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

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Part 1

The patient road: disease burden and quality of care of meningioma patients and their caregivers

Chapter 2

Impaired health-related quality of life in meningioma patients – a systematic review

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ABSTRACT

While surgical and radiotherapeutic improvements increased life expectancy of meningioma patients, little is known about these patients health-related quality of life (HRQoL). Therefore, the objectives of this systematic review were to assess HRQoL in meningioma patients, the methodological quality of the used questionnaires (COSMIN criteria) and the reporting-level of patient-reported outcomes (PRO) in the included studies (ISOQOL criteria). Nineteen articles met our inclusion criteria. HRQoL was measured with 13 different questionnaires, three validated in meningioma patients. According to our predefined cut-off, HRQoL data was reported sufficiently in 5/19 studies. Both findings hamper interpretation of the PRO results. In general, meningioma patients reported clinically worse HRQoL than healthy controls. Although meningioma patients had better HRQoL than glioma patients, this difference was not clinically relevant. Radiotherapy seemed to improve some domains of HRQoL on the short-term, while HRQoL decreased to pre-radiotherapy levels on the long-term. Tumor resection increased HRQoL, but long-term follow-up showed persistent reduced HRQoL compared to healthy controls. These results suggest an impaired HRQoL in meningioma patients, even years after anti-tumor treatment. Results of this systematic review warrant high quality prospective studies, better instruments to assess HRQoL and improved level of reporting for this group of patients.

Key words: Meningioma; Health-related Quality of Life; Patient-reported outcome; Questionnaires; Reporting level

INTRODUCTION

Meningiomas are the most prevalent tumors of the central nervous system (36.4%), originating from the arachnoid cap cells[1], with an incidence rate of 7.86 per 100,000 population[2]. About 90% of meningiomas are benign (WHO grade I)[3]. Depending on the location of the mass, patients may suffer from a wide variety of somatic and psychological symptoms, such as epileptic seizures, visual loss, cognitive symptoms, psychiatric symptoms and neuropathies.[3] In addition, the majority of patients suffer from more general symptoms, such as tiredness, sleep problems and psychosocial problems. Both the disease-specific and more general symptoms may cause limitations of daily activities and consequently participation restrictions, which is reflected in a deterioration of patients' health-related quality of life (HRQoL).

During the last two decades, new radiation and surgical techniques have improved the treatment of meningioma patients (MP). In modern case series, meningioma patients have a near normal 5 and 10 years life expectancy (5 year survival 92%, expected survival 94%; 10 year survival 81%, expected survival 86%), but often suffer from moderate to severe neurological deficits, even 5 years after surgery (67%)[4]. Parallel to these improvements in therapy and life expectancy, a shift is occurring in treatment objectives; from survival and radical tumor removal to patient performance and HRQoL.[5] Indeed, one should now start to measure the net clinical benefit of meningioma therapy.[6]

HRQoL is a multidimensional concept covering generally valued aspects of life (defined as health or health-related), such as in the physical, social and psychological domains, as well as disease-specific signs and symptoms caused by the disease and its treatment.[7] HRQoL should be patient-reported since doctor-reported and patient-reported HRQoL results differ significantly and patients are thought to be the best source of information on their own HRQoL.[8] HRQoL can be measured using generic (e.g. SF-36, EQ-5D, FACT-G, EORTC QLQ-C30, MDASI)[9–14] or disease-specific questionnaires (e.g. FACT-BR, EORTC QLQ-BN20, MDASI-BT).[14–16] However, neither in clinical practice, nor in research this is done frequently in meningioma patients.

The main objective of this systematic review was to assess HRQoL in meningioma patients. In addition, we assessed the methodological quality of the used HRQoL questionnaires as well as the level of reporting of the patient-reported outcomes (PROs) in the included studies.

MATERIALS AND METHODS

Search Strategy and paper selection

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[17].

Search Strategy

A literature search was conducted in the following electronical databases: Embase, MEDLINE, Web of Science, CINAHL, PsychInfo, Academic Search Premier, COCHRANE and ScienceDirect up to October 2015. Search terms used were "meningioma", "quality of life" and terms formulated to exclude case reports and studies with animals only (see supplementary Table 1 for the search strategy in MEDLINE). The search strategy was adapted for the other electronical databases. Reference lists of included articles were scanned for additional studies.

Paper selection

Inclusion criteria were the following: original peer-reviewed articles measuring patient-reported HRQoL in meningioma patients (whole population or reported separately as a subpopulation) using a questionnaire. Both observational and interventional studies, either retrospective or prospective, were included. Exclusion criteria were as follows: articles not in English, case reports (up to five patients), reviews, studies with only animals and studies including a main population of patients younger than 18 years old. Two independent reviewers (AHZN and MCMP) screened all titles and abstracts for eligibility. Disagreement was resolved with discussion and consensus and when discussion failed to lead to consensus, a third researcher mediated (LD).

Data extraction

Information was extracted per included article by two independent researchers (AHZN and MCMP) on study design, main inclusion criteria and subject characteristics: mean age at time of intervention, percentage women, percentage WHO grade I, II or III tumors, location of tumor and functional status. In addition, when applicable, type of intervention and Simpson Grade were noted. Regarding study outcomes, the timing of HRQoL assessments, the used questionnaire and the HRQoL outcomes (mean and when reported the standard deviation) itself were extracted. Data are presented for all studies separately. No meta-analysis was performed due to the small number of studies and heterogeneity of the studies in population (different tumor grades, tumor location), intervention (surgery, radiotherapy, wait-and-scan) and outcomes (different HRQoL questionnaires used). Assessment of reporting level of included articles and quality assessment of used questionnaires

Assessment of reporting level of PROs in the included articles

The level of reporting of the PRO data in the included articles was assessed by two researchers independently (AHZN and MCMP) following the criteria for patient-reported outcomes of the International Society of Quality Of Life Research (ISOQOL)[18]. The criteria were adapted for non-randomised studies and are presented in Supplementary Table 2. A maximum of 16 points could be scored and the predefined cut-off for sufficient reporting was 11/16 points, which is in line with previous work.[19]

Quality assessment of used questionnaires

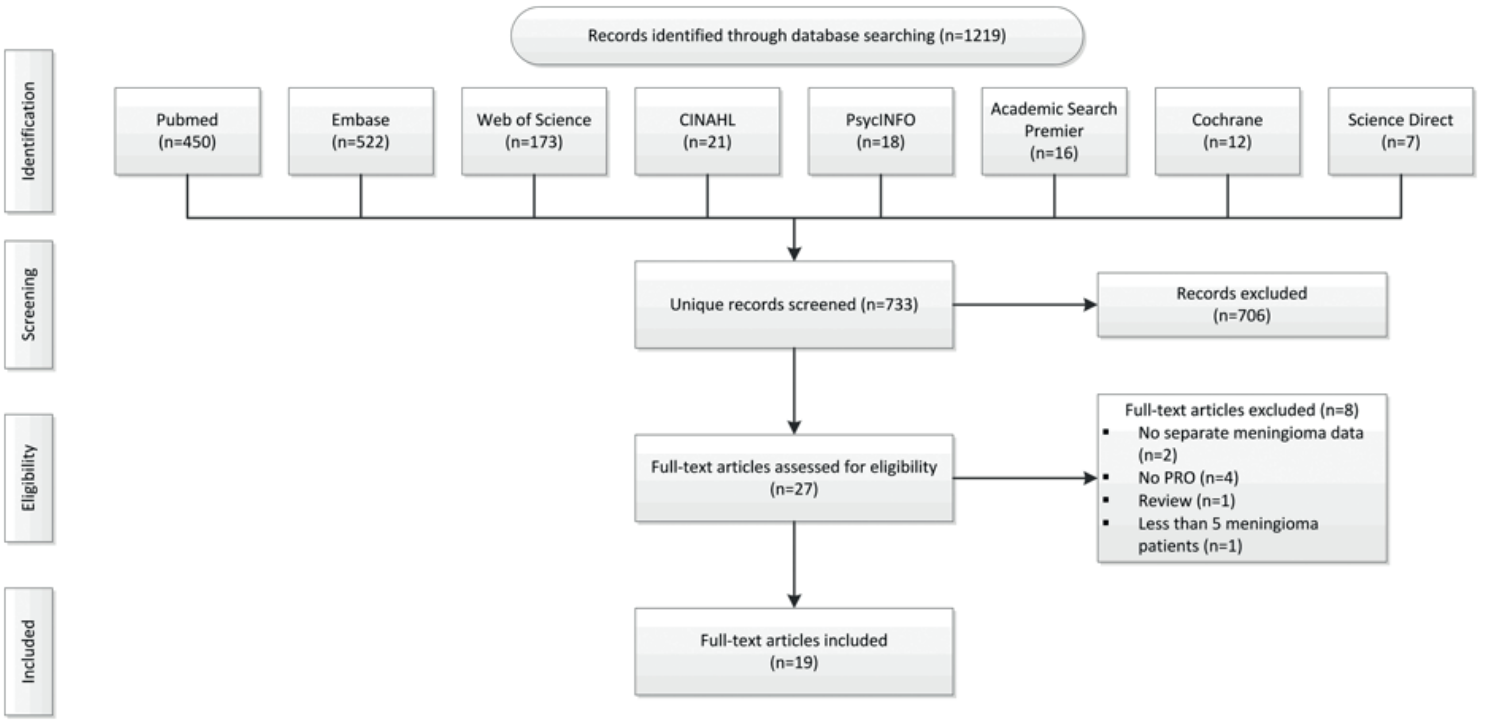
Quality of the used questionnaires was assessed by two researchers independently (MCMP and LD) using the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) criteria[20]. In short, the following aspects were evaluated for meningioma patients or patients with other acquired brain injuries: content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects and interpretability.

RESULTS

Study characteristics

Titles and abstracts of 733 unique articles were screened, resulting in 27 eligible articles. These articles were read full-text and 19 met our inclusion criteria[21–40]. Flow diagram of record analysis and article inclusion is depicted in Figure 1. Study characteristics are presented in Table 1. Of the 19 included articles, four studies used a longitudinal[21,22,29,38] and 15 a cross-sectional study design[23–28,30–34,36,37,39,40]. Six studies included only patients with WHO grade I meningioma[23,30–32,36,38], four studies also included patients with WHO grade II or III meningioma[21,22,25,29] and nine studies did not report the WHO grade[24,26–28,33,34,37,39,40]. Study population size ranged between 16 and 155 meningioma patients (median 47 patients). Seven studies compared the results of meningioma patients with normative data of healthy controls (HC)[21,23,29–32,34], one study compared results of meningioma patients with normative data of healthy controls and (brain) cancer patients[25], one study compared meningioma patients with glioma patients[33] and eight studies presented only results for meningioma patients[22,24,26–28,36–40]. Surgery was the primary intervention in 13 studies[21–28,33,34,36–40], of which two compared HRQoL results before and after surgery[21,22]. Radiotherapy was the primary intervention in three studies[29–31], of which one compared HRQoL results before and after radiotherapy.[29] A wait-and-scan approach was the primary treatment modality in one study.[32]

Fig. 1 Flow diagram of record analysis and article inclusion.



Data extraction

Data of the included studies is depicted in Supplementary Table 4, significant and/or clinically relevant results as described in the original articles are presented here.

Meningioma vs. normative data healthy controls

In general, meningioma patients reported worse HRQoL compared to healthy controls before surgery. Overall health status was lower (study specific questionnaire (SSQ): MP 74±2, HC 91±2, $p<.0001$; SF-36: MP 53±25, HC 66±21, $p=.030$)[21,32] and also the following subdomains: physical health (SSQ: MP 27±1, HC 37±3, $p<.0001$)[21], patient satisfaction with medical care (SSQ: MP 5±2, HC 7±2, $p<.001$)[21], self-care (SSQ: MP 14±2, HC 20±1, $p<.0001$)[21] and vitality (SF-36: MP 56±19, HC 66±23, $p=.043$)[32]. Postoperatively, studies reported both worse and better HRQoL scores in meningioma patients compared to healthy controls. About 3.4 years after surgery meningioma patients had more role limitations caused by physical problems (SF-36: MP 50, HC 65, $p<.05$)[23], while they had less role limitations 6 months after surgery (SF-36: MP 77, $p=.01$)[25]. Compared to healthy controls, meningioma patients still scored worse 6 months after tumor removal on cognitive functioning (EORTC QLQ-C30: MP 79, $p=.02$), yet better on physical functioning (EORTC QLQ-C30: MP 80, $p=.01$) and social functioning (EORTC QLQ-C30: MP 84, $p<.01$).[25] Data for healthy controls was not described in this article by Konglund et al.[25]

Meningioma vs. glioma patients and normative data of cancer and brain cancer patients

HRQoL of meningioma patients and glioma or (brain) cancer patients was compared using the EORTC QLQ-C30 and QLQ-BN20 questionnaires. Compared to glioma patients (GP), meningioma patients scored better on cognitive functioning (MP 73±25, GP 64±28, $p=.008$), social functioning (MP 81±26, GP 64±34, $p<.001$), physical functioning (MP 75±20, GP 66±29, $p=.02$), future uncertainty (MP 28±21, GP 39±24, $p=.003$), motor dysfunction (MP 24±23, GP 34±33, $p=.02$) and communication deficits (MP 16±23, GP 30±31, $p<.001$).[33] Compared to brain cancer patients (all grades), meningioma patients scored also better on cognitive functioning (MP 79, $p=.02$) and emotional functioning (MP 82, $p=.04$), but meningioma patients had more insomnia (MP 28, $p=.01$).[25] Compared to the general cancer population, meningioma patients scored better on the following domains of the EORTC QLQ-C30 and QLQ-BN20: physical functioning (MP 80, $p=.01$), role functioning (MP 77, $p=.02$), emotional functioning (MP 82, $p=.04$) and social functioning (MP 84, $p=.03$) but worse on cognitive functioning (MP 79, $p=.02$). Data for healthy controls was not described in this article by Konglund et al.[25]

Table 1 – Study characteristics of included studies

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Miao (2010)[21]	Prospective	Meningioma patients histologically confirmed and operated	Meningioma patients: 147 Controls: 96, age-matched	Meningioma patients median age: 43 (5-77) Controls Median age: 42 (range N/A)	Meningioma patients: 59% Controls: 67%	I: 80% II: 7% III: 6%	Parasagittal: 3% Falcine: 16% Convexity: 39% Olfactory groove: 9% Sphenoid ridge: 13% Clivus: 5% Intraventricular: 6% Cerebellum: 4% Other: 4%	0: 8% I: 18% II: 20% III: 27% IV: 27% V: -	N/A	Surgery	Before and after surgery, not further specified
Jakola (2012)[22]	Prospective	Meningioma patients, histologically confirmed, aged ≥ 18 years	Meningioma patients: 46	Meningioma patients mean age: 55±13	Meningioma Patients: 67%	I: 83% II: 17%	Convexity: 24% Parasagittal or falcine: 33% Supratentorial skull base: 35% Infratentorial: 8%	I-II: 66% III: 17% IV-V: 17%	KPS: 85±11	Surgery	Before surgery: 1-3 days Short term after surgery: 6 weeks Long term after surgery: 10-58 months

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Waagemans (2010)[23]	Cross-sectional	Meningioma patients: histologically confirmed WHO grade I, without signs of tumor recurrence for at least 1 year after last intervention	Meningioma patients: 89 Controls: 89, age-, sex-, educational level-matched	Meningioma patients mean age: 58±13 Controls mean age: 58±13	Meningioma patients: 74% Controls: 74%	I: 100%	Convexity: 51% Skull base: 45% Tentorium/falx: 20% Orbital: 7% Olfactory tract: 3%	I: 23% II: 34% III: 13% IV: 24% V: 3% Unknown: 3%	N/A	Surgery	After surgery: at least 1 year after last intervention (mean 3.4 years)
Mathiesen (2007)[34]	Cross-sectional	Meningioma patients: petroclival tumors, larger than 30mm.	Meningioma patients: 16	Meningioma patients mean age: 54 (SD N/A)	Patients: 69%	MIB+ <2%: 94% 6%>: 6%	Petroclival tumors	I: 4% II: 38% III: 7% IV:52% V: -	N/A	Surgery	Postoperative, at least 1 year after surgery (mean 66 months)
Neil-Dwyer (2000)[24] Neil-Dwyer (2001)*[40] Lang (1999)*[39] (same study population and results)	Cross-sectional	Meningioma patients: petroclival tumors arising medial to the 5th cranial nerve	Meningioma patients: 19 (*17)	Meningioma patients age range: 29-63	Meningioma patients: 79%	N/A	Petroclival tumors	N/A	N/A	Surgery	Postoperative, at least 1 year after surgery

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Konglund (2012)[25]	Cross-sectional	Meningioma patients, ≥60 years, elective surgery	Meningioma patients: 47	Meningioma patients median age: 70 (60-84)	Meningioma patients: 65%	I: 94% II: 4% Missing: 2%	Convexity: 44% Skull base: 33% Parasagittal: 11% Tentorial: 9% Intraventricular: 2%	I: 35% II: 39% III: 13% IV: 13%	KPS <50: 2% 50-70: 9% >70: 89%	Surgery	Postoperative, 6 months after surgery
Shin (2013)[33]	Cross-sectional	Patients ≥18 years, histologically diagnosed brain tumor: meningioma, glioma and other tumors	Meningioma patients: 107	All patients: mean age 48 (18-81)	All patients: 57%	N/A	N/A	N/A	All patients: KPS ≤70: 11% >70: 89%	Surgery	Postoperative, not further specified
Mohsenipour (2001)[26]	Cross-sectional	Meningioma patients, neurosurgical treatment	Meningioma patients: 82	Meningioma patients: mean age 61±15	Meningioma patients: 65%	N/A	Convexity: 72% Petrosal: 12% Cerebropontine: 4% Multiple: 4% Spinal: 9%	N/A	N/A	Surgery	Postoperative, not further specified
Kalkanis (2000)[27]	Cross-sectional	Meningioma patients, undergone craniotomy	Meningioma patients: 155	Meningioma patients: mean age 59±14	Meningioma patients: 66%	N/A	N/A	N/A	N/A	Surgery	Postoperative, mean time after surgery 33 months (0-165)

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Salo (2002)[28]	Cross-sectional	Brain tumor patients, ≥16 years, diagnosed by imaging	Meningioma patients: 31	All patients: 49 (20-82)	Meningioma patients: 61%	N/A	Intracranial Left: 46% Right: 35% Bilateral: 14% Undefined: 4%	N/A	N/A	Surgery	Preoperative
Henzel (2013)[29]	Prospective	Meningioma patients, ≥18 years, ECOG performance status ≥2, KPS≥70%, life expectancy>2 years.	Meningioma patients: 52	Meningioma patients median age: 57 (40-81)	Meningioma patients: 75%	Known of previous operated 42/52 I: 79% II: 17% III: 5%	Medial wing sphenoid: 56% Petroclival: 15% Tentorial: 6% Petroclival up to sphenoid bone: 12% Falx cerebi: 8% Optic nerve sheath: 2% Olfactory: 2%	N/A	N/A	SRT (42/52 previous surgery)	Before SRT, last day of SRT, thereafter biannually
Kangas (2012)[30]	Cross-sectional	Meningioma patients, WHO grade I, treated with radiotherapy	Meningioma patients: 70	Meningioma patients: 57±12	Meningioma patients: 77%	I: 100%	N/A	N/A	N/A	Radiotherapy	After RT, mean 1.7 years

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Van Nieuwenhuizen (2007)[31]	Cross-sectional	Meningioma patients, WHO grade I	Meningioma patients only surgery: 18 Meningioma patients: surgery and radiotherapy: 18 Healthy controls: 18, age- and sex-matched	Meningioma patients surgery only: 63±12 Meningioma patients surgery and radiotherapy: 63±11	Meningioma patients surgery only: 84% Meningioma patients surgery and radiotherapy: 89%	I: 100%	N/A	N/A	KPS Surgery only: 83±20 Surgery and radiotherapy: 71±18 Barthel Surgery: 17±1 Surgery and radiotherapy: 17±2	Surgery with or without RT	Postoperative, at least 1 year after surgery Surgery only: mean 3.3±2.0 years after surgery Surgery and RT: mean 3.3±1.9 years after surgery
Van Nieuwenhuizen (2013)[32]	Cross-sectional	Meningioma patients: radiologically suspected WHO grade I, who have not received surgery or radiotherapy	Meningioma patients: 21 Controls: 21	Meningioma patients: 63±14 Controls: 62±14	Meningioma patients: 81% Controls: 76%	I: 100%	Convexity: 38% Tentorium/Falx: 24% Skull base: 38%:	N/A	KPS 80 (40-100)	No intervention	Pre-operative
Bunevicius (2014)[37]	Cross-sectional	Adult patients admitted for brain tumor surgery	Meningioma patients: 77	All patients: 56±15	All patients: 69%	N/A	N/A	N/A	N/A	Before surgery	Pre-operative

Table 1 – (continued)

Author (year)	Study design regarding PRO results	Main inclusion and exclusion criteria	Patients and controls	Age (years)	Gender (% women)	WHO grade	Location tumor	Simpson grade	Functional status	Primary Intervention	Moment of measurement
Krupp (2009)[36]	Cross-sectional	Meningioma patients, supratentorial, WHO grade I, surgically treated	Meningioma patients: 91	Meningioma patients: 56±10	Meningioma patients: 66%	I: 100%	Convexity: 46% Sphenoid ridge: 21% Parasagittal, falx: 20% Frontal cranial base: 13%	N/A	N/A	Surgery	Postoperative (mean 15 months, range 10-19 months)
Curey (2012)[38]	Prospective	Tuberculum sellae meningioma, surgically treated with the superior interhemispheric approach	Meningioma patients: 20	Meningioma patients: 59±11	Meningioma patients: 85%	I: 100%	Tuberculum sellae meningioma	I or II: 95%	N/A	Surgery	Pre-operative and postoperative at 6 months

Percentages do not add up to 100% due to rounding
KPS: Karnofsky Performance Score
N/A: not assessed or not reported
(S)RT: (stereotactic) radiotherapy

HRQoL in meningioma patients before and after intervention

Long-term (10-58 months postoperative) general HRQoL improved significantly after surgery (EQ-5D: mean improvement 0.09, p=.040; SSQ: preoperative 74±2, postoperative 85±2, p<.0001)[22] and also on the following domains: physical health (SSQ: preoperative 27±1, postoperative 36±2, p<.0001)[21], patient satisfaction with medical care (SSQ: preoperative 5±2, postoperative 7±1, p=.01)[21], self-care (SSQ: preoperative 14±2, postoperative 16±3, p=.04)[21] and olfactory function (impact of surgery on VAS score for olfactory function +5.7±2.2).[38] Patients who had undergone surgery before radiotherapy (OP+RT) had significantly better mental health (SF-36) compared to patients who only received radiotherapy (RT), both before radiotherapy (OP+RT 43, RT 32, p=.04), at the end of radiotherapy (OP+RT 42, RT 29, p=.014) and at 6/12/18/24 months follow up (6 months: OP+RT 45, RT 36; 12 months: OP+RT 43, RT 33; 18 months: OP+RT 44, RT 31; 24 months: OP+RT 42, RT 34, all p=.004)[29]. Moreover, the addition of RT to surgery resulted in worse scores on the following domains: physical functioning (OP+RT 55±55, RT 73±33, p=.05), role limitations caused by physical functioning (OP+RT 34±39, RT 61±43, p=.03) and on the physical component score (OP+RT 33±11, RT 52±12, p=.007).[31] However, these differences could be explained by the longer disease length for patients treated with OP+RT compared to those treated with OP only (7.6 versus 3.0 years after diagnoses, respectively).[31]

Factors negatively influencing HRQoL in meningioma patients

A larger tumor size (p=.037), higher histological grade (p=.011) and tumor recurrence (p=.018) were all associated with lower overall HRQoL.[21] In addition, larger tumor size was associated with more physical mobility impairment.[21,26] The presence of a meningioma was associated with emotional well-being in a univariable analysis (r=-0.14, p=.048); however this association was not confirmed in the multivariable analysis.[37] Waagemans et al. found that meningioma patients who used anti-epileptic drugs had lower scores on physical health (p<.01), social functioning (p<.05), mental health (p<.05), vitality (p<.01) and overall health status (p<.05) when compared to healthy controls.[23] They also found significant associations between impaired HRQoL and problems in neurocognitive functioning (executive functioning, information processing, verbal memory, psychomotor speed).[23] Furthermore, shorter time since diagnosis (p=.013), more posttraumatic stress (p=.005), confusion (p=.000) and tumor location in the left hemisphere (p=.009) were negatively associated with HRQoL in meningioma patients.[30]

Factors positively influencing HRQoL in meningioma patients

A longer follow-up was associated with better HRQoL outcomes (SF-36); meningioma patients scoring on more than 4 subscales below the 25th percentile of normative data of healthy controls had a mean follow-up period of 2.9 years, whereas patients scoring less than 4 subscales below the 25th percentile had a mean follow-up period of 5.4 years (p<.05).[34] Furthermore, less emotional impairment was associated with longer follow-up time after surgery (IHD-NS).[26]

Table 2 – Assessment of PRO-reporting level of included studies

			Methods (6pnt)		Results (3pnt)			Discussion (4pnt)				
Author (year)	**Title and abstract (1pnt)**	**Introduction Background and Objectives (1pnt)**	**Outcomes (4pnt)**	**Statistical methods (2pnt)**	**Participant flow / missing data (1pnt)**	**Baseline data (1pnt)**	**Outcomes and estimation (1pnt)**	**Limitations (1pnt)**	**Generalizability (1pnt)**	**Interpretation (2pnt)**	**Protocol / copy of instrument (1pnt)**	**Total points (Max 16 points)**
Miao (2010)[21]	1	1	2	1	1	0	0	0	1	0	1	8
Jakola (2012)*[22]	1	0	3	2	1	1	1	1	1	2	1	14
Waagemans (2010)*[23]	1	1	3	1	1	1	1	1	1	1	1	13
Mathiesen (2007)[34]	1	0	1	0	1	0	0	0	1	1	1	6
Neil-Dwyer (2000)[24]	1	0	2	0	0	0	1	0	1	0	1	6
Neil-Dwyer (2001)[40]	1	0	1	0	0	0	1	1	0	1	1	6
Lang (1999)[39]	1	0	3	0	0	0	1	1	0	1	1	8
Konglund (2012)[25]	1	0	1	1	0	0	1	0	1	1	1	7
Shin (2013)[33]	1	1	2	1	0	0	1	1	0	1	1	9
Mohsenipour (2001)[26]	1	0	2	1	0	0	1	0	1	0	1	7
Kalkanis (2000)[27]	1	0	3	1	1	0	1	0	0	0	1	8
Salo (2002)[28]	1	1	0	1	0	0	1	0	0	1	1	6
Henzel (2013)[29]	1	0	1	1	1	1	1	0	0	1	1	8
Kangas (2012)*[30]	1	1	3	1	0	1	1	0	1	1	1	11
Van Nieuwenhuizen[31] (2007)*	1	1	3	1	1	1	1	0	1	1	1	12
Van Nieuwenhuizen (2013)*[32]	1	0	3	1	1	1	1	0	1	1	1	11
Bunevicius (2014)[37]	1	0	2	1	1	0	0	0	1	1	1	8
Krupp (2009)[36]	1	0	3	1	1	1	1	0	0	1	1	10
Curey (2012)[33]	1	0	2	0	0	1	1	0	0	1	1	7
Percentage of studies scoring maximum score per criterium	100%	32%	0%	5%	53%	42%	84%	26%	58%	5%	100%	Mean 8 points

* Articles with sufficient reporting level (predefined cut-off ≥ 11 points)

Assessment of reporting level of PRO data in the included articles

Reporting level of PRO data in the included studies is depicted in Table 2. Median reporting level score was 8 points (range: 6-14 points) and in five articles PRO data could be classified as sufficiently reported (≥11 points).[22,23,30–32] All articles described the PRO in the title or abstract and included or cited the used questionnaire. However, most articles did not report the PRO methods (none), used statistical methods (for missing data, 5%)[22] or how the results should

be interpreted (e.g. presenting the number of patients with a minimal important change or describing the cut-off for normal scores for the used scale, 5%).[22] On all other criteria, 26% to 84% of the articles scored the highest possible score.

Quality assessment of used questionnaires

Of the 13 used questionnaires three questionnaires were validated in meningioma patients, the FACT-G/FACT-BR[14] and a study-specific QOL questionnaire (SSQ)[41]. In addition, five questionnaires were (partially) validated for other types of acquired brain injury or brain cancer: EQ-5D[42,43], SF-36[44], EORTC QLQ-C30 and QLQ-BN20[15,45] and the IHD(NS)[46]. Validity and reliability varied among all questionnaires and none of the questionnaires met all requirements as specified in the COSMIN criteria. Data are presented in Supplementary Table 3.

DISCUSSION

Although HRQoL is an important outcome for meningioma patients, this systematic literature review showed that only a few studies are published describing HRQoL in this patient group. Of those published, unfortunately, the level of PRO reporting of most articles was of low quality; only three HRQoL questionnaires have been validated in meningioma patients and only one study has reported minimal important changes of the PRO results, all hampering interpretation of HRQoL results. Nevertheless, based on the available results we can conclude that in general meningioma patients had a clinically relevant worse HRQoL than healthy controls. Tumor resection improved HRQoL, but long-term follow-up still showed reduced HRQoL compared to healthy controls. In addition, meningioma patients seemed to have a better HRQoL than (brain) cancer patients after surgery, although, this difference was not clinically relevant. These results suggest an impaired HRQoL in some meningioma patients even years after tumor resection.

In general, meningioma patients reported worse HRQoL than healthy controls both before and after surgery. However, because of the few available studies, the use of different questionnaires and low PRO reporting level, PRO results could not be pooled and results could not be compared for patients with different tumor location (e.g. convexity vs. skull base). When comparing results of the EORTC QLQ-C30 of postoperative meningioma patients[25,33] with normative data of healthy controls[47], meningioma patients had a clinically relevant lower score on the following domains: physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning and insomnia. In different studies meningioma patients scored both better and worse on overall health status and fatigue. Likewise, when comparing preoperative results of the SF-36 for meningioma patients with matched controls (age, sex and education) in a small study, meningioma patients had clinically significant more

role limitations caused by physical and emotional problems, worse general health and less vitality.[32] However, these clinically relevant differences between meningioma patients and healthy controls disappeared after surgery[23,31], except for the role limitations caused by physical problems[23]. These seemingly confounding findings may be the result of psychological mechanisms of coping with surgery and illness, which may lead to a positive mental change, also called posttraumatic growth, a known phenomenon generally found in long-term follow-up of patients with different types of cancer or acquired brain injury[48–50]. In addition, a mental change often causes a "response shift", i.e. a change in patient's internal standards, values and consequently perception of HRQoL.[47]

Results of the included studies further showed that, compared to glioma patients, meningioma patients generally had a statistically significant better HRQoL. One study however, showed that meningioma patients had more insomnia than glioma patients.[33] When comparing scores of newly diagnosed glioblastoma patients with scores of meningioma patients on the EORTC QLQ-C30 and QLQ-BN20 questionnaires[25,33], these scores were surprisingly similar between both patient groups.[52] Although differences in 11 HRQoL domains were statistically significant, these results were not clinically relevant. Moreover, meningioma patients experienced more pain and visual problems than other brain cancer patients.[52] Compared with a meta-analysis on SF-36 data in rheumatoid arthritis patients, the study of Waagemans et al. showed that meningioma patients scored similar on the mental and physical component score five years after tumor removal.[53] This implies that five years after tumor removal HRQoL scores of meningioma patients are similar to that of a chronic disease and substantially lower than HRQoL scores of healthy controls.[53]

Results on the impact of different therapies on both the survival and HRQoL/cognition may be used to determine the net clinical benefit of specific therapies.[6] This information is important for clinical decision-making and patient-tailored therapy. Although two studies showed a statistically significant improvement in HRQoL after surgery, this improvement was not clinically relevant in one study and not interpretable in the other study as characteristics of the used questionnaire were not presented.[21,22] Patients who underwent radiotherapy perceived a clinically relevant reduction in role limitations caused by physical problems immediately after radiotherapy and a clinically relevant reduction in role limitations caused by emotional problems 6 months after radiotherapy. However, both of these differences disappeared after 2 years of follow-up[29], suggesting that HRQoL returns to pre-radiotherapy levels on the long-term. However, studies in low grade glioma patients give strong evidence that radiotherapy causes long-term (after 6 years) cognitive problems and a decline in HRQoL[54–56]. These results, while not in all respects comparable with meningioma patients due to different radiation fields and/or techniques, suggest that meningioma patients who receive radiotherapy might also experience a decline in HRQoL and cognitive performance on the long-term. As the results of the

impact of surgery and radiotherapy are not conclusive and potentially suffer from confounding by indication, prospective studies are needed to investigate the impact of treatment on both HRQoL and cognition on the long-term.

PRO reporting of the included articles was on average of low quality. While the used study design, data acquisition methods, and analysis of the results may be correctly performed, it was not adequately described by the authors. As patient and tumor characteristics (e.g. WHO grade, tumor location) were often not fully reported, and HRQoL data not stratified for these characteristics, generalizability of the results is hampered.

Studies comparing HRQoL results after radiotherapy and surgery may suffer from confounding by indication, as patients who are only treated with radiotherapy may have a worse prognosis due to unfavourable tumor location (close to critical structures) and/or higher WHO grade (WHO grade II and III). Moreover, most studies did not report whether to have included consecutive patients in a predefined time period and did not describe characteristics of non-responders. Since reasons for patients not to participate in a study are frequently poor health status and age[57], this could result in an overestimation of HRQoL of meningioma patients in the included studies. Another major limitation of the included studies is that no article clearly reported the PRO data registration and intended collection schedule, while both can influence results[58]. Self-report tools suffer more from patients' cognitive deficits than interviews, while both may be hampered by aphasia.[6] Interpretation of HRQoL results depends on the intended moment of measurement, short-term or long-term, which may lead to different outcomes and interpretations. Indeed Jakola and colleagues showed that compared with preoperative HRQoL, the mean improvement of patients HRQoL was not significantly improved 6 weeks after surgery, while it was improved 10-58 months after surgery.[22]

There is great variety of available HRQoL questionnaires and a lack of argumentation for choosing a particular questionnaire, prohibiting comparison of results between studies. The most commonly used questionnaires were the SF-36[9,10], the FACT-G and FACT-BR[14] and the EORTC QLQ-C30[12] and QLQ-BN20[15] questionnaires. Of these questionnaires the FACT-G and FACT-BR were also validated in meningioma patients. In addition, the minimal important change is determined for the SF-36, FACT and EORTC questionnaires, which is necessary for critical appraisal of found differences. Currently, the SF-36, FACT and EORTC questionnaires seem most suitable for measuring HRQoL in meningioma patients.

In conclusion, this systematic review describes 19 studies reporting on HRQoL in meningioma patients. Most questionnaires that were used to assess HRQoL were not validated in meningioma patients and the reporting quality of the PRO data in the included studies was on average of low quality, both hampering interpretation of the results. In contrast to the current

impression of patients and physicians, data are still insufficient and not conclusive on the effect of interventions on HRQoL in meningioma patients. To improve clinical-decision making, more high-quality evidence is needed on the effect of meningioma and its different treatment modalities on HRQoL. Therefore, new prospective studies, validated meningioma-specific instruments to assess HRQoL in meningioma patients and improved level of reporting seem warranted. Current data suggests that, even though tumor removal through surgery may be beneficial, some meningioma patients have long term clinically significant impaired HRQoL.

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SUPPLEMENTS

Supplementary Table 1 – Search strategy for MEDLINE

Search terms: Meningioma, quality of life and terms to exclude studies with only animals and case reports
(((“Meningioma”[MesH] OR “Meningioma”[Tw] OR “Meningiomas”[Tw] OR “Meningiomatosis”[Tw] OR “Meningiomatoses”[Tw] OR “Meningeal Neoplasms”[MeSH] OR “Meningeal Neoplasms”[Tw] OR “Meningeal Neoplasm”[Tw]) AND (“Quality of Life”[mesh] OR “Health Surveys”[mesh] OR “Questionnaires”[Mesh] OR “Self Report”[mesh] OR “Patient Outcome Assessment”[mesh] OR “Health Status Indicators”[mesh] OR “Quality of Life”[tw] OR “QoL”[tw] OR “HRQL”[tw] OR “HRQOL”[tw] OR “PQoL”[tw] OR “AQoL”[tw] OR “subjective wellbeing”[tw] OR “subjective well-being”[tw] OR “Patient Reported Outcome”[tw] OR “Patient Reported Outcomes”[tw] OR “patient reported”[tw] OR “PRO”[tw] OR “PROs”[tw] OR “PROM”[tw] OR “PROMs”[tw] OR “health survey”[tw] OR “health surveys”[tw] OR “Questionnaires”[tw] OR “questionnaire”[tw] OR “Self reports”[tw] OR “Self report”[tw] OR “Self-reported”[tw] OR “Patient Outcome Assessments”[tw] OR “Patient Outcome Assessment”[tw] OR “health status indicator”[tw] OR “health status indicators”[tw] OR health status indicat*[tw] OR “outcome instrument”[tw] OR “outcome instruments”[tw] OR “health score”[tw] OR “health scores”[tw] OR health scor*[tw])) **NOT** (“Animals”[mesh] NOT “Humans”[mesh]) NOT (“Case Reports”[pt] NOT “Clinical Trial”[pt]))

The search strategy was adapted for the following electronical databases: Embase, Web of Science, CINAHL, PsychInfo, Academic Search Premier, COCHRANE and ScienceDirect.

Supplementary Table 2 – adapted ISOQOL-recommended PRO reporting standards for non-randomised clinical studies

Title and abstract	The PRO should be identified as an outcome in the abstract	1 point
Introduction, background and objectives	The PRO hypothesis should be stated and should specify the relevant PRO domain(s) if applicable	1 point
Methods		
Outcomes registration	The mode of administration of the PRO tool and the methods of collecting data (e.g., telephone, other) should be described	1 point
	The rationale for choice of the PRO instrument used should be provided	1 point
	Evidence of PRO instrument validity and reliability should be provided or cited	1 point
	The intended HRQL data collection schedule should be provided	1 point
Statistical methods	There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested	1 point
	Statistical approaches for missing data should be explicitly stated, and the extent of missing data should be stated	1 point
Results		
Participant flow (a diagram is strongly recommended)	The reasons for missing data on PRO scores should be explained	1 point
Baseline data	The study patients' characteristics should be described	1 point
Outcomes and estimation	Results should be reported for all PRO domains (if multi-dimensional) and items identified by the reference instrument (i.e., not just those that are statistically significant)	1 point
Discussion		
Limitations	The limitations of the PRO components of the study should be explicitly discussed	1 point
Generalizability	Generalizability issues uniquely related to the PRO results should be discussed, if applicable	1 point
Interpretation	The clinical significance of the PRO findings should be discussed	1 point
	The PRO results should be discussed in the context of the other clinical studies	1 point
Other information		
Protocol	A copy of the instrument should be included if it has not been published previously*	1 point
		Maximum: 16 points

* When the used instrument has previously been published, 1 point is given.

Supplementary Table 3 – Quality assessment of used questionnaires

Questionnaire	Articles	Domains	Population validated in	Content validity	Internal consistency	Criterion validity	Construct Validity	Agreement	Reliability	Responsive-ness	Floor and ceiling effects	Interpre-tability
EQ-5D	Jakola (2012)[22]	N/A	Glioma* / stroke	-	0	-	+	-*	0	-*	-*	?
SF-36	Bunevicius (2014)[37] Waagemans (2010)[23] Mathiesen (2007)[34] Neil-Dwyer (2000)[24] Henzel (2013)[29] van Nieuwenhuizen (2007 & 2013)[31,32]	PF, RP, BP, GH, VT, SF, RE, MH	Stroke patients	-	-	?	-	0	0	0	-	?
FACT-G	Kangas (2012)[30]	PWB, SWB, EWB, FWB	Brain tumor Meningioma	-	+	-	?	0	-	0	0	?
FACT-Br	Kalkanis (2000)[27] Kangas (2012)[30]	N/A	Brain tumor Meningioma	+	+	-	?	0	+	0	0	?
SSQ	Miao (2009)[21]	PH, PS, PSMC, SC	Brain tumor Meningioma	+	?	0	0	0	0	?	0	0
EORTC QLQ-C30	Konglund (2012)[25] Shin (2013)[33]	QOL, PF, RF, EF, CF, SF, FA, NV, PA, DY, SL, AP, CO, DI, FI	Brain cancer	+	0	0	0	0	0	+	0	0
EORTC QLQ-BN20	Konglund (2012)[25] Shin (2013)[33] Van Nieuwenhuizen (2007)[31]	FU, VD, MD, CD, BHA, BSE, BDR, BHL, BIS, BWL, BBC	Brain cancer	+	+	-	-	0	0	+	-	?
Freiburg questionnaire on coping with illness	Krupp (2009)[36]	N/A	Not described	0	0	0	0	0	0	0	0	0
Questions on life satisfaction survey	Krupp (2009)[36]	N/A	Cancer patients	0	0	0	0	0	0	0	0	0
VAS score for olfaction	Curey (2012)[33]	N/A	Chronic rhinosinusitis	0	0	0	0	0	0	0	0	0
NHP	Mohsenipour (2001)[26] Salo (2002)[28]	N/A	Chronic diseases	0	0	0	0	0	0	0	0	0
IHD	Mohsenipour (2001)[26]	N/A	Brain tumor	?	?	-	0	0	-	0	0	0
Sintenon's 15D	Salo (2002)[28]	N/A	Hospitalized patients, not further specified	0	0	0	0	0	0	0	0	0

Supplementary Table 3 – Quality assessment of used questionnaires

SF 36 domains and subscales: physical functioning (PF), role limitation caused by physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation caused by emotional problems (RE), mental health (MH), physical component scale (PSC), mental component scale (MSC)

FACT-G domains: Physical well-being (PWB), Social well-being (SWB), Emotional well-being (EWB), Functional well-being (FWB)

SSQ domains: Physiological (PH), Psychological (PS), Patient satisfaction with medical care (PSMC), Self-care (SC)

EORTC QLQ-C30 subscales and symptoms: general health status (QOL), physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF), fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), financial difficulties (FI)

EORTC QLQ-BN20 subscales and symptoms: future uncertainty (FU), visual disorder (VD), motor dysfunction (MD), communication deficit (CD), headaches (HA), seizures (SE), drowsiness (DR), hair loss (HL), itchy skin (IS), weakness of legs (WL), bladder control (BC)

NHP domains: emotional reactions (EM), energy (EN), pain (P), physical mobility (PM), social isolation (SO), sleep (SL)

+ Rating: criteria met and adequate analysis for content validity, internal consistency, criterion validity, construct validity, reproducibility, responsiveness, floor and ceiling effects, interpretability.

? Rating: doubtful design or method was used or description of analysis was lacking.

- Rating: criteria not met, despite adequate design and method.

0 Rating: no information presented on patients with meningioma, acquired brain injury or other brain tumors

Supplementary Table 4 – Patient-reported outcomes per study

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Surgery						
Miao (2010)[21]	Before and after surgery, not further specified	SSQ Physiological (PH) Psychological (PS) Patient satisfaction with medical care (PSMC) Self-care (SC)	Meningioma patients Total: 74±2 PH: 27±1 PS: N/A PSMC: 5±2 SC: 14±2	Meningioma patients Total: 85±2 PH: MNG 36±2 PS: N/A PSMC: 7±1 SC: 16±3	Healthy controls Total: 91±2 PH 37±3 PS: N/A PSMC: 7±2 SC: 20±1	Follow-up vs. baseline: Meningioma patients scored higher on all domains during follow-up: Total and PH (p=.0001), SC (p=.004), PSMC (p=.01) At baseline meningioma patients score worse than controls: Total, PH and SC (p=.0001), PSMC (p=.001)
Jakola (2012)[22]	Before surgery: 1-3 days Short term after surgery: 6 weeks Long term after surgery, 10-58 months	EQ-5D Change in index value defined as clinical significant > 0.10	Meningioma patients mean scores: All patients: 0.7±0.3 Skull base: 0.6 (SD N/A) Other location: 0.8 (SD N/A) Patients experiencing improvement or unchanged HRQoL at follow-up: 0.6 Patients experiencing deterioration at follow-up: 0.8	Meningioma patients: Short-term: Mean improvement: 0.06 (95% CI, -0.03–0.16) Clinical improvement: 44% Clinically unchanged: 37%, Clinically deteriorated: 19% Long-term: Mean improvement: 0.09 (95% CI, 0.00–0.17) Clinical improvement: 49% Clinically unchanged: 31% Clinically deteriorated: 20%	N/A	Long term vs. baseline: Mean long term improvement in all patients (95% CI 0.00-0.17, p=.040) Preoperative scores were higher for patients experiencing deterioration of HRQOL vs. patients with a unchanged or improved HRQL (p=.049)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Waagemans[23] (2010)	After surgery: at least 1 year after last intervention (mean 3.4 years)	SF-36:	Meningioma patients: PF: 71 RP: 50 BP: 67 GH: 57 VT: 56 SF: 70 RE: 72 MH: 69	N/A	Normative data of Dutch healthy controls PF: 74 RP: 65 BP: 67 GH: 63 VT: 61 SF: 77 RE: 79 MH: 73	Meningioma vs. control postoperative: meningioma patients have more role limitations caused by physical health problems (p<.05)
Mathiesen[34] (2007)	Postoperative, at least 1 year after surgery (mean 66 months)	SF-36	Meningioma patients: PSC: 39 MSC: 45 Below mean of normative data: PF 50%, RP 50%, BP 68%, GH 74%, VT62%, SF 56%, RE 25%, MH 50% Below 25th percentile: PF 50%, RP 44%, BP 30%, GH 18%, VT 30%, SF 61%, RE 25%, MH 25%	N/A	Normative data of normal aged and sex-adjusted Swedish population	Meningioma vs. control Mean time between surgery and SF-36 examination was 2.9 years for patients reporting more than 4 subscale items below the 25th percentile and 5.4 years for patients reporting less than 4 subscale items (p<.05)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Neil-Dwyer (2000)[24] Neil-Dwyer (2001)[40] Lang (1999)[39] Same study study population and results	Postoperative, at least 1 year after surgery	SF-36	Meningioma patients: Individual scores below accepted norms: PF: 56% RP: 61% BP: 39% GH: 56% VT: 72% SF: 61% RE: 56% MH: 44%	N/A	N/A	N/A

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Konglund (2012)[25]	Postoperative, 6 months after surgery	EORTC QLQ-C30 EORTC QLQ-BN20	Meningioma patients EORTC QLQ-C30: QoL: 74 (95% CI, 68-82) PF: 80 (95% CI, 74-88) RF: 77 (95% CI, 69-89) EF: 82 (95% CI, 75-89) CF: 79 (95% CI, 74-87) SF: 84 (95% CI, 79-92) FA: 22 (95% CI, 16-28) NV: 2 PA: 14 (95% CI, 6-23) DY: 10 (95% CI, 3-12) SL: 28 (95% CI, 18-40) AP: 5 (95% CI, 1-9) CO: 14 (95% CI, 4-21) DI: 8 (95% CI, 1-15) FI: 4 QLQ-BN20: mean score 26.7	N/A	Normative data of the Norwegian population for cancer patients, brain cancer patients, and healthy controls	Meningioma vs. cancer patients Meningioma patients scored better than cancer patients on PF (p=.01), RF (p=.02), EF (p=.04), SF (p=.03) and worse than cancer patients on CO (p=.01). Meningioma vs. brain cancer Meningioma patients scored better than brain cancer patients on CO (p=.02), EF (p=.04) and worse on SL (p=.01) Meningioma vs. healthy controls Meningioma patients scored better than healthy controls on PF (p=.01), RF (p=.01), SF (p<.01), yet poorer CF (p=.02)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients		Results: follow-up results	Results: healthy controls	Significant differences
Shin (2013)[33]	Postoperative, not further specified	EORTC QLQ-C30 EORTC QLQ-BN20	Meningioma EORTC QLQ-C30 PF:75±20 RF:75±25 EF:74±21 CF:73±25 SF: 81±26 QOL: 58±24 FA:34±20 NV:9±14 PA:24±24 EORTC QLQ-BN20 FU:28±21 VD:31±27 MD:24±23 CD:16±23	Glioma EORTC QLQ-C30 PF:66±29 RF:65±36 EF:68±25 CF:64±28 SF:64±34 QOL:51±26 FA:40±26 NV:14±19 PA:26±30 EORTC QLQ-BN20 FU:39±24 VD:22±26 MD:34±33 CD:30±31	N/A	N/A	Meningioma vs. glioma EORTC QLQ-C30 Meningioma patients scored significantly better than glioma patients on PF (p=.02), SF (p<.001), CF (p=.008). EORTC QLQ-BN20 Meningioma patients scored significantly better than glioma patients on FU (p=.003), MD (p=.02) and CD (p<.001)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients		Results: follow-up results	Results: healthy controls	Significant differences
Mohsenipour (2001)[26]	Postoperative, not further specified	IHD(NS) Score: None QoL impairment (no): 0 Mild (mi): 1-8 Moderate (mod): 9-16 Severe (sev): 17-38 NHP	Meningioma NHP Energy Pain Emotional Sleep Social isolation Physical mobility NHP total IHD Communication Physical condition Autonomic funct. Independence Psych. Funct. Social isolation IHD total	Percentages No/mi/mod/sev 52/11/15/22 65/11/15/10 42/34/12/12 40/21/32/7 79/12/4/5 50/15/17/18 21/40/27/12 No/mi/mod/sev 32/55/10/4 34/21/23/22 49/28/22/1 9/54/26/1 0/57/31/12 40/48/9/4 1/59/24/16	N/A	N/A	Meningioma patients Emotional impairment decreased significantly with increasing time after the date of operation. Physical mobility impairment increased significantly with age. Size of tumor correlated significantly with impairment in physical mobility.
Kalkanis (2000)[27]	Postoperative, mean time after surgery 33 months (0-165)	Adapted FACT-BR (26 out of 53 questions)	Descriptive data of 26 questions: percentage of subjects answering each question with 'not at all', 'a little bit', 'somewhat','quite a bit', 'very much'.		N/A	N/A	N/A

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Salo (2002)[28]	Preoperative	Sintenon's 15D NHP	Meningioma patients Sintenon's 15D: 0.86 (n=32) NHP median values Energy: 0 Pain: 8.8 Emotional: 6.2 Sleep: 27 Social isolation.: 0 Mobility: 0	N/A	N/A	N/A
Bunevicius (2014)[37]	Pre-opreative	SF-36	Meningioma In a univariable analysis having a meningioma was correlated with the emotional well-being subscale (-0.14, p=0.048). However this association was not found in the multivariable analysis.	N/A	N/A	Meningioma There is a significant negative correlation between meningioma and emotional well-being (p=.048). However this association was not found in the multivariable analysis.

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Krupp (2009)[36]	Postoperative (mean 15 months, rang 10-19)	Freiburg Questionnaire on Coping with Illness Questions on Life Satisfaction Survey Both in German	Meningioma: Coping strategies: Single and female meningioma patients suffer report more often a depressive coping stile (p<.05) than those who are married or have a partner or are who are men. Female patients report more concerning spirituality (p<.05) Satisfaction with life: Meningioma patients living as a single report less satisfaction with life than those who are marries (p<.05), with single men reporting lower satisfaction than single women (p<.05). Elderly report more satisfaction with disease-related health ((p<.05) and less satisfaction with sexuality (p<.001)	N/A	N/A	Coping strategies: Marital status and gender influence coping strategies. Satisfaction with life: Marital status, gender and age influence satisfaction with life
Curey (2012)[33]	Preoperative and postoperative at 6 months	VAS score for olfaction	Meningioma: Normal olfaction: 85% Hyposmia: 10% Anosmia: 5%	Meningioma long-term: Preserved olfactory function: 50% Hyposmia; 3/20 Anosmia: 7/20 VAS score: 5.7±2.2 (95% CI 4.1-7.3)	N/A	Meningioma patients: long term olfactory function is significantly worse than preoperative olfactory function (95% CI, 4.1-7.3)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results		Results: healthy controls	Significant differences
Radiotherapy							
Henzel (2013)[29]	Before SRT, last day of SRT, thereafter biannually	SF-36	Meningioma PF: 63 RP:42 BP:64 GH:53 VT:45 SF:71 RE:46 MH:57	Domain PF RP BP: GH: VT: SF: RE: MH:	After/6/12/18/24 months 61/72/67/66/64 31/51/57/46/42 59/67/61/57/59 56/55/54/53/50 43/48/45/47/44 67/72/67/69/65 40/60/55/47/50 59/61/57/58/56	German normal population PF: 86 PR: 84 BP:79 GH:68 VIT:63 SF:89 RE:90 MH:74	Meningioma At baseline (p=.004) the end of RT (p=.014) and in each follow-up (p=.004) the values for MCS were better in patients who received previous surgery
Kangas (2012)[30]	After RT, mean 1.7 years	FACT-G FACT-BR	Meningioma: PWB: 23±5 SWB: 21±6 EWB: 19±5 FWB: 21±5 FACT-G: 83±15 FACT-BR: 57±12 FACT-G/FACT-BR: 140±24	N/A		Percentile norms US cancer sample 50%/25% PWB: 23/18 SWB: 23/19 EWB: 20/16 FWB: 20/14 FACT-G: 83/70	Meningioma Patients with tumors of the left hemisphere scored significantly lower (19.3±5.7) than patients with a tumor of the right hemisphere (22.5±3.9) on the FACT-FWB (p=.009)

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients		Results: follow-up results	Results: healthy controls	Significant differences
Van Nieuwenhuizen (2007)[31]	Postoperative, at least 1 year after surgery Surgery only: mean 3.3±2.0 years after surgery Surgery and RT: mean 3.3±1.9 years after surgery	SF-36 EORTC QLQ-BN20	Meningioma: Surgery only SF36 PF: 73±33 RP: 61±43 BP: 67±40 GH: 61±25 VT: 61±31 SF: 70±34 RE: 78±41 MH: 72±24 PCS: 45±13 MCS: 52±12 EORTC QLQ-BN20 FU: 23±26 VD: 15±22 MD: 17±26 CD: 21 ±30 HD: 24±23 SZ: 6±18 DR: 22±31 HL: 6±13 IS: 24±35 WL: 12±23 CB: 14±24	Surgery and Radio therapy SF36 PF: 55±55 RP: 34±39 BP: 56±24 GH: 45±27 VT: 44±21 SF: 67±24 RE: 73±43 MH: 71±23 PCS: 33±11 MCS: 51±13 EORTC QLQ-BN20 FU: 29±26 VD: 28±28 MD: 27±25 CD: 19±21 HD: 41±42 SZ: 13±28 DR: 33±32 HL: 15±26 IS: 24±38 WL: 24±34 CB: 19±33	N/A	Normative data for healthy controls SF36 PF: 74±25 RP: 63±34 BP: 62±25 GH: 65±18 VT: 62±18 SF: 71±26 RE: 75±36 MH: 70±19 PCS: 45±12 MCS: 49±12	Surgery vs. surgery and radio therapy Meningioma patients treated with surgery and with radiotherapy scored lower than patients treated with surgery alone on PF (p=.05), RP (p=.03), PCS (p=.007). This difference disappeared when corrected for duration of disease.

Supplementary Table 4 – (continued)

Author/year	Moment of measurement	Questionnaire	Results: baseline patients	Results: follow-up results	Results: healthy controls	Significant differences
Wait-and-scan						
Van Nieuwenhuizen (2013)[32]	Pre-operative	SF-36	Meningioma PF: 68±26 RP: 52±42 BP: 59±27 GH: 53±25 VT: 56±19 SF: 75±24 RE: 78±40 MH: 74±23	N/A	Normative data for healthy controls PF: 70±31 RP: 69±45 BP: 65±29 GH: 66±21 VT: 66±23 SF: 80±23 RE: 89±30 MH: 78±21	Meningioma vs. Healthy controls Meningioma patients scored lower than healthy controls on GH (p=.030) and VT (p=.043)

SF 36 domains and subscales: physical functioning (PF), role limitation caused by physical problems (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role limitation caused by emotional problems (RE), mental health (MH), physical component scale (PSC), mental component scale (MSC)
FACT-G: Physical well-being (PWB), Social well-being (SWB), Emotional well-being (EWB), Functional well-being (FWB)
SSQ: Physiological (PH), Psychological (PS), Patient satisfaction with medical care (PSMC), Self-care (SC)
EORTC QLQ-C30 subscales and symptoms: general health status (QOL), physical functioning (PF), role functioning (RF), emotional functioning (EF), cognitive functioning (CF), social functioning (SF), fatigue (FA), nausea and vomiting (NV), pain (PA), dyspnoea (DY), insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI), financial difficulties (FI)
EORTC QLQ-BN20 subscales and symptoms: future uncertainty (FU), visual disorder (VD), motor dysfunction (MD), communication deficit (CD), headaches (BHA), seizures (BSE), drowsiness (BDR), hair loss (BHL), itchy skin (BIS), weakness of legs (BWL), bladder control (BBC)
N/A: not assessed or not report