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

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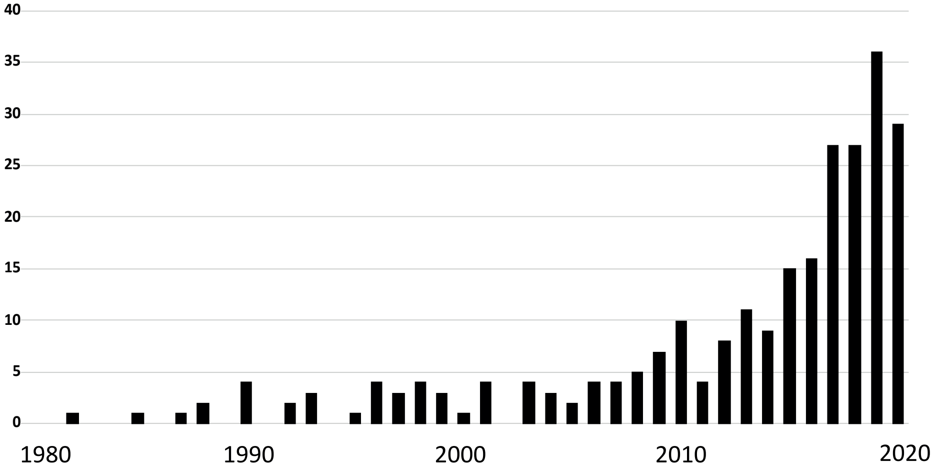
Chapter 11.1

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.