Journal of Neuro-Oncology (2020) 148:109–116
https://doi.org/10.1007/s11060-020-03501-z

CLINICAL STUDY

Symptomatic peritumoral edema is associated with surgical outcome: a consecutive series of 72 supratentorial meningioma patients ≥ 80 years of age

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Received: 6 March 2020 / Accepted: 13 April 2020 / Published online: 22 April 2020

Abstract

Purpose To assess the association of peritumoral brain edema (PTBE) with postoperative outcome in old (≥ 80 years) meningioma patients.

Methods All supratentorial meningioma patients (≥ 80 years old) who underwent surgery between 2010 and 2018 were retrospectively identified. Patients were classified into poor (≤ 40), intermediate (50–70), or good (≥ 80) preoperative Karnofsky Performance Status (KPS) subgroups. Outcome was evaluated at 3 months and at last follow-up within the first year after surgery, and categorized as improved, stable, or deteriorated. Three-dimensional volumetric assessment of tumor and PTBE volume was conducted. Volumes were categorized as small (< 10 cm^3), medium (10–50 cm^3), large (> 50 cm^3).

Results Seventy-two patients (mean age 83 ± 3 years, median 83; median follow-up 3 years) were included. The mean tumor volume was 39 ± 31 cm^3 (median 27), and mean PTBE volume was 57 ± 79 cm^3 (median 27). The mean preoperative KPS and at last follow-up was 58 ± 16 (median 60) and 59 ± 30 (median 70). Thirty-three patients were classified as improved, 16 as stable, and 23 deteriorated; eleven patients died within the first year. Large PTBE volume was more common for patients with poor preoperative status ($p = 0.001$). However, patients with large PTBE and poor preoperative status improved most frequently following surgery ($p = 0.037$ at 3 months, $p = 0.074$ at last follow-up). Large PTBE volume was not associated with treatment-associated complications ($p = 0.538$) or mortality ($p = 0.721$). A decision support tool to predict outcome was developed ($p = 0.038$).

Conclusion Elderly patients with large PTBE volumes usually had a poor preoperative performance status, but appeared to benefit most often from surgery.

Keywords Edema volume · Elderly · Meningioma · Outcome · Resection · Tumor volume

Abbreviations

EI	Edema index
KPS	Karnofsky Performance Scale
MRI	Magnetic resonance imaging
PTBE	Peritumoral brain edema
WHO	World Health Organization

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11060-020-03501-z) contains supplementary material, which is available to authorized users.

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Introduction

Elderly patients are considered to be more prone to treatment-related morbidity after neurosurgery [11]. Due to the demographic developments, there has been increasing interest in the clinical outcome and identification of prognostic factors in elderly (≥ 80 years old) meningioma patients [1–3, 7, 9, 13].

Meningioma-associated symptoms are often caused by the peritumoral brain edema (PTBE). However, data on the influence of PTBE on patients' outcome—especially in an elderly patient population—are limited. In prior studies, PTBE has generally been associated with poor surgical outcomes [4–8, 10, 12, 14–16]. Given that only few of the previous studies have focused on elderly meningioma patients, our aim was to assess whether PTBE affects surgical outcome of this fragile and rapidly growing patient group [4, 5, 7, 10, 12]. To this end, we evaluated the association of PTBE with postoperative morbidity and mortality, considering the tumor location and patients' preoperative status as possible confounders. We hypothesized that larger PTBE volumes are associated with poor surgical outcome in very old (≥ 80 years old) meningioma patients [4, 7, 10, 12]. Furthermore, we aimed to introduce an easy-to-use classification system and preliminary patient-centered decision support tool for improving preoperative patient counseling and estimating postoperative outcome.

Methods

Patients

All consecutive patients with histologically-confirmed supratentorial meningioma, who had undergone resection between 2010 and 2018, were retrospectively identified. The inclusion criteria were: (1) patient's age ≥ 80 years old at surgery, (2) clinical follow-up data (within 12 postoperative months), and (3) preoperative magnetic resonance imaging (MRI). Patients who had undergone surgery for tumor recurrences were excluded. The study protocol was approved by the institutional review board.

Clinical data

Clinical data were extracted from the electronic patient records. The retrieved data included the following information: patient characteristics (e.g. age at surgery, sex, tumor location, etc.), histopathology, and surgery-associated morbidity. The patients' pre- and postoperative performance status were assessed by the Karnofsky Performance Scale (KPS). Patients were classified into three subgroups based on their preoperative KPS: poor (KPS ≤ 40), intermediate (KPS 50–70), and good (KPS ≥ 80) status. Histopathological tumor grading followed the World Health Organization (WHO) classification system [9].

Magnetic resonance imaging

When multiple meningiomas were present, only the tumor for which the initial resection was performed was considered in the analyses. Maximum diameters were measured on the T1 + contrast sequences. Three-dimensional volumetric assessments of tumor and PTBE volumes were conducted by importing the data to the neuronavigation (Brainlab Elements®, Brainlab AG, Germany). Volumes were then delineated and calculated via the semi-automatic and integrated SmartBrush® function. The tumor volume was calculated based on the T1 + contract sequences (slice thickness 1 mm) (Fig. 1), and the PTBE volume was additionally delineated by the fused T2-sequences (slice thicknesses ranged from 1 to 5 mm). The tumor's dural tail was not included for measurements. An edema index (EI) was calculated as the ratio between tumor and edema volume.

Follow-up

According to the standardized follow-up protocol, patients are routinely scheduled for a 2- to 3-month postoperative follow-up visit. Afterwards, WHO grade 1 patients usually have follow-up brain MRIs at 2, 5 and 10 years. The WHO grade 2

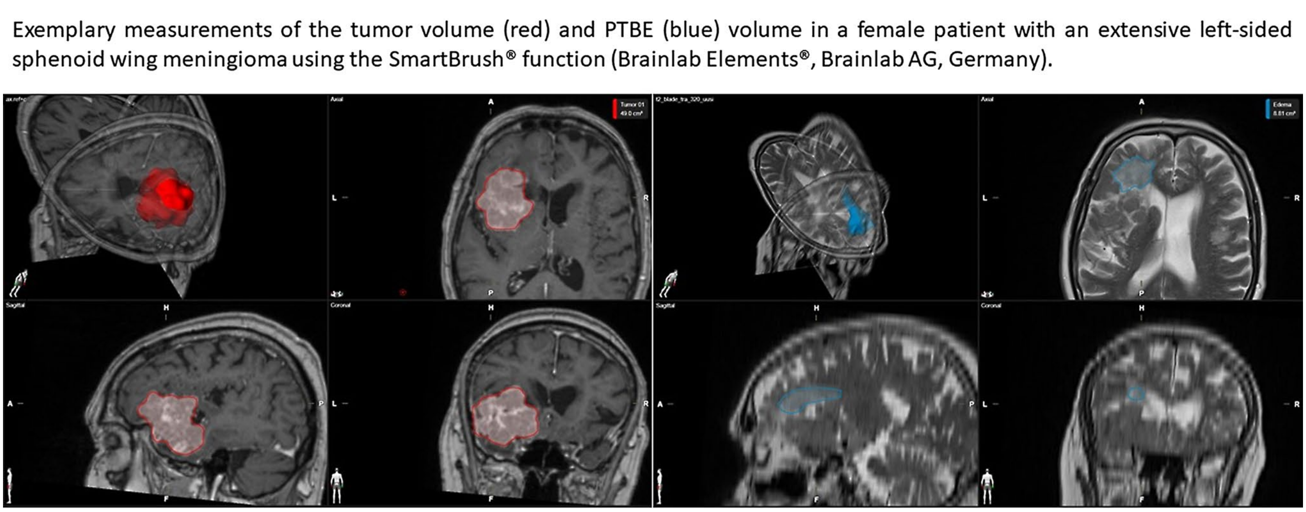

Fig. 1 Tumor and PTBE volume measurements

and 3 patients, as well as patients with partial resection, have annual follow-up MRIs for up to 5 years.

The primary outcome measure was the KPS score at 3 months and at last available follow-up within the first year (either at 3, 6 or 12 months after surgery). The secondary outcome measures were the treatment-associated mortality and morbidity. The date of death was retrieved from the patient record system; surgery/tumor-related mortality was assessed within the first twelve postoperative months. If a patient died within the first year, the postoperative KPS was recorded as "0" for the corresponding follow-up date. Treatment-associated morbidity was classified into major (i.e. intracerebral hemorrhage, hemiparesis/new neurological deficits, pneumonia, pulmonary embolism) and minor complications (i.e. wound infection, cerebrospinal fluid fistula, urinary tract infection).

Decision support tool

A scoring system was applied to create a simple tool for improving preoperative patient counseling and decision-making. Good, intermediate, and poor preoperative status (KPS) corresponded to 1, 2, and 3 points, respectively. Tumor and PTBE volumes were categorized as small (< 10 cm^3), medium (10–50 cm^3), and large (> 50 cm^3); this arbitrary categorization was agreed by three study neurosurgeons prior to any statistical analyses. Small, medium, and large PTBE volumes corresponded to 1, 2, and 3 points, respectively. The scores of both were then added to a final score ranging from 2 to 6 points. Based on these sum scores, patients with a total score of 2 points were classified as Class A, patients with 3–4 points as Class B, and patients with 5–6 points as Class C (Table 1).

Statistics

The patients' sex, tumor location, WHO grade, and complications were assessed as categorical values. Age and volume-based parameters were assessed as continuous, and outcome (i.e. KPS changes between pre- and postoperative status) was categorized as improved, stable, or deteriorated. All variables were tested for normality. The correlation analyses (Chi-squared for categorical parameters, Spearman's correlation for continuous parameters, Kruskal–Wallis test for group analyses) were conducted using SPSS Statistics Version 24 (IBM Cooperation, USA). The significance level was $p \leq 0.05$.

Results

Patients

Four patients were excluded due to the lack of preoperative MRI data. Therefore, the study population consisted of 72 patients (24 males, 48 females). The mean age at surgery was 83 ± 3 years old (median 83, range 80 to 96). The mean preoperative KPS score was 58 ± 16 (median 60, range 20 to 100) at the time of admission. Surgical indications were neurological symptoms (n = 67), tumor growth (n = 3) on follow-up imaging, and unknown (n = 2). The most common symptoms included a suspicion of meningioma-related cognitive decline (n = 29) and motor deficits (n = 15) (Supplementary Table 1).

The preoperative performance status subgroups consisted of 18 (25%) poor, 43 (60%) intermediate, and 11 (15%) good clinical status patients. The mean preoperative KPS scores were 37 ± 6 (median 40, range 20 to 40) for poor, 61 ± 7 (median 60, range 50 to 70) for intermediate, and 84 ± 7 (median 80, range 80 to 100) for good clinical status patients. The performance status subgroups did not differ in age ($p = 0.686$, Kruskal–Wallis test), sex ($p = 0.236$, Chi-squared), WHO grade ($p = 0.475$, Chi-squared), and location ($p = 0.396$, Chi-squared).

Meningiomas

The meningiomas were most often located on the convexity (39%) and in the olfactory groove (18%). The most frequently compressed brain lobes were the frontal (67%) and temporal lobes (19%). In total, 11% of patients had multiple intracranial meningiomas. The majority of meningiomas (74%) were of WHO grade 1 (Supplementary Table 1).

Follow-up

All patients (n = 62) who did not die before the first scheduled follow-up visit were clinically assessed at least once within the first postoperative year (Supplementary Table 2). Fifty-three (85%) patients were assessed at 3 months; for 25 (36%) patients, this was the only postoperative visit during the first year. Nineteen (31%) patients were assessed at 6 months, and 29 (48%) at 12 months. Thirty-three (53%) patients were assessed more than once during the first year. Overall, the last KPS within the first postoperative year was recorded for 35 (49%) patients at 3 months, for seven (10%) at 6 months, and for 30 (42%) patients at 12 months (Supplementary Table 2). The overall mean follow-up was 4 ± 3 years (median 3, range 0–9 years). At least one postoperative MRI within the first year was available for 42 (58%) patients. Complete tumor removal was seen in 33/42 (79%) cases.

Morbidity and mortality

Within the first year, 11 (15%) patients died. Ten deaths occurred within the first three postoperative months, and one patient died 8 months after surgery. According to our

Table 1 Decision support tool

Class system	
Preoperative status	Score
Good (KPS ≥ 80)	1
Intermediate (KPS 50–70)	2
Poor (KPS ≤ 40)	3
PTBE volume	Score
Small (< 10 cm^3)	1
Medium (10–50 cm^3)	2
Large (> 50 cm^3)	3
Class	Sum score
A	2
B	3–4
C	5–6
Patient characteristics—all patients (n = 72)	
Median age at surgery (range) (years)	83 (80–96)
Median preoperative KPS score (range)	60 (20–100)
Median tumor volume (range) (cm^3)	27 (1–141)
Median PTBE volume (range) (cm^3)	27 (0–409)
Median EI	1:1
Patient characteristics—class A (n = 11)	
Median age at surgery (range) (years)	83 (80–86)
Median preoperative KPS score (range)	80 (80–100)
Median tumor volume (range) (cm^3)	16 (7–63)
Median PTBE volume (range) (cm^3)	0 (0–14)
Median EI	1:0
Patient characteristics—class B (n = 30)	
Median age at surgery (range) (years)	83 (80–89)
Median preoperative KPS score (range)	60 (30–70)
Median tumor volume (range) (cm^3)	25 (1–107)
Median PTBE volume (range) (cm^3)	4 (0–49)
Median EI:	1:1
Patient characteristics—class C (n = 31)	
Median age at surgery (range) (years)	83 (80–96)
Median preoperative KPS score (range)	50 (20–70)
Median tumor volume (range) (cm^3)	38 (3–141)
Median PTBE volume (range) (cm^3)	109 (15–409)
Median EI	1:3

EI Edema index, *KPS* Karnofsky Performance Scale, *PTBE* Peritumoral brain edema

records, 34 (47%) patients suffered from postoperative complications. Of these, 14 (19%) suffered from major, 13 (18%) from minor, and seven (10%) patients suffered from both types of complications. The most frequent major complications were intracerebral hemorrhage (n = 11) and pneumonia (n = 7), and major complications were associated with a deteriorated clinical outcome (KPS decrease) at 3-month ($p \leq 0.001$, Chi-squared) and at the last follow-up visit within the first year after surgery (p = 0.004, Chi-squared). Major complications associated with an increased 90-days- (p = 0.003, Chi-squared) and 1-year mortality (p = 0.003, Chi-squared). There was no association between the patients' preoperative clinical status and the risk of major complications (p = 0.170, Chi-squared).

Postoperative KPS change

The mean postoperative KPS score was 59 ± 30 (median 70, range 0–100) at the last follow-up visit within the first postoperative year. At 3 months, the mean postoperative KPS was 57 ± 30 (median 60, range 0–100), including the patients who had died. Based on the last available KPS score within 12 months, 33 (46%) patients improved, 16 (22%) were stable, and 23 (32%) deteriorated. The highest proportion (61%) of patients with KPS improvement was recorded for the poor preoperative status subgroup. The intermediate and good preoperative status subgroups improved less often (47% and 18% of the patients, respectively). Including only those patients for whom KPS data was available at 3 months after surgery, the improvement was also most frequent in the poor status subgroup in comparison to the intermediate and good subgroups (63% vs. 13% and 27%). Anecdotally, five (7%) patients had a postoperative KPS of 100 at the last follow-up. In patients (n = 23) for whom a KPS was available at 3 and 12 months, KPS scores were similar at both visits (mean KPS 70 ± 22, median 70, range 30–100 vs. mean KPS 73 ± 18, median 70, range 30–100; p = 0.088, paired t-test).

Tumor and PTBE volumes

The mean tumor volume was 37 ± 31 cm^3 (median 27 cm^3, range 1 to 141 cm^3), and the mean PTBE volume was 56 ± 79 cm^3 (median 27 cm^3, range 0 to 409 cm^3), resulting in a mean EI of 1:3 (median 1:1) (Table 1). The measured volumes correlated (p = 0.001, Spearman's correlation); in other words, large tumors had large PTBEs. The highest proportion of large tumor and PTBE volumes (> 50 cm^3) were found in poor preoperative status patients (KPS ≤ 40), and the PTBE volume was associated with the patients' preoperative status (p = 0.001, Chi-squared) (Fig. 2) (Supplementary Table 3a and 3b).

Patients with large tumor and PTBE volumes benefitted (i.e. improved) most frequently from surgery (Supplementary Table 4). Specifically, larger PTBE volumes were associated with an improved outcome at 3 months after surgery (p = 0.037, Kruskal–Wallis test). At the last follow-up visit within the first 12 months after surgery, this association did not reach significance (p = 0.074, Kruskal–Wallis test). The tumor volume, in contrast, was neither associated with the patients' outcome at 3 months (p = 0.263, Kruskal–Wallis test) nor at the last follow-up within the first 12 months (p = 0.106, Kruskal–Wallis test). Similarly, the EI did not correlate with outcome at 3 months (p = 0.115, Kruskal–Wallis test) nor at the last follow-up (p = 0.185, Kruskal–Wallis test). Neither the tumor nor PTBE volumes were associated with major complications (p = 0.241; p = 0.538, Kruskal–Wallis test) or with the 90-day (p = 0.672; p = 0.961, Kruskal–Wallis test) and 1-year mortality (p = 0.667; p = 0.721, Kruskal–Wallis test) (Supplementary Table 4).

Neither volumes correlated with age (p = 0.956 and p = 0.433, Spearman's correlation), sex (p = 0.738; p = 0.327, Kruskal–Wallis test), WHO grade (p = 0.269; p = 0.325, Kruskal–Wallis test), tumor lateralization (p = 0.446; p = 0.054, Kruskal–Wallis test), or tumor location (p = 0.625; p = 0.313, Kruskal–Wallis test).

Decision support tool

Patients in the Class C had a clinical benefit most often (63%) from surgery at 3-months (63% vs. 24% and 27%; p = 0.044, Chi-squared) and at last follow-up within the first year (65% vs. 37% and 18%; p = 0.038, Chi-squared) compared to those assigned to the Classes B and A (Table 2). In other words, Class C patients (i.e. poor KPS and large PTBE volume) were much more likely to improve after surgery than Class A patients (i.e. good KPS and small PTBE volume) (Table 2, Fig. 3). The mean KPS improvement was highest for the Class C patients (Table 2).

We found no associations between the PTBE volume and 90-day mortality (p = 0.806, Chi-squared), 1-year mortality (p = 0.618, Chi-squared), major complications (p = 0.124, Chi-squared) or KPS deterioration (p = 0.326, Chi-squared).

Discussion

The main findings include several novelties: (1) patients with large PTBE volumes benefitted most often and most drastically from surgery, (2) patients with large PTBE volumes were most often in poor preoperative condition; in our patient cohort, the PTBE volume—not the tumor—was the decisive factor determining the patients' preoperative status, and (3) large PTBE volume was not associated with treatment-related complications or mortality, as previously suggested (Supplementary Table 5) [4, 6–8, 10, 12, 14–16]. Rather, they were associated with an increased potential of benefitting from surgery [4–8, 10, 12, 14–16].

Thus far, only a few studies have focused on the influence of PTBE volume on patients' outcome (Supplementary Table 5) [4–8, 10, 12, 14–16]. The majority of these studies concluded that an increased PTBE was associated with poor outcome [4–8, 10, 12, 14–16]. Two studies also reported that PTBE was correlated with an increased cortical meningioma infiltration [14, 15]. Since total resection of infiltrating meningiomas is likely to cause focal lesions, this could partially explain the increased risk of worse outcome. In our study, very old meningioma patients were selected for surgery mostly when symptomatic. The symptoms appeared often to be related to PTBE. Therefore, patients with large PTBEs were frequently in poor condition preoperatively, but

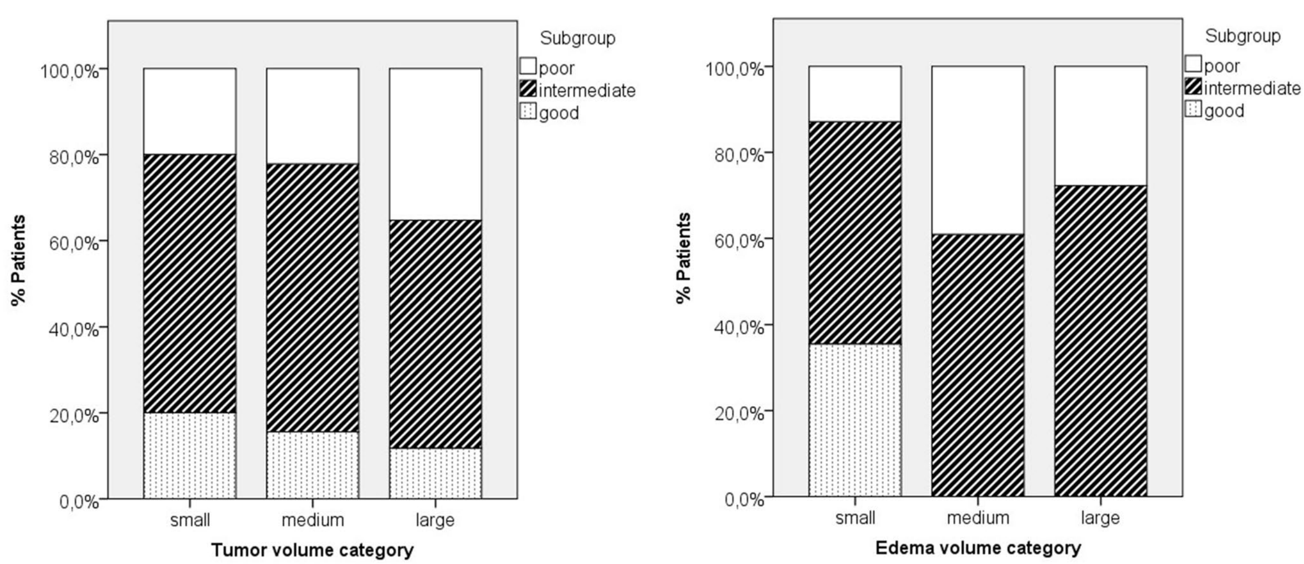

Fig. 2 Tumor and PTBE volumes stratified by preoperative subgroups

Table 2 Decision support tool and outcome

Clinical outcome at 3 months—patients			
Improved (%)[a]	26 (41)		
Stable (%)[a]	11 (17)		
Deteriorated (%)[a]	26 (41)		
90-days mortality (%)	10 (14)		
Clinical outcome at last follow-up within the first 12 months—patients			
Improved (%)	33 (46)		
Stable (%)	16 (22)		
Deteriorated (%)	23 (32)		
Major complications (%)	21 (29)		
1-year mortality (%)	11 (15)		
Clinical outcome at 3 months—classes			
	Class A (n = 11)	Class B (n = 25)	Class C (n = 27)
Improved (%)[a]	3 (27)	6 (24)	17 (63)
Stable (%)[a]	3 (27)	6 (24)	2 (7)
Deteriorated (%)[a]	5 (46)	13 (52)	8 (30)
90-days mortality (%)	1 (9)	5 (17)	4 (13)
Clinical outcome at last follow-up within the first 12 months—classes			
	Class A (n = 11)	Class B (n = 30)	Class C (n = 31)
Improved (%)	2 (18)	11 (37)	20 (65)
Stable (%)	5 (46)	7 (23)	4 (13)
Deteriorated (%)	4 (36)	12 (40)	7 (23)
1-year mortality (%)	1 (9)	6 (20)	4 (13)
Major complications (%)	1 (9)	12 (40)	8 (26)
Mean KPS change (SD)	15 (26)	15 (32)	17 (27)
Median KPS change (range)	0 (10–20)	0 (0–70)	10 (0–60)
Mean KPS improvement (SD)	15 (7)	15 (6)	30 (16)
Median KPS improvement (range)	15 (10–20)	20 (10–50)	20 (10–60)
Correlation analyses—classes			
Factor		p value	
Clinical outcome at 3 months		***0.044***	
Clinical outcome at last FU within first year		***0.038***	
90-days mortality		0.806	
1-year mortality		0.618	
Major complications		0.124	

The bold lines indicate the subheadings and significant p-values

KPS Karnofsky Performance Scale, *SD* standard deviation

[a]Follow-up data not available for all patients

as soon as the PTBE-caused tumor was totally or partially removed, their clinical status improved. This postoperative improvement occurred rather quickly, namely within the first postoperative weeks or months (Fig. 3). Given that there is more room for improvement in patients with poor preoperative KPS than patients with no or only few preoperative symptoms, it is conceivable that even in the case of resection-related focal brain lesions, very old and symptomatic patients with large PTBE volumes are still likely to benefit from surgery. Therefore, even if the tumor infiltrates the edematous brain, the surgical outcome can be beneficial from a patient's perspective.

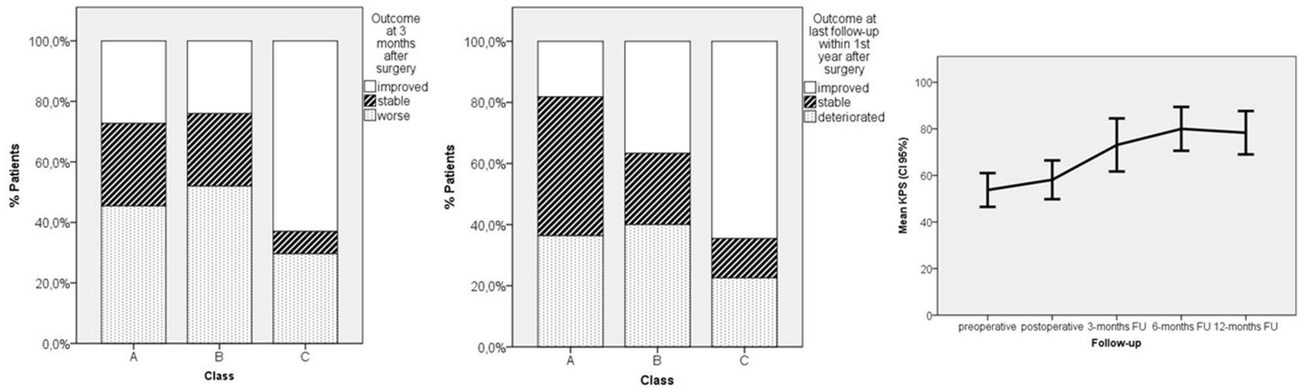

Fig. 3 Class and postoperative outcome

Our simple KPS and PTBE-based classification may help to identify those patients who have the highest likelihood of benefitting from surgery. Previously, the use of the SKALE (Sex, KPS, American Society of Anesthesiology (ASA) Class, Location of Tumor, and Peritumoral Edema) grading system has been suggested to predict surgery-related mortality in very old meningioma patients [7, 12]. The SKALE system includes five independent parameters (Sex, KPS, ASA, Location, Edema), and the total score ranges from 0 to 18 [7, 12]. It has been found that lower SKALE scores were associated with 1-year mortality [7, 12]. The authors concluded that surgery should be deemed reasonable only for old patients (≥ 80 years) with a score of ≥ 8 [12]. Although the SKALE system may appear similar to our proposed classification system, there are several important differences. First, both of the earlier studies used mortality as their outcome measure, whereas we aimed to identify patients with a potential to improve from surgery [7, 12]. When we applied the SKALE system to our patients, only 39 (54%) had a score of ≥ 8. In other words, if the SKALE system had been followed, 33 (46%) of our patients would not have been operated on. Of these 33 patients, eight died, 19 (58%) improved (KPS) and another six (18%) showed an unchanged status during the first postoperative year. Whether these eight deaths could have been avoided by abandoning surgery is debatable, as the natural history of symptomatic meningiomas in this age group is unknown. Also, even though the patients with a SKALE score of < 8 were more likely to die within the first year of surgery (8/33 vs. 3/39, $p = 0.052$, Chi-squared), the accuracy of predicting mortality within the first year after surgery was only 61%, and the SKALE score failed to reliably predict neurological improvement for our patients ($p = 0.478$, Chi-squared). Moreover, the edema assessment of SKALE is based on conventional axial MRI measurements, and does not include volumetric data. In order to more reliably factor PTBE volume in as a parameter for treatment decision-making and risk assessments in meningioma patients, we believe that semi-automatic and fully automatic volume-based assessments may increase the reliability and standardize these measurements. By using neuronavigation software volumetric assessments were easy and feasible. This widely usable approach could help to standardize volume measurements.

Nearly two-thirds of the Class C patients had a functional benefit from surgery. Hence, our decision support tool, which is easy to use and can therefore be effortlessly applied, may help to form a shared treatment decision with the patients and their relatives. For old, symptomatic meningioma patients, it is perhaps more important to estimate the likelihood of benefitting than the likelihood of death, as quality of life and life expectancy in these patients are already compromised. However, our results are preliminary; in order to establish the proposed classification, further retrospective or even prospective studies are required.

Our study has several limitations. First, this type of retrospective study inherently includes a selection bias. Those patients with larger PTBEs and associated symptoms are more likely to be recommended for surgery. Thus, no conclusions with regard to asymptomatic patients may be drawn. In fact, in our series of very old meningioma patients, only five (7%) were asymptomatic prior to surgery. Moreover, unidentified factors may have further contributed to the selection bias. Second, the follow-up was not standardized, as our routine follow-up protocol was not applied as rigorously as usual. However, we were able to collect the outcome data for all patients. As we only evaluated the KPS and mortality, the follow-up data is perhaps sufficient and reliable. Third, postoperative MRI was not available for all patients. Therefore, we could not objectively assess the extent of resection. Based on operation notes, total resection was achieved in 80% of the cases, which equals the MRI findings of those 58% of patients with postoperative MRI. Total resection, however, is not necessarily the primary goal in very old meningioma patients. Similarly, studying meningioma recurrence in this aged patient population may have little relevance. Fourth, due to the cohort size, negative results (i.e. no associations) need to be cautiously interpreted. Fifth, no proper cognitive assessments were done prior to and after surgery, although 40% of patients were operated based on the assumption that the meningioma related to cognitive symptoms. We believe that this is an important aspect to be addressed in future studies, as the factors behind cognitive symptoms in elderly can be diverse. In some cases, a cortical biopsy for dementia in local anesthesia prior to a major surgery could possibly aid in decision-making. Of the 29 patients with suspected meningioma-related cognitive symptoms, twelve (41%) improved in KPS.

Conclusions

Old meningioma patients with large PTBE usually had a poor preoperative performance status, but appeared to benefit most often and most drastically from surgery. Contrary to previous studies, large PTBE volumes were not associated with higher complications rates or mortality [4, 6–8, 10, 12, 14–16]. Thus, even patients with poor performance status could benefit from surgery. We developed a simple, patient-centered decision support tool, which may help to identify patients with the highest potential for postoperative improvement.

Funding Ilari Rautalin received personal research grants from the Maire Taponen Foundation and Uulo Arhio Foundation. The foundations have no personal or institutional financial interests concerning this study.

Compliance with ethical standards

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

Ethics approval The study protocol was approved by the institutional review board.

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