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

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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].

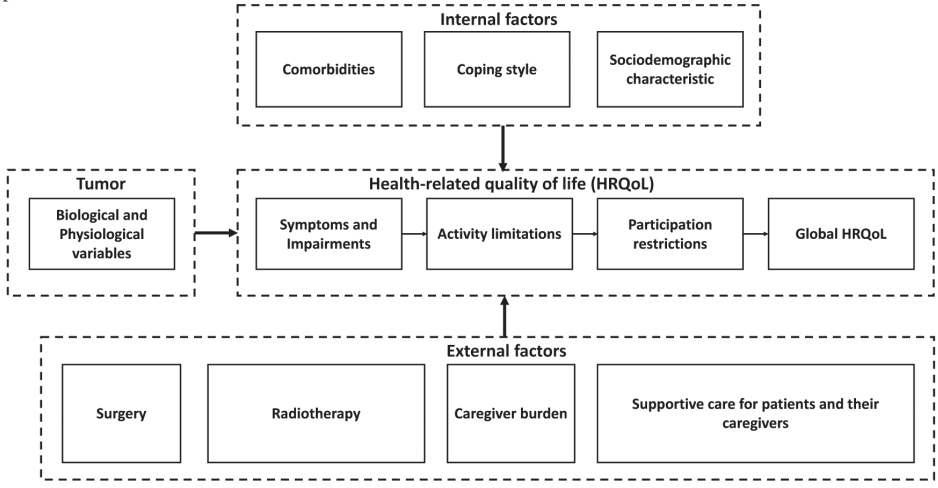
Despite Cushing's efforts, it is still not the standard to measure surgical outcomes and publish the results in the public domain. In recent years there have been great national and international efforts to measure outcomes in neurosurgery structurally[41,42]. In the Netherlands, the Dutch Society of 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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