Sterile Gelatin Film Reduces Cortical Injury Associated With Brain Tumor Re-Resection

Colin J. Przybylowski, MD [*]
Veronica So, BS [‡]
Kaylee DeTranaltes, BS [‡]
Corey Walker, MD [*]
Jacob F. Baranoski, MD [*]
Kristina Chapple, PhD [§]
Nader Sanai, MD [*]

[*]Ivy Brain Tumor Research Center, Department of Neurosurgery, Barrow Neurological Institute, Phoenix, Arizona; [‡]College of Medicine, University of Arizona, Phoenix, Arizona; [§]Department of Biostatistics, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

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Correspondence:
Nader Sanai, MD,
Barrow Neurological Institute,
350 W. Thomas Rd.,
Phoenix, AZ 85013, USA.
Email:
nader.sanai@barrowbrainandspine.com

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BACKGROUND: Recurrent intracranial tumors frequently require re-resection. Dural adhesions to the cortex increase the morbidity and duration of these revision craniotomies.
OBJECTIVE: To describe the use of commercially available sterile gelatin film to prevent meningocerebral adhesions and decrease the rate of surgically induced ischemia from revision craniotomy.
METHODS: This retrospective cohort study examined patients with recurrent glioma, meningioma, and metastasis who underwent re-resection at least 30 d following their initial tumor resection. Cortical surface tissue ischemia after re-resection on diffusion-weighted magnetic resonance imaging was compared for patients with (gelatin film group) and without (nongelatin film group) a history of gelatin film placement at the conclusion of their initial tumor resection.
RESULTS: A total of 84 patients in the gelatin film group were compared to 86 patients in the nongelatin film group. Patient age, sex, tumor pathology, tumor volume, tumor eloquence, laterality of surgical approach, history of radiotherapy, and time interval between resections did not differ between groups. Radiographic evidence of cortical ischemia following reoperation was less prevalent in the gelatin film group (13.1% vs 32.6%; $P < .01$). In multivariate logistic regression analysis, no gelatin film ($P < .01$) and larger tumor size ($P = .02$) predicted cortical surface ischemia following revision craniotomy. Postoperative complications in the gelatin film and nongelatin film group otherwise did not differ.
CONCLUSION: Routine placement of commercially available sterile gelatin film on the cortex prior to dural closure is associated with decreased surgically induced tissue ischemia at the time of revision tumor craniotomy.

KEY WORDS: Brain tumor, Recurrence, Gelatin film, Dural graft

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Gelatin film is a commercially available implant that has been shown to be an effective barrier to prevent scarring and adhesions between soft tissue layers.[1-4] It is commonly used in decompressive hemicraniectomy to prevent adhesions between the musculocutaneous flap and cerebral cortex, which facilitates soft tissue dissection during subsequent cranioplasty.[1] Decreased soft tissue scarring to the pial surface in these operations has been proven to lower operative time and morbidity.[1,5-9] This same concept can be applied to patients with high-grade intracranial tumors, who frequently require revision craniotomy.[10-12] Dural adhesions to the cortex in revision craniotomy for recurrent intracranial tumors can lead to disruption of the pial surface or tearing of cortical veins, causing focal cortical injury. Here, we describe the placement of sterile gelatin film over the exposed cortex at the conclusion of the initial tumor resection to prevent meningocerebral adhesion formation and decrease the rate of surgically induced cortical ischemia from the subsequent revision craniotomy.

ABBREVIATIONS: AVM, arteriovenous malformation; **CI,** confidence interval; **CSF,** cerebrospinal fluid; **DWI,** diffusion-weighted imaging; **MR,** magnetic resonance; **OR,** odds ratio; **WHO,** World Health Organization

METHODS

Patient Selection

This is a retrospective review of 170 consecutive patients with recurrent intracranial high-grade gliomas (World Health Organization [WHO] grade III-IV),

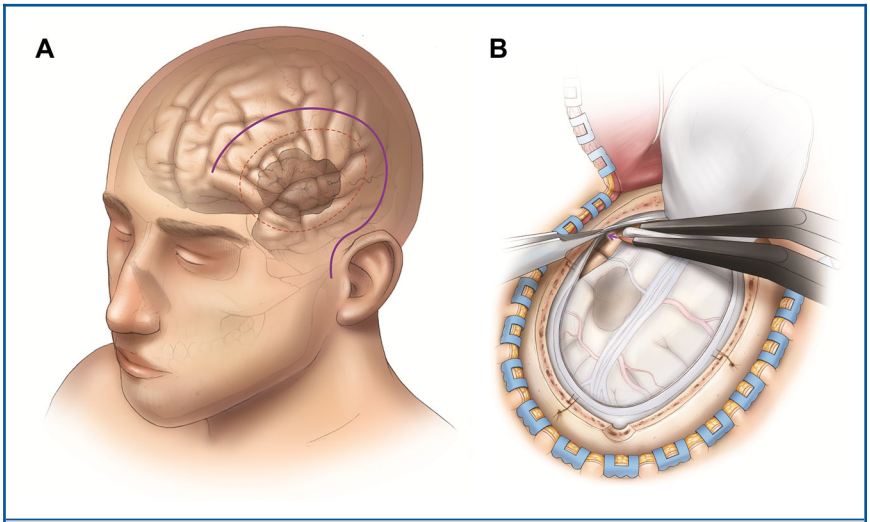

FIGURE 1. **A**, *Representative illustration of gelatin film placement for a high-grade intracranial tumor located within the insular lobe.* **B**, *At the conclusion of the tumor resection, a piece of sterile gelatin film is cut to a size slightly larger than the dural opening. It is then placed over the cortex and tucked underneath the dural edges circumferentially.*

high-grade meningiomas (WHO grade II-III), and metastases treated with 170 revision resections at our institution from 2013 to 2016. The neuropathology department used WHO guidelines for histopathological diagnosis.[13] Inclusion criteria included age >18 yr; history of an initial craniotomy for high-grade glioma, meningioma, or metastasis; and ≥30 d between the initial and revision tumor resection. Exclusion criteria included patients with multifocal lesions, gliomatosis cerebri, or tumor recurrence at a site distant from the initial craniotomy. The institutional review board approved this study. Informed patient consent for the analysis was not required because of the retrospective nature of the study; all patients or their guardians consented to undergoing the procedures described in the study.

Gelatin Film Placement

At the conclusion of the tumor resection, commercially available sterile gelatin film (Pfizer, New York, New York) is brought into the operative field. It is cut to a size slightly larger than the dural opening and irrigated with bacitracin-saline. It is carefully placed over the exposed cortex and tucked under the dural edges, extending approximately 1 to 2 cm beyond the dural opening (Figure 1). The closure of the dura, plating of the bone flap, and closure of the remaining tissue layers are then continued in standard fashion.

Clinical and Radiographic Data

The use of gelatin film during the patient's initial tumor resection was determined via independent review of operative reports in the medical record system. Patients were then divided into 2 groups for comparison: the "gelatin film group" and "nongelatin film group." The decision to utilize gelatin film was based on surgeon practice, such that surgeons either did or did not utilize gelatin film for all of their respective cases within the study period. The use of gelatin film did not alter dural closure technique or choice of suture material.

Clinical and radiographic outcomes data following revision craniotomy were then collected from electronic medical records while blinded to the patient's history of gelatin film placement. Neurological examinations and clinical follow-up were performed by an attending neurosurgeon at 3, 6, and 12 mo postoperatively for all patients. Acute postoperative neurological deficits were not compared between groups, since these findings could be significantly confounded by subcortical injury related to tumor resection. Because postoperative seizures could be the result of cortical surface ischemia and irritation, the incidence of new or worsening seizures was compared between groups. All preoperative and postoperative magnetic resonance (MR) imaging studies were retrospectively reviewed. All postoperative MR imaging studies were confirmed to have been completed within 24 h of the revision tumor resection. Tumor volumes were measured with manual segmentation with region-of-interest analysis as previously described.[14] Infratentorial tumors included in this study were limited to those within the cerebellum. Tumor eloquence was defined by radiographic location.[15] Diffusion-weighted imaging (DWI) was analyzed to determine the presence of postoperative cortical surface ischemia underneath the revision craniotomy site. Any positive DWI signal underneath the revision craniotomy site was considered positive for postoperative cortical surface ischemia. Subcortical tissue ischemia related to tumor resection (ie, deep vessel injury or white matter retraction injury) was not analyzed for this study. Figure 2 shows 2 representative case examples of positive cortical surface ischemia.

Statistical Analyses

Counts with percentages and means with standard deviations were used to describe the sample. Independent samples *t*-tests and Pearson chi-square tests were used to compare gelatin film and nongelatin film cohorts. Odds ratios (ORs) were reported with 95% CIs as measures of effect size. The following variables were log transformed to account for skew: tumor volume and days between initial and revision resections. The means of these variables are reported; however, the *P*-values for

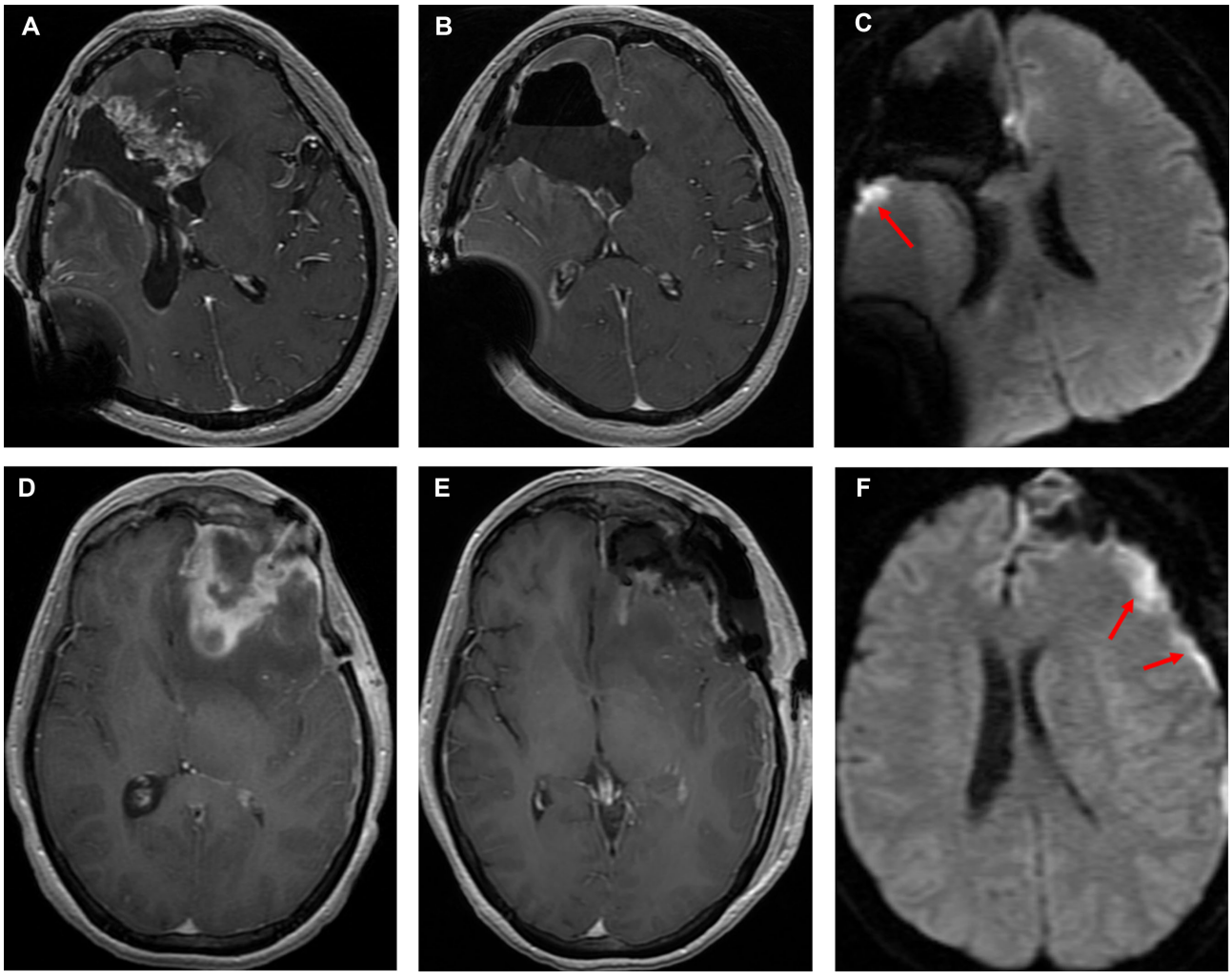

FIGURE 2. *Representative case examples showing positive cortical surface ischemia.* **A**, *Preoperative axial T1-weighted with contrast MR image of a recurrent right frontal high-grade intracranial glioma.* **B**, *Postoperative axial T1-weighted with contrast MR image demonstrating a complete resection.* **C**, *Postoperative axial diffusion-weighted MR image demonstrating cortical surface ischemia adjacent (posterior) to the corticectomy site (red arrow).* **D**, *Preoperative axial T1-weighted with contrast MR image of a recurrent left frontal intracranial metastasis.* **E**, *Postoperative T1-weighted with contrast MR image demonstrating an excellent resection.* **F**, *Postoperative axial diffusion-weighted MR image demonstrating cortical surface ischemia underneath the superior aspect of the frontotemporal craniotomy (red arrows).*

these comparisons are based on *t*-tests using log-transformed variables. A logistic regression model was used to analyze for predictors of cortical surface ischemia. Predicted probabilities from this model were used in a receiver operating characteristic analysis.

RESULTS

The study cohort consisted of a total of 170 patients, including 84 patients in the gelatin film group and 86 patients in the nongelatin film group (Table 1). All patients had a history of an initial craniotomy for high-grade glioma, meningioma, or metastasis at our institution and presented with disease recurrence requiring re-opening of the craniotomy for resection. Patients in the gelatin film and nongelatin film groups did not differ by age (mean 56.8 vs 58.3 yr; $P = .49$), sex (52.4% vs 59.3% male; $P = .36$), number of days between the initial and revision resection (mean 385.3 vs 277.6 d; $P = .25$), or history of radiotherapy (75.0% vs 83.7%; $P = .16$), respectively. Tumor characteristics, including pathology ($P = .59$), tumor volume (mean 20.2 vs 22.3 cm^3; $P = .43$), laterality (48.8% vs 45.3% right-sided; $P = .65$), supratentorial location (91.7% vs 90.7%; $P = .82$), and eloquent location (46.4% vs 38.4%; $P = .29$), also did not significantly differ between the gelatin film and nongelatin film

TABLE 1. Patient and Tumor Characteristics

	Entire cohort (n = 170)	Gelatin film group (n = 84)	Nongelatin film group (n = 86)	*P* value
Age (yr)	57.5 ± 14.3	56.8 ± 14.9	58.3 ± 13.8	.49
Male sex	95 (55.9%)	44 (52.4%)	51 (59.3%)	.36
Days between initial and revision resection	330.8 ± 340.1	385.3 ± 408	277.6 ± 247.4	.25
History of radiotherapy	135 (79.4%)	63 (75.0%)	72 (83.7%)	.16
Pathology				.59
High-grade glioma	123 (72.4%)	62 (73.8%)	61 (70.9%)	
High-grade meningioma	16 (9.4%)	9 (10.7%)	7 (8.1%)	
Metastasis	31 (18.2%)	13 (15.5%)	18 (20.9%)	
Tumor volume (cm^3)	21.3 ± 24.9	20.2 ± 21.5	22.3 ± 27.9	.43
Supratentorial location	155 (91.2%)	77 (91.7%)	78 (90.7%)	.82
Tumor laterality				.65
Right	80 (47.1%)	41 (48.8%)	39 (45.3%)	
Left	90 (52.9%)	43 (51.2%)	47 (54.7%)	
Eloquent location	72 (42.4%)	39 (46.4%)	33 (38.4%)	.29

Variables are presented as: n (%) or mean ± SD.

TABLE 2. Postoperative Clinical and Radiographic Complications

	Gelatin film group (n = 84)	Nongelatin film group (n = 86)	*P* value
Clinical			
CSF leak	3 (3.6%)	4 (4.7%)	.72
Infection	6 (7.1%)	7 (8.1%)	.81
New/worsening seizures	2 (2.4%)	4 (4.7%)	.42
Radiographic			
Cortical surface ischemia	11 (13.1%)	28 (32.6%)	<.01[a]

[a]Statistically significant ($P < .05$).
Variables are presented as n (%).

TABLE 3. Summary of Multivariate Logistic Regression Analysis Predicting Cortical Surface Ischemia

	P value	OR	95% CI
Days between resections	.64	0.89	0.55 to 1.44
History of radiotherapy	.27	1.86	0.62 to 5.56
Pathology (reference metastasis)			
High-grade glioma	.13	2.68	0.74 to 9.74
High-grade meningioma	.43	2.10	0.33 to 13.38
Increasing tumor volume	.02[a]	1.55	1.08 to 2.21
Supratentorial location	.39	0.51	0.11 to 2.40
Side, right	.98	0.99	0.44 to 2.23
Eloquent location	.07	0.42	0.17 to 1.08
No gelatin film	<.01[a]	3.57	1.53 to 8.36

[a]Statistically significant ($P < .05$).
Model AUC (95% CI): 0.83 (0.77-0.89).
AUC: area under receiver operating characteristic curve; CI: confidence interval; OR: odds ratio.

groups, respectively. The mean clinical follow-up times for the gelatin and nongelatin film groups were 3.2 and 2.9 yr, respectively.

Postoperative clinical and radiographic complications are summarized in Table 2. The rates of postoperative cerebrospinal fluid (CSF) leak (3.6% vs 4.7%; $P = .72$), infection (7.1 vs 8.1%; $P = .81$) and new or worsening seizures (2.4% vs 4.7%; $P = .42$) did not significantly differ between the gelatin film and nongelatin film groups, respectively. Radiographic evidence of cortical ischemia following revision craniotomy was less prevalent in the gelatin film group compared to the nongelatin film group (13.1% vs 32.6%, respectively; $P < .01$).

After adjusting for age and sex, the multivariate logistic regression model showed that increasing tumor volume ($P = .02$; OR: 1.55, 95% CI 1.08-2.21) and no gelatin film placement at the time of the initial craniotomy ($P < .01$; OR 3.57, 95% CI 1.53-8.36) were independent predictors of cortical surface ischemia following revision craniotomy (Table 3).

DISCUSSION

High-grade gliomas, high-grade meningiomas, and brain metastases frequently recur despite maximal resection and adjuvant therapy.[10-12] Revision craniotomy is commonly performed in the management of recurrent intracranial tumors and is often complicated by dural adhesions to the cortex. This study demonstrates that placement of gelatin film over the cortex at the conclusion of the initial tumor resection can decrease the rate of surgically induced cortical ischemia from the subsequent revision craniotomy.

In revision craniotomy, meningocerebral adhesions can lead to overmanipulation of the cortex or tearing of cortical veins during surgical exposure (Figure 3A). We hypothesize that the placement of gelatin film decreased the formation of

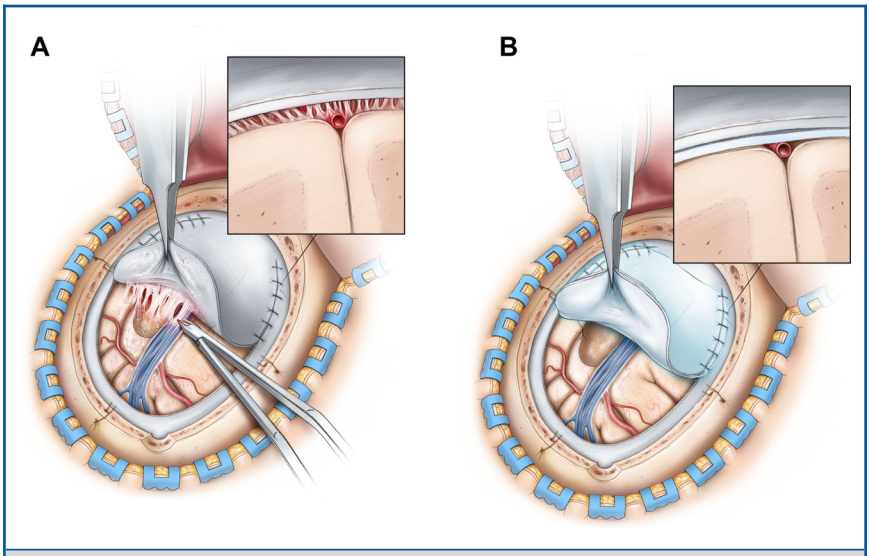

FIGURE 3. **A**, *Representative illustration of a revision craniotomy in which no gelatin film was placed over the cortex during the initial tumor resection. Significant adhesions to the dura, cortex, and superficial veins often must be dissected when opening the dura.* **B**, *Representative illustration of a revision craniotomy in which gelatin film was placed over the cortex during the initial tumor resection. The gelatin film prevents meningocerebral adhesion formation and allows the dura to be opened without difficulty.*

meningocerebral adhesions in the gelatin film group, thus accounting for the lower rate of cortical surface ischemia (Figure 3B). We also observed that larger tumor volume was an independent predictor of cortical surface ischemia. This is likely the result of the larger cortical exposures required for larger tumor resections, rendering more cortical surface exposed to possible injury. Further, for patients in the gelatin film group, the surgeon may be less likely to successfully cover the entire cortical surface with gelatin film with larger cortical exposures.

Gelatin film has an approximate thickness of 0.075 mm and maintains its structural integrity for 2 to 5 mo in the body before slowly resorbing.[1] It is simple to handle in the operating room and does not stick to itself when folded. The use of dural repair grafts is common following tumor resection, but only gelatin film is protective against meningocerebral adhesion formation. Because postoperative morbidity is associated with decreased overall survival in patients with high-grade intracranial tumors, the avoidance of cortical injury during surgical exposure is critical in these revision craniotomy procedures.[16-19]

Gelatin film has proven utility in the neurosurgical field as a barrier to prevent soft tissue scarring to the cortex. Oladunjoye et al[1] described 62 consecutive patients who underwent hemicraniectomy in which gelatin film was placed between the dural repair graft and the musculocutaneous flap. They reported an excellent epidural plane established by the gelatin film barrier in 60 of 62 cases (97%). Sharp dissection of the temporalis muscle was only needed in 2 cases, both of which were the result of the gelatin film not covering the graft in the caudal temporal space. The use of gelatin film in their series did not affect the operative length (mean 2 h and 27 min), infection rate (6.5%), or estimated blood loss (mean 213 cc) compared to recent hemicraniectomy series. Nishizawa et al[3] have also described the use of gelatin film for a 2-staged arteriovenous malformation (AVM) resection. At the conclusion of the first stage of their resection, they placed gelatin film over the remaining AVM nidus and draining vein. During the subsequent second stage of the procedure, they found no adhesions from the AVM to the surrounding parenchyma.

One disadvantage of using gelatin film following intracranial tumor resection is the added cost. This cost may be partially negated by decreased operating room time during subsequent revision craniotomy due to ease of dural opening. However, operating room time data was unable to be accurately collected for this study. Additionally, industry and insurance contracts will vary significantly among institutions, which decreases the generalizability of such a comparison. Another possible disadvantage of using gelatin film is that patients may be at increased risk of infection or adverse biological reaction considering that it is a nonautologous implant. This is particularly true for high-grade tumor patients considering that many of them undergo multiple operations as well as radiotherapy. However, no increased risk of infection was seen by Oladunjoye et al,[1] nor in the current series.

Limitations

This study is limited by its exposure to the referral and treatment biases of our institution and surgeons, including the subjective decision of whether or not gelatin film was used. There may be also additional factors that could lead to cortical surface

ischemia following revision craniotomy not accounted for in our analysis. Specifically, it is possible that cortical surface ischemia was related to a surgical event other than the dural opening. While tumor pathology was controlled in the multivariate analysis for cortical surface ischemia, unaccounted for differences in the goals and size of exposure between intra-axial and extra-axial tumors could have affected outcomes. Additionally, the retrospective nature of this study limits our ability to compare surgeons' opinions on the ease of dural opening in both groups. Key outcome measures not included in this study were the length of the dural opening and the patterns of adhesion formation (dural edges, corticectomy site) for the gelatin film and nongelatin film groups. These would require a prospective analysis and are outside the scope of this retrospective study. Nonetheless, we describe the use of a commercially available biomaterial to protect the cortex during the surgical exposure of revision tumor resection. The use of gelatin film following intracranial tumor resection is safe, quick, and can easily be integrated into any neurosurgeon's clinical practice.

CONCLUSION

Routine placement of a commercially available sterile gelatin film on the cortex prior to dural closure was associated with decreased surgically induced tissue ischemia at the time of revision tumor craniotomy and did not lead to increased risk of infection or CSF leak in patients with recurrent intracranial tumors.

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REFERENCES

1. Oladunjoye AO, Schrot RJ, Zwienenberg-Lee M, Muizelaar JP, Shahlaie K. Decompressive craniectomy using gelatin film and future bone flap replacement. *J Neurosurg*. 2013;118(4):776-782.
2. McGhee MA, Dornhoffer JL. The effect of gelfilm in the prevention of fibrosis in the middle ear of the animal model. *Am J Otol*. 1999;20(6):712-716.
3. Nishizawa S, Ryu H, Yokoyama T, Kitamura S, Uemura K. Intentionally staged operation for large and high-flow cerebral arteriovenous malformation. *J Clin Neurosci*. 1998;5(Suppl):78-83.
4. Matsumura G, Shin'oka T, Ikada Y, Sakamoto T, Kurosawa H. Novel anti-adhesive pericardial substitute for multistage cardiac surgery. *Asian Cardiovasc Thorac Ann*. 2008;16(4):309-312.
5. Bulters D, Belli A. Placement of silicone sheeting at decompressive craniectomy to prevent adhesions at cranioplasty. *Br J Neurosurg*. 2010;24(1):75-76.
6. Lee CH, Cho DS, Jin SC, Kim SH, Park DB. Usefulness of silicone elastomer sheet as another option of adhesion preventive material during craniectomies. *Clin Neurol Neurosurg*. 2007;109(8):667-671.
7. Missori P, Polli FM, Peschillo S, D'Avella E, Paolini S, Miscusi M. Double dural patch in decompressive craniectomy to preserve the temporal muscle: technical note. *Surg Neurol*. 2008;70(4):437-439; discussion 439.
8. Miyake S, Fujita A, Aihara H, Kohmura E. New technique for decompressive duraplasty using expanded polytetrafluoroethylene dura substitute–technical note. *Neurol Med Chir*. 2006;46(2):104-106; discussion 106.
9. Vakis A, Koutentakis D, Karabetsos D, Kalostos G. Use of polytetrafluoroethylene dural substitute as adhesion preventive material during craniectomies. *Clin Neurol Neurosurg*. 2006;108(8):798-802.
10. Sanai N, Berger MS. Recent surgical management of gliomas. *Adv Exp Med Biol*. 2012;746:12-25.
11. Rogers L, Barani I, Chamberlain M, et al. Meningiomas: knowledge base, treatment outcomes, and uncertainties. A RANO review. *J Neurosurg*. 2015;122(1):4-23.
12. Arbit E, Wronski M, Burt M, Galicich JH. The treatment of patients with recurrent brain metastases. A retrospective analysis of 109 patients with nonsmall cell lung cancer. *Cancer*. 1995;76(5):765-773.
13. Louis DN, Perry A, Reifenberger G, et al. The 2016 World Health Organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820.
14. Smith JS, Cha S, Mayo MC, et al. Serial diffusion-weighted magnetic resonance imaging in cases of glioma: distinguishing tumor recurrence from postresection injury. *J Neurosurg*. 2005;103(3):428-438.
15. Pouratian N, Bookheimer SY. The reliability of neuroanatomy as a predictor of eloquence: a review. *Neurosurg Focus*. 2010;28(2):E3.
16. Rahman M, Abbatematteo J, De Leo EK, et al. The effects of new or worsened postoperative neurological deficits on survival of patients with glioblastoma. *J Neurosurg*. 2017;127(1):123-131.
17. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg*. 2011;115(1):3-8.
18. Patel CK, Vemaraju R, Glasbey J, et al. Trends in peri-operative performance status following resection of high grade glioma and brain metastases: the impact on survival. *Clin Neurol Neurosurg*. 2018;164(Jan):67-71.
19. Oppenlander ME, Wolf AB, Snyder LA, et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. *J Neurosurg*. 2014;120(4):846-853.