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

Zamanipoor Najafabadi, A.H.

Citation

Zamanipoor Najafabadi, A. H. (2022, January 13). *Treating Meningioma: does the patient benefit?: A paradigm shift from tumor to patient*. Retrieved from https://hdl.handle.net/1887/3249735

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

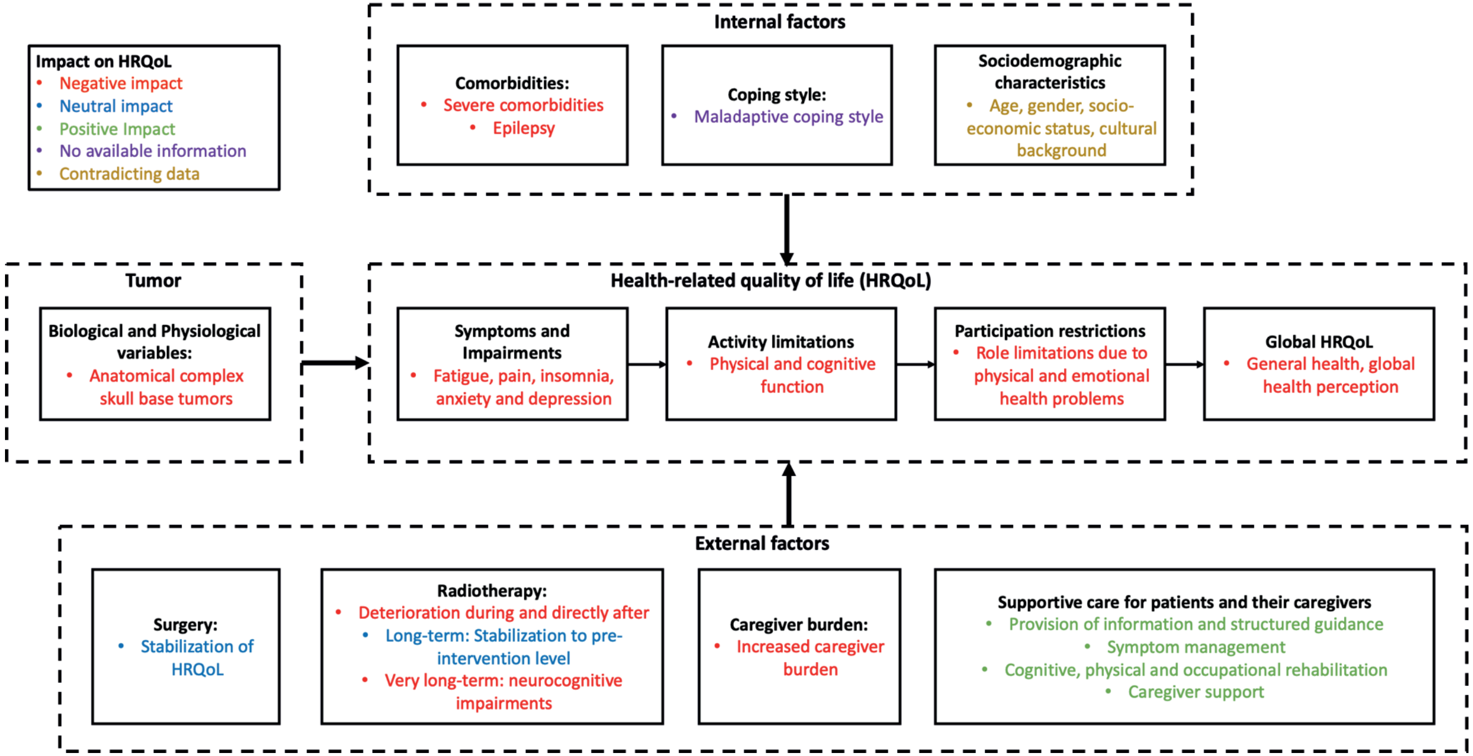
Based on the results of **Chapter 8**, we encourage referral of patients with spheno-oribital meningioma for surgery, even patients with minimal hyperostosis or visual impairments, as our results show that good visual outcomes can be achieved and maintained after pterional surgery. Moreover, we make 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 coordinating 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.