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Genomic alterations associated with postoperative nodular leptomeningeal disease after resection of brain metastases

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Abstract

OBJECTIVE—The relationship between brain metastasis resection and risk of nodular leptomeningeal disease (nLMD) is unclear. This study examined genomic alterations found in brain metastases with the aim of identifying alterations associated with postoperative nLMD in the context of clinical and treatment factors.

METHODS—A retrospective, single-center study was conducted on patients who underwent resection of brain metastases between 2014 and 2022 and had clinical and genomic data available. Postoperative nLMD was the primary endpoint of interest. Targeted next-generation sequencing of > 500 oncogenes was performed in brain metastases. Cox proportional hazards analyses were performed to identify clinical features and genomic alterations associated with nLMD.

RESULTS—The cohort comprised 101 patients with tumors originating from multiple cancer types. There were 15 patients with nLMD (14.9% of the cohort) with a median time from surgery to nLMD diagnosis of 8.2 months. Two supervised machine learning algorithms consistently identified *CDKN2A/B* codeletion and *ERBB2* amplification as the top predictors associated with postoperative nLMD across all cancer types. In a multivariate Cox proportional hazards analysis

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

Disclosures

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

Supplemental Information

Online-Only Content

Supplemental Figs. 1 and 2. https://thejns.org/doi/suppl/10.3171/2023.5.JNS23460.

including clinical factors and genomic alterations observed in the cohort, tumor volume (× 10 cm^3; HR 1.2, 95% CI 1.01–1.5; p = 0.04), *CDKN2A/B* codeletion (HR 5.3, 95% CI 1.7–16.9; p = 0.004), and *ERBB2* amplification (HR 3.9, 95% CI 1.1–14.4; p = 0.04) were associated with a decreased time to postoperative nLMD.

CONCLUSIONS—In addition to increased resected tumor volume, *ERBB2* amplification and *CDKN2A/B* deletion were independently associated with an increased risk of postoperative nLMD across multiple cancer types. Additional work is needed to determine if targeted therapy decreases this risk in the postoperative setting.

Keywords

brain metastasis; surgery; *CDKN2A* ; *CDKN2B* ; *ERBB2* ; leptomeningeal disease; oncology

Brain metastases are the most common intracranial patients with solid cancers will develop brain metastases.[1] Although novel systemic agents offer promising control of CNS disease,[2–5] control of brain metastases and prevention of CNS dissemination remain a challenge. Local control of brain metastases can be achieved with resection via a craniotomy, and the addition of adjuvant postoperative radiation therapy has been shown to decrease rates of local recurrence.[6–9]

One concern with resection, however, is a potential risk of developing nodular leptomeningeal disease (nLMD) postoperatively. Some studies have demonstrated that resection is associated with higher rates of CNS dissemination compared with treatment with stereotactic radiosurgery (SRS).[10,11] Previously identified risk factors for the development of leptomeningeal disease (LMD) postoperatively include breast cancer histology, posterior fossa location, piecemeal resection, the presence of multiple lesions, and hemorrhagic and cystic features.[12–17] However, the risk factors highlighted are inconsistent among studies. Furthermore, there has been a paucity of studies examining genomic alterations associated specifically with postoperative LMD. This study aimed to identify genomic alterations associated with nLMD in the context of clinical and treatment factors.

Methods

Study Design

This was a retrospective cohort study conducted at a single academic center (University of California, San Francisco [UCSF]). After obtaining approval from the UCSF IRB, we searched the institutional tumor registry for adult patients who had undergone resection of intracranial brain metastases between 2014 and 2022. Inclusion criteria were patients who 1) were ≥ 18 years of age at the time of surgery, 2) underwent a craniotomy for brain metastasis resection, 3) had gene sequencing data available for analysis, 4) had pathology-confirmed malignant tissue present in resected specimens, and 5) had an electronic medical record with available documentation of clinical and imaging outcomes for > 1 month. Patients were excluded if they did not have gene sequencing performed, had only radiation necrosis on pathology, or had dura mater–based lesions. Resection was pursued after a multidisciplinary discussion between a neurosurgeon, radiation oncologist, and oncologist. The IRB waived

the requirement for written informed consent for this retrospective observational study. Genomic data were collected for clinical purposes.

Patient, Treatment, and Tumor Variables

Patient variables included age at surgery, race/ethnicity, sex, preoperative Karnofsky Performance Status (KPS), minority status (all non-Caucasian), and date of death. Tumor variables included primary cancer type, tumor side, tumor location, tumor volume (estimated using the [length × width × height]/2 method previously validated for assessing tumor volume[3]), intratumoral hemorrhage on preoperative imaging, cystic appearance on preoperative imaging, number of brain metastases at the time of surgery, and the presence of extracranial disease at the time of surgery. Extracranial disease status was based on results from either CT imaging of the body with and without contrast or total-body PET imaging performed for staging purposes within 1 month of the surgery date. Treatment variables included extent of resection (gross-total resection [GTR] vs subtotal resection [STR] of the enhancing disease), treatment with checkpoint inhibitors or other targeted therapy, prior radiation therapy to the index brain metastasis (i.e., progressive brain metastases), number of metastases resected at the index surgery, and type of postoperative local radiation therapy. Prior radiation treatment was defined as upfront treatment of brain metastases prior to the index surgery. Preoperative SRS as a form of perioperative adjuvant therapy was not used in the cohort.

Next-generation sequencing of all brain metastasis specimens using a Clinical Laboratory Improvement Amendments (CLIA)–certified assay was performed on the coding regions of 529 oncogenes as well as select introns of 47 genes as part of clinical care only. These data were extracted from the medical record for retrospective analysis. An oncoplot of genomic alterations observed in the cohort is depicted in Supplemental Fig. 1. Genomic analysis was performed at the discretion of the treating oncologist in the first half of the study period (2014–2018) and for all resected brain metastases at the institution in the second half of the study period (2019–2022).

Clinical Outcomes of Interest

The main outcome of interest for the study was the occurrence of postoperative nLMD as defined by prior studies.[18,19] Examples are shown in Fig. 1. Because not all patients underwent CSF sampling at the time of suspected LMD occurrence, MRI criteria were used for defining LMD, as has been previously published.[19] In brief, nLMD was defined as new focal extra-axial nodular enhancing lesions in contact with the meninges or ependyma. These were distinct from intra-axial recurrences that did not have pial invasion with dural contact. Previously defined “linear” or “classical” LMD with sugarcoating enhancement along cranial nerves and sulci were not included as events. Diagnoses were based on MRI features only. For the purposes of this study, nLMD diagnosis required 1) documentation by an attending neuroradiologist, 2) agreement by the treating oncologist or neuro-oncologist, and 3) verification by the lead author (R.A.M.).

Statistical Analysis

Statistical analyses were performed in JMP Pro (version 16.0, SAS Institute Inc.). Demographic data and baseline characteristics were collected and analyzed in a standard fashion. The Kaplan-Meier method was used to visualize time to postoperative nLMD from the date of surgery. Univariate and multivariate Cox proportional hazards and nominal logistic regression analyses were performed to identify variables associated with nLMD. Odds ratios (nominal regression) and hazard ratios (Cox proportional hazards model) and their 95% CIs were computed. Multivariate regression analyses were performed with variables demonstrating $p < 0.05$ on univariate analysis. The level of significance was $p < 0.05$ for all analyses.

The Bootstrap Forest and Boosted Tree platforms in JMP, two supervised machine learning algorithms based on decision trees, were used to screen genomic alterations associated with postoperative nLMD (n = 101 patients). All genes reported in Supplemental Fig. 1 were used for the models. The bootstrap forest algorithm builds a collection of recursive partitioning trees by repeatedly boot-strapping the data. In-bag subsets are used to build a partitioning tree, and predictions are made using out-of-bag subsets of patients. The final predictive model is based on a majority input from 100 trees. The Boosted Tree platform builds an additive decision tree by fitting a sequence of smaller decision trees, called layers. The final prediction for an observation is the sum of the predictions for that observation over all the layers in the model. Missing categorical values within the database were imputed as a separate level of the variable, and missing continuous values within the database were assigned values via an optimal split algorithm. Area under the receiver operating characteristic (AUROC) curves were reported for the two models, and the top three predictors with the biggest effect on the model were reported and assessed with traditional univariate analysis for their association with nLMD.

Finally, JMP's Partition platform was used to create a decision tree using genomic and clinical variables associated with nLMD identified in the multivariate logistic regression analysis. The partition algorithm searches all possible splits of predictors (*CDKN2A/B* codeletion, *ERBB2* amplification, and tumor volume) to best predict a response (occurrence of nLMD). Groups identified on the recursive partition analysis were used to create Kaplan-Meier plots to confirm the relevance of these groups for predicting postoperative LMD.

Results

Summary of Cohort

The cohort comprised 101 patients undergoing resection of 102 brain metastases with genomic data available. There was 1 patient who underwent resection of 2 separate brain metastases during the same operation. Cohort details can be found in Table 1. The median age at surgery was 66 years, and the cohort comprised 51 females and 50 males (50.5% and 49.5% of the cohort, respectively). The most common primary cancer types were melanoma (n = 27 patients, 26.7%), non–small cell lung cancer (NSCLC) (n = 26, 25.7%), and breast adenocarcinoma (n = 12, 11.9%). The most common tumor locations were in the frontal lobe (n = 32, 31.4%), parietal lobe (n = 26, 25.5%), and temporal lobe (n = 17, 16.7%).

Fourteen brain metastases (13.7%) were infratentorial in the cerebellum, while 88 (86.3%) were supratentorial. The median number of brain metastases at the time of index surgery was 1, and extracranial disease was present at the time of index surgery in 72 patients (71.3%). The median tumor volume of the resected brain metastasis was 14.8 cm^3. The median preoperative KPS was 80 (range 40–100).

Details of treatment for the cohort are displayed in Table 1. GTR and STR were attained for 85 (84.2%) and 16 (15.8%) brain metastases, respectively. Prior intracranial radiation therapy had been used in 21 cases (20.8%), and postoperative adjuvant radiation therapy was used in 91.1% of the cohort. Eighty-nine cases underwent focal radiation therapy (SRS, stereotactic radiation therapy [SRT], or brachytherapy), and 3 underwent whole-brain radiation therapy (WBRT). For patients receiving postoperative SRS or SRT, the median dose was 30 Gy (range 16–40 Gy) delivered in a median number of 5 fractions (range 1–10 fractions), with 57 patients (71.3%) receiving fractionated therapy to the resection cavity. For patients receiving postoperative WBRT, doses included 30 Gy in 10 fractions (n = 2) and 35 Gy in 14 fractions (n = 1). For patients receiving brachytherapy, all received cesium-131 with a mean dose of 89.4 mCi. There were 9 patients who did not receive adjuvant radiation therapy. For 7 patients, CNS-penetrating systemic therapy was pursued instead, and for 2 patients, preoperative radiation therapy had been given within a month of surgery.

The mean follow-up was 12.6 months. Postoperative nLMD occurred in 15 patients (14.9%), with a median time from surgery to nLMD of 8.2 months. The censored 6-, 12-, and 24-month nLMD-free survival rates were 91.5%, 86.1%, and 74.1%, respectively. Use of adjuvant SRS/SRT, brachytherapy, WBRT, and no adjuvant radiation therapy was associated with nLMD rates of 15% (n = 12), 22.2% (n = 2), 0% (n = 0), and 11.1% (n = 1), respectively. In patients treated with prior radiation therapy, the risk of nLMD was 23.8% (5 of 21 patients). By the last follow-up, 25 patients had died and the median time of survival from surgery was not reached. The median time to local progression was not reached, and 16 patients (15.8%) had local progression on follow-up. The 6- and 12-month local progression-free survival rates were 90.4% and 84.3%, respectively.

Genomic Alterations Associated With Postoperative nLMD in the Cohort

First, bootstrap forest and boosted tree analyses were performed to help screen for genomic alterations associated with the occurrence of postoperative nLMD. All genomic alterations observed in the cohort were used for analysis. Alterations in *ERBB2*, *CDKN2A/B*, *PTEN*, and *RB1* were within the top three genomic changes predictive of LMD using either statistical method (Fig. 2). *ERBB2* amplification and *CDKN2A/B* codeletion were the top factors across both models.

Next, analyses of the time to postoperative nLMD were performed incorporating the top three genomic alterations identified in either the bootstrap forest or boosted tree analyses (*ERBB2*, *CDKN2A/B* codeletion, *PTEN*, and *RB1*). Of the genes evaluated, *CDKN2A/B* codeletion (median time not reached, log-rank p = 0.007), *ERBB2* amplification (median 13.8 months vs not reached, p = 0.009), and *PTEN* mutations (median 15.3 months vs not reached, p = 0.009) were each independently associated with a shorter time to nLMD (Fig. 3). *RB1* alterations were not significantly associated with time to nLMD, and thus this

alteration was not included for further analyses. Patients with alterations in *CDKN2A/B*, *ERBB2*, or *PTEN* had a significantly decreased time to postoperative nLMD (presence vs absence: median 15.3 months vs not reached, log-rank $p < 0.0001$) (Fig. 3). *CDKN2A/B* codeletion, *ERBB2* amplification, and *PTEN* mutations were seen across multiple cancer types and account for 80% of postoperative nLMD cases (12 of the 15 cases) despite these mutations only being observed in 35.6% of the cohort. *CDKN2A/B* codeletion was seen in 22.2% of melanoma, 30.8% of NSCLC, 16.7% of breast adenocarcinomas, 20% of gastrointestinal (GI) cancers, 16.7% of renal cell carcinoma (RCC), and 5.9% of other cancer types (occurred in urothelial cancer). *ERBB2* amplification was seen in 7.7% of NSCLC, 33.3% of breast adenocarcinoma, and 20% of GI cancers. For GI cancers, 50% of gastric cancer tumors (1 of 2 cases), 20% of colon cancer tumors (1 of 5 cases), and no esophageal cancer tumors (0 of 3 cases) harbored an *ERBB2* amplification. *PTEN* mutations were seen in 18.5% of melanoma, 7.7% of NSCLC, 8.3% of breast adenocarcinoma, 30% of GI cancers, 16.7% of RCC, 66.7% of gynecological cancers, and 5.9% of other cancer types.

A Cox proportional hazards analysis using both clinical and genomic factors was performed to evaluate factors associated with time to nLMD diagnosis (Table 2). Univariate analysis found that increased tumor volume, *ERBB2* amplification, *CDKN2A/B* codeletion, and *PTEN* mutation were associated with postoperative nLMD. On multivariate analysis, tumor volume ($\times 10$ cm^3; HR 1.2, 95% CI 1.01–1.5; $p = 0.04$), *CDKN2A/B* codeletion (HR 5.3, 95% CI 1.7–16.9; $p = 0.004$), and *ERBB2* amplification (HR 3.9, 95% CI 1.1–14.4; $p = 0.04$) were associated with decreased time to postoperative nLMD (Supplemental Fig. 2). *PTEN* alterations were no longer significantly associated with nLMD in the multivariate model. A recursive partitioning analysis was performed using these three variables to divide patients into LMD risk groups. Four risk groups were identified, with groups 1, 2, and 3 having an elevated LMD risk, while group 4 had a decreased LMD risk (Fig. 4A). Group 1 patients (n = 20) harbored tumor with *CDKN2A/B* codeletion and had a postoperative nLMD rate of 35% on follow-up. Group 2 patients (n = 9) lacked *CDKN2A/B* codeletion but had tumors ≥ 42 cm^3 and a postoperative nLMD rate of 44%. Group 3 patients (n = 5) lacked *CDKN2A/B* codeletion, had tumors < 42 cm^3 but harbored *ERBB2* amplification, and had a post-operative nLMD rate of 40%. Group 4 patients (n = 67) lacked *ERBB2* amplification and *CDKN2A/B* codeletion, had tumors < 42 cm^3, and had a postoperative nLMD rate of 3%. Compared with group 4 patients, group 1, 2, and 3 patients had a decreased time to postoperative nLMD (group 1 vs 4: $p < 0.0001$; group 2 vs 4: $p = 0.0003$; group 3 vs 4: 0.0004) (Fig. 4B). There were no significant differences between groups 1, 2, and 3.

Discussion

LMD is considered an end-stage event for patients with metastatic disease and is associated with poor prognosis. Prior studies have defined two phenotypes of LMD: a linear, sugarcoating subtype thought to be secondary to hematological spread and another nodular subtype thought to be iatrogenic, attributed to microscopic tumor spillage at the time of resection.[10,15,20] Although risk factors for predicting LMD after resection of a brain metastasis have included breast cancer histology, infratentorial location, piecemeal tumor resection, number of brain metastases, and intratumoral hemorrhage or cystic features,

results are mixed across studies and the subtype of LMD has not always been clearly differentiated.[12,13,15–17] Furthermore, prior studies have not explored if genomic alterations within brain metastases are associated with the risk of postsurgical nLMD.

In this study, the rate of nLMD in the cohort was 14.9%, with censored 6-, 12-, and 24-month nLMD-free survival rates of 91.5%, 86.1%, and 74.1%, respectively. These rates are comparable to those in prior studies, which have reported rates ranging from 5% to 31%.[8,12,14–17] Genomic alterations present in brain metastases were found to be associated with postoperative nLMD. Amplification of *ERBB2* (i.e., HER2), *CDKN2A/B* codeletion, and mutations in *PTEN* were associated with nLMD in univariate analyses. When combining these genomic alterations with patient and treatment factors in a Cox proportional hazards model, *CDKN2A/B* codeletion and *ERBB2* amplification were still associated with postoperative nLMD in addition to increased resected tumor volume. Furthermore, these genomic alterations occurred across multiple primary cancer types, suggesting that general screening for these aberrations in resected brain metastases may be relevant for guiding follow-up imaging and potentially even treatment management. Finally, recursive partition analysis revealed three groups of patients at increased risk of postoperative nLMD: group 1: presence of *CDKN2A/B* codeletion; group 2: tumor volume ≥ 42 cm^3 and *CDKN2A/B* intact; and group 3: presence of *ERBB* mutation with *CDKN2A/B* intact and tumor volume < 42 cm^3.

CDKN2A (i.e., cyclin-dependent kinase inhibitor 2A) and *CDKN2B* (i.e., cyclin-dependent kinase inhibitor 2B) are tumor suppressor genes located on 9p21, which undergoes homozygous deletion in about 15% of all human cancers.[21,22] *CDKN2A* and *CDKN2B* encode for p16 and p15, two cell cycle checkpoint proteins that interact with CDK4 and CDK6 to regulate and inhibit cell cycle progression. Codeletion of these two genes has been associated with worse prognosis in other oncological settings including intracranial glioma and meningioma. In fact, the presence of homozygous *CDKN2A/B* deletion is now a diagnostic criterion for WHO grade 4 astrocytoma in the new WHO 2021 classification system of CNS tumors and is associated with worse prognosis in patients with isocitrate dehydrogenase (IDH)–wild-type glioblastoma.[23,24] Furthermore, the cell cycle regulatory axis involving CDK4 and CDK6 is potentially targetable with available inhibitors such as ribociclib, palbociclib, and abemaciclib.[25]

There have been little data linking *CDKN2A* or *CDKN2B* alterations to postoperative nLMD. However, *CDKN2A* is frequently altered in brain metastases across several cancer types. For example, Huang and colleagues found that *CDKN2A* and *CDKN2B* were frequently altered in breast and NSCLC brain metastases.[26,27] Interestingly, rates of *CDKN2A* and *CDKN2B* alterations in our cohort were similar to or higher than those observed in brain metastases by Huang and colleagues (*CDKN2A*: NSCLC 30.8% vs 32.9%, breast 25% vs 8.7%; *CDKN2B*: NSCLC 30.8% vs 21%, breast 16.7% vs 6.4%).[26,27] Additionally, *CDKN2A* deletion in melanoma patients is associated with an increased risk of brain metastasis development.[28–30] Finally, *CDKN2A* genomic alterations are frequently observed metastatic cells obtained from the CSF of patients with leptomeningeal metastases[31,32] and have been detected in circulating tumor DNA from CSF obtained from patients with LMD secondary to melanoma.[33] Further work is needed to compare

rates of 9p21 loss or *CDKN2A/B* codeletion between brain metastases, primary tumors, and extracranial metastatic sites to determine if this gene locus is truly associated with the brain metastatic cascade. Interestingly, recent work has noted that loss of 9p21 (with associated loss of *CDKN2A* and *CDKN2B*) is a marker of immune checkpoint therapy resistance.[22,44] Thus, the contribution of these alterations to the interplay between immune escape mechanisms and brain seeding requires further exploration.

ERBB2 amplification was also found to be associated with postoperative nLMD in the present cohort. *ERBB2* encodes for HER2, a receptor tyrosine kinase found across several cancer types but most prevalent in breast cancer. It activates via hetero- or homodimerization with another ERBB member, leading to activation of numerous pathways including the PI3K-AKT-mTOR or RAS pathways. Prior work has demonstrated that patients with HER2+ breast cancer frequently develop brain metastases,[34,35] albeit over a longer time frame compared with triple-negative breast cancer. Prior reports have reported *ERBB2* alterations across many cancer types, the majority of which are amplifications (reportedly about 60% of *ERBB2* alterations).[36,37] *ERBB2* amplification occurs most frequently in esophagogastric cancers (11%–20%) and breast cancer (10%–20%), with lower rates observed in other GI cancers (e.g., colorectal 2%–3%, esophageal 5%–10%) and NSCLC (2%–3%).[36,38–40] When compared with these previously published rates in primary cancers, it appears that *ERBB2* amplification in the present cohort was more prevalent in brain metastases from breast cancer (33.3%) as well as NSCLC (7.7%), with mixed findings in the GI cancer subgroup depending on the primary cancer origin (i.e., gastric vs colon).

Breast cancer overall has been reported to be a risk of LMD after resection of brain metastases. However, there have been limited data clarifying this risk based on HER2 status. Some prior work has demonstrated that HER2 status is associated with a decreased risk of LMD after surgery and improved survival after LMD diagnosis.[16,34,41,42] Press et al., for example, found that within a subgroup of patients who underwent resection of a breast cancer brain metastasis, HER2+ was associated with a decreased risk of LMD.[16] However, this analysis was limited to 21 breast cancer patients and did not differentiate nodular versus linear forms of LMD, limiting comparison to the present study. Furthermore, in the present study, *ERBB2* mutations were analyzed across multiple cancer types, with mutations seen in not only breast cancer but also NSCLC and GI cancers. More work with larger cohorts of patients is needed to clarify this finding within breast cancer patients specifically.

Moving forward, it is important to identify patients who are at increased risk of postoperative nLMD in order to evaluate treatment measures that may mitigate this risk. *CDKN2A/B* alterations are potentially targetable via CDK inhibitors, and mutations in HER2 have a variety of targeted therapies that may be relevant for treatment in the perioperative setting. Validation of our findings in larger cohorts may also justify inclusion of molecular status in the discussion about treatment planning when there is equipoise between resection before SRS to the cavity and SRS alone for a brain metastasis. Recent work has also demonstrated that SRS performed prior to resection may help decrease the risk of local recurrence and potentially LMD.[43] Additionally, if postoperative RT is selected, larger radiation fields or inclusion of the surgical tract to a resection cavity may be implemented to potentially decrease the risk of nLMD during follow-up. Additional work

is thus needed to examine whether escalated therapy in high-risk patients, such as those identified in this study, may help lower postoperative nLMD rates.

Limitations

There are a number of limitations with the current study. This study is a retrospective study and was limited by recall bias, heterogeneity in cancer types, and management during a patient's oncological course. We could only evaluate patients who had adequate documentation of clinical details with available genomic and imaging data collected for clinical purposes. Genomic information on primary tumors was not readily collected as part of clinical care and thus was not available for analysis. Although en bloc resection has been previously identified as being protective against LMD, reliable documentation of this was not consistently performed, and it was difficult to assess in a retrospective manner. Additionally, given the relatively infrequent occurrence of nLMD postoperatively (n = 15), the study may be underpowered to detect all genomic alterations associated with leptomeningeal dissemination. The mean follow-up of 12.6 months and the possibility of misdiagnosis based on imaging features alone may have limited the detection of nLMD in the cohort. Furthermore, given the limited number of patients for each cancer type, subgroup analyses based on primary cancer were not attempted. Further confirmatory work is therefore needed in larger cohorts of patients with brain metastases.

Conclusions

In this cohort of 101 patients with brain metastases from multiple cancer types, increased tumor volume, mutations in *ERBB2*, and *CDKN2A/B* codeletion were associated with an increased risk of postoperative nLMD. Partitioning analysis revealed three separate groups of patients (group 1: presence of *CDKN2A/B* codeletion, group 2: tumor volume ≥ 42 cm^3 and *CDKN2A/B* intact, and group 3: presence of *ERBB2* mutation with *CDKN2A/B* intact and tumor volume < 42 cm^3) with similar rates and timing of postoperative nLMD. These three groups of patients were all at increased risk of postoperative nLMD compared with patients lacking these features. Additional work is needed to examine whether targeted therapy relevant to these genomic alterations may lower the risk of postoperative nLMD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS

AUROC	area under the receiver operating characteristic
GI	gastrointestinal
GTR	gross-total resection
KPS	Karnofsky Performance Status
LMD	leptomeningeal disease

nLMD	nodular LMD
NSCLC	non–small cell lung cancer
RCC	renal cell carcinoma
SRS	stereotactic radiosurgery
SRT	stereotactic radiation therapy
STR	subtotal resection
WBRT	whole-brain radiation therapy

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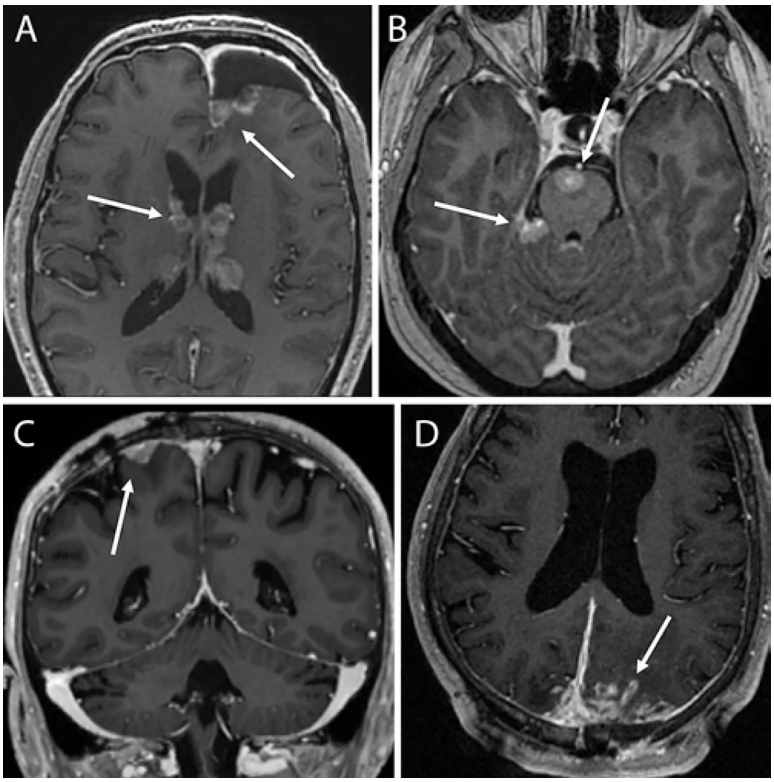

FIG. 1.

Axial (**A, B, and D**) and coronal (**C**) MR images showing examples of postoperative nLMD (*arrows*). Sites of nLMD were outside prior radiation fields.

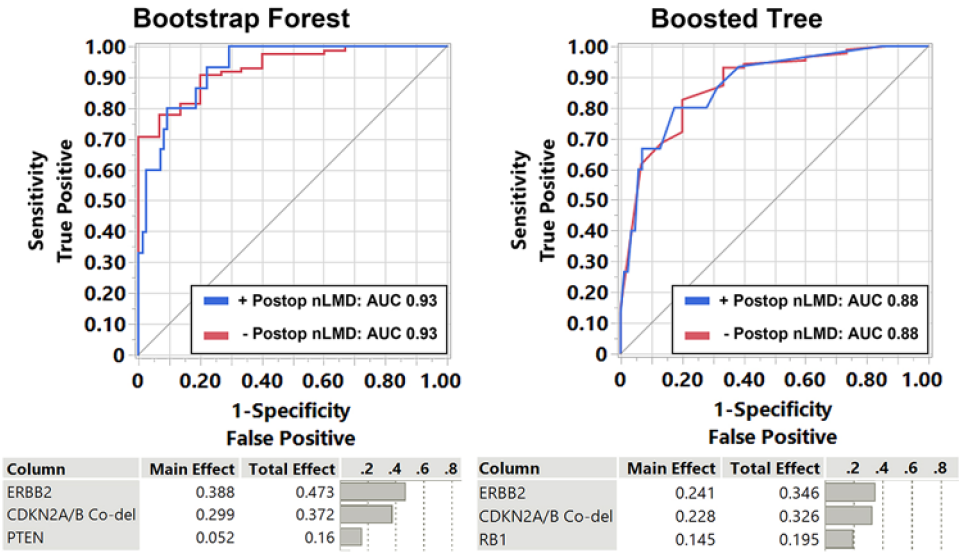

FIG. 2.

Two supervised machine learning algorithms (bootstrap forest and boosted tree analyses) identify genomic alterations associated with postoperative nLMD. For both models, all mutations observed in the cohort were included for analysis. For the bootstrap forest analysis, the model was found to have an AUROC curve of 0.93 and identified *ERBB2* mutations, *CDKN2A/B* codeletion, and *PTEN* mutations as the top three contributing factors. For the boosted tree analysis, the model had an AUROC curve of 0.88 and identified *ERBB2* mutations, *CDKN2A/B* codeletion, and *RB1* mutations as the top three contributing factors. Figure is available in color online only.

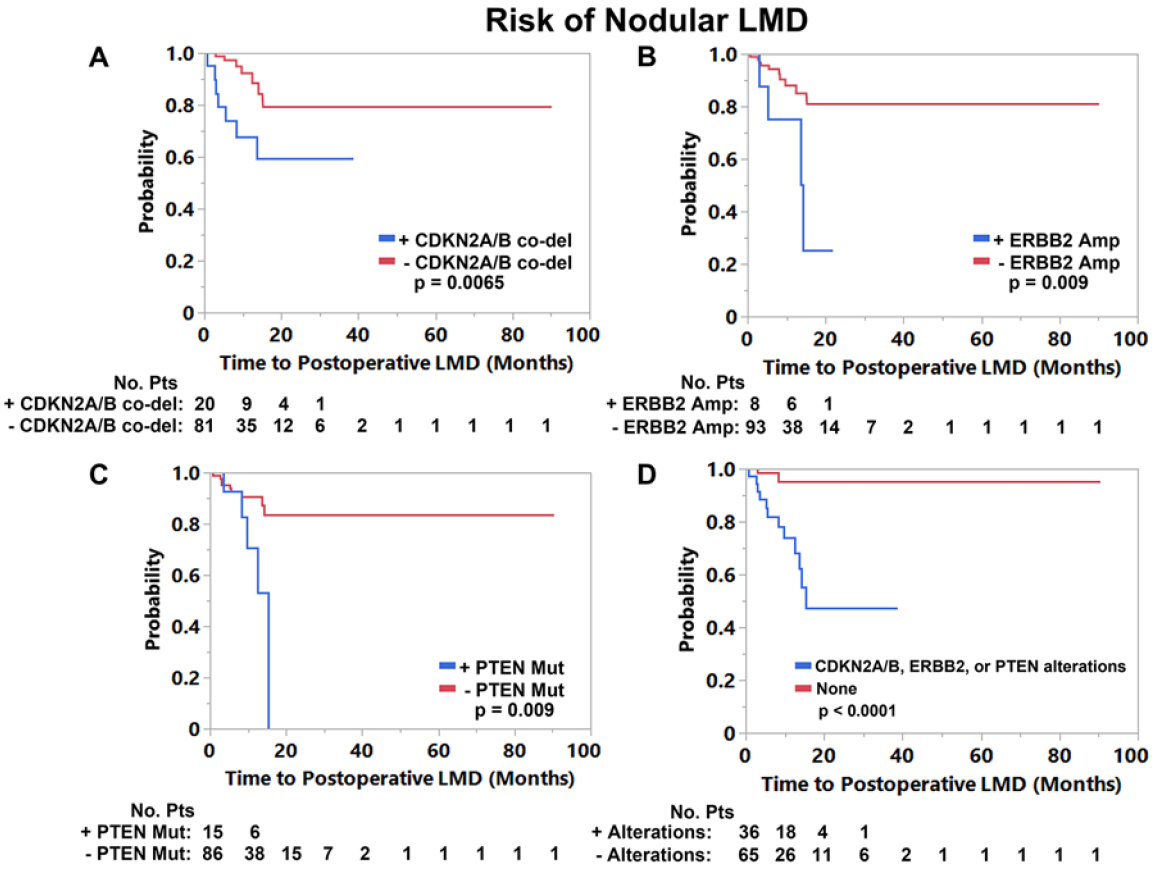

FIG. 3.

Analyses of time to postoperative nLMD by genomic alterations. **A–C:** *CDKN2A/B* codeletion (co-del) (A), *ERBB2* amplification (Amp) (B), and *PTEN* mutations (Mut) (C) were associated with a decreased time to nLMD diagnosis. **D:** Patients with alterations in any of the three genes of interest had a significantly higher risk of developing nLMD ($p < 0.0001$). Pts = patients. Figure is available in color online only.

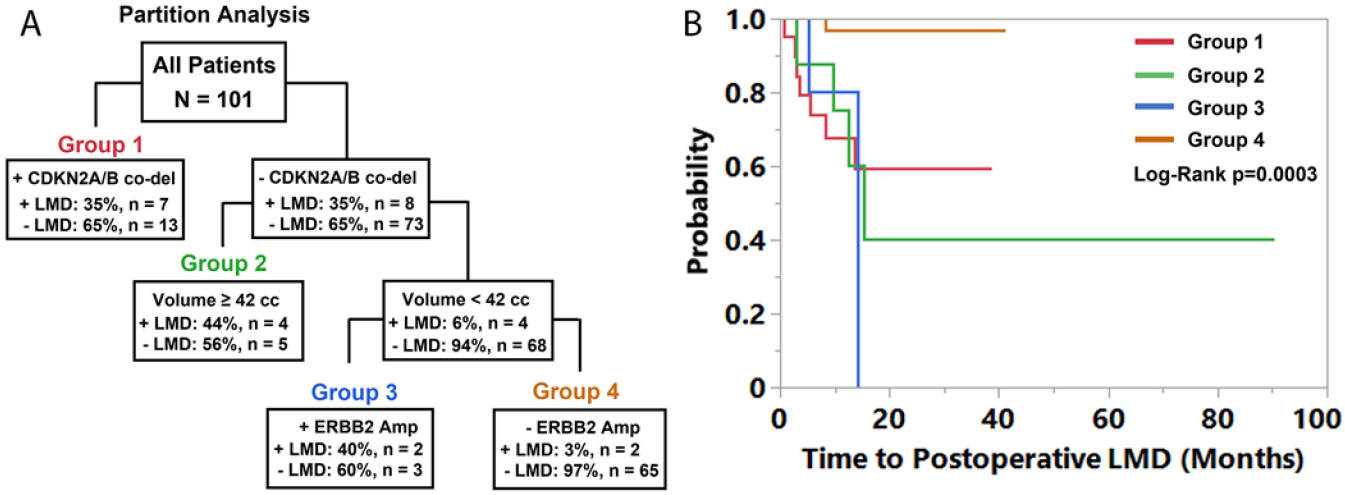

FIG. 4.

Recursive partition analysis to identify groups at risk of postoperative nLMD. **A:** Groups were differentiated based on *CDKN2A/B* codeletion, resected tumor volume, and *ERBB2* mutation status. Groups 1, 2, and 3 were at increased risk of nLMD, while group 4 was at decreased risk. **B:** The time to postoperative nLMD based on these partitioned groups was also significant (log-rank p = 0.0003). cc = cm^3. Figure is available in color online only.

TABLE 1.

Patient, tumor, and treatment characteristics for the cohort

	Value
No. of patients	101
No. of metastases	102
Primary cancer type	
Melanoma	27 (26.7)
NSCLC	26 (25.7)
Breast	12 (11.9)
GI	10 (9.9)
RCC	6 (5.9)
Gynecological	3 (3.0)
Other	17 (16.8)
Median (range) age, yrs	66.3 (27.1–84.9)
Sex	
Female	51 (50.5)
Male	50 (49.5)
Race/ethnicity	
White/Caucasian	76 (75.2)
Asian/Pacific Islander	13 (12.9)
Hispanic/Latino	7 (6.9)
Black/African American	3 (3.0)
American Indian/Alaska Native	2 (2.0)
Median (range) preop KPS	80 (40–100)
Location	
Frontal	32 (31.4)
Parietal	26 (25.5)
Temporal	17 (16.7)
Cerebellum	14 (13.7)
Occipital	13 (12.7)
Side	
Rt	53 (52.0)
Lt	48 (47.1)
Midline	1 (1.0)
Median (range) time from BM diagnosis to op, mos	0.3 (0–62.7)
Median (range) tumor vol, cm^3	14.8 (0.3–109.9)

	Value
Median (range) no. of BMs at op	1 (1–18)
Multiple craniotomies	17 (16.8)
Cystic features	18 (17.8)
Intratumoral hemorrhage	49 (48.5)
Systemic disease status	
Present	72 (71.3)
Not present	29 (28.7)
Extent of resection	
GTR	85 (84.2)
STR	16 (15.8)
Prior RT	21 (20.8)
Periop adjuvant RT	
SRS/SRT	80 (79.2)
Brachytherapy	9 (8.9)
WBRT	3 (3.0)
None	9 (8.9)
Checkpoint or targeted therapy	81 (80.2)
Postop nLMD	15 (14.9)
Local CNS progression	16 (15.8)
Distant CNS progression	47 (46.5)
Death	25 (24.8)
Mean (range) follow-up, mos	12.6 (1.3–90.2)

BM = brain metastasis; RT = radiation therapy.

Values are given as number of patients or metastases (%) unless otherwise indicated.

TABLE 2.

Univariate and multivariate Cox proportional hazards analyses for predicting time to postoperative nLMD

	Univariate		Multivariate	
	HR (95% CI)	**p Value**	**HR (95% CI)**	**p Value**
Age	2.6 (0.4 to 26.3)	0.38		
Male (vs female)	0.8 (0.3 to 2.3)	0.61		
Minority	0.9 (0.2 to 3.2)	0.85		
Primary cancer				
Melanoma	Reference			
NSCLC	0.8 (0.2 to 2.8)	0.26		
Breast	0.7 (0.1 to 3.6)	0.65		
Gastrointestinal	0.6 (0.07 to 4.8)	0.60		
Renal cell carcinoma	*			
Gynecological	2.0 (0.4 to 10.3)			
Other	*			
Preop KPS	0.2 (0.02 to 1.8)	0.13		
Multiple craniotomies	1.2 (0.3 to 4.4)	0.76		
Time from BM diagnosis to op	4.2 (0.1 to 35.6)	0.28		
No. of BMs at op	0.02 (7.2e-6 to 2.2)	0.20		
Tumor vol (× 10 cm^3)	1.2 (1.04 to 1.4)	0.007	1.2 (1.01–1.5)	0.04
Cystic	0.7 (0.2 to 3.1)	0.62		
Intratumoral hemorrhage	0.5 (0.2 to 1.5)	0.22		
Systemic disease absent	2.7 (0.9 to 7.8)	0.07		
Extent of resection (GTR vs STR)	3.4 (0.4 to 25.8)	0.25		

	Univariate		Multivariate	
	HR (95% CI)	**p Value**	**HR (95% CI)**	**p Value**
Prior RT	2.8 (0.9 to 8.3)	0.07		
Postop RT type		0.75		
Local RT	Reference			
WBRT	*			
None	0.7 (0.1 to 5.5)			
Checkpoint inhibitor therapy	1.8 (0.6 to 5.4)	0.29		
Targeted inhibitor therapy	1.4 (0.5 to 4.2)	0.54		
Location		0.14		
Frontal	Reference			
Cerebellum	1.3 (0.3 to 7.0)			
Parietal	0.3 (0.03 to 2.5)			
Occipital	3.2 (0.9 to 11.1)			
Temporal	0.8 (0.2 to 4.2)			
ERBB2 mutation	4.2 (1.3 to 13.4)	0.02	3.9 (1.1–14.4)	0.04
CDKN2A/B codeletion	3.9 (1.4 to 11.1)	0.01	5.3 (1.7–16.9)	0.004
PTEN mutation	3.9 (1.3 to 11.9)	0.02	2.9 (0.8–10.3)	0.10

*There were no LMD events in the group, precluding HR calculation.