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Association of *CDKN2A* alterations with increased postoperative seizure risk after resection of brain metastases

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Abstract

OBJECTIVE—Seizures are common and significantly disabling for patients with brain metastases (BMs). Although resection can provide seizure control, a subset of patients with BMs may continue to suffer seizures postoperatively. Genomic BM characteristics may influence which patients are at risk for postoperative seizures. This work explores correlations between genomic alterations and risk of postoperative seizures following BM resection.

METHODS—All patients underwent BM resection at a single institution, with available clinical and sequencing data on more than 500 oncogenes. Clinical seizures were documented pre- and postoperatively. A random forest machine learning classification was used to determine candidate genomic alterations associated with postoperative seizures, and clinical and top genomic variables were correlated with postoperative seizures by using Cox proportional hazards models.

RESULTS—There were 112 patients with BMs who underwent 114 surgeries and had at least 1 month of postoperative follow-up. Seizures occurred preoperatively in 26 (22.8%) patients and postoperatively in 25 (21.9%). The Engel classification achieved at 6 months for those with preoperative seizures was class I in 13 (50%); class II in 6 (23.1%); class III in 5 (19.2%), and class IV in 2 (7.7%). In those with postoperative seizures, only 8 (32.0%) had seizures preoperatively, and preoperative seizures were not a significant predictor of postoperative seizures (HR 1.84; 95% CI 0.79–4.37; p = 0.156). On random forest classification and multivariate Cox analysis controlling for factors including recurrence, extent of resection, and number of BMs, *CDKN2A* alterations were associated with postoperative seizures (HR 3.22; 95% CI 1.27–8.16;

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Conception and design: Morshed, Cummins, Berger, Theodosopoulos, Hervey-Jumper, Aghi. Acquisition of data: Morshed, Cummins, Garcia, Saggi, Chung, Theodosopoulos, Chang, Hervey-Jumper, Aghi. Analysis and interpretation of data: Morshed, Cummins, Garcia, Saggi, Chung, Goldschmidt, Berger, Aghi. Drafting the article: Morshed, Cummins, Saggi, Chung, Hervey-Jumper. Critically revising the article: Morshed, Garcia, Nguyen, Chung, Goldschmidt, Berger, Theodosopoulos, Chang, Aghi. Reviewed submitted version of manuscript: Morshed, Cummins, Nguyen, Saggi, Chung, Goldschmidt, Theodosopoulos, Chang, Daras, Aghi. Approved the final version of the manuscript on behalf of all authors: Morshed. Statistical analysis: Morshed, Cummins, Nguyen, Saggi. Administrative/technical/material support: Berger, Chang. Study supervision: Morshed, Berger, Daras.

Disclosures

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

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p = 0.014). Melanoma BMs were associated with higher risk of postoperative seizures compared with all other primary malignancies (HR 5.23; 95% CI 1.37–19.98; p = 0.016). Of 39 BMs with *CDKN2A* alteration, 35.9% (14/39) had postoperative seizures, compared to 14.7% (11/75) without *CDKN2A* alteration. The overall rate of postoperative seizures in melanoma BMs was 42.9% (15/35), compared with 12.7% (10/79) for all other primary malignancies.

CONCLUSIONS—*CDKN2A* alterations and melanoma primary malignancy are associated with increased postoperative seizure risk following resection of BMs. These results may help guide postoperative seizure prophylaxis in patients undergoing resection of BMs.

Keywords

brain metastasis; seizure; *CDKN2A* ; genetics; machine learning; tumor

Seizures are a common and disabling clinical feature of brain metastases (BMs), occurring in up to 20% of patients with BMs at presentation.[1,2] Seizures secondary to BMs can significantly reduce quality of life and neurocognitive function for patients.[3] In patients with BMs presenting with seizures, resection can offer favorable seizure control in up to 90% of cases.[4] Resection of BMs can furthermore confirm a pathological diagnosis, and genomic testing of resected BMs can facilitate targeted therapies, which improve overall survival.[5–7] BM genomic sequencing also provides the opportunity to correlate clinical outcomes such as postoperative seizure occurrence with genomic alterations.

Although postoperative antiseizure prophylaxis is generally given to minimize the risk of persistent or new postoperative seizures, the seizures may persist in a significant portion of patients.[4,8,9] Identification of at-risk patients based on genomic alterations may help guide antiseizure therapy in this population. Although previous work has explored clinical risk factors for postoperative seizures and a small number of molecular variables such as *KRAS* and *EGFR* mutation status have been explored,[8] there has yet to be a more comprehensive analysis of genomic alterations that correlate with seizures in the postoperative period. Alterations in the *PI3K-AKT-mTOR* pathway, for instance, have been previously associated with seizures in gliomas,[10] focal cortical dysplasia,[11] and posttraumatic epilepsy.[12] *BRAF* alterations have likewise been associated with low-grade, epilepsy-associated tumors.[13,14] Identifying genomic alterations that correlate with seizures in BMs may both expedite personalized therapy for patients and identify potential molecular drivers of epilepsy more broadly. We therefore explored the relationship between clinical seizures and oncogenomic alterations in patients following resection of BMs.

Methods

Study Design

All patients with resection of a pathologically confirmed intracranial BM at a single academic institution between January 2019 and June 2022 were retrospectively reviewed. IRB approval was obtained, with need for informed consent waived for this retrospective observational study. Inclusion criteria were as follows: patients who 1) had pathology confirmed malignant tissue present at time of BM resection for a supratentorial BM without evidence of radiation necrosis; 2) had available gene-sequencing data for the coding regions

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in > 500 oncogenes routinely obtained in tumor specimens for clinical purposes;[13] 3) had an electronic medical record with available imaging and documentation of clinical outcomes; and 4) had at least 1 month of postoperative clinical follow-up. Patients were excluded for the following reasons: 1) if the resected BM was infratentorial, or 2) if they received a diagnosis of leptomeningeal disease prior to the date of surgery. Resection was considered after multidisciplinary discussion between a neurosurgeon, radiation oncologist, and oncologist.

Patient and Tumor Variables

Next-generation sequencing of all BM specimens was performed on the coding regions of 529 oncogenes and select introns of 47 genes as part of clinical care within a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory.[13] Data were extracted from the medical record for analysis. The 172 genomic alterations detected in at least 1 sample across all patients are depicted in Table 1. Preoperative and postoperative seizures and use of anticonvulsants were extracted from the medical record, and Engel class as a measure of postoperative seizure control was determined at 6 months postoperatively from electronic medical record notes. Postoperative seizures were determined by presence of seizures between the time of hospital discharge after BM resection and the end of follow-up. Thus, seizures in the acute postoperative period possibly related to surgery itself were not included.

Preoperative variables included patient age; sex; self-reported race; previous craniotomy history; dates of primary malignancy diagnosis, BM diagnosis, and surgery; presence or absence of systemic malignancy at surgery; immune checkpoint inhibitor; or history of targeted cancer therapy. Tumor variables included primary malignancy identified on BM pathological examination; location (frontal, parietal, temporal, or occipital lobe); laterality; cystic tumor (yes/no); preoperative intratumoral hemorrhage (yes/no); preoperative intratumoral susceptibility-weighted imaging (SWI) artifact indicative of blood products; history of prior radiation to the resected BM; and total number of BMs at time of surgery. Surgical variables included extent of resection (gross-total resection vs subtotal resection) and volume of resected tissue. Postoperative variables included local and distant CNS tumor recurrence; postoperative radiation (none, local radiation [CyberKnife or Gamma Knife], brachytherapy, or whole-brain radiation therapy [WBRT]); use of postoperative checkpoint inhibitors or targeted therapy; and follow-up duration.

Statistical Analyses

Analyses were performed using R version 4.2.1. All genomic variables were first fed into random forest (RF) models to determine candidate genomic alterations associated with postoperative seizures. Data were split into 70% training and 30% validation data sets. The *randomForest()* function from the *randomForest* package was applied to training data, with number of trees set to 501 and 4 variables randomly sampled at each split. Genes without alterations across all tumors were excluded from analysis, giving 172 genetic variables of interest in the RF models. Model accuracy with different hyperparameters was iteratively assessed to determine optimal hyperparameter values. Given that the initial RF models for postoperative seizures revealed class imbalance toward the outcome of no seizure (100%

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prediction of no seizures), data oversampling was used with the *ovun.sample()* function from the *ROSE* package to oversample to 100 samples in the training data set. The RF model was applied to the 30% validation data set to determine and maximize model accuracy. The top 10 variables of importance were determined from the optimized RF model by the mean decrease in the Gini index of importance. The Gini index represents a measure of the relative importance of variables to classification in the RF model.[15] Thus, a greater reduction in the mean Gini index in a model with high accuracy implies that a variable contributes highly to accurately predicting the outcome of interest (which was seizure in this study). The top 10 genomic variables from RF modeling associated with postoperative seizures were then included in Cox proportional hazards models for survival analysis in postoperative seizures.

Associations between predictor variables (clinical and genomic) and postoperative seizures were assessed using Cox proportional hazards models from *Survival* and *Survminer* R packages. All clinical variables and the top 10 genomic variables from RF modeling were included in univariate analysis. Variables with $p < 0.05$ on univariate analysis were incorporated into multivariate analysis.

Results

The cohort consisted of 112 patients who underwent 114 surgeries for resection of 114 BMs—2 patients underwent resection of 2 metastases (Table 2). Primary malignancy diagnoses for each BM included melanoma for 30.7% (n = 35); non–small cell lung cancer (NSCLC) for 28.1% (n = 32); breast for 11.4% (n = 13); gastrointestinal for 7.9% (n = 9); renal cell carcinoma for 5.3% (n = 6); gynecological for 4.4% (n = 5); and other cancer types in 12.3% (n = 14). The average patient age at time of surgery was 63.2 ± 13.6 years. Fifty-five (48.2%) patients were female. Extracranial systemic malignancy at the time of surgery was present in 84 (73.7%). The median resected tumor volume was 12.8 (range 0.3–109.9) cm^3, and the median number of BMs at surgery was 2 (range 1–25 BMs). Tumors had cystic features in 18 (15.8%) cases and preoperative intratumoral hemorrhage in 61 (53.5%). Gross-total resection was achieved in 95 (83.3%). The median duration of postoperative clinical follow-up was 8.0 (range 1.2–90.2) months. Postoperative adjuvant therapies included immune checkpoint inhibitors in 40 (35.1%) and targeted therapy in 44 (38.6%). Postoperative radiation therapies included brachytherapy in 10 (8.8%), local stereotactic radiosurgery in 79 (69.3%), and WBRT in 3 (2.6%). Local tumor progression occurred postoperatively in 16 (14.0%) at a median time of 4.2 (range 0.7–15.3) months postoperatively and distant progression in 57 (50.0%) at a median time of 3.6 (range 0.4–15.1) months postoperatively.

Seizure occurred preoperatively in 26 (22.8%) cases and postoperatively in 25 (21.9%). The first postoperative seizure occurred at a median time of 3.8 (range 0.4–10.7) months postoperatively. All patients with preoperative seizure received subsequent antiseizure medication prior to surgery. All patients were discharged postoperatively with an antiseizure medication, typically levetiracetam, in the absence of a contraindication. Duration of postoperative antiseizure prophylaxis was typically 30 days in those with no history of seizures and was discontinued on a case-by-case basis in those with preoperative seizure. Of patients with a postoperative seizure, 15 (60.0%) occurred while on antiseizure prophylaxis

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and 10 (40.0%) occurred after cessation of antiseizure prophylaxis. Seizure control at 6 months postoperatively in the 26 cases with preoperative seizures was Engel class I in 13 (50%); class II in 6 (23.1%); class III in 5 (19.2%), and class IV in 2 (7.7%).

Postoperative Seizures: Genomic and Clinical Associations

RF classification revealed that the top 10 genomic variables predictive of postoperative seizures were alterations in *CDKN2A*, *CD74-ROS1* translocation, *PTEN*, *BRAF*, *ATRX*, *MITF*, *TERT*, *EGFR*, *CHEK2*, and *PREX2* (Fig. 1). These top 10 genomic variables were included with all clinical variables in univariate Cox survival analysis. Univariate analysis demonstrated that *CDKN2A* (HR 3.08; 95% CI 1.39–6.78; p = 0.00537); *CD74-ROS1* (HR 9.69; 95% CI 2.22–42.33; p = 0.00253); *BRAF* (HR 2.70; 95% CI 1.07–6.81; p = 0.035); *MITF* (HR 4.34; 95% CI 1.02–18.59; p = 0.048); and *TERT* (HR 2.56; 95% CI 1.17–5.61; p = 0.019) alterations were significantly associated with postoperative seizures (Table 3). On univariate analysis, clinical variables associated with increased risk of postoperative seizures included history of previous craniotomies (HR 3.63; 95% CI 1.62–8.13; p = 0.00174); distant intracranial progression (HR 2.63; 95% CI 1.10–6.30; p = 0.031); and number of BMs at surgery (HR 1.12; 95% CI 1.04–1.20; p = 0.00344). Local tumor progression was not a significant predictor of postoperative seizures (HR 1.93; 95% CI 0.77–4.82; p = 0.162). Melanoma as the primary malignancy was associated with postoperative seizures (HR 3.97; 95% CI 1.78–8.87; p = 0.00778). Preoperative seizures were not a significant predictor of postoperative seizures (HR 1.84; 95% CI 0.79–4.37; p = 0.156). Adjuvant postoperative therapies had no significant impact on postoperative seizure risk, including immune checkpoint inhibitors, targeted therapy, brachytherapy, local stereotactic radiosurgery, or WBRT (p > 0.300).

On multivariate analysis, *CDKN2A* alterations (HR 3.22; 95% CI 1.27–8.16; p = 0.014) and *CD74-ROS1* translocation (HR 14.06; 95% CI 1.52–130.44; p = 0.020) were associated with increased risk of postoperative seizures. Only 2 patients had *CD74-ROS1* translocation, both of whom (100%) had postoperative seizures. Of 39 BMs with *CDKN2A* alteration, 35.9% (14/39) were associated with postoperative seizures, compared to 14.7% (11/75) without *CDKN2A* alteration. Time to first postoperative seizure was also different between patients harboring a *CDKN2A* alteration compared to those without this alteration (log-rank p = 0.014, Fig. 2A). Details on the specific *CDKN2A* alterations observed as well as seizure semiology are listed in Table 4. Overall, there was not a significantly different rate of postoperative seizures based on the type of *CDKN2A* alteration. Melanoma primary malignancy was associated with increased risk of postoperative seizures on multivariate analysis (HR 5.23; 95% CI 1.37–19.98; p = 0.016) (Fig. 2B). The overall rate of postoperative seizures in melanoma BMs was 42.9% (15/35), compared with 12.7% (10/79) for all other primary malignancies.

The relationship between *CDKN2A* alterations and local and distant intracranial disease progression was also assessed. *CDKN2A* alterations were associated with both local (HR 2.63; 95% CI 1.01–6.84; p = 0.047) and distant (HR 1.91; 95% CI 1.13–3.25) intracranial tumor progression postoperatively. As previously described, of all 25 patients with postoperative seizures, 60.0% (15/25) occurred while they were receiving antiseizure

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prophylaxis and 40.0% (10/25) occurred after cessation of antiseizure prophylaxis. Of patients with *CDKN2A* alteration and postoperative seizure, a similar 64.3% (9/14) were on antiseizure prophylaxis and 35.7% (5/14) were not at the time of their first seizure. Associations with preoperative seizures were also assessed. Given that no genomic associations were found with preoperative seizures ($p > 0.150$ for all) and clinical factors reflected those recently described in a similar cohort,[8] this analysis was not included.

Discussion

This study explores the relationship between genomic alterations and postoperative seizures in 114 brain metastases with targeted analysis of > 500 oncogenomic alterations. Seizures occurred preoperatively in 26 (22.8%) cases and postoperatively in 25 (21.9%). RF classification and subsequent multivariate Cox proportional hazards analysis revealed that *CDKN2A* gene alterations (HR 3.22; 95% CI 1.27–8.16; $p = 0.014$) were associated with postoperative seizures. Compared with other primary malignancies, melanoma BMs were associated with a higher risk of postoperative seizures following resection (HR 5.23; 95% CI 1.37–19.98; $p = 0.016$). Increased risk of postoperative seizures with melanoma BMs occurred independent of hemorrhage or blood products on SWI. These results provide insight into at-risk patients who may require more intensive antiepileptic therapy postoperatively.

CDKN2A and Postoperative Seizures

The most robust genomic alteration associated with postoperative seizures seen in the cohort involved mutations in *CDKN2A*. The postoperative seizure rate was 35.9% (14/39) for BMs with *CDKN2A* alteration and 14.7% (11/75) for BMs without *CDKN2A* alteration. *CDKN2A* alteration–associated postoperative seizures occurred across primary malignancies, including in melanoma (n = 7), NSCLC (n = 3), pancreatic cancer (n = 2), renal cell carcinoma (n = 1), and breast cancer (n = 1). The *CDKN2A* gene on chromosome 9p21 encodes several unique proteins that act as tumor suppressors, including two well-described proteins involved in cell cycle regulation: $p16^{INK4a}$ and $p14^{ARF}$. Protein $p16^{INK4a}$ is an inhibitor of cell growth through inhibition of CDK4 and CDK6, which when uninhibited act to promote RB protein–mediated cell turnover.[16] Therefore, p16 halts cell cycle progression and cell growth via downstream RB inhibition. Protein $p14^{ARF}$ likewise limits cell growth through a separate mechanism via MDM2 inhibition and the resultant p53 activation.[16]

Unsurprisingly, *CDKN2A* gene alterations (including deletion, mutation, or silencing) are thus associated with increased risk of both primary malignancies such as melanoma and pancreatic cancer at the germline level and with increased risk of BM from primary malignancies.[17–19] Recent work has also found that *CDKN2A/B* codeletion is associated with both local and distant intracranial tumor recurrence following resection of BMs.[20] However, there is limited evidence directly correlating *CDKN2A* alterations or its protein products ($p16^{INK4a}$ or $p14^{ARF}$) with seizures. In the glioma literature, *CDKN2A* deletion has been associated with both higher tumor grade and shorter overall survival.[21,22] *CDKN2A* deletion, often with codeletion of *CDKN2B*, is also a hallmark of pleomorphic

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xanthoastrocytomas,[23] which present with seizures in > 70% of cases.[24,25] It is plausible that *CDKN2A* deletion in BMs leads to downstream expression of proteins on tumor cells that increase seizure risk by interactions with local cortical tissue. For example, *CDKN2A* activity has been shown to reduce cell-cell adhesion by altering expression of transmembrane proteins such as E-cadherin.[26] Alterations in *CDKN2A* may therefore increase tumor epileptogenicity by allowing tumor–cortical interactions via tumor cadherin expression.[27] Further work is needed to elucidate the molecular mechanisms of tumor-induced epilepsy, but these results indicate possible downstream epileptogenic changes resulting from decreased *CDKN2A* activity.

Independent of mechanism, it is notable that *CDKN2A* alterations are associated with increased risk of postoperative seizures, particularly in combination with recent work associating *CDKN2A/B* codeletion with local and distant CNS progression.[20] These findings point toward generally increased CNS aggressiveness in BMs harboring *CDKN2A* alterations. *CDKN2A* alterations were significantly associated with postoperative seizures on multivariate analysis when incorporating local and distant progression in analysis (HR 3.22; 95% CI 1.27–8.16; p = 0.014). Distant CNS progression was a significant predictor of postoperative seizures on univariate (HR 2.63; 95% CI 1.10–6.30; p = 0.031) but not multivariate analysis (HR 1.00; 95% CI 0.36–2.78; p = 0.994). Local CNS progression was not a significant predictor of postoperative seizures (HR 1.93; 95% CI 0.77–4.82; p = 0.162). Similarly, using Cox analysis to assess time to intracranial tumor progression, *CDKN2A* alterations were associated with both local (HR 2.63; 95% CI 1.01–6.84; p = 0.047) and distant (HR 1.91; 95% CI 1.13–3.25) intracranial tumor progression postoperatively. *CDKN2A/B* codeletion was also associated with both local (HR 4.62; 95% CI 1.78–12.02; p = 0.002) and distant (HR 1.99; 95% CI 1.14–3.49; p = 0.016) intracranial tumor progression in this cohort.

Primary Malignancy and Postoperative Seizures

The only clinical factor that was a significant predictor of postoperative seizure risk on multivariate analysis was primary malignancy, with melanoma carrying a higher risk of postoperative seizures compared with all other primary malignancies (HR 4.81; 95% CI 1.24–18.59; p = 0.023); see Fig. 2B. Higher rates of seizures with melanoma BMs compared to other primary malignancies have been previously reported.[1,28] The overall rate of postoperative seizures in melanoma BMs was 42.9% (15/35) compared with 12.7% (10/79) for all other primary malignancies. For reference, analyses were also carried out for risk of postoperative seizures with melanoma versus each of the other primary malignancies. In these analyses, NSCLC was associated with a lower risk of postoperative seizures compared with melanoma on multivariate analysis (HR 0.14; 95% CI 0.02–0.86; p = 0.034), and other comparisons of primary malignancy were nonsignificant, probably because of smaller sample sizes for other primary malignancies. These results further support a particularly high rate of postoperative seizures in patients with a primary malignancy of melanoma.

Recommendations for Antiseizure Prophylaxis After Resection of BMs

The sole previous randomized trial focusing on antiseizure prophylaxis after resection of brain metastases showed no significant reduction in seizures in the perioperative setting.[29] A

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similar null result for antiseizure prophylaxis after resection has been found when grouping all brain tumors.[30] However, it should be noted that no randomized study has assessed longer-term postoperative seizure rates after BM resection, which may be much higher than in the immediate postoperative period. Indeed, the one randomized study on antiseizure prophylaxis after BM resection found a clinically relevant seizure rate of just 3% within 7 days postoperatively,[29] compared with 21.9% of all patients in this study who had clinically identified postoperative seizures with a median follow-up of 8.0 months. Identifying which patients are at risk for long-term postoperative seizures may guide effective individualized treatment, thereby avoiding unnecessary adverse effects of antiseizure medication in those at low risk, while preventing the morbidity of seizures in those at higher risk. In addition to effectively reducing the morbidity of seizures, there is evidence that antiseizure prophylaxis may improve survival in patients with glioblastoma.[31,32] There could also be survival benefit in preventing postoperative seizures in those at high risk following resection of brain metastases, a topic that deserves further study. This work indicates that both patients with *CDKN2A* alterations and those with primary malignancy of melanoma are at relatively high risk for seizures following BM resection, and thus may be most likely to benefit from antiseizure prophylaxis. Further work is needed to see if escalating antiepileptic therapy in these patients impacts outcomes.

Seizure rates of > 20% in this study exceeded previous reports on patients with BMs (< 15%).[1,33] Given the association between melanoma and seizures, the high rate of patients with melanoma (30.7%) compared to rates of approximately 10% reported in the literature is likely to have contributed to a higher seizure rate.[34] Rapidly evolving systemic therapies and increasing life expectancy in patients with BM may further increase the likelihood of long-term postoperative seizures. Although there was a mild effect of number of BMs on risk of postoperative seizures on univariate analysis (HR 1.12; 95% CI 1.04–1.20), this relationship did not persist on multivariate analysis ($p = 0.131$). Notably, the risk of postoperative seizures may be > 10% following craniotomy independent of the pathology being treated, perhaps due to mechanisms such as cortical trauma or postoperative gliosis.[35] Across all patients who receive a craniotomy, postoperative seizure rates have been found to be influenced by factors such as preoperative seizures and the specific lesion being treated.[35,36]

Limitations

Primary limitations of this study include its retrospective methodology and its relatively small sample size with many genetic variables assessed for statistical associations. We attempted to account for the large number of genomic variables by first determining candidate genomic alterations with RF machine learning modeling. A multitude of clinical variables may also confound the associations determined by this study. We note that antiseizure regimens were not standardized across all patients. The definition of seizures encompassed only overt clinical seizures. Comprehensive EEG data were not available to correlate with observed seizures or to detect subclinical seizures. The cohort that presented with seizures, although derived from a large group, was not large enough to provide adequate power to assess tumor or treatment subgroups. Additionally, several demographic and morphological variables that probably modified the threshold for seizures

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were unavailable in the database of medical records included in this study. These variables included demographic factors (e.g., family history of seizures, medications known to provoke seizures) and pathological factors such as presence of cortical hemosiderin deposits, acute or chronic edema, and gliosis.

Conclusions

In this study of patients undergoing resection of brain metastases, *CDKN2A* alterations were associated with increased risk of postoperative seizures. Further studies with larger sample sizes of brain metastases with genomic testing are needed to validate these findings. Correlation of intrinsic genomic features in brain metastases may further advance our understanding of seizure development and improve personalized therapy for patients.

ABBREVIATIONS

BM	brain metastasis
NSCLC	non–small cell lung cancer
RF	random forest
WBRT	whole-brain radiation therapy

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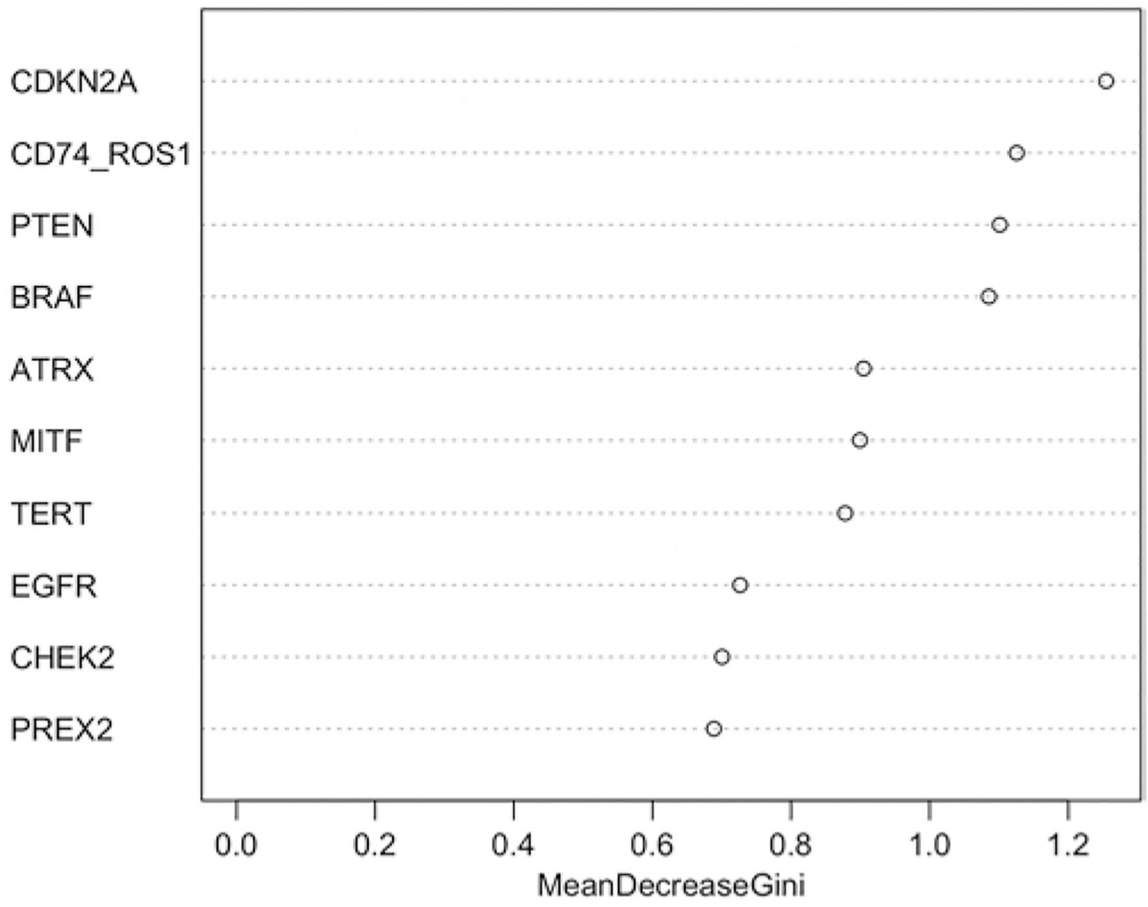

FIG. 1.

CDKN2A identified as the top genomic variable associated with postoperative seizures on RF classification.

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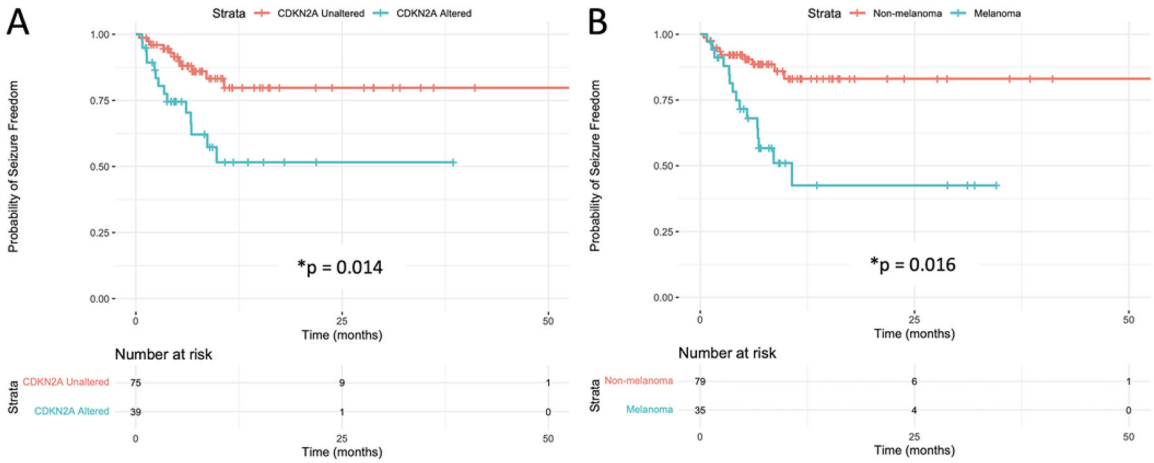

FIG. 2.

Kaplan-Meier curves for postoperative seizure freedom after resection of brain metastases by (**A**) *CDKN2A*-altered versus *CDKN2A*-unaltered BMs (log-rank test, p = 0.014) and (**B**) by melanoma versus nonmelanoma primary malignancy (log-rank test, p = 0.016).

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TABLE 1.

List of gene alterations in BMs included in analyses

AGBL1-NTRK3	*BRCA1*	*CIC*	*ERBB4*	*IKZF3*	*MLH1*	*NRIP1*	*RAC1*	*STK11*
AKT1	*BRCA2*	*COL1A1*	*ESR1*	*INPP4B*	*MRE11*	*NTRK1*	*RAD51*	*TBX3*
ALK	*CASR*	*COL2A1*	*FAT1*	*JAK1*	*MSH3*	*PAK1*	*RARA*	*TERT*
AMER1	*CBL*	*CREBBP*	*FBXW7*	*KDM5C*	*MSH6*	*PALB2*	*RASA2*	*TET2*
APC	*CCND1*	*CTNNB1*	*FGF3*	*KDM6A*	*MTOR*	*PBRM1*	*RB1*	*TFED*
ARAF	*CCND3*	*CUL3*	*FGF4*	*KDR*	*MUTYH*	*PDGFRA*	*RBM10*	*THSD4-NTRK3*
ARHGAP35	*CCNE1*	*DAXX*	*FGF19*	*KEAP1*	*MYC*	*PIK3CA*	*RNF43*	*TP53*
ARID1A	*CD74-ROS1*	*DCC*	*FGFR1*	*KIT*	*MYCL*	*PIK3R1*	*RUNX1*	*TRAF7*
ARID2	*CD79A*	*DDX3X*	*FGFR3*	*KMT2A*	*NAV3*	*PIK3R2*	*SETBP1*	*TSC1*
ARID5B	*CDH1*	*DICER1*	*FH*	*KMT2B*	*NCOR1*	*PMS2*	*SETD2*	*VEGFA*
ASXL1	*CDK4*	*DNAH12-RAF1*	*FLT1*	*KMT2C*	*NF1*	*PPM1D*	*SF3B1*	*VHL*
ATM	*CDK6*	*DNMT3A*	*FLT3*	*KMT2D*	*NF2*	*PPP6C*	*SLIT2*	*ZFHX3*
ATR	*CDK8*	*EGFR*	*FOXA1*	*KRAS*	*NFE2L2*	*PREX2*	*SMAD2*	
ATRX	*CDK12*	*EIF1AX*	*GATA1*	*LRP1B*	*NFKBIE*	*PRKDC*	*SMAD4*	
BAP1	*CDKN2A*	*ELF1-FOXO1*	*GATA3*	*LZTR1*	*NIPBL*	*PTCH1-GLI1*	*SMARCA4*	
BARD1	*CDKN2B*	*ELF3*	*GLMN*	*MAP2K1*	*NKX2–1*	*PTEN*	*SMARCAL1*	
BCORL1	*CDKN2A/B* codeletion	*EML4-ALK*	*GNA11*	*MED12*	*NOTCH1*	*PTPN11*	*SPEN*	
BLM	*CHD1*	*EPHA3*	*GNAS*	*MET*	*NOTCH2*	*PTPRB*	*SPRED1*	
BMPR1A	*CHD5*	*ERBB2*	*GRIN2A*	*MGA*	*NOTCH3*	*PTPRK*	*SPTA1*	
BRAF	*CHEK2*	*ERBB3*	*IDH1*	*MITF*	*NRAS*	*PTPRT*	*STAG2*	

Alterations with a hyphen between genes denote fusions (i.e., *AGBL1-NTRK3, CD74-ROS1, DNAH12-RAF1, ELF1-FOXO1, EML4-ALK, PTCH1-GLI1*, and *THSD4-NTRK3*). All other genes include all previously defined pathogenic genomic alterations in the gene of interest.

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TABLE 2.

Clinical and tumor characteristics

Characteristic	Value
Age in yrs	63.2 ± 13.6
Female sex (%)	55 (48.2%)
Race	
Asian/Pacific Islander	15 (13.2%)
African American/Black	4 (3.5%)
Caucasian/White	84 (73.7%)
Hispanic/Latino	9 (7.9%)
Native American/Alaskan Native	2 (1.8%)
Primary malignancy, no. (%)	
Melanoma	35 (30.7%)
NSCLC	32 (28.1%)
Breast	13 (11.4%)
GI	9 (7.9%)
RCC	6 (5.3%)
Gyn	5 (4.4%)
Other	14 (12.3%)
Hepatocellular	2 (1.8%)
Prostate	2 (1.8%)
Pancreatic	2 (1.8%)
Sarcoma, undifferentiated	2 (1.8%)
Spindle cell	1 (0.9%)
Pulmonary SCC	1 (0.9%)
Acinic cell carcinoma	1 (0.9%)
Parotid cell carcinoma	1 (0.9%)
Carcinoma, undifferentiated	1 (0.9%)
Urothelial	1 (0.9%)
Location	
Frontal	42 (36.8%)
Parietal	35 (30.7%)
Temporal	22 (19.3%)
Occipital	15 (13.2%)
Lt side (%)	53 (46.5%)
Hx of multiple craniotomies	22 (19.3%)
Resected tumor vol in cm^3, median (range)	12.8 (0.3–109.9)
Extent of resection (%)	
GTR	95 (83.3%)
STR	19 (16.7%)

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Characteristic	Value
Local progression	16 (14.0%)
Distant progression	57 (50.0%)
Prior radiation	30 (26.3%)
Postop radiation	
None	22 (19.3%)
Brachytherapy	10 (8.8%)
Local radiotherapy	79 (69.3%)
WBRT	3 (2.6%)
Cystic tumor	18 (15.8%)
Hemorrhagic tumor	61 (53.5%)
No. of BMs at surgery, median (max)	2 (25)
Systemic disease present	84 (73.7%)
Preop Sz	26 (22.8%)
Checkpoint inhibitor postop	40 (35.1%)
Targeted therapy postop	44 (38.6%)
Time from malignancy Dx to BM Dx, median mos (range)	22.2 (0.0–353.4)
Time from BM Dx to surgery, median mos (range)	0.4 (0.0–62.8)
Duration of follow-up, median mos (range)	8.0 (1.2–90.2)

Dx = diagnosis; GI = gastrointestinal; GTR = gross-total resection; Gyn = gynecological; Hx = history; max = maximum; RCC = renal cell carcinoma; SCC = small cell carcinoma; STR = subtotal resection; Sz = seizure.

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TABLE 3.

Postoperative seizures: clinical and genomic associations assessed by Cox proportional hazards

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	**p Value**	**HR (95% CI)**	**p Value**
Age	1.02 (0.96–1.01)	0.178		
Sex; male vs female	1.15 (0.53–2.53)	0.723		
Race; minority vs nonminority	0.86 (0.36–2.05)	0.728		
Primary malignancy				
Nonmelanoma	Reference	Reference	Reference	Reference
Melanoma	**3.97 (1.78–8.87)**	**0.000778**	**5.23 (1.37–19.98)**	**0.016**
Location				
Frontal	Reference	Reference		
Parietal	1.89 (0.74–4.81)	0.181		
Temporal	0.66 (0.18–2.49)	0.539		
Occipital	1.26 (0.38–4.20)	0.703		
Side; rt vs lt	1.28 (0.58–2.83)	0.538		
Hx of multiple craniotomies	**3.63 (1.62–8.13)**	**0.00174**	1.74 (0.64–4.78)	0.280
Resected tumor vol in mL	0.98 (0.96–1.01)	0.160		
Extent of resection; STR vs GTR	2.00 (0.84–4.79)	0.120		
Local progression	1.93 (0.77–4.82)	0.162		
Distant progression	**2.63 (1.10–6.30)**	**0.031**	1.00 (0.36–2.78)	0.994
Prior radiation	1.55 (0.67–3.61)	0.305		
Postop radiation				
None	Reference	Reference		
Brachytherapy	1.26 (0.30–5.32)	0.755		
Local radiotherapy	0.64 (0.24–1.76)	0.387		
WBRT	1.36 (0.16–11.70)	0.778		
Cystic tumor	0.69 (0.21–2.32)	0.552		
Hemorrhagic tumor	1.67 (0.74–3.78)	0.222		
Preop SWI artifact; significant vs trace/none	1.40 (0.60–3.24)	0.438		

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Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
No. of BMs	**1.12 (1.04–1.20)**	**0.00344**	1.07 (0.98–1.17)	0.131
Systemic disease present	1.08 (0.45–2.60)	0.861		
Preop Sz	1.84 (0.79–4.37)	0.156		
Checkpoint inhibitor postop	1.28 (0.58–2.82)	0.543		
Targeted therapy postop	1.45 (0.66–3.18)	0.357		
Time from BM Dx to surgery	1.01 (0.97–1.04)	0.710		
Time from malignancy Dx to BM Dx	1.00 (0.99–1.01)	0.983		
Genes				
CDKN2A	**3.08 (1.39–6.78)**	**0.00537**	**3.22 (1.27–8.16)**	**0.014**
CD74-ROS1	**9.69 (2.22–42.33)**	**0.00253**	**14.06 (1.52–130.44)**	**0.020**
PTEN	1.96 (0.78–4.90)	0.152		
BRAF	**2.70 (1.07–6.81)**	**0.035**	1.34 (0.39–4.59)	0.646
ATRX	3.47 (0.81–14.91)	0.095		
MITF	**4.34 (1.02–18.59)**	**0.048**	2.23 (0.43–11.50)	0.338
TERT	**2.56 (1.17–5.61)**	**0.019**	0.62 (0.19–1.99)	0.418
EGFR	0.31 (0.04–2.28)	0.248		
CHEK2	1.12 (0.15–8.27)	0.914		
PREX2	2.27 (0.53–9.67)	0.267		

Boldface type indicates statistical significance.

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TABLE 4.

CDKN2A alteration pathogenicity and postoperative seizures

Deletion	Sz Frequency	Sz Semiology
CDKN2A deep deletion (n = 3) *CDKN2A* exon 1 deletion (n = 1) *CDKN2A/B* deletion (n = 26)	10 of 30 patients (33.3%)	• Gaze deviation & hemibody convulsions followed by postictal hemiparesis (n = 1) • Generalized tonic-clonic Sz (n = 3) • Unilat upper-extremity & face convulsions (n = 1) • Unilat arm convulsions generalized to tonic-clonic Sz followed by transient postictal hemiparesis (n = 1) • Hemibody convulsions followed by transient postictal hemiparesis (n = 2) • Transient episodes of altered mental status determined as likely Szs (n = 1) • Transient aphasia followed by gaze deviation (n = 1)
Point Mutations/Frameshifts/Translocation	**Sz Frequency**	**Sz Semiology**
CDKN2A p.M54fs (frameshift mutation; n = 1) *CDKN2A* p.L78fs (frameshift mutation; n = 1) *CDKN2A* p.R103fs (frameshift mutation; n = 1) *CDKN2A* p.P114L (missense mutation; n = 1) *CDKN2A* p.A102E (missense mutation; n = 1) *CDKN2A* p.R80* (nonsense mutation; n = 2) *CDKN2A* p.R58* (nonsense mutation; n = 1) *CDKN2A* inactivating translocation (n = 1)	4 of 9 (44.4%)	• Transient unilat hand numbness followed by upper-extremity weakness (n = 1) • Transient receptive aphasia w/ corresponding epileptiform activity on EEG (n = 1) • Generalized tonic-clonic Sz (n = 1) • Transient unilat upper-extremity weakness & altered mental status (n = 1)

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