



NF2 mutation status and tumor mutational burden correlate with immune cell infiltration in meningiomas

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Abstract

Background The tumor microenvironment is an emerging biomarker of underlying genomic heterogeneity and response to immunotherapy-based treatment regimens in solid malignancies. How tumor mutational burden influences the density, distribution, and presence of a localized immune response in meningiomas is unknown.

Methods Representative hematoxylin and eosin slides were reviewed at 40X to assess for the density of inflammatory cells. Lymphocytes and macrophages were quantified in the following ordinal manner: 0 = not present, 1 = 1–25 cells present, and 2 = greater than 26 cells present. Immune cell infiltrate grade was scored for both scattered and aggregated distributions. Next generation targeted sequencing was performed on all meningiomas included in this study.

Results One hundred and forty-five meningiomas were evaluated in this study. Lymphocytes were observed in both scattered (95.9%) and aggregated (21.4%) distributions. A total of 115 (79.3%) meningiomas had 1–25 scattered lymphocytes, and 24 (16.6%) had > 25 scattered lymphocytes, and 6 (4.1%) had no scattered lymphocytes. Twenty (13.8%) meningiomas had 1–25 aggregated lymphocytes. Eleven (7.6%) had > 25 aggregated lymphocytes and 114 (78.6%) had no aggregated lymphocytes. Six (4.1%) meningiomas had 1–25 aggregated macrophages, 5 (3.4%) had > 25 aggregated macrophages, and 134 (92.4%) had no aggregated macrophages. Density of aggregated lymphocytes and aggregated macrophages were associated with higher tumor grade, $P = 0.0071$ and $P = 0.0068$, respectively. Scattered lymphocyte density was not associated with meningioma grade. The presence of scattered lymphocytes was associated with increased tumor mutational burden. Meningiomas that did not have scattered lymphocytes had a mean number of single mutations of 2.3 ± 2.9 , compared with meningiomas that had scattered lymphocytes, 6.9 ± 20.3 , $P = 0.03$. *NF2* mutations were identified in 59 (40.7%) meningiomas and were associated with increased density of scattered lymphocytes. *NF2* mutations were seen in 0 (0%) meningiomas that did not have scattered lymphocytes, 46 (40.0%) meningiomas that had 1–25 scattered lymphocytes, and 13 (54.2%) meningiomas that had > 25 scattered lymphocytes, $P = 0.046$.

Conclusions Our findings suggest that distribution of immune cell infiltration in meningiomas is associated with tumor mutational burden. *NF2* mutational status was associated with an increasing density of scattered lymphocytes. As the role of immunotherapy in meningiomas continues to be elucidated with clinical trials that are currently underway, these results may serve as a novel biomarker of tumor mutational burden in meningiomas.

Keywords Meningioma · Immunotherapy · Sequencing · Inflammation · Biomarker

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Introduction

Meningiomas are extra-axial brain tumors with an estimated prevalence of approximately 2–7.5 in 100,000 [1–3]. While the majority of meningiomas are WHO grade I and are classically associated with a benign outcome, 5–7% of meningiomas are atypical (WHO grade II), and 1–3% are classified as anaplastic (WHO grade III). A typical and

anaplastic meningioma grades are associated with worse clinical courses with reported 10-year survival rates of 79% and 34.5%, respectively [4]. However, while patients with Grade I meningiomas typically experience favorable oncological outcomes compared with higher grade tumors, Grade I meningiomas recur for a subset of patients, warranting further examination of histopathological features of low-grade meningiomas that may be associated with recurrence [5]. Higher-grade meningiomas may also be treated with adjuvant radiotherapy depending upon neuropathological features of the tumor such as brain invasion. Emerging insight into the underlying genomic heterogeneity of meningiomas is valuable to develop novel treatment paradigms for lesions that portend dismal clinical sequela.

Accumulating evidence suggest that the immune microenvironment mediates tumorigenesis and cancer progression [6–8]. For example, macrophage infiltration has been reported in all three grades of meningiomas with higher grade tumors expressing more numerous macrophages [9]. Interestingly, M1 macrophages have shown to exhibit anti-tumoral effects with low M1:M2 ratios reported in higher grade and recurrent meningiomas [10]. To further understand immune cell microenvironment in meningiomas, we quantified pathological evidence of macrophage and lymphocyte infiltration and examined the association between underlying mutational status and inflammatory response in meningiomas. Further understanding of how mutational influences immune response may augment our understanding of the pathogenesis of high-grade meningiomas, as well as help guide the emerging role of immunotherapy in meningiomas.

Methods

Study cohort

This study was reviewed and approved by the human subjects institutional review board and complied with HIPAA (Health Insurance Portability and Accountability Act of 1996) guidelines. Informed consent was waived. We reviewed the electronic health record for patients diagnosed with a meningioma who underwent neurosurgical resection at our institution between the years of 1995 and 2017. We identified 145 patients with available archival formalin-fixed, paraffin-embedded (FFPE) tissue. A board-certified neuropathologist reviewed histopathological diagnosis, grade, and purity of each case according to 2016 WHO guidelines [11].

Next-generation targeted sequencing

We performed next-generation targeted sequencing in a large series of 145 meningiomas. DNA was extracted from

representative FFPE tissue using Maxwell FFPE Plus DNA Purification Kit (Promega, Madison, WI). DNA libraries were generated from tissue using the AmpliSeq OncoPrint Comprehensive research panel versions 2.0 and 3.0 (ThermoFisher Scientific, Waltham, MA) as described previously [12]. Sequencing data analysis was performed using Torrent Suite (versions 5.6.0. and 5.8.0.) (ThermoFisher Scientific, Waltham, MA) and Ion Reporter (versions 5.2, 5.6, and 5.8) (ThermoFisher Scientific, Waltham, MA).

Histopathologic analysis of immune infiltration

WHO grade was determined by review of at least five board certified neuropathologist. A single board-certified neuropathologist with over 20 years of experience performed the quantification of immune cells. Representative hematoxylin and eosin (H&E) slides were reviewed at 40X for the density of inflammatory cells. Lymphocytes and macrophages were quantified using an ordinal scale: 0 = not present, 1 = 1–25 cells, and 2 = greater than 26 cells (Fig. 1). Immune cell infiltrate grade was assessed for both scattered and aggregated distributions (Fig. 2).

Statistical analysis

Statistical analysis performed using JMP Pro 14.2 (SAS Institute Inc., Cary, NC). Fisher's exact test used to detect statistical differences in categorical variables; *t* test used for continuous variables. $P \leq 0.05$ used for statistical significance.

Results

Clinical characteristics of 145 meningiomas included in Table 1. Data on a sub-set of these tumors have been previously reported; however, none of these studies included data on immune characterization [13–16]. We were limited to the content of our targeted sequencing panel and were not able to assess known meningioma driver genes, such as TRAF, KLF4, and POLR2A [17, 18]. The genes included in this study are shown in Supplementary Table 1.

Lymphocytes were observed in both scattered (95.9%) and aggregated (21.4%) distributions, Fig. 1. A total of 115 (79.3%) meningiomas had 1–25 scattered lymphocytes, whereas 24 (16.6%) had > 25 scattered lymphocytes, Fig. 2a. A total of 20 (13.8%) meningiomas had 1–25 aggregated lymphocytes, whereas 11 (7.6%) had > 25 aggregated lymphocytes, Fig. 2b. There were 77 cases that were primary and 68 cases that were recurrent (Table 1). There were no significant differences in scattered lymphocytes, aggregated lymphocytes, or aggregated macrophages between primary and recurrent tumors ($P > 0.05$, for all).

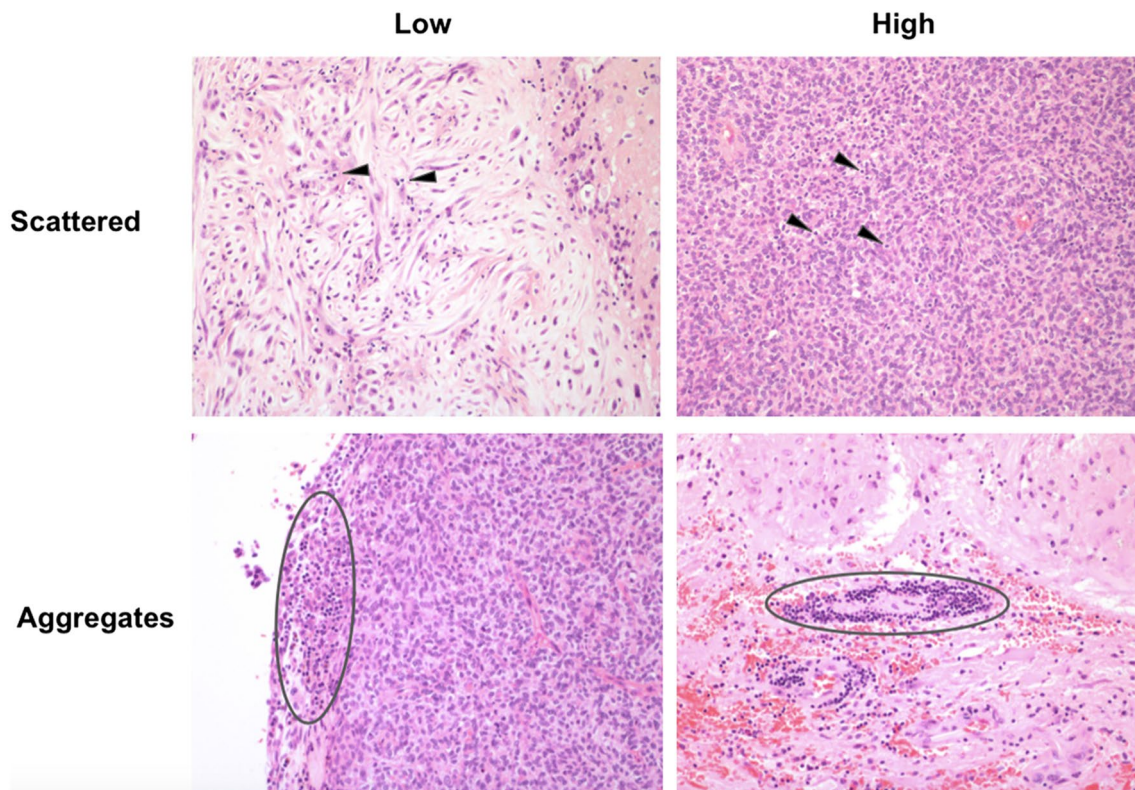


Fig. 1 H&E at 40X demonstrating density of scattered (arrowheads) and aggregate (circled) lymphocytes in meningioma

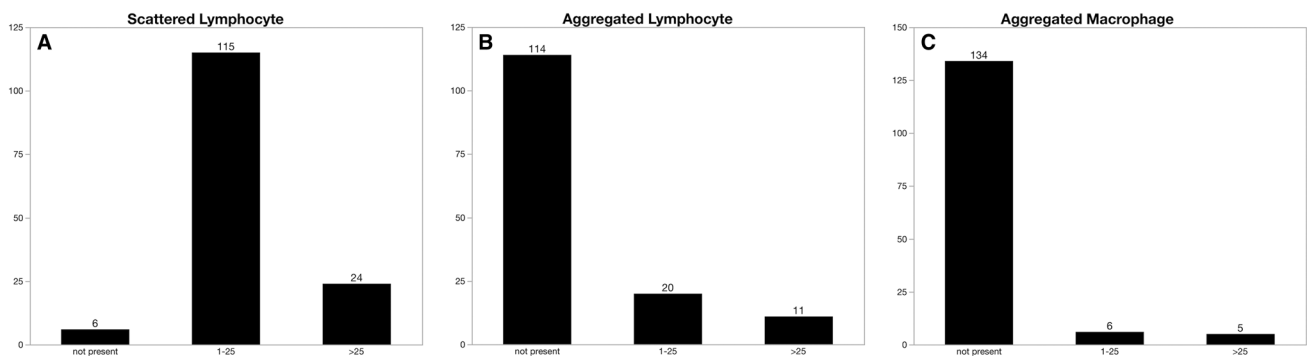


Fig. 2 Bar graphs of **a** scattered lymphocyte, **b** aggregated lymphocyte, and **c** aggregated macrophage distributions binned by not present, 1–25, >25. Values above bars are data counts

No meningioma specimens had scattered macrophages. A total of 6 (4.1%) meningiomas had 1–25 aggregated macrophages, whereas 5 (3.4%) had >25 aggregated macrophages, Fig. 2c. Density of aggregated lymphocytes ($P=0.0071$, Fisher's exact) and aggregated macrophages ($P=0.0068$, Fisher's Exact) were significantly associated with higher grade meningiomas, Table 2. Scattered lymphocyte density was not associated with meningioma grade. An example of meningioma specimens exhibiting

high focal aggregation of lymphocytes and macrophages is shown in Fig. 3.

The presence of scattered lymphocytes was associated with increased tumor mutational burden.

The mean number of single nucleotide variants was 6.7 ± 19.9 (range 0–192). Mean number of single nucleotide variants was 2.3 ± 2.9 for meningiomas that did not have scattered lymphocytes compared to 6.9 ± 20.3 for meningiomas that did have scattered lymphocytes ($P=0.03$). Mean

Table 1 Clinical characteristics

Clinical characteristics	
Age	
Median (IQR)	60.7 (49.0, 70.9)
Range	20.3–95.7
Sex (female)	95 (65.5)
WHO grade	
I	43 (29.7%)
II	93 (64.1%)
III	9 (6.2%)
Occurrence	
Primary	77 (53.1%)
Recurrent	68 (46.9%)
Mitotic count	
Median (IQR)	1 (0, 5)
Ki-67	
Median (IQR)	20 (10, 30)

Data in parenthesis represent percentage in column, unless otherwise indicated

Table 2 Immune infiltration by meningioma grade

	Grade I	Grade II	Grade III	<i>P</i> value*
Scattered lymphocyte				0.6
Not present	2 (33.3)	4 (66.7)	0 (0)	
1–25	32 (27.8)	74 (64.4)	9 (7.8)	
> 25	9 (37.5)	15 (62.5)	0 (0)	
Aggregated lymphocyte				0.0071
Not present	38 (33.3)	73 (64.0)	3 (2.6)	
1–25	3 (15.0)	14 (70.0)	3 (15.0)	
> 25	2 (18.2)	6 (54.6)	3 (27.3)	
Aggregated macrophage				0.0068
Not present	42 (31.3)	86 (64.2)	6 (4.5)	
1–25	1 (16.7)	5 (83.3)	0 (0)	
> 25	0 (0)	2 (40.0)	3 (60.0)	

Bold values indicate statistical significance ($P < 0.05$)

Data in parenthesis represent percentage in row

**P* value within row, Fisher's exact test

number of single nucleotide variants was 7.1 ± 20.7 for meningiomas that did not have aggregate macrophages present compared to 1.7 ± 1.2 for meningiomas that did have aggregate macrophages ($P = 0.004$).

A total of 59 (40.7) meningiomas harbored NF2 mutations. AKT1, SMO, and PIK3CA mutations were identified in 8 (5.6%), 4 (2.8%), and 4 (2.8%), respectively. NF2 mutation status was associated with increased density of scattered lymphocytes. NF2 mutations were seen in 0 (0%) meningiomas that did not have scattered lymphocytes, 46 (40.0%) meningiomas that had 1–25 scattered lymphocytes,

and 13 (54.2%) meningiomas that had > 25 scattered lymphocytes ($P = 0.046$, Fisher's exact). Among the 11 cases with aggregate macrophages, an NF2 mutation was seen in only 1 (9.1%) case ($P = 0.03$, Fisher's exact). There was no significant association between scattered lymphocytes, aggregated lymphocytes, or aggregated macrophages and AKT1, SMO, and PIK3CA mutations status.

Discussion

Meningiomas are extra-axial tumors that reside outside of the blood–brain barrier. Systemic immune regulators can infiltrate these tumors [19]. While there has been considerable interest in studying immune-mediated processes to guide immunotherapies in other brain tumors such as gliomas [19–21], there is also a growing interest in assessing the immune system response to meningiomas and multiple immunotherapies trials are currently underway [19, 22]. Further understanding the complex association between immune infiltration and genomic mutations may help to increase our understanding of the complex role of inflammation in the tumor microenvironment as well as guide emerging immunotherapies for treating meningiomas.

Patterns of immune infiltrates in meningioma have been qualitatively described. They include a variety of cells including B and T lymphocytes, macrophages, plasma cells, and mast cells. Macrophages are found in all meningioma grades; however, they tend to have greater density in grades II and III lesions [9]. Grund et al. found that higher grade meningiomas with invasion of the pial–glial basement membrane exhibited greater degrees of microglial cells that expressed CD14 or CD163 [23]. These results support our finding of increased aggregated macrophages in higher grade meningiomas in the present study.

Similarly, CD4+ and CD8+ T lymphocytes are found in both low- and high-grade meningiomas, and tend to exhibit greater density in atypical and anaplastic meningiomas [9, 24]. Interestingly, increased presence of infiltrating CD8+ T cells has been shown to correlate with increased survival in meningiomas, as well as breast and lung cancer [25–27]. Higher PD-L1 +/CD68 – expression has been shown to be associated with reduced overall survival. Increased expression of CD68 –, PD-L1 + cells is correlated with meningioma grade [28]. Elevated PD-L1 expression in high-grade meningiomas has been found in numerous studies, suggesting that immune checkpoint inhibitors may be useful in treating aggressive high-grade meningiomas [29–32].

Several studies have evaluated how systemic serum markers of inflammation mediate immune response against meningiomas. Comtesse et al. found that patients with meningiomas exhibited an elevated serum antibody level to numerous antigens compared with healthy individuals,

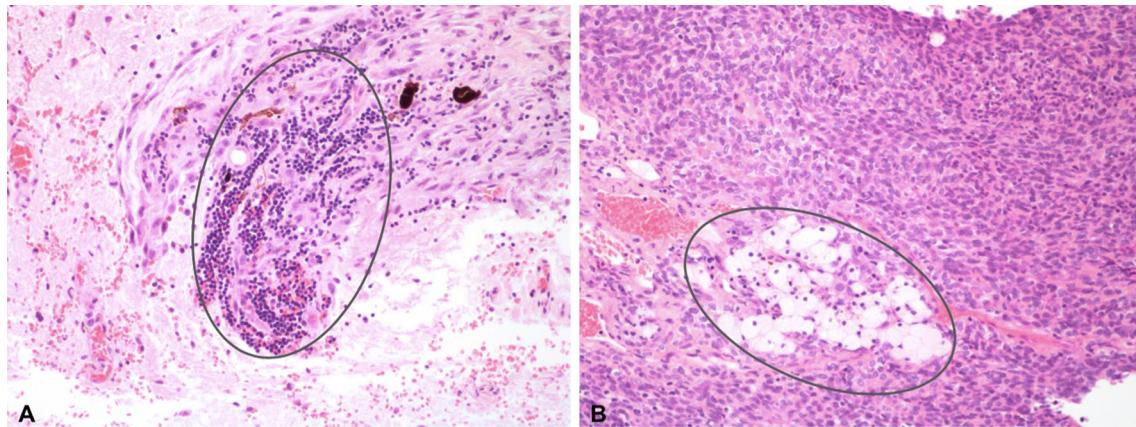


Fig. 3 H&E at 40X demonstrating high aggregate lymphocyte (a) and macrophage (b) distributions (circled) seen in meningioma

supporting that meningioma do in fact elicit a systemic immune response. CD69, a surface marker of natural killer cells and lymphocyte activation, may be elevated in the serum of patients with meningiomas [33].

We modeled our immune cell infiltration quantification after the study by Keren et al., which described the impact of tumor infiltrating immune cells in cold (no infiltration), mixed (scattered immune cells), and compartmentalized (aggregated immune cells) on tumor behavior and prognosis in breast cancer [34]. Keren et al. demonstrated that the compartmentalized immune cell phenotype was associated with increased survival compared with the mixed phenotype [34]. Linking underlying genomic status with tumor immune microenvironment features may further our understanding of the complex interplay between inflammation and tumor progression and aide in patient stratification and developing immunotherapies in the future. The results from this study suggest that potentially clinically relevant information is provided by studying the spatial arrangement of immune infiltration in the context of genomic heterogeneity in meningiomas.

Our results suggest that meningiomas that harbor more mutations generate increased levels of neoantigens that result in a more marked immune response. Meningiomas with scattered lymphocyte infiltration had threefold mutational burden compared with meningiomas without lymphocyte infiltration. Indeed, meningiomas with high tumor mutational burden may display higher susceptibility to immunotherapies compared with tumors with low mutational burden. Prior studies have shown that tumors with greater tumor mutational burden tend to have higher immunogenicity, which leads to a more robust repertoire of neoantigens and confers susceptibility to immunotherapies [35, 36]. There are a few studies that have examined the association between tumor mutational burden and immune response in meningiomas [37]. These findings may be useful in the

selection of clinical trial candidates for the application and development of immunotherapeutic strategies in high-grade meningiomas, as seen in gliomas [20, 38].

While the role of cancer immunotherapy continues to expand in the treatment of advanced cancers such as melanoma [39], lung cancer [40], and glioma [20, 21, 38], the role of immunotherapy in the treatment of meningiomas must still be elucidated. Interestingly, a recent case report documented an incidental 24% decrease in meningioma volume in a patient receiving nivolumab for concomitant stage IV lung adenocarcinoma, providing preliminary evidence for the efficacy of a single-agent monoclonal antibody targeting PD-1 in treating meningiomas [41].

Clinical trials aimed at determining the efficacy nivolumab (NCT03173950), pembrolizumab (NCT03279692), avelumab (NCT03267836), and nivolumab with and without ipilimumab in combination with multifraction stereotactic radiosurgery (NCT03604978) are currently underway in patients with meningiomas. These studies, as well as clinical trials that utilize other checkpoint inhibitors against targets such as cytotoxic T lymphocyte-associated protein 4 (CTLA4), will be important for determining the role of immune checkpoint inhibitors in patients with high-grade meningiomas.

Limitations and future directions

The main limitation of the present study was the inability to quantify specific immune cell populations beyond the distinction between lymphocytes and macrophages that was permitted by H&E stains. Meningiomas can be invaded by a wide variety of immune cells and future studies are required to perform advanced immunohistochemical staining to quantify specific cell types to correlate with molecular findings. In particular, CD4, CD8, CD25, and FOXP3 are important immune cell markers that have been

described in distinct meningioma phenotypes that should be investigated in the context of genomic alterations [24, 31, 42, 43]. Immune cells expressing immune checkpoint molecules such as PD-1, CTLA-4, and Tim-3 should be examined in the context of genomic alterations. Moreover, prior studies have provided evidence for the prognostic significance of activity of immune cells at the tumor border; such focused evaluation ought to occur in meningiomas [34]. Given the lack of differentiation of immune cell sub-phenotypes using immunohistochemistry, the present study serves to provide preliminary data with regard to the correlation of macrophage and lymphocyte patterns with tumor mutational status. Future work will include immunohistochemical interrogation of specific immune cell markers to further elucidate the role of immune cell infiltration in meningiomas.

Given the nature of the surgical resections, it was difficult to determine the location that each histological specimen originated from within the tumor. Future work should focus on methods by which to document the location of histological specimens within the tumor such as deeper aspects versus sections at the brain–tumor interface.

Conclusion

There are limited treatment options for patients with meningiomas in the recurrent setting [44, 45]. Immunotherapy is currently being explored in clinical trials as an adjuvant modality for treating aggressive meningiomas that recur after neurosurgical resection. However, there is an unmet need to sufficiently characterize the association between genomic heterogeneity and immune response in meningiomas. The present study revealed that both tumor mutational burden and *NF2* mutation status are correlated with density of lymphocytic infiltration. These findings may serve as a novel biomarker to guide the emerging role of immunotherapy in high-grade meningiomas.

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Author contributions JWR—manuscript drafting, data collection, critical revision, reviewed final manuscript, and submitted on behalf of the authors; CMG—manuscript drafting, statistical analysis, and reviewed final manuscript; JL—data collection, data analysis, and reviewed final manuscript; HA—data analysis and reviewed final manuscript; MP—data analysis and reviewed final manuscript; MU—data analysis and reviewed final manuscript; YK—data analysis and reviewed final manuscript; RBM—data analysis and reviewed final manuscript; JB—data analysis and reviewed final manuscript; MD—data analysis and reviewed final manuscript; RS—reviewed final manuscript and data analysis; RKS—reviewed final manuscript, study supervision, and critical revision; MF—data collection, reviewed final manuscript, study supervision, and critical revision.

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Compliance with ethical standards

Conflicts of interest Dr. Joshua Bederson (a Significant Contributor in this study and Chair of the Department of Neurosurgery) owns equity in Surgical Theater, LLC [manufacturer of the Surgical Navigation Advanced Platform (SNAP) system that may be used for intraoperative image guidance in the study]. The remaining authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Ethical approval This study was by the Icahn School of Medicine at Mount Sinai Institutional Review Board, and we certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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