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

Zamanipoor Najafabadi, A.H.

Chapter 3

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

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Amir H. Zamanipoor Najafabadi
Pim B. van der Meer
Florien W. Boele
Martin J.B. Taphoorn
Martin Klein
Saskia M. Peerdeman
Wouter R. van Furth
Linda Dirven
On behalf of the Dutch Meningioma Consortium

ABSTRACT

Background

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

Objective

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

Methods

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

Results

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

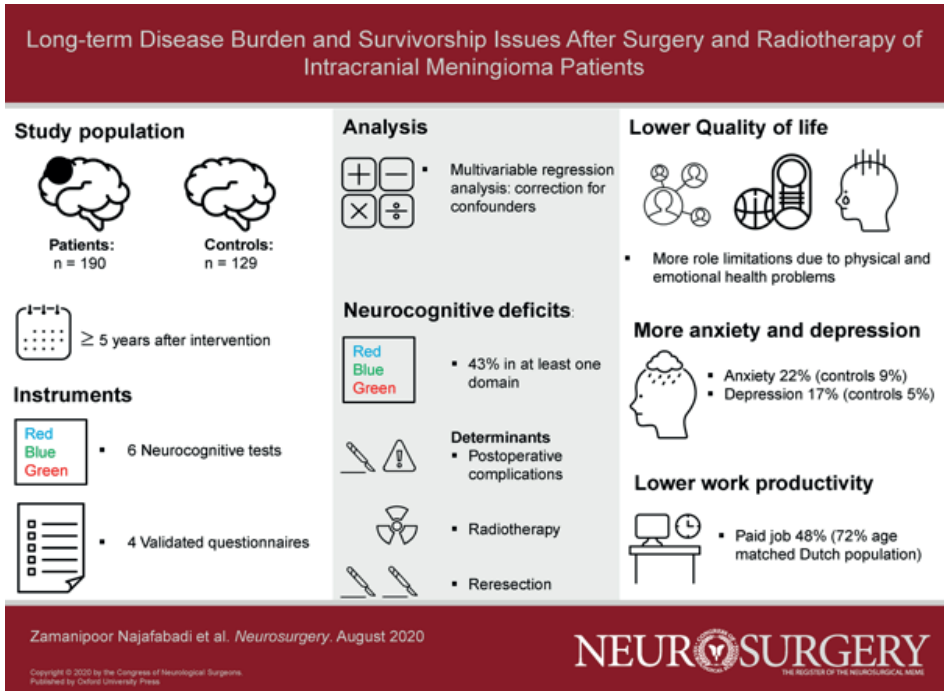
Conclusion

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

Keywords

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

VISUAL ABSTRACT



INTRODUCTION

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

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

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

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

METHODS

Participants

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

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

Procedures

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

Questionnaires

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

Neuropsychological assessment

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

Statistical Analysis

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

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

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

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

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

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

RESULTS

Demographics

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

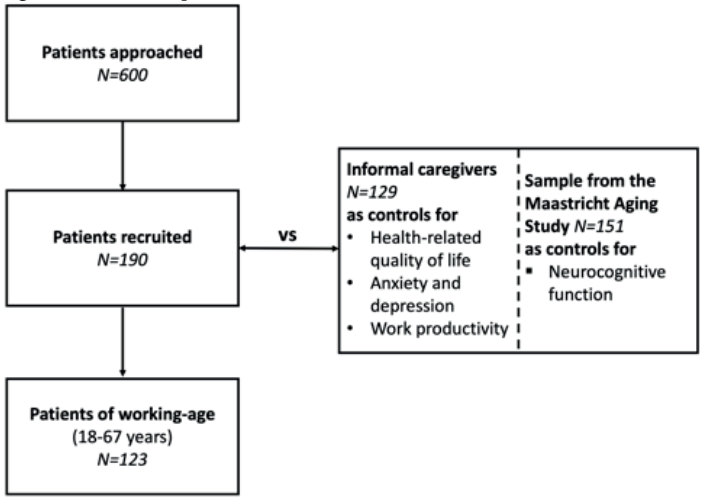
Table 1: Sociodemographic and clinical characteristics of meningioma patients and controls (i.e. informal caregivers and controls from the MAAS study)

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

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

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

Figure 1. Flow chart of patients and controls



Health-related quality of life (HRQoL)

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

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

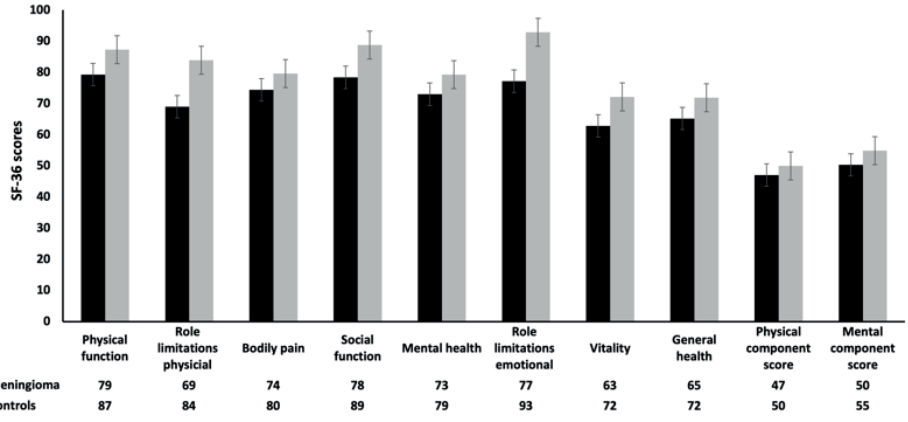
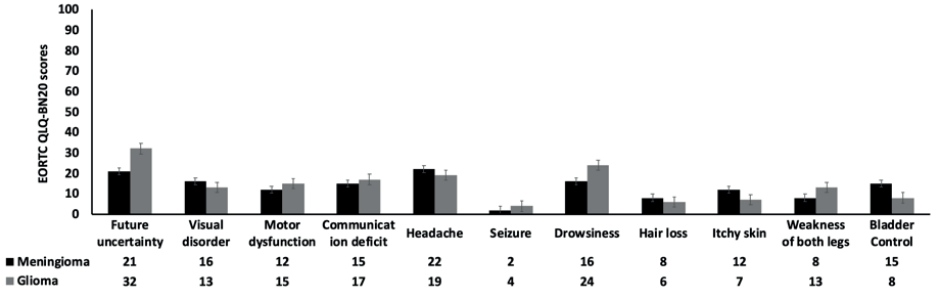


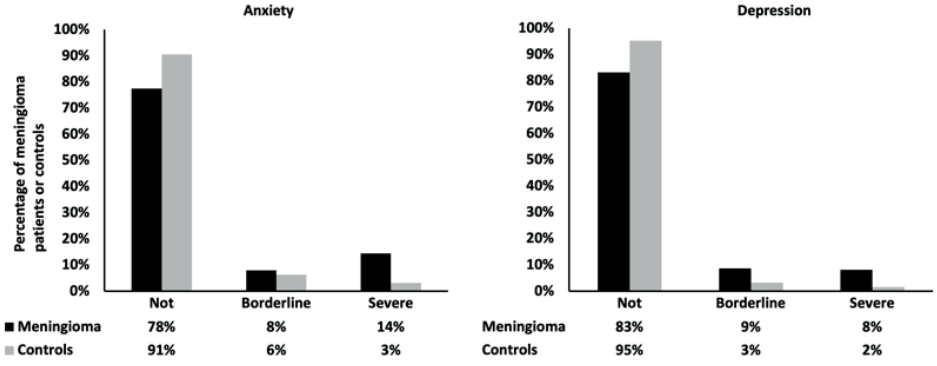
Figure 3. EORTC QLQ-BN20 scores for meningioma patients (median 9 years after treatment) and for glioblastoma patients participating in the AVAglio study at baseline (i.e. comparison group for this analysis), presented as bar charts and absolute scores.



Anxiety and depression

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

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

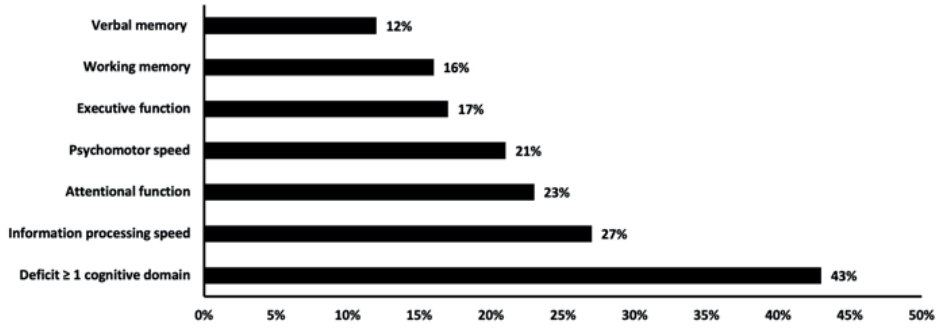


Neurocognitive functioning

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

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

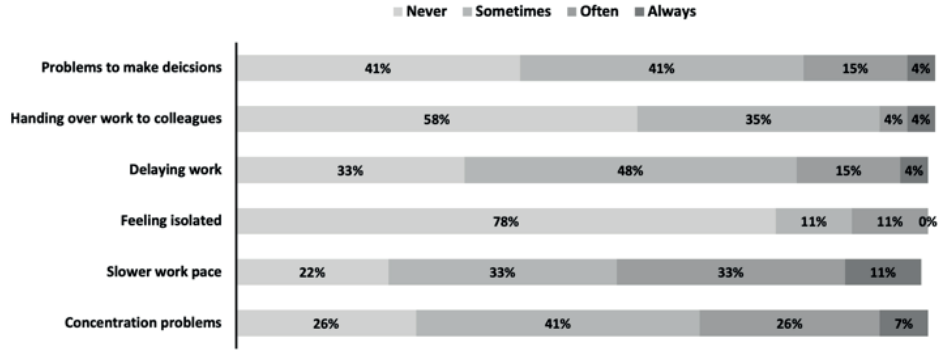
Figure 5. Percentage of patients with a clinically relevant neurocognitive deficit, (difference in z-score greater than -1.5 compared to the mean of controls), separately for each domain and in at least 1 domain.



Work productivity

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

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



Impact of surgery and radiotherapy on HRQoL and neurocognition

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

DISCUSSION

Key results

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

Limitations

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

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

Interpretation

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

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

Generalizability

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

Conclusions

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

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Conflicts of interest:

None of the authors declares a conflict of interest

Prior presentations:

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

Ethics committee approval:

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

Contributorship:

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

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SUPPLEMENTS

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

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

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

Sample size calculation

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

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

Rationale propensity score regression analysis

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

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

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

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

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

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

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

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

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

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

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

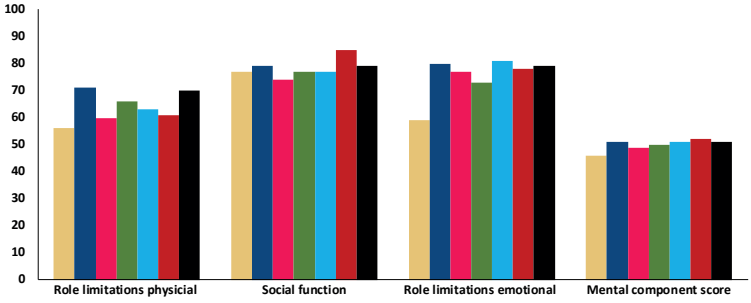
Supplemental Digital Content 8. Propensity score adjusted differences between meningioma patients and controls for the cognitive domains executive functioning, verbal memory and working memory.

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

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

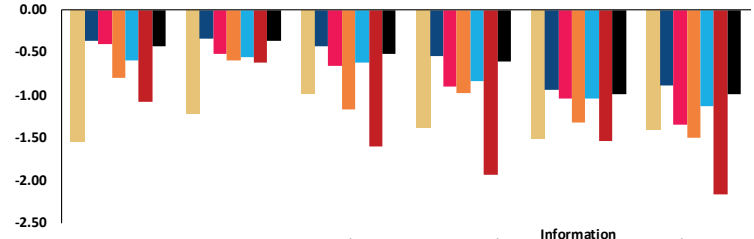
	Attention			Information processing speed			Psychomotor functioning		
	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value	Difference	(95%CI)	p-value
Radiotherapy (ref. active MRI surveillance)	-2.04	(-4.45 to 0.36)	0.01	-0.05	(-1.08 to 0.98)	0.92	-0.21	(-1.65 to 1.24)	0.78
Radiotherapy (ref. active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

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



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

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



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