and long-term. More studies are needed to discriminate the effect of tumor type and surgery, specifically craniotomy, but also radiotherapy on patient-reported fatigue.

Study limitations

A limitation of this study is the limited number of patients included, which hampers comparison between the different subgroups (e.g. specific tumor locations and use of anti-epileptic drugs). Patients with WHO grade II and III meningioma, as well as with neurofibromatosis type 2 were excluded. Due to the low patient number, none of the included patients had recurrent or multiple meningioma. Both issues may hamper the generalizability of the results of this study. Moreover, the issues as identified during the semi-structured interviews may be subject to the interpretation of the researcher. In addition, only issues covered by HRQoL questionnaires

used in published studies including meningioma patients were included and discussed during the semi-structured interviews. Questionnaires not already used in meningioma research, but of possible relevance for this patient group are missed, for instance the MDASI and its specific brain module (MDASI-BT), and the FACT-MNG.[3, 6, 45] However, patients were also asked to report missing relevant issues during the interviews, so issues missing in existing HRQoL questionnaires were likely to be identified. Lastly, information on educational background and social-economic status were not collected in this study, while both may influence patients' perception on HRQoL issues.[43,44]

Conclusions

In conclusion, existing HRQoL questionnaires are only partially relevant for meningioma patients and they lack several relevant issues for this patient group. Agreements between patients and HCPs on issue relevance and importance was poor. Differences in relevance of HRQoL questionnaires and importance of issues were found between convexity and skull base meningioma patients, and patients interviewed before and after surgery. Therefore, the use of just one of the existing HRQoL questionnaires in studies including a heterogeneous group of meningiomas may be troublesome. Hence, we are currently developing a meningioma-specific PROM, measuring HRQoL, by including meningioma patients irrespective of cranial tumor location and treatment phase. Based on the collected data there are multiple options for the construct and structure of the PROM. On the one hand, such a PROM may exist of just one core questionnaire, covering the majority of relevant issues for all meningioma patients, by heterogeneous patient sampling. A drawback is that this may result in a long questionnaire, increased patient burden and subsequently lower response rates. A PROM existing of a core questionnaire covering the issues relevant to all patients, complemented with modules for certain meningioma subgroups, may resolve this problem. Which option is best, will be based on the data collected in our currently ongoing study, while keeping in mind that the PROM should be relevant for the majority of meningioma patients and have a low response burden.

Funding:

No funding was received for this research.

Conflict of Interest:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Acknowledgements:

The authors would like to thank J.W. Schoones for his help with the systematic literature search.

Presentation:

This work has not been presented at any national or international meeting.

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SUPPLEMENTS

Supplementary Table 1 – Search strategy for MEDLINE

Search terms: Meningioma, quality of life and terms to exclude studies with only animals and case reports
(((“Meningioma”[MesH] OR “Meningioma”[Tw] OR “Meningiomas”[Tw] OR “Meningiomatosis”[Tw] OR “Meningiomatoses”[Tw] OR “Meningeal Neoplasms”[MeSH] OR “Meningeal Neoplasms”[Tw] OR “Meningeal Neoplasm”[Tw]) **AND** (“Quality of Life”[mesh] OR “Health Surveys”[mesh] OR “Questionnaires”[Mesh] OR “Self Report”[mesh] OR “Patient Outcome Assessment”[mesh] OR “Health Status Indicators”[mesh] OR “Quality of Life”[tw] OR “QoL”[tw] OR “HRQL”[tw] OR “HRQOL”[tw] OR “PQoL”[tw] OR “AQoL”[tw] OR “subjective wellbeing”[tw] OR “subjective well-being”[tw] OR “Patient Reported Outcome”[tw] OR “Patient Reported Outcomes”[tw] OR “patient reported”[tw] OR “PRO”[tw] OR “PROs”[tw] OR “PROM”[tw] OR “PROMs”[tw] OR “health survey”[tw] OR “health surveys”[tw] OR “Questionnaires”[tw] OR “questionnaire”[tw] OR “Self reports”[tw] OR “Self report”[tw] OR “Self-reported”[tw] OR “Patient Outcome Assessments”[tw] OR “Patient Outcome Assessment”[tw] OR “health status indicator”[tw] OR “health status indicators”[tw] OR health status indicat*[tw] OR “outcome instrument”[tw] OR “outcome instruments”[tw] OR “health score”[tw] OR “health scores”[tw] OR health scor*[tw])) **NOT** (“Animals”[mesh] NOT “Humans”[mesh]) NOT (“Case Reports”[pt] NOT “Clinical Trial”[pt]))

The search strategy was adapted for the following electronical databases: Embase, Web of Science, CINAHL, PsychInfo, Academic Search Premier, COCHRANE and ScienceDirect.

Supplementary Table 2 – Subject characteristics: different treatment phase

	All patients (n=20)	Before surgery (n=5)	After Surgery < 2 years (n=9)	After surgery ≥ 2 years (n=6)	*p*-value
Age in years at interview, median (range)	57 (39-73)	67 (43-69)	56 (44-68)	55 (39-65)	0.73
Sex, n (% female)	15 (75%)	4 (80%)	7 (78%)	4 (67%)	0.85
Tumor Location, n (%)					0.61
Convexity	10 (50%)	3 (60%)	5 (56%)	2 (33%)	
Skull base	10 (50%)	2 (40%)	4 (44%)	4 (67%)	
Karnofsky Performance Status, median (range)	95 (70-100)	100 (70-100)	90 (70-100)	100 (80-100)	0.11
Charlson Comorbidity Index, n (%)					0.15
0	15 (75%)	4 (80%)	5 (56%)	6 (100%)	
1-2	4 (20%)	1 (20%)	3 (33%)	0 (0%)	
>2	1 (5%)	0 (0%)	1 (11%)	0 (0%)	
Midline shift present, n (%)	4 (20%)	1 (20%)	2 (22%)	1 (17%)	0.96
Edema present, n (%)	16 (80%)	5 (100%)	7 (78%)	4 (67%)	0.38
Corticosteroid use, n (%)	3 (15%)	2 (40%)	1 (11%)	0 (0%)	0.16
Antiepileptic drug use, n (%)	3 (15%)	1 (20%)	1 (11%)	1 (17%)	0.90
Surgical resection, n (%)	15 (75%)	-	9 (100%)	6 (100%)	0.70
Simpson grade I	7 (35%)	-	5 (56%)	2 (33%)	
Simpson grade II	6 (30%)	-	3 (33%)	3 (50%)	
Simpson grade III	0 (0%)	-	0 (0%)	0 (0%)	
Simpson grade IV	2 (10%)	-	1 (11%)	1 (17%)	
Simpson grade V	0 (0%)	-	0 (0%)	0 (0%)	
Patients with Surgical complications, number (%)	4 (20%)	1 (17%)	1 (11%)	2 (40%)	0.71
Number of infections	3 (15%)	0 (0%)	1 (11%)	2 (40%)	
Number of cardiovascular complications	1 (5%)	1 (17%)	1 (11%)	0 (0%)	
Number of neurological complications	1 (5%)	0 (0%)	0 (0%)	0 (0%)	
Number of pulmonal complications	1 (5%)	0 (0%)	0 (0%)	1 (20%)	
Postsurgical radiotherapy, n (%)	2 (10%)	0 (0%)	1 (11%)	1 (17%)	0.65

n: number.

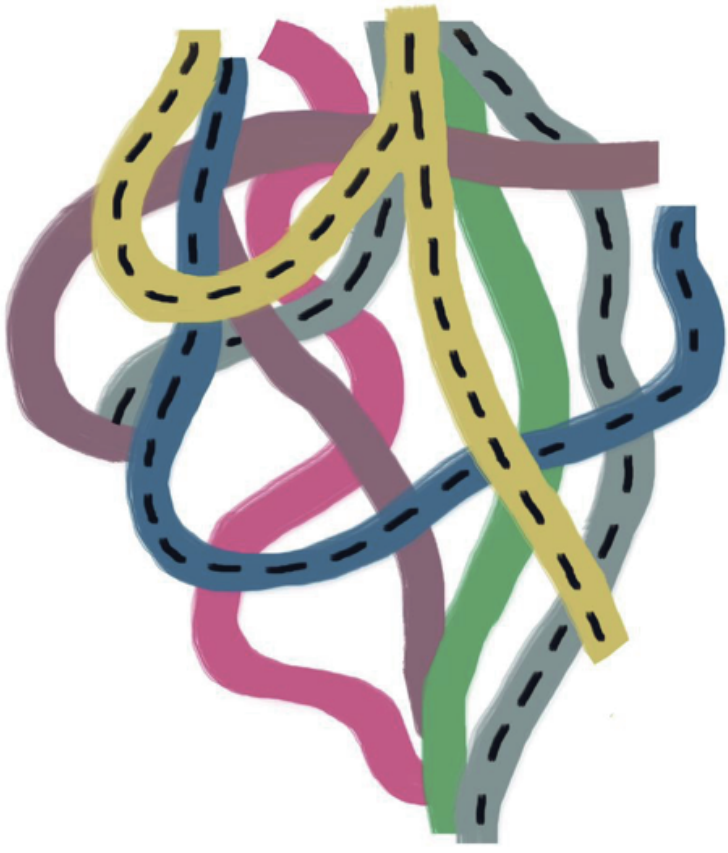
Supplementary Table 3 - Subject characteristics: different tumor location

	All patients (n=20)	Convexity (n=10)	Skull base (n=10)	*p*-value
Age in years at interview, median (IQR)	57 (48-67)	62 (53-68)	50 (44-66)	.06
Sex, number (% female)	15 (75%)	7 (70%)	8 (80%)	1.00
Time since clinical diagnosis in months, median (IQR)	23 (5-51)	18 (4-55)	30 (5-59)	.74
Karnofsky Performance Status, median (IQR)	95 (80-100)	95 (90-100)	95 (80-100)	.74
Charlson Comorbidity Index, n (%)				.59
0	15 (75%)	8 (80%)	7 (70%)	
1-2	4 (20%)	2 (20%)	2 (20%)	
>2	1 (5%)	0 (0%)	1 (10%)	
Midline shift present, n (%)	4 (20%)	2 (20%)	2 (20%)	1.00
Edema present, n (%)	16 (80%)	7 (70%)	9 (90%)	.58
Corticosteroid use, n (%)	3 (15%)	2 (20%)	1 (10%)	1.00
Antiepileptic drug use, n (%)	3 (15%)	2 (20%)	1 (10%)	1.00
Moment of interview				.61
Before surgery	5 (25%)	3 (30%)	2 (20%)	
After surgery < 2 year	9 (45%)	5 (50%)	4 (40%)	
After surgery ≥ 2 years	6 (30%)	2 (20%)	4 (40%)	
Surgical resection, n (%)	15 (75%)	7 (70%)	8 (80%)	.69
Simpson grade I	7 (35%)	4 (40%)	3 (30%)	
Simpson grade II	6 (30%)	2 (20%)	4 (40%)	
Simpson grade III	0 (0%)	0 (0%)	0 (0%)	
Simpson grade IV	2 (10%)	1 (10%)	1 (10%)	
Simpson grade V	0 (0%)	0 (0%)	0 (0%)	
Patients with Surgical complications, n (%)	4 (20%)	2 (20%)	2 (20%)	1.00
Number of infections	3 (15%)	1 (10%)	2 (20%)	
Number of cardiovascular complications	1 (5%)	1 (10%)	0 (0%)	
Number of neurological complications	1 (5%)	0 (0%)	1 (10%)	
Number of pulmonal complications	1 (5%)	0 (0%)	1 (10%)	
Postsurgical radiotherapy, n (%)	2 (10%)	2 (20%)	0 (0%)	0.24

n: number. IQR: interquartile range

Part 2

Understanding and predicting outcomes of meningioma patients



Chapter 7

TRIPOD statement: a preliminary pre-post analysis of reporting and methods of prediction models

BMJ Open, 2020;10: e041537.

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ABSTRACT

Objectives

To assess the difference in completeness of reporting and methodological conduct of published prediction models before and after publication of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement.

Methods

In the seven general medicine journals with the highest impact factor, we compared the completeness of the reporting and the quality of the methodology of prediction model studies published between 2012 and 2014 (pre-TRIPOD) with studies published between 2016 and 2017 (post-TRIPOD). For articles published in the post-TRIPOD period, we examined whether there was improved reporting for articles (1) citing the TRIPOD Statement, and (2) published in journals that published the TRIPOD Statement.

Results

A total of 70 articles were included (pre-TRIPOD: 32, post-TRIPOD: 38). No improvement was seen for the overall percentage of reported items after the publication of the TRIPOD Statement (pre-TRIPOD 74%, post-TRIPOD 76%, 95% CI of absolute difference: -4% to 7%). For the individual TRIPOD items, an improvement was seen for 16 (44%) items, while 3 (8%) items showed no improvement and 17 (47%) items showed a deterioration. Post-TRIPOD, there was no improved reporting for articles citing the TRIPOD statement, nor for articles published in journals that published the TRIPOD statement. The methodological quality improved in the post-TRIPOD period. More models were externally validated in the same article (absolute difference 8%, post-TRIPOD: 39%), used measures of calibration (21%, post-TRIPOD: 87%) and discrimination (9%, post-TRIPOD: 100%), and used multiple imputation for handling missing data (13%, post-TRIPOD: 50%).

Conclusions

Since the publication of the TRIPOD Statement, some reporting and methodological aspects have improved. Prediction models are still often poorly developed and validated and many aspects remain poorly reported, hindering optimal clinical application of these models. Long-term effects of the TRIPOD statement publication should be evaluated in future studies.

Key words

Diagnostic, Prediction, Prognostic, Reporting, TRIPOD, Methodology.

Strengths and limitations of this study

- This is the first study to assess the completeness of reporting and methodological conduct of prediction models published before and after publication of the TRIPOD statement.
- A limitation of this study is the short time period evaluated and therefore future studies are needed to assess the long-term effects on completeness of reporting and methodological conduct.
- Causality between publication of the TRIPOD statement and the found results cannot be established due to confounding.

INTRODUCTION

Prediction models cover both prognostic models, which aim to predict the risk of future outcomes, and diagnostic models, which aim to assess the presence or absence of a condition.[1] They provide information for differential diagnosis, additional testing and for patient selection on treatment. Interest in prediction models has sharply increased over the last two decades, translating to new methodological developments, especially regarding performance assessment of these models[2–4]. In addition, clinical guidelines are increasingly recommending the use of prediction models,[5,6] and consequently implementation of these models in clinical practice for individualised diagnostic and therapeutic decisions has surged.[7–10]

Previous systematic reviews on the quality of published prediction models have identified poor reporting and many methodological shortcomings in the development and validation of these models.[11–13] In response to these reviews, the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement was developed.[14] The TRIPOD Statement provides reporting recommendations for articles that describe the development and external validation of prediction models, aiming to enhance reporting transparency and hence interpretability, reproducibility, and clinical usability of these models.[14] Although the TRIPOD Statement primarily focuses on reporting and not on methods, current accepted methods for the development and validation of prediction models are discussed in the accompanied Explanation and Elaboration document.[15]

The primary aim of this study was to assess the difference in completeness of reporting and methodological conduct of published prediction models before and after publication in high impact general medicine journals.

METHODS

Systematic literature search

We selected the seven general medicine journals with the highest Web of Knowledge impact factor in 2017: *New England Journal of Medicine (NEMJ), Journal of the American Medical Association (JAMA), The Lancet, the British Medical Journal (The BMJ), Annals of Internal Medicine, PLOS Medicine, and BMC Medicine*. Articles on prediction models published in these journals before publication of the TRIPOD Statement (pre-TRIPOD: 01 January 2012 – 31 December 2014) and after publication of TRIPOD statement (post-TRIPOD: 01 January 2016 – 31 December 2017) were identified by a PubMed search string (Supplementary text 1). Articles published in 2015 were excluded from the search, as the TRIPOD Statement was published in 2015 and we regard this as a transition period. Titles and abstracts were screened by one

reviewer (AHZN). Full-text articles were screened by two independent reviewers (AHZN and CLR) and disagreement was resolved by discussion and consensus with a senior author (MvD).

Article and model selection

Original articles with the primary aim of developing and/or validating multivariable models, both prognostic and diagnostic, were included. We excluded etiological studies, genetic marker studies, and model impact studies, as these are not covered by the TRIPOD Statement. Included articles were classified as 1) development, 2) development and external validation, 3) external validation, and 4) extension/updating of models. For articles addressing multiple models but not explicitly recommending a single model, the model with the most predictors was evaluated. For instance, Hippisley-Cox (2013) described model A, B and C for the prediction of future risk of cardiovascular disease, with model B being the same as model A with the addition of several predictors and interactions and model C being the same as model B with the addition of one variable. In this case model C was evaluated.

Assessment of adherence to TRIPOD criteria

In 2018, authors of the TRIPOD Statement published a TRIPOD adherence assessment form and adherence scoring rules, which were also used in our study. [16–18] The TRIPOD Adherence form is a measurement tool developed for authors who want to evaluate the adherence of prediction model studies to TRIPOD, e.g. over time or in a certain medical domain. In general, when multiple aspects were described within a TRIPOD item, all aspects needed to be reported to score a point for that item. For instance, the item title contains four sub-items (e.g. i. identifying the study as development and/or validation of a ii. prediction model with iii. description of target population and iv. outcome) and all four aspects need to be reported to score a point for this specific item. For all items and aspects of the checklist it was assessed whether it was reported in the main article or supplementary materials. The main analyses were based on items reported in either the main text or supplements. Each article was only assessed for items applicable to the study (i.e. development and/or external validation, or incremental value study). Scores for reporting level were calculated by assigning a single point for each reported item applicable to the study and total reporting level scores were converted to percentages based on the maximum possible score, and followed published scoring rules for the TRIPOD Adherence form.[16,17]

Assessment of study characteristics and used methods

In addition to the completeness of reporting following the TRIPOD statement, we assessed specific study characteristics and methods used in the included articles. To this end, we developed a comprehensive data extraction form based on previous studies, current methodological consensus, and the TRIPOD Exploration and Elaboration document (Supplementary text 1).[11,13,15,19–22] In summary the following topics were assessed: general study characteristics (i.e.

diagnostic-prognostic and study topic), handling of missing data, model development methods, type of external validation and updating, and performance measures. To facilitate interpretation of the results section, main recommendations of the TRIPOD Exploration and Elaboration document are presented in Table 1. Assessment of these items was performed by two independent reviewers (AHZN and CLR) and a senior author (MvD) where necessary. In addition, for all articles published in the post-TRIPOD period, we extracted whether authors cited or referred to the TRIPOD Statement, provided the completed checklist, if the article was published in a journal that published the Statement (*The BMJ*, *Annals of Internal Medicine*, *BMC Medicine*), or was published in a journal that clearly stated in the author guidelines that they required TRIPOD adherence for submitted work at the time of writing this manuscript (*The BMJ, JAMA, and PLOS Medicine*). While all included journals (except for the *NEJM*) encouraged authors to follow the Equator Network guidelines, which includes the TRIPOD checklist, in their author instructions, only *The BMJ, JAMA and PLOS Medicine* required adherence to the Equator network guidelines and also required to include a filled-out checklist at the time of submission.

Table 1: Recommended methods and analyses for the development and validation of prediction models including supportive references

Methodology		
Handling of missing data	It is generally advised to use multiple imputation for handling of missing data. Complete case analysis, single or mean imputation are inefficient methods to estimate coefficients	[47–49]
Selection and retaining of predictors in multivariable models	Predictor selection and retaining is preferably based on clinical knowledge and previous literature, instead of significance levels in univariable or stepwise analysis.	[22,26,27]
Internal validation	It is advised to internally validate the model to assess optimism in performance and reduce over-fitting. An efficient method is bootstrapping; split-sample validation should be avoided.	[25,26]
Calibration	It is advised to assess the calibration of a model at external validation. The preferred method is a calibration plot, with intercept and slope, and not statistical tests (e.g. Hosmer-Lemeshow), as a plot retains the most information on possible miscalibration.	[22,26,27,50]
External validation	External validation of models is needed for rigorous assessment of performance. The preferred external validation population is fully independent.	[28,51]

Analysis and reporting of results

Reporting levels are presented as percentages, stratified by journal, and for comparison the absolute difference in percentages with 95% confidence intervals are reported. Analyses were performed with IBM SPSS statistics (version 23.0, Armonk, NY, USA). Main results of the completeness of both reporting and methods are reported in text and detailed results are reported in the (Supplementary) Tables. Comparisons were made between articles I) Pre- and Post-TRIPOD, II) post-TRIPOD between articles published in journals that published and did not publish the TRIPOD, III) between articles published in journals that require TRIPOD

adherence or not, IV) citing vs. not citing the TRIPOD, and V) providing vs. not providing a completed TRIPOD checklist. Furthermore, to estimate changes over time regardless of the TRIPOD statement, a comparison was made between pre-TRIPOD articles and post-TRIPOD articles not citing the TRIPOD.

RESULTS

Characteristics of included studies

The PubMed search string retrieved 481 articles, of which the full-text of 119 were read and 70 met our inclusion criteria (pre-TRIPOD: 32 articles, post-TRIPOD: 38 articles, Figure 1, Supplementary Text 1). Most of the included articles were published in *The BMJ* (n=38), and least in *The Lancet* (n=3) and NEJM (n=1). In both the pre- and post-TRIPOD period the majority of articles described prognostic models (as opposed to diagnostic models) and this increased in the post-TRIPOD period (pre-TRIPOD: 59%, post-TRIPOD: 89%) (Table 2). In the post-TRIPOD period the percentage of articles describing both the development and validation of a model (pre-TRIPOD: 31%, post-TRIPOD: 39%) or solely the external validation (pre-TRIPOD: 13%, post-TRIPOD: 26%) increased too. Thirty-two percent of articles only described the development of a prediction model without external validation in the post-TRIPOD period, compared to 44% in the pre-TRIPOD period.

Figure 1: Flow chart of search results and selection procedure

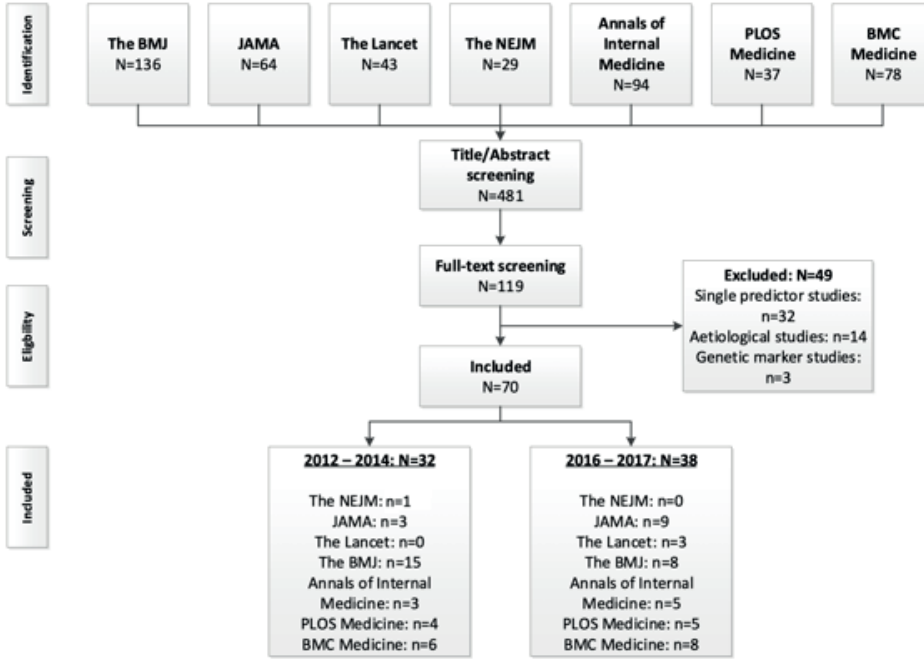


Table 2: Characteristics of included studies

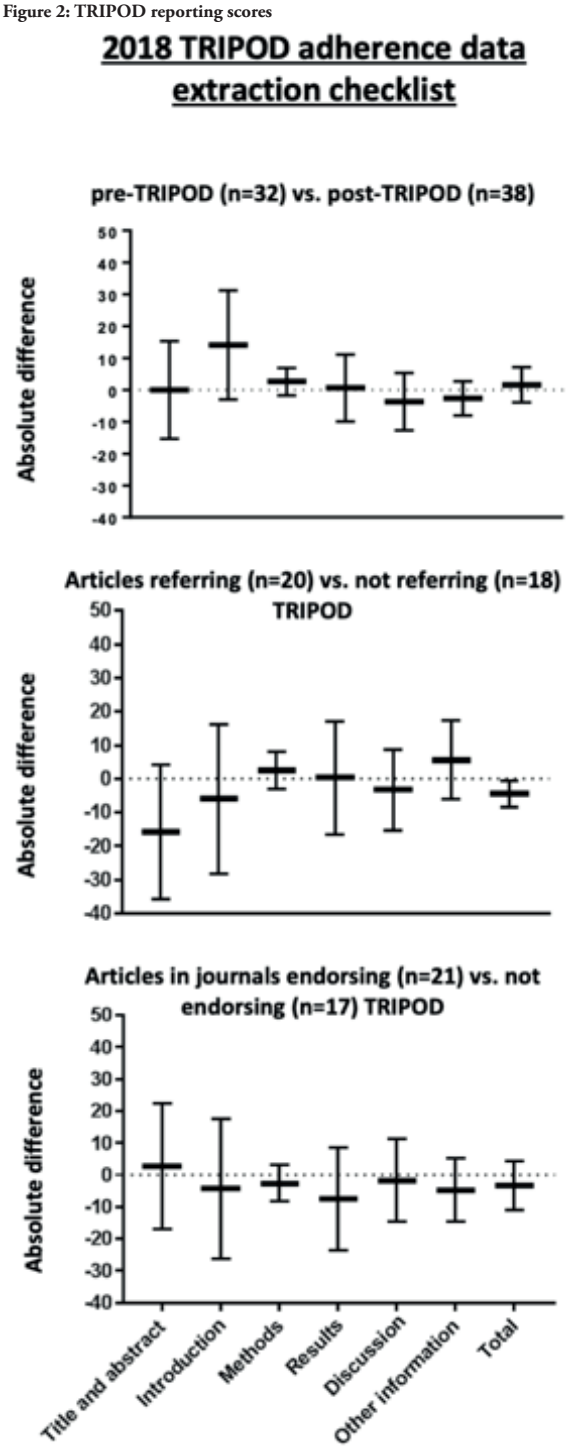
	Before 2015 (n=32) number, (%)	After 2015 (n=38) number, (%)
Diagnostic/Prognostic		
Diagnostic	13 (41%)	4 (11%)
Prognostic	19 (59%)	34 (89%)
Type		
Development	14 (44%)	12 (32%)
Validation	4 (13%)	10 (26%)
Development and Validation	10 (31%)	15 (39%)
Update	4 (13%)	1 (3%)
Setting		
General population and Primary care	18 (56%)	18 (47%)
Secondary care	14 (44%)	20 (53%)
Design		
Cohort	26 (81%)	31 (82%)
RCT	1 (30%)	4 (11%)
Cohort and RCT	2 (6%)	3 (8%)
Case-Control	3 (9%)	0 (0%)
Topic		
(Cardio)vascular	12 (38%)	16 (42%)
Oncological	3 (9%)	8 (21%)
Other	17 (53%)	14 (37%)

The majority of models were developed and/or validated using data from observational cohorts (pre-TRIPOD: 81%, post-TRIPOD: 82%) compared to other study designs such as randomised trials. More than half of the articles published in the post-TRIPOD period referred to the TRIPOD Statement (n=20, 53%) and were published in journals that published the TRIPOD Statement (n=21, 55%). The TRIPOD Statement was cited in 48% of articles published in journals that published the TRIPOD, and in 59% of articles in journals that did not publish TRIPOD.

Assessment of adherence to TRIPOD statement

Using the 2018 TRIPOD Adherence assessment form, a minimal non-significant increase in the overall percentage of reported items was found comparing the pre-TRIPOD period (74%) with the post-TRIPOD period (76%, absolute difference 2%, 95% CI: -4% to 7%, Figure 2, Supplementary Table 1), with no clear trend over the years (Supplementary Figure 1). Results were similar for the comparison between pre-TRIPOD articles and post-TRIPOD articles not citing the statement (76%, absolute difference 2%, 95%CI: -5% to 9%). An improvement

Figure 2: TRIPOD reporting scores



for 16 of the individual TRIPOD items (44% of items, Supplementary Table 2) was seen, while 3 (8%) of items showed no improvement and 17 (47%) items showed a decrease in the percentage of articles appropriately reporting the item. Post-TRIPOD, for articles referring vs. not referring to the statement, published in journals that published vs. did not publish the statement, and published in journals that required adherence to the statement vs. did not require adherence to the statement, no difference in the completeness of reporting was observed (Supplementary Tables 3-5). Five articles presented the completed TRIPOD checklist in the supplementary material and the overall percentage of reporting for these articles was 80%. The percentage of articles reporting TRIPOD items in their supplement is presented in Supplementary Table 6.

Assessment of specific TRIPOD items

Abstract

In both the pre-TRIPOD (16%) and post-TRIPOD period (8%), most abstracts did not report all the proposed sub-items (TRIPOD item 2).

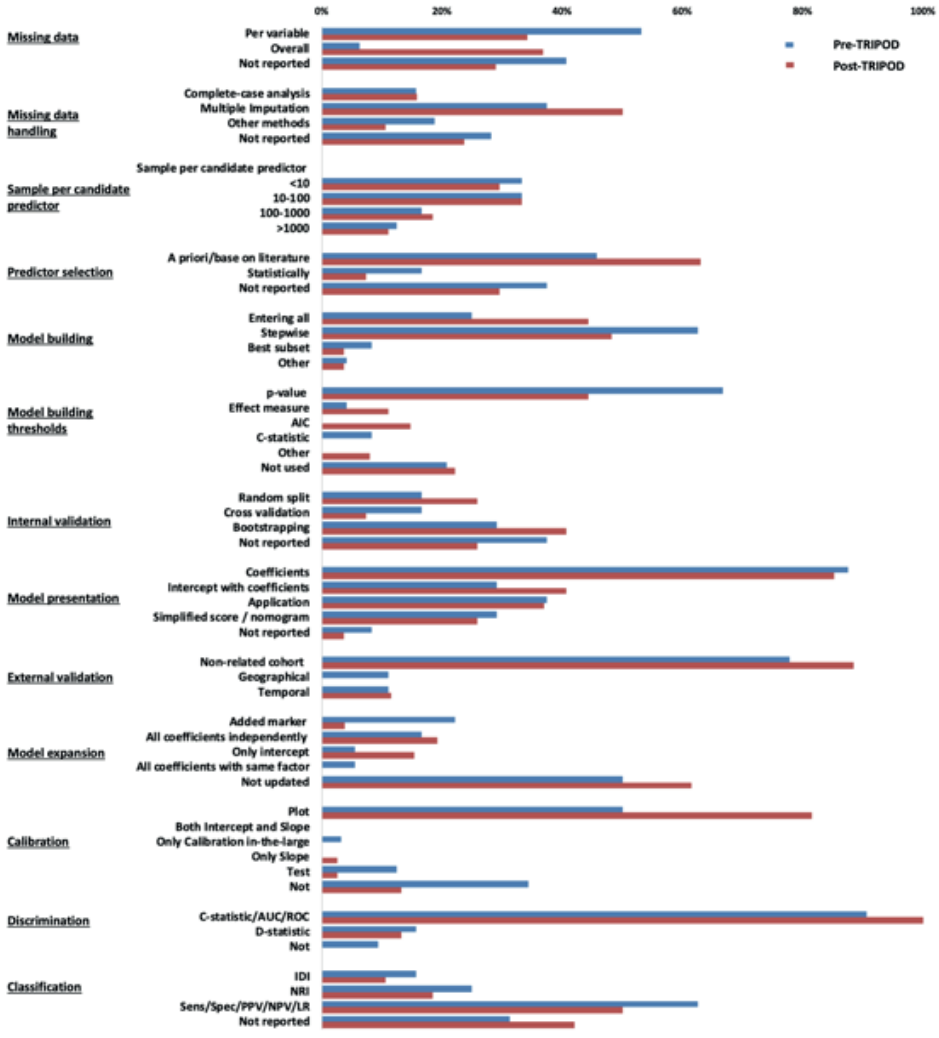
Reporting of missing data

In general, the reporting of missing data (TRIPOD item 13b) improved from 59% in the pre-TRIPOD period to 71% in the post-TRIPOD period, though fewer studies reported missingness per predictor in the post-TRIPOD period (pre-TRIPOD: 53%, post-TRIPOD: 37%, Figure 3 and Supplementary Table 7). Most studies did not report the reason for missing data (pre-TRIPOD: 84%, post-TRIPOD: 95%).

Model development and presentation

In the post-TRIPOD period, proper description of the characteristics of study participants (TRIPOD item 13b) was less often reported (37%) than in the pre-TRIPOD period (50%). In the post-TRIPOD period, method of predictor selection (TRIPOD-item 10b) was more often reported (70%) than in the pre-TRIPOD period (62%), as was internal validation (TRIPOD-item 10b) of the developed model (pre-TRIPOD 62%, post-TRIPOD 74%). If performed, unadjusted analyses were less often reported (TRIPOD item 14b) in the post-TRIPOD period (64%) than in the pre-TRIPOD period (86%). In the post-TRIPOD period, the full model (i.e. intercept or baseline hazard and all regression coefficients: TRIPOD-item 15a) was presented more frequently (41%), compared with the pre-TRIPOD period (29%). However, in both eras some studies still reported no information at all on the final model (pre-TRIPOD 8%; post-TRIPOD 4%, Figure 3 and Supplementary Table 8). To improve clinical usability (TRIPOD-item 15b), more than one third of studies reported to have developed a web application (pre-TRIPOD: 38%, post-TRIPOD: 37%) and some studies provided a simplified clinical risk score or nomogram (pre-TRIPOD: 29%; post-TRIPOD: 26%).

Figure 3: Comparison of used methods in the pre-TRIPOD and post-TRIPOD period



Performance measures

The percentage of studies reporting calibration (TRIPOD-item 16) of the model increased from 66% in the pre-TRIPOD period to 87% in the post-TRIPOD period. Discrimination (TRIPOD-item 16), was reported by all studies in the post-TRIPOD period and by 91% of studies in the pre-TRIPOD period. Measures of classification were reported less frequently in the post-TRIPOD period (pre-TRIPOD: 69%, post-TRIPOD: 58%). Measures of clinical usefulness like decision curve analysis were only reported by 2 (6%) studies in the pre-TRIPOD period and 7 (21%) studies in the post-TRIPOD period. Measures of overall performance like

the Brier score or R^2 were infrequently reported in both periods (pre-TRIPOD: 19%, post-TRIPOD: 21%). Detailed results are depicted in Supplementary Table 7.

Assessment of methods

Handling of missing data

Multiple imputation was the most frequently performed approach for handling missing data (pre-TRIPOD: 38%, post-TRIPOD: 50%). The number of studies that used a complete case analysis remained constant and was 16% in both the pre- and post-TRIPOD period.

Model development

Post-TRIPOD, the number of studies that included predictors based on significance levels in univariable analysis decreased (pre-TRIPOD: 67%, post-TRIPOD: 44%, Figure 2 and Supplementary Table 8) as well as the number of studies using stepwise methods to retain predictors (pre-TRIPOD: 63%, post-TRIPOD: 48%). In general, a larger number of candidate predictors was used in the post-TRIPOD period (median: 25), compared with pre-TRIPOD period (median: 20). Internal validation was more frequently performed in the post-TRIPOD period (74%) compared with the pre-TRIPOD period (62%). When internal validation was performed, bootstrapping was the most frequently used method in both time periods with an increase from 29% in the pre-TRIPOD period to 41% in the post-TRIPOD period.

Performance measures

The majority of studies presented measures of calibration (pre-TRIPOD: 66%, post-TRIPOD: 87%) and discrimination (pre-TRIPOD: 91%, post-TRIPOD: 100%, Figure 3 and Supplementary Table 7).A calibration plot and this increased in the post-TRIPOD period (pre-TRIPOD: 50%, post-TRIPOD: 82%)). Discrimination was primarily assessed with the C-statistic and Area Under the Curve (AUC) methods (pre-TRIPOD: 91%, post-TRIPOD: 100%). Measures of classification were reported in more than half of the studies (pre-TRIPOD: 69%, post-TRIPOD: 58%),mostly assessed with diagnostic test summary statistics (i.e. sensitivity, specificity and positive and negative predictive values) (pre-TRIPOD: 63%, post-TRIPOD: 50%) and to a lesser extent the integrated discrimination improvement (IDI; pre-TRIPOD: 16%, post-TIRPOD: 11%) or the net reclassification improvement (NRI; pre-TRIPOD 25%, post-TRIPOD: 18%).

External validation and model updating

Most external validation studies performed the validation in individuals fully unrelated to the development cohort (pre-TRIPOD 78%, post-TRIPOD: 88%, Figure 3 and Supplementary Table 9). Models were updated with an additional predictor in 4 (13%) studies before the TRIPOD statement and in 1 (3%) study after the TRIPOD statement.

DISCUSSION

No significant improvement in the overall reporting quality of prediction models published in the seven general medicine journals with the highest impact factor was found in the post-TRIPOD period, according to the TRIPOD Adherence form. However, an improvement in general methodological conduct was found. Notably, more studies described external validation of a model, reported information on missing data, used multiple imputation methods instead of complete case analysis for handling of missing data, selected and maintained variables in multivariable models based on clinical relevance instead of statistical cut-offs, and assessed both discrimination and calibration measures. While improvement was found for almost half of the TRIPOD items, no improvement or a deterioration was found for the other half of the items.

Recommendations on reporting and methods

Though improvements over time in specific aspects of reporting and methods were apparent, there is room for further progress. While an increase in studies reporting the percentage of missing data in the post-TRIPOD period was observed, the amount of missingness was often not reported per predictor, yet this is important for the assessment of clinical usability of the model.[15] Multiple imputation was the most frequently performed method for handling missing data, which generally is the preferred approach.[23] Reporting of all coefficients of the final multivariable model and intercept, which is necessary for external validation and clinical use of models, increased over time.[22] Although widely discouraged, a number of studies in both the pre-TRIPOD and post-TRIPOD period included predictors in multivariable prediction models based on data-driven selection methods such as univariable significance and/or stepwise methods. Such methods increase the risk of overfitted and poorly calibrated models.[11,22–26] Instead, it is advised to select predictors based on clinical knowledge and previous literature.[27] While the percentage of studies that both developed and externally validated a model increased over time, still more than 30% of articles only described the development of a model. External validation in a fully independent cohort is strongly recommended, as model performance might significantly decrease in cohorts other than the development cohort.[28] Assessment of both calibration and discrimination also increased, which is necessary in order to judge a model's predictive accuracy. Calibration refers to the agreement between absolute predicted and observed outcomes and the majority of studies used the preferred calibration plot.[29] Discrimination, a relative measure on the ability to distinguish between patients with and without the outcome, was reported by almost all studies.[29]

Comparison with other reporting guidelines

A large number of reporting guidelines have been published for various study types.[19,30–33] Mixed results on the effect of these guidelines on the completeness of reporting have been found.[34–38] While an overall modest improvement in reporting was described for randomised

controlled trials after publication of the CONSORT statement and by the STARD statement for diagnostic studies, no clear improvement was described for observational studies by the STROBE statement and prognostic marker studies by the REMARK guideline as described by the authors of these studies.[34–38] These findings pose the question how the introduction and publication of these guidelines can optimally impact the research field. For both the CONSORT and STARD statement, journals endorsing the statement showed a higher level of reporting compared with journals not endorsing these statements. Nevertheless, this was not found for the REMARK guideline, nor in our study for the TRIPOD statement.[34,37,38] Evidence of a relation between citing the statement and reporting level is also limited, as no association between this was found for the STARD nor in our study.[38] Requiring authors to provide and publish the completed checklist might help to improve reporting levels, as we found that the small numbers of studies providing the checklist reported more items on average. Therefore, we do not only recommend journals to ask authors to submit the completed checklist upon submission, but also require authors to publish it as a supplement, and reviewers and editors to control the provided checklist. However, as endorsing, citing and providing the checklist seems to have only a small effect on the reporting quality, we believe it is even more important to train methodologists and clinicians to interpret and use the checklist. This is supported by the results that even studies that provided the completed checklist, still did not report all items of the TRIPOD statement in analysis of reporting. Documents such as the TRIPOD Exploration and Elaboration document facilitate proper interpretation, but we believe that the threshold to use this detailed document might be too high for the unexperienced researcher. Other possibilities to familiarize authors with the checklist should be explored, such as collaborative efforts of educational institutions and the TRIPOD committee to train researchers and clinicians. Online training courses might be of added value to reach a large target group.

Comparison with other reviews on the completeness of reporting and methodological conduct of prediction models

Previous studies, published between 2012 and 2014, concluded poor reporting and use of methods for prediction models.[11,13,20,21] Comparing our results with a study assessing reporting and methods of prediction studies published in 6 high impact general medicine journals in 2008, improvement since then is clear for both methods and reporting. Considering methods more studies are externally validated, compose calibration plots to assess calibration and use multiple imputation for handling missing data. Improvement in reporting is also apparent as more studies report calibration and discrimination measures. Furthermore, a recently published article assessed the reporting quality of prediction models published in 37 clinical domains in 2014 using the 2018 TRIPOD Adherence assessment form, which found similar results to our Pre-TRIPOD results.[17] As we only included articles published in high impact general medicine journals it is difficult to generalize these results to the entire medical academic research field. We could argue that the improvement we observed might be an overestimation

if general medical journals adopted the TRIPOD guidelines and new methodological insights with more speed and rigour. However, the opposite might also be true as these high impact general medicine journals already had high methodological standards before the TRIPOD statement publication.[11,13,16,21,35,36,39,40]

Strengths and Limitations

A limitation of the current study is that the evaluation of studies was limited to the first two years after the TRIPOD statement publication. It may take some years before a reporting guideline is widely disseminated and accepted and the full impact is measurable. However, to somewhat overcome this problem we did not include any articles published in 2015, as the TRIPOD statement was published in January 2015 and we therefore saw this as a transition period. In addition, a previously published study on the effect of STARD found significant improvement within two years after publication.[38] Furthermore it is not possible to causally attribute the reported changes to the TRIPOD statement, as the results might be confounded by other developments in the last decade, such as publication of multiple series on the conduct of prediction models, publication of other guidelines such as the REMARK guideline for tumor marker prognostic studies, and a general increase in the numbers of published prediction models.[41–43] One may also expect that authors who work in the field of prediction models are aware of the publication of the TRIPOD statement, especially those who publish in high impact general medicine journals. A strength of the study is that the actual used methods for the development, description, validation and updating of prediction models were also assessed. While reporting and used methods are inherently related, the focus is different. A poorly developed model may be described fully and transparently in a manuscript and score high on reporting quality and vice versa a well-developed model may have poor reporting.[16] Furthermore, we have facilitated comparison to future TRIPOD reviews by using the 2018 TRIPOD Adherence assessment form. Although both reporting and methods were comprehensively assessed, we might have missed interesting items for evaluation, especially as the field of prediction models is continuously developing. We also did not assess the risk of bias of the included studies with the PROBAST risk of bias assessment tool, as it would be not feasible to score the included articles according to the PROBAST, since to do so subject-specific knowledge is required and the included studies span a wide range of clinical subjects. Furthermore, as the PROBAST only gives suggestions for signalling questions and no scoring rules, it does not completely fit with the aim to assess the actual used methods of the included studies. Furthermore, it would have been of interest to compare articles published in journals that between January 2016 and December 2017 obligated authors to complete the TRIPOD checklist, however this information was not available.

Unanswered questions and future research

Future studies should focus on the long-term effects of the TRIPOD statement publication on reporting quality and methods, using the 2018 TRIPOD Adherence form to allow for comparisons over time using the same adherence assessment tool. In addition, effects of the statement should be assessed in different medical fields for which a pre-TRIPOD baseline measurement is already performed.[16] Earlier studies on the effect of other reporting guidelines showed that the effect of these guidelines may be smaller or larger in specific medical fields.[34,40]

A new emerging field is the development of prediction models using artificial intelligence, machine learning and deep learning methods. In addition, more often omics data is used as predictors for these models.[44] While these models have many similarities with traditional regression methods, they differ in some aspects and may require specific guidelines on reporting.[44,45] Accordingly, the TRIPOD-AI tool has recently been announced and is underway.[46] Similarly, reporting guidelines for prediction model impact studies are missing.

With the increasing number of reporting guidelines and lack of clear evidence that all guidelines improve reporting quality, research should be conducted to find methods to optimise the form, use and impact of these guidelines. With this in mind, there should also be focus on the overlap between different reporting guidelines. Prediction models can be reported following the TRIPOD statement, the STARD statement for diagnostic test accuracy studies, and REMARK for prognostic tumor marker studies. As an increasing amount of studies contain multiple goals, analyses and data sources, it may be difficult to adhere to all applicable and relevant guidelines within the maximum word count. This holds especially for the abstract section of articles.

Conclusion

No improvement was found comparing the post-TRIPOD period with the pre-TRIPOD period in the overall reporting quality of prediction models published in the seven general medicine journals with the highest impact factor. Comparison of articles published before the TRIPOD statement with non-TRIPOD citing articles published after the TRIPOD statement, yielded similar results as the main pre-post comparison, further suggesting a lack of direct impact of the TRIPOD statement on overall reporting levels. However improvement was found in various specific aspects methodological conduct. More studies described external model validations, reported information on missing data, used multiple imputation methods for handling of missing data, reported the full prediction model and reported information on performance measures. However, there is still room for improvement in both the reporting and used methods of these models, as prediction models are still erroneously developed and validated and many aspects remain poorly reported, hindering optimal use of these models in clinical decision making. Long-term effects of the TRIPOD statement publication should be

evaluated in future studies, ideally using the same 2018 TRIPOD Adherence assessment form to allow for comparisons over time.

Contributorship:

AHZN conceived the study. AHZN, MvD, CLR, and EWS developed the study design with input from FWD, PH, LH, KGMM, WCP, GSC. AHZN and CLR screened the literature and performed the data-extraction. AHZN performed the statistical analysis and wrote the first and successive drafts of the manuscript. AHZN, CLR, FWD, PH, LH, KGMM, WCP, GSC, EWS, MvD interpreted the data, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript.

Funding:

AHZN and CLR were supported by personal Leiden University Medical Center MD/PhD Scholarships. MvD was supported by a grant from the Dutch Kidney Foundation (16OKG12). GSC is supported by the NIHR Biomedical Research Centre, Oxford and Cancer Research UK programme grant (C49297/A29084).

Competing interests:

GSC, KGMM, and EWS are members of the TRIPOD group. All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no other support from any organisation for the submitted work than the grants reported in the funding section; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval:

Not required

Data sharing:

All datasets that were used are retrievable following the instruction of the original papers.

Transparency:

The lead author (AHZN) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Patient and Public Involvement:

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Dissemination declaration:

Not applicable.

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SUPPLEMENTS

Supplementary Table 1: TRIPOD reporting scores for all included articles

	Before % n=32	After % n=38	Absolute difference of percentages (95% CI)
Title and abstract	25	25	0 (-15 to 15)
Introduction	69	83	14 (-3 to 31)
Methods	80	83	3 (-2 to 7)
Results	66	67	1 (-10 to 11)
Discussion	89	85	-4 (-13 to 5)
Other information	100	97	-3 (-8 to 3)
Total	74	76	2 (-4 to 7)

Supplementary Table 2: TRIPOD reporting scores for individual TRIPOD items

TRIPOD item	pre-TRIPOD %	post-TRIPOD %	TRIPOD item	pre-TRIPOD %	post-TRIPOD %
1	34	42	**10d**	69	71
2	16	8	**10e**	56	50
3a	78	84	**11**	96	95
3b	59	82	**12**	75	71
4a	97	100	**13a**	94	95
4b	91	95	**13b**	50	37
5a	97	95	**13c**	53	65
5b	97	97	**14a**	100	97
5c	100	60	**14b**	86	64
6a	97	97	**15a**	27	42
6b	97	95	**15b**	65	61
7a	88	87	**16**	66	68
7b	94	100	**17**	40	73
8	100	100	**18**	94	97
9	28	24	**19a**	82	75
10a	63	84	**19b**	100	95
10b	19	39	**20**	75	68
10c	67	100	**22**	100	97

Supplementary Table 3: TRIPOD reporting scores for articles published after TRIPOD statement referring vs not referring to the statement

	TRIPOD not referred % n=18	TRIPOD referred % n=20	Absolute difference of percentages (95% CI)
Title and abstract	33	18	-16 (-36 to 4)
Introduction	86	80	-6 (-28 to 16)
Methods	82	84	2 (-3 to 8)
Results	67	67	0 (-17 to 17)
Discussion	87	83	-3 (-15 to 9)
Other information	94	100	6 (-6 to 17)
Total	76	76	-1 (-8 to 7)

Supplementary Table 4: TRIPOD reporting scores for articles published after TRIPOD statement in journals that published and did not publish the TRIPOD statement

	TRIPOD not endorsed % n=17	TRIPOD endorsed % n=21	Absolute difference of percentages (95% CI)
Title and abstract	24	26	3 (-17 to 22)
Introduction	85	81	-4 (-26 to 18)
Methods	84	82	-3 (-8 to 3)
Results	71	63	-7 (-24 to 9)
Discussion	86	84	-2 (-15 to 11)
Other information	100	95	-5 (-15 to 5)
Total	78	75	-3 (-11 to 4)

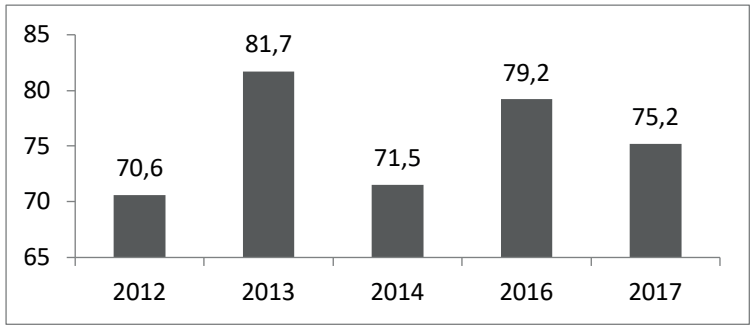
Supplementary Table 5: TRIPOD reporting scores for articles published after TRIPOD statement in journals that require adherence to the TRIPOD statement and journals that do not require to the adherence statement

	TRIPOD not required % n=16	TRIPOD required % n=22	Absolute difference of percentages (95% CI)
Title and abstract	25	25	0 (-21 to 21)
Introduction	81	84	3 (-20 to 26)
Methods	83	83	0 (-6 to 6)
Results	66	67	1 (-16 to 19)
Discussion	90	81	-8 (-20 to 3)
Other information	100	95	-5 (-15 to 5)
Total	76	76	0 (-8 to 9)

Supplementary Table 6: Percentage articles reporting TRIPOD items in supplementary material

TRIPOD item	Supplement %
1	0
2	0
3a	0
3b	0
4a	7
4b	7
5a	10
5b	6
5c	33
6a	13
6b	0
7a	36
7b	0
8	3
9	9
10a	12
10b	13
10c	14
10d	1
10e	0
11	4
12	24
13a	21
13b	30
3c	17
14a	2
14b	40
15a	40
15b	35
16	0
17	17
18	0
19a	0
19b	0
20	0
22	1

Supplementary figure 1: Average overall TRIPOD reporting levels in percentage per year



Supplementary Table 7: Performance measures and missing data in all studies

	Before 2015 (n=32) Number (%)	After 2016 (n=38) Number (%)
Calibration		
Plot	16 (50%)	31 (82%)
Intercept and Slope	0 (0%)	0 (0%)
Calibration in-the-large	1 (3%)	0 (0%)
Slope	0 (0%)	1 (3%)
Test	4 (13%)	1 (3%)
Not	11 (34%)	5 (13%)
Discrimination		
C-statistic / AUC	29 (91%)	38 (100%)
D-statistic	5 (16%)	5 (13%)
Not	3 (9%)	0 (0%)
Classification		
IDI	5 (16%)	4 (11%)
NRI	8 (25%)	7 (18%)
Sens. Spec. PPV. NPV. LR. ROC	20 (63%)	19 (50%)
Not reported	10 (31%)	16 (42%)
Clinical usefulness		
Decision curve analysis	2 (6%)	8 (21%)
Not reported	30 (94%)	30 (79%)
Overall performance		
Brier	2 (6%)	3 (8%)
R2	4 (13%)	5 (13%)
Adequacy statistic	1 (3%)	2 (5%)
Not reported	26 (81%)	28 (74%)
Missing data reporting		
Per variable	17 (53%)	13 (34%)
Overall	2 (6%)	14 (37%)
Not reported	13 (41%)	11 (29%)
Type and reason of missing data		
Type reported	3 (9%)	2 (5%)
Reason reported	5 (16%)	2 (5%)
Missing data handling		
Complete-case analysis	5 (16%)	6 (16%)
Multiple Imputation	12 (38%)	19 (50%)
Other methods	6 (19%)	4 (11%)
Not reported	9 (28%)	9 (24%)

Supplementary Table 8: Model development and presentation

	Before 2015 (n=24) Number (%)	After 2016 (n=27) Number (%)
Sample per candidate predictor		
<10	8 (33%)	8 (30%)
10-100	8 (33%)	9 (33%)
100-1000	8 (17%)	5 (19%)
>1000	3 (13%)	3 (11%)
Unknown number of predictors	0 (0%)	1 (4%)
Unknown number of outcomes	1 (4%)	1 (4%)
Model Type		
Linear	1 (4%)	0 (0%)
Logistic	16 (67%)	15 (56%)
Cox	6 (25%)	10 (37%)
Points	0 (0%)	2 (7%)
Other	1 (4%)	0 (0%)
Predictor Selection		
A priori knowledge / based on literature	11 (46%)	17 (63%)
Statistically	4 (17%)	2 (7%)
Not reported	9 (38%)	8 (30%)
Model building		
Entering all	6 (25%)	12 (44%)
Stepwise	15 (63%)	13 (48%)
Best subset	2 (8%)	1 (4%)
Other	1 (4%)	1 (4%)
Model building thresholds		
p-value	16 (67%)	12 (44%)
Effect measure	1 (4%)	3 (11%)
R	0 (0%)	1 (4%)
Manually	0 (0%)	1 (4%)
AIC	0 (0%)	4 (15%)
C-statistic	2 (8%)	0 (0%)
Other	0 (0%)	0 (0%)
Not used	5 (21%)	6 (22%)
Internal validation		
Random split	4 (17%)	7 (26%)
Cross validation	4 (17%)	2 (7%)
Bootstrapping	7 (29%)	11 (41%)
Not reported	9 (38%)	7 (26%)
Model presentation		
Coefficients	21 (88%)	23 (85%)
Intercept with coefficients	7 (29%)	11 (41%)
Application	9 (38%)	10 (37%)
Simplified score / nomogram	7 (29%)	7 (26%)
Not reported	2 (8%)	1 (4%)

Supplementary Table 9: External validation and updating

	Before 2015 (n=18) Number (%)	After 2016 (n=26) Number (%)
External validation		
Fully independent	14 (78%)	23 (88%)
Geographical	2 (11%)	0 (0%)
Temporal	2 (11%)	3 (12%)
Model updating		
Added marker	4 (22%)	1 (4%)
All coefficients independently	3 (17%)	5 (19%)
Only intercept	1 (6%)	4 (15%)
All coefficients with same factor	1 (6%)	0 (0%)
Not updated	9 (50%)	16 (62%)

Supplementary text 1: Protocol

Article selection

Search strategy:

("The New England journal of medicine"[Journal] OR "Lancet (London, England)"[Journal] OR "BMJ (Clinical research ed.)"[Journal] OR "*JAMA*"[Journal] OR "PLOS Medicine"[Journal] OR "*Annals of Internal Medicine*" [Journal] OR "*BMC Medicine*"[Journal]) AND (predict*[ti] OR prognost*[ti] OR diagnostic*[ti] OR "risk score"[ti]) NOT ("Animals"[mesh] NOT "Humans"[mesh]) NOT (("case reports"[ptyp] OR "case report"[ti]) NOT ("Review"[ptyp] OR "clinical study"[ptyp] OR "case series"[tw]))

Articles included

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Assessment of study characteristics, used methods and specific reporting items

3 Background and Objectives	
3a: Type of predictive study	1. Prognostic 2. Diagnostic
3a: Topic Study	1. (Cardio)vascular 2. Oncological 3. Surgical 4. Other
3b: Model development and validation	1. Development 2. Validation 3. Development and Validation 4. Updating
4 Source of Data	
4a: Study design	1. RCT 2. Prospective cohort 3. Retrospective cohort 4. Nested case-control 5. Non-nested case-control
5 Participants	
5a: Study Setting	1. General population 2. Primary care 3. Secondary care
6 Outcome	
6a: Definition outcome	1. What is the outcome? 2. What is the time frame?
6a: Type of outcome	1. Dichotomous, 2. Continuous 3. Ordinal 4. Nominal 5. Time to event
9 Missing Data	
9 Type	1. MAR 2. MCAR 3. MNAR
9 Reason	Reason missing data
9 Handling	1. Complete-case analysis 2. Single imputation 3. Multiple imputation 4. Missing indicator method 5. Last observation carried forward 6. Mean imputation 7. Other

10 Statistical Analysis and Methods	
10a: Analysis of predictors	1. Categorical 2. Linear: kept linear 3. Linear: dichotomized 4. Linear: categorized 5. Linear: polynomial transformation 6. Linear: spline transformation, 7. Linear: interaction 8. Linear: log-transformation 9. Other (multiple options possible)
10b: Type of Model	1. Linear 2. Logistic 3. Ordinal 4. Nominal 5. Survival 6. Poisson 7. Points 8. Other
10b: Selection Predictors	1. A priori knowledge 2. Based on the literature 3. Statistically (multiple options possible)
10b: Model building procedure	1. Entering all predictors 2. Forward selection 3. Backward selection 4. Best subset
10b: Statistical thresholds for model building	1. p-value: threshold 2. AIC/BIC 3. R^2 4. C-statistic/AUC 5. HR 6. Manually
10b: Internal Validation methods	1. Apparent 2. Random split 3. Cross-validation 4. Bootstrapping (multiple options possible)
10d: External Validation methods	1. Temporal validation 2. Geographical validation 3. Fully independent 4. Other (Multiple options possible)
10d: Performance Calibration	1. Test 2. Slope 3. Intercept and slope 4. Calibration in-the-large 5. Plot (multiple options possible)

10d: Performance Discrimination	1. C-statistic / AUC after Development 2. C-statistic / AUC after Internal validation 3. C-statistic / AUC after external validation 4. D-statistic
10d: Performance Classification	1. Sensitivity / Specificity 2. Positive Predictive Value / Negative Predictive Value 3. Likelihood ratio (multiple options possible)
10d: Performance Other	1. IDI 2. NRI 3. Decision curve analysis (multiple options possible)
10d: Performance Overall	1. Brier 2. 2. R^2
10e: Model Updating	1. Intercept 2. all coefficients changed with same factor 3. Re-estimation all coefficients independently 4. 2+ selection of additional predictors 5. 3+ Reestimation all coefficients

13 Participants	
13a: Number of Participants	1. Number of participants with and without outcome
13b: Missing Values	Reported for 1. Any value 2. Per predictor 3. For predictors in general 4. For outcome (multiple options possible)

15 Model Specification	
15a Intercept or baseline hazard	
15a: Coefficients	Coefficients reported: 1. All univariate 2. Univariate of included predictors in final model 3. All multivariate 4. Multivariate of predictors included in final model (multiple option possible)
15a: Number of predictors	Number of predictors in final model
15a: Use of model	Use of model reported as: 1. Only regression coefficients 2. Intercept with regression coefficients 3. Simplified score (incl. nomogram or app) (multiple options possible)

Chapter 8

Determinants and predictors of the long-term disease burden in meningioma

Journal of Neuro-Oncology, 2021;151(2):201-210

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ABSTRACT

Introduction

Meningioma is a heterogeneous disease and patients may suffer from long-term tumor- and treatment-related sequelae. To help identify patients at risk for these late effects, we first assessed variables associated with impaired long-term health-related quality of life (HRQoL) and impaired neurocognitive function on group level (i.e. determinants). Next, prediction models were developed to predict the risk for long-term neurocognitive or HRQoL impairment on individual patient-level.

Methods

Secondary data analysis of a cross-sectional multicenter study with intracranial WHO grade I/II meningioma patients, in which HRQoL (Short-Form 36) and neurocognitive functioning (standardized test battery) were assessed. Multivariable regression models were used to assess determinants for these outcomes corrected for confounders, and to build prediction models, evaluated with C-statistics.

Results

Data from 190 patients were analyzed (median 9 years after intervention). Main determinants for poor HRQoL or impaired neurocognitive function were patients' sociodemographic characteristics, surgical complications, reoperation, radiotherapy, presence of edema, and a larger tumor diameter on last MRI. Prediction models with a moderate/good ability to discriminate between individual patients with and without impaired HRQoL (C-statistic: 0.73, 95%CI: 0.65 to 0.81) and neurocognitive function (C-statistic: 0.78, 95%CI: 0.70 to 0.85) were built. Not all predictors (e.g. tumor location) within these models were also determinants.

Conclusions

The identified determinants help clinicians to better understand long-term meningioma disease burden. Prediction models can help early identification of individual patients at risk for long-term neurocognitive or HRQoL impairment, facilitating tailored provision of information and allocation of scarce supportive care services to those most likely to benefit.

Key words

Meningioma; health-related quality of life; neurocognitive functioning; predictors; determinants; risk factors

INTRODUCTION

Although over 95% of meningioma patients have a non-malignant WHO grade I or II tumor[1], these patients still suffer from a clinically relevant disease burden, even after tumor resection, which can persist over time[2–6]. Compared with controls, meningioma patients report on average worse health-related quality of life (HRQoL) up to nine years after surgery[3,4]. Approximately 40% of patients have neurocognitive impairments, although these impairments are often not considered clinically meaningful[5–7]. However, not all meningioma patients have poor outcomes and it is currently unclear which factors are related to the long-term disease burden, while it might help to better understand the disease burden in meningioma patients. In the clinical setting, early identification of patients at high risk for a long-term disease burden facilitates timely provision of information and rehabilitation, and allocation of scarce supportive care services to those most likely to obtain benefit.

A limited number of published studies have reported a variety of variables associated with increased meningioma disease burden in the first years after treatment, primarily focusing on sociodemographic (e.g. higher age and lower educational level), tumor (e.g. larger tumor diameter and higher WHO grade) and treatment characteristics (e.g. higher Simpson grade and receiving radiotherapy)[3,7]. However, there are no published studies on the possible factors associated with the long-term disease burden (≥5 years). This distinction is important as patients might suffer from different issues during the treatment phase, then they do on the longer term (i.e. survivorship issues). First, some aspects of treatment toxicity only become apparent on the long-term, e.g. neurocognitive impairments caused by radiotherapy[2,8–11]. Second, patients learn to adapt to the disease-related symptoms and change their coping strategies over time, influencing patients' perception of their disease burden[2,12]. Finally, on the long-term patients might face growth of tumor remnant or recurrence of disease, sometimes requiring intervention.[13]

A methodological limitation of most published studies determining associations between certain risk factors and outcomes is the lack of distinction between determinants and predictors[14]. A determinant is an individual variable that on group-level is independently associated with the outcome of interest, corrected for confounding (e.g. the association between sex or tumor location with the long-term disease burden). Prediction models on the other hand use multiple variables together (i.e. patient, tumor and treatment characteristics) to predict for an individual patient the risk to develop a certain outcome of interest. Although both reflect patients' future outcomes, determinants are variables with an assumed causal relationship to the outcome of interest (e.g. postoperative complications may have a negative impact on a patient's long-term HRQoL), while predictors are solely used to predict the outcome of interest (e.g. hospitalization length may be predictive for diminished HRQoL on the long-term), without assuming causality.

We aimed to assess in meningioma patients determinants for the long-term disease burden, defined as impaired HRQoL and neurocognitive function at a median of 9 years after the last intervention. Furthermore, we have built prediction models to identify individual patients with a high risk around the time of intervention to suffer from a long-term impairment in HRQoL or neurocognitive function.

METHODS

Participants

This is a secondary analysis of a multicenter cross-sectional study, assessing the long-term disease burden in meningioma patients.[15] Consecutive meningioma patients were recruited from the neurology, neurosurgery and radiation oncology outpatient clinics of two academic hospitals and one large non-academic teaching hospital between July 2016 and April 2019. Patients were eligible if the end of their anti-tumor treatment was at least 5 years prior to recruitment, or in case of active MRI surveillance, at least five years after diagnosis. Furthermore, patients had to be 18 years or older; with a histologically confirmed WHO grade I or II meningioma in case of surgery, and an MRI-based clinically suspected meningioma in case of radiotherapy only or active MRI surveillance. Exclusion criteria for study participation were history of whole brain radiotherapy, diagnosis with a neurodegenerative disease (including neurofibromatosis type II), or patients not proficient in the Dutch language.

Procedures

Information on tumor and treatment was obtained from patient's charts, and sociodemographic information was obtained at the beginning of the assessments (questionnaires and neurocognitive testing) from patients themselves. Radiological variables, such as tumor size and location, were assessed and recorded by the researchers to ensure uniformity of measurement. Clinician observed level of function was assessed using the Karnofsky Performance Score (KPS).

Patient-reported outcome measures

HRQoL was measured with the validated Short-Form Health Survey (SF-36), which yields 8 domain scores and two component scores (physical component summary (PCS) and mental component summary (MCS), ranging from 0 to 100, with higher scores representing better HRQoL[16–18].

Neuropsychological assessment

Neuropsychological performance was assessed with a comprehensive battery of neuropsychological tests by trained research assistants and nurses: Digit-Symbol Substitution Test, Auditory Verbal Learning Test, Categoric Word Fluency Test,, Concept Shifting Test, Memory Com-

parison Test, and Stroop Colour-Word Test.[9,10,19] Based on these tests, scores for the following neurocognitive domains were calculated: verbal memory, executive functioning, working memory, information processing speed, psychomotor functioning, and attention[9,10,19]. Each domain was transformed into Z-scores, using means and standard deviations from a reference sample from the Maastricht Aging Study (MAAS; large longitudinal study on the psychological and biological determinants of cognitive aging), matched on group-level for age, sex and educational level[20].

Statistical Analysis

Multivariable regression analyses were performed to: 1) estimate the association between individual determinants, corrected for confounders, and impaired HRQoL and neurocognitive function, 2) build prediction models which could be used to predict the risk for impaired HRQoL or neurocognitive function for an individual patient based on patient-, tumor-, and treatment-related characteristics around diagnosis and the intervention. Although for both analyses multivariable regression analyses are used, the statistical considerations and interpretation differ considerably. First, for the development of prediction models, only variables measured at baseline (around diagnosis and intervention) were included because the aim is to predict a future outcome. To assess determinants, variables later in the disease course were also considered (e.g. peritumoral edema before study assessment). Second, the outcomes of interest were dichotomized for the development of prediction models, as this facilitates use in clinical practice (i.e. does a patient have an impairment or not). For the analyses of determinants, outcomes were kept as continuous variables, as this increases statistical power.

Based on minimally clinically important differences as reported in the literature, HRQoL physical and mental component scores were dichotomized as follows: poor physical component score was defined as a score <46.4 and poor mental component score as a score <47.0.[21] Impaired neurocognitive functioning was defined as a z-score<1.5 in at least one out of six domains.[22]

For all statistical tests, SPSS 23 (SPSS Inc, Chicago, IL) was used, and P less than .05 was considered statistically significant.

Analysis of Determinants

For the assessment of determinants, multivariable linear regression analyses were performed assessing the causal relationship between determinants (independent variable) and 5 outcomes (dependent variables): the SF-36 physical and mental component score (HRQoL), and z-scores for verbal memory, executive function, and attention (neurocognitive function). To reduce the number of analyses, only these 3/6 neurocognitive domains were chosen, as earlier analyses of this sample showed that patients primarily suffer from impairments in these domains[15].

Separate multivariable analyses were run for each association between a single determinant and a single outcome, corrected for possible confounders. A-priori confounders were chosen for each analysis, based on prior knowledge and defined as associated with both the determinant and outcome, but not lying in the causal path between the determinant and outcome. Results were expressed as beta (β) with 95% confidence intervals (CI).[14]

Analysis of Predictors

For prediction analyses we developed two multivariable logistic regression models for the following two dichotomous outcomes (dependent variables): impaired HRQoL (physical component score <46.4 or mental component score <47.0) and impaired neurocognitive function (z-score<1.5 in at least one out of six domains). Based on the literature, clinically relevant variables were analyzed in univariable logistic regression analysis: gender, age, educational level, Charlson Comorbidity Index, tumor location and size, treatment characteristics (i.e. first resection, second resection, complications, radiotherapy), Simpson grading, WHO grade, years since diagnosis, and for the model predicting neurocognitive function also hand dominance. Variables were selected for multivariable analyses based on statistical significance in univariable regression analysis.[3,4,7,23–29] A $p<0.20$ as selection criterion was used to limit chances of overfitting. Sensitivity analyses were performed with a cut-off of $p<0.15$. We assessed the discrimination for each model, using the area under the receiver-operating curve (AUC) including 95% confidence interval (CI). For each model we provided two patient examples showing how to calculate the absolute risk of impaired HRQoL or neurocognitive function for an individual patient.

RESULTS

A total of 190 patients (female: n=149, 78%) were included in the analyses with a median follow-up since intervention of 9 years (IQR: 7-12 years) (Table 1). Patients were on average 63 (SD: 12) years old. Tumors were located on the skull base in 92 patients (48%), the cerebral convexity in 93 patients (49%) and other intracranial locations in 5 patients (3%). The majority of operated patients were classified with a WHO grade I meningioma (88%). Surgery was first line treatment in 168 (88%) patients, 36 (19%) received radiation.

A total of 93 (49%) patients suffered from impaired HRQoL (PCS: n=78, 41%; MCS n=47, 53%), and 81 (43%) from objective neurocognitive deficits. A total of 127 (67%) suffered from a HRQoL impairment, *or* neurocognitive deficit.

Table 1: Sociodemographic and clinical characteristics of the included meningioma patients

	Meningioma Patients n=190
Age, years	63 (SD 12)
Sex (Female)	149 (78%)
Academic hospital (vs. nonacademic teaching hospital)	142 (75%)
Meningioma Location	
Skull base	92 (48%)
Convexity	93 (49%)
Other	5 (3%)
Time since diagnosis, years	10 (8-12)
Tumor size before intervention, mm	38 (26-50)
Tumor size before study, mm	0 (0-16)
Tumor growth on last MRI before study	10 (5%)
Number of meningiomas ≥2	26 (14%)
Active MRI surveillance	12 (6%)
Surgery as initial treatment	168 (88%)
Complication first surgery (operated patients: n=168)	63 (38%)
Second surgery	13 (7%)
Time since first surgery, years	9 (7-12)
Simpson Grade (operated patients: n=168)	
Grade I-III	109 (65%)
Grade IV-V	40 (24%)
Unknown	19 (11%)
WHO grade (operated patients: n=168)	
Grade I	148 (88%)
Grade II	12 (7%)
Unknown	8 (5%)
Radiotherapy*	36 (19%)
Radiotherapy as initial treatment	10 (5%)
Adjuvant radiotherapy	26 (14%)
Time since radiotherapy, years	8 (6-9)
Karnofsky Performance Status at time of study	100 (90-100)
Self-perceived neurocognitive impairment at time of study	94 (49%)
Self-reported motor dysfunction at time of study	55 (29%)
Dexamethasone use for symptoms at any moment during the care trajectory	22 (12%)
Physical rehabilitation	37 (19%)
Cognitive rehabilitation	8 (4%)
Psychological support	21 (11%)
Other supportive care	10 (5%)
Educational level	

Table 1: Sociodemographic and clinical characteristics of the included meningioma patients (continued)

	Meningioma Patients n=190
Primary/Secondary	40 (21%)
Tertiary: technical/vocational	85 (45%)
Academic	59 (31%)
Not provided	6 (3%)
Charlson Comorbidity Index	
0	127 (67%)
1≥	63 (23%)
Right handed	147 (77%)

* Radiotherapy techniques changed over time in each participating center, but all patients treated with radiotherapy received fractioned radiation.

Table 2: Determinants for Health-related Quality of Life as measured with the Short-from 36 (SF-36), separately for the physical and mental component score

	Physical component score β (95%CI)	Mental component score β (95%CI)
Sex female (ref: male)	**-2.521 (-6.393 to 1.351)**	0.066 (-4.182 to 4.315)
Age, years	-0.113 (-0.248 to 0.023)	-0.016 (-0.165 to 0.133)
Tumor location, skull base (ref: convexity)	2.832 (-0.410 to 6.073)	2.603 (-0.974 to 6.180)
Tumor size before last intervention, mm	0.085 (-0.017 to 0.187)	0.023 (-0.086 to 0.132)
Tumor size before study, mm	**-0.235 (-0.450 to -0.020)**	0.20 (-0.211 to 0.252)
Tumor growth on last MRI before study, yes (no)	0.571 (-1.479 to 2.626)	0.816 (-1.396 to 3.029)
Edema on last MRI before study, yes (ref: no)	-2.798 (-10.988 to 5.392)	4.801 (-4.077 to 13.678)
First resection, yes (ref: no)	1.438 (-5.564 to 8.439)	3.072 (-4.852 to 10.997)
First resection complications, yes (ref: no)	-1.873 (-5.596 to 1.851)	-0.444 (-4.648 to 3.760)
Second resection, yes (ref: no)	-1.325 (-8.290 to 5.640)	1.610 (-6.590 to 9.811)
Simpson grade first resection IV/V (ref: I-III)	-1.241 (-3.001 to 0.519)	1.693 (-0.216 to 3.602)
WHO Grade II (ref: I)	-0.027 (-6.657 to 6.603)	-4.843 (-11.988 to 2.301)
Radiotherapy, yes (ref: no)	-2.950 (-7.837 to 1.936)	-3.327 (-9.083 to 2.429)
Karnofsky performance score	**0.374 (0.170 to 0.578)**	**0.388 (0.133 to 0.643)**
Hand dominance, right (ref: left)	-3.117 (-7.694 to 1.460)	1.168 (-3.815 to 6.152)
Charlson Comorbidity Index	**-3.308 (-4.624 to -1.992)**	-0.021 (-1.560 to 1.517)
Educational level (1: primary/secondary, 2: tertiary vocational, 3: academic)	**2.703 (0.540 to 4.867)**	0.762 (-3.512 to 5.036)
Years since diagnosis	-0.460 (-0.500 to 0.410)	-0.090 (0.720 to 0.400)

β represent the decrease or increase in physical or mental component score. For continuous determinants this is per 1-point increase in the determinant, unless otherwise specified. For categorical variables a comparison is made with a reference category.

Determinants

HRQoL

Determinants for a lower physical component score (Table 2) were female sex (ref: male, β=-2.52, 95% CI: -6.39 to 1.35), increase in Charlson Comorbidity Index (β=-3.31 for each point increase, 95% CI: -4.62 to -1.99), larger tumor size before study participation (β=-0.23, 95% CI: -0.45 to -0.02), a lower educational level (β=2.70, 95% CI: 0.54 to 4.87), and lower KPS (β=0.37, 95% CI: 0.17 to 0.58). Determinant for a lower mental component score (Table 2) was lower KPS (β=0.39, 95% CI: 0.13 to 0.64). Tumor location, tumor size before intervention, surgical complications, reoperation, and radiotherapy were no determinants for HRQoL (Table 2).

Neurocognitive function

Determinants for decreased neurocognitive function (Table 3) for all three selected domains were radiotherapy (range β: -1.06 to -0.47), second resection (range β: -2.34 to -0.62), higher age (range β: -0.05 to -0.03), and lower educational level (range β: 0.31 to 0.91). Determinant for both decreased executive function and attention was lower KPS (range β: 0.06 to 0.07). Determinants for worse executive function were maximum tumor size (β=-0.03 for each mm tumor, 95% CI: -0.05 to -0.01) and edema on the last MRI before study participation (ref: no edema β=-0.84, 95% CI: -1.70 to -0.01). Determinant for decreased attention was complications of first resection (β=-0.76, 95%CI: -1.42 to -0.10). Tumor location, tumor size before intervention were no determinants for neurocognitive function (Table 3).

Prediction models

HRQoL impairments

Using a p-value cut-off <0.20 in univariable analyses, the following variables were included in the multivariable prediction model: age, tumor size before intervention, surgery, surgical complications, Charlson Comorbidity Index and educational level (Table 4). This model showed an AUC of 0.72 (95%CI: 0.63 to 0.80) (Supplementary Figure 1). Sensitivity analysis resulted in a model with the same variables, except for age, with also a similar AUC of 0.72. The full prediction model to calculate the absolute risk of impaired HRQoL is presented in Supplementary Table 1.

Neurocognitive impairments

Using a p-value cut-off <0.20 in univariable analyses, the following variables were included in the multivariable prediction model: age, tumor size before intervention, reresection, radiotherapy, Charlson Comorbidity Index and educational level (Table 5). This model showed an AUC of 0.78 (95%CI: 0.70 to 0.85) (Supplementary Figure 1). Sensitivity analysis resulted in the same model with the same variables and hence the same AUC. The full prediction model to calculate the absolute risk of impaired neurocognitive function is presented in Supplementary Table 2.

Table 3: Determinants for neurocognitive functioning as measured with a standardized test battery for the three previously determined most relevant domains in this patient population

	Verbal memory β (95%CI)	Executive function β (95%CI)	Attention β (95%CI)
Sex female (ref: male)	**0.442 (0.140 to 0.744)**	0.107 (-0.332 to 0.546)	0.341 (-0.350 to 1.032)
Age, years	**-0.025 (-0.036 to -0.014)**	**-0.048 (-0.063 to -0.032)**	**-0.042 (-0.067 to -0.018)**
Tumor location, skull base (ref: convexity)	0.034 (-0.223 to 0.290)	-0.122 (-0.499 to 0.255)	0.010 (-0.588 to 0.608)
Tumor size before last intervention, mm	-0.004 (-0.012 to 0.004)	-0.005 (-0.015 to 0.006)	-0.004 (-0.022 to 0.014)
Tumor size before study, mm	-0.007 (-0.023 to 0.009)	**-0.028 (-0.051 to -0.005)**	-0.024 (-0.065 to 0.016)
Tumor growth on last MRI before study, yes (ref: no)	-0.250 (-1.336 to 0.836)	0.019 (-0.194 to 0.231)	0.170 (-0.181 to 0.521)
Edema on last MRI before study, yes (ref: no)	-0.281 (-0.892 to 0.330)	**-0.844 (-1.701 to -0.014)**	-0.605 (-2.023 to 0.813)
First resection, yes (ref: no)	**0.693 (0.130 to 1.256)**	-0.069 (-0.850 to 0.714)	-0.279 (-1.606 to 1.048)
First resection complications, yes (ref: no)	-0.228 (-0.553 to 0.097)	-0.357 (-0.761 to 0.047)	**-0.758 (-1.415 to -0.101)**
Second resection, yes (ref: no)	**-0.623 (-1.188 to -0.057)**	**-1.025 (-1.815 to -0.236)**	**-2.336 (-3.680 to -0.993)**
Simpson grade first resection IV/V (ref: I-III)	0.094 (-0.040 to 0.229)	0.040 (-0.147 to 0.227)	0.163 (-0.167 to 0.492)
WHO Grade II (ref: I)	0.372 (-0.104 to 0.847)	0.185 (-0.530 to 0.899)	0.038 (-1.108 to 1.184)
Radiotherapy, yes (ref: no)	**-0.469 (-0.866 to -0.071)**	**-0.666 (-1.224 to -0.107)**	**-1.063 (-2.036 to -0.090)**
Karnofsky performance score	0.012 (-0.006 to 0.030)	**0.060 (0.035 to 0.085)**	**0.069 (0.025 to 0.113)**
Hand dominance, right (ref: left)	**0.520 (0.167 to 0.873)**	0.359 (-0.168 to 0.886)	0.213 (-0.693 to 1.065)
Charlson Comorbidity Index	-0.019 (-0.128 to 0.090)	-0.125 (-0.285 to 0.036)	-0.133 (-0.383 to 0.116)
Educational level (1: primary/secondary, 2: tertiary vocational, 3: academic)	**0.305 (0.139 to 0.471)**	**0.510 (0.265 to 0.756)**	**0.913 (0.528 to 1.297)**
Years since diagnosis	-0.007 (-0.045 to 0.031)	-0.033 (-0.090 to 0.023)	-0.06 (-0.140 to 0.030)

β represent the decrease or increase in z-score. For continuous determinants this is per 1-point increase in the determinant, unless otherwise specified. For categorical variables a comparison is made with a reference category.

Table 4: Prediction model development for impaired Health-related quality of life

	Univariable analysis Odds Ratio (95%CI)	Multivariable model based on statistical significance only Odds Ratio (95%CI)
Sex female (ref: male)	1.024 (0.505 to 2.076), p=.947	
Age, years	**1.018 (0.992 to 1.044), p=.173**	0.997 (0.964 to 1.030)
Tumor location, skull base (ref: convexity)	0.801 (0.446 to 1.437), p=.456	
Tumor size before last intervention, mm	**0.982 (0.964 to 1.001), p=.061**	0.980 (0.959 to 1.002)
First resection yes (ref: no)	**0.408 (0.158 to 1.052), p=.064**	0.438 (0.117 to 1.637)
First resection complications yes (ref: no)	**2.066 (1.102 to 3.873), p=.024**	1.924 (0.900 to 4.114)
Second resection yes (ref: no)	1.406 (0.411 to 4.804), p=.587	
Simpson grade first resection IV/V (ref: I-III)	1.502 (0.724 to 3.118), p=.275	
WHO Grade II (ref: I)	1.772 (0.537 to 5.845), p=.348	
Radiotherapy yes (ref: no)	1.610 (0.575 to 3.421), p=.216	
Charlson Comorbidity Index	**1.520 (1.117 to 2.069), p=.008**	1.338 (0.930 to 1.925)
Educational level (1: primary/secondary, 2: tertiary vocational, 3: academic)	**0.535 (0.351 to 0.816), p=.004**	0.428 (0.255 to 0.717)
Years since diagnosis	1.036 (0.953 to 1.127), p=.406	

Health-related quality of life impairment is defined as a physical component score < 46.4 *or* mental component score < 47.0)
P-values are only showed for the univariable analysis, as they were used for development of the multivariable model that was based on statistical significance.

Table 5: Prediction model development for Neurocognitive deficits

	Univariable analysis Odds Ratios (95%CI)	Multivariable model based on statistical significance Odds Ratios (95%CI)
Gender female (ref: male)	1.089 (0.540 to 2.196), p=.813	
Age, years	**1.036 (1.008 to 1.064), p=.011**	1.024 (0.987 to 1.063)
Tumor location, skull base (ref: convexity)	1.072 (0.598 to 1.923), p=.816	
Tumor size before last intervention, mm	**1.019 (1.000 to 1.039), p=.048**	1.022 (0.998 to 1.047)
First resection yes (ref: no)	0.729 (0.299 to 1.777), p=.487	
First resection complications yes (ref: no)	1.500 (0.805 to 2.794), p=.201	
Second resection yes (ref: no)	**4.574 (1.191 to 17.572), p=.027**	2.662 (0.488 to 14.528)
Simpson grade first resection IV/V (ref: I-III)	1.121 (0.540 to 2.325), p=.760	
WHO Grade II (ref: I)	2.148 (0.651 to 7.092), p=.210	
Radiotherapy yes (ref: no)	**2.011 (0.956 to 4.230), p=.066**	2.819 (0.925 to 8.585)
Hand dominance, right (ref: left)	0.659 (0.289 to 1.505), p=.323	
Charlson Comorbidity Index	1.135 (0.877 to 1.468), p=.336	
Educational level (1: primary/secondary, 2: tertiary vocational, 3: academic)	**0.412 (0.265 to 0.641), p=.000**	0.359 (0.206 to 0.628)
Years since diagnosis	**1.103 (1.011 to 1.203), p=.027**	1.130 (0.982 to 1.301)

Neurocognitive deficit is defined as a z-score<1.5 in at least one neurocognitive domain
P-values are only showed for the univariable analysis, as they were used for development of the multivariable models that was based on statistical significance

Examples

Example patients and calculations are provided for both prediction models in Supplementary Table 1 and 2. Furthermore, using the predicted risk for HRQoL impairment, the sample was divided into tertiles (i.e. three equally large groups: low-risk, medium-risk, high-risk). Of the patients in the low-risk group 27% suffered an HRQoL impairment, 40% in the medium-risk group, and 70% in the high-risk group. Using the predicted risk for neurocognitive impairment to divide patients in risk groups, 9% of patients in the low-risk group suffered from a neurocognitive impairment, 47% in the medium-risk group, and 60% of patients in the high-risk group.

DISCUSSION

Results of this study indicate that determinants for the long-term disease burden in meningioma patients on group level are 1) sociodemographic characteristics: sex, age and educational level, 2) treatment characteristics: complications of surgery, reoperation, radiotherapy, 3) tumor characteristics: diameter and peritumoral edema at the time of study, and 4) clinican-reported level of functioning (i.e. KPS). Furthermore, we have developed prediction models to predict whether an individual patient will suffer from long-term HRQoL or neurocognitive impairment using easily accessible patient chart information, which showed moderate to good discriminative ability to differentiate between those with and without clinically relevant impairments in HRQoL or neurocognitive function on the long term. We reported that 67% of patients suffered from impaired HRQoL or neurocognitive deficits. For these patients, rehabilitation and supportive care options should be available, even on the long-term, as the need for these supportive treatments was underlined in a previous study in meningioma patients.[30] In this study we focused on readily available variables as determinants and predictors, facilitating use in daily clinical practice.

Interpretation: meningioma literature on determinants for disease burden

Information on determinants might be useful for clinicians to better understand the impact of both the tumor and treatment on the long-term outcomes of patients. We report that a complicated treatment course with surgical complications, the need for reoperation and radiotherapy, are associated with long-term neurocognitive impairments and less with HRQoL impairments, which is in line with the literature on (low grade) glioma patients.[9,31] On a group-level, meningioma patients therefore deserve extra attention regarding neurocognitive deficits and early referral for neurocognitive rehabilitation. Furthermore, results of this study showed that tumor activity at the time of study, defined as the presence of edema and a larger tumor diameter on the last MRI before study participation, were negatively associated with patients' executive

function. A larger tumor diameter was also associated with decreased physical function. This is in line with previous meningioma studies reporting in the first years after treatment that factors negatively influencing overall HRQoL and neurocognitive function were higher histological grade, a larger tumor size and peritumoral edema.[23,25,32] However, we found no association between WHO grade and HRQoL or neurocognitive function, which might be explained by the low number of patients with WHO grade II tumors in our study (7%). Indeed, based on the WHO 2016 classification of central nervous system tumors, WHO grade II tumors occur in up to 20% of patients[1]. Our results may therefore not be completely generalizable, as we have a slight underrepresentation of patients with WHO grade II tumors. Two previous studies reported, using univariable analyses only, that tumor location and tumor laterality were associated with neurocognitive function, while in the current study no association was observed after correction for confouders.[7,25,27,28] These results have implications for our understanding of the disease burden in meningioma, as generally it is thought that patients with skull base lesions, compared with convexity tumors, suffer from worse HRQoL after surgery.[3]

Interpretation: prediction models for individual meningioma patients

Prediction models were developed to estimate which patient develops a long-term impairment in HRQoL or neurocognitive function. Until now there have been no prediction models developed for the short- or long-term disease burden of meningioma patients. Not only does the disease burden changes over time, as HRQoL and neurocognitive impairments become more prominent after 5 years of follow-up.[3–5,15,29] It has also been acknowledged that patients enter a chronic disease state in the long-term, with specific long-term survivor issues.[3,4] With good survival rates of this patient population, a prediction model for the long-term disease burden is of particular interest. Two separate models were built, one for long-term problems in HRQoL and one for neurocognitive impairments. These models showed that higher age, lower educational level, presence of comorbidities as measured with the Charlson Comorbidity Index, larger tumor size before intervention, surgical complications, the need for reresection, initiation of radiotherapy, and years since diagnosis were predictors for long-term impairments. Although these variables together help to predict these future outcomes, not all of these variables were independently related to the measured outcomes (i.e. determinants), such as tumor location. This emphasizes the difference between predictors and determinants. While determinants are variables causally related to the outcome of interest, predictors are solely used to predict the outcome of interest, without assuming causality. Hence, predictors can be determinants, act as a proxy for a determinant, or have no causal relationship at all with the long-term disease burden.

Limitations

The measured outcomes in this study are nine years after the last intervention. Therefore, the studied patients might have experienced other major health issues and undergone large extra-

cranial treatments between the period of meningioma treatment and study participation, which could impact their long-term HRQoL and neurocognitive function. Furthermore, a limitation of the current study is the lack of external validation of the models. Prediction models that are only internally validated might be overfitted with externally validated models showing lower performance measures. This might especially hold true for the models predicting HRQoL, as it is strongly subjected to the sociocultural context and different health care systems. Cross-cultural validation is therefore warranted. Furthermore, due to the cross-sectional nature of our study, we were unable to assess determinants and predictors for a change in HRQoL or neurocognitive function over time. Previous studies have shown that baseline HRQoL also acts as predictor for long-term HRQoL, which is a more precise measure of functioning than the KPS.[3] In the light of lack of a validated meningioma-specific HRQoL instrument, we used the SF-36 to measure HRQoL, as this is the most frequently used HRQoL instrument in meningioma literature and in other diseases, facilitating comparability of our results.[3] However, HRQoL issues specific to this patient group might therefore be missing[2]. Previous research has indeed shown that existing HRQoL questionnaires currently used in meningioma patients do not fully cover all relevant issues, supporting the need to develop and validate a meningioma-specific HRQoL questionnaire.

Implications for clinical practice

The found determinants can help clinicians to better understand the long-term HRQoL and neurocognitive impairments of patients, as both the impact of the tumor and the treatment they initiate may affect patients' functioning and well-being. The prediction models can be used to identify individual patients at baseline with a high risk to suffer from a long-term disease burden, which enables tailored provision of information and allocation of scarce supportive care services to those most likely to obtain benefit. Our results emphasize that predictors are not per se determinants, and that causal attributions shouldn't be given to predictors. We recommend external validation in the country of the population of interest before clinical use of the described prediction models.

Acknowledgements:

We would like to acknowledge the research nurses of the LUMC/HMC Neurosurgery department for their help with the data collection.

Funding:

AHZN was supported by a personal MD/PhD grant of the Leiden University Medical Center. No specific funding was received for this project.

Conflicts of interest:

None of the authors declares a conflict of interest

Prior presentations:

The results described in this manuscript have not been presented at any conferences.

Ethics committee approval:

This cross-sectional study was approved by the medical ethical committees of all participating centers (NL54866.029.15).

Consent to participate:

Participants provided informed consent before study procedures

Consent for publication:

All authors have reviewed and given consent to this submission of this manuscript.

Availability of data:

Upon request (please direct to amir@lumc.nl) the used code for the analysis can be provided.

Code availability:

Upon request (please direct to amir@lumc.nl) the used code for the analysis can be provided.

Contributorship:

LD, FWB, and SM designed the original study of which data was used for this report. Data collection was performed by AHZN and PBvdM. AHZN initiated the assessment of the reported study questions and performed data analysis with input from LD. AHZN wrote the first and successive versions of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the drafts of the paper, and approved the final version. LD supervised the project. AHZN had full access to all the data in the study and had final responsibility for the decision to submit for publication.

The generation of this manuscript has been supported by the Dutch Meningioma Consortium which at time of submission of this manuscript consisted of Florien W. Boele, Linda Dirven, Wouter R. van Furth, Martin Klein, Johan Koekkoek, Frank Lagerwaard, Pim B. van der Meer, Saskia M. Peerdeman, Jaap C. Reijneveld, Martin J.B. Taphoorn, Amir H. Zamanipoor Najafabadi.

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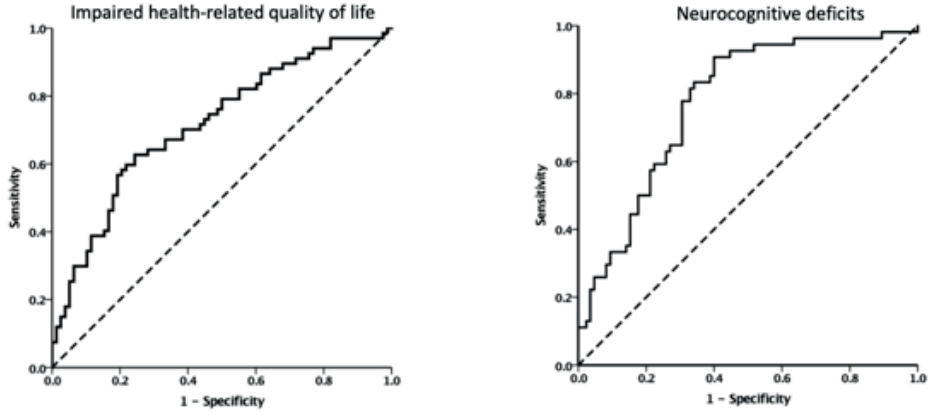
SUPPLEMENTS

Supplementary Figure 1: Receiver Operating Curves (ROC) for the developed multivariable models and Area Under the ROC (AUC)



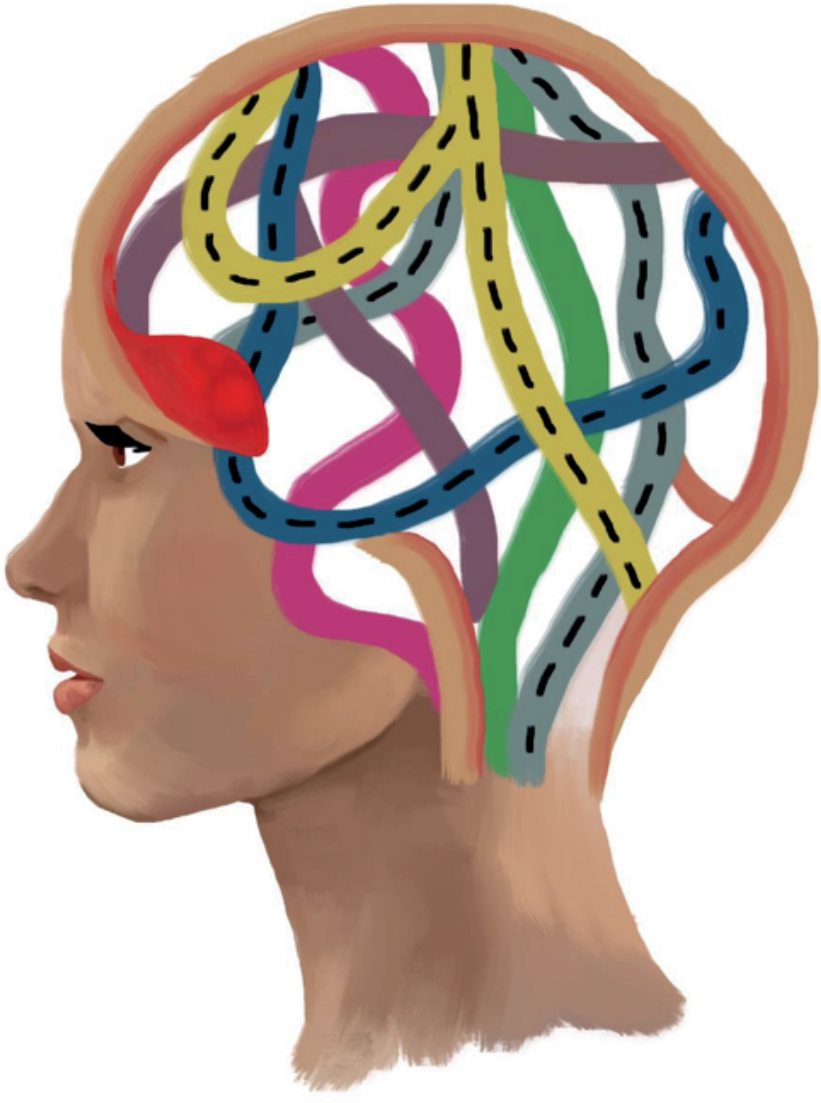
Model Health-related quality of life: AUC 0.717 (95%CI 0.633 to 0.801)
Model Neurocognitive deficits: AUC 0.775 (95%CI 0.696 to 0.853)

Supplementary Table 1: Health-related Quality of Life (HRQoL)

Formula for full risk score:	y=2.997 + (-0.003x age in years) + (-0.020 x largest tumor diameter before first intervention) + (-0.826 x surgery[yes]) + (0.655 x surgical complications[yes]) + (0.291 x Charlson Comorbidity Index) + (-0.849 x education level)
Explanation:	2.997 is the intercept of the model. Largest tumor diameter before first intervention was measured in mm. Charlson comordidity index ranges from 0 to 30). Education is classified as (1=primary/secondary, 2=tertiary vocational, 3 academic).
Formula for impaired HRQoL	HRQoL= $1/1+e^{-y}$
Example 1:	80 years old patients with a skull base tumor of a maximum diameter of 44 millimetre who received surgery, with surgical complications, with a Charlson Comorbidity Index of 6, who only followed primary education: y=2.997 + (-0.003 x 80) + (-0.020 x 44) + (-0.826 x 1) + (0.655 x 1) + (0.291 x 6) + (-0.849 x 1) =2.603 Chance for impaired HRQoL = $1/1+e^{-2.603}$=93%
Example 2:	40 years old patients with a skull base tumor of a maximum diameter of 11 millimetre who received only surgery, without a surgical complications, with a Charlson Comorbidity Index of 2, who followed academic education: y=2.997 + (-0.003 x 40) + (-0.020 x 11) + (-0.826 x 1) + (0.655 x 0) + (0.291 x 2) + (-0.849 x 3) =-0.134 Chance for impaired HRQoL = $1/1+e^{0.134}$=47%

Supplementary Table 2: Neurocognitive function

Formula for full risk score:	y=-2.212 + (0.024x age in years) + (0.022 x largest tumor diameter before first intervention) + (0.979x reresection[yes]) + (1.036 x radiotherapy[yes]) + (-1.023 x education level) + (0.123 x years since diagnosis).
Explanation:	2.212 is the intercept of the model. Largest tumor diameter before first intervention was measured in mm. Education is classified as (1=primary/secondary, 2=tertiary vocational, 3 academic).
Formula for impaired neurocognitive function:	Impaired neurocognitive function = $1/1+e^{-y}$
Example 1:	80 years old patient with a maximum tumor diameter of 44 millimetre who was operated twice and received radiotherapy, who only followed primary education, 9 years after diagnosis: y=-2.212 + (0.024x80) + (0.022 x 44) + (0.979 x 1) + (1.036 x 1) + (-1.023 x 1) + (0.123 x 9)=2.775. Chance for impaired neurocognitive function = $1/1+e^{-2.775}$=94%
Example 2:	40 years old patients with a maximum tumor diameter of 11 millimetre who was operated twice and who followed academic education, 9 years after diagnosis: y=-2.212 + (0.024x40) + (0.022 x 11) + (0.979 x 1) + (1.036 x 0) + (-1.023 x 3) + (0.123 x 9)=-1.993. Chance for impaired neurocognitive function = $1/1+e^{1.993}$ =12%



Chapter 9

Visual outcomes endorse surgery of patients with spheno-orbital meningioma with minimal visual impairment or hyperostosis

Acta Neurochirurgica, 2021;163(1): 73-82

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Wouter R. van Furth

ABTRACT

Background

Most spheno-orbital meningioma series span multiple decades and predictors of visual outcomes have not yet been systemically assessed. We describe visual outcomes in a recent cohort and assess predictors of postoperative visual outcomes.

Methods

Consecutive case series operated by a team of a neurosurgeon and orbital surgeon between May 2015 and January 2019. Best corrected visual acuity (BCVA), visual fields (static perimetry), and relative proptosis were measured pre- and postoperatively at 3/6/12 months after which it was assessed yearly. Predictors were assessed with linear regression analysis.

Results

Nineteen patients (all WHO grade I) were operated by the pterional approach (median follow-up: 2.4 years). Preoperative visual acuity deficits (n=10) normalized in 70% and improved in 10% (median preoperative: 0.8, postoperative: 1.2, p=0.021). Preoperative visual field deficits (n=8) normalized in all patients (preoperative: -6.5dB, postoperative: -1.5dB, p=0.008). Preoperative proptosis (n=16) normalized in 44% and improved in 56% (preoperative: 5mm, postoperative: 2mm, p<0.001). BCVA and visual fields remained stable at longer follow-up in 95% of patients, while 21% showed progression of proptosis. Predictors for worse longer-term (>12 months) BCVA were worse preoperative BCVA (p=0.002) and diagnosis of multiple meningioma (p=0.021). Predictors for worse longer-term visual fields were higher diameter of hyperostosis (p=0.009) and higher Simpson grade (p=0.032). Predictor for short-term (3 months) proptosis was preoperative proptosis (p=0.006).

Conclusion

We recommend surgery, even of patients with minimal visual impairment or hyperostosis, as patients who present with deteriorated visual function or extensive hyperostosis are less likely to have postoperative visual outcomes restored to normal.

Key words

Spheno-orbital, meningioma, surgery, vision, hyperostosis

INTRODUCTION

Spheno-orbital meningioma (SOM) are tumors originating from the sphenoid ridge, primarily characterised by hyperostosis of the lesser and/or greater sphenoid wing.[1,2] In addition, the majority of patients have an intradural meningioma, often described as a thin "carpet-like" or "en-plaque" tumor, which can be more extensive including cavernous sinus involvement and an intraorbital component.[2–4] Due to its location, the majority of patients present with visual deficits, and/or proptosis.[5]

Due to the low incidence of SOM, current series in the literature describe smaller and larger patient series often covering multiple decades, while surgical techniques have improved over the years.[1,2,12,3,4,6–11] In these series, surgery has proven its value with improvement of visual function (10-73%) and proptosis (50-93%).[1–3,6–9,11,12] Nevertheless, many papers only describe the pre- and postoperative visual acuity and proptosis, neglecting patients' visual fields deficits, while this is strongly associated with patients' health-related quality of life.[3,4,6,7,9,11] In addition, predictors of visual outcomes have not yet been systematically assessed. Identification of these predictors may optimise the decision and timing of surgical treatment and tailor postsurgical ophthalmological follow-up.

Therefore, we aimed to describe visual outcomes, complications and recurrence in a recent cohort of surgically treated SOM patients in a high-volume referral centre with a dedicated multidisciplinary team. In addition, we systematically assessed predictors of short- and longer-term postoperative best corrected visual acuity (BCVA), visual fields, and proptosis

METHODS

Study setting and subject selection

Consecutive (i.e. no case selection) spheno-orbital meningioma patients operated between June 2015 and January 2019 in the Leiden University Medical Center (LUMC) in Leiden the Netherlands were described in this study. A set team of a neurosurgeon (WRvF) and orbital/oculoplastic surgeon (SWG) operated patients and followed patients at their multidisciplinary outpatient clinic. SOM was defined as an inner sphenoid-ridge meningioma with hyperostosis of at least the lesser or greater sphenoid wing with an intradurual meningioma. Patients were excluded if previously operated. In our center the usual first line treatment of SOM consists of surgery, with radiotherapy reserved for recurrent tumors. This study was reviewed and approved by the LUMC-LDD medical ethics committee as part of a larger study protocol (G19.011).

Surgical technique

The pterional approach was used in all cases. Patients were positioned in the supine position, with the head extended and rotated to the contralateral side. An interfascial temporal flap was developed to expose the skull.[13] Neuronavigation was used to verify extension of bony resection. Hyperostotic bone of the orbital roof and lateral orbital wall was microscopically decompressed from the maxillary strut to the optic strut using the eggshell technique, which comprises thinning of bone to softly peel the layer of bone around critical structures. If involved the optic canal was decompressed in total length. The meningo-orbital band was cut to fully expose the superior orbital fissure (Figure 1). Intradural meningioma was removed, but no attempts were made to remove intracavernous sinus meningioma. Intraorbital meningioma was resected by the orbital surgeon and periorbita was partially resected, or incised, to reduce proptosis. Common grafting techniques (cranial periosteum, donor or artificial material) was used for watertight dural reconstruction. If indicated, the lateral orbital wall was reconstructed with titanium mesh, or patient-specific 3D-printed PEEK (polyetheretherketone) implant to prevent pulsatile enopthalmos and/or adhesion of the temporal muscle to the periorbita. Abdominal fat, or gelatine-based artificial material was used to fill-up the defect. The surgical technique was somewhat modified over time based on developing experiences and new insights.

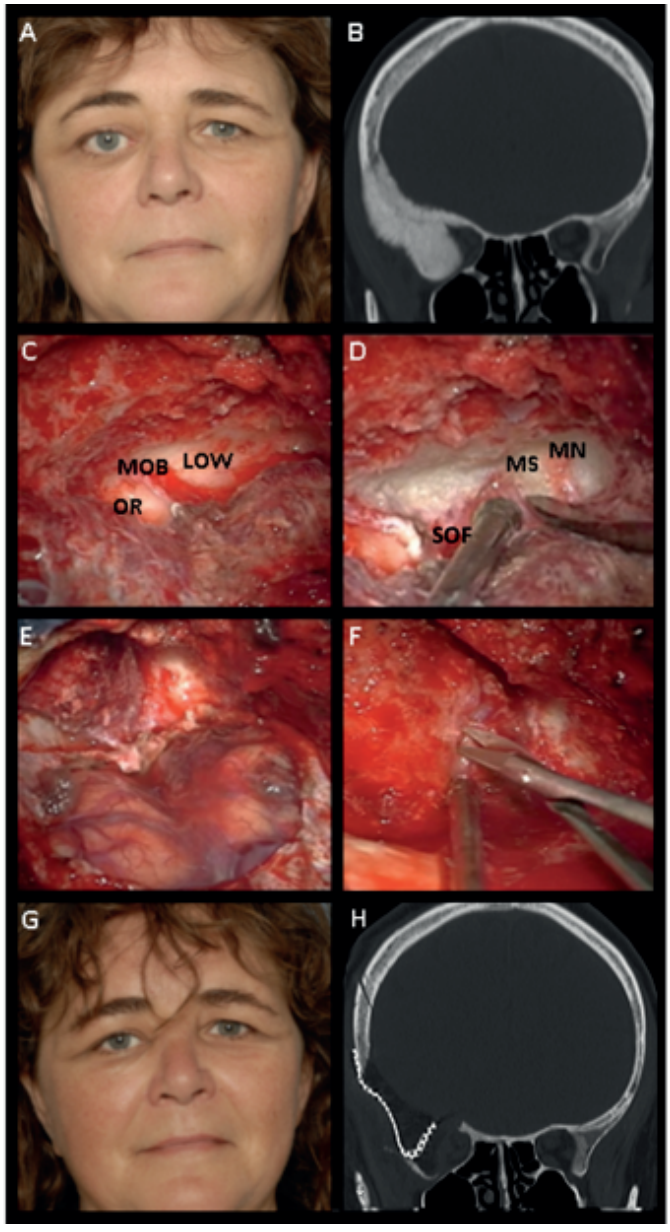
Data collection

Demographic characteristics were collected from the electronic patient charts. Patients underwent both computed tomography (CT) and gadolinium contrast-enhanced magnetic resonance imaging (MRI) both before and after surgery (postoperative: after 6 months and then yearly.) Multiple visual outcomes were measured preoperatively, and postoperatively at 3, 6, and 12 months, after which patients were seen yearly in the multidisciplinary outpatient clinic of both surgeons. Best corrected visual acuity (BCVA) was measured with the Snellen chart. Patient's visual fields were investigated using the Zeiss Humphrey visual field analyser, described as Mean Deviation (MD) in decibel (dB). Proptosis was determined by measuring axial globe position using a double-prism exopthalmometer, comparing the affected eye with the unaffected eye.[14]

Statistical Analysis

Outcomes after surgery are described as the percentage of patients with deteriorated, stable, improved or normalized BCVA, visual fields and proptosis. Preoperative outcomes were compared with direct postoperative outcomes using the Wilcoxon signed rank test. Individual patient data is graphically depicted over time for all outcomes in graphs. Furthermore, median values were calculated for all patients together and for those patients with and without preoperative visual acuity deficits (cut-off for deficit 0.8 or lower), visual field deficits (cut-off for deficit -5dB or lower)[15], or proptosis (cut-off for clinically relevant proptosis 2mm or more). No cut-offs for improvement on the individual patient level were set, as clinical interpretation

Figure 1: Example of Spheno-Orbital meningioma patient management



A: Patient presented with a relative proptosis of 8 mm of the right eye, BCVA of 0.6 and a visual field deficit of -6.50dB. **B:** Hyperostosis of both the orbital roof and lateral orbital wall is shown on the CT scan in bone setting. **C/D:** Pictures of the microsurgical decompression. MOB = Meningo-Orbital Band. OR = Orbital Roof. LOW = Lateral Orbital Wall. MS = Maxillary Strut. MN = Maxillary Nerve. **E:** A Simpson grade I resection was achieved after intradural and intraorbital meningioma resection. **F:** After resection of intraorbital meningioma, vertical cuts were made in the periorbita to reduce proposes. **G:** Postoperative facial picture showed clear reduction of proptosis. Her BCVA normalised (1.20) as well as the visual field deficit (-0.33dB) **H**: CT scan in bone setting showed reduction of hyperostotic bone and reconstruction of the lateral orbital wall with titanium mesh. Figures published with permission of the patient after written informed consent.

of improvement is highly dependent on the preoperative status (e.g. visual acuity improvement of 0.0 to 0.4 vs 1.0 to 1.4). Instead, the above-mentioned cut-offs were used both preoperatively and postoperatively and distinction was made between postoperative improvement and normalization of visual outcomes. Predictors of BCVA, visual fields and proptosis were assessed by univariable linear regression analysis, separately for the direct postoperative outcomes (3 months) and outcomes at longest follow-up. No multivariable analysis was performed due to the small number of patients. IBM SPSS Statistics version 23.0 (Armonk, NY, USA) was used for all statistics and a p-value lower than 0.05 was considered statistically significant.

RESULTS

Subjects

During the study period, 20 patients were operated, but one patient was lost to follow-up, as the patient died due to comorbidities not related to the SOM or surgery. The remaining 19 patients were described in this study (median age: 47.0, 97% female). All patients suffered from unilateral disease. See table 1 for a description of all baseline characteristics. Median follow-up time between diagnosis and surgery was 7.2 months, as a short wait-and scan regimen was chosen as initial treatment for patients who only presented with proptosis without any visual deficits. Median follow-up time after surgery was 2.4 years (IQR: 1.3 to 3.3).

Surgical techniques

In all cases the pterional approach was used, including decompression of the lateral orbital wall and superiorior orbital fissure (Table 2). The principles of the used surgical technique modified somewhat over time; the meningo-orbital band was cut in the last 10 patients (38%) to facilitate full exposure of the superior orbital fissure. Furthermore, in the first couple of operated patients the optic canal and orbital roof were only decompressed if preoperative CT showed extensive hyperostosis of these structures and/or a patient presented with visual acuity or visual field deficits. In the last 12 patients the orbital roof and optic canal were decompressed in all patients. Resection of the anterior clinoid process, decompression of the foramen rotundum, ovale and spinosum were only performed when clinically indicated. In the first patients, reconstruction of the lateral orbital wall was performed with titanium mesh, while in recent patients patient-specific 3D-printed PEEK implants were used for reconstruction. Gross total resection, i.e. resection of meningioma tissue and hyperostotic bone, was achieved in 14 patients (74%). A subtotal resection was achieved in 5 (26%) patients, due to extensive hyperostosis over the skull base.

Table 1: Baseline characteristics of Spheno-orbital meningioma patients

	LUMC cohort (n=19)
Gender, female	18 (95%)
Age at surgery, years	47.0 (45.0-50.0)
Time between diagnosis and surgery in months	7.2 (3.4-8.9)
Hyperostosis diameter (mm)	31.0 (24.0-35.0)
Soft tissue diameter (mm)	11.0 (8.0-18.0)
Simpson Grade	
Grade I	6 (32%)
Grade II	9 (47%)
Grade III	0 (0%)
Grade IV	4 (21%)
Extent of resection	
Full resection	15 (79%)
Subtotal resection	4 (21%)
WHO grade I	19 (100%)
WHO subtypes	
Meningothelial	15 (79%)
Transitional	3 (16%)
Secretory	1 (5%)
Number of tumors	
1	13 (69%)
2	3 (16%)
3	0 (0%)
4	1 (5%)
5	2 (11%)
Postoperative proton radiotherapy	2 (11%)
Postoperative photon radiotherapy	1 (5%)
Reoperation	2 (11%)
Follow-up length in years	2.4 (1.3-3.3)

Continuous outcomes are described as median value and interquartile range. Dichotomous outcomes are described as number and percentages. Percentages might not add up to 100% due to rounding.
Extent of resection was determined intraoperatively and on postoperative CT and MRI scan. A subtotal resection was defined as residual meningioma tissue or hyperostosis.

Visual outcomes

Ten (53%) patients suffered from a decrease in BCVA, which normalized in 7 (70%) after surgery, improved in 1 (10%) and remained unchanged in 2 (20%, preoperative BCVA: 0.0 and 0.7) patients. Median BCVA before surgery was 0.8 (IQR: 0.7 to 1.5), which improved postoperatively to 1.2 (IQR: 1.0 to 1.5, p=0.021), and remained stable in all patients at 1-year follow-up (1.2, IQR: 1.0 to 1.5) and longer follow-up (1.2, IQR: 1.0 to 1.5). Eight (42%) patients had preoperative visual field deficits, which normalized in all (100%) patients after

Table 2: Surgical techniques

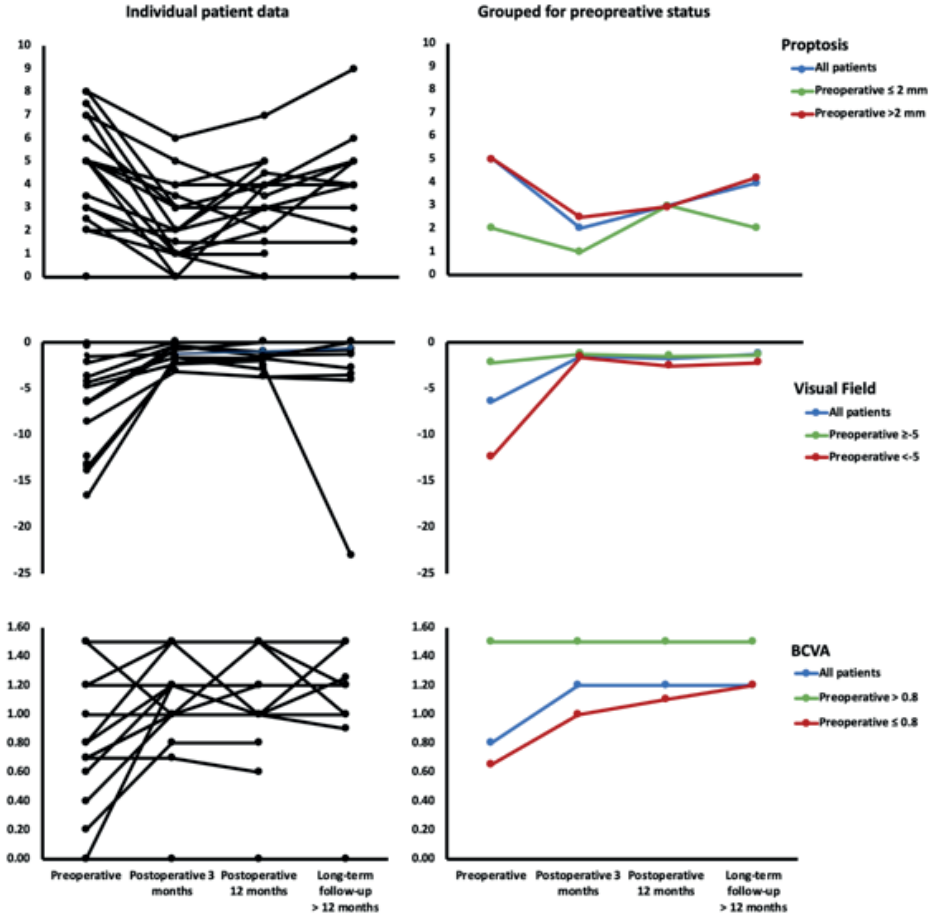
	LUMC cohort (n=19)
Resection hyperostotic bone	
Lateral orbital wall	19 (100%)
Orbital roof	
Complete	10 (53%)
Partial	5 (26%)
Not	4 (21%)
Anterior clinoid process	1 (5%)
Decompression of foramina	
Superior orbital fissure	19 (100%)
Optic canal	
Complete (full-length)	7 (37%)
Partial	5 (26%)
Not	7 (37%)
Foramen rotundum	1 (5%%)
Foramen ovale	0 (0%)
Foramen spinosum	1 (5%)
Resection of soft-tissue structures	
Meningo-orbital band	10 (53%)
Intraorbital meningioma	10 (53%)
Periorbita management	
Cuts	4 (22%)
Stripping	7 (37%)
Nothing	8 (42%)
Reconstruction	
Patient-specific 3D PEEK implant	3 (16%)
Titanium mesh reconstruction	12 (63%)
No reconstruction performed	4 (21%)
Periumbilical fat filling	11 (58%)

PEEK: polyetheretherketone. Percentages might not add up to 100% due to rounding.

surgery. Median visual field before surgery was -6.5dB (IQR: -12.9 to -3.0), which improved postoperatively to -1.5dB (IQR: -2.2 to -0.7, p=0.03) and remained stable in seven (88%) patients at 1-year follow-up (all patients: -1.7dB, IQR: -2.5 to -1.1) and longer follow-up (all patients: -1.3dB, IQR: -3.2 to -0.3). One patient suffered from a strong deterioration (-23.1dB) after 1-year follow-up. Sixteen (84%) patients presented with proptosis preoperatively, which normalized in seven (44%) and improved in nine (54%) patients. Median relative proptosis before surgery was 5mm (IQR: 3.0 to 6.5), which improved postoperatively to 2mm (IQR: 1.0 to 3.3, p<0.01). However, four of these patients (25%) suffered from deterioration

at one-year follow-up (all patients: 3mm, IQR: 2 to 4) and one patient (6%) at longer follow-up (all patients: 4mm, IQR: 2 to 5). Individual patient data over time of BCVA, visual fields and proptosis are depicted in figure 2. In addition, median values are provided for all patients together and separately for patients with and without preoperative visual acuity deficits, visual field deficits and proptosis.

Figure 2: Proptosis, Visual Fields and Visual Acuity: individual patient data and grouped for patients with preoperative deficits



Pre-and postoperative measures of proptosis, visual fields and visual acuity are depicted for individual patients and grouped for all patients and patients with and without preoperative deficits. Proptosis was measured with a Hertel exopthalmometer in mm**.** Visual fields were measured with the Humphrey visual field analyser, described as Mean Deviation (MD) in decibel (dB). Visual acuity was measured with the Snellen chart.

Complications and reintervention

Patients suffered from the following postoperative complications: transient (n=3) and permanent (n=3) hypesthesia of the maxillary nerve, transient deficit of the frontal branch of the facial nerve with consequently asymmetry of the eyebrows (n=3), wound abscess requiring debridement of the wound (n=1), preseptal orbital cellulitis (n=1) which was successfully treated with antibiotics, and oscillopsia during chewing (n=1) for which eventually a patient-specific 3D-printed PEEK reconstruction was performed. No complications of the other cranial nerves or surgical mortality were observed. After 1-year follow-up two patients developed MRI established growth of residual tumor, for which one patient received photon radiotherapy 1.5 years after surgery and one patient received proton beam therapy 4.0 years after surgery. As stated before, one patient suffered from strong deterioration of visual fields (-23.1dB), requiring reresection and proton beam therapy, which improved and stabilized the patient's visual field deficit (-10.0dB). One patient required reresection for the development of ophthalmoplegia, which improved the patient's symptoms. In these four patients the optic canal was decompressed in one and the orbital roof in three patients.

Predictors of short- and longer-term postoperative visual acuity, visual fields and proptosis

Short-term: Predictor for worse short-term postoperative BCVA was worse preoperative BCVA: for each point lower preoperative BCVA, postoperative BCVA was 0.49 lower (95%CI: -0.21 to -0.77, p=0.002). No predictors were identified for short-term visual fields. Predictor of worse postoperative proptosis was worse preoperative proptosis: for each additional mm preoperative proptosis, postoperative proptosis was 0.47 mm higher (95%CI: 0.16 to 0.78, p=0.006). Detailed information about predictors of short-term outcomes is provided in Supplementary Table 1.

Longer-term: Predictors for worse longer-term BCVA were worse preoperative BCVA (β=-0.49, 95%CI: -0.21 to -0.77, p=0.002), and the number of tumors: for each extra diagnosed meningioma, postoperative BCVA was -0.14 lower (95%CI: -0.26 to -0.02, p=0.021). Predictors for worse postoperative visual fields were the maximum diameter of preoperative hyperostosis: for each additional mm preoperative hyperostosis, postoperative visual fields were 0.39dB lower (95%CI: -0.67 to -0.12, p=0.009); and Simpson grade: for each grade increase in Simpson grade, postoperative visual fields were 3.71dB lower (95%CI: -6.63 to -0.78, p=0.017). No predictors were identified for longer-term proptosis. Detailed information about predictors of longer-term outcomes is provided in Supplementary Table 2.

DISCUSSION

In a recent cohort of spheno-orbital meningioma patients operated by a dedicated team of a neurosurgeon and orbital surgeon in a high-volume referral center good visual outcomes were achieved and maintained with modest morbidity and no mortality. Postoperative visual acuity and visual fields endorsed surgery of patients with SOM, even with minimal visual impairment or hyperostosis, as we showed with our regression analysis that preoperative visual deficits and the maximum diameter of hyperostosis were predictors of poorer outcome.

Results of this mono-center study were in line with published studies of the last two decades, which reported improvement of vison in 37-87% of patients, visual fields in 17-88%, proptosis in 60-100%, and permanent complications in 22-44% of patients.[2,6,8,16–19] We reported improvement of visual acuity in 80% and visual fields in 100% of patients with stable outcomes in 95% of these patients during our modest follow-up period. Proptosis was also improved in all patients, however 21% reported deterioration at longer follow-up. We observed permanent complications in 32%. Despite the good visual outcomes, 21% of patients showed progression requiring reresection, which was comparable to the outcomes (22-48%) of recently published studies by other groups.[9,16,17,20]

Predictors of postoperative vision

Based on our results, multiple data driven recommendations can be made to optimize surgery and postsurgical follow-up for SOM patients (Table 3). Our results suggest that it might be beneficial to operate patients, even with minimal visual impairment or hyperostosis, to prevent the development of visual deficits, that might not completely resolve after surgery (i.e. strongest predictor for postoperative visual outcomes were preoperative visual function and hyperostosis), which is in line with conclusions reported in published literature [3,4,6,9,11,17,18,21]. Our, relatively short, follow up results suggest early surgery has a lasting change on the clinical course of the disease, with persisting good visual outcomes in the majority of patients. Patients with normal visual function, operated for their proptosis, maintained good visual outcomes after surgery. While surgery of patients with minimal visual symptoms seems intuitive and was recommended by other case series, these studies did not systematically assess predictors of postoperative visual outcomes. [3,4,6,9,11,17,18,21]. As these tumors tend to invade the bone near the foramina of the cranial nerves, early surgery might prevent extensive hyperostosis, narrowing of formina, and consequently cranial nerve deficits.[1,6] Indeed it is reported that optic canal and intraorbital involvement are predictors for postoperative visual deficits.[21] Nevertheless we also acknowledge that surgery itself imposes a risk of new visual and cranial nerve deficits.[2,16] Especially in very old patients, patients with severe comorbidities, or patients with extensive disease resulting in full blindness, the benefits of surgery might not always outweigh the risk of complications. However, in general we believe that the risk for new complications might

be smaller when patients are operated on early in their disease course, as cranial nerves are less vulnerable when compression is less severe. Our results also indicate that patients diagnosed with multiple intracranial meningioma were at higher risk for postoperative visual acuity deficits. Therefore, we advise a more intensive multidisciplinary postsurgical follow-up for these patients, to identify objective or subjective postoperative visual deterioration as early as possible, enabling early reresection. The need for repeat intervention was high in this group.

Surgical approaches

Although multiple surgical approaches have been described for SOM surgery, the pterional approach is the most used approach in these patients, and also used for all patients described in this study.[2,6,7,11,19,22] Advantages of pterional craniotomy are wide exposure and access to the anterior, middle and temporal cranial fossa, and therefore ability to resect the hyperostotic bone and soft-tissue tumor as radically as possible. Recently, multiple endoscopic approaches have been described for anterior skull base pathology, such as the supraorbital, and the combined endonasal and transorbital approach.[23–29] Three studies described a total of 12 SOM patients operated with the endonasal transorbital approach.[27,28,30] The endonsasal approach was used for decompression of the medial part of the optic canal. Further decompression of the hyperostotic bone and tumor removal was accomplished with the transorbital approach.[27,28,30] Compared with endonasal approach only, this combined approach enabled resection of more laterally located pathology.[27] Overall these case series showed stabilisation of visual function with moderate to good reduction of proptosis. Proposed advantages are the less invasive approach with cosmetically pleasing results. However, gross total resection is often not possible, and therefore these approaches should be preserved for selected patients with suspected benign meningioma with minimal intradural growth and in whom relief of symptoms through decompression of the optic canal is the primary goal.[30] In these cases residual tumor can be controlled by radiotherapy.[30]

Hyperostotic bone resection, dealing with periorbita, and reconstruction techniques

In the last decades a paradigm shift has occurred in skull base surgery from aiming maximum surgical resection to optimizing patient outcomes and health-related quality of life.[31,32] A maximum resection of hyperostotic bone is advocated to reduce proptosis, to restore visual function and minimize progression. However, there is no consensus on the degree of bony resection, the need to resect invaded periorbit and the need for reconstruction of the lateral orbital wall. We agree with earlier reports that cavernous sinus involvement is a contra-indication for gross-total resection.[1,6,17,22] Some of the same reports advise no decompression of superior orbital fissure tumor involvement. However, with transection of the meningo-orbital band, full decompression of the superior orbital fissure is possible.[33] It remains controversial whether resection of bone should be limited to clearly visible hyperostotic bone or whether decompression of the

optic canal and possible other foramina should be performed routinely for preservation of good visual function.[17] We recommend resection of at least the orbital roof and lateral orbital wall, and decompression of the optic canal, and superior orbital fissure to prevent further deterioration of visual outcomes and improve proptosis (Table 3). Although standard resection of the anterior clinoid process is performed by others, we only advise to resect this structure in case of hyperostosis to prevent early postoperative progression, as no cranial nerves are directly affected by hyperostosis of the anterior clinoid proces.[1–3,11,17,34] Another debate is the need for resection of the periorbit. While this should clearly be done when the periorbit is invaded with tumor, it is advocated by some to preserve the periorbita to prevent pulsatile enopthalmos. However, we agree with others that resection of the periorbit is critical to maximally reduce proptosis. Based on our own experience and the reported literature, we advise reconstruction with titanium mesh or customized patient-specific 3D PEEK implants to prevent (pulsatile) enopthalmos, especially in case of periorbita resection.[3,6–8,10,11,17,34] Other groups have reported to actually not perform reconstruction to provide an even greater reduction of proptosis.[1,2,19]

Table 3 – Recommendations for surgical indication, surgical technique and patient follow-up

Current practice	Recommendations	Evidence current study	Literature supporting recommendation
Indication for surgery			
• Significant visual symptoms or proptosis	• Prevention of visual deficits by early surgery, even of patients with minimal visual impairment or hyperostosis	• Worse preoperative deficits were related to worse postoperative outcomes	• [3,4,6,9,11,17,18,21]
Surgical technique			
• Resection of hyperostotic bone • Limited resection intraorbital meningioma and periorbita • Reconstruction is some patients	• Maximum resection of hyperostotic bone: at least the lateral orbital wall, orbital roof, optic canal, and superior orbital fissure • Maximum intraorbital meningioma resection, including periorbita • Reconstruction with titanium mesh or customized 3d-printed PEEK implant	• Need for reresection or radiotherapy was observed in patient without decompression of orbital roof and optic canal • Simpson grade was predictive for long-term visual field deficits • Reconstruction with titanium mesh or 3D-printed PEEK implant showed good postoperative proptosis results	• [2,11,16,18] • [11,17,20,38–40] • [8,11,16–18,34,41]
Patient follow-up			
• Routine meningioma follow-up	• More frequent follow-up of patients with multiple meningioma	• Tumor number was predictive for long-term visual acuity	• No relevant literature

Progression and Adjuvant treatment

In this case series with limited follow-up length, 21% of patients needed reintervention. Two patients showed established tumor growth without the development of new visual deficits. These patients were treated with radiotherapy to halt the tumor growth. While radiotherapy is associated with optic neuropathy, extra-ocular muscle dysfunction and pituitary insufficiency[16,20], irradiation was chosen over reoperation, as the growing tumor remnants were deemed difficult to fully resect. Especially with the introduction of proton beam therapy, irradiation might be less harmful than reoperation for cases with residual disease or tumor regrowth without symptoms of newly developed visual deficits.[35] However, in the two patients with newly developed visual deficits due to postoperative tumor growth, reoperation was chosen in an attempt to decompress the optic system to improve the visual function of the patient. These percentages and treatment strategies for recurrent disease are in line with other case series.[2,16,34,36] Although our case series did not include any patients with a WHO grade II tumor, other authors advise upfront radiotherapy for these patients.[16,37]

Strengths and limitations

Strengths of this study are the use of a recent cohort of SOM patients operated by a dedicated set team of a neurosurgeon and orbitoplastic surgeon for assessment of short- and longer-term visual outcomes. Furthermore, we prospectively comprehensively assessed visual outcomes, not only reporting visual acuity, but also standardised measurement of visual fields. Only few studies have been published reporting results of visual fields, while this is a significant symptom for patients, highly correlated with their health-related quality of life.[15] Another strength is the assessment of predictors for postoperative visual outcomes, enabling formulation of recommendations for SOM surgery and patient follow-up. However, due to the small number of patients no multivariable analysis was performed and ideally our results should be validated in a larger (international) dataset, to ensure robustness of the results. Although we did not perform a direct comparison between patients with an early vs. late stage disease, we formulated that surgery of patients with minimal visual impairment or hyperostosis might provide better postoperative results, as predictors of worse postoperative visual outcomes were worse preoperative visual acuity and a larger diameter of proptosis. While more intuitive, a direct comparison of early vs. later surgery was not possible due to the small patient sample and might actually not be preferred as it does not take into account the extent of disease and visual status at diagnosis. Longer follow-up is needed to assess more accurate recurrence rates and the long-term outcomes after reresection and radiotherapy.

Conclusions

The aim of surgery for spheno-orbital meningioma should be to optimize visual outcomes and health-related quality of life. As spheno-orbital meningioma is a rare disease with significant treatment variation, sound comparison of different treatment strategies and outcomes can only

be performed through international collaboration and harmonized data collection. In lack of that, we present outcome data of our recent small series and make an argument for surgical intervention of spheno-orbital meningiomas, even in patients with limited visual impairments or hyperostosis, as worse preoperative visual acuity, and greater diameter of hyperostosis were predictors of poorer visual outcome.

Funding:

The Leiden University Medical Center provided financial support in the form of a personal MD/PhD grant funding for AHZN. The sponsor had no role in the design or conduct of this research.

Acknowledgements:

None

Conflicts of interest:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethics approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This cross-sectional study was approved by the medical ethical committees of the Leiden University Medical Center as part of a larger study protocol (G19.011).

Informed consent:

Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authorship:

AHZN, SWG, and WRvF designed the study, and collected data. AHZN performed data analysis and wrote the first and successive versions of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the drafts of the

paper, and approved the final version. AHZN had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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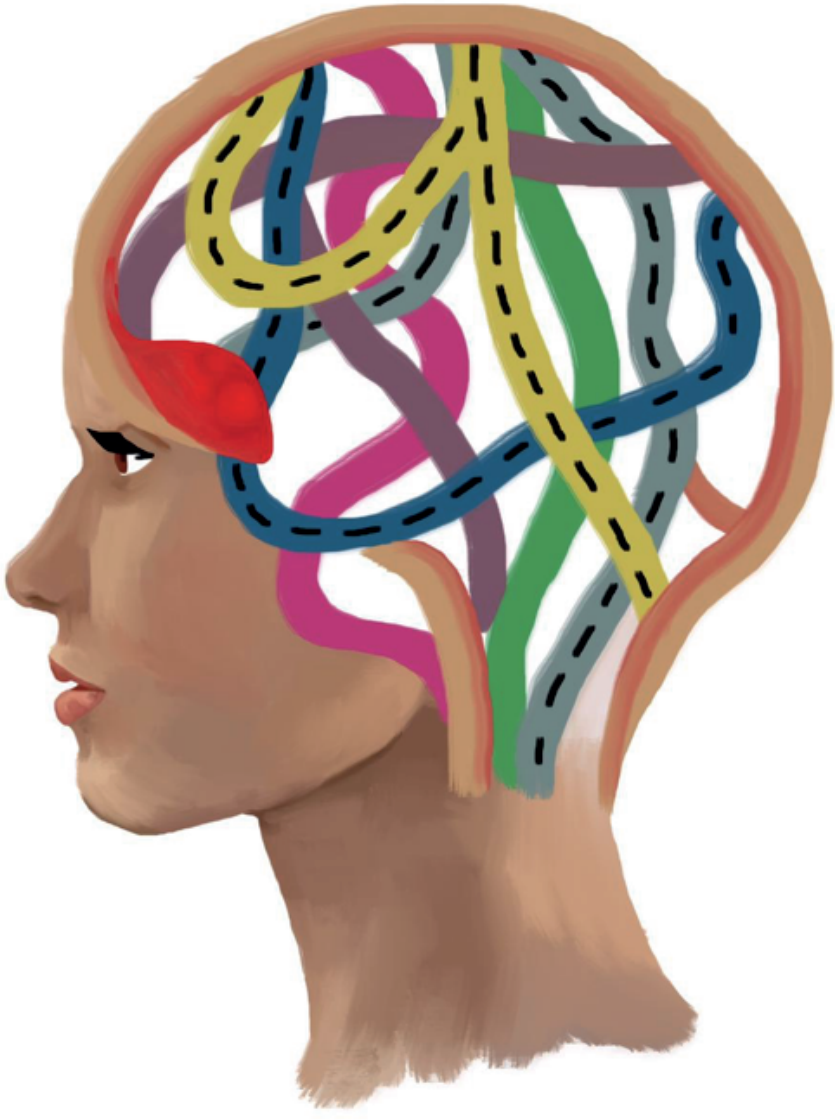
SUPPLEMENTS

Supplementary Table 1: baseline predictors for short-term (3-months) postoperative best corrected visual acuity (BCVA), visual fields and proptosis

	Beta	95%CI	p-value
BCVA			
Tumor diameter in mm	-0.007	-0.026 to 0.012	0.458
Diameter hyperostosis in mm	-0.005	-0.026 to 0.016	0.630
Simpson grade (I-V)	-0.067	-0.237 to 0103	0.416
Number tumors	-0.120	-0.245 to 0.005	0.059
BCVA (Snellen chart)	0.487	0.207 to 0.766	0.002
Age at surgery in years	0.002	-0.019 to 0.023	0.874
Visual Fields			
Tumor diameter in mm	0.041	-0.074 to 0.156	0.441
Diameter hyperostosis in mm	-0.040	-0.123 to 0.044	0.316
Simpson grade (I-V)	-0.020	-0.885 to 0.844	0.959
Number tumors	-0.175	-0.660 to 0.309	0.439
Visual field mean deviation in dB	0.098	0.098 to 0.230	0.124
Age at surgery in years	-0.023	-0.089 to 0.044	0.466
Proptosis			
Tumor diameter in mm	0.049	-0.039 to 0.136	0.255
Diameter hyperostosis in mm	0.039	-0.056 to 0.133	0.399
Simpson grade (I-V)	0.343	-0.437 to 1.123	0.366
Number tumors	-0.124	-0.764 to 0.516	0.687
Proptosis in mm	0.466	0.156 to 0.775	0.006
Age at surgery in years	-0.083	-0.170 to -0.004	0.059

Supplementary Table 2: baseline predictors for long-term (median 2.4 years) postoperative best corrected visual acuity (BCVA), visual fields and proptosis

	Beta	95%CI	p-value
Visual Acuity			
Tumor diameter in mm	-0.004	-0.024 to 0.015	0.634
Diameter hyperostosis in mm	0.004	-0.017 to 0.025	0.716
Simpson grade (I-V)	-0.080	-0.248 to 0.089	0.332
Number tumors	-0.143	-0.261 to -0.024	0.021
BCVA (Snellen chart)	0.489	0.210 to 0.767	0.002
Age at surgery in years	-0.005	-0.026 to 0.015	0.596
Visual Fields			
Tumor diameter in mm	-0.009	-0.366 to 0.348	0.959
Diameter hyperostosis in mm	-0.393	-0.670 to -0.116	0.009
Simpson grade (I-V)	-3.705	-6.633 to -0.777	0.017
Number tumors	0.508	-2.231 to 3.247	0.695
Visual field mean deviation in dB	0.331	-0.313 to 0.975	0.284
Age at surgery in years	0.174	-0.170 to 0.519	0.294
Proptosis			
Tumor diameter in mm	0.066	-0.054 to 0.186	0.262
Diameter hyperostosis in mm	0.035	-0.097 to 0.166	0.557
Simpson grade (I-V)	0.514	-0.551 to 1.580	0.323
Number tumors	0.415	-0.442 to 1.272	0.321
Proptosis in mm	0.364	-0.140 to 0.867	0.146
Age at surgery in years	-0.048	-0.178 to 0.082	0.446



Chapter 10

Trends in cerebrospinal fluid leak rates following the extended endoscopic endonasal approach for anterior skull base meningioma: a meta-analysis over the last 20 years

Acta Neurochirurgica, 2021;163(3):711-719

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ABSTRACT

Objective

The extended endoscopic approach provides unimpaired visualization and direct access to ventral skull base pathology, but is associated with cerebrospinal fluid (CSF) leak in up to 25% of patients. To evaluate the impact of improved surgical techniques and devices to better repair skull base defects, we assessed published surgical outcomes of the extended endoscopic endonasal approach in the last two decades for a well-defined homogenous group of tuberculum sellae and olfactory groove meningioma patients.

Methods

Random-effects meta-analyses were performed for studies published between 2004 (first publications) and April 2020. We evaluated CSF leak as primary outcome. Secondary outcomes were gross total resection, improvement in visual outcomes in those presenting with a deficit, intraoperative arterial injury, and 30-day mortality. For the main analyses, publications were pragmatically grouped based on publication year in three categories: 2004-2010, 2011-2015, and 2016-2020.

Results

We included 29 studies describing 540 patients with tuberculum sellae and 115 with olfactory groove meningioma. The percentage patients with CSF leak dropped over time from 22% (95% CI: 6-43%) in studies published between 2004 and 2010, to 16% (95% CI: 11-23%) between 2011 and 2015, and 4% (95% CI: 1-9%) between 2016 and 2020. Outcomes of gross total resection, visual improvement, intraoperative arterial injury, and 30-day mortality remained stable over time

Conclusions

We report a noticeable decrease in CSF leak over time, which might be attributed to the development and improvement of new closure techniques (e.g. *hadad bassagasteguy flap*, and *gasket seal*), refined multilayer repair protocols, and lumbar drain usage.

Keywords

Meningioma, endoscopic surgery, skull base, cerebrospinal fluid leak

INTRODUCTION

In the last two decades the limits of endoscopic endonasal skull base surgery have been investigated. Current extended approaches allow exposure of the area between the olfactory groove and the odontoid process for resection of different pathologies (e.g. meningioma and chordoma).[1,2] Originally used for transsphenoidal surgery of sellar pituitary tumors, resection of tuberculum sellae meningioma and later of olfactory groove meningioma were intuitive steps in the evolution of the extended endoscopic approach.[3–5]

With the addition of the extended endoscopic approach to the arsenal of the surgeon, certain tumors can be approached from below with unimpaired visualization and direct access to the pathology - with minimal exposure and manipulation of unaffected critical neurovascular structures.[6] In patients with tuberculum sellae and olfactory groove meningioma there is evidence that in selected patients the endoscopic approach results in better visual outcomes compared with the transcranial approach with overall low complication rates.[7] However, these extended approaches result in large dural defects and an increased risk of cerebrospinal fluid (CSF) leak in up to 25% of patients.[7] In order to address this risk, various techniques to prevent CSF leaks have been described and optimized by surgeons over the years, using lumbar drains and based on the principle of multilayer closure with autologous and synthetic materials.[8,9] Landmark developments were the description of the vascularized pedicled *Hadad-Bassagasteguy flap,* its modification to a "rescue flap", and more recently the gasket seal closure technique.[10–12] As these extended approached are still relatively new and are used for uncommon pathologies, a learning curve has been described by multiple groups.[13,14]

To evaluate the impact of these modifications and a possible learning curve, we evaluated outcomes of the extended endoscopic endonasal approach in the last two decades for a well-defined homogenous group of patients with tuberculum sellae and olfactory groove meningioma in terms of CSF leak and other surgical outcomes using a meta-analyses approach.

METHODS SECTION

Article selection and data extraction

A previously published literature search in Pubmed and Embase considering publications after 2004 (first paper) on outcomes of tuberculum sellae and olfactory groove meningioma patients operated with the extended endoscopic and transcranial approach was updated on 19-04-2020.[7] Details of this search strategy are provided in the original publication.[7] Articles eligible for the current analyses were studies describing original data of the extended endoscopic approach in at least 5 patients and articles were excluded describing a combined surgical approach,

a pediatric patient population (<18 years old), or outcomes of re-operations. The following data points were extracted from each publication: publication year, study period, study size, mean or median age, tumor location, and the outcomes of interest: number of patients with gross total meningioma resection, improvement in visual outcomes in those with preoperative deficits, CSF leak, intraoperative arterial injury, and all-cause 30-day mortality.

Risk of bias assessment

We have adapted the New-Castle Ottawa Scale for risk of bias assessment. This scale is scored out of 6 and assesses sample selection, outcome reporting, and comparability between treatment arms. As no comparative studies were assessed in our study, we omitted the latter domain.

Main Analyses

For the main analyses, we pragmatically grouped publications based on publication year in three categories (2004-2010, 2011-2015, and 2016-2020). As in earlier years fewer publications were published, we chose the first category to span a year longer than the other categories. We evaluated the percentage patients with a CSF leak as primary outcome. Secondary outcomes were the percentage patients with a gross total meningioma resection, improvement in visual outcomes in those with preoperative deficits, intraoperative arterial injury, and 30-day mortality.

Sensitivity Analyses

We also performed multiple sensitivity analyses to assess the robustness of the results and the possible effects of information bias, classification bias, and selection bias.

First, as publications from the same year might cover different study periods, we categorized studies in three categories based on the median calendar year of the described study period: 2000-2005, 2006-2010, and 2011-2015.

Second, we performed analyses separately for patients with tuberculum sellae meningioma and olfactory groove meningioma. Although the analyses with only patients with olfactory groove meningioma should be interpreted with caution, as the number of studies and patients within some analyses is very small.

Third, we compared publications that specifically described routine use of pedicled nasoseptal flaps (e.g. *Hadad-Bassagasteguy flap)* with those that did not describe routine use of these flaps. No other comparisons were made concerning closure techniques, due to paucity of data on other well-defined techniques.

Fourth, we compared publications that specifically described the routine use of lumbar drains to prevent CSF leaks with those that did not describe routine use of lumbar drains.

Used statistics

Random-effect estimates with 95% confidence intervals were calculated using the DerSimonian and Laird method.[15] A Freeman-Tucky double arcsine transformation was performed to include studies with 0% or 100% outcomes.[16] I^2 statistics were used for quantification of between-study heterogeneity. If multiple patient groups (e.g. patients with tuberculum sellae and olfactory groove meningioma) were described separately within one publication, each group was entered separately in the analyses to account for the heterogeneity between the groups with the use of the random-effects model. No formal statistics were assessed to obtain p-values for the performed comparisons, as none of the comparisons were described in the original studies. Comparison of different patient groups could be strongly affected by differences in patient and tumor characteristics, which are often confounders for the comparisons. Instead results are reported for each group, including 95% confidence intervals (95%CI), describing the accuracy of the aggregated results within the group.[17] Publication bias was assessed by generating a funnel plot for the main analyses with and without the Duval and Tweedie trim-and-fill method.[18] Analyses were performed with Stata version 16.1 (Statacorp).

RESULTS SECTION

Study characteristics

A total of 2285 articles were screened for title and abstract and of 241 articles the full-text was read to assess eligibility. We eventually included 29 studies describing 36 groups of patients consisting of 540 patients with tuberculum sellae meningioma patients and 115 with olfactory groove meningioma (Figure 1 and Supplementary Table 1). The median age was 54 years (interquartile range (IQR): 52-59) and the median percentage of male patients included was 24% (IQR: 14-33%). Risk of bias scores for individual studies are depicted in Supplementary Table 1. Four studies (11%) were classified as low risk of bias on both sample selection and outcome reporting. Fifteen studies (42%) scored low risk of bias only on sample selection and five (8%) only on outcome reporting.

Trends over time

The percentage patients with a CSF leak dropped over time from 22% (95% CI: 6-43%) in studies published between 2004 and 2010, to 16% (95% CI: 11-23%) between 2011 and 2015, and 4% (95% CI: 1-9%) between 2016 and 2020 (Figure 2). Outcomes of gross total resection, visual improvement, intraoperative arterial injury, and 30-day mortality remained stable over time (Figure 2). Impact of publication bias was limited for these outcomes, as there was limited asymmetry in the funnel plots without any major change in effect estimates using the trim and fill method (Supplementary Figure 1).

Figure 1: Flow chart of article screening and selection

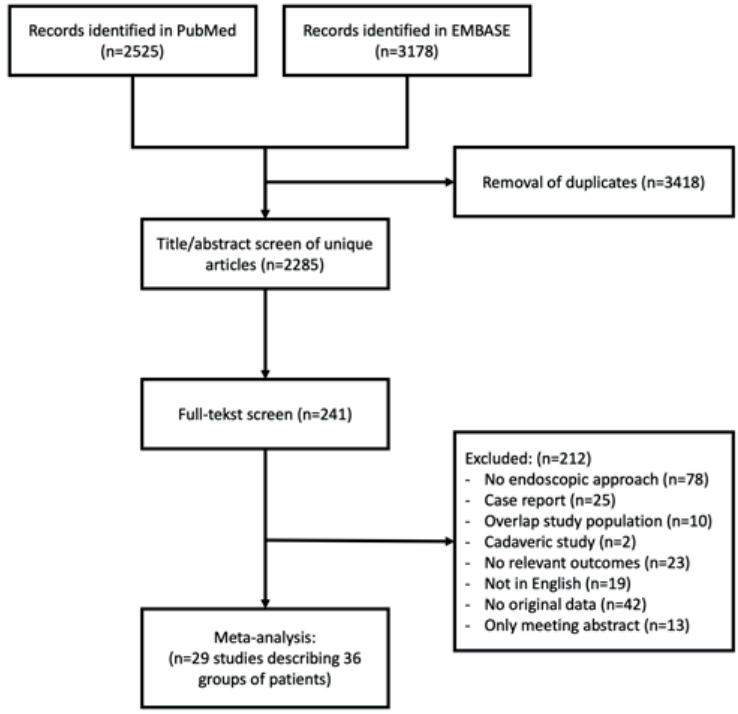
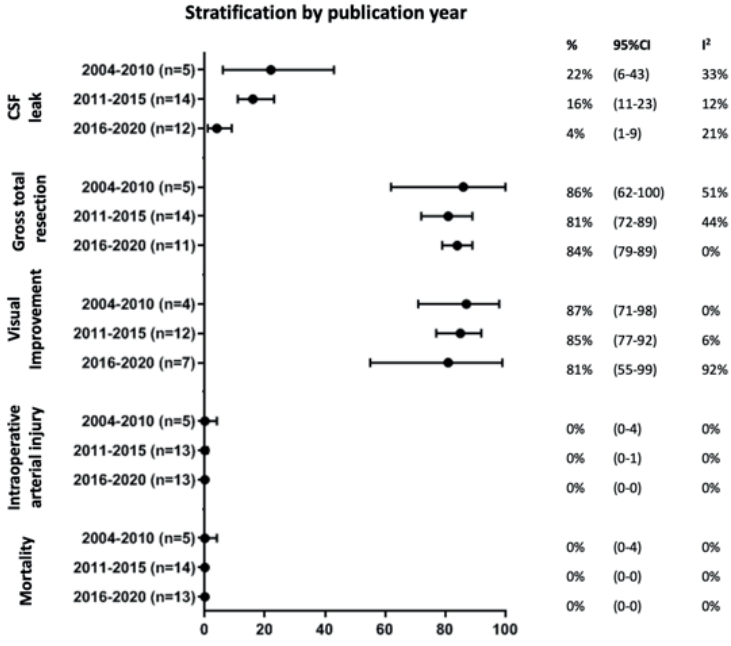
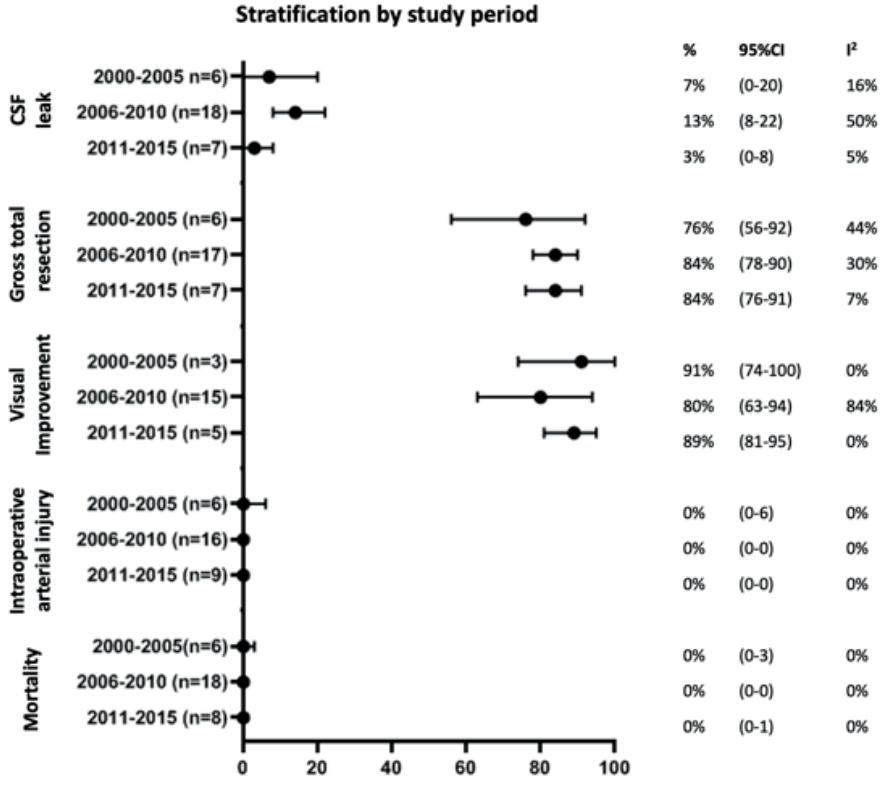


Figure 2. Outcomes stratified by publication year



Results were similar for the sensitivity analyses using study period instead of publication year, except for CSF leak: 7% (95%CI: 0-20) of patients from studies conducted between 2000 and 2005, compared with 13% (95%CI: 8-22%) between 2006 and 2010, and 3% (95%CI: 0-8%) between 2011 and 2015 (Figure 3). Results did not differ for the sensitivity analyses only including case series describing patients with tuberculum sellae meningioma (Figure 4), or olfactory groove meningioma, although the latter should be interpreted with caution as the number of studies and patients within some analyses is very small (Supplementary Figure 2)

Figure 3. Sensitivity analyses: outcomes stratified by study period (median calendar year of reported study period)



In articles clearly describing the routine use of a pedicled nasoseptal flap, CSF leak was reported in 3% (95%CI: 0-8%) of patients, compared with 12% (95%: 6-19%) in those articles that did not describe routine use of a pedicled flap (Figure 5). In articles describing the routine use of lumbar drains, CSF leak was reported in 1% (95%CI: 0-4%) of patients, compared with 14% (95%CI: 9-19%) in those articles that did not describe routine use of lumbar drains (Figure 5). In the three articles describing routine use of the gasket seal closure technique, CSF leak was reported in 9% (95%CI: 0-46%). Note that all three studies were published by the same group.[19–21]

Figure 4. Sensitivity analyses: outcomes stratified by publication year, only including patients with tuberculum sellae meningioma

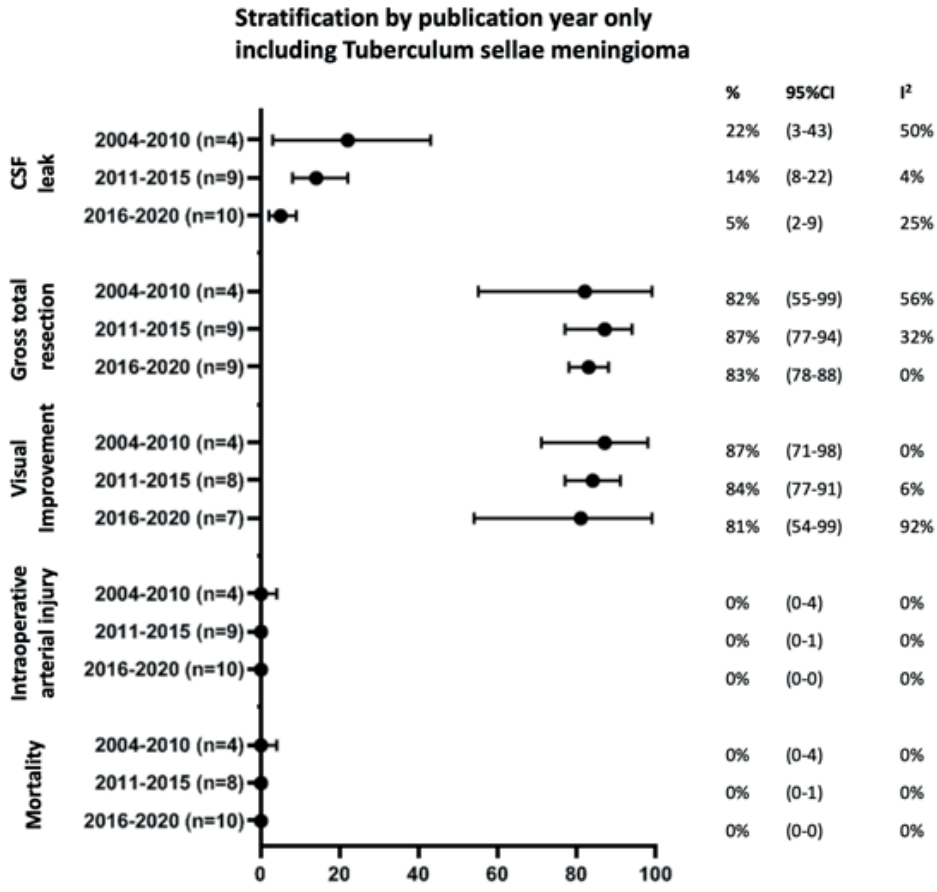
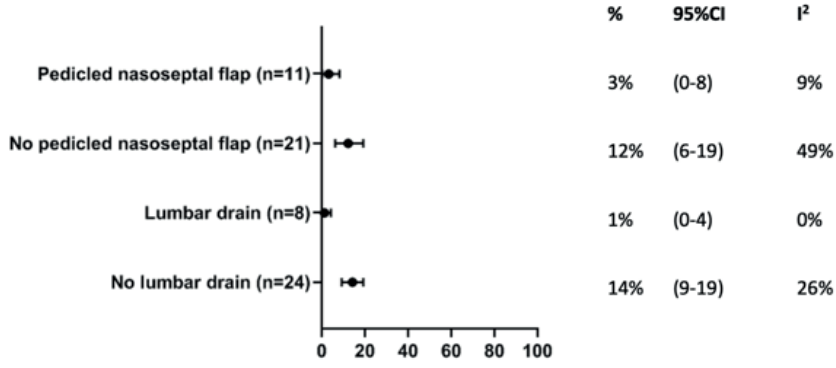


Figure 5. CSF leak in studies which clearly reported routine use of a pedicled nasoseptal flap, and which reported routine use of lumbar drains



DISCUSSION

Results of the main meta-analyses indicate that the percentage patients suffering from a CSF leak after extended endoscopic endonasal surgery for a tuberculum sellae or olfactory groove meningioma has decreased from 22% since publication of the first described case series to 4% in recent case series. Classifying studies on the actual described study period showed that the percentage CSF leak first increased and then decreased to percentages lower than the first published case series. We speculate this is because the first cases were highly selected and performed and described by very experienced endoscopic surgeons and pioneers of the extended endoscopic approach, while hereafter the approach found a broadened indication for use and was performed by an early majority of practitioners at various stages of their learning curve.[22] Gross total resection and improvement in visual function was achieved in approximately 85% of patients in all evaluated time periods. Similarly, outcomes of intraoperative arterial injury and mortality were stable over time, both outcomes occurring in almost no patients. These outcomes are fairly similar to meta-analyses of the transcranial approach for patients with tuberculum sellae and olfactory groove meningioma, with the exception that studies suggest that superior visual outcome might be achieved with the extended endoscopic approach in selected patients.[7,23,24]

Compared with previously published meta-analyses, our results show indeed that the percentage CSF leak has decreased in the last decade with a 2011 analysis of anterior skull base meningioma reporting CSF leak in 32% of patients and a 2013 analysis of tuberculum sellae meningioma reporting CSF leak in 21% of patients.[24,25] This improvement in the percentage CSF leak might be attributed to the development and improvement of new closure techniques, including the vascularized pedicled *Hadad-Bassagasteguy flap,* and the gasket seal closure technique.[10,11] Due to its vascularization from the posterior sphenopalatine artery, the *Hadad-Bassagasteguy flap* is a fast healing flap with a large area coverage and large arc of rotation.[11] Its use as part of multilayer closure techniques, including synthetic materials, fat and fascia lata is adopted by many groups to decrease the chance of CSF leak.[6,8,26–28] Indeed, we describe that the percentage CSF leak in studies routinely using the *Hadad-Bassagasteguy flap* was 3%. In addition, multiple groups have published graded repair protocols, based on anticipated defect size and location, and intraoperative CSF leak grade to reduce unnecessary preparation of a pedicled nasoseptal flap, especially with the development of the rescue-flap.[12,29,30] Primarily described by the Cornell group, the gasket seal closure technique consisting of fascia lata and a bone buttress or other implant (e.g. *MEDPOR)* provides another technique for watertight closure of defects with excellent outcomes.[10]

Standard use of lumbar drains to prevent CSF leaks is controversial as complications such as pneumocephalus and infections might not outweigh the potential benefit, especially as the

percentage patients with a CSF leak has reduced with the development and improvement of closure techniques.[31,32] However, a recent randomised controlled trial suggests that perioperative lumbar drain use combined with nasoseptal flap repair (in the context of dural defects >1cm^2 and high flow intra-op CSF leak), further decreases CSF rhinorrhoea rates (21% vs 8%) without an increased risk of complications, such as infections.[8] Direct lumbar drain complications occurred in 4%, consisting of postoperative spinal headaches requiring a blood patch and retained catheter requiring no intervention.[8] These results suggest that the use of lumbar drains could play an important role in the prevention of CSF leaks in high risk cases, such as intradural meningioma resection.[8,14,33] The effectiveness of lumbar drains is underpinned in the current meta-analyses, as we report that CSF leak only occurred in 1% of patients in studies that routinely used a lumbar drain.

The decrease in CSF leak might also be attributed to a surgical learning curve. However no clear improvement in the percentage patients with a gross total resection or improvement in visual outcomes was observed. This is in contrast with studies on the learning curve within a single large referral center, which showed improvement of both outcomes.[13,32] Subcomponents of skull base surgery might demand particular surgical techniques, which run on different surgical curves.[14] In addition, different surgical groups, of whom the publications were analysed in this meta-analyses, might be at different positions of their own respective learning curves. Regarding CSF leaks, it is actually described that a learning curve was only observed for complex skull base closure and closures of high-flow leaks, and not for small defects.[32] Similarly, for complex outcomes such as gross total resection and hormonal cure, a learning curve is described even after the first 200 cases, while not being described for surgical complications.[14] Unfortunately the number of studies describing a center-specific learning curve is limited and could therefore not be analyzed separately in our study, limiting sound analyses of a potential surgical learning curve.

Strengths and limitations

A limitation of this study is the small number of published studies with small, possibly highly selected, patient groups, and therefore selection bias and publication bias cannot be ruled out. However, to address selection bias to the best of our ability, we performed multiple sensitivity analyses which generally showed results in line with the main analyses, adding to the robustness of the results. Furthermore, we expect the possible impact of publication bias to be limited, as heterogeneity was seen in the reported outcomes, and asymmetry in the funnel plots was limited without any major changes in effect estimates using the trim and fill method. Nevertheless, the bar to submit and publish outcomes worse than the first reports, might have affected our outcomes. While we were able to perform analyses with studies routinely using a vascularized pedicled nasoseptal flap, we did not perform a separate analysis with studies routinely using gasket seal closure techniques, as these studies were almost all from the same surgical

group.[19–21] Furthermore, the analyses for patients with olfactory groove meningioma included a very limited number of studies, limiting the accuracy of the results and therefore readers are advised to interpret these results with caution. We acknowledge that our results might not be generalizable to patients with other pathologies than meningioma (e.g. chordoma, craniopharyngioma) as we chose to analyze a homogenous group of patients with tuberculum sellae and olfactory groove meningioma and did not include outcomes of other pathologies. Finally, analyses were performed on study-level, and therefore we were not able to compare patients and tumor characteristics between publications. We encourage the international neurosurgical community to share individual patient-data for individual patient-data meta-analysis, which also provides results stratified for different tumor locations in more detail, enables analyses of outcomes currently rarely reported in literature, and may allow for comparison of the transcranial approach with the extended endoscopic approach.

Conclusions

We report a noticeable decrease in CSF leak over time, which might be attributed to the use of lumbar drains, development and improvement of new closure techniques (e.g. *hadad bassagasteguy flap*, and *gasket seal*) and integration of these techniques within multilayer and graded repair protocols (Figure 6). No improvement was observed for the percentage patients with a gross total resection, improvement in visual outcomes in those with preoperative deficits, intraoperative arterial injury, and 30-day mortality. An area for further research is understanding practice variations in skull base repair techniques and their corresponding CSF leak rates. Future multicentre studies aim to address this.[34]

Funding:

No funding was received for this project. DZK and HJM are funded by the Wellcome / EPSRC Centre for Interventional and Surgical Sciences (WEISS). HJM is funded by the National Institute of Health Research University College London Biomedical Research Centre.

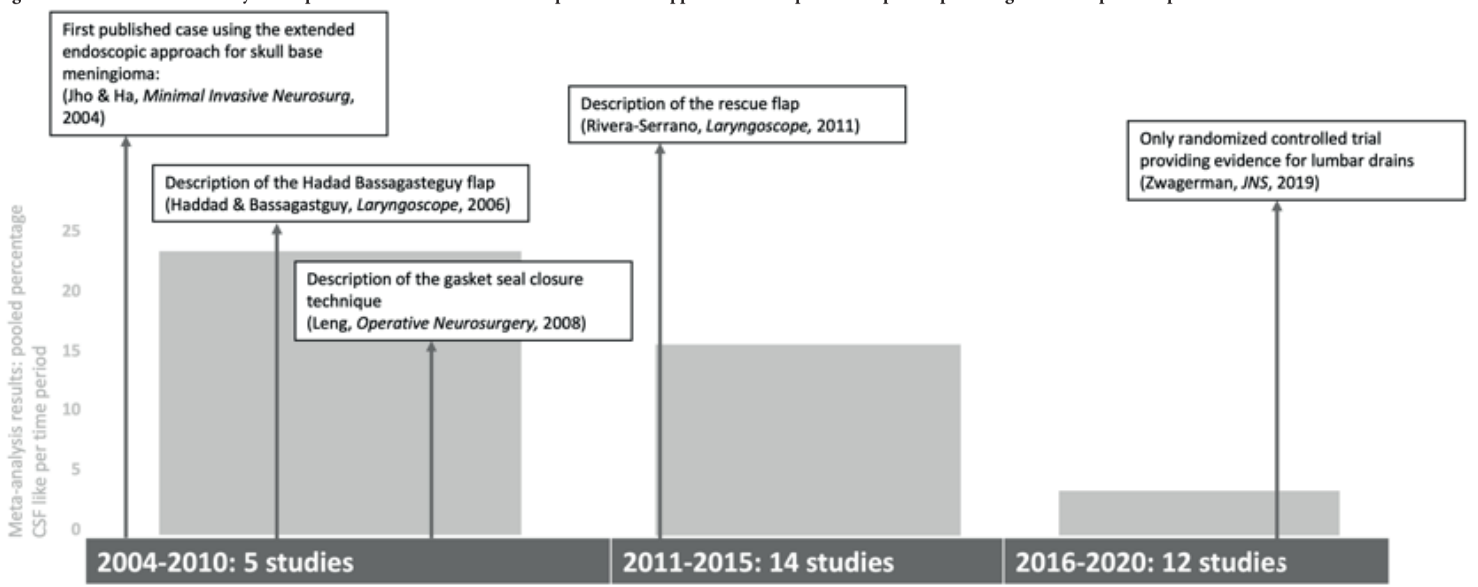
Acknowledgements:

We would like to acknowledge Tom L. Ouwehand and Joseph P. Castlen for their help with the original data extraction.

Conflicts of interest:

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Figure 6: Timeline of selected key developments for the extended endoscopic skull base approach. Bars represent the pooled percentage CSF leak per time period"



Ethics approval

No medical ethical approval was needed for this study.

Contributorship:

Data collection was performed by DZK, AHZN, ISM. Study inception was by AHZN, DZK, WRvF, HJM. AHZN performed data analysis. AHZN wrote the first and successive version of the manuscript. All authors contributed to the interpretation of the results, intellectual content, critical revisions to the drafts of the paper, and approved the final version. AHZN and DZK had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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SUPPLEMENTS

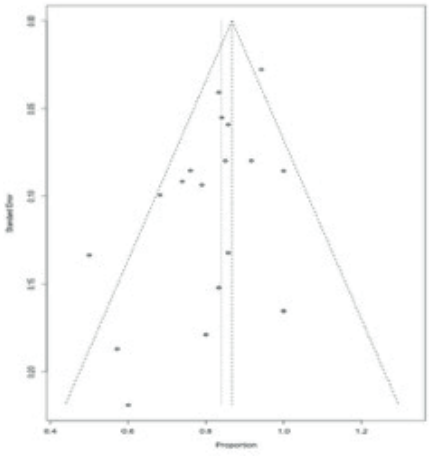
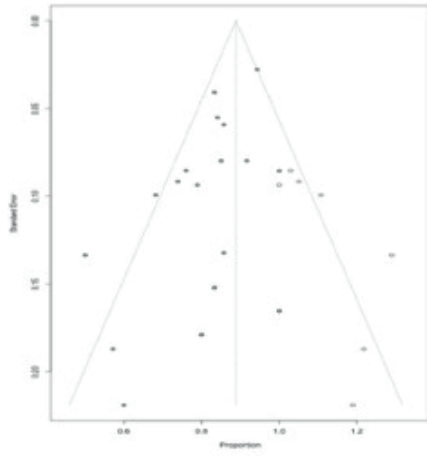
Supplementary Table 1: study characteristics

Author	Publication year	Hadad-flap	Gasket seal	Drain	OGM	TSM	Age	% male	% WHO I	Mean size
Cook	2004	No	no	no		3	40	0%		
De Devitiis	2008	No	no	no	4		49	25%	100%	
De Devitiis	2008	No	no	no		7		20%		
Fatemi	2009	No	no	no		14	51	29%		
Wang	2010	No	no	no		12	57	33%	100%	
Bowers	2011	No	no	no		5	58	20%		12
Bohman	2012	yes	no	no		5	53	40%		
Chowdhury	2012	No	no	yes		6	40	33%		
Ogawa	2012	No	no	no		19	59	26%	89%	
Padhye	2012	No	no	no	8		52	25%	100%	41
Padhye	2012	No	no	no		3	66	0%	100%	9
Gadgil	2013	yes	no	no		5	51	40%	1020%	6
Khan	2014	yes	no	no		20	66	30%	100%	12
Khan.	2014	yes	no	no	15				67%	
Koutourousiou	2014	no	no	no		70	57	16%	100%	
Koutourousiou	2014	no	no	no	50		57	36%	20%	
Al-meida	2015	no	no	no	10		53	30%		36
Banu	2015	yes	yes	yes	6		67	0%		20
Ceylan	2015	yes	no	no		23	53	19%		
Bander	2016	yes	yes	yes		17	54	35%		6
Catapano	2016	yes	no	yes		7				
Hayhurst	2016	no	no	no		7	46	43%	100%	
Hayhurst	2016	no	no	no	9		50	11%	100%	
Zoli	2016	no	no	no		35			97%	
Elshazly	2017	yes	no	no		25	54	16%	100%	5
Hayashi	2017	yes	no	yes		22	58	32%		
Linsler	2017	no	no	yes		6	64	0%	67%	2
Bernat	2018	yes	no	no		20	59			
Bernat	2018	yes	no	no	6		59			
Kong	2018	yes	no	yes		84	54	24%		
Kuga	2018	no	no	no		7	54	0%		3
Liu 1	2018	yes	no	no	5		51	20%		33
Magill	2018	no	no	no		44				
Ottenhausen	2018	no	yes	yes	2		79	0%		11
Ottenhausen	2018	no	yes	yes		30	57	37%		7
Song	2018	no	no	yes		44	53	14%	91%	6

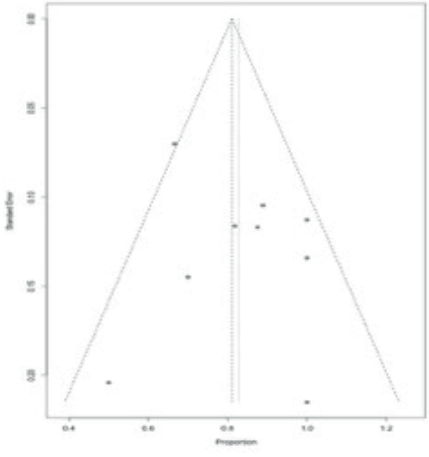
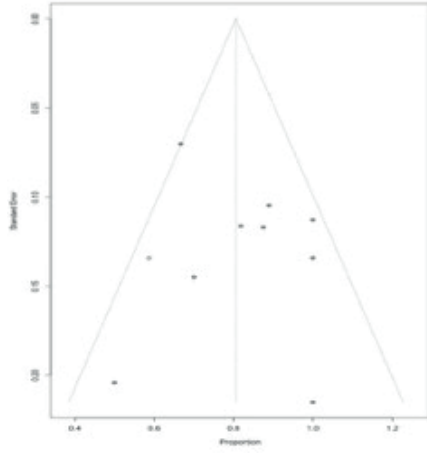
Mean FU	Risk of bias (mNOS)	% Gross toal resection	% visual improvement	% CSF leak	% arterial injury	% mortality
	3	100%	100%	0%	0%	0%
10	3	100%	0%	25%	0%	0%
	4	86%	71%	57%	0%	0%
27	6	50%	82%	29%	0%	0%
25	3	92%	92%	8%	0%	0%
	3	60%		20%	0%	0%
12	4	80%	80%	20%	0%	0%
7	4	83%	83%	17%	0%	0%
36	3	79%	74%	5%	0%	0%
	3	88%	25%	38%	0%	0%
3	3	100%	100%	0%	0%	0%
15	4	80%	100%	20%	0%	0%
	3	85%	82%	10%	0%	5%
	4	82%	80%	7%	0%	0%
29	3	94%	86%	27%	1%	1%
33	3	67%	93%	30%	2%	0%
54	4	70%		10%	0%	0%
19	5	50%	100%	17%	0%	0%
	3	74%	70%	9%		0%
25	5					
39	4	86%		14%	14%	0%
39	5	57%		0%	14%	0%
39	5	89%		0%	0%	0%
58	4	86%	18%	17%	0%	0%
21	6	76%	88%	8%	0%	0%
	4	68%	83%	0%	0%	0%
15	5	83%	67%	0%	0%	0%
38	5	0%		0%	0%	0%
38	5	0%		0%	0%	0%
28	5	83%	85%	5%	0%	1%
19	6	100%	100%	14%	0%	0%
15	5	100%		20%	0%	0%
46	5			11%		0%
42	5	100%	0%	0%	0%	0%
42	5					
27	5	84%	98%	2%	0%	0%

Supplementary Figure 1: Raw and Trim & Fill funnel plots of the assessed outcomes
1) Gross total resection:

Tuberculum Sellae Meningioma

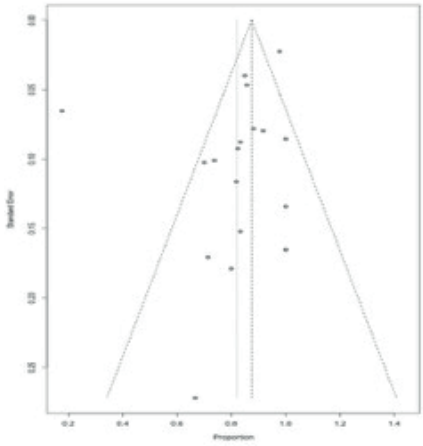
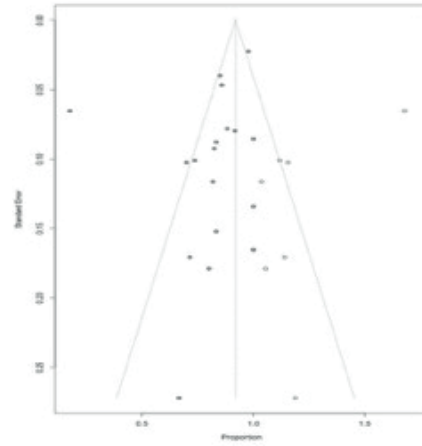
Raw funnel plot	Trim & fill funnel plot
	

Olfactory Groove Meningioma

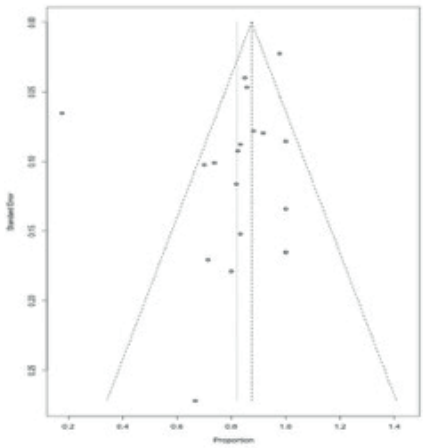
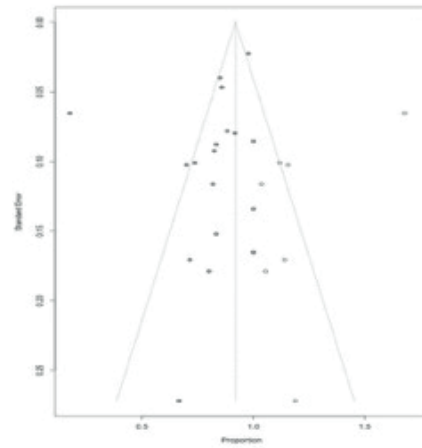
Raw funnel plot	Trim & fill funnel plot
	

2) **Visual Improvement:**

Tuberculum Sellae Meningioma

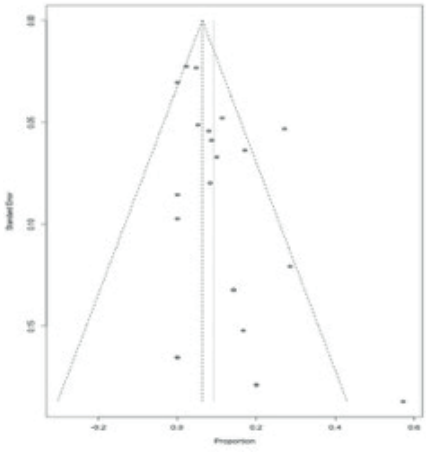
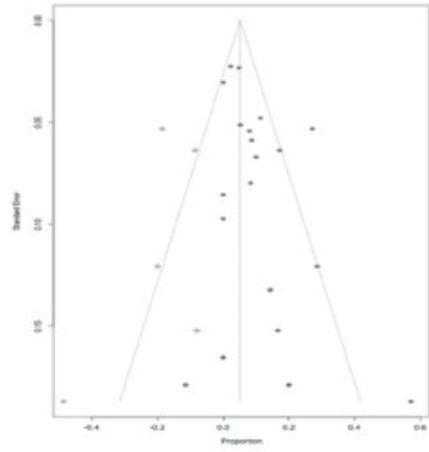
Raw funnel plot	Trim & fill funnel plot
	

Olfactory Groove Meningioma

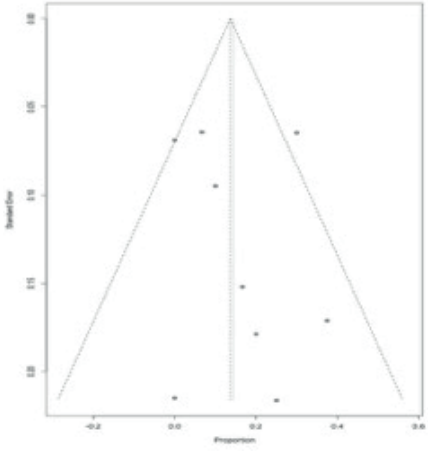
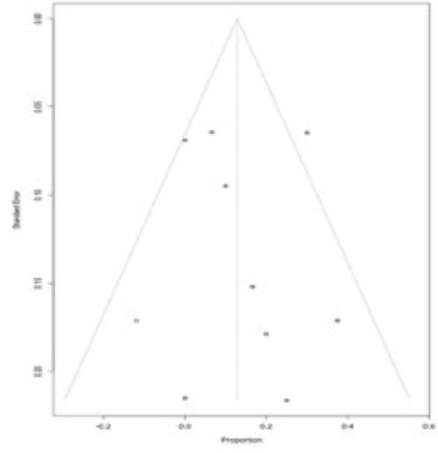
Raw funnel plot	Trim & fill funnel plot
	

3) Post-operative cerebrospinal fluid (CSF) leak

Tuberculum Sellae Meningioma

Raw funnel plot	Trim & fill funnel plot
	

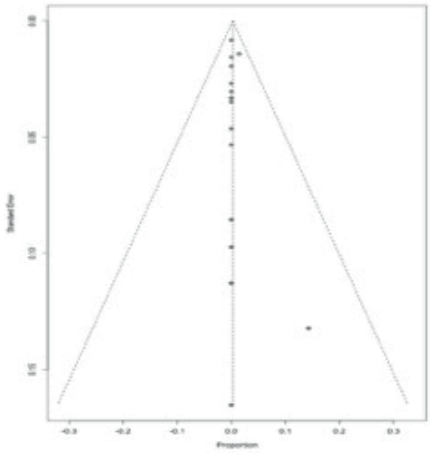
Olfactory Groove Meningioma

Raw funnel plot	Trim & fill funnel plot
	

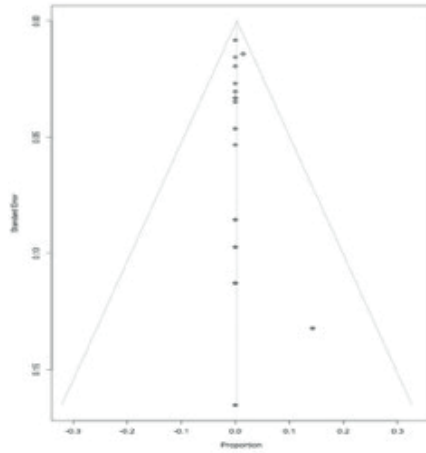
4) Intraoperative arterial injury:

Tuberculum Sellae Meningioma

Raw funnel plot

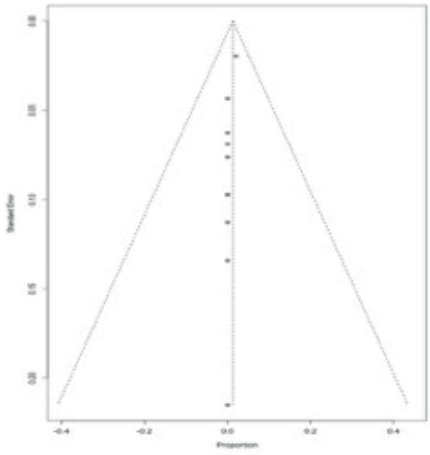


Trim & fill funnel plot

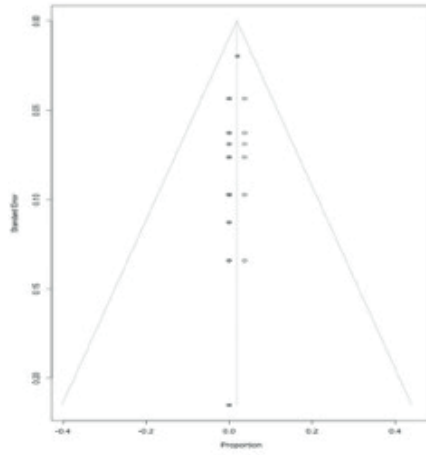


Olfactory Groove Meningioma

Raw funnel plot

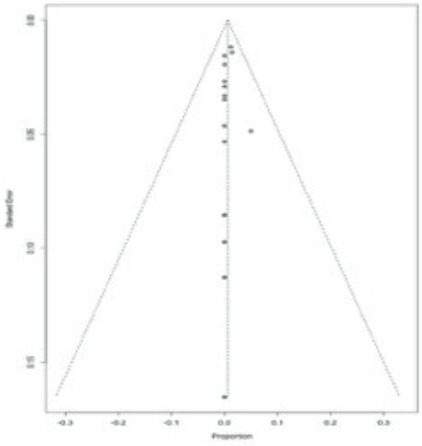
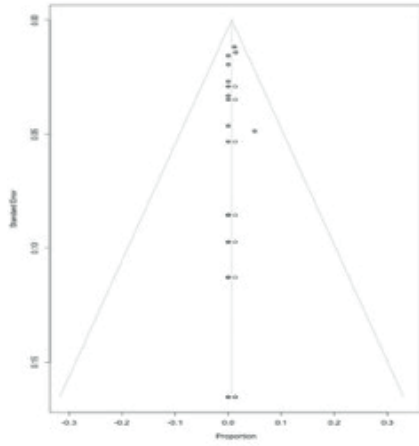


Trim & fill funnel plot

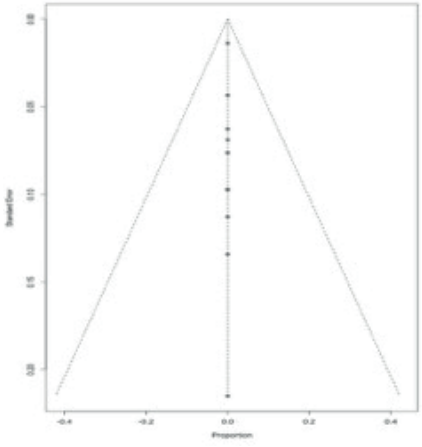
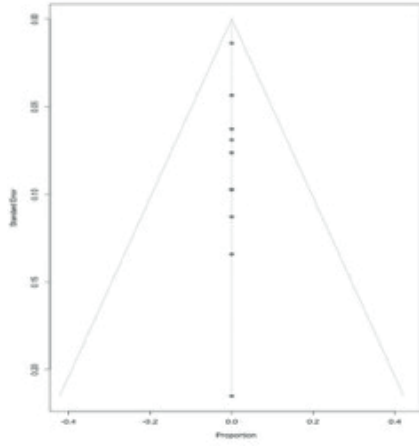


5) 30-day mortality:

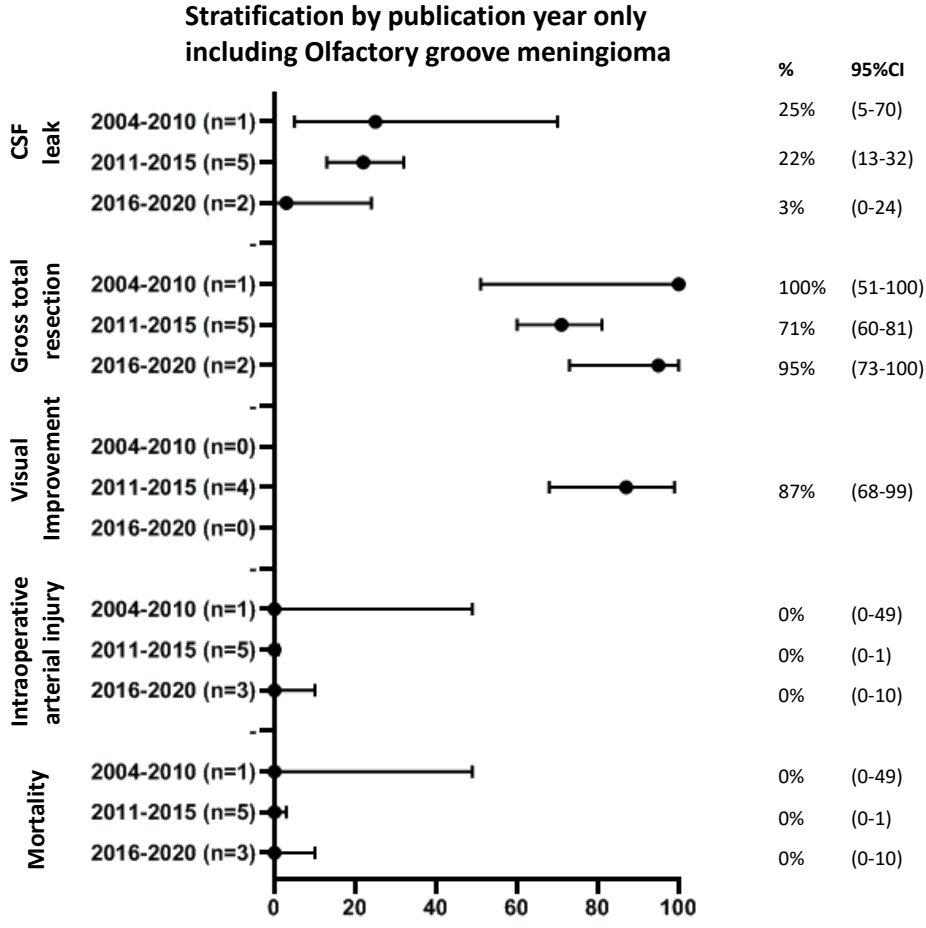
Tuberculum Sellae Meningioma

Raw funnel plot	Trim & fill funnel plot
	

Olfactory Groove Meningioma

Raw funnel plot	Trim & fill funnel plot
	

Supplementary Figure 2: Results for patients with Olfactory groove meningioma



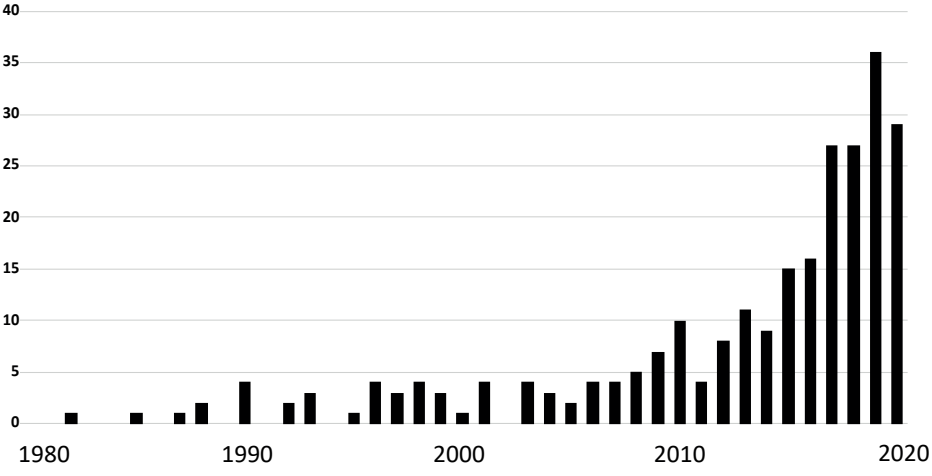
Chapter 11.1

General Discussion: paradigm shifts in the road to optimize meningioma care and research

INCREASE OF MENINGIOMA STUDIES EVALUATING PATIENT-CENTERED OUTCOMES: A SHIFT FROM TUMOR TO PATIENT

During the period in which the studies described in this thesis were conducted, a large increase was observed in the number of publications evaluating patient-centered outcomes, such as health-related quality of life (HRQoL, Figure 1). The increase in knowledge on the impact of a meningioma itself and its treatment on the functioning and well-being of patients was needed and welcomed not only by meningioma patients, but also their caregivers and healthcare providers. For too long, meningioma was described as a benign disease, curable with total tumor resection, thereby neglecting the impact of tumor and treatment on patient functioning and well-being shortly after treatment and in the long-term. Multiple editorials were published in the early nineties and the beginning of this century by renowned and respectful neurosurgeons recommending a shift from tumor to patient. Consequently, there was an increase in the number of studies focusing on the immediate impact of treatment on patient-centered outcomes. However, it took another two decades before the first results on the (very) long-term outcomes were published (**Chapter 2 and 3**)(1,2).

Figure 2: Number of articles indexed in PubMed retrieved with the search strategy ("meningioma"[tiab] AND ("quality of life "[tiab] or "functioning"[tiab]))



In **Chapter 2,** we evaluated articles published up to 2015, describing HRQoL in meningioma patients. At that time, a total of nineteen studies were published on this topic that met our inclusion criteria. In general, published articles described that meningioma patients report worse HRQoL than healthy controls both before and after intervention. Radiotherapy seemed to result in a transient improvement in HRQoL, while it decreased to pre-radiotherapy levels after a couple of years of follow-up. Surgery seemed to improve HRQoL outcomes; however,

longer-term follow-up after surgery showed persistent lowered HRQoL compared with controls. A major limitation of these studies was the small study populations, ranging between 16 and 155 patients, prohibiting subgroup analyses, and assessing the relationship between different treatment modalities and outcomes. Moreover, most studies assessed outcomes up to only one year after intervention. Lastly, outcomes were often only evaluated with a generic HRQoL instrument, thus failing to measure issues that may be particularly relevant for meningioma patients. Therefore, a study comprehensively evaluating the long-term meningioma disease burden seemed warranted.

MEASURING THE ROAD: A SHIFT FROM CLINICIAN-REPORTED OUTCOMES TO PATIENT-REPORTED OUTCOMES (PROS) IN MENINGIOMA

The articles included in the systematic review described in **Chapter 2** measured HRQoL with 13 different PROMs. Only three of these PROMs were validated in meningioma patients. Hence, it was not surprising that most items of these 13 PROMs were not considered relevant by meningioma patients (**Chapter 6**). Indeed, we showed that for 12 PROMs, more than 40% of items were deemed irrelevant by meningioma patients. For the thirteenth PROM, the EQ-5D, 4 out of 5 items were deemed relevant by patients. Although the EQ-5D measures aspects of functioning, the questionnaire is meant to be a utility measure for economic analysis. The low number of items deemed relevant in the used questionnaires can be explained by the fact that often generic PROMs were used, such as the SF-36, which were developed for common chronic conditions, such as asthma, cardiovascular disease, and rheumatoid arthritis(3,4). Brain tumor patients differ from patients with these chronic conditions, as they harbor specific neurological and psychological symptoms, not reflected by generic or even cancer-specific PROMs(5,6). Indeed only 57% and 33% of the EORTC QLQ-C30 and FACT-G items were marked relevant by meningioma patients, which are both generic cancer PROMs **(Chapter 6)**. Even brain tumor-specific PROMs, typically developed for and validated in glioma patients and/or patients with metastatic brain tumors, were not considered completely relevant for meningioma patients, as patients assessed only 35% of the items of the EORTC QLQ-BN20 and 40% of the FACT-Br as relevant **(Chapter 6)**. This underlines that the disease burden in meningioma patients differs from patients with glioma and metastatic brain tumors. Not only are these distinctly different tumor entities, meningioma patients also receive other treatment regimens (e.g., no standard use of radiotherapy and chemotherapy), possibly resulting in different toxicity profiles and subsequently different issues as experienced by patients. Moreover, WHO grade I and II meningioma patients have a near-normal life expectancy, and hence survivorship issues are of particular relevance in this patient group. Therefore, the results of **Chapter 2** warrant the development of a meningioma-specific patient-reported outcome measure (PROM).

THE ROAD DOESN'T STOP AFTER INTERVENTION: A SHIFT FROM SHORT-TERM TO SURVIVORSHIP ISSUES

As mentioned, there is a paucity of data on patient-centered outcomes in the longer term. In **Chapter 3**, we described the long-term outcomes of meningioma patients. Patients were assessed at least 5 years, with a median follow-up of 9 years, after their last meningioma intervention or diagnosis in case of solely a wait-and-scan follow-up strategy. We compared outcomes between meningioma patients and controls, and corrected the results for clinically relevant confounders. Measured outcomes were HRQoL, anxiety and depression, neurocognitive functioning, and work productivity. The following sections describe how our results relate to the published literature on patient-centered outcomes in WHO grade I/II meningioma in the short-term, and if available, the longer term. Of note, only results that are both statistically significant and clinically relevant are discussed.

Health-related Quality of Life (HRQoL)

In general, compared with controls or normative data, meningioma patients reported worse HRQoL both before and after intervention. The difference between patients and controls was largest before intervention, likely reflecting both the tumor's physiological impact and the diagnosis's psychological effect (7,8). After intervention, worse HRQoL was more likely to be reported in the very long-term (4-9 years after diagnosis or intervention)(9–14). Whereas patients in the period before intervention primarily reported symptoms and impairments, postoperatively, and especially in the very long-term, patients suffered more from participation restrictions. This is in line with existing survivorship frameworks, which describe that patients experience bodily impairments around the period of diagnosis and treatment, while in the long-term they adapt to these functional impairments. Nevertheless, they still experience disruptions of their social roles. Detailed information of the studies and results on which the above conclusions are based are provided in the following paragraphs.

Patients suffered from various symptoms before meningioma treatment, such as anxiety, depression, and fatigue, of which fatigue is the most prevalent symptom(15,16). One study showed that 23/53 (43%) patients suffered from general or mental fatigue after diagnosis, as measured with the Multidimensional Fatigue Inventory (MFI)-20(15). Moreover, vitality (SF-36) was clinically relevant lower in 21 patients with radiologically suspected meningioma than 21 controls, matched for age, sex, and educational level(7). The same study showed that meningioma patients also reported clinically relevant lower general health scores. Another study showed that 52 patients had more role limitations due to emotional health problems (SF-36) before irradiation compared with non-corrected normative data(8). Overall, these findings depict the

impact of a space-occupying intracranial lesion and the uncertain and stressful period around diagnosis for meningioma patients.

Whereas patients in the period before intervention primarily report symptoms and impairments, patients suffer from impairments and participation restrictions in the first years after intervention. In two larger size studies (1722 patients on average 0.6 years after surgery, and 89 patients on average 3 years after surgery), patients reported a clinically relevant lower score for role limitations due to physical health problems (SF-36) compared to controls matched for sociodemographic variables(9,11). Two studies with small sample sizes (n<25 patients) found no differences between patients and controls after correction for confounders, probably due to the small study population(12,14). At a median of 4 years after surgery, 291 patients reported clinically relevant lowered perceived cognitive function (EORTC QLQ-C30) compared with normative data. The difference between patients and normative data became larger with increasing follow-up length (120 months follow-up after surgery vs. less than 120 months follow-up)(17).

In the very long-term (**Chapter 3**), participation restrictions were the most relevant issues, as reflected by role limitations due to health problems. At a median of 9 years after intervention, comparing 190 patients (12 WHO grade II) with 129 controls, patients reported clinically relevant more role limitations due to physical health problems and role limitations due to emotional health problems (SF-36), even after correction for age, sex, gender, educational level, and comorbidities. These very long-term outcomes are particularly relevant for meningioma patients, as they have a near-normal life expectancy (18). However, these outcomes are also affected by normal physiological processes of aging, including reduced physical and mental reserves, and the development of unrelated comorbidities.

Anxiety and Depression

As described, some patients already report anxiety and depression prior to treatment. Indeed, one study reported that before treatment, 23% of meningioma patients suffered from severe anxiety and 10% from severe depression as measured with the HADS(16). In our long-term study, we found fairly similar results measured with the HADS: 14% of patients suffered from severe anxiety and 8% from severe depression after a median of 9 years after treatment (**Chapter 3**). Moreover, we found that meningioma patients had increased odds to suffer from clinically relevant anxiety or depression compared with controls. We and others hypothesize that the increased preoperative levels of anxiety and depression in brain tumor patients, including meningioma patients, might be caused by the acute stress and uncertainty of a brain tumor diagnosis, which often requires major intracranial tumor surgery(16,19). Postoperatively and in the long-term, patients might suffer from future uncertainty, as the tumor might require

reintervention(20). In general, symptoms of depression, such as apathy are associated with tumors located in the frontal lobes(16,21).

The symptom burden, including anxiety and depression, may impact patient's functioning, activities in daily life, and their perceived global health status, as described by the WHO ICF model and studies in patients with brain tumors, including meningioma(22–25). Anxiety and depression are especially associated with both self-reported and objective neurocognitive deficits(23). Preoperative higher levels of anxiety and depression were also associated with lower 5-year overall survival rates in meningioma patients, independent of sex, age, functional status, extent of resection, tumor location, WHO grade, and history of depression(26). These results emphasize that although clinically relevant severe anxiety and depression are not frequently occurring symptoms, they profoundly impact patient well-being and survival.

Neurocognitive functioning

A study of 48 asymptomatic meningioma patients found no clinically relevant differences in any of the evaluated neurocognitive domains between patients and controls matched for age, sex, and education(27). These results suggest that small tumors that cause no neurological deficits or other symptoms are also unlikely to cause any relevant subclinical neurocognitive deficits. In contrast, a study preoperatively compared patients with a clear surgical indication with controls found that 20-42% of patients suffered from deficits in different cognitive domains(28). These impairments were most frequently found in the domains psychomotor speed (42%) and cognitive flexibility (40%)(28). Twelve months after surgery, 17-33% of the same patient cohort suffered from neurocognitive deficits. Improvement in neurocognitive functioning was seen in 3% to 30% of patients in different domains within the first 12 months (28). As described in **Chapter 3,** a total of 43% of patients suffered from a clinically relevant neurocognitive deficit in at least 1 of the 6 measured domains in the very long-term (average of 9 years follow-up), most often in the domains information processing speed (27%) and attention (23%). In general, these studies show that both in the short- and long-term, patients primarily suffer from neurocognitive deficits in domains that can be classified as executive functions. These functions require control over multidimensional processes, which are not located in specific brain locations. These findings are in line with the theorem that these functions are diffusely distributed over the brain, connected by large white matter networks, which come together at so-called central hubs(29,30). This could also explain why no association was found between tumor location and neurocognitive deficits (**Chapter 9**).

Work productivity

Out of the 190 meningioma patients assessed in **Chapter 3**, 123 (65%) were aged between 18 and 67 years and considered to be of working age. At the time of assessment, 50% of meningioma patients had a paid job, compared with 72% of the net average working-age

Dutch population. These results are similar to a Swedish study with 956 meningioma patients, reporting that within the first two years after surgery, 57% of patients returned back to work.(31) In **Chapter 3**, we describe the main reasons reported by patients not to have a paid job: being a homemaker (female patients 15%, male patients 0%) or poor health condition (both male and female patients: 24%). When having a paid job, patients reported more often obstacles at work (46%) than controls (17%). The following problems at work were reported to occur sometimes to always: impaired concentration (74%), slower work pace (78%), feelings of isolation (22%), delaying work (67%), the need for someone to take over their work (42%), and problems to make decisions (59%). Possible determinants for not returning back to work were a previous history of depression, sick leave in the year before surgery, and surgical complications.(31,32) In general, there is only very limited data available on work productivity in meningioma patients. Hence, this should be a topic of future research.

Overall, **Chapter 3** emphasizes that patient functioning and well-being should not only be evaluated and monitored in the short-term, but also when clinical follow-up visits become less frequent over time. The findings from the literature and our study suggest that short- and long-term issues are different; whereas patients are likely to suffer from issues associated with the tumor and short-term treatment effect in the early disease stages, other issues become more relevant later in the disease course and reflect long-term treatment effects (e.g., neurocognitive dysfunction after radiotherapy) as well as survivorship issues (e.g., problems with role functioning). Moreover, the finding that meningioma patients still have a significant disease burden many years after the last anti-tumor treatment has led to the insight that meningioma should be regarded as a chronic condition with life-long limitations.

BEYOND THE PATIENT: THE CAREGIVER ROAD

Sherwood and colleagues have described a conceptual model of caregiver burden in primary malignant brain tumor patients.(33,34) According to this model, the patient disease characteristics (including tumor, treatment, functional, cognitive, and neuropsychiatric status) alongside the caregiver personal characteristics (e.g., personal or social attributes) impact caregiver burden. The caregiver burden may consequently affect caregivers' overall health and wellbeing (e.g., HRQoL).(33,34) In **Chapter 4**, we analyzed the caregiver burden according to this model and described that up to 35% of meningioma informal caregivers reported a clinically relevant caregiver burden. This was the first study describing the caregiver burden in meningioma. This burden was indeed associated with lower levels of HRQoL and higher levels of anxiety and depression in caregivers. While the caregiver burden was related to the patient's HRQoL, it was not determined by the patient's neurocognitive functioning, nor their sociodemographic, tumor or treatment status. These results emphasize that the caregiver

burden is inherently part of the chronic nature of meningioma. Moreover, it shows that the caregiver burden in meningioma is most strongly influenced by modifiable factors, such as patient's HRQoL, and less by non-modifiable factors, such as tumor and sociodemographic characteristics. As caregiver and patient wellbeing are strongly interlinked, supportive care should be directed to both patients and their informal caregivers.

Compared with other patient groups, the meningioma caregiver burden tends to be higher than caregiver burden in patients with traumatic brain injury, epilepsy, Parkinson's disease, multiple sclerosis, and lung cancer, but lower than the caregiver burden in stroke, dementia, and dialysis, most likely related to the severity of the disease of the patient and the time period at which informal caregivers had to adjust to their new situation.(35–43) These findings emphasize the clinical relevance of the caregiver burden in meningioma and warrant attention for the caregiver as well.

THE PATIENT ROAD: A SHIFT FROM DESCRIBING TO UNDERSTANDING

Biological variables as determinants for HRQoL and neurocognitive functioning: tumor characteristics and comorbidities

Several studies attempted to identify determinants for the long-term disease burden in terms of lowered HRQoL and impaired neurocognitive deficits, to better understand the disease burden. In contrast with many published studies, we used an etiological approach, in which we only correct for established confounders, instead of multivariable regression analyses including all measured variables. The latter provides results in terms of variables associated independently from other variables with the outcomes of interest. However, it might also result in overcorrection, by correcting for variables that lay in the causal path between the determinant and outcome of interest. For instance, correction for peritumoral edema for the association between tumor growth rate and neurocognitive functioning might result in overcorrection, as vasogenic edema is caused by tumor growth and might directly be related to neurocognitive impairments. Hence, this may fade the association between tumor growth and neurocognitive functioning.

In **Chapter 9** we described that a larger tumor size at the time of study participation is a determinant for lowered HRQoL and impaired neurocognitive functioning at a median of 9 years after the last meningioma intervention or diagnosis in case of a wait-and-scan approach. Moreover, we found edema on the last MRI before study participation to be a determinant for impaired neurocognitive functioning. We did not find an association between other tumor characteristics, such as tumor location (convexity vs. skull base) and tumor size before intervention, and long-term HRQoL or neurocognitive functioning. Similarly, in five previously

published studies (range study size: 21 to 249 patients) no differences in HRQoL (EQ-5D or EORTC QLQ-C30) or neurocognitive functioning were found for patients with different tumor locations, preoperative tumor size, or WHO grade(13,14,28,44,45). While preoperative tumor edema has not been associated with postoperative HRQoL scores, it has been associated with neurocognitive deficits(14). One smaller study of 52 patients with anterior skull base meningioma showed an association between a simpler anatomical tumor location (i.e., minimal optic canal involvement, carotid artery encasement, sella turcica involvement, or bone hyperostosis) and postoperative improvement in overall HRQoL (EQ-5D). In contrast, patients with a complex anatomical tumor location had postoperative deterioration in HRQoL scores(46). These findings suggest that a simple distinction between convexity and skull base tumors is of limited value. We hypothesize that this is also the reason why we did not identify an association between tumor location and HRQoL or neurocognitive functioning. Detailed information on the anatomical location and proximity to critical structures seems therefore needed when evaluating the effect of tumor location on HRQoL.

In **Chapter 9** we also found an association between higher comorbidity burden measured with the Charlson Comorbidity Index and lower HRQoL scores. Only one other study investigated the association between comorbidities and HRQoL in meningioma patients. This study in 133 elderly patients (aged 55-85) showed that those classified as ASA (American Society of Anesthesiologists classification) class 4 (i.e. more serious comorbidities) reported lower HRQoL (SF-36) than those classified as ASA class 1 (i.e., no comorbidity)(47).

Sociodemographic characteristics as determinants for HRQoL and neurocognitive functioning

In **Chapter 9**, we further described that female patients had lower HRQoL scores, but better neurocognitive functioning, compared with male patients. Moreover, older age was associated with impaired neurocognitive functioning. Higher educational level was associated with both better HRQoL and neurocognitive functioning. Other studies that have examined the association between sociodemographic characteristics and HRQoL showed conflicting results. In 249 operated meningioma patients, older age (>55 years) was associated with a clinically relevant HRQoL (EORTC QLQ-C30) improvement one year after surgery (absolute difference ≥ 10% on at least one scale), while no associations were found for sex or socioeconomic status(45). In contrast, a study in 133 older meningioma patients (55-85 years) showed that increasing age resulted in a lower physical component score as measured with the SF-36(47). In 52 patients treated with radiotherapy, neither age nor sex was a determinant for HRQoL(8). Regarding neurocognitive functioning, older age, and lower educational level have consistently been associated with poorer neurocognitive functioning(28).

Surgery as a determinant for HRQoL and neurocognitive functioning

Several studies have described the short-term impact of surgery on the symptomatology, level of functioning in daily life, and societal participation of meningioma patients. Regarding the symptom burden, surgery was found to have a small impact on fatigue. One study described that 68% of 34 patients reported fatigue before surgery, which decreased to 57% one year after surgery, as measured with the MFI-20(15). Similarly, the percentage of patients with anxiety reduced from 23% before surgery to 10% after one-year follow-up, as measured in 52 patients with the HADS(16). The same study showed that the percentage of patients with depression was similar at both time points (10% before surgery vs. 12% after surgery)(16). Furthermore, in 249 patients, surgery resulted in a clinically relevant (absolute difference ≥10%) improvement in headache (19%) and seizures (12%), and patients' global health status (21%) as measured with the EORTC QLQ-C30 at one-year follow-up. However, no clinically relevant changes were observed for other brain tumor-specific symptoms as measured with the MDASI-BT(45). Regarding neurocognitive deficits, 20-42% of 261 patients suffered from a deficit in various domains preoperatively, which improved for the different domains in 8-28% of 82 patients who were followed longitudinally up to three months after surgery(28). In another study, 54 patients with skull base meningioma were assessed both preoperatively and one year after surgery using a standardized test battery showing that for all assessed tests, patients showed improvement or stabilization in neurocognitive functioning on group level(48). Another study used the SF-36 and found in 78 patients that surgery resulted in a clinically relevant improvement in societal participation, reflected by improvements in role limitations due to physical health problems and role limitations due to emotional health problems at one-year follow-up(49). Overall, surgery results in improvements on all WHO ICF levels in the short-term. These results are probably a mixed effect of treatment, improvement of preoperative symptoms, presence or absence of postoperative deficits, personal, social and environmental attributes, and psychological effects of the diagnosis and (successful) treatment.

Improved postoperative levels of functioning have also been reported in the longer term. In 54 patients 2.5 years after surgery, postoperative scores on the EQ-5D were almost clinically relevant improved (EQ-5D change: 0.09, cut-off for clinical relevance: ≥ 0.10). The results of the same study at the individual patient level confirmed these results, showing that most patients maintained or improved in their overall EQ-5D scores after surgery: a clinically relevant improvement was found for 25 (49%) patients, while a deterioration was found in only 10 (20%) patients(44). Regarding skull base meningioma, two studies with 52 (grade II: 8%) and 58 skull base meningioma patients showed stable functioning and HRQoL within the first year after surgery, as measured with the EQ-5D and EORTC QLQ-C30, respectively(46,50). Nevertheless, these results need to be interpreted with caution as the likelihood of performing surgery is inherently associated with the location of the meningioma on the skull base.

The possible impact of surgery had not yet been evaluated for outcomes in the very long-term, including HRQoL and neurocognitive functioning. In our long-term disease burden study (**Chapter 3**) we found that compared with patients who were treated once with surgery (n=155), patients who needed reoperation (n=13) suffered from worse executive functioning, verbal memory, and attention. Similarly, patients who suffered from surgical complications (n=63) suffered from more attention deficits than patients who did not suffer from complications (n=105). However, only the association between reoperation and attention was clinically relevant. We observed no associations between different treatment modalities or complications with long-term HRQoL outcomes. We hypothesize that the association between surgery-related factors and long-term impairments is stronger for neurocognitive deficits than lowered HRQoL, as response shift may occur for HRQoL outcomes. Indeed, patients might change in their evaluation of a construct (i.e., HRQoL) as a result of a change in their internal standards of measurement, and their values or definition of the construct. For example, patients may accept their functional deficits caused by the treatment and its complications in the longer term, impacting how they evaluate their higher levels of functioning (i.e., activities in daily life and participation restrictions). In contrast, adaptation to neurocognitive deficits is less feasible, and neurocognitive deficits caused by treatment sometimes only become apparent in the very long-term.

Radiotherapy as a determinant for HRQoL and neurocognitive functioning

Overall, radiotherapy seems to have a negative effect on HRQoL in the short-term, after which HRQoL scores recover to pre-treatment levels at around 2 years after radiotherapy(8,51). After three years of follow-up, adjuvant radiotherapy seems to cause lowered HRQoL compared with controls matched for sociodemographic variables(12). However, in the very long-term (**Chapter 3**), no clinically relevant differences were found between patients treated with surgery as first-line treatment, patients treated with radiotherapy as first-line treatment, and patients treated with postoperative radiotherapy. Moreover, no association was found between radiotherapy use and neurocognitive functioning in the first years after treatment, and only significant but not clinically relevant associations were found in the very long-term (**Chapter 3**)(12,52,53). Details of the above-described impact of radiotherapy on HRQoL and neurocognitive functioning are elaborated in the following paragraphs.

Compared with normative data, 52 meningioma patients reported clinically relevant lower HRQoL scores for all SF-36 domains before radiotherapy. HRQoL scores further decreased during radiotherapy, after which they improved markedly to reach pre-radiotherapy levels after 2 years follow-up. The 10 patients who were solely treated with radiotherapy reported a clinically relevant worse mental component score both before, during, and after radiotherapy compared with the 42 patients who were surgically treated before receiving radiotherapy(8). It

should be noted though that these results were not corrected for differences at baseline, as treatment with primary radiotherapy was reserved for patients with small tumors causing minor symptoms, patients who favored radiotherapy over surgery, and patients with anatomically inoperable tumors.

One study showed that the addition of radiotherapy to surgery resulted in more activity limitations and participation restrictions in the mid-long-term. In this study, 18 meningioma patients treated with both surgery and radiotherapy were compared with 18 patients treated with surgery alone, matched for age, sex, and educational level(12). After a median of 3 years follow-up, patients treated with additional radiotherapy reported clinically relevant lower physical function, more role limitations due to physical health problems, and a lower score on the physical component score (all SF-36 domains), than those treated with surgery alone. No differences were found for brain tumor-specific symptoms (EORTC QLQ-BN20). However, these results should be interpreted with caution, as the patient groups were small and already differed significantly at baseline in their Karnofsky Performance Status (KPS) score, and the results were not corrected for this difference (12). Both studies found no differences in neurocognitive functioning between the groups.

In the very long-term (**Chapter** 3), radiotherapy did no longer seem to impact HRQoL and neurocognitive functioning at group level. At a median of 9 years after intervention neurocognitive functioning scores were statistically significant lower for patients who were treated with radiotherapy alone (n=10), and those who were treated with a combination of surgery and postoperative radiotherapy (n=26), compared with patients treated with only surgery (n=141). However, these differences did not reach thresholds for clinical relevance. The lack of clinically relevant association between radiotherapy and the long-term disease burden is somewhat surprising, as the above-described studies with shorter follow-up showed overall a negative impact of radiotherapy on the level of HRQoL. Moreover, in patients with low-grade glioma, radiotherapy toxicity in terms of neurocognitive deficits actually only became apparent on the very long-term, after more than 10 years of follow-up (54). The relatively small subgroup of patients treated with radiotherapy alone or with adjuvant radiotherapy could be an explanation for our findings.

REPORTING QUALITY: PAVING THE ROAD FOR TRANSPARENT PUBLICATIONS

In **Chapters 2 and 7,** we showed that many published studies do not report study aspects necessary to properly understand the study results and implement the results in clinical practice. The systematic review described in **Chapter 2** showed that the average reporting quality of studies

measuring PROs in meningioma patients, as evaluated with the ISOQOL criteria, is low. This is in line with similar systematic reviews on studies in patients with glioma, metastatic brain tumors, and lymphoma(55–57). Aspects often reported poorly are the reasons why certain PROMs are selected, information on how to interpret PROMs, and a description of clinical relevance of the results next to statistical significance. One might expect that the quality of reporting is lower in a niche field, such as meningioma, as these studies are often published in lower impact journals. High(er) impact general medicine journals often require the use of reporting guidelines, and the authors who publish in these journals therefore should adhere to these(58–60). However, we also evaluated the quality of reporting of non-meningioma prediction models in high impact general medical journals in **Chapter 7**. Although the systematic review described in **Chapter 7** focused on different outcomes (e.g., survival and cardiovascular outcomes) and evaluated another specific reporting guideline, namely the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statement, focusing on the reporting of prediction models, the quality of reporting of the studies included in this review was also low. Interestingly, results were not better for studies explicitly referring to the TRIPOD statement, or for studies published in journals requiring TRIPOD adherence. Items poorly reported even after the TRIPOD publication were, among others, characteristics of study population (37%), predictor selection (70%), and description of the full prediction model (42%). Especially the lack of reporting of the full prediction model provides an important barrier for any further validation or use of the model. These results are in line with publications evaluating the implementation of other important guidelines, such as the CONSORT (Consolidated Standards of Reporting Trials) statement for clinical trials, the STARD (Standards for Reporting Diagnostic accuracy studies) statement for diagnostic studies, the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) statement for observational studies, and the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) guideline for prognostic marker studies. Although studies evaluating the impact of these reporting guidelines showed an improvement in some of the relevant aspects, many study aspects were still poorly reported(61–63). Improvement in the level of reporting is therefore warranted.

ORGANIZING THE PATIENT ROAD

Before drafting the current Dutch guideline for meningioma care (i.e., "*Oncoline richtlijn intracranieel meningeoom*"), the Dutch Comprehensive Cancer Organization (IKNL) conducted a survey to identify the needs of patients and their informal caregivers in current meningioma care trajectories(64). The survey results showed a large unmet need in the guidance and support of meningioma patients and their informal caregivers. Moreover, the survey identified a large knowledge gap on current bottlenecks in meningioma care trajectories and what patients

actually seek in terms of guidance and support. Based on these results, we performed semi-structured interviews and focus groups with meningioma patients, their informal caregivers, and healthcare providers to identify additional issues in the meningioma care trajectories and possible solutions for these issues. The results of this study are described in **Chapter 5**. First of all, patients, partners, and healthcare providers reported the lack of information on care processes, interventions, and outcomes as a large unmet need. Furthermore, patients and partners experienced insufficient guidance and support throughout the process, including care for friends and family members who functioned as informal caregivers. Finally, they believed that screening and referral for rehabilitation are not optimal. Healthcare workers described that they have limited possibilities for referral to physiatrists for rehabilitation. Although it might seem a simple approach, the addition of a case manager to current care trajectories was identified by all groups as the solution with possibly the biggest benefit(65,66). Case managers can provide information on care processes and possible outcomes, thereby reducing symptoms of anxiety and future uncertainty. Case managers can also manage patient's and caregiver's expectations regarding activity limitations and be a contact point for everyday questions(66). Furthermore, they are able to provide continuity of care and oversee all the care processes, including possible gaps in care and the need for referral for supportive care, such as psychological care or help by social workers, supporting patients to regain their role in society(66). Through these processes, patients will be better involved in their own care, feel more in control of their situation, and receive appropriate supportive care where needed, eventually aiming to improve their global HRQoL(65,66).

Spheno-orbital surgery: a multidisciplinary road

Resection of spheno-orbital meningioma is often perceived as very challenging, due to the hyperostosis of the sphenoid bone and proximity to the skull base foramina harboring the cranial nerves. In **Chapter 8**, we describe in our modestly sized study that pterional surgery, performed by a team of a neurosurgeon and orbital surgeon, resulted in long-lasting improvements in visual outcomes and proptosis. Preoperative best-corrected visual acuity (BCVA) deficits normalized in 70% of patients, and improved in 10%. Preoperative visual field deficits normalized in all patients. Preoperative proptosis normalized in 44% and improved in 56% of patients. BCVA and visual fields remained stable at longer follow-up (> 1 year) in 95% of patients, while proptosis remained stable in approximately 80% of patients. These results are in line with a meta-analysis on this topic(67). Predictors for worse longer-term (defined as >12 months) BCVA were worse preoperative BCVA and diagnosis of multiple meningioma. Predictors for worse longer-term visual fields were higher diameter of hyperostosis and higher Simpson grade. With the clear association between visual deterioration preoperatively and worse postoperative outcomes, we advise intensive ophthalmological monitoring and early referral for surgery of these patients by ophthalmologists. Although others already advised

early referral and surgery based on their clinical experience, we provided scientific evidence supporting this message (68–75).

Taking the road from above or below

In the last two decades, the extended endoscopic endonasal approach has been improved for resection of anterior skull base meningioma. Previous systematic reviews have shown similar outcomes for the endoscopic endonasal and transcranial open approach in total resection grade (approximately 80%) and the percentage of severe complications (approximately 0-5%) (76,77). The biggest drawback is the higher percentage CSF-leak, which in previous studies has been reported to occur in up to 20% of anterior skull base meningioma patients(78). However, in **Chapter 10**, we reported by means of a meta-analysis a clear drop in CSF leak from 22% in the first reported case series to 4% in the most recently reported case series. Contribution to this drop is the development of graded multilayer repair protocols using a variety of flaps, synthetic materials, fat, and fascia lata(79). Especially the use of the pedicled nasoseptal flap, the Hadad-Bassagasteguy flap, and its modification to a "rescue flap", has proven to be a great method to prevent CSF leak for surgical resection of this intradural pathology. Due to its vascularization from the posterior sphenopalatine artery, the Hadad-Bassagasteguy flap is a fast healing flap with a large area coverage, and a large arc of rotation(80,81). Indeed, we showed that CSF leak was lower when the Hadad-Bassagasteguy flap was used (3%) than when it was not used (12%). The gasket seal closure technique also provided low CSF leak, namely in 9% of patients. This percentage is probably slightly higher than the Hadad-Bassagasteguy flap, as it is often used in complicated cases with large dural defects. Controversy exists on using lumbar drains to prevent CSF leak, as complications such as pneumocephalus and infections might not outweigh the potential benefit, especially with the current low CSF leak rate(82,83). Nevertheless, the only grade A evidence to prevent CSF leaks stems from a randomized controlled trial showing that perioperative lumbar drain usage combined with a nasoseptal flap further reduces the percentage CSF leak (21% vs. 8%) without an increased risk for complications and pneumocephalus(84). With similar outcomes in terms of resection grade and complication risk, and the lowered percentage CSF leak, the extended endoscopic endonasal technique becomes a more attractive option to resect anterior skull meningioma in selected patients.

Chapter 11.2

Practical implications and future directions.

PRACTICAL IMPLICATIONS

With this thesis, we aimed to provide information that could readily be implemented in clinical practice to improve our current care trajectories for meningioma patients and their caregivers. Moreover, the results may have implications for future clinical research in patients with intracranial lesions, more specifically meningioma. Although some of the formulated recommendations have been described in other medical fields, our results confirm that these recommendations are also relevant for the meningioma research field. In this part we will focus on the practical implications of the results of this thesis, while areas for future research are described in the next part.

Implications for clinical care

Informing patients and caregivers

While already in the early nineteenth-century dr. Codman and dr. Cushing collected data on the short-term outcomes of their procedures to inform their future patients, information on long-term functioning in meningioma lacked before the studies (**Chapter 3 and 4**) described in this thesis. Outcomes on long-term functioning are of particular relevance for this patient group, as meningioma patients have a near-normal life expectancy(18). The current unmet need for information on treatment outcomes was underlined in our focus groups with meningioma patients, their informal caregivers, and healthcare providers (**Chapter 5**). Based on the results described in this thesis and other published literature, we provide in Table 1 the most important results regarding patient functioning and the impact of surgery, which could be used for patient and caregiver education. The information may not only be important for treatment decision-making, but also for decision-making to participate in research. Patients should be well-informed on the possible benefits and adverse effects of (new) treatment strategies before providing informed consent for treatment or research participation. The impact of radiotherapy is not described in Table 1, as we believe that there is currently not sufficient published data to provide reliable conclusions on the impact of irradiation on patient outcomes in both the short- and long-term.

Understanding the meningioma disease burden

Meningioma is a very heterogeneous disease, and consequently, outcomes might differ strongly between patients. In addition to the literature, the results of **Chapters 3, 4, and 9** help to better understand the long-term disease burden. Not only did we show that patients have lowered HRQoL scores and impaired neurocognitive deficits compared with controls, we also evaluated determinants for these outcomes, using an etiological approach. Based on the results presented in the mentioned chapters and other published studies on similar topics, we have filled out the WHO ICF framework of functioning (Figure 2), which provides clinicians and researchers with an overview of our current knowledge of the meningioma disease burden, including

determinants related to the disease burden, and external modifiable factors. In **Chapter 3**, we showed that patients treated with a single operation reported the best long-term outcomes. Although a small proportion of patients is not eligible for primary surgery, it is the mainstay of treatment for meningioma, and optimal surgical treatment is therefore warranted(85). The good patient-centered outcomes probably reflect the great development in meningioma surgery in the last two centuries with emphasis on patient functioning instead of gross total resection(1,86,87). We also showed in **Chapter 5** that the caregiver burden and patient disease burden are strongly interlinked, and hence, the caregiver should be actively included the care decisions and processes. Supportive care should therefore not only be directed to the patient, but also their informal caregiver, as decreasing the caregiver burden may possibly improve the patient disease burden and vice verca.

Predicting the meningioma disease burden in clinical practice

In **Chapter 9** we have developed separate prediction models to predict an individual patient's risk of developing long-term lowered HRQoL or impaired neurocognitive functioning. Information used for these prediction models is readily available in clinical information systems. The prediction models showed that higher age, lower educational level, presence of comorbidities as measured with the Charlson Comorbidity Index, larger tumor size before intervention, surgical complications, the need for reresection, initiation of radiotherapy, and years since diagnosis, were predictors for long-term lowered HRQoL and impairments in neurocognitive functioning. Of note, as these prediction models are currently based on WHO grade I and II meningioma patients treated in tertiary referral centers in the Netherlands, we recommend external validation of these models in different settings, populations, or countries before further use in clinical practice. When validated, these models could be used to provide tailored information on long-term outcomes and for allocation of scarce and expensive supportive care resources.

Measuring PROMs in clinical practice

In clinical care, the results obtained with PROMs create a dialogue between patients and physicians on patient-relevant topics, which have shown to result in improved communication, adequate monitoring of patient functioning over time, continuity of care, and also patient well-being (6,66,88–91). The results in **Chapter 5 and 6** emphasize the importance of measuring patient functioning in clinical practice using PROMs in addition to clinician-reported outcomes, such as the performance status (e.g., KPS). First, in **Chapter 6** we report a large discrepancy between patients and healthcare providers on what they report as relevant outcomes for patients. In **Chapter 5** we further described that patient-partner dyads themselves report that they believe that routine use of PROMs in clinical practice is of added value to strengthen the patient voice. Among other, it facilitates discussion on topics that are not routinely discussed in clinical practice. Moreover, when completed before their visit to the

outpatient clinic, it enables healthcare workers to better prepare their clinic. Hence, PROM measurement might even be time-efficient in clinical practice. PROMs might also be used as a screening instrument to identify symptoms and problems that could be improved after referral to other healthcare workers, such as neurocognitive problems, and problems with (instrumental) activities of daily living I(ADL). With the current lack of meningioma-specific PROMs, we recommend using a combination of a generic and more neuro-oncology specific PROMs to capture issues on all possibly relevant aspects. A broad approach enables comparison with other patient groups, while it also provides sufficient relevant information on the individual patient level. While meningioma-specific PROMs are being developed and validated, the results of the study described in **Chapter 6** could also be used to construct item lists using items from item banks, such as the EORTC and PROMIS.

Spheno-orbital meningioma surgery

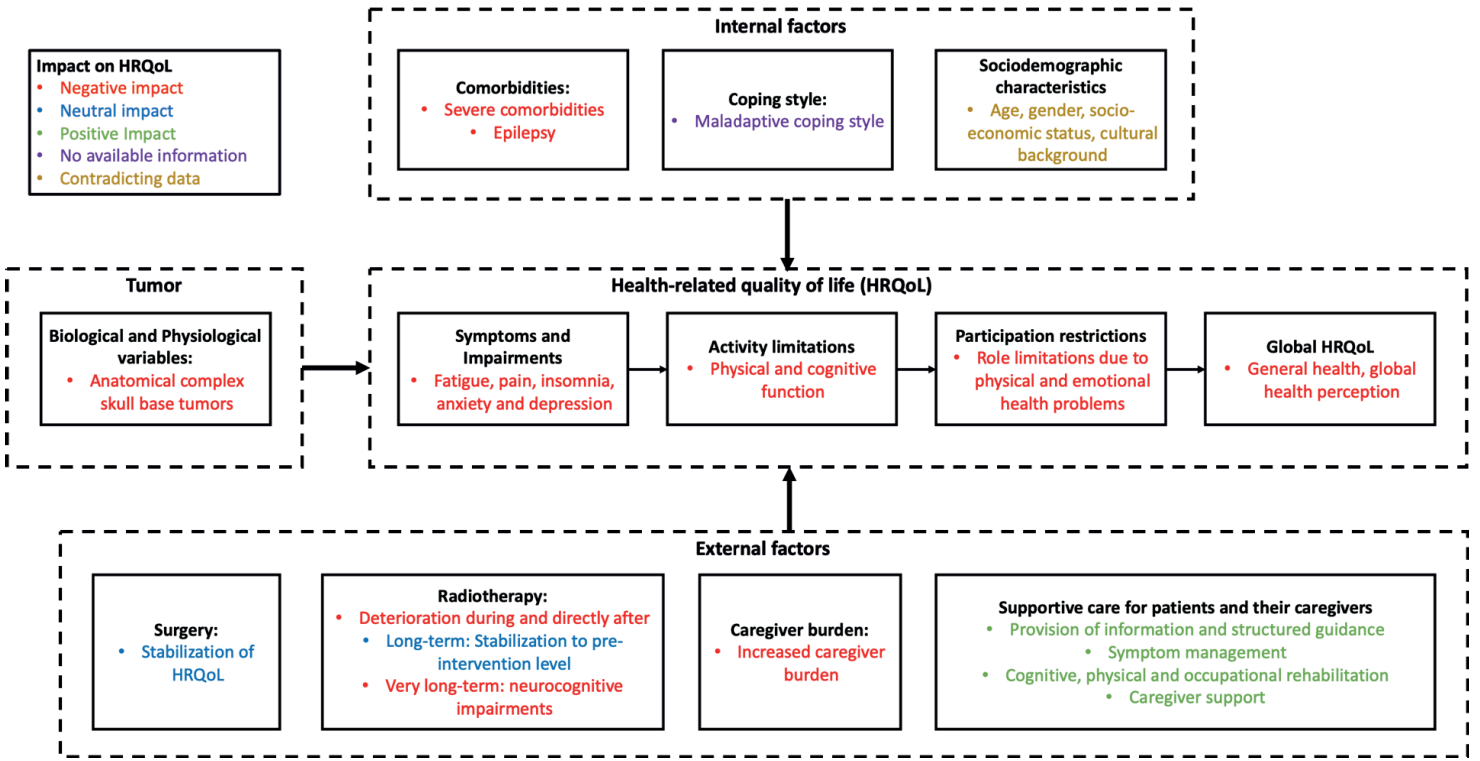
Based on the results of **Chapter 8**, we encourage referral of patients with spheno-oribital meningioma for surgery, even patients with minimal hyperostosis or visual impairments, as our results show that good visual outcomes can be achieved and maintained after pterional surgery. Moreover, we make an argument for early referral and early surgery, as the predictors of worse postoperative visual outcomes were worse preoperative visual acuity and greater diameter of hyperostosis. Based on the clinical experience in our relatively high-volume referral center and the existing literature, we advise transection of the meningo-orbital band to facilitate decompression of the superior orbital fissure, which encompasses multiple cranial nerves (92). In addition, we advise to always resect hyperostotic bone of the lateral orbital wall, orbital roof, and optic canal (70,71,75,93–95). The addition of an orbitoplastic surgeon to the neurosurgical team helps to resect intraorbital meningioma involvement, as they are trained in surgery of this complex anatomical location. To prevent (pulsatile) enophthalmos, reconstruction should be performed with titanium mesh or 3d-printed PEEK (polyetheretherketone) implants (70,71,73,75,93,96–98). Others have described to perform no orbital reconstruction to reach optimal restoration of proptosis. However, we believe that minimal residual proptosis is less bothersome than (pulsatile) enophthalmos. Moreover, the results **in Chapter 8** showed that while we performed orbital reconstruction, proper long-lasting decrease of proptosis was still achieved. We believe, in contrast to some published reports (99,100), that the use of new endoscopic approaches, such as the transorbital approach and the combined endoscopic and transorbital approach, should be preserved for selected patients with suspected benign meningioma with minimal intradural growth, and in whom relief of symptoms through decompression of the optic canal is the primary goal. These recommendations are underlined with our observations that tumor remnants tend to grow rapidly postoperatively, underlining the importance of a maximum safe resection, i.e., to resect as much as possible without causing new neurological or cranial nerve deficits.

Table 1. Summary of relevant outcomes in clinical practice for meningioma patients who received surgery as their primary treatment and their caregivers during the disease course

	Before intervention *(results of literature)*	**Short-term and mid-term after surgery (up to 5 years after surgery)** *(results of literature)*	**Long-term (at least 5 years of the last intervention)** *(results of this thesis)*
Health-related quality of life (HRQoL)	Patients primarily suffer from fatigue, lowered vitality and general health, and role limitations due to emotional health problems(7,8,15).	Patients primarily suffer from role limitations due to physical health problems(9,11). Up to 20% of patients report improvement in at least one HRQoL domain, but primarily stabilization of HRQoL scores is reported(15,16,45).	Patients primarily suffer from role limitations due to emotional and physical health problems
Neurocognitive functioning	20-42% of patients suffer from a deficit in at least one cognitive domain, but the specific domains differ. Most frequently impairments in psychomotor speed (42%) and cognitive flexibility are reported (40%)(28).	17-33% of patients suffer from a deficit in at least one cognitive domain, although the specific domains differ. Improvement in neurocognitive functioning is seen in 3 to 30% of patients in different domains within first 12 months(28).	43% of patients suffer from neurocognitive deficits in at least one domain. Most frequently impairments in information processing speed (27%) and attention (23%) are reported
Anxiety and Depression	17-23% of patients suffer from patient-reported severe anxiety and 10% from severe depression(16,26).	10% of patients suffer from patient-reported severe anxiety and 12% from severe depression(16,26). After surgery up to 10% of patients report improvement in anxiety compared with before surgery(16).	14% of patients suffer from severe anxiety, and 8% from severe depression.
Work productivity	79% of Swedish patients aged between 16 and 60 years had a paid job(31).	57% of Swedish patients aged between 16 and 60 years had a paid job(31). Of those with a paid job preoperatively, 33% was not able to go back to work 10 months after surgery(32).	43% of patients aged between 18 and 67 had a paid job, compared with 72% of the net average working-age Dutch population.
Caregiver burden	No published data available	No published data available	Up to 35% of informal caregivers report a clinically relevant caregiver burden in at least one domain. This burden is associated with lower HRQoL, and more anxiety and depression in those caregivers.

**Improvement concerns clinically relevant improvement*

Figure 2. Framework for Health-related quality of life (HRQoL) in WHO grade I/II intracranial meningioma patients.



Extended endoscopic endonasal surgery for anterior skull base meningioma

With the development of new reconstruction techniques, a decrease in CSF leak for anterior skull base meningioma in the last two decades was observed (**Chapter 10**). Hence this approach has become even more attractive to resect anterior skull base meningioma. This holds especially for patients whose tumor pushed the optic apparatus upwards with lateral extension less than 50% over the carotids, as it enables tumor resection without crossing the optic system or carotids. Compared with the transcranial approach, endoscopic resection of these tumors might result in better visual outcomes (76,78). Instead of the Hadad-Bassagasteguy flap, we recommend the use of a free mucosal flap for smaller dural defects to prevent unnecessary nasal mucosal damage. Although recommended by others (84), we believe that with the low percentage CSF leak using these advanced reconstruction techniques, there is no role for standard perioperative use of lumbar drains(101,102).

Implications for clinical research

Patient involvement in PRO development and use of PROMs for outcome evaluation

As patients and clinicians report different symptoms and other aspects of functioning as relevant, the results of **Chapter 6** underline the importance of including patients in the development of new PROMs, as clinicians may not always be aware of all issues patients experience during the disease course, or may not realize which aspects have most impact on patients' life. This holds especially true for survivorship issues, as these were not studied before the studies presented in this thesis (**Chapters 2,3,4**), hampering healthcare workers to be fully aware of these issues. Unfortunately, PROMs, regardless of the medical field, are still sometimes developed with minimal patient involvement. When PROMs are used in clinical research, it enables to comprehensively evaluate the impact of treatment in a truly patient-centered fashion. It also facilitates to determine the net clinical benefit of treatment (i.e., weighing the benefits of treatment against the side-effects) as both eventually impact patient functioning.

The difference between prediction and assessment of determinants

In **Chapter 9**, we showed that not all predictors for outcomes such as neurocognitive functioning and HRQoL are determinants and vice versa. These findings align with the great body of work on this topic published by methodologists (103–106). However, the time has come to also make a clear distinction between predictors and determinants in the neuro-oncological and neurosurgical field. We strongly advise our colleagues to determine the actual aim of the study before applying certain statistical methods, such as multivariable regression analyses. If the aim is to assess determinants, only variables should be used in the multivariable model that are causally associated with both the determinant and outcome, and do not lay in the causal path between the determinant and outcome. These variables are preferably chosen based on clinical knowledge or previous work on the topic. This is different for prediction models. Predictors are

often used altogether with other predictors within multivariable prediction models to predict an individual patient's risk for developing a certain outcome at a specific time point in the future. Hence predictors are not determinants per se, but can also be a proxy of a determinant or just be associated with the outcome without assumptions of causality.

The difference between statistical significance and clinical relevance

The studies summarized in the systematic review of **Chapter 2** primarily reported statically significant results, while significant results are not per se also clinically relevant. We advise to only formulate firm conclusions based on results that are both statistically significant and clinically relevant. Similarly, statistically significant results should only be implemented in clinical practice when also clinically relevant. For example, in **Chapter 3**, we report that there were significant differences between patients and controls for 5 domains/component HRQoL scores, of which only two were also clinically relevant.

Use of reporting guidelines

Studies can be excellently performed and analyzed. Nevertheless, if they are poorly reported, interpretation and clinical usability is hampered, as shown in **Chapters 2 and 7**. We therefore encourage authors to report their study according to the applicable reporting guideline, as can be found on the website of the EQUATOR Network (https://www.equator-network.org), which is an international initiative to promote transparent and high quality reporting by making published reporting guidelines easy accessible for researchers. Even in cases where researchers can only collect and analyze their data with major limitations, transparent reporting facilitates that other researchers can build on their research. While many general medicine journals have endorsed these reporting guidelines, and require the use of these guidelines as prerequisite for publication, it is time for more topic-specific journals to also require authors to adhere to reporting guidelines in order to improve the level of reporting. In addition, asking reviewers to check adherence to reporting guidelines may improve the level of reporting. More generally, medical doctors shouldn't only be taught on methodology and statistics, but also on the importance of proper reporting.

FUTURE DIRECTIONS

Improving the patient and caregiver road

The ultimate goal is to provide care that adds value to patients and their caregivers in terms of improved outcomes and experiences, as described in the framework for Value-Based Healthcare (VBHC) by prof. Michael Porter and prof. Elizabeth Teisberg. To this end, it is essential to evaluate current care systems structurally and adapt them if needed. In figure 3, we propose an approach for care transition and continuous care evaluation for meningioma patients, adapted

from Porter's VBHC framework. These adaptations are based on our experiences with the focus group study, as described in **Chapter 5**. This adapted framework consists of 7 steps: 1) assess the need for any changes and problems in current care trajectories, 2) define the boundaries of the evaluated care and involve all stakeholders, 3) identify possible solutions for these problems, 4) decide indicators for iterative evaluation, 5) integrate care processes into a formalized care trajectory, 6) expand excellent care services geographically, and 7) parallel to steps 1 to 6: build an information platform for monitoring patients and care trajectories throughout the whole process. This adapted model differs from the original model, as we emphasize more on preparation steps to evaluate whether a change is needed, who should be involved, and what should be measured. By doing so, we can accomplish long-lasting sustainable changes. Although the original model describes as a first step to organize teams into integrated practice units (IPU), this is not so straightforward for rare diseases where healthcare workers can be involved in the care of different patient groups and hence take part in multiple IPUs. Before the actual measurement of outcomes and costs as described in the original model, we believe that we first need to evaluate which outcomes should be measured, ensuring comprehensive measurement of patient-relevant outcomes and experiences. Steps 5, 6, and 7 were already described in Porter's original model and were incorporated in the current framework without any adaptations.

In relation to step 1, the results described in the studies conducted as part of this thesis, together with the currently available literature, emphasize that meningioma patients and their informal caregivers suffer from functional impairments in both the short- and long-term (**Chapters 2 and 3**). These impairments are not sufficiently addressed in current care trajectories (**Chapter 5**). Moreover, patients indicated that they lack continuous guidance and support (**Chapter 5**)(6,65). Hence, we believe that there is a need to formalize and improve meningioma care trajectories to address these problems and improve care for patients and their caregivers.

Second, the limited available literature on the caregiver burden did show a strong interdependent relationship between patient and caregiver functioning. This finding emphasizes the need for integrative care targeting both patients' and their caregivers' needs. For WHO grade I/II intracranial meningioma, a large multidisciplinary team seems needed to address patient and caregiver needs, including: neurosurgeons, neurologists, radiation oncologists, ENT-surgeons, ophthalmologists, neuroradiologists, pathologists, endocrinologist, physiatrists, psychologists, case managers, and nurse specialists. Importantly, we believe it is more feasible to organize an integrated practice unit around delivered care than around a patient group, as healthcare workers tend to be involved in the care of different patient groups, for whom they deliver similar care. Hence, we propose that two integrated practice units are needed for the care of meningioma patients. One IPU is needed for patients with non-skull base meningioma in strong collaboration with a neuro-oncology IPU, as it involves the same healthcare workers

and patterns of care. Similarly, another IPU is needed for patients with skull base meningioma, as the care of these patients resembles the care of patients with pituitary adenoma, chordoma, vestibular schwannoma, and other skull base lesions.

Third, interventions should be considered that improve patient and caregiver functioning on all three WHO ICF levels: I) symptoms and impairments, II) activity limitations, III) and participation restrictions. We believe that this is not only achieved by improving tumor interventions, such as surgery and radiotherapy, but also by improving supportive care options, such as (cognitive) rehabilitation or occupational therapy (**Chapter 5)**.

Different clinical outcome assessment modalities serve different purposes. Hence, we believe that a core outcome set for continuous outcome evaluation should encompass not only clinician-reported outcomes, observer-reported outcomes, and performance outcomes, but also PROMs to ensure that the patient experience is incorporated. In addition, following the VBHC principles, key performance indicators are needed, such as time between diagnosis and surgery, surgical complications, and time back to work. Importantly, outcomes should be measured against the costs of care, as added value can be achieved by improving outcomes for similar or less costs, or stabilizing outcomes while reducing costs.

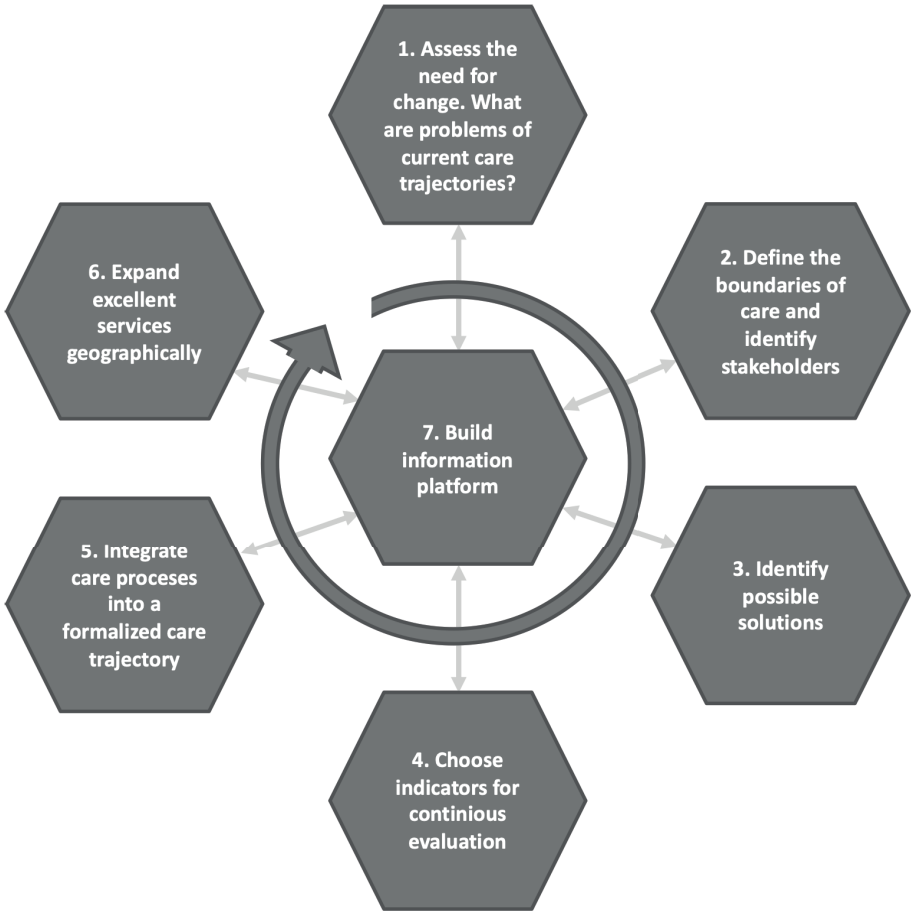
Fifth, according to the VBHC principles and the results of **Chapter 5**, a formalized integrative care trajectory is needed with strong collaboration between all involved stakeholders. Within such a formalized care trajectory all stakeholders can work together to improve the identified problems and implement interventions to improve patient and caregiver functioning, while outcomes are continuously evaluated and acted upon. Patients and informal caregivers deserve a prominent role in the process of reforming and formalizing current care trajectories as they are an important stakeholder.

Sixth, care services should expand geographically within the Netherlands and Europe to ensure that developed expertise is accessible for a large group of patients. This is especially relevant for meningioma care, as not all centers can provide all possible treatment possibilities. For example, not all centers have endoscopic skull base surgeons, experience with for instance spheno-orbital meningioma patients, or access to a radiosurgery facility.

Seventh, an information platform is needed to follow patients throughout their care trajectory, and to routinely measure the clinical core outcome set and key performance indicators. Preferably such an information platform is integrated within existing electronic patient file systems, enabling healthcare workers to truly incorporate the measured outcomes into their clinical practice. This will not only help clinicians to coordinate patient care, but also to monitor

patient functioning over time. Moreover, it assists in evaluating the impact of treatment and identifying the need for supportive care.

Figure 3. Adaptation of Porter's Value Based Healthcare (VBHC) steps for care transformation and continuous care evaluation



Interventions to improve symptoms and impairments

Regarding symptoms and impairments in brain tumor patients, there is mostly evidence for the effectiveness of interventions directed to symptoms of anxiety and depression, fatigue, and neurocognitive deficits, which are among the most frequently reported symptoms by meningioma patients. As a first step, evaluation of symptoms through PROMs is needed to identify patients with a certain degree of symptoms (**Chapter 5**). The presence of neurocognitive deficits should be evaluated with a neuropsychological test battery administered by a trained administrator. Where possible, and if needed, patients should be referred to the right healthcare worker for their symptoms. Case managers could play a pivotal role in coordinat-

ing this process (**Chapter 5**). Regarding symptoms of anxiety and depression, national and international guidelines advise treatment with a combination of pharmacological and psychological treatment, which is also applicable to patients with brain tumors(24). Regarding fatigue, the lack of improvement with psychostimulants (such as modafinil) (107–109) has redirected the focus of research to treatable contributing factors, such as anemia and altered sleep hygiene(110). For example, there is strong evidence from a meta-analysis of randomized controlled trials in cancer patients that exercise effectively reduces cancer-related fatigue(111). Understanding the biological substrates of fatigue in meningioma patients is needed to develop more effective interventions for this disabling symptom. Regarding neurocognitive deficits, an extensive cognitive rehabilitation program focusing on attention, memory, and neurocognitive function showed improvement in neurocognitive function and a decrease in self-reported mental fatigue at 6 months follow-up in glioma patients(112). These interventions still need to be evaluated in meningioma patients. As improvement of neurocognitive functions is difficult, preservation of neurocognitive function is of equal or even greater importance. Prevention is even better than cure, and less toxic treatment options should therefore be explored, such as more precise irradiation protocols, broadened indications for proton beam therapy, and improved microsurgical techniques(113). Furthermore, adaptive e-health programs focusing on the improvement of a specific outcome, e.g., neurocognitive functioning, are promising(24). Indeed, online neurocognitive rehabilitation programs are more accessible and more tailored to the patient, requiring less time-consuming visits to the outpatient clinic, if available at all. Currently, a randomized controlled trial is being performed to evaluate the effectiveness of such an application in patients with primary intracranial tumors, including meningioma(114).

Interventions to improve activity limitations and participation restrictions

Problems with activities, and consequently participation in society, are especially present in the longer term **(Chapter 2 and 3**). These limitations might be improved with multidisciplinary rehabilitation therapy, including occupational therapy. In patients with non-acquired brain injury this type of intervention has been suggested to improve instrumental activities of daily living (IADL) and consequently patient participation in society(115). Especially the use of occupational therapy has been suggested to improve role limitations, as it focuses on assisting with IADL, enabling patients to retake their roles in society(116). Compared with glioblastoma or stroke patients, it has been suggested that meningioma patients may actually reach better outcomes, being an extra-axial pathology with less direct damage on brain parenchyma(117,118). Although the above-mentioned studies suggest that traditional multidisciplinary rehabilitation may improve functional outcomes in meningioma patients, this is not yet widely implemented in this patient population, largely due to cost, availability, and difficulty identifying those who will benefit (65,66,116). Future research should therefore focus on identifying which aspects of traditional multidisciplinary rehabilitation have a profound impact on the functioning and well-being of meningioma patients, and which patients benefit the most from an intervention.

Interventions to improve caregiver burden

A Cochrane review published in 2019 identified eight interventional studies aiming to improve caregiver well-being in those caring for patients with brain or spinal cord tumors, but not meningioma patients(119). These interventions primarily focused on providing information, training for caregiver skills, and psychosocial support. However, only limited evidence was found for improvement of caregiver distress, caregiver mastery, and caregiver HRQoL. So, there is still a large unmet need to identify interventions to improve the caregiver burden. Emerging innovative fields that may address patient's and caregiver's needs are the use of e-health, enabling personalized therapy through adaptive online programs, and the use of case managers in formalized care trajectories focused to improve patient and caregiver functioning on all three WHO ICF levels (24,65,66). In patients with pituitary tumors it has been shown that psychoeducation programs with patient-partner dyads not only improve patients' HRQoL, but also decrease the caregiver burden and caregiver depression symptoms (120). There is a strong need to evaluate these innovative supportive care options in the meningioma population, including their caregivers. The need for supportive care might further decrease with the improvement of meningioma treatment protocols, including more tailored wait-and-scan follow-up, surgery, radiotherapy, and systematic therapy, resulting in improved outcomes in both the short- and long-term.

Improving surgical care

Less invasive and multiportal approaches have been developed in the last decades, such as the extended endoscopic endonasal approach as described in this thesis, and the combined endoscopic endonasal transorbital approach for spheno-orbital meningioma(121,122). Challenged by the anatomic boundaries, neurosurgeons have always tried to develop new surgical approaches and techniques to improve outcomes (86,123). Historically this might have led to morally debatable techniques, such as the frontal lobe lobotomy for psychiatric diseases, and in more recent years the use of very extensive transcranial approaches for complete meningioma resection. In current times, guidelines exist to methodologically and ethically guide surgical development and to ensure transparency of these developments, such as the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework(124). These guidelines advise standardized data collection on surgical technique and outcomes, central data registration, and ethical oversight, to regulate these developments and ensure that the patient actually benefits from these new techniques.

An emerging field to facilitate surgical improvement is the use of robot-assisted and computer-assisted surgery(125). Driven by artificial intelligence, it could, among other things, assist in the preoperative planning of surgical approach, intraoperative decision making, and more precise microsurgical dissection. Moreover, it could assist, for instance through the use of

augmented reality systems, in the training of surgeons to become more quickly more skilled surgeons(126–128).

While surgery is the mainstay treatment for meningioma, the question remains when to perform surgery. Although surgery aims to relieve symptoms and is needed for tissue diagnosis, it encompasses a risk of complications too. More personalized and evidence-based wait-and-scan follow-up schemes facilitate tailored follow-up of meningioma patients, which also helps to time meningioma intervention(129). This is particularly important, as the number of asymptomatic meningioma diagnoses is rising with the increase in neuro-imaging.

Improving radiotherapy and targeted therapy options

Patients with an inoperable meningioma or poor health condition might be treated with radiotherapy, especially patients with smaller tumors. The role of upfront adjuvant radiotherapy in addition to surgery for WHO grade II is still debatable. Currently, two phase III trials (RTOG 0539/NCT00895622 and EORTC 22042/NCT00626730) compare upfront adjuvant radiotherapy with a wait-and-scan follow-up in completely resected WHO grade II tumors(130,131). In addition, the role of particle-based therapies will need to be further crystallized in future studies, especially the added benefit in terms of neurological and neurocognitive outcomes, and survivorship issues in long-term survivors.

Targeted therapy might claim a more prominent role in future meningioma care than it currently does(132). Driven by the vast expanding field and understanding of the molecular profile of meningioma, new systemic therapeutic regimens have been developed, which are currently being evaluated using innovative and adaptive trials designs, such as umbrella trials, basket trials, and combined phase IIa/IIb/III trials(131). An example is the umbrella trial A071401/NCT02523014 evaluating SMO, AKT1, and FAK inhibitors in patients with residual, progressive, or recurrent meningioma (all WHO grades) with targetable alterations in SMO, AKT1, and NF2, respectively. These molecular markers are primarily harbored by skull base meningioma, for whom the addition of systematic molecular therapies is especially beneficial, due to anatomically complicated location for complete surgical resection(132–134). Moreover, these systemic therapies could be very relevant for WHO grade II and III meningioma. Unfortunately, these tumors less often harbor these molecular alterations(135).

Raising the bar for meningioma research

Large prospective registries

Randomized controlled trials on meningioma surgery are challenging due to multiple reasons. First of all, healthcare providers and patients must believe that there is equipoise between different treatment options to justify that patients can be randomized. Currently, healthcare providers often have a strong preference for a specific treatment modality (e.g., surgery or

radiotherapy), or surgical approach (e.g., craniotomy or endoscopic endonasal), which they also might impose on the patient. Consequently, clinicians refrain from recruiting patients for such studies and patients choose to not participate in these studies. This is likely due to multiple factors. First, surgeons might not have access to all possible treatment modalities. For example, a patient with a 1.5 cm symptomatic cavernous sinus meningioma might be treated with either surgery or radiosurgery (e.g., gamma-knife radiotherapy). However, not all hospitals may have radiosurgery facilities. Second, surgeons might not be trained to perform certain surgical approaches, or might not be equally skilled to perform two different surgical approaches. The same 1.5 cm symptomatic cavernous sinus meningioma might be operated by an extended endoscopic endonasal approach or a peterional approach. While all skull base surgeons learn transcranial skull base approaches, not all are trained in extended endoscopic approaches. Moreover, different surgeons might perform the same surgical approach with slightly different techniques, hampering comparability of the evaluated procedure. Third, based on conventional clinician-reported outcomes, such as tumor control and neurological functioning, different meningioma treatment options might not only seem to be in equipoise, but to actually all have clinically good outcomes. Hence, it might seem that there is no need to evaluate which treatment option is best. For instance, both surgery and radiosurgery have been proven to provide excellent tumor control for 85% to 95% of meningioma patients with smaller meningioma within the first 5 years of treatment respectively, with neurological complications occurring in less than 10% of patients for both interventions(18,136).

Nevertheless, different treatment modalities could still impact patient-reported outcomes differently, emphasized by the finding in this thesis that there is a poor correlation between clinician- and patient-reported outcomes (**Chapter 3**). Importantly, the above-described barriers not only hamper randomization, but also generalizability of RCT results, and implementation in clinical practice. What is the added value to prove that a certain treatment modality or surgical technique is superior if a patient does not have access to a center with that treatment option, or a surgeon who is skilled and experienced to successfully perform a certain surgical approach? Another major barrier for performing RCTs in this patient group is that for both clinician-reported and patient-reported outcomes, results in the very long-term are of equal interest as short-term outcomes, since patients having near-normal survival rates. One would need at least a decade of follow-up to monitor outcomes of this often slowly progressing disease. Although studies in patients with low-grade glioma have proven that such studies are feasible, they require a huge investment of human and financial resources (137). Moreover, the relevance of the specific research question might become less relevant over time.

Based on the above-described barriers, it seems more feasible to set-up large international registries than a randomized controlled trial to measure outcomes of different treatment strategies and surgical approaches. First of all, such a registry will provide insight into current practice

variation, which is inherent to the current neurosurgical field with access to different treatment modalities, equipment, and differences in neurosurgical training. Detailed and standardized data collection is needed for clinical outcome assessment, including clinician-reported, patient-reported, observed-reported, and performance outcomes. The collected information will facilitate the development of classification systems to provide a more granulated indication for specific treatment options. Using the data collected in these registries, different treatment modalities or surgical techniques can be compared.

The barriers mentioned for an RCT, namely that surgeons often have a strong preference for a certain treatment modality or approach, might also be an opportunity for a natural experiment, where patients are treated with different modalities or approaches based on patient's geographic location (i.e., a natural experiment). Using such a natural experiment, one can compare outcomes of the different treatments or approaches. An excellent and successful example of such a study is the population-based low-grade glioma study in Norway, where patients were more likely to be treated with first-line biopsy or resection based on their zip-code and the affiliated hospital(138). In such a study, patients treated with different treatment strategies tend to be similar, as the choice for a certain treatment was not based on clinically relevant variables influencing the outcomes, but variables unrelated to the clinical condition or outcome, namely patients zip-code. However, treatment success is not only determined by the provided intervention, but also by the quality of the whole care trajectory, which hampers comparability between different centers. By comparing naturally occurring practice variation, not only different treatments are compared, but also different centers with different health cultures and possibly differences in quality of health care. Hence, it is important to also collect detailed data on key performance indicators for that intervention and other procedures performed by the healthcare team, as it facilitates to compare centers on the quality of the delivered care, detangling outcomes differences based on the actual treatment strategy and quality of care.

While non-RCT designs can sometimes substitute RCTs to compare different treatment strategies or approaches, comparison of actual interventions will still be hampered by confounding by indication, meaning that patients with certain characteristics are more likely to receive a certain treatment. Therefore, the reason to choose a certain treatment or surgical approach over another should also be collected in detail. This allows a better understanding of variables that determine treatment choice. Through a better understanding of treatment decisions and with the use of sophisticated analyses methods, we will be able to correct to the best of our ability for these confounders, and hence collect more information on the best treatment strategies for individual patients.

Future research should specifically be directed to evaluate and develop new methods to evaluate treatment effectiveness in rare diseases (e.g., previous example of optimal strategy for cavernous

sinus meningioma), where only a small number of patients are available for comparison of different treatment modalities or strategies.

Eventually, with the availability of high-quality registries, equipoise of different treatment possibilities might be proven, and healthcare providers might feel the need to create the highest quality evidence through RCTs. Going back to the example of the symptomatic 1.5 cm cavernous sinus meningioma, multiple treatment modalities and surgical techniques could be compared head-to-head. However, with the limited number of patients harboring such a tumor, we need to prioritize which questions need to be answered first. Moreover, we need to explore possibilities for smart RCT designs, such as adaptive trials, cohorts with multiple embedded RCT's, and patient-preference RCTs.

Initiatives to standardize the design, analysis, reporting, and interpretation of COAs and specifically PROMs in meningioma

For all study types, including registries and RCTs, it is important to standardize the design, analyses, and reporting of methods and results to the highest possible quality standards to ensure comparability, transparency, and clinical usability of study results. Multiple initiatives exist to this end, such as the Response Assessment in Neuro-Oncology (RANO) criteria for meningioma(139,140). While these often focus primarily on clinician-reported outcomes, such as tumor response, there are currently also international efforts to standardize the measurement of PROs for adult brain tumor patients, including meningioma, in clinical trials and practice(141).

For proper clinical outcome assessment in meningioma patients, a disease-specific PROM is needed, as patients have distinct symptoms, different from other conditions. Therefore, we are currently developing and validating a meningioma-specific HRQoL instrument(6). This instrument will be developed and validated cross-culturally to facilitate implementation in different cultures, enabling comparison of HRQoL across languages, countries, and cultures. Moreover, we are involved in the development of a minimum core outcome set for meningioma (https://www.thecosmicproject.org). Furthermore, progress has been made in the field of oncology and brain tumors in the standardization of the use, analysis, reporting, and interpretation of PROMs. Guidelines exist for including PRO assessments in clinical trial protocols (The Standard Protocol Items: Recommendations for Interventional Trials-PRO extension [SPIRIT-PRO])(142). Recently the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium published the first international standards for the analysis and interpretation of PROs in cancer clinical trials, focusing on the development of well-defined PRO aims, use of appropriate statistical methods for specific research objectives, and standardizing terminology and handling of missing data(143). To improve reporting of PROs in publications of randomized controlled trials,

the Consolidated Standards of Reporting Trials Statement-PRO extension (CONSORT-PRO) has been developed(144). Additionally, The International Society of Quality of Life Research (ISOQOL) reporting standards were published, distinguishing reporting for PROs defined as a primary or secondary outcome measure(145). Future studies should evaluate if these guidelines are implemented in meningioma research and if implementation of these guidelines will result in improvement in the use, analysis, and reporting of PROs in research and practice.

Chapter 11.3

Summary.
Treating meningioma: does the patient benefit?

TREATING MENINGIOMA: DOES THE PATIENT BENEFIT?

Intracranial meningioma surgery has led the way for many neurosurgical developments in the last two centuries with the ultimate goal to safely resect this tumor. In the last decade, through Clinical Outcome Assessment, and especially PRO measurement, we, among others, have initiated a shift in focus from tumor to patient (**Chapter 2 and 3**). Hence, we argue that the current goal of treatment is not only to safely resect the tumor, but also to improve patient functioning and caregiver well-being.

Although both radiotherapy and surgery result in excellent tumor control in meningioma up to a diameter of 3 cm, we believe that radiotherapy cannot replace first-line meningioma surgery in most patients. In contrast with surgical resection, radiotherapy doesn't resolve neurological deficits per se, but primarily prevents further growth of tumor (remnants). Hence, we believe that radiotherapy should be reserved for cases where patients are poor surgical candidates, even in patients with tumor regrowth after surgery. Patients might be poor surgical candidates due to extensive comorbidities, or an anatomically inaccessible tumor. Although we did not find a clinically relevant association between radiotherapy and the long-term disease burden of meningioma patients, strong statistical associations were found in our study, and clinically relevant associations are expected in larger study populations (**Chapter 3**). Moreover, as reported in the discussion, other studies report a detrimental effect of radiotherapy on neurocognitive functioning. Hence, we believe that patients do not readily benefit from radiotherapy.

Regarding surgery, we advocate for early meningioma surgery to increase the patient benefit. Patients with a smaller meningioma without any anatomical interaction with cranial nerves or blood vessels have a higher chance to be successfully treated with a single meningioma resection. Hence, they are less likely to suffer from surgical complications and report to have better long-term neurocognitive functioning (**Chapter 3**), compared with patients who needed multiple surgeries or who suffered from surgical complications. Moreover, in patients with anterior skull base meningioma, we show that predictors for worse postoperative visual outcomes are worse preoperative visual outcomes (**Chapter 9**), indicating that patients benefit the most from surgery when performed early in the disease course, before they develop symptoms or before further progression of symptoms occurs. Hence, we propose to not only operate patients with a symptomatic meningioma or radiologically established fast growing meningioma, as advised in Dutch and international guidelines, but also to operate patients with an asymptomatic meningioma or slowly growing meningioma in younger and older patients with a normal life expectancy.

Endoscopic endonasal surgery (i.e., surgery through the nose) has increasingly become popular in the last two decades, adding a new approach to the surgical arsenal. With the development of new closure techniques in the last two decades, such as the Hadad-Bassegasteguy flap, to reduce the risk of cerebrospinal fluid (CSF)-leak, it is even a more attractive option to operate anterior and middle skull base meningioma. Indeed, we showed that the percentage of patients with a CSF-leak has decreased in recent years and is lower in patients who received advanced closure techniques, such as the Hadad-Bassegasteguy flap (**Chapter 10**). Nevertheless, assessment of the proper indication to operate patients with the endoscopic endonasal approach is paramount. We do not believe that patients benefit from this approach because it is minimally invasive, as still parts of the skull base need to be drilled out. Moreover, patients report significant nasal morbidity due to removal and manipulation of nasal structures, especially the nasal mucosa. We believe that patients primarily benefit from this approach in case the tumor pushes critical neurovascular structures upwards and laterally, such as the optic system, enabling tumor resection without crossing nerves and vascular structures. This Pittsburg group first described this adagium.

While surgery improves functioning in the first years, patients still have impaired functioning, compared with matched controls, in the long-term. Most importantly, we describe in the very long-term, on average nine years after treatment or diagnosis, that patients suffer from participation restrictions in terms of role limitations with friends, family, and at work (**Chapter 3**). Often, we do not pay enough attention to these problems at outpatient clinic visits, especially as visits are less frequent in the long-term. Importantly, patient and informal caregiver (i.e., close relatives and friends) functioning are strongly interlinked (**Chapter 4**). These long-term issues should be addressed in formalized Value Based Healthcare (VBHC) meningioma care trajectories as described in the future directions of this thesis. The studies in this thesis suggest that such a trajectory could benefit from the use of 1) case managers, 2) implementation of patient-reported outcome measures, 3) prediction models assisting in the identification of individual patients at high risk for long-term lowered functioning, and 4) a holistic approach taking into account both the patient and their informal caregivers. A case manager could help patients during the period of diagnosis and treatment, which is a hectic and uncertain period for patients and their informal caregivers (**Chapter 5**). They can also assist patients and their caregivers with retaking their roles in society. They oversee the whole care process and, where needed, refer a patient to other healthcare workers. Throughout the disease course the use of PROMs will help clinicians and case managers identify the problems that patients and caregivers experience (**Chapter 6**). This enables more focused outpatient clinic visits, facilitates patients doctor communication, and eventually patient outcomes. Importantly, we established that patients and healthcare providers describe different outcomes and care processes as relevant (**Chapter 5 and 6**). This underlines the importance of PROMs implementation in clinical practice. Ultimately, patients evaluate their level of functioning,

and especially societal participation, as relevant in the long-term. Patients are less interested in conventional treatment outcomes, such as degree of tumor resection and length of hospital stay (**Chapter 5**). To implement the above-described advices, we also need to consider that meningioma is a heterogeneous disease, as these tumors grow throughout the whole central nervous system. Hence patients present with different symptoms, based on tumor location and tumor characteristics, requiring different surgical approaches and treatment protocols. Not all patients will experience a complicated disease course. Prediction models can help identify patients at high risk for impaired functioning, facilitating optimal use of often scarce and expensive supportive care recourses, such as (neuro)psychological guidance and group therapy (**Chapter 8**). However, the developed prediction models for long-term impaired functioning require validation, before implementation in clinical practice (**Chapter 7**).

In conclusion, although progress in the treatment of meningioma has been made in the last decades, we have to challenge ourselves to continuously optimize meningioma treatment with an increased focus on patient-relevant outcomes. The role of radiation therapy needs to be more crystalized, so it can selectively be used in poor surgical candidates, to limit the number of patients suffering from long-term complications of radiotherapy. Development and evaluation of new systematic therapies, based on patient's molecular tumor profile, will provide additional treatment options for meningioma patients who are poor candidates for surgery and/or radiotherapy. Ultimately, patients benefit from formalized meningioma care pathways, including a crucial role for case managers. New study designs may facilitate the evaluation of different treatment options, in this relatively rare disease. Guidelines, like the IDEAL statement, guide clinicians to develop and evaluate new surgical techniques following modern methodological and ethical standards. International guidelines will assist researchers to standardize their analyses and reporting, facilitating implementation of study results in clinical practice. However, during these exciting times with excellent treatment and methodological developments, we shouldn't forget for whom these developments are meant. Empowering the patients' voice, will help us navigate the road to future studies and Value-Based Healthcare.

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Hoofdstuk 11.4

Samenvatting. Heeft de patiënt baat bij de behandeling van een meningeoom?

HEEFT DE PATIËNT BAAT BIJ DE BEHANDELING VAN EEN MENINGEOOM?

Intracraniële meningeoomchirurgie heeft de weg vrijgemaakt voor veel neurochirurgische ontwikkelingen in de afgelopen twee eeuwen. Hierbij was het doel om deze tumor op een veilige manier zo volledig mogelijk te reseceren. In de afgelopen jaren is internationaal een verschuiving teweeggebracht waarbij de focus van de tumor naar de patiënt verplaatst is. Dit is mede mogelijk gemaakt door ons onderzoek, waarbij naar het functioneren en welzijn van meningeoom patiënten gekeken is. Middels vragenlijsten over onder andere kwaliteit van leven, zogenaamde patiënt-gerapporteerde uitkomstmaten (**Hoofdstukken 2 en 3**), hebben we deze uitkomsten in kaart gebracht. Op basis van dit onderzoek kunnen we stellen dat het huidige doel van de behandeling niet alleen gericht is op het veilig verwijderen van de tumor, maar ook om het functioneren en welzijn van zowel de patiënt als de naasten te verbeteren.

Hoewel zowel radiotherapie als chirurgie resulteren in goede controle van meningeomen tot een diameter van 3 cm, zijn wij van mening dat de meeste patiënten toch gebaat zijn bij chirurgie als eerste behandeling. Dit is omdat radiotherapie niet per se de neurologische klachten van patiënten doet verbeteren, maar in de eerste plaats verdere groei van tumor(restanten) verhindert. Chirurgie daarentegen kan ook verlichting van symptomen geven. Daarom pleiten wij ervoor dat radiotherapie behouden dient te blijven voor patiënten die door hun algemene gezondheid slechte kandidaten zijn voor chirurgie, zelfs indien het patiënten betreft met tumorgroei na een eerdere operatie. Hoewel we statistisch een sterk verband vonden tussen radiotherapie en een toegenomen ziektelast op de lange termijn, was dit verband niet klinisch relevant (**Hoofdstuk 3**). Waarschijnlijk hebben we deze relatie niet gevonden, omdat het aantal patiënten dat behandeld werd met radiotherapie in onze studie klein was. De resultaten zullen dus bevestigd moeten worden in een grotere onderzoeksgroep. Bovendien beschrijven andere onderzoeken een nadelig effect van radiotherapie op het neurocognitief functioneren. Daarom zijn wij van mening dat radiotherapie niet de eerste behandelkeuze moet zijn.

Wat chirurgie betreft, pleiten wij voor het vroeg opereren van een meningeoom om het voordeel voor de patiënt te vergroten. Patiënten met een kleiner meningeoom, dat niet dichtbij de hersenzenuwen of bloedvaten ligt, hebben een grotere kans op een volledige resectie zonder complicaties. Zodoende tonen ze betere neurocognitieve functies op de lange termijn dan patiënten die meerdere operaties behoeven of die complicaties ondervinden van de operatie (**Hoofdstuk 3**). Bovendien hebben we aangetoond bij patiënten met een meningeoom van de voorste/middelste schedelbasis dat de belangrijkste voorspeller voor slechtere visus na de operatie visusproblemen voor de operatie was (**Hoofdstuk 9**). Deze bevinding geeft aan dat patiënten het meeste baat hebben bij chirurgie wanneer dit vroeg in het ziekteverloop plaatsvindt, voordat symptomen ontstaan of de symptomen verder toenemen. Daarom stellen we

voor om niet alleen volgens de richtlijn patiënten met een symptomatisch meningeoom of radiologisch vastgesteld snelgroeiend meningeoom te opereren, maar ook jongere en oudere patiënten met een normale levensverwachting met een asymptomatisch meningeoom of een langzaam groeiend meningeoom.

Endoscopische endonasale chirurgie (d.w.z. chirurgie via de neus) is de afgelopen twee decennia steeds populairder geworden. Met de ontwikkeling van nieuwe sluitingstechnieken, zoals de Hadad-Bassegasteguy-flap, is het risico op liquorlekkage (lekkage van hersenvocht) verkleind. Hierdoor is deze benadering een nog aantrekkelijkere optie geworden om een meningeoom van de voorste of middelste schedelbasis te opereren. We hebben inderdaad aangetoond dat het percentage patiënten met een liquorlek de afgelopen jaren is afgenomen en lager is bij patiënten bij wie geavanceerde sluitingstechnieken gebruikt zijn, zoals de Hadad-Bassegasteguy-flap (**Hoofdstuk 10**). Desalniettemin is de indicatiestelling om patiënten te opereren met de endoscopische endonasale benadering van groot belang. De toegevoegde waarde van deze benadering is niet omdat deze minimaal invasief is, aangezien nog steeds delen van de schedelbasis worden weggeboord en patiënten bovendien significante neusklachten rapporteren als gevolg van het verwijderen en manipuleren van de binnenzijde van de neus, en dan vooral klachten met betrekking tot het neusslijmvlies (zoals een verminderd reukvermogen). Wij vinden dat vooral patiënten baat hebben bij deze aanpak in het geval het meningeoom de hersenzenuwen en bloedvaten naar boven en opzij duwt, zoals de oogzenuwen, waardoor tumorresectie mogelijk is zonder dat de instrumenten langs deze structuren geplaatst worden. Hiermee voorkomen we manipulatie van zenuwen en vaten en daarmee uitval van de hersenzenuwen of een bloeding. De Pittsburg-groep beschreef dit adagium voor het eerst.

Hoewel chirurgie het functioneren van de patiënt met een meningeoom in de eerste jaren na operatie verbetert, hebben patiënten op de lange termijn nog steeds een verminderd functioneren. Op de lange termijn, gemiddeld negen jaar na behandeling of diagnose, rapporteren patiënten vooral participatiebeperkingen, wat zich uit in beperkingen op het werk en binnen sociale kringen (**Hoofdstuk 3**). Vaak is hier weinig aandacht voor op de polikliniek, des te meer daar patiënten zoveel jaren na de operatie niet standaard en met lange tussenpozen op de poli gezien worden. Belangrijk is ook dat niet alleen het functioneren en welzijn van de patiënt wordt geëvalueerd, maar ook dat van de naaste familieleden en vrienden, omdat uit ons onderzoek is gebleken dat deze sterk met elkaar samenhangen (**Hoofdstuk 4**). Aandacht hiervoor kan gegeven worden in geformaliseerde zorgpaden. Waardegedreven zorg is hierbij essentieel, opdat we zorg leveren waar de patiënt wat aan heeft. De onderzoeken in dit proefschrift suggereren dat een dergelijk zorgpad verbetert met het gebruik van 1) casemanagers, 2) implementatie van patiënt-gerapporteerde uitkomstmaten, 3) voorspelmodellen die helpen bij de identificatie van individuele patiënten met een hoog risico op een verminderd functioneren op de lange termijn, en 4) een holistische benadering waarbij rekening wordt gehouden

met zowel de patiënt als zijn/haar naasten. Een casemanager zou patiënten kunnen helpen tijdens de periode van diagnose en behandeling, wat een hectische en onzekere periode is voor patiënten en hun naasten (**Hoofdstuk 5**). Tevens kan een casemanager patiënten en hun naasten bijstaan met de re-integratie in de sociale kringen en op het werk. Zij overzien het hele zorgtraject en verwijzen waar nodig een patiënt naar andere zorgverleners. In het zorgpad zal het gebruik van patiënt-gerapporteerde uitkomstmaten clinici en casemanagers helpen bij het identificeren van de problemen die patiënten en zorgverleners ervaren (**Hoofdstuk 6**). Dit maakt meer gerichte polikliniekbezoeken mogelijk, vergemakkelijkt de communicatie tussen de zorgverlener en de patiënt, en verbetert uiteindelijk de uitkomsten van de zorg. Belangrijk is dat we hebben vastgesteld dat patiënten en zorgverleners verschillende uitkomsten en zorgprocessen als relevant beschrijven (**Hoofdstuk 5 en 6**). Dit onderschrijft het belang van patiënt-gerapporteerde uitkomstmaten. Uiteindelijk beoordelen patiënten hun niveau van functioneren, en vooral het maatschappelijk participeren als relevant op de lange termijn. Patiënten zijn minder geïnteresseerd in conventionele behandelresultaten, zoals de mate van tumorresectie en de opnameduur (**Hoofdstuk 5**), wat wel als relevant wordt beschouwd door zorgverleners. Om de hierboven beschreven adviezen te implementeren, moeten we er ook rekening mee houden dat het meningeoom een heterogene ziekte is. Aangezien deze tumoren in het hele centrale zenuwstelsel kunnen ontstaan, ervaren patiënten verschillende symptomen. Echter zullen niet alle patiënten een gecompliceerd ziekteverloop ervaren. Voorspelmodellen kunnen helpen bij het identificeren van patiënten met een hoog risico op een verminderd functioneren op de lange termijn, waardoor optimaal gebruik kan worden gemaakt van vaak schaarse en dure ondersteunende middelen, zoals de inzet van (neuro)psychologen en groepstherapie (**Hoofdstuk 8**). Deze voorspelmodellen moeten echter wel eerst gevalideerd worden voordat ze in de klinische praktijk kunnen worden geïmplementeerd (**Hoofdstuk 7**).

Concluderend: hoewel vooruitgang is geboekt in de behandeling van meningeoompatiënten in de afgelopen decennia, moeten we onszelf blijven uitdagen om de behandeling van deze patiëntengroep verder te optimaliseren met de focus op patiëntrelevante uitkomsten. Zo moet de rol van radiotherapie verder worden uitgekristalliseerd, en alleen worden toegepast bij patiënten die niet geopereerd kunnen worden vanwege de ernstige bijwerkingen van radiotherapie op de lange termijn. De ontwikkeling van nieuwe therapieën, gebaseerd op het moleculair tumorprofiel van de patiënt, zal aanvullende behandelingsopties creëren voor meningeoompatiënten die niet in aanmerking komen voor chirurgie en/of radiotherapie. Uiteindelijk heeft de patiënt er baat bij dat de behandeling in geformaliseerde zorgpaden plaatsvindt met een sterke rol voor casemanagers. Nieuwe onderzoeksopzetten zijn nodig om de verschillende behandelingsopties op een efficiëntere manier te evalueren bij deze relatief zeldzame ziekte. Nieuwe richtlijnen helpen clinici bij het ontwikkelen en evalueren van nieuwe chirurgische technieken volgens moderne methoden en moderne medisch ethische normen. Internationale richtlijnen helpen onderzoekers met het standaardiseren van hun onderzoeksopzet, statische analyses en rapport-

eren van uitkomsten, wat helpt om studieresultaten in de klinische praktijk te implementeren. Echter, we mogen niet vergeten voor wie deze spannende ontwikkelingen op het gebied van behandeling en methodologie bedoeld zijn. Door de patiënt sterker te betrekken in onderzoek en verbeterinitiatieven in de zorg, kunnen we de weg naar doelmatige waardegedreven zorg sneller bereiken.

List of publications (30-10-2021)
Curriculum Vitae
Dankwoord

LIST OF PUBLICATIONS

1. **Zamanipoor Najafabadi AH**, Peeters MCM, Lobatto DJ, Groen JLG, Broekman MLD, Peerdeman SM, Peul WC, Taphoorn MJB, Dirven L, van Furth WR. Impaired health-related quality of life of meningioma patients - a systematic review. Neuro Oncol. 2017;17(9):897–907.
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CURRICULUM VITAE

Amir Hossein Zamanipoor Najafabadi was born on the 7th of March 1994, in Karaj, Iran. Together with his parents he arrived in the Netherlands in 1995 and grew up in Leiderdorp. He completed high school in 2012 by obtaining his gymnasium diploma summa cum laude from the Visser 't Hooft Lyceum in Leiden. During the last two years of high school, he attended courses at the Leiden University as part of the Leiden Pre-University College, where his interest in research was sparked. In 2012 he obtained his Pre-University College diploma cum laude. In the same year, Amir started Medical School at the Leiden University. In 2013 he was selected for the MD/PhD program and started studying the role of the visual system in migraine under supervision of Prof. M.D. Ferrari at the department of Neurology in het LUMC. In 2015 he obtained his Bachelor of Medicine cum laude. During this time period he developed a great interest in neuro-anatomy and the anatomy of the head and neck, working as a dissection assistant at the Department of Anatomy and Embryology of the LUMC.

In 2016 Amir obtained a personal PhD grant from the LUMC enabling two years of full-time research as a PhD student at the Department of Neurosurgery and Neurology under the supervision of Prof. Wilco Peul, Dr. Wouter van Furth and Dr. Linda Dirven. During this period, he also joined the Department of Clinical Epidemiology to be trained as a Clinical Epidemiologist. Since 2016, he is the course coordinator of the Leiden Endoscopic Skull Base Dissection course, which he organizes with course directors Dr. Wouter van Furth and Dr. Christos Georgalas. During his PhD he was involved with various Value-Based Healthcare projects for patients with skull base pathologies, for which he received an award from Bewustzijnsproject Nederland.

In 2019, Amir started internships (co-schappen). He obtained his medical degree in May 2021 cum laude. From the 1st of July 2021, he started working as a resident (ANIOS) at the Department of Neurosurgery in the Haaglanden Medical Center.

DANKWOORD

Prof. Wilco Peul. Dank je voor de vrijheid en steun die ik gekregen heb binnen jouw afdeling om mijzelf te mogen ontplooien als onderzoeker. We delen de liefde voor de epidemiologie en de passie om de kwaliteit van chirurgisch onderzoek te verbeteren. Er is nog een lange en uitdagende weg te gaan.

Dr. Wouter van Furth. Wat ooit begon als een plan om de anatomie van spheno-orbitale meningeomen te onderzoeken heeft geresulteerd in dit proefschrift, inclusief een hoofdstuk over dit meningeoomtype, waar onze speciale interesse naar uit gaat. Dank je voor de geweldige begeleiding, waar ik niet alleen de vruchten van geplukt heb tijdens het onderzoek, maar ook mijn coschappen. Ik spreek van geluk je als mentor te mogen hebben.

Dr. Linda Dirven. Ik vind het bewonderenswaardig hoe je met engelengeduld mij begeleid hebt en waar nodig ook geholpen hebt met kaderen. Ik heb onwijs veel mogen leren van jouw expertise op het gebied van patiënt-gedreven onderzoek en de neuro-oncologie. Ik kijk terug naar een geweldige periode met bijzondere congresavonturen, soms in een wolkenkrabber in Toronto, soms op een opblaasmatras achter een chocoladefabriek.

Prof. Nienke Biermasz en hypofyse team. Hoewel het proefschrift over meningeomen gaat, heb ik het geluk dat ik ook vele projecten met jullie heb mogen uitvoeren voor patiënten met hypofysetumoren. Jullie zijn koplopers op het gebied van waardegedreven zorg en ik heb dan ook veel inspiratie kunnen putten uit onze samenwerking.

Prof. Saskia Peerdeman. Dank je wel voor het aan mij toevertrouwen van de MEGA-studie. Het was een erg vruchtbare samenwerking.

Drs. Daniel Lobatto. Kamergenoot en altijd luisterend oor. Wat was het ploegen in het begin. Maar laten we vooral ook nu trots zijn! Dank je dat ik altijd gebruik kan maken van je ervaringen op het gebied van onderzoek, klinische zorg, maar ook het leven buiten het ziekenhuis. Jij loopt altijd twee stappen voor op mij, hoewel ik je de laatste stap nog niet zo snel na zal doen.

Prof. Friedo Dekker en Dr. Merel van Diepen. Jullie hebben letterlijk het zaadje voor de epidemiologie in mij geplant vanuit de vakken Academische Wetenschappelijke Vorming. Ik ben erg dankbaar dat ik als gast bij jullie onderzoeksgroep mocht aansluiten. Waar sommigen methodologen met de vingers wijzen naar de clinici, zorgen jullie voor een fijne samenwerking met als resultaat klinische epidemiologie waar de patiënt en dokter echt wat aan heeft.

Prof Frits Rosendaal en collegae van de afdeling Klinische Epidemiologie. Dank voor de vele leerzame momenten.

Prof. Martin Taphoorn en het neuro-oncologie team van het LUMC en HMC. Het was een waar genoegen om met jullie samen te mogen werken voor de verschillende studies van dit proefschrift. Kwaliteit van leven is nu eindelijk "*hot and happening*"!

Drs. Stijn van der Meeren. De brug naar de oogheelkunde heb ik al vroeg in het onderzoek mogen slaan. Dank voor de vele brainstormsessies en discussies, niet alleen op het gebied van onderzoek, maar ook breder. Er is meer dan de geneeskunde.

Marijke, Pim, Quirien, Marthe, Friso, Fleur, Kwong, Florien. Het is ongelofelijk hoe wij energie en inspiratie putten uit het onderzoek en elkaar. De finishlijn gaan we halen.

Neurochirurgen, arts-assistenten, (onderzoeks)verpleegkundigen en secretariaat van het Universitair Neurochirurgisch Centrum Holland. Dank jullie wel voor het fijne leerklimaat, waarin ik mij vrij en gewaardeerd voel te zijn wie ik ben.

Dear international colleagues and meningioma researchers. I'm amazed by the developments in the last decade. Let's keep the momentum going, as there is so much to win for this patient group.

Headache minions. Zo hadden jullie opeens een eerstejaars gup te midden van jullie. Mogen er nog vele gezellige maaltijden volgen.

Mini United Nations. Jan, Mona, Willem. I'm so thankful to have you guys in my life. Research is not just about output, but also building friendships. Thank you for your kindness.

Mathijs, Pleun, Karien, en Anne-Tess. Ik snap niet hoe jullie mijn eeuwige gezeur uithouden. Mogen er nog vele barbecues volgen! Misschien zelfs wat papers?

Annemijn en Janine. Dank voor jullie onvoorwaardelijke vriendschap.

Patiënten en naasten. Jullie vormen de kern van dit proefschrift. Dank voor jullie deelname en steun.

Marcin. From the moment I've met you, my road in life has turned for the better. Thank you for grounding me and showing a world outside of medicine.

Anna. Het is geweldig hoe jij je eigen pad opgegaan bent. Ik had nooit gedacht dat onze werelden zouden kruizen. De kaft is prachtig geworden!

Mamma en pappa. Jullie staan aan de basis van mijn succes. Dagelijks sta ik stil bij jullie dappere keuzes. Ik hoop dat jullie trots zijn. Ik ben ieder geval erg trots op jullie.