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Long-term health-related quality of life and neurocognitive functioning after treatment in skull base meningioma patients

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OBJECTIVE Patients with skull base meningioma (SBM) often require complex surgery around critical neurovascular structures, placing them at high risk of poor health-related quality of life (HRQOL) and possibly neurocognitive dysfunction. As the survival of meningioma patients is near normal, long-term neurocognitive and HRQOL outcomes are important to evaluate, including evaluation of the impact of specific tumor location and treatment modalities on these outcomes.

METHODS In this multicenter cross-sectional study including patients 5 years or more after their last tumor intervention, Short-Form Health Survey (SF-36) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-BN20 questionnaires were used to assess generic and disease-specific HRQOL. Neurocognitive functioning was assessed with standardized neuropsychological assessment. SBM patient assessments were compared with those of 1) informal caregivers of SBM patients who served as controls and 2) convexity meningioma patients. In addition, the authors compared anterior/middle SBM patients with posterior SBM patients and anterior/middle and posterior SBM patients separately with controls. Multivariable and propensity score regression analyses were performed to correct for possible confounders.

RESULTS Patients with SBM (n = 89) with a median follow-up of 9 years after the last intervention did not significantly differ from controls (n = 65) or convexity meningioma patients (n = 84) on generic HRQOL assessment. Statistically significantly but not clinically relevantly better disease-specific HRQOL was found for SBM patients compared with convexity meningioma patients. Anterior/middle SBM patients (n = 62) had significantly and clinically relevantly better HRQOL in SF-36 and EORTC QLQ-BN20 scores than posterior SBM patients (n = 27): physical role functioning (corrected difference 17.1, 95% CI 0.2–34.0), motor dysfunction (−10.1, 95% CI −17.5 to −2.7), communication deficit (−14.2, 95% CI −22.7 to −5.6), and weakness in both legs (−10.1, 95% CI −18.8 to −1.5). SBM patients whose primary treatment was radiotherapy had lower HRQOL scores compared with SBM patients who underwent surgery on two domains: bodily pain (−33.0, 95% CI −55.2 to −10.9) and vitality (−18.9. 95% CI −33.7 to −4.1). Tumor location and treatment modality did not result in significant differences in neurocognitive functioning, although 44% of SBM patients had deficits in at least one domain.

CONCLUSIONS In the long term, SBM patients do not experience significantly more sequelae in HRQOL and neurocognitive functioning than do controls or patients with convexity meningioma. Patients with posterior SBM had poorer HRQOL than anterior/middle SBM patients, and primary treatment with radiotherapy was associated with worse HRQOL. Neurocognitive functioning was not affected by tumor location or treatment modality.

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KEYWORDS skull base meningioma; quality of life; neurocognitive function; anterior skull base meningioma; convexity meningioma; oncology

ABBREVIATIONS EORTC QLQ-BN20 = European Organisation for Research and Treatment of Cancer, brain neoplasm module; HRQOL = health-related quality of life; SBM = skull base meningioma; SF-36 = 36-item Short-Form Health Survey.

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Meningiomas are central nervous system tumors that arise from the arachnoid cap cells.[1] Approximately 95% of meningiomas are located intracranially, and 20%–30% are located at the skull base.[1,2] These tumors are often closely related to critical neurovascular structures, such as cranial nerves, vessels, and the brainstem. Another characteristic of skull base meningiomas (SBMs) is the distinct growth pattern, often associated with diffuse growth.[3,4] Both characteristics complicate total resection and increase the risk of devastating complications, perhaps to a greater extent compared with convexity meningiomas.[5,6]

Due to the near-normal survival of meningioma patients, long-term neurocognitive and HRQOL-related outcomes have become increasingly important to evaluate, as they reflect the patients' functioning and well-being.[7] Previous studies, including our own, have reported that intracranial meningioma patients have impaired health-related quality of life (HRQOL) and neurocognitive functioning not only in the short term[5,8,9] but also up to 10 years after intervention.[10,11] Tumor location is thought to play a pivotal role in long-term outcomes of meningioma.[1] Yet further research that includes a more granulated classification of tumor location, taking into account different skull base locations, is needed to accurately assess the impact of specific tumor location on HRQOL and neurocognitive functioning, especially in the long term (> 5 years).

Compared with convexity meningioma patients, SBM patients are treated with different and more invasive surgical approaches and receive postoperative radiotherapy for tumor remnants or regrowth more often.[4] While reports about nonmeningioma skull base tumors have shown that treatment modality has an effect on long-term HRQOL scores and neurocognitive functioning of patients,[12,13] this has not yet been assessed for SBM. Due to the relation of SBM with critical neurovascular structures, we expect to find long-term neurological sequelae and hence a decreased HRQOL in SBM patients compared with healthy controls and convexity meningioma patients.[14] Conversely, we expect convexity meningioma patients to perform worse on neurocognitive functioning due to the lesions' extensive cortical involvement.

Published data on the effect of precise tumor location at the skull base and different treatment modalities on patients' functioning and well-being are crucial. This will inform clinicians and patients in clinical practice, facilitate treatment decisions based on patient-centered outcomes, and help the distribution of expensive and scarce supportive care resources to patients with the highest need. Thus, the main purpose of this study was to assess the level of HRQOL and neurocognitive functioning of SBM patients after treatment in the long term. Preferably the disease burden is measured with both generic and disease-specific HRQOL instruments and objective neuropsychological assessment.[15] To this end, we compared patient-centered outcomes in SBM patients with controls and convexity meningioma patients. Secondary analyses were performed to compare HRQOL and neurocognitive functioning between patients with anterior/middle SBM and those with posterior SBM. Furthermore, outcomes were reported descriptively for the most frequently observed tumor locations within the skull base. Finally, we assessed the impact of specific treatments on HRQOL and neurocognitive functioning in patients with SBM and in anterior/middle and posterior SBM patients separately.

Methods

Study and Participants

This is a subgroup analysis of a multicenter cross-sectional study, in which meningioma patients were included prospectively if 1) they had a histologically confirmed WHO grade I or II meningioma in surgical cases, or an MRI-based clinically suspected meningioma in patients undergoing radiotherapy or wait-and-scan; 2) the end of the primary antitumor treatment was at least 5 years prior to recruitment; and 3) they were ≥ 18 years of age.[11] Indication for treatment was based on the Dutch national standards published on Richtlijnendatabase, which is in line with the European Association of Neuro-Oncology guideline for the diagnosis and treatment of meningiomas.[16,17] Consecutive patients were recruited between July 2016 and April 2019 from the neurosurgery, neurology, and radiation oncology outpatient clinics of two academic hospitals and one large non–academic teaching hospital (Leiden University Medical Center, Haaglanden Medical Center, and Amsterdam University Medical Centers, location VUmc), all in the Netherlands. In this study, we did not include SBM patients treated with a wait-and-scan approach due to the small sample size of SBM patients (n = 4). From the original cohort, informal caregivers from SBM patients were included in this study as controls, since we only compared SBM patients with controls.

Procedures

Detailed information on patient recruitment and data collection has been reported in a previous publication.[11] The study was approved by the medical ethical committees of all participating centers. All participants, including informal caregivers, consented to participate in the study before they were assessed. HRQOL questionnaire administration and neurocognitive evaluation was performed for study purposes only. Clinical characteristics, including presenting symptoms, were extracted from the electronic patient records.

Patient-Reported Outcome Measures

Patients completed the 36-item Short-Form Health Survey (SF-36), a generic measure of HRQOL, with higher scores (range 0–100) representing better HRQOL. The SF-36 covers eight domains and comprises 2 component scores (Supplementary Table 1). Brain tumor–specific HRQOL was measured using the European Organisation for Research and Treatment of Cancer, brain neoplasm module (EORTC QLQ-BN20). The EORTC QLQ-BN20 contains 4 multiitem and 7 single-item scales, with higher scores (range 0–100) representing higher symptom burden (Supplementary Table 1). Similar to previously published studies, the clinically relevant cutoff was set at 10 points for both the SF-36 domains and the EORTC QLQ-BN20 scales.[18,19] For the mental and physical component scales (MCS and PCS) of the SF-36 these cutoffs were set, re-

spectively, at 4.6 and 3.0 points.[20] The SF-36 questionnaire was also completed by patients' informal caregivers.

Neurocognitive Assessment

A standardized and frequently used test battery was used for neurocognitive assessment, consisting of the Auditory Verbal Learning Test, Concept Shifting Test, Memory Comparison Task, Categorical Verbal Fluency Test, Digit Symbol Substitution Test, and the Stroop Color and Word Test.[11] Assessment of these tests' scores allowed estimation of the following domains: executive functioning, verbal memory, working memory, psychomotor functioning, information processing speed, and attention. Z-scores were calculated for each neurocognitive domain with means and standard deviations from a reference sample from the Maastricht Aging Study (a large longitudinal study on the psychological and biological determinants of cognitive aging). These data, which are representative of the general population, were matched on group level for age, sex, and educational level.[21] Differences in z-scores were considered clinically relevant if greater than –1.5 for each domain.[22]

Comparison Groups

Main Comparisons

For SBM patients, there were two comparison groups: 1) informal caregivers of SBM patients who served as controls (comparison of generic HRQOL [SF-36] and neurocognitive functioning), and 2) convexity meningioma patients (comparison on both disease-specific [EORTC QLQ-BN20] and generic [SF-36] HRQOL and neurocognitive functioning). Controls were included in this study to provide information on the extent of issues SBM patients may experience. The informal caregivers of SBM patients were selected as controls to assess the effect of the disease itself on the level or HRQOL and neurocognitive functioning of patients, as informal caregivers are indirectly affected by the disease course but do not suffer from the tumor and its treatment.

Secondary Comparisons

HRQOL scores and neurocognitive functioning were compared between 1) patients with anterior/middle SBM and those with posterior SBM (SF-36 and EORTC QLQ-BN20), 2) controls and patients with anterior/middle SBM (SF-36), and 3) controls and patients with posterior SBM (SF-36). For this purpose, the Al-Mefty classification of meningioma location was used.[23] In addition, outcomes were described for the three most frequently observed SBM locations using descriptive statistics only: patients with tuberculum sellae, medial sphenoid wing, and cerebellopontine angle meningioma. No statistical comparisons were made between these three subgroups because of the small number of patients with each tumor location. Finally, we assessed the impact of specific treatments on HRQOL and neurocognitive functioning in patients with SBM and separately for patients with anterior/middle SBM and patients with posterior SBM.

Statistical Analysis

Descriptive statistics were used to describe baseline characteristics and to present uncorrected outcomes. To compare presenting symptoms and outcomes between SBM patients and controls and convexity meningioma patients, as well as between anterior/middle SBM and posterior SBM patients, independent t-tests and multivariable regression analyses corrected for previously established confounders (i.e., age, sex, education level and comorbidities) were used.[5,12] In the multivariable regression analyses, HRQOL (SF-36 and EORTC QLQ-BN20) scale and component scores and neurocognitive functioning domain scores were the dependent outcomes. Patient group was an independent variable. The number of confounders allowed into the different models was in accordance with the number of patients included in each analysis. Outcomes of HRQOL (SF-36) and neurocognitive functioning of patients with tuberculum sellae, medial sphenoid wing, and cerebellopontine angle meningiomas were only presented as raw scores, as the sample size for these analyses was too small to include confounding factors.

The effects of surgery and radiotherapy were assessed in SBM patients and anterior/middle and posterior SBM patients separately, for all SF-36 HRQOL scales and neurocognitive functioning domains, using propensity score regression analyses to adjust for previously established confounders (i.e., age, tumor size at the moment of intervention, tumor location, Simpson grade), which is considered appropriate for studies with relatively small sample sizes.[10,24,25] More specifically, the following comparisons were performed: 1) surgery as initial treatment versus radiotherapy as initial treatment; 2) treatment with only surgery versus surgery with adjuvant radiotherapy; 3) surgery with adjuvant radiotherapy versus radiotherapy as initial treatment; 4) postoperative complication(s) during first surgery versus no complication(s); and 5) one surgery versus reoperation.

For all statistical tests, IBM SPSS version 25 (IBM Corp.) was used, and $p < 0.05$ was considered statistically significant. No correction for multiple testing was performed as the analyses were hypothesis driven, and established methods to correct for multiple testing can inflate confidence intervals.[26] The hypotheses were formed after the primary analysis in our first report but before performing the analyses of the subgroups as reported in this article.[11] In this report, we focused on results that were both statistically significant and clinically relevant.

Results

Demographics

The total study population consisted of 190 meningioma patients, of whom 89 were SBM patients (female: 77/89, 87%) and could be included in the present analysis (Fig. 1). There were 62 SBMs located at the anterior/middle skull base and 27 located at the posterior skull base. The three most frequently observed SBM locations were the tuberculum sellae in 18 (20%) of 89 patients, the inner (medial) sphenoid wing in 16 (18%), and the cerebellopontine angle in 9 (10%). The mean age of all SBM patients was 62 years (SD 11 years), and median follow-up was 9 years (range 5.1–20.8 years). Of all surgically removed SBMs (84/89, 94%), 90% (76/84) were WHO grade I. Surgery was the

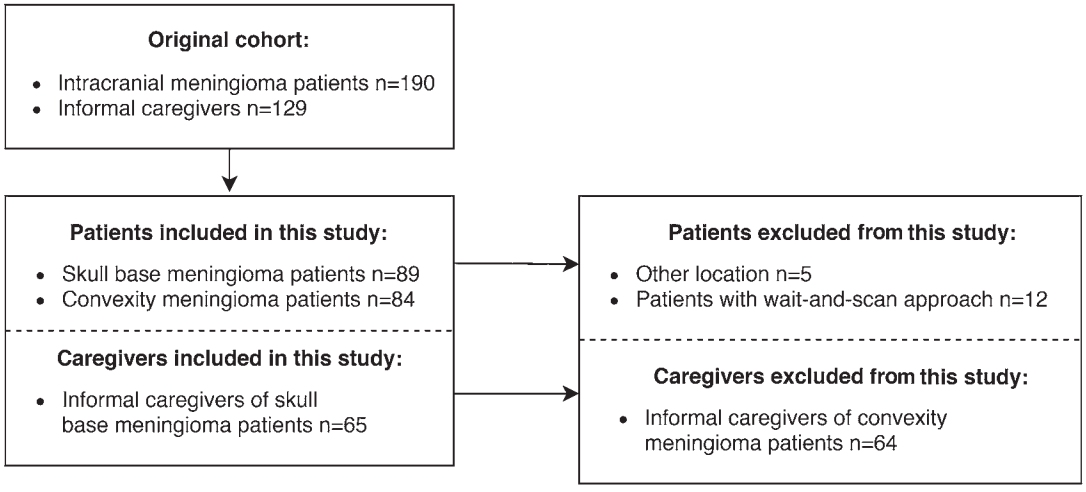

FIG. 1. Flowchart of patients and controls.

initial treatment in 71% (63/89) of SBM patients. At first surgery, 44% (39/89) experienced a complication, which varied from minor (e.g., urinary tract infection) to severe (e.g., deep venous thrombosis) (see Supplementary Table 2 for an overview). The three most common complications were CSF leak (9/89, 10%) and meningitis and deep venous thrombosis (both in 3/89, 3%). Twenty-six patients (26/89, 29%) received radiotherapy; in 6 of these patients (23%), it was the only treatment, and in the remaining patients it was used as adjuvant treatment after resection. Reresection was performed in 7 (8%) of the 89 patients.

We compared SBM patients with 65 controls and 84 convexity meningioma patients. See Table 1 for an overview of the baseline sociodemographic and clinical characteristics of both patient groups and controls. In short, compared with convexity meningioma patients, SBM patients accounted for significantly more females (87% vs 70%, $p = 0.01$), received radiotherapy more often (29% vs 8%, $p < 0.01$), and experienced more complications of both radiotherapy (12% vs 0%, $p < 0.01$) and surgery (44% vs 27%, $p = 0.04$). Compared with convexity meningioma patients, SBM patients had a significantly smaller tumor size at the time of intervention (median 36 vs 42 mm, $p < 0.01$) but a significantly larger tumor size at the time of study participation (median 7 vs 0 mm, $p < 0.001$).

See Supplementary Tables 3 and 4 for baseline characteristics of patients with anterior/middle SBM, posterior SBM, tuberculum sellae, medial sphenoid wing, and cerebellopontine angle meningioma separately.

Presenting Symptoms as Reported in the Medical Records

Compared with convexity meningioma patients, SBM patients reported motor deficits (17% vs 3%, $p < 0.01$), cognitive complaints (11% vs 1%, $p < 0.01$), and epilepsy (23% vs 11%, $p = 0.04$) significantly less often as presenting symptoms but reported visual deficits significantly more often (7% vs 37%, $p < 0.001$). In anterior/middle SBM patients, sensory deficits occurred statistically significantly less often in comparison with posterior SBM patients (3% vs 22%, $p = 0.03$), and visual deficits occurred significantly more often as well (47% vs 15%, $p < 0.01$). See Supplementary Table 5 for percentages and p values of all presenting symptoms.

Health-Related Quality of Life

SBM Patients Versus Controls and Convexity Meningioma Patients

Regarding generic HRQOL (SF-36), no significant differences were observed between patients with an SBM and controls, or between patients with an SBM and convexity meningioma (Fig. 2). Regarding brain tumor–specific HRQOL, available for SBM and convexity meningioma patients, we found that SBM patients had significantly better scores on 2 of the 11 EORTC QLQ-BN20 scales: drowsiness (corrected difference –5.9, 95% CI –9.7 to –2.1) and hair loss (–3.1, 95% CI –5.9 to –0.3), although these differences were not clinically relevant (Fig. 3).

Anterior and Middle Versus Posterior SBM

Comparing anterior/middle SBM patients with posterior SBM patients, we found a statistically significant and clinically relevant difference in role limitations due to physical functioning in favor of anterior/middle SBM patients (corrected difference 17.1, 95% CI 0.2–34.0) as measured with the SF-36 (Fig. 2). In line with the previous results, posterior SBM patients had worse HRQOL scores (SF-36) than controls, while no differences were found between anterior/middle SBM patients and controls (see Supplementary Table 6).

When looking at the EORTC QLQ-BN20 results, anterior/middle SBM patients reported statistically significant lower symptom burden than posterior SBM patients on 4 of 11 scales as follows: motor dysfunction (–10.1, 95% CI –17.5 to –2.7), communication deficit (–14.2, 95% CI –22.7 to –5.6), weakness in both legs (–10.1, 95% CI –18.8 to –1.5), and hair loss (–8.1, 95% CI –13.8 to –2.4), of which all were also clinically relevant, except for hair loss (Fig. 3). See Supplementary Tables 7 and 8 for the corrected differences with 95% CIs for all HRQOL scales.

TABLE 1. Sociodemographic and clinical characteristics of patients and controls (informal caregivers)

	SBM Patients (n = 89)	Controls (n = 65)*	p Value (SBM vs controls)	Convexity Meningioma Patients (n = 84)	p Value (SBM vs convexity)
Mean age (SD), yrs	62 (11)	61 (13)	0.820	63 (11)	0.707
Female sex	77 (87)	21 (32)	<0.001	59 (70)	0.009
Median follow-up time (range), yrs	9 (5–21)			8 (5–17)	0.166
Academic hospital	68 (76)			59 (70)	0.535
Meningioma location detailed					
Olfactory groove	5 (6)			–	
Planum sphenoidale	5 (6)			–	
Tuberculum sellae	18 (20)			–	
Diaphragma sellae	1 (1)			–	
Anterior clinoid process	5 (6)			–	
Inner (medial) sphenoid wing	16 (18)			–	
Outer (lateral) sphenoid wing	7 (8)			–	
Cavernous sinus	4 (5)			–	
Meckel's cave	1 (1)			–	
Petroclival	8 (9)			–	
CPA	9 (10)			–	
Foramen magnum	2 (2)			–	
Cerebellar tentorium	8 (9)			–	
Cerebral convexity				55 (65)	
Sagittal sinus superior				4 (5)	
Falx				21 (25)	
Cerebellar convexity				4 (5)	
Sx at presentation (multiple options possible per patient)					
Epilepsy	10 (11)			19 (23)	0.040
Motor deficit	3 (3)			14 (17)	0.004
Sensory deficit	8 (9)			5 (6)	0.480
Visual deficit	33 (37)			6 (7)	<0.001
Cognitive impairment	1 (1)			9 (11)	0.008
Other	33 (37)			28 (33)	0.694
Mean time since 1st Sx (SD), yrs	12 (5)			11 (5)	0.207
Mean time since diagnosis (SD), yrs	11 (3)			10 (3)	0.193
Median tumor size before intervention (range), mm	36 (11–97)			42 (6–87)	0.008
Median tumor size before study (range), mm	7 (0–49)			0 (0–33)	<0.001
Tumor growth on last MRI before study	3 (3)			6 (7)	0.210
≥2 meningiomas	16 (18)			10 (12)	0.284
Surgically treated	84 (94)			83 (99)	0.107
Op as initial treatment	63 (71)			77 (92)	
Complication after 1st op†	39 (44)			23 (27)	0.042
2nd op	7 (8)			6 (7)	0.791
3rd op	1 (1)			1 (1)	0.943
Median time since 1st surgery (SD), yrs	10 (3)			9 (3)	0.087
Simpson grade 1st surgery					0.011
I–III	51 (61)			57 (69)	
IV or V	27 (32)			13 (16)	
Unknown	6 (7)			13 (16)	
WHO grade 1st surgery†					0.225
I	76 (90)			71 (86)	
II	4 (5)			8 (10)	

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TABLE 1. Sociodemographic and clinical characteristics of patients and controls (informal caregivers)

	SBM Patients (n = 89)	Controls (n = 65)*	p Value (SBM vs controls)	Convexity Meningioma Patients (n = 84)	p Value (SBM vs convexity)
WHO grade 1st surgery† (*continued*)					
Unknown	4 (5)			4 (5)	
Radiotherapy	26 (29)			7 (8)	<0.001
Radiotherapy only	6 (7)			1 (1)	
Adjuvant radiotherapy	20 (22)			6 (7)	
Mean time since radiotherapy (SD), yrs	8 (3)			7 (2)	0.396
Complications of radiotherapy‡	3 (3)			0 (0)	0.001
Mean KPS score at time of study (SD)	95 (9)			96 (8)	0.706
Self-reported cognitive deficit at time of study	46 (52)			38 (45)	0.443
Self-reported motor deficit at time of study	23 (26)			26 (31)	0.396
Seizures in last 3 mos before study	3 (3)			3 (3)	0.575
Antiepileptic drug use at any time during care trajectory	33 (37)			49 (58)	0.003
Dexamethasone use for Sx at any time during care trajectory	11 (12)			10 (12)	0.575
Physical rehabilitation	17 (19)			19 (23)	0.490
Cognitive rehabilitation	2 (2)			5 (6)	0.211
Psychological support	9 (10)			12 (14)	0.355
Other supportive care	5 (6)			5 (6)	0.879
Education level			0.088		0.576
Primary/secondary	18 (20)	8 (12)		19 (23)	
Tertiary: technical/vocational	42 (47)	28 (43)		37 (44)	
Academic	28 (31)	28 (43)		23 (27)	
Not provided	1 (1)	1 (2)		5 (6)	
CCI			0.278		0.549
0	67 (75)	44 (68)		51 (61)	
≥1	22 (25)	20 (31)		29 (35)	
Not provided	0 (0)	1 (1)			
Right-handed	71 (80)	49 (75)	0.128	60 (71)	0.383

CCI = Charlson Comorbidity Index; CPA = cerebellopontine angle; KPS = Karnofsky Performance Status; Sx = symptoms.
Values are presented as the number of patients (%) unless stated otherwise.
* Informal caregivers of all SBM patients.
† n = 84 for SBM patients and n = 83 for convexity meningioma patients.
‡ n = 26 for SBM patients and n = 7 for convexity meningioma patients.

Neurocognitive Functioning

Overall, SBM patients showed similar levels of neurocognitive functioning as controls and convexity meningioma patients. Also, we did not find any statistically significant or clinically relevant difference in the six neurocognitive functioning domains between anterior/middle and posterior SBM patients. See Supplementary Table 9 for the corrected differences with 95% CI for all neurocognitive domains.

Skull Base Meningioma

In total, 39 (44%) of the 89 patients had neurocognitive dysfunction in at least one of six measured domains. In 15 (17%) of the 89 patients, problems occurred in one domain; in 7 patients (8%), in two domains; in 6 patients (7%), in three domains; in one patient (1%), in four domains; in 3 patients (3%), in five domains; and in 3 patients (3%), in all six domains. Difficulty with information processing speed occurred most frequently, with an occurrence of 26% (23/89). See Fig. 4 for all six domains and the occurrence of deficits in ≥ 1 domain.

Anterior and Middle SBM

Of all anterior/middle SBM patients, 27/62 (44%) had a neurocognitive deficit in at least one of six domains. Eleven patients experienced problems in one domain (18%), 5 in two domains (8%), 5 in three domains (8%), 0 in four domains, 2 in five domains (3%), and 3 in all six domains (5%). The most frequently observed cognitive deficit was difficulty with information processing speed (14/62, 23%).

Posterior SBM

Twelve (44%) of 27 patients with posterior SBM experi-

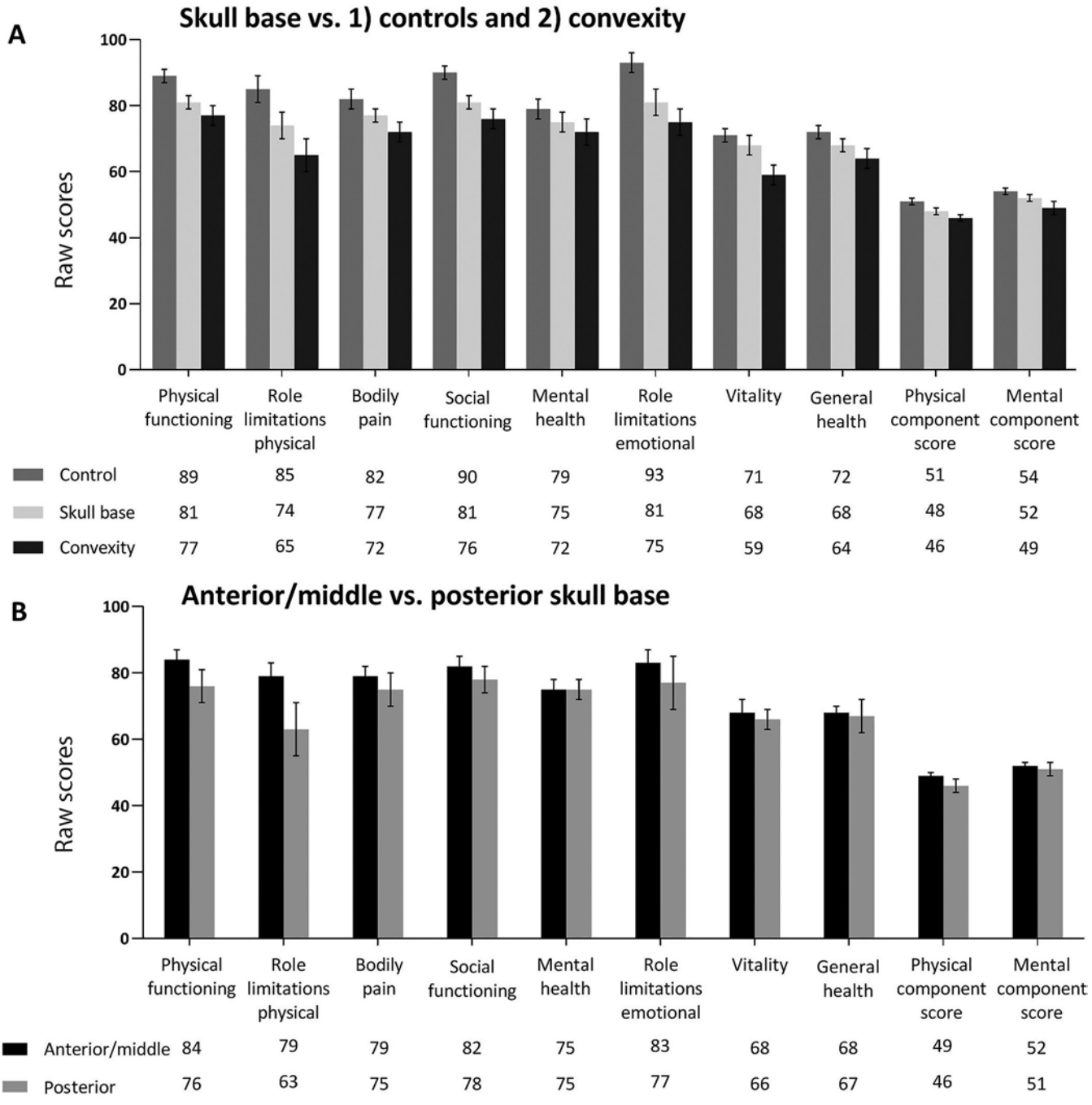


FIG. 2. Raw mean scores with their standard error, presented as bar charts and actual scores, on all SF-36 HR-QOL domains and components for SBM patients versus 1) informal caregivers and 2) convexity meningioma patients (**A**) and for anterior and middle SBM patients versus posterior SBM patients (**B**).

enced neurocognitive dysfunction in one or more domains. Problems in one domain occurred in 4 patients (15%); in two domains in 2 patients (7%); and three, four, or five domains in 1 patient (1/27, 4%). No patients had deficits in all six domains. As in the other patient groups, information processing speed was the most frequently occurring deficit in posterior SBM patients (9/27, 33%). See Fig. 4 for all six domains and the occurrence of deficits in at least one domain in patients with anterior/middle and posterior SBM separately. See also Fig. 5 for SF-36 HRQOL scores and neurocognitive functioning of tuberculum sellae, medial sphenoid wing, and cerebellopontine angle meningiomas separately.

Impact of Surgery and Radiotherapy

HRQOL

Comparing initial treatment with surgery or radiotherapy only, SBM patients whose primary treatment was ra-

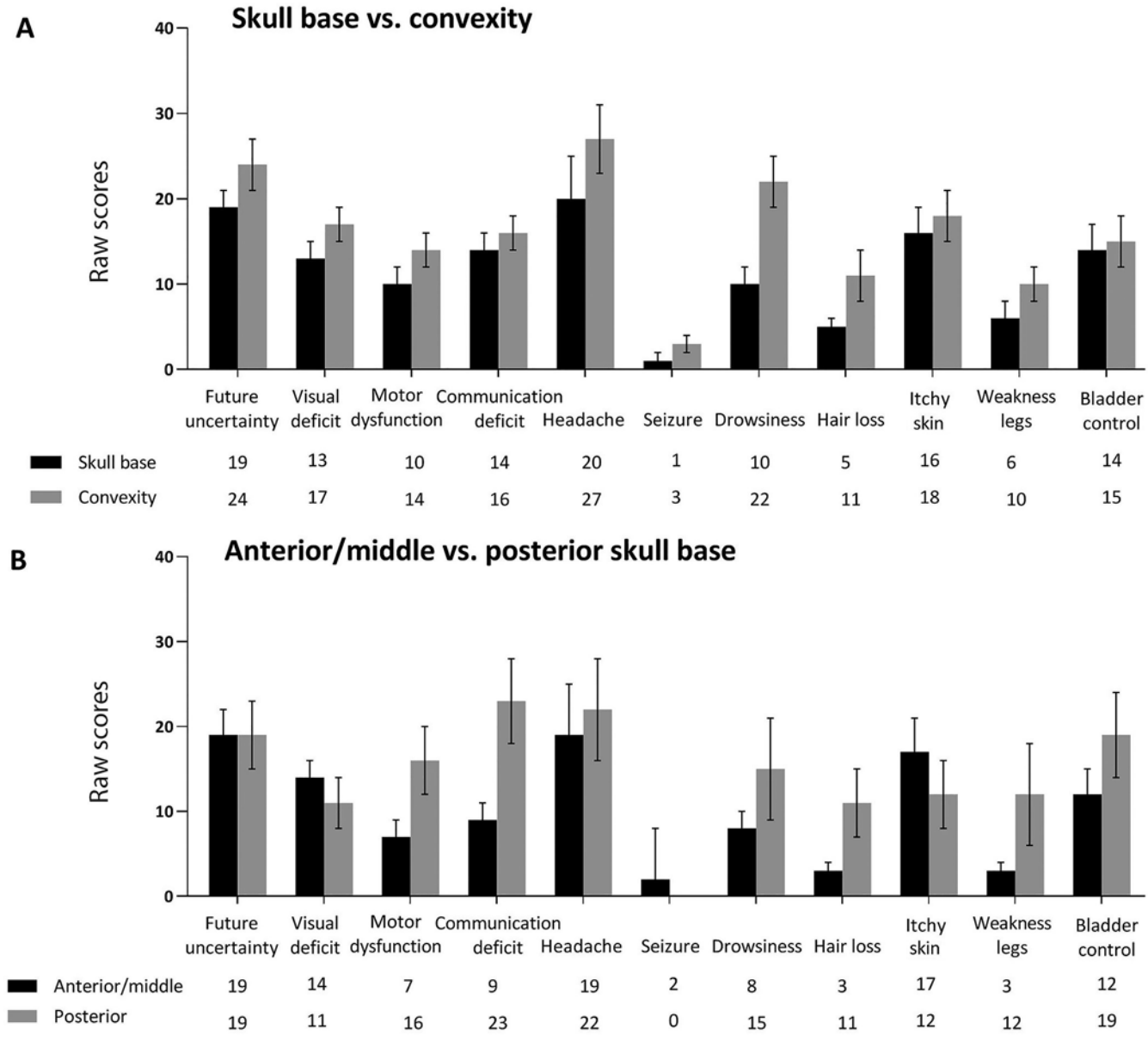


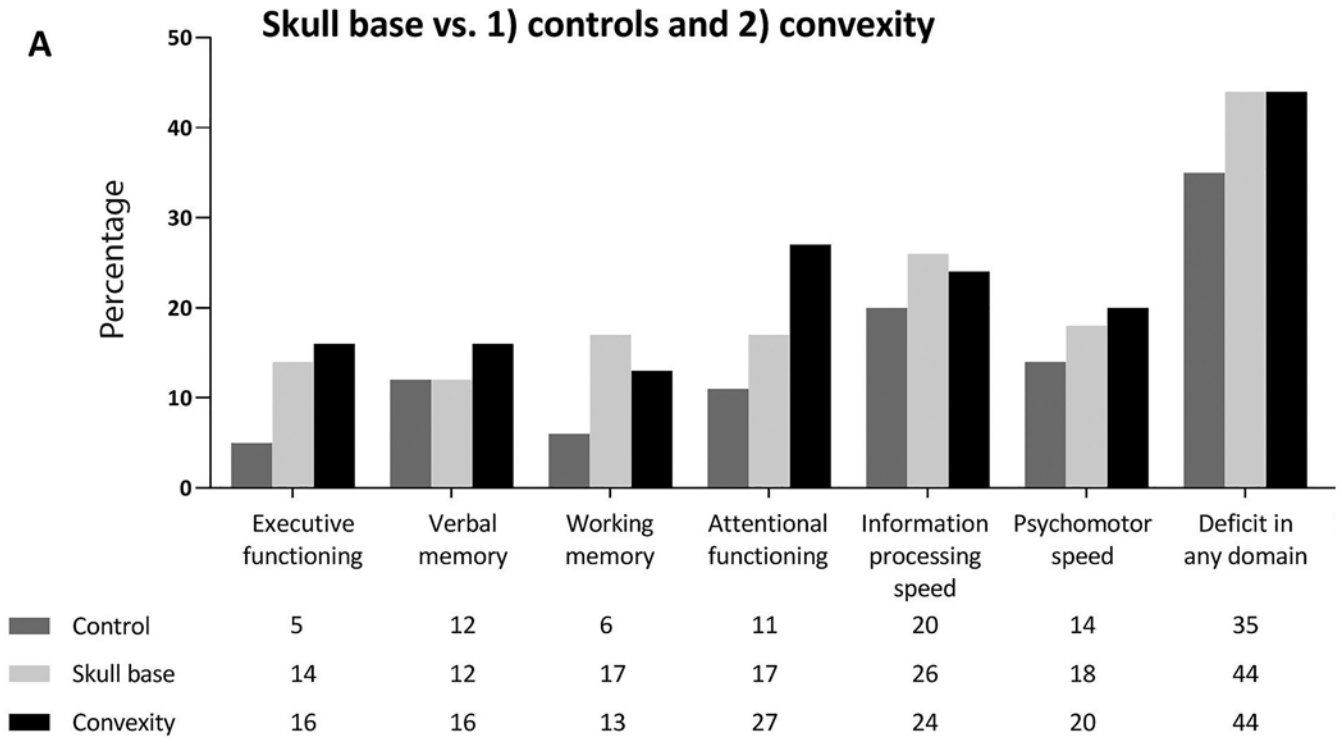
FIG. 3. Raw mean scores with their standard error presented as bar charts and actual scores on the EORTC QLQ-BN20 for SBM patients compared with convexity meningioma patients (**A**) and for anterior and middle SBM patients compared with posterior SBM patients (**B**).

diotherapy scored both clinically relevantly and statistically significantly worse on bodily pain (corrected difference –33.0, 95% CI –55.2 to –10.9) and vitality (–18.9, 95% CI –33.7 to –4.1) than SBM patients treated with surgery as primary treatment. On the other scales, no significant differences were found in SBM patients. In addition, long-term HRQOL scores were not different for SBM patients operated on only once and those who were operated on multiple times, between SBM patients who had and did not have postoperative complications, between SBM patients treated with only surgery and those also treated with adjuvant radiotherapy, or between SBM patients treated with surgery and adjuvant radiotherapy and those treated with radiotherapy as initial treatment.

Posterior SBM patients treated with radiotherapy only had worse HRQOL scores (SF-36) on bodily pain, vitality, and general health than those treated with surgery only. No differences were found between the other treatment groups in posterior SBM patients. Treatment did not result in differences in HRQOL scores for anterior/middle SBM patients.

Neurocognitive Functioning

Verbal memory was significantly worse in SBM patients primarily treated with radiotherapy compared with initial treatment with surgery (corrected difference –1.2, 95% CI –2.0 to –0.4). Using adjuvant radiotherapy after surgery was associated with significantly worse execu-



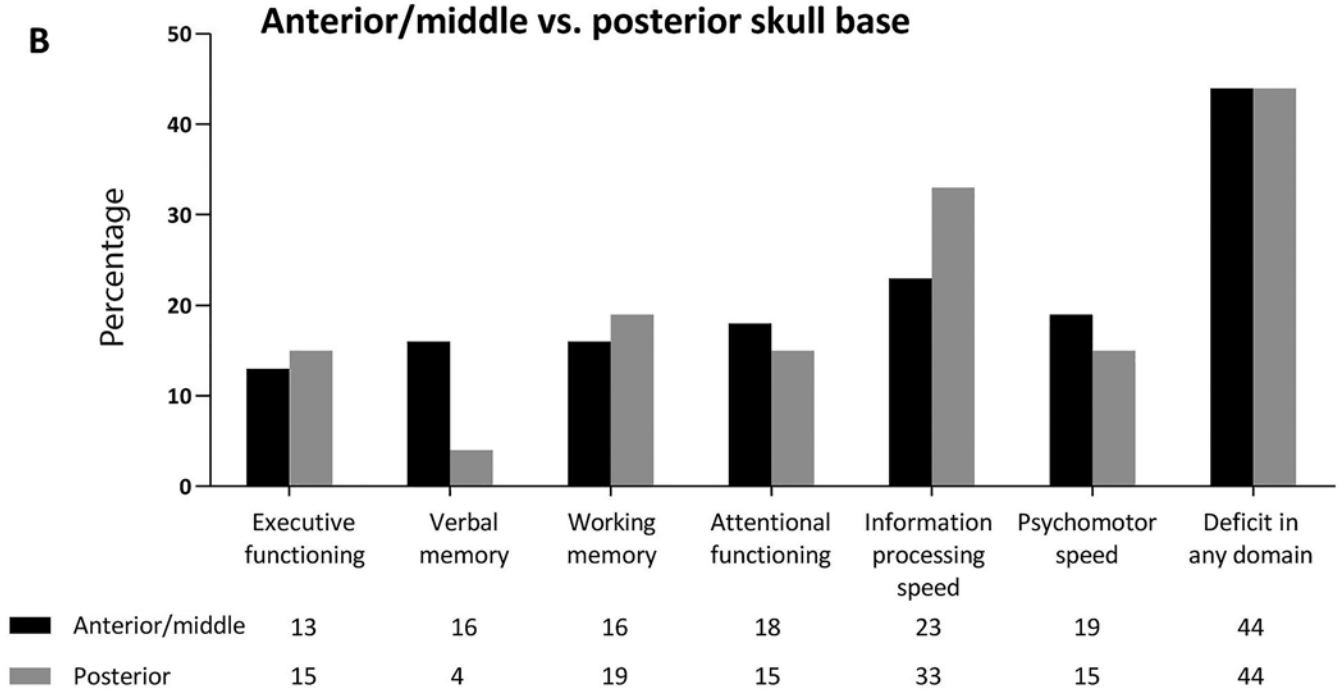
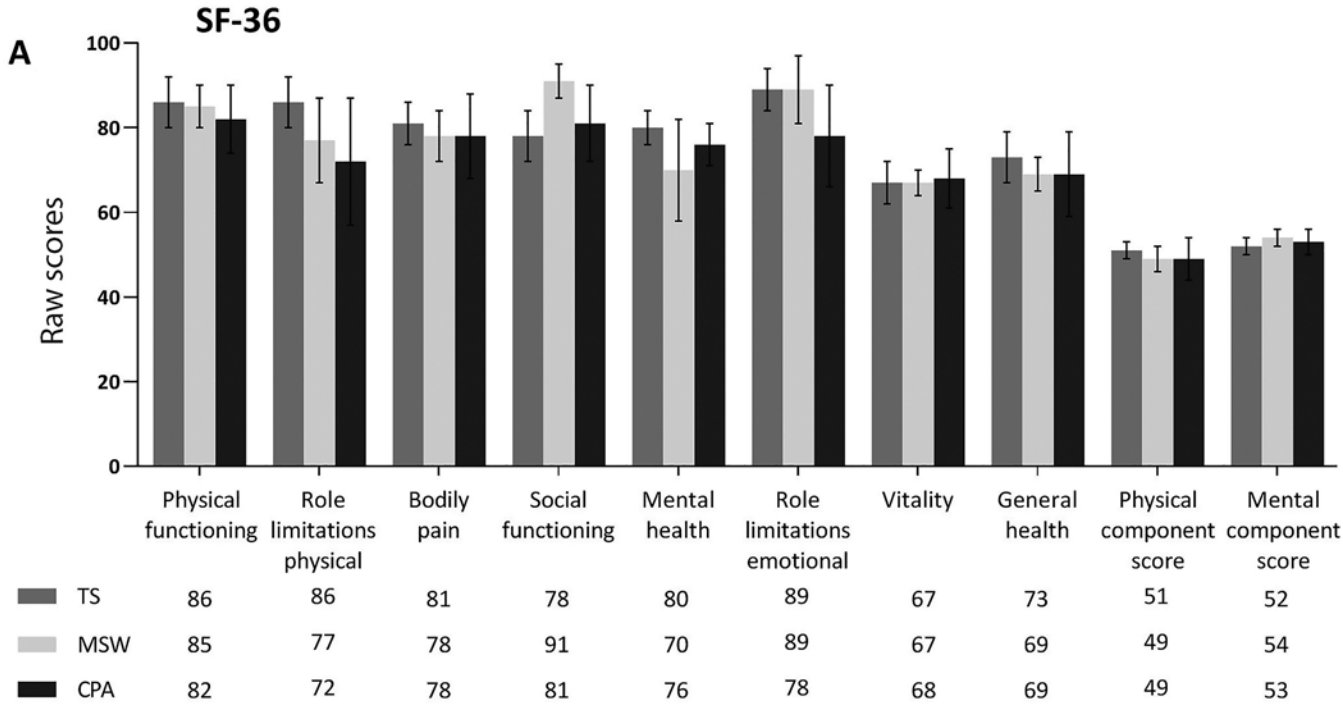


FIG. 4. The percentage of SBM patients with a clinically relevant neurocognitive deficit (difference in z-score ≤ 1.5 compared with the mean of controls) versus 1) informal caregivers and 2) convexity meningioma patients (**A**) and the percentage of anterior and middle SBM patients versus posterior SBM patients (**B**) separately for each domain, and in any domain.

tive functioning (–0.9, 95% CI –1.5 to –0.2) and attention (–1.1, 95% CI –2.1 to –0.2) in SBM patients compared with treatment with surgery only. However, none of these differences were found to be clinically relevant. Neurocognitive functioning did not differ between SBM patients operated on only once and those who were operated on multiple times, between SBM patients who did and did not have postoperative complications, or between SBM patients treated with surgery and adjuvant radiotherapy and those treated with radiotherapy as initial treatment.



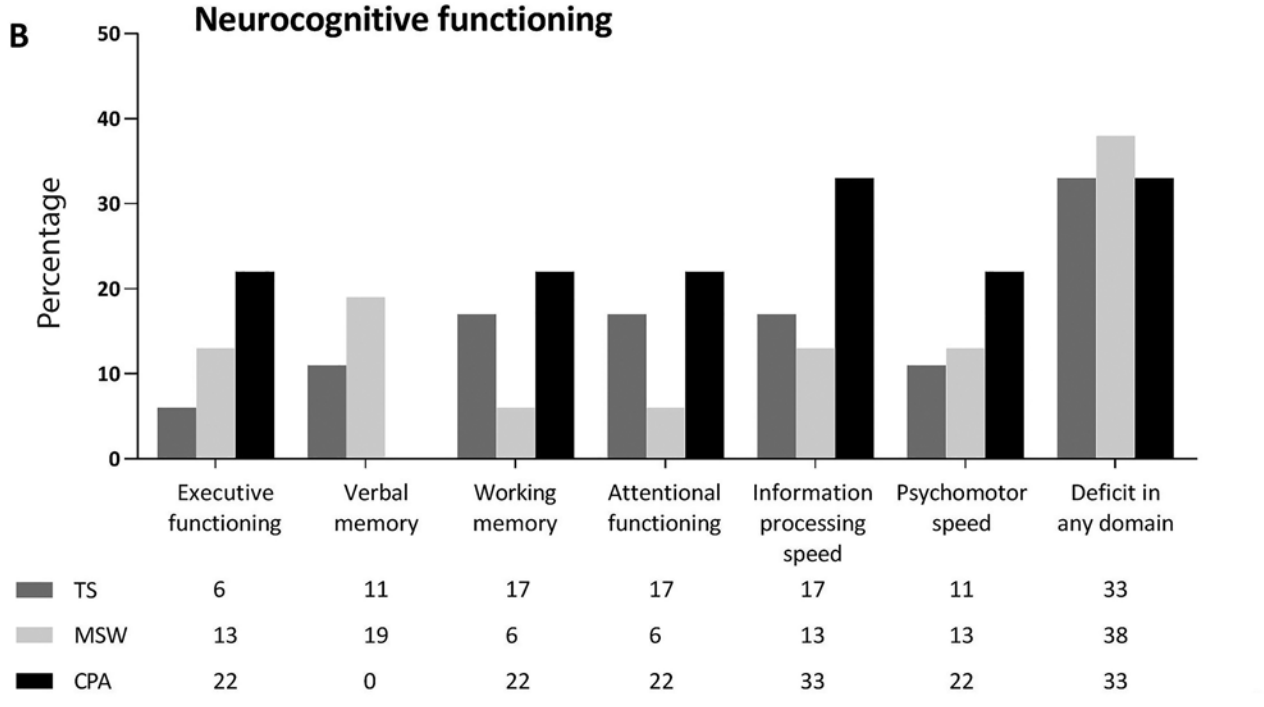


FIG. 5. Raw mean scores with their standard error, presented as bar chart and as actual scores on all SF-36 HRQOL domains and components (**A**) and the percentage of patients with a clinically relevant neurocognitive deficit (difference in z-score ≤ −1.5 compared with the mean of controls) (**B**) separately for each domain and in any domain for tuberculum sellae (TS), medial sphenoid wing (MSW), and cerebellopontine angle (CPA) meningiomas separately.

In both anterior/middle and posterior SBM patients, no differences in neurocognitive functioning were found comparing different treatment strategies.

See Table 1 for sample size per treatment group. For the corrected differences with 95% CIs for the impact of the different treatment strategies in all SBM patients and in anterior/middle SBM and posterior SBM patients separately, see Supplementary Tables 10–12.

Discussion

As the survival of meningioma patients is near normal due to improvements in treatment in recent decades, long-term neurocognitive and HRQOL-related outcomes have become increasingly important to evaluate, as they reflect patients' functioning and well-being.[7] Our results show that in the long term (approximately 10 years after the last intervention), SBM patients do not have significantly lower HRQOL scores or more neurocognitive deficits than controls or convexity meningioma patients. When looking at the tumor location in more detail, we see that posterior SBM patients have poorer HRQOL than anterior/middle SBM patients. In SBM patients, receiving radiotherapy was associated with worse HRQOL scores. Neurocognitive functioning was not affected by tumor location or treatment modality.

Compared with patients with convexity meningioma, SBM patients had similar disease-specific and generic HRQOL scores, which was against our expectations. However, previously published reports showing a difference between convexity meningioma patients and SBM patients did not fully correct for possible confounders (age, sex, education level, and comorbidities) and did not always consider clinical relevance of their findings.[5] In our analyses and results, we did take these factors into account, which can explain the fact that we did not find any relevant differences. We did find that a more detailed differentiation of tumor location within the skull base was associated with differences in HRQOL, as anterior/middle SBM patients reported significantly and clinically relevantly better role functioning and fewer neurological deficits than posterior SBM patients. These results emphasize the need to assess patient-centered outcomes for meningioma with different tumor locations using a more granulated classification than convexity versus skull base.

In our previous report, we found a significant and relevant difference in role limitations due to physical and emotional functioning between all intracranial meningioma patients and controls.[11] However, this difference was not found when comparing SBM patients with controls. Our conclusion was based on estimates that were corrected for confounders and the differences needed to be both statistically significant and clinically relevant. When we look at the raw scores only, the data show worse HRQOL and neurocognitive functioning in convexity meningioma compared with SBM patients in all scales and domains. Therefore, it is likely that the original cohort, in which both SBM and convexity meningioma patients were in the same group, had poorer outcomes that, on a group level, resulted in significant and clinically relevant differences from controls.[11]

Previous articles have not shown consistent findings regarding the late effect of radiotherapy on HRQOL and neurocognitive functioning in meningioma and glioma. The latent period of radiotherapy toxicity can be years, which can be a reason for the fact that previous studies with a shorter follow-up (mean follow-ups of 3.3 [SD 2.0], 3.4 [SD 2.0] years, and 0.9 years) did not report a negative impact of radiotherapy on patient-centered outcomes,[5,8,27] while others with a longer follow-up period did find correlations (mean follow-up of 12 years, range 6–28 years).[12] Our study has a long follow-up time (median of 8 years after radiotherapy, range 5–17 years), and all included patients treated with radiotherapy at least 5 years prior to recruitment, which is likely one of the reasons we did find a negative effect of radiotherapy on HRQOL and neurocognitive functioning.

SBM patients treated with radiotherapy compared with patients treated with surgery scored significantly and clinically relevantly worse on generic and disease-specific HRQOL assessments and neurocognitive functioning. The difference in the observed outcomes could be explained by tumor complexity, as SBMs with complex anatomy that is near critical structures are preferably treated with radiotherapy rather than surgery. Having a more complex meningioma 1) leads to more damage by the meningioma itself,[9,10] 2) requires more aggressive surgery when treated surgically, 3) more often leads to subtotal resection, and 4) requires radiotherapy as primary treatment and as adjuvant treatment more often. Furthermore, at the time of the study (median of 9 years after treatment), the size of the meningioma of those treated with radiotherapy was significantly larger than that of those treated with surgery (median 26.5 mm vs 0.0 mm, $p < 0.001$). This is not corrected for in the propensity score regression analyses, as this was not a possible confounder at the time of treatment assignment.[28] All of these factors potentially cause more substantial functioning deficits.[29,30]

Some symptoms can be ascribed to the anatomical location of the tumor (e.g., higher incidence of visual impairments in anterior SBM patients). This is not as straightforward in cases of neurocognitive functioning. Cerebral cortex functioning is not always one-on-one related to tumor location but is more diffusely distributed over the brain surface, interconnected by large white matter tract networks, which come together at so-called central hubs that participate in different cortical functions and with different cortical locations.[31–34] This could be one reason why we have found no significant or clinically relevant differences in neurocognitive functioning when comparing different tumor locations. However, we did consistently find problems with information processing speed in SBM patients. This neurocognitive domain reflects the time it takes to complete a mental task and is thus not a domain that relies on one particular cortical structure. As meningiomas are not infiltrative tumors, problems with neurocognitive functioning are more likely to be due to the increased intracranial pressure caused by the tumor or by damage caused by resection or radiotherapy. While radiotherapy toxicity can become apparent after years, the impact of surgery could either be permanent or resolve in the long term.

Although not significantly or clinically relevantly different from controls or convexity meningioma patients, a large proportion (44%) of SBM patients had long-term neurocognitive dysfunction. For patients with neurocognitive deficits, different interventions are available to minimize the burden, of which cognitive rehabilitation is most evidence based.[35,36] Examples of cognitive rehabilitation that are shown to be effective in improving cognitive test performance in intracranial tumor patients are computerized and compensation training.[37–39] To improve patient functioning, the use of case managers might especially be of added value. They guide patients over time, identify needs for supportive care, and organize referrals for

rehabilitation and psychological support.[40] Furthermore, our center is also implementing a patient and partner education program that was originally developed for patients with pituitary tumors, which has been shown to improve psychological well-being and other aspects of HRQOL.[41]

Strengths and Limitations

In this report we compared HRQOL and neurocognitive functioning between meningioma patients with tumors in different locations in a more granulated way than most published reports, and hence provided insights in patients' long-term functioning and well-being that were not previously described. Our median follow-up time was 9 years, which is longer than that in most other studies reporting median follow-up to a maximum 4 years.[5,9,42] Furthermore, the amount of missing data was minimal, since all assessments were performed on the same day by a trained researcher. We used patients' informal caregivers as the control group. This filters out the neurocognitive and psychological consequences other than from the tumor and its treatment, since informal caregivers are indirectly affected by the course of the disease and everything around it. The difference between patients and the general population is therefore expected to be even bigger, since the burden on caregivers is also substantial and should not be underestimated.[43]

A limitation is that this was a relatively small observational study, prohibiting causal inferences and increasing the risk of confounding. To correct for possible confounders, we used multivariable and propensity score regression analyses. These types of analyses are considered appropriate for the current sample size and result in estimates for each association independent of possible confounders. There is, however, also a possibility for inclusion bias, since only the patients who gave consent to participate in the study were included, and we recruited patients in large referral centers in which treatment is more common than a wait-and-scan approach. Another limitation is that the questionnaires used to assess the HRQOL are not developed for or validated in meningioma patients, which may lead to omission of disease-specific issues. Nevertheless, we showed in a previous study that the combination of generic and more brain tumor–specific questionnaires covers most relevant HRQOL issues for meningioma patients.[44] Also, although we did assess the presence of epilepsy and motor and cognitive deficits at the time of the assessments, we did not evaluate other important symptoms such as visual or sensory deficits, which may also have an impact on HRQOL and neurocognitive outcomes. Lastly, both WHO grade I and II patients were included, and their different clinical paths may also impact their functioning and well-being differently. Although previous research showed no differences in HRQOL scores between WHO grade I and II tumors, subgroup analyses are not possible in this study due to the limited number of patients with WHO grade II tumors.[45]

Conclusions

Treatment for SBM patients has improved over time,[6] but until now little was known about the location-specific disease burden of long-term survivors. Yet, given improving survival times, long-term outcomes become even more relevant. This study has shown that in the long term, SBM patients do not have significantly lower HRQOL or more neurocognitive deficits than controls or convexity meningioma patients. Anterior/middle SBM patients reported better generic and disease-specific HRQOL than posterior SBM patients. Neurocognitive functioning was not affected by tumor location or treatment modality. SBM patients treated with radiotherapy showed lower HRQOL scores than surgically treated patients. The availability of this information facilitates informing the patient about the impact of the tumor and its treatment on their long-term functioning and well-being. Therefore, the results of this study may help to optimize patients' and healthcare providers' expectations, facilitate treatment decisions based on patient-centered outcomes, and facilitate the distribution of expensive and scarce supportive care resources to patients with the highest need.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Fisher, Zamanipoor Najafabadi, Taphoorn, Dirven, van Furth. Acquisition of data: Zamanipoor Najafabadi, van der Meer. Analysis and interpretation of data: Fisher, Zamanipoor Najafabadi. Drafting the article: Fisher. Critically revising the article: Zamanipoor Najafabadi, van der Meer, Boele, Peerdeman, Peul, Dirven, van Furth. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fisher. Statistical analysis: Fisher. Study supervision: Zamanipoor Najafabadi, van Furth.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables 1–12. https://thejns.org/doi/suppl/10.3171/2021.4.JNS203891.

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