



Post-operative cardiovascular complications and time to recurrence in meningioma patients treated with versus without pre-operative embolization: a retrospective cohort study of 741 patients

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Received: 17 July 2018 / Accepted: 4 September 2018
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Abstract

Purpose Preoperative embolization of radiographically suspected meningiomas is often performed to facilitate tumor resection. Its effects on the subsequent disease course of meningioma patients have not been studied in detail and randomized trials are lacking. The purpose of this study was to explore associations of preoperative meningioma embolization with postoperative outcome.

Patients and methods Patients undergoing resection of an intracranial meningioma at the University Hospital Zurich 2000–2013 (N=741) were reviewed for the inclusion of pre-operative embolization in the management strategy. Annotations included demographics, radiographic, surgical, histological and hematological parameters, cardiovascular risk factors, pre- and postoperative neurological function and gene methylation-based classification. Binary regression and Cox proportional hazards models were applied to determine factors associated with outcome.

Results Pre-operative embolization was performed in 337 patients (42%). Cardiovascular events after surgery comprised mostly deep vein thrombosis (N=39) and pulmonary embolisms (N=64). On multivariate analyses of post-operative cardiovascular adverse events controlling for established risk factors, there were associations with embolization (OR 2.38, 95% CI 1.37–4.00), and with female gender (OR 2.18, 95% CI 1.17–4.08). Recurrence-free survival (RFS) of embolized patients was less favorable among patients with WHO grade II or grade III meningiomas (median RFS: 4.3 vs. 7.0 years, P=0.029) or in patients with intermediate or malignant gene methylation subtype meningiomas (median RFS: 2.0 vs. 8.2 years, P=0.005).

Conclusion Pre-operative meningioma embolization may cause adverse outcomes. Randomized trials to determine benefit-risk ratios are warranted to clarify the role of pre-operative embolization for the treatment of meningioma patients.

Keywords Embolism · Embolization · Meningioma · Post-operative · Recurrence · Thrombosis

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11060-018-2996-0>) contains supplementary material, which is available to authorized users.

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Introduction

Meningiomas are the most common primary intracranial tumors in adults [1]. The World Health Organization (WHO) classification of tumors of the central nervous system assigns grades I–III based on histological criteria [2]. WHO grade I meningiomas are histologically benign and commonly treated with surgery alone, whereas WHO grade II and grade III meningiomas are characterized by microscopic signs of atypia and malignancy, recur frequently and are therefore often treated with post-operative radiotherapy [2–4].

Pre-operative tumor embolization utilizing microparticles is often performed to reduce blood loss during surgery and facilitate resection. Since prospective efficacy studies are lacking, controversy exists as to whether the risk of an additional procedure is justified [5, 6]. Skepticism also arises regarding the frequent observation of cellular atypia and mitotic activity in peri-necrotic areas after embolization, which may mislead neuropathologists to overestimate tumor grade and subsequently provoke unnecessary adjuvant treatment [7, 8].

Meningioma surgery is associated with moderate or severe morbidity in a substantial fraction of patients [9–12]. The risk of post-operative thrombosis and pulmonary embolism after meningioma resection exceeds that of other brain tumors [11–14]. Underlying causes that have been identified include duration of surgery, older age, comorbidities and surgical complications [11, 12], but a potential role of pre-operative tumor embolization has not been studied in detail.

Here we report the post-operative outcomes in a cohort of 741 consecutive meningioma patients according to whether or not they underwent pre-operative embolization. Outcomes were assessed in multivariate models that control for established prognostic factors.

Patients and methods

Subject selection and study design

Supplementary Fig. 1 details the primary analysis population. A total of 779 consecutive patients that underwent neurosurgery for intracranial meningioma at the University Hospital Zurich between 2000 and 2013 were identified by an automated search of the electronic chart system [9] and classified based on whether pre-surgical tumor embolization was performed within 1 month before surgery (group A), or not (group B). Thirty-eight patients were excluded from further analysis because of a time

from embolization of more than 1 month before surgery (N = 9), embolization after surgery (N = 3), or a follow-up time of < 3 months after surgery in the absence of death (N = 26).

Gene methylation classification

For methylation analysis, Illumina 450 k Human BeadChip (Illumina, San Diego, CA) arrays were employed. Samples were assessed within the discovery cohort of the pivotal study defining methylation subgroups [15].

Pre-operative meningioma embolization

Tumor embolization was performed under general anesthesia utilizing a 5F diagnostic catheter (Cook Medical, Bloomington, IN) for access through the right femoral artery by a modified Seldinger technique. Six-vessel angiography was performed prior to the introduction of a microcatheter for superselective angiographic analysis of the blood supply of the meningioma, followed by polyvinyl alcohol particle (PVA)-based embolization with microparticles measuring 45–150 μm in diameter (Embozene® Microspheres; Celonova, San Antonio, TX). PVA injection was ceased when stagnation of blood flow in the terminal segment of respective arteries was achieved and all accessible feeder arteries were embolized. Tumor devascularization was confirmed on magnetic resonance imaging (MRI, Fig. 1a) or computed tomography (CT) within 48 h following the endovascular intervention. Enhanced mitotic activity in embolization-induced peri-necrotic tumor portions was not referenced for histopathological grading (Fig. 1b).

Variables

Clinical data were obtained by review of medical reports. Imaging data were reevaluated with a focus on maximal tumor diameter, hemorrhage and absence or presence of edema. Gross total resection (GTR) was defined as the absence of contrast enhancement on post-operative computed tomography (CT) or MRI scans. For safety analyses of the embolization procedure, events were considered related until surgery or for a maximum of 3 months. Adverse neurological outcome was defined as post-operative new onset of neurological symptoms, or as a worsening of neurological symptoms that persisted at least 3 months after surgery. Adverse cardiovascular outcome was defined as any of the following events within 3 months after surgery: pulmonary embolism, deep vein thrombosis, sinus vein thrombosis, ischemic stroke, myocardial infarction, and cardiovascular death or sudden death of unexplained cause. Time to recurrence was defined as the time to re-intervention, including

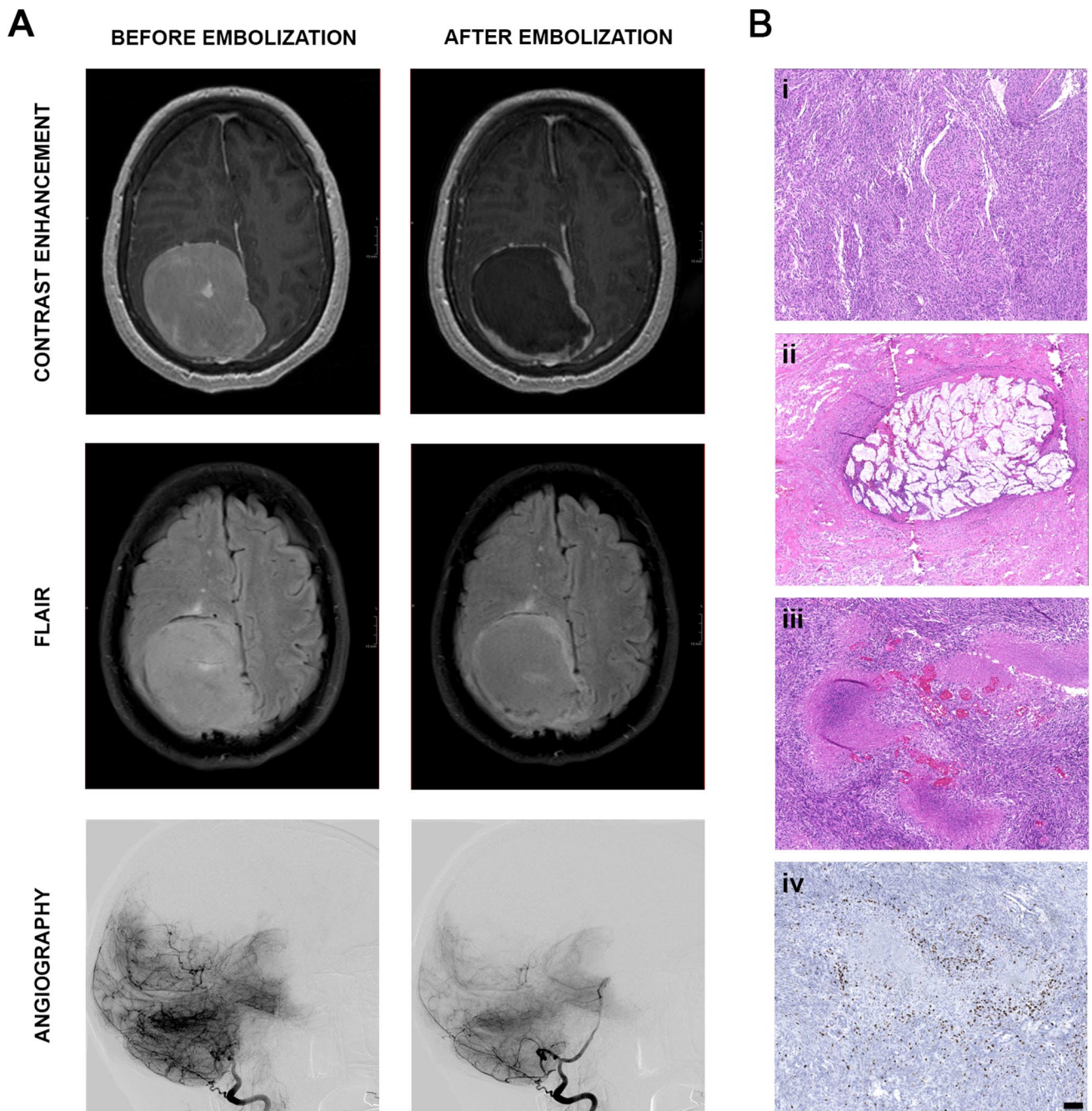


Fig. 1 Imaging and histopathological effects of meningioma embolization. **a** MRI and angiography of the internal carotid artery before and after embolization of a parasagittal meningioma. Contrast enhancement was assessed on T1-weighted sequences. FLAIR, fluid attenuated inversion recovery. **b** Histopathological stainings of (i) a non-embolized portion of a transitional meningioma (WHO grade I,

hematoxylin and eosin stain [H&E]), (ii) embolization material (PVA particles 45–150 μm) in a meningioma feeder artery (H&E), (iii) embolization-induced necrosis and micro-bleeds (H&E) and (iv) perinecrotic proliferation, Ki-67 immunohistochemistry stain. Scale bar: 100 μm

re-resection, radiotherapy or systemic therapies, or death from meningioma progression. Post-operative radiotherapy of residual tumor was not classified as recurrence.

Statistical methods

The Chi Square test was performed for analyses of nominal and ordinal variables and the Mann–Whitney U test was performed for continuous variables. Binary logistic regression

was performed for multivariate testing of factors associated with neurological outcome or cardiovascular complications of meningioma surgery and Cox proportional hazards models were applied to determine factors associated with recurrence-free survival.

Results

Study population

The study population of 779 patients with histologically confirmed intracranial meningioma was previously characterized in the context of post-operative epilepsy risk [9]. Here, only patients with a minimum post-operative follow-up time of at least 3 months were included in analyses of neurological and cardiovascular outcome (N = 741). This population included 337 patients (42.3%) who underwent pre-operative tumor embolization (group A) and 404 patients (57.7%) who did not (group B) (Supplementary Fig. 1). The median time to surgery was 2 days and the vast majority of embolized patients underwent embolization within 1 week prior to surgery (N = 308, 91.4%, Supplementary Fig. 2A). During a median follow-up time of 69 months (95% confidence interval [CI] 64–75), 167 patients (22.5%) experienced progressive or recurrent disease and 124 patients (16.7%) died.

Clinical characteristics of patients with versus without pre-operative tumor embolization

The clinical characteristics of patients in group A versus group B are summarized in Table 1. Age, gender, tumor location and presence of multiple meningiomas were balanced between both groups. Group A contained more WHO grade II or grade III versus grade I tumors, and of the 9 histological WHO grade I variants, only psammomatous meningiomas were less frequent in group A versus group B (1.0% vs. 3.4%, $P=0.042$) (Supplementary Table 1). On imaging scans obtained prior to surgery, meningiomas in group A were larger and more frequently accompanied by peritumoral edema. Within group A, peritumoral edema was detected less frequently after versus before embolization. More detailed analyses of imaging scans in group A versus group B revealed similar rates for hyperostosis, intraosseous growth, extracranial growth or infiltration of venous sinuses in both groups. Yet, group A versus group B was associated with lower rates of calcification (22.3% vs. 32.2%, $P=0.003$) and of radiographic gross total resection (69.1% vs. 80.3%, $P=0.001$), and with higher rates of post-operative brain edema (55.0% vs. 34.8%, $P=0.006$) and intraaxial growth (9.3% vs. 5.5%, $P=0.052$) (Supplementary Table 2). Furthermore, Simpson grade 1 resection was

Table 1 Clinical characteristics of meningioma patients with versus without pre-operative tumor embolization

	Embolization		P
	Yes (group A) N = 337 (42.3%)	No (group B) N = 404 (57.7%)	
Age at diagnosis: years			
Median (years)	57	59	0.99
Range (years)	19–88	18–87	
Gender: N (%)			
Male	103 (30.6)	130 (32.2)	0.64
Female	234 (69.4)	274 (67.8)	
WHO grade: N (%)			
I	258 (76.6)	348 (86.1)	0.001
II	63 (18.7)	51 (12.6)	
III	16 (4.7)	5 (1.2)	
Location ^a : N (%)			
Convexity	64 (19.0)	94 (23.3)	0.16
Parasagittal	64 (19.0)	58 (14.4)	0.087
Skull base	123 (36.6)	126 (31.2)	0.12
Posterior fossa	36 (10.7)	41 (10.1)	0.80
Other	4 (1.2)	16 (4.0)	0.023
Multiple meningiomas: N (%)			
Yes	46 (13.4)	69 (17.1)	0.17
No	291 (86.6)	335 (82.9)	
Maximal diameter: mm			
At embolization ^b : mm			
Median	46	n.a.	0.51 ^g
Range	8–107		
At surgery ^c : mm			
Median	47	31	<0.001
Range	23–90	10–96	
Edema: N (%)			
At embolization ^d			
Yes	169 (78.6)	n.a.	<0.001 ^h
No	46 (21.4)		
At surgery ^e			
Yes	194 (60.1)	147 (43.2)	<0.001
No	129 (39.9)	193 (56.8)	
Duration of surgery ^f : Minutes			
Median	270	210	<0.001
Range	40–810	40–755	
Simpson grade ^g : N (%)			
1	52 (24.8)	84 (35.7)	0.011
2	103 (49.0)	107 (45.5)	
3	18 (8.6)	19 (8.1)	
4	28 (13.3)	24 (10.2)	
5	9 (4.3)	1 (0.4)	
Tumor recurrence during follow-up: N (%)			
Yes	87 (25.8)	80 (19.8)	0.051
No	250 (74.2)	324 (80.2)	

^aN=626, not including patients with multiple meningiomas

^bDocumentation available in N = 215 patients

Table 1 (continued)^cDocumentation available in N = 638 patients^dDocumentation of edema before embolization and before surgery available for comparison in N = 215 patients^eDocumentation available in N = 663 patients^fDocumentation available in N = 445 patients^gDocumentation available in N = 610 patients^hComparison with values in the same patients at surgery

achieved at lower rates in embolized patients, the median operation time was 1 h longer compared to the no embolization group, and embolization was linked to a higher rate of recurrent or progressive tumor growth during follow-up (Table 1), indicating higher surgical complexity of patients selected for preoperative embolization, e.g., due to a smaller fraction of patients with convexity meningiomas and larger tumor size in the embolization group.

Complications from meningioma embolization

Any patients that underwent embolization for a radiographically suspected intracranial meningioma were included in safety analyses of the embolization procedure, regardless of whether surgery was done subsequently (N = 358). Acute potentially life threatening or disabling complications from embolization occurred in 5 patients (1.4%), including stroke (N = 3), intratumoral hemorrhage (N = 1) and serial generalized epileptic seizures (N = 1). Furthermore, two patients suffered mild transient neurological symptoms with gradual onset within 24 h from embolization and good response to anti-edematous therapy, consisting of hemianopia and aphasia, respectively. One patient with Marfan syndrome suffered an aortic dissection 2 months after the embolization. There was no fatal complication.

Neurological outcome after meningioma resection by embolization status

Adverse neurological events within 3 months after surgery were more frequent in group A versus group B (57.0% vs. 44.8%, P = 0.001). Supplementary Table 3 summarize the most common post-operative neurological events by study group. Rates of trigeminal neuralgia, sensorimotor deficits, visual deficits, early symptomatic seizures, neurocognitive deficits, central nervous system (CNS) infections and craniotomy were similar in both groups, but cranial nerve palsy, hydrocephalus and intracranial hemorrhage as well as post-operative new onset epilepsy were more frequent in group (A) Patients with pre-operative epilepsy were balanced between group A versus group B (29.2% vs. 35.0%, P = 0.091); however, a smaller fraction of patients with pre-operative epilepsy became seizure free after surgery in group

Table 2 Cardiovascular risk profile of patients with versus without pre-operative embolization

	Embolization		P
	Yes (group A) N = 337 (42.3%)	No (group B) N = 404 (57.7%)	
Number of cardiovascular risk factors			
0–1	227 (67.4)	275 (68.1)	0.84
> 1	110 (32.6)	129 (31.9)	
Cardiovascular risk factors: N (%)			
Diabetes	31 (9.2)	29 (7.2)	0.32
Arterial hypertension	100 (29.7)	112 (27.7)	0.56
Dyslipidemia	24 (7.1)	35 (8.7)	0.44
Positive family history	71 (21.1)	95 (23.5)	0.43
Smoking	79 (23.4)	102 (25.2)	0.57
Body mass index > 30 kg/m ²	78 (23.1)	79 (19.6)	0.23
Pre-operative cardiovascular events: N (%)			
Yes	24 (7.1)	29 (7.2)	0.98
No	313 (92.9)	375 (92.8)	
Myocardial infarction	7 (2.1)	7 (1.6)	0.56
Stroke	8 (2.4)	12 (2.7)	0.83
Sinus vein thrombosis	0 (0.0)	0 (0.0)	n.a
Pulmonary embolism	6 (1.8)	9 (2.0)	0.86
Deep vein thrombosis	5 (1.5)	9 (2.0)	0.62

A versus group B (51.7% vs. 64.4%, P = 0.048). We have also analyzed residuals of adverse neurological events 1 year post-operatively. Among 686 patients with a follow-up of at least 1 year, 316 (46.1%) were in group A and 370 (53.9%) in group (B) In group A versus group B, 69 (21.8%) versus 67 (18.1%) patients had residuals from adverse neurological events associated with surgery (P = 0.22).

Adverse cardiovascular events after meningioma resection by embolization status

Cardiovascular risk factors were balanced between both groups, including the number of risk factors (P = 0.84) and pre-operative cardiovascular events (P = 0.98, Table 2). Adverse cardiovascular events after surgery were more frequent in group A versus group B (17.5% vs. 8.2%, P < 0.001). Ischemic stroke, myocardial infarction and sinus vein thrombosis occurred at similar rates in both groups, but patients in group A suffered more deep vein thromboses and pulmonary embolisms, and group A was associated with a higher rate of death (Supplementary Table 3). Post-operative hematological parameters did not differ in group A versus group B, except for slightly lower median values for platelet counts (P = 0.002) and hematocrit (P < 0.001) (Supplementary Table 4).

Multivariate and subgroup analyses

We applied a binary logistic regression model controlling for demographics, WHO grade and imaging characteristics to test whether pre-operative tumor embolization is a predictor of cardiovascular outcome (Table 3). Univariate analyses of the association of variables included in this model are summarized in Supplementary Table 5. An association with higher cardiovascular risk was identified for group A (odds ratio [OR] 2.38, 95% CI 1.37–4.00, $P=0.002$) and female gender (OR 2.18, 95% CI 1.17–4.08, $P=0.014$). No association was identified for age, WHO grade, tumor size, presence of multiple meningiomas, radiographic extent of resection or cardiovascular risk factors. Factors that were tested as additional single variables in this model are summarized in Supplementary Table 6: Tumor location at the skull base (OR 2.33, 95% CI 1.40–3.86, $P=0.001$) and adverse neurological outcome (OR 1.75, 95% CI 1.05–2.86, $P=0.032$) were associated with inferior cardiovascular outcome. In reverse, parasagittal tumor location (OR 0.44, 95% CI 0.20–0.98, $P=0.045$) and thrombocyte levels of 220/nl or higher on post-operative blood cell counts (OR 0.55, 95% CI 0.29–1.05, $P=0.069$) correlated with lower cardiovascular risk. No association was identified for the presence or absence of pre-operative neurological deficits ($P=0.43$), pre-operative brain edema ($P=0.93$), post-operative brain edema ($P=0.64$), duration of surgery ($P=0.31$) tumor calcification ($P=0.47$), post-operative epilepsy ($P=0.26$), intraaxial growth ($P=0.37$), or post-operative hematocrit levels ($P=0.40$) (Supplementary Table 6). Group A was associated with inferior cardiovascular outcome in most subgroups, but not in male patients, patients with multiple meningiomas or patients with posterior fossa meningiomas

Table 3 Multivariate analyses of predictors for adverse cardiovascular outcome after meningioma resection

Multivariate model	Cardiovascular events	
	Odds ratio and 95% CI	P
Group A versus group B	2.38 (1.37–4.00)	0.002
Cardiovascular risk factors: 0–1 versus 2+	0.68 (0.41–1.13)	0.14
Demographics		
Age: 18–54 versus 55+	0.76 (0.46–1.27)	0.29
Gender: female versus male	2.18 (1.17–4.08)	0.014
WHO grade: I versus II/III	1.22 (0.61–2.43)	0.58
Imaging characteristics		
Max diameter: 40+ versus <40	1.05 (0.63–1.78)	0.84
Multiple meningiomas: yes versus no	1.11 (0.56–2.19)	0.77
Radiographic extent of resection: gross total versus incomplete	0.84 (0.48–1.47)	0.34

N = 612 patients with complete datasets were included

(Supplementary Fig. 3). Among embolized patients, a time to surgery of 1 week or less versus longer intervals were not associated with cardiovascular outcome (OR 0.61, 95% CI 0.23–1.63, $P=0.32$), and applying receiver operator characteristics (ROC) curve analyses to cardiovascular outcome identified no predictive cut-off for the time interval between embolization and surgery (sensitivity 58%, specificity 46%, Supplementary Fig. 2B).

Similar analyses evaluating risk factors for adverse neurological outcome 3 months after surgery were also performed and similarly identified associations with embolization (OR 1.85, 95% CI 1.30–2.63, $P=0.001$), whereas radiographic gross total resection was associated with better neurological outcome (OR 0.59, 95% CI 0.39–0.87, $P=0.006$), with no significant interaction between both predictors ($P=0.17$). Further details are summarized in Supplementary Tables 7 and 8, and Supplementary Fig. 3.

Recurrence-free survival by embolization status

Tumor recurrence during the entire follow-up period was documented in 167 patients, including 87 of 337 patients (25.8%) in group A and 80 of 404 patients (19.8%) in group B ($P=0.052$). The median recurrence-free survival (RFS) was 12 years in patients with embolization and not reached in patients without embolization ($P=0.043$). Multivariate analyses applying a Cox proportional hazards model of shorter RFS that controlled for the established prognostic factors outlined in Table 3 rendered WHO grade II or grade III versus grade I the strongest factor associated with shorter RFS (HR 3.83, 95% CI 2.30–6.37, $P<0.001$). Therefore, we also performed analyses segregated by WHO grade.

The RFS in group A versus group B did not differ in patients with WHO grade I meningiomas ($P=0.89$, Fig. 2a). Among patients with WHO grade II or grade III meningiomas, the RFS was 4.3 years in group A versus 7.0 years in group B ($P=0.029$, Fig. 2b) and outcome with respect to RFS was less favorable in group A versus group B in a similar Cox model (HR 1.92, 95% CI 0.97–3.79, $P=0.062$).

Molecular tumor characteristics may predict the clinical course more accurately than histology alone, and such approaches to re-classify meningiomas include genome-wide methylation signatures that are more closely associated with recurrence than histological WHO grading [15]. Gene methylation-based classification of prognostic molecular subtypes was available from 81 patients, including 41 patients assigned to the benign subtype and 40 patients with an intermediate ($N=35$) or malignant ($N=5$) gene methylation pattern. Paralleling the prognostic role of WHO grading, an intermediate or malignant versus benign gene methylation pattern was the strongest factor associated with shorter time to re-intervention when replacing WHO grade in the Cox model utilizing the variables outlined in Table 3

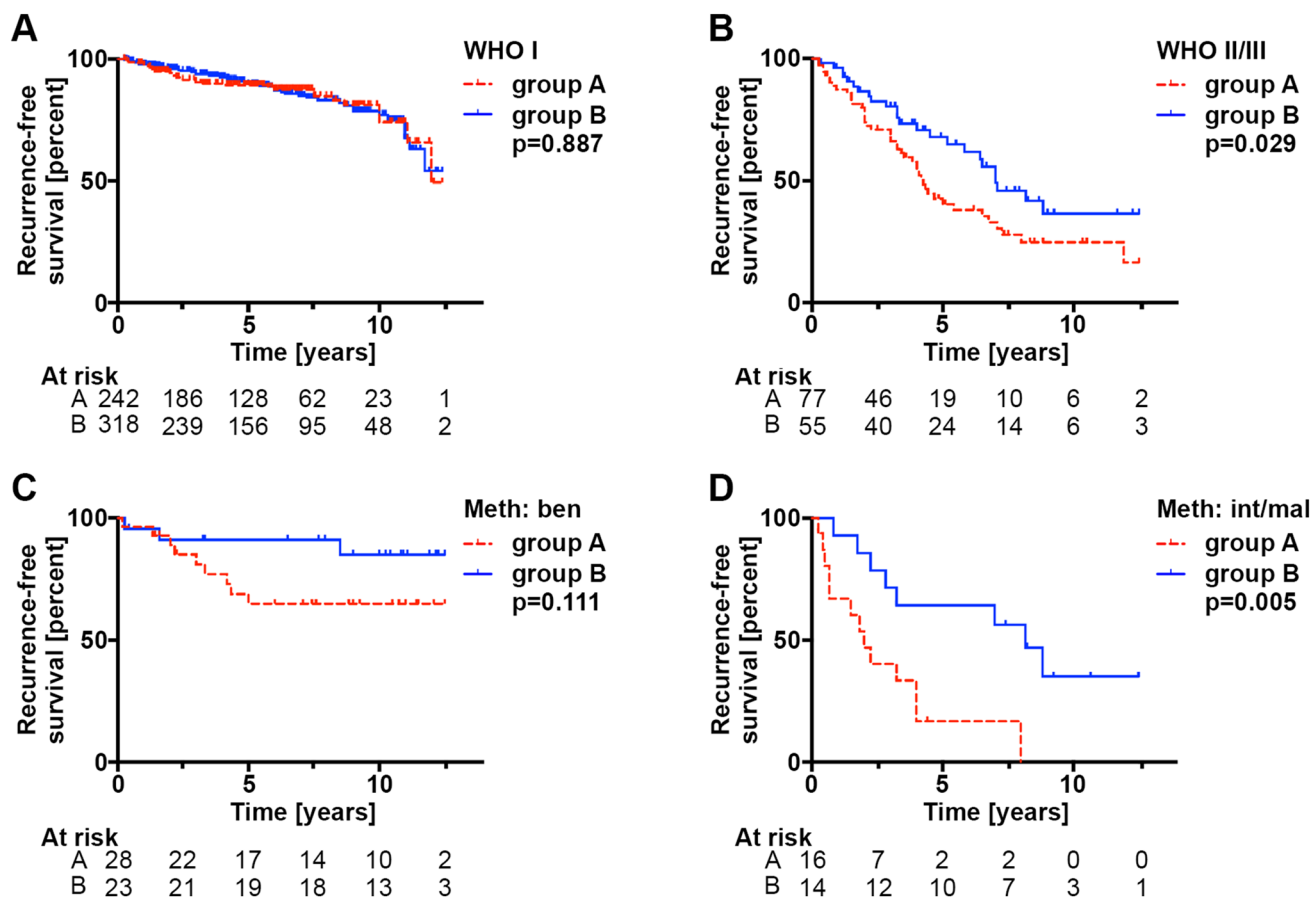


Fig. 2 Recurrence-free survival in patients with pre-operative embolization (group A) versus without embolization (group B). **a** WHO grade I (N=606); **b** WHO grade II (N=114) or grade III (N=21);

c benign (ben) gene methylation subtype (N=41); **d** intermediate (N=36) or malignant (N=5) gene methylation subtype. The log rank test was applied to assess differences in time to re-intervention

(HR 8.66, 95% CI 3.00–25.05, $P < 0.001$). The RFS in group A versus group B did not differ in patients with benign subtype meningiomas ($P = 0.11$, Fig. 2c). Among patients with intermediate or malignant subtype meningiomas, the time to re-intervention was 2.0 years in group A versus 8.2 years in group B ($P = 0.005$, Fig. 2d) and outcome was less favorable in group A versus group B in a similar Cox model (HR 4.08, 95% CI 0.91–18.21, $P = 0.066$).

Discussion

Here we have analyzed the post-operative outcomes of 741 consecutive patients with histologically diagnosed meningioma, including 337 patients that underwent pre-operative tumor embolization versus 404 patients who did not undergo embolization. Moreover, molecular meningioma subtypes with better prognostic accuracy compared to histological WHO grading [15] were defined by genome-wide methylation arrays in 81 patients.

Outcome parameters after surgery included the likelihood of adverse cardiovascular events within 3 months, persistence of neurological deficits with peri-operative new onset at 3 months and at 1 year after surgery, and recurrence-free survival as defined by the time to re-intervention or tumor-related death as a clinically relevant indicator. Multivariate analyses controlling for established prognosticators of outcome after meningioma surgery identified pre-operative embolization as an important risk factor for post-operative cardiovascular adverse events. Embolization was also associated with a higher rate of neurological adverse events after surgery, but no difference in the rate of neurological deficits 1 year after surgery. Recurrence-free survival was less favorable with embolization in patients with WHO grade II or grade III meningiomas, and with intermediate or malignant gene methylation patterns, but not in patients with WHO grade I or benign methylation subtype meningiomas.

Prospective studies of the effects of embolization in meningioma patients are scarce [16] and mostly restricted to small series without comparator groups [5]. Previous reports of retrospective cohorts focused on intraoperative blood loss,

complication rates and comparison of these parameters with the use of different embolization materials [17–22]. Reports on associations of embolization with post-operative neurological outcomes are limited, with associations of embolization with cardiovascular adverse events or tumor recurrence not previously reported. To date, two recent studies explored associations of post-operative cardiovascular risk in meningioma patients [11, 12]. In contrast to these studies, we did not detect associations of duration of surgery, older age and comorbidities with cardiovascular risk on multivariate analyses. Similar to previous reports, adverse neurological outcome was associated with cardiovascular risk and there was a previously not reported strong association of female gender.

In our cohort, procedure-related complications from embolization occurred at low rates compared to previous studies [23], indicating a high level of experience of the interventional neuroradiologists. The use of PVA for embolization in all patients of our cohort and uniform standards of post-operative prophylaxis of thromboembolism [24] may have prevented confounding of the data by heterogeneous algorithms of care.

Limitations of our study include the retrospective design and imbalances of key prognostic factors, albeit these were not prognostic on multivariate and subgroup analyses. The lack of an independent neuropathology review furthermore retains the possibility that the larger fraction of WHO grade II and grade III meningiomas among embolized patients were caused by misinterpretation of histological changes induced by the embolization procedure [7, 8]. Yet, the shorter RFS with embolization among patients with WHO grade II or grade III meningiomas was confirmed utilizing an observer-independent molecular classification approach [15], which was more powerful in detecting survival differences than histological classification.

Reasons for the shorter RFS with embolization are elusive, but the induction of mitotic activity that is commonly observed around necrotic tumor fractions after embolization may have contributed to accelerated tumor growth. Furthermore, larger tumor size and edema on pre-operative imaging scans were associated with the decision to perform embolization. These indicators of less favorable disease courses and of more challenging surgery were reflected by a longer duration of surgery and have likely contributed to the higher rate of neurological deficits and shorter RFS in embolized patients, albeit embolization was identified as the most relevant prognostic factor on multivariate models of neurological outcome and RFS. Moreover, the extent of devascularization achieved, or changes on diffusion weighted images are additional factors that may have been associated with outcome, but such data were not available. Compared to clinical practice in most centers, the rate of embolization in our cohort was relatively high, thus potentially limiting the

generalizability of our results. The high rate of embolization results from Zurich being a referral center over many years and potentially a bias towards offering this intervention to patients rather frequently. There certainly was a belief in benefit from embolization because of reducing bleeding risk.

The reasons for the higher rate of cardiovascular events remain elusive. In consideration of the lack of an association with the cardiovascular risk profile of patients or with hematological parameters, we speculate that systemic factors released from necrotic tissue after embolization may have contributed to higher rates of thromboembolism in patients undergoing meningioma embolization. However, other factors that have not been assessed may have confounded our analyses, including steroid use or immobilization time after surgery.

In conclusion, the adverse outcomes with embolization reported here emphasize the necessity of randomized trials to determine when the benefit outweighs the risk of pre-operative meningioma embolization and which patients may potentially benefit. Future prospective studies should include standardized assessments of the extent of devascularization and other clinically relevant outcome parameters beyond estimated blood loss, such as health-related quality of life, disability scores and neurological functioning.

Funding There was no funding for this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the regional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. IRB No.: KEK-ZH-2014-0087.

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