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Original Article

Clinicopathologic Factors Associated with Tumor Necrosis after Preoperative Embolization of Meningiomas

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Objective: Preoperative embolization of meningiomas induces necrosis prior to surgery and facilitates resection. Lack of contrast enhancement on postembolization MRI correlates with pathological findings of necrosis and can be used to assess embolization efficacy. This study aimed to examine clinicopathologic factors associated with tumor necrosis after embolization.

Methods: A total of 119 patients with intracranial meningioma who underwent 145 surgical resections between 2010 and 2019 at our institute were reviewed. Inclusion criteria for the study were preoperative embolization with trisacryl gelatin microspheres (Embosphere) or absorbable gelatine sponge (Gelfoam). Postembolization Gd-enhanced T1-weighted and angiographic imaging, and histopathologic examination results were reviewed to evaluate the effectiveness of embolization.

Results: In all, 66 patients satisfied the inclusion criteria. In total, 36 patients were embolized with Embosphere and 30 patients were embolized with Gelfoam. Patients embolized with Embosphere had a significantly higher necrosis rate (NR) than patients with Gelfoam (21% vs. 7.1%, $P < 0.01$). The 36 Embosphere patients were analyzed regarding clinicopathologic factors associated with NR. Tumors in 12 patients were located in the parasagittal/falx region; these patients had a significantly lower NR compared with tumors in other locations (10.6% vs. 26.2%, $P = 0.016$). In all, 13 patients had feeders arising from only the middle meningeal artery (MMA), which was associated with a significantly higher NR (29.3% vs. 14.4%, $P = 0.015$). In total, 11 patients had meningeal feeders arising from internal carotid artery (ICA), which was associated with a significantly lower NR (9.0% vs. 26.3%, $P < 0.01$).

Conclusion: This study showed embolization agent, tumor location, and blood supply were important factors predicting necrosis after preoperative embolization.

Keywords: preoperative embolization, meningioma, embosphere, tumor necrosis, necrosis rate

Introduction

Meningiomas are highly vascularized tumors that arise from leptomeninges. When symptomatic, they are typically treated with surgical resection, which has morbidity and mortality rates of 30% and 4%, respectively.[1] Preoperative embolization of meningiomas was initially described by Manelfe et al.[2] in 1973. More recently, it has been proposed as an adjunct treatment to reduce intraoperative complications, decrease surgical time, and increase the ability to obtain a total resection, as embolization may reduce intraoperative blood loss and cause softening of the tumor tissue.[3,4] However, its advantages and indications still remain unclear.

Although there is no consensus on how to measure the efficacy of embolization, previous studies have frequently used operative duration, estimated blood loss (EBL), Simpson grade, prognosis, hardness of tumors.[5–7] In addition, studies have found that lack of contrast enhancement on postembolization MRI correlates with pathological findings of necrosis and can be used to assess efficacy[5,8]; however, few studies have focused on the factors influence necrosis after preoperative embolization. Therefore, this

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study aimed to examine clinicopathologic factors associated with tumor necrosis in embolized meningiomas.

Materials and Methods

Patient selection

We retrospectively reviewed 119 patients who underwent 145 intracranial meningioma surgical resections at the Kagawa University Faculty of Medicine from January 2010 to March 2019. Among these, 97 received preoperative embolization, based on a multidisciplinary risk–benefit assessment. Patients with imaging characteristics indicative of hypervascularization and who were expected to be able to embolize safely were generally selected for preoperative embolization. This study included only those who underwent preoperative embolization with 300–500 µm trisacryl gelatin microspheres (Embosphere, Nippon Kayaku, Tokyo, Japan) or an absorbable gelatine sponge (Gelfoam, Pfizer, New York, NY, USA). Feeders originating from the external carotid artery were embolized with them as a first choice. Feeder originating from internal carotid artery (ICA) circulation were embolized with n-butyl cyanoacrylate (n-BCA). Platinum coils for feeder occlusion were selected when we could not utilize enough catheter or there was a risk of using other materials. Patients embolized with n-BCA or coils and those with inadequate data were excluded. Finally, 66 patients were included for analysis. Image-guided navigation was performed in selected patients using preoperative MRI that included Gd-enhanced T1-weighted images.

This study was conducted in accordance with the principles of Declaration of Helsinki and approved by the institutional review board of the Kagawa University Faculty of Medicine (approval number 2019-078). The requirement for informed consent was waived for this study as all patient identifiers were removed and the data were collected retrospectively.

Image analysis

Before procedures, CT, MRI, and angiography were performed in all patients. Tumor location was categorized as follows: skull base (sphenoid ridge, petrous, middle fossa, and planum sphenoidale), convexity, parasagittal/falx. Vascularization of the meningioma was assessed by angiography of the internal and external carotid arteries and vertebral artery. Tumoral blood supply was categorized as follows: simple feeder, tumor staining at middle meningeal artery (MMA) only; and complex feeder, tumor staining at several branches of external carotid artery or ICA. ICA feeders were classified as pial artery or meningeal branch of the ICA such as the meningohypophyseal trunk, inferolateral trunk, or ophthalmic artery. Postembolization total angiographic occlusion was defined as complete lack of contrast opacification of the tumor blush. As a measure of embolization effectiveness, necrosis rate (NR) of the tumor was defined as the percent reduction in the enhanced tumor volume on postembolization navigation MRI (2D, spin echo, TE = 12, TR = 400 ms, FOV 23 cm, Slice Thickness = 3 mm, interleaved, Image Matrix = 256 × 154, NEX = 1). Pre-embolization tumor volume was calculated by subtracting the uncontrasted volume (such as cyst) from the total tumor volume. We computed the volumetric measurements of tumor volume or necrosis using the StealthStation Surgical Navigation System (Medtronic, Minneapolis, Minnesota, USA).

Embolization technique

Preoperative embolization procedures were performed using high-resolution biplane digital subtraction angiography (Allura Xper FD20/20; Philips, Amsterdam, Netherlands). Patients were given local anesthesia for insertion of a right femoral 5F sheath. A bolus of heparin was administered after sheath placement. Then, a 5F guiding catheter was advanced to the origin of external carotid artery. The feeding vessel to the tumor was identified and then catheterized using a coaxial microcatheter–microguide wire combination. The microcatheter was positioned as close as possible to the tumor. Superselective angiography was performed to ensure no dangerous anastomoses; if present, coil placement was considered to avoid inadvertent embolization of normal vessels. Gelfoam was the main embolic agent used before March 2015; 300–500 µm Embosphere was mainly used thereafter. Embosphere was diluted 1:2 or 1:4 with contrast medium and normal saline. Gelfoam was manually cut into small pieces and diluted with contrast medium and normal saline. To avoid reflux during slow injection of embolic agent, embolization was performed using a blank roadmap. Embolization was ceased once contrast stasis or a small amount of reflux was observed. The tumor feeder was proximally occluded with pushable platinum coils. Finally, angiography of external carotid artery and ICA was performed to assess the postembolization result. Procedure-related complication was defined as any abnormal radiological finding or neurological deficit during or after embolization.

Table 1 Patient clinicopathological characteristics

	Total n = 66	Embosphere n = 36	Gelfoam n = 30	P value
Age (years)	65 ± 15	65 ± 15	66 ± 15	0.85
Sex (women/men)	43/ 23	27/9	16/14	<0.01
Location				
Skull base	18 (27%)	5 (14%)	13 (43%)	<0.01
Convexity	32 (48%)	19 (53%)	13 (43%)	
Parasagittal/falx	16 (24%)	12 (33%)	4 (13%)	
Tumor volume (cm^3)	35 ± 28	38 ± 32	31 ± 23	0.34
Total angiographical occlusion	31 (47%)	18 (50%)	13 (43%)	0.16
Interval between embolization and MRI	3 days	3 days	3 days	
Cases with absence of necrosis	20 (30%)	5 (14%)	15 (50%)	<0.01
NR	15 ± 18%	21%	7%	<0.01
NR in convexity meningiomas	19% (n = 32)	28% (n = 19)	7% (n = 13)	<0.01

NR: necrosis rate

Surgical resection

Surgical resection was performed within 7 days after embolization unless embolization complication arose. Perioperative data and pathologic features were recorded including EBL, World Health Organization (WHO) grade and Ki67-labeling index.

Statistical methods

Statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Univariate analysis was conducted using the Mann–Whitney U test or chi-square test for parametric data; non-parametric data were compared using the Kruskal–Wallis test. Spearman's correlation coefficient was used to assess association between variables. P <0.05 was considered significant.

Results

Patient clinicopathologic characteristics

The baseline characteristics of 66 study patients are shown in **Table 1**. Mean patient age was 65 ± 15 years. The most common tumor location was convexity (n = 32), followed by skull base (n = 18) and parasagittal/falx (n = 16). In all, 36 patients were embolized with Embosphere and 30 with Gelfoam (**Table 1**). The Embosphere and Gelfoam groups significantly differed with respect to sex and tumor location. The proportion of patients with absence of necrosis was significantly higher in the Gelfoam group than the Embosphere group (50% vs. 14%, P <0.01). NR was 21% in the Embosphere group, 7.1% in the Gelfoam group; this difference was significant (P <0.01). NR in convexity meningiomas was significantly higher in the Embosphere group than the Gelfoam group (28% vs. 7%, P <0.01).

Embosphere group subanalysis

The Embosphere group comprised of 36 patients, 27 women and nine men with a mean age of 65 ± 15 years. Mean NR was 21.4 ± 19.6%. Radiographic, angiographic, and surgicopathologic factors that were assumed to be potentially involved in NR were examined in 36 patients. **Table 2** shows the radiographic factors associated with necrosis in the Embosphere group. Tumor location was skull base in five patients, convexity in 19 patients and parasagittal/falx in 12 patients. There was significant difference in NR between three locations (P = 0.038). Parasagittal/falx had a significantly lower NR compared with tumors in other locations (10.6% vs. 26.8%, P = 0.014). Mean tumor volume was 38 ± 32 cm^3, which also was not associated with NR (r = 0.06). Patients with tumor volume >30 cm^3 (18 patients) and those with tumor volume <30 cm^3 (18 patients) had similar NR (23.2% and 18.9%, respectively; P = 0.62).

Table 3 shows the angiographic factors associated with necrosis in the Embosphere group. Tumor vascularity was grade 1 in 13 patients, grade 2 in 18 patients, and grade 3 in 5 patients; NR did not significantly differ between grades. The tumor-feeder were the ipsilateral MMA (n = 30), bilateral MMA (n = 6), meningeal branch of the ICA (n = 11), pial artery (n = 8), superficial temporal artery (n = 7), occipital artery (n = 3), deep temporal artery (n = 3), and accessory meningeal artery (n = 2). In all, 13 patients

Table 2 Radiographic factors associated with necrosis in the Embosphere group

		Number of cases	NR		P value
			Average (%)	Stdev. (%)	
		n = 36	21	19.6	
Location	Skull base	5	19.8	18.1	0.038
	Convexity	19	27.9	21	
	Parasagittal/falx	12	10.6	13.1	
Tumor volume	Average = 37.8 ± 32.3 cm^3				
	<30 cm^3	18	18.9	19.3	0.62
	>30 cm^3	18	23.2	20.1	

NR: necrosis rate; +: yes; –: no

had simple feeder; these patients had a significantly higher NR than the 23 patients with complex feeders (30.9% vs. 16%, P = 0.015). Patients with feeders from the meningeal branch of the ICA had a significantly lower NR than those who did not (9.2% vs. 26.7%, P <0.01). The presence of pial feeders did not affect NR (19.5% vs. 21.5%, P = 0.66).

Angiographic characteristics of convexity and parasagittal/falx meningiomas were analyzed. Patients of parasagittal/falx meningiomas were less simple MMA than convexity meningiomas (25% vs. 58%, P < 0.01). Parasagittal/falx meningiomas had more meningeal branch of the ICA than convexity meningiomas (42% vs. 16%, P <0.01).

Table 3 additionally shows the angiographic and post-embolization factors associated with necrosis in the Embosphere group. The target vessels embolized were the ipsilateral MMA (n = 31), bilateral MMAs (n = 4), deep temporal artery (n = 2), superficial temporal artery (n = 2), accessory meningeal artery (n = 2), and occipital artery (n = 1). The average volume of Embosphere delivered was 6.68 mL; this was not associated with NR (r = 0.27). Complete angiographical occlusion of feeding vessels was achieved in 18 patients and associated with significantly higher NR (31% vs. 11.1%, P <0.01). Tumor location with complete angiographic occlusion was 4 falx/parasagittal and 13 convexity; vascularization was simple MMA in 13 and only 1 from the ICA. These characteristics might influence NR.

After embolization, the body temperature of 14 patients increased by ≥1°C; this was associated with higher NR (27.7% vs. 16.8%, P = 0.036). The median interval from embolization to MRI and resection was 3 days and 4 days, respectively.

Table 4 shows the surgicopathologic factors associated with necrosis in the Embosphere group. Average EBL was 453 mL and not associated with NR (r ≤0.01). Patients with EBL <300 mL had an insignificantly higher NR (26.3% vs 16.6%, P = 0.15). Total resection was achieved in 13 patients; these patients had a significantly higher NR than patients with subtotal resection (31.1% vs. 15.3%, p = 0.03). The number of patients with WHO 1 and 2 grade tumors was 13 and 23, respectively; no significant difference in NR was found between grades (22.1% vs. 19.5%, P = 0.66). Median Ki-67 index was 5 and not associated with NR (r = 0.12).

Complication

No postprocedural hemorrhage or cranial nerve palsies occurred. Only one patient in Embosphere group experienced worsening of symptoms after embolization (**Fig. 1**).

Discussion

Effectiveness of embolization

The efficacy of preoperative embolization has been analyzed by numerous investigators.[1,5,8–11] There are no definite procedural indications because its benefits remain unclear. Occlusion of tumor arteries not anatomically accessible during the surgical approach is one theoretical advantage. Another is induction intratumor necrosis, which may result in tumor softening, aiding resection, and decreasing the need for brain retraction.[12] This study aimed to examine the clinicopathologic factors that affect tumor necrosis. NR was calculated and used as an index to estimate the degree of necrosis.

Review articles

Only four previous studies have assessed NR after preoperative embolization.[5,9,10,13] These utilized an MRI-based

Table 3 Angiographic and post-embolization factors associated with necrosis in the Embosphere group

		Number of cases	NR		P value
			Average (%)	Stdev. (%)	
		n = 36	21	19.6	
Simple MMA	+	13	29.3	20.1	0.015
	–	23	14.4	16.7	
Meningeal branch of the ICA	+	11	9	12.9	<0.01
	–	25	26.3	19.8	
Pial feeder	+	8	19.5	20.1	0.66
	–	28	21.5	19.7	
Amount of Embosphere	Average = 6.68 mL				
	≤5 mL	18	17.4	17	0.27
	>5 mL	18	24.7	21.7	
Result of embolization	Partial	18	11.1	15.8	<0.01
	Total	18	31	18.1	
Increase in body temperature	+	14	27.7	18.2	0.036
	–	22	16.8	19.6	

ICA: internal carotid artery; MMA: middle meningeal artery; NR: necrosis rate; +: yes; –: no

Table 4 Surgicopathologic factors associated with necrosis in the Embosphere group

		Number of cases	NR		P value
			Average (%)	Stdev (%)	
		n = 36	21	19.6	
EBL	Average = 453 mL				
	<300 mL	19	26.3	21.2	0.15
	>300 mL	17	16.6	16.9	
WHO grade	1	13	22.1	16.2	0.28
	2	23	19.5	24	
Ki-67 index	Median = 5				
	≤5	20	17.9	16.3	0.53
	<5	16	25	22.9	
Result of resection	Partial	23	15.3	16.3	0.03
	Total	13	31.1	21.4	

EBL: estimated blood loss; NR: necrosis rate; WHO: World Health Organization

method to compare volume of non-enhancing tumor regions before and after embolization. In a prospective study, Bendszus et al.[9] concluded that embolization only had an effect on EBL in patients with complete tumor devascularization, defined as >90% reduction in NR, and that preoperative tumor embolization was of limited value with respect to effect on clinical outcome or EBL compared with surgical therapy alone. In contrast, a retrospective study by Ali et al.[5] concluded that greater extent of embolization as quantified by NR resulted in decreased EBL and improved postsurgical outcome. Catapano et al.[13] concluded that NR was a better predictor of EBL.[13] Jo et al.[10] examined skull base meningiomas only; they found ICA feeding vessels were associated with ineffective embolization and effective embolization (NR >75%) was associated with low EBL.

Embolic agent

Microspheres, including trisacryl gelatin microspheres (Embosphere), are a recently introduced embolization agent that has several advantages: consistent shape and size and compressibility, which helps to prevent the catheter blockage.[12,13] In this study, although the rate of total angiographic occlusion was almost the same between Embosphere and Gelfoam groups, the NR was significantly higher in the Embosphere group than the Gelfoam group. This shows that Embospheres more easily penetrate in the tumor. It is considered that characteristics such as

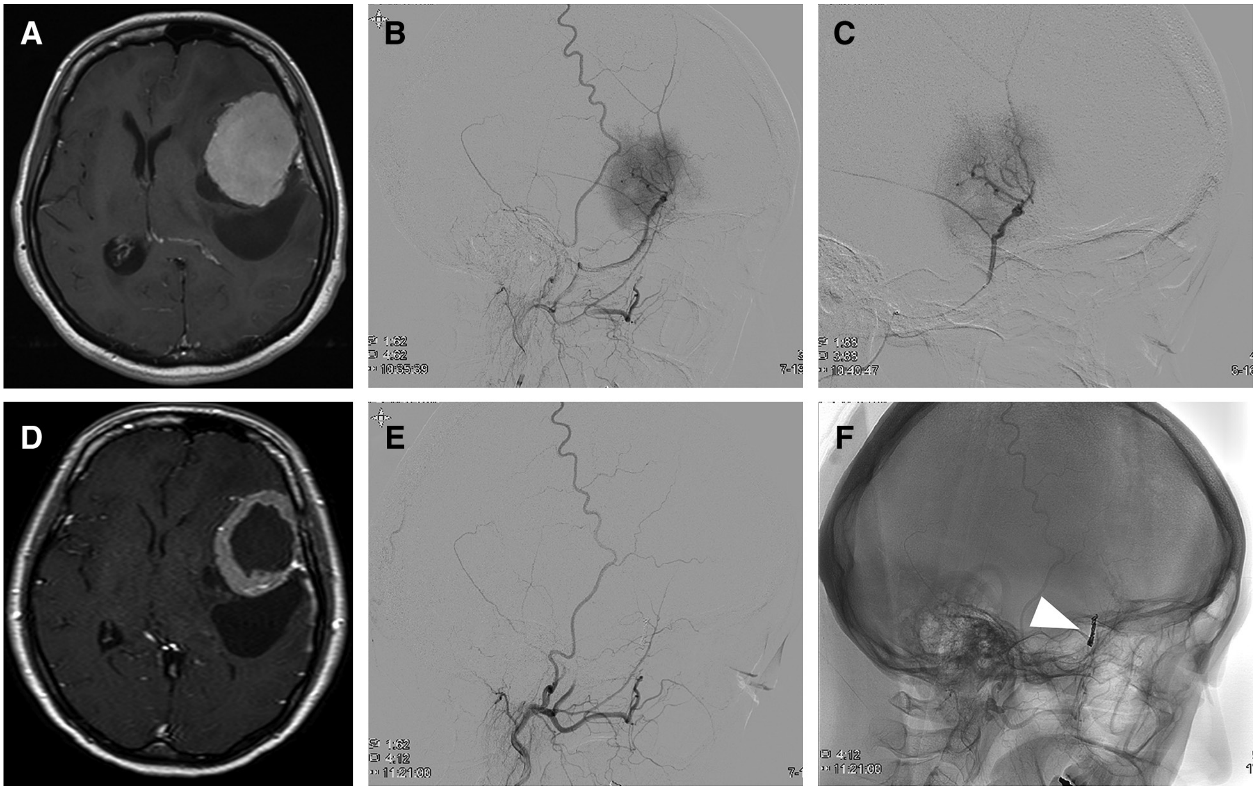

Fig. 1 A 41-year-old woman with sphenoid ridge meningioma: (**A**) Pre-embolization gadolinium enhanced T1-weighted image. (**B**) Lateral view of left external carotid artery angiography. The sole feeding artery was middle MMA. (**C**) Superselective MMA angiography and embolization with Embosphere (NR was 42%). (**D**) Postembolization gadolinium enhanced T1-weighted image. (**E**) Postembolization external carotid artery angiography showing complete occlusion (**F**) Lateral view shows proximal occlusion of the MMA by pushable coils (white arrowhead). MMA: middle meningeal artery; NR: necrosis rate

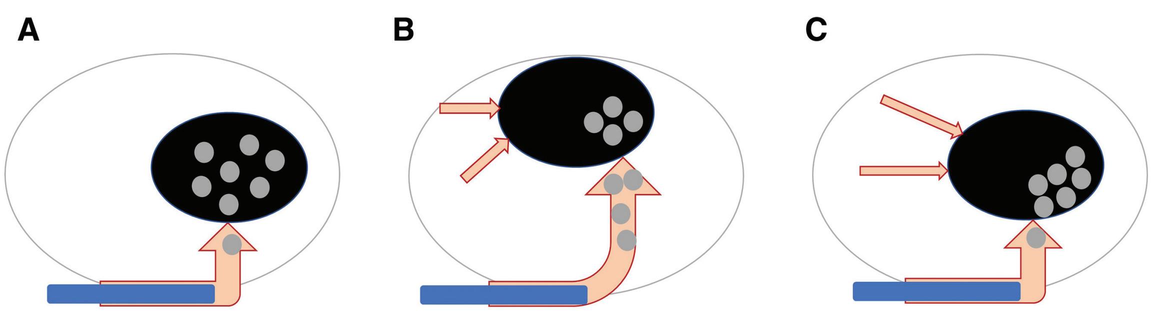

Fig. 2 Illustrative meningioma model: (**A**) Convexity meningioma with simple feeder artery. Microsphere penetration throughout the entire tumor is easily achieved. (**B**) Parasagittal/falx meningioma. Most tumors have complex feeder supply and microcatheter is positioned distant from the tumor. Microsphere penetration into the tumor is poor. (**C**) Meningioma with meningeal feeders from the ICA. Complex feeder supply to the tumor results in poor penetration of microspheres. ICA: internal carotid artery

consistent shape and size and compressibility of Embosphere have a significant effect on NR.

Smaller embolization particles are associated with a higher rate of postembolization tumor necrosis; however, they have an increased risk for intratumoral hemorrhage or advancement into small vessels supplying cranial nerves.[11,14] We therefore did not use 100–300 µm Embosphere or other small-sized agents. Ali et al. used microsphere and polyvinyl alcohol particles (100–300 µm and 300–500 µm, respectively) and found a mean 25% NR that was similar to ours (21%).[5] We therefore conclude that 300–500 µm Embosphere is safe and effective.

In selecting an embolic agent, the pros of preoperative embolization have to be carefully weighed against the cons of an additional intervention, with its inherent risks and potential complications such as stroke. If we expect large necrosis after embolization, it may be good choice to use Embosphere positively; however, if necrosis is not expected, we should aim only proximal occlusion of tumor arteries.

Tumor location

Patients with Parasagittal/falx meningiomas had a significantly lower NR than the other locations. Parasagittal/falx meningiomas typically have more complex feeders than convexity meningiomas. Furthermore, it is difficult to get a microcatheter close enough to the tumor in parasagittal/falx meningioma patients. These factors are presumed to be the cause of the low NR (**Fig. 2B**). The use of lower profile microcatheters may be a solution: they are able to be advanced closer to the tumor. On the other hand, patients of convexity meningioma with only simple feeders are more likely to result in necrosis (**Fig. 2A**).

Feeding artery

Meningiomas are commonly supplied by external carotid artery branches, which are easily accessible by selective microcatheterization.[15] ICA branches and pial feeders supplying the tumor may also be embolized, although these vessels are typically more difficult to access and their embolization is associated with complications.[16–18] In this study, patients with a tumor able to be embolized via a MMA feeder alone had a higher NR; tumors with meningeal branch of the ICA had lower NRs, respectively. Jo et al.[10] also concluded that ICA feeding vessels including pial and meningeal vessels were associated with ineffective embolization. These data suggest that embolization of tumors with complex feeders arising from the ICA may not be worth the risk with embolization (**Fig. 2C**).

After embolization, patients with a postembolization increase in body temperature >1°C showed a high NR. Fever is an indicator of necrosis and common after embolization; it is caused by an inflammatory response to the necrotic or ischemic tumor tissue.[19–21]

Surgical resection

In this study, NR was not significantly associated with intraoperative EBL. We conclude that EBL was possibly related to other tumor characteristics and the craniotomy itself, in agreement with a previous report.[22] However, we showed that higher NR was associated with easier tumor removal and higher rate of complete resection.

In the present study, there was a higher percentage of WHO grade 2 patients compared to natural history. The histopathologic findings of necrosis, commonly found in meningiomas that have been embolized, may be confused with more aggressive and higher-grade lesions.[23] Postembolization changes may have affected the pathological findings in this study. Recently, it is our policy not to take necrosis findings into account in the WHO grade when performing embolization.

Limitation

The main limitations of this study are its small sample size and single-center retrospective design. In addition, the study was not standardized or randomized. Patient selection for embolization was based on surgeon’s preference; and there were no specific criteria. Gerfoam and Embosphere groups were not randomized but were separated by time. Embolization procedures were performed by multiple neurointerventionalists; therefore, there were some biases, such as the surgeon’s skill and experience. There are confounding factors associated with NR. Future studies using quantitative analyses could provide more detailed information.

Conclusions

Embolization with Embospheres (300–500 µm) is effective and safe prior to meningioma resection. Tumor location and feeding artery predict intratumoral necrosis after embolization. Parasagittal/falx location and meningeal feeder from the ICA are significant negative predictive factors of tumor necrosis. A simple feeder originating from only the MMA is a positive predictive factor of tumor necrosis. Embolization should be performed in selected patients taking tumor location and bloody supply into account.

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Disclosure Statement

All authors have no conflict of interest.

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