Original Article

Adjuvant radiotherapy and outcomes of presumed hemorrhagic melanoma brain metastases without malignant cells

Yuanxuan Xia[1], Leila A. Mashouf[1], Russell Maxwell[1,2], Luke C. Peng[2], Evan J. Lipson[3],
William H. Sharfman[3], Chetan Bettegowda[1], Kristin J. Redmond[2], Lawrence R. Kleinberg[2],
Michael Lim[1,2,3]

[1]Department of Neurosurgery, Johns Hopkins Medical Institutes, [2]Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins Medical Institutes, [3]Department of Oncology, Johns Hopkins Medical Institutes, Baltimore, Maryland, USA

E-mail: Yuanxuan Xia - yxia17@jhmi.edu; Leila A. Mashouf - lmashouf@jhu.edu; Russell Maxwell - rmaxwe13@jhmi.edu; Luke C. Peng - Lpeng14@jhmi.edu;
Evan J. Lipson - evanlipson@jhmi.edu; William H. Sharfman - Sharfwi@jhmi.edu; Chetan Bettegowda - cbetteg1@jhmi.edu;
Kristin J. Redmond - kjanson3@jhmi.edu; Lawrence R. Kleinberg - KLEINLA@jhmi.edu; *Michael Lim - mlim3@jhmi.edu
*Corresponding author

Abstract

Background: Patients with melanoma can present with a hemorrhagic intracranial lesion. Upon resection, pathology reports may not detect any malignant cells. However, the hemorrhage may obscure their presence and so physicians may still decide whether adjuvant radiotherapy should be applied. Here, we report on the outcomes of a series of patients with melanoma with hemorrhagic brain lesions that returned with no tumor cells.

Methods: All melanoma patients who had craniotomies from 2008 to 2017 at a single institution for hemorrhagic brain lesions were identified through retrospective chart review. Those who had pathology reports with no malignant cells were analyzed. Recurrence at the former site of hemorrhage and resection was the primary outcome.

Results: Ten patients met inclusion criteria, and the median follow-up time was 8.5 (1.8–27.3) months. At the time of craniotomy, the median number of brain lesions was 3 (1–25). Two patients had prior craniotomies, eight had prior radiation, and six had prior immunotherapy to the lesion of interest. After surgery, one patient received stereotactic radiosurgery (SRS) to the resection bed. Only one patient developed subsequent melanoma at the resection site; this patient developed the lesion recurrence once and had not received postoperative SRS.

Conclusion: Although small foci of metastatic disease as a source of bleeding for some patients cannot be excluded, melanoma patients with a suspected hemorrhagic brain metastasis that shows no tumor cells on pathology may benefit from close observation. The local recurrence risk in such cases appears to be low, even without adjuvant radiation.

Key Words: Brain metastasis, hemorrhage, melanoma, negative pathology, stereotactic radiosurgery

INTRODUCTION

Worldwide, the incidence of brain metastases is increasing in patients with advanced solid tumors and this is in part due to better systemic therapies and increased surveillance with improved imaging modalities.[13,28] Melanoma has one of the highest tendencies to develop brain metastases with a prevalence of nearly 45% in patients with stage IV melanoma and 75% upon autopsy.[3,11,21,30] This predisposition has been attributed to the cancer's highly angiogenic, immunoevasive, and proliferative nature.[5] These characteristics also contribute to the high frequency of hemorrhage in melanoma brain metastases.[6,25,30] In a retrospective review of 905 brain tumor cases, melanoma metastases had the highest rate of hemorrhage at 50.0% while the second most frequent was oligodendroglioma at 35.7%.[19]

When a hemorrhagic brain lesion is discovered in a patient with melanoma, it is commonly presumed to be a melanoma metastasis. Typically, standard of care involves surgical resection and, once pathology confirms melanoma, a regimen of stereotactic radiosurgery (SRS) is prescribed to significantly reduce the risk of local recurrence.[18,23] However, in rare cases, these lesions have no detectable malignant cells.[18,20] Instead, pathology reports show evidence for radiation necrosis (if prior radiation treatment) or more ambiguous findings of gliosis and inflammatory infiltrate. While postoperative SRS has been established for melanoma brain metastases, the role of adjuvant radiotherapy has not been addressed for hemorrhagic lesions that return no detectable tumor cells by pathologic examination.

In an effort to minimize unnecessary side effects, only close interval observation is often used when no tumor is found after resection. However, there is a risk for misdiagnosis in hemorrhagic lesions since their bloody composition may dilute out malignant cells. Moreover, the necrotic features of melanoma have been known to make it difficult to diagnose on pathology.[2] In fact, there is no exclusive set of immunohistochemical markers that definitively diagnose melanoma.[26] To address these challenges, this case series explores the outcomes of brain lesions suspicious for metastatic melanoma that lack conclusive pathological evidence.

MATERIALS AND METHODS

This retrospective series received institutional review board approval. Medical records were reviewed for all patients with melanoma who underwent craniotomy by a senior author between 2008 and 2017. Inclusion criteria for relevant cases were patients (1) over 18 years of age, (2) with a history of melanoma, (3) presenting with hemorrhagic intracranial lesions, and (4) with surgical specimens reporting no tumor by pathological examination. Data on patient demographics (age at diagnosis, age at relevant surgical resection, sex), characteristics of melanoma disease (BRAF mutation status, extent of metastasis), intracranial disease course (age at relevant brain lesion diagnosis, total number, and location of brain lesions), previous treatments, presenting symptoms, surgical parameters (relevant lesion and size, pathology report, extent of resection), treatment after relevant surgery, and outcomes of interest were collected from electronic medical records. Relevant pathology reports were categorized as either radiation necrosis if "treatment effect" was recorded or gliosis and inflammatory infiltrate if such findings were recorded in the pathology reports. The primary outcome measure was pathology-confirmed melanoma at the site of resection that previously reported no tumor. Secondary outcome measures included other metastatic intracranial sites before last date of follow-up. Systemic treatments before or after the relevant surgery were considered to affect the lesion of interest. All analyses were performed in STATA SE 14 (StataCorp, College Station, TX, USA) and statistical significance was defined as $P \leq 0.05$.

RESULTS

During the study period, 69 separate craniotomy cases were performed to resect 77 lesions in patients with melanoma. Among them, 10 cases (13.9%) of individual patients met the inclusion criteria. All cases that produced surgical specimens reporting no tumor were also hemorrhagic lesions. Two of these patients had *de novo* lesions that quickly hemorrhaged while the other eight had hemorrhages in lesions that were already documented. The median age at the date of surgery was 62.9 years. Patient demographic information is summarized in Table 1. The median number of brain lesions at the time of craniotomy was 3 (1–25). Eight of 10 patients had prior treatment with SRS or whole-brain radiation therapy to the lesion of interest. The median dose of prior SRS to the lesion of interest was 20.0 (18–24) Gy. Table 2 reports individual disease characteristics of each case and relevant information regarding each lesion. Five of the 10 patients had melanoma with BRAF mutations while 1 was unknown because the patient was treated before regular BRAF testing and Food and Drug Administration approval of medications targeting melanoma with BRAF mutations. Nine of the 10 patients had metastases to additional visceral organs at the time of craniotomy for the lesion of interest. Five patients had surgical resection of intracranial melanoma disease before hemorrhagic lesion of interest, but only two of these five were resections of the same lesion location. In all cases, prior craniotomies for lesions were gross total resections. Surgical outcomes are reported in Table 3. After surgical resection of the lesion of interest, only one patient had postoperative

SRS to their lesion and this patient did not develop a local lesion recurrence. One patient who did develop local lesion recurrence that proved to be melanoma had not received postoperative SRS. Four of the 10 patients died by the time of data collection while 2 were lost to follow-up. The median follow-up time after negative pathology surgery was 8.5 (1.8–27.3) months while it has been reported that the median time from first craniotomy to diagnosis of recurrence is 6.7 months in patients with recurrent brain metastases.[4,14] After censoring Cases 7

and 9 for loss of follow-up, median survival after negative pathology surgery was 12.8 (1.9–27.3) months.

Illustrative cases

Case 4 — Local tumor development after a lesion with ambiguous pathology

This 70-year-old male patient had two separate primary cutaneous diagnoses: one lesion in the left upper abdomen and another on the upper back. Both lesions were wild-type BRAF. Over the following 18 months, the patient developed multiple systemic cutaneous lesions that were resected. Two years after his primary diagnosis, a lesion was discovered in his left cingulate gyrus. SRS was applied to this lesion and the patient was given immunotherapy with ipilimumab. Despite treatment, the patient's systemic disease progressed and alternative immunotherapy was initiated with combined nivolumab and lirilumab 16 months after brain metastases were found. Four and 8 months later, lesions in the right postcentral gyrus and right medial occipital lobe were found, respectively, and SRS was promptly applied to both (20 Gy each). The right medial occipital lesion hemorrhaged shortly after SRS but was managed conservatively for 8 months until the patient struck his head during a fall. His lesion subsequently expanded, became symptomatic, and required surgical intervention. Neuroimaging identified a 2.3-cm lesion with a 3.9 cm surrounding cystic area [Figure 1a]. Craniotomy was performed with pathology specimens reporting chronic inflammation and hemosiderin-laden macrophages without viable tumor cells [Figure 1b]. Postoperative SRS was planned but canceled due to an unclear clinical picture that suggested possible treatment effect rather than true tumor. Nonetheless, the patient was continued on nivolumab and lirilumab. Two months after surgical

Table 1: Summary of general patient demographics and clinical characteristics

Characteristic	Value
Male	7
Female	3
Median age at relevant date of surgery (years)	62.9±11.2
No. of brain lesions	
Median	3
Range	1-25
BRAF status	
Wild-type	4
Mutant	5
Unknown	1
Prior treatment[a]	
Chemotherapy	2
Immunotherapy	8
WBRT	2
SRS	8
Surgical resection	5
Median survival from date of surgery (months)[b]	12.8 (1.9-27.3)

WBRT: Whole-brain radiation therapy, SRS: Stereotactic radiosurgery. [a]Prior treatment for any metastatic intracranial disease. [b]Cases 7 and 9 censored due to loss of follow-up and Cases 2, 3, 6, and 8 still alive at time of data collection

Table 2: Individual disease characteristics and surgical parameters

Case No.	Age at diagnosis of brain metastasis (years), gender	BRAF status	Organs with metastasis	No. intracranial lesions	Lesion of interest location (max dimension at surgery, cm)	Prior treatment for intracranial melanoma disease[a]	Prior treatment for intracranial lesion of interest[a]	Prior SRS and surgical resection parameters for lesion of interest[a]
1	42.8, M	Mutant	Lung, liver, spleen	4	R temporal (3.2)	T, I, WBRT, SRS, S	T, SRS	SRS (24 Gy)
2	50.5, M	Mutant	Liver	1	R temporal (2.1)	T, I, S, SRS	I, SRS	SRS (20 Gy)
3	67.1, M	WT	Lung	1	L frontal (>3.5)	S, SRS, I	S, SRS, I	S (GTR), SRS (21 Gy)
4	72.2, M	WT	Lung	3	R median occipital (3.9)	I, SRS	I, SRS	SRS (20 Gy)
5	51.4, M	WT	Bladder	6	R precuneus (3.2)	I, T, C, SRS	I, C, SRS	SRS (20 Gy)
6	67.2, F	Mutant	Lung	5	L frontal (1.9)	S, SRS, I	S, SRS, I	S (GTR[b]), SRS (24 Gy)
7	55.2, M	Mutant	Liver, lung	1	L occipital (2.7)	T	T	
8	70.3, F	WT	Lung	4	L frontal (3.6)	C, I, SRS	None	
9	41.4, M	Mutant	Spine, peritoneum	25	L frontal (3.5)	T, I, WBRT	T, I, WBRT	
10	58.4, F	Unknown	No others	4	R frontal (2.0)	S, SRS	SRS	SRS (18 Gy)

[a]C: Systemic chemotherapy, I: Systemic immunotherapy, T: Systemic targeted therapy (BRAF inhibitors, MEK inhibitors), WBRT: Whole-brain radiation therapy, SRS: Stereotactic radiosurgery, S: Surgical resection, GTR: Gross total resection, STR: Subtotal resection. [b]Piecemeal gross total resection

Table 3: Surgical outcomes

Case No.	Pathology findings from unclear hemorrhagic lesion	GTR vs. STR[a]	Treatment to lesion of interest after surgical resection[a]	Tumor development[c] (time from surgery, months)	Treatment for tumor development[a]	Survival from surgery (months)
1	Radiation necrosis	STR[b]	C	None		2.5
2	Radiation necrosis	GTR	I	None		23.9, alive
3	Radiation necrosis	GTR	None	None		8.7, alive
4	Gliosis and infiltrate	GTR	I	Local (2.2)	S, C	7.4
5	Gliosis and infiltrate	GTR	C	None		1.9
6	Gliosis and infiltrate	GTR	None	Distant (11.3)	SRS, I	16.9, alive
7	Gliosis and infiltrate	GTR	T	None		5.9[d]
8	Gliosis and infiltrate	GTR	I	Distant (8.0)	SRS, C	8.3, alive
9	Gliosis and infiltrate	GTR	SRS, I, T	None		1.8[d]
10	Gliosis and infiltrate	GTR	I, C	Distant (1.2)	SRS, S	27.3

[a]C: Systemic chemotherapy, I: Systemic immunotherapy, T: Systemic targeted therapy (BRAF inhibitors, MEK inhibitors), WBRT: Whole-brain radiation therapy, SRS: Stereotactic radiosurgery, S: Surgical resection, GTR: Gross total resection, STR: Subtotal resection. [b]Stereotactic biopsy. [c]Local=confirmed melanoma metastasis developed at site of ambiguous pathology, distant=confirmed melanoma metastasis developed elsewhere in intracranial CNS. [d]Lost to follow-up
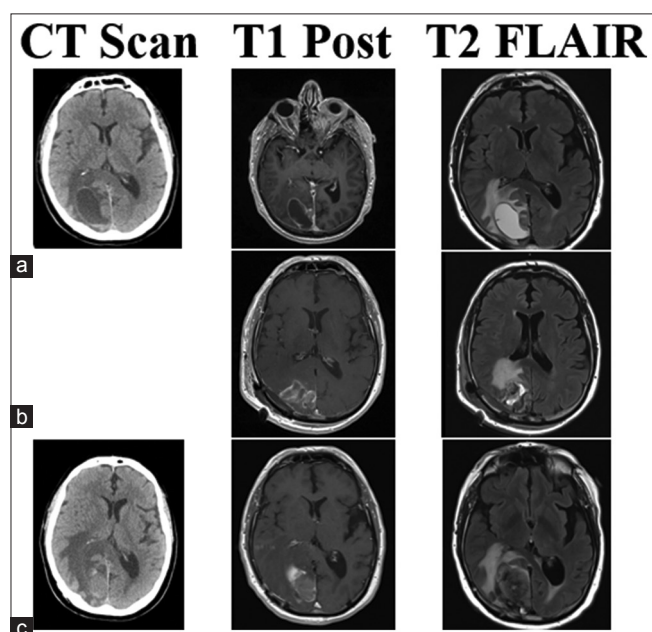

Figure 1: CT, T1 post-contrast, and T2 Flair images for illustrative Case 4. This patient's lesion in the right occipital lobe was treated with SRS (20 Gy) less than 1 month before hemorrhage with nivolumab and lirilumab immunotherapy. (a) Imaging of the hemorrhagic lesion that produced samples with chronic inflammation and no viable tumor cells. Post-operative MRI shows gross total resection in (b), no CT was performed at the time. The lesion recurred and hemorrhaged in 4 months as seen in (c). The second surgery produced samples with melanoma tumor cells and confirmed the lesion as metastasis

resection, imaging detected a recurrence of the right medial occipital lesion and this lesion hemorrhaged 2 months later [Figure 1c]. The patient required surgery again, and pathology from this second craniotomy confirmed melanoma. Therefore, temozolomide chemotherapy was administered and SRS was planned but not performed due to clinical deterioration and multiple hospitalizations. Three months after this second craniotomy, imaging detected another recurrence at the

same location but, at this point, the patient elected for palliative care.

Case 6 – No local tumor development after a lesion with ambiguous pathology

This 63-year-old female patient had a primary diagnosis of BRAF-positive cutaneous melanoma, although the specific lesion that became melanotic was unclear due to the patient's extensive history of multiple compound nevi and skin lesions. Over the following 4 years, the patient had local surgical resection of several cutaneous lesions. Metastases developed in the patient's lungs and brain and neuroimaging first detected three separate lesions in the left frontal, right deep parieto-occipital, and left occipital lobes 4 years after the patient's primary diagnosis. These lesions progressed, and the patient's left frontal lobe lesion eventually caused cognitive deficits that required surgical intervention [Figure 2a]. Gross total resection was performed and pathologic examination of the resected tissue confirmed melanoma. Postoperative SRS to the surgical resection bed (24 Gy) and the two occipital lesions (20 Gy each) was administered and systemic immunotherapy with nivolumab was initiated. Targeted therapy with cobimetinib and vemurafenib was briefly attempted but discontinued due to side effects. Two new left temporal lesions developed for which SRS was also administered. Eighteen months after the initial craniotomy, the original left frontal lesion started to progress again and hemorrhaged, causing cognitive deficits and a 1.9-cm lesion that required surgery [Figure 2b]. This second craniotomy produced pathology specimens that were negative with reports of "brain with gliosis and inflammation." Tumor cells were not identified. Postoperatively [Figure 2c], SRS was only applied to the two left temporal lesions and a new right temporal lesion. At the time of writing this case series, this patient continues to be followed at this institution 17 months since the surgery of interest with a total of six brain lesions.
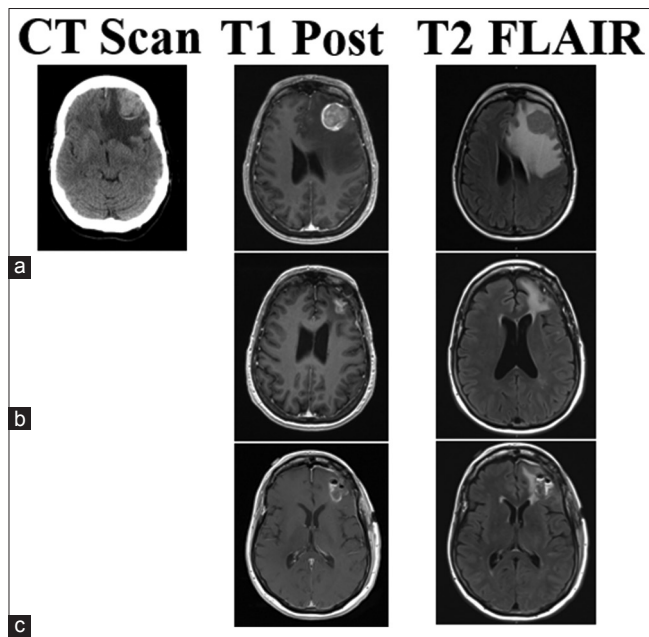
Figure 2: CT, T1 post-contrast, and T2 Flair images for illustrative Case 6. This patient's lesion of interest in the left frontal lobe progressed (a) and required surgery, which produced samples confirming melanoma metastasis. Postoperative SRS (24 Gy) was given with systemic nivolumab immunotherapy. However, the lesion recurred and hemorrhaged in 18 months (b), requiring a second resection with postoperative imaging shown in (c). No CTs were performed. This second surgery produced samples of gliosis, inflammation, and no tumor cells so no SRS was applied. There has been no local recurrence to date

DISCUSSION

Melanoma brain metastases hemorrhage more frequently than all other types of primary and secondary brain tumors.[11,19] Their highly angiogenic and proliferative nature contribute to a dismal median overall survival of 4–6 months in patients with melanoma following diagnosis of brain metastases.[5,9,11] Usually, hemorrhagic lesions in melanoma patients are presumed to be brain metastases and, when symptomatic, their standard of care involves surgical resection followed by SRS.[18,23] However, when hemorrhagic samples detect no tumor cells and are reported to be radiation necrosis or inflammatory gliosis, the role of adjuvant SRS is unknown. There is a risk that the hemorrhagic nature of these lesions makes detecting tumor cells more difficult and, therefore, adjuvant SRS may still be considered despite negative sample findings. We sought to bring clarity to this difficult clinical scenario by examining the outcomes of this case series.

In this series of 10 melanoma patients, 3 patients (Cases 1–3) had a hemorrhagic lesion consistent with radiation necrosis while 7 (Cases 4–10) had ambiguous findings of gliosis and inflammatory infiltrate. Only one lesion (Case 4), originally noted as gliosis and inflammatory infiltrate, had a local recurrence that proved to be melanoma. In cases of true metastatic melanoma

to the brain, adjuvant radiotherapy, usually in the form of SRS, is administered to increase both the rates of intracranial disease control and patient survival time.[9] When radiation necrosis is the cause of a new intracranial lesion, treatment options include surgical resection of symptomatic lesions, corticosteroids, anticoagulants, and hyperbaric oxygen.[22] Here, SRS was not administered by default because these lesions had no viable tumor cells. Adjunct radiotherapy was only given to 1 of the 10 lesions because, in that case, the 2 additional lesions that were simultaneously resected were confirmed to be melanoma. Of the nine other lesions that did not receive SRS, only one had a local melanoma recurrence (Case 4). In Patchell *et al.*'s prospective study comparing surgical resection with and without adjuvant radiotherapy, local recurrence occurred in 46% of cases where no postoperative radiation was administered.[24] In comparison, the low rate of local recurrence in our case series suggests that adjuvant radiotherapy is not necessary in cases of hemorrhagic lesions where no tumor cells are detected. Though beneficial when tumor is confirmed,[10] SRS does increase the risk of several complications, foremost among them radiation necrosis with rates ranging from 2% to 10%[29] to nearly 50% for recurrent lesions.[12,16] For clinicians who encounter this ambiguous scenario, close interval observation may be most appropriate.

In the one case of this series with local recurrence, the preoperative therapies that were given may have influenced the hemorrhage that occurred. Recently, data have suggested that immunotherapy combined with SRS increases overall survival and is associated with higher complication rates including hemorrhage and radiation necrosis.[1,7,11,18] Immunotherapy combined with radiotherapy may accelerate the rate of radiation necrosis.[1] In an attempt to evaluate the growing role of this combined treatment for melanoma brain metastases, Kaidar-Person *et al.* found in 58 patients that adding immunotherapy to radiotherapy extended overall survival from 6 to 15 months ($P = 0.0013$).[18] They also found that in terms of intracranial complications, combination treatment had a higher rate of radiation necrosis (8/29 combination vs. 0/29 SRS-only) and a higher rate of hemorrhage though this was not significant (7/29 combination vs. 2/29 SRS-only, $P = 0.14$). Though Kaidar-Person *et al.*'s analysis did not include Fisher's exact test for comparing radiation necrosis, the analysis would have resulted in significance at $P = 0.01$. Similarly, Colaco *et al.* evaluated 180 patients with any brain metastases (31.1% melanoma) treated with SRS and showed that those who also received immunotherapy, as opposed to chemotherapy or targeted therapy, had a higher risk for radiation necrosis (odds ratio = 2.40, $P = 0.03$).[7] In this case series of hemorrhagic lesions, 5 of 10 patients had both immunotherapy and SRS before their operation of interest, including 2 of the 3 patients

who had lesions with evidence of radiation necrosis. As more melanoma patients are given combination immunotherapy and radiotherapy for intracranial disease,[27] rates of hemorrhage and potentially negative samples may increase.

The bloody nature of hemorrhagic lesions can simultaneously make pathologic diagnoses more challenging and also reduce local recurrence risks by facilitating better resections. Tumor cells that are actually in a lesion may be missed since hemorrhage may obscure or dilute them from samples. In Illustrative Case 4, the prolonged 8-month period of non-surgical management after the lesion of interest had hemorrhaged may have complicated detection of any actual tumor cells present. Indeed, brain lesions in the setting of systemic cancer are not necessarily treated surgically. Surgical resection is often reserved for symptomatic or large lesions while asymptomatic or small lesions may be observed or treated with only radiotherapy.[8] On the other hand, hemorrhagic lesions that are surgically treated often provide an easily identified dissection plane for efficient resection, which allows for better extent of resections and minimizes the risk of leaving tumor cells behind.[15,31] Yoo *et al.* found that in 21 patients with various confirmed metastatic brain tumors that hemorrhaged, only 2 patients (9.5%) had local recurrence after complete resection regardless of adjuvant radiotherapy.[31] In this case series, gross total resection was achieved in all patients' hemorrhagic lesions except for one where stereotactic biopsy was performed. Moreover, for the two patients who had prior craniotomies for the lesion of interest, gross total resection was also performed. Finally, the etiology of intratumoral hemorrhage may involve vascular endothelial growth factor and matrix metalloproteinases, which can disrupt a lesion's blood supply and cause subsequent tumor cell necrosis, thereby reducing the risk for local recurrence.[17,31] Considering these factors and the findings of the current case series, patients with a history of melanoma that present with a presumed hemorrhagic brain metastasis with no detected tumor cells may not need to be treated with adjuvant radiotherapy.

This case series should be considered exploratory: due to the rare nature of this phenomenon, this study encompasses a small sample size with experience from only one institution. Further studies with larger sample sizes and prospective designs are warranted to better define the risk of melanoma recurrence in a suspected hemorrhagic metastasis with no tumor cells on pathologic examination. In addition, a subsequent local recurrence that proves to be melanotic does not necessarily imply that tumor cells were always present but missed during the initial resection. Rather, the local recurrence of true melanoma could be independent of the original lesion, since patients with melanoma have ongoing systemic disease that can generate new metastases. Nonetheless,

the aim of this study was to evaluate the risk of local recurrence and whether adjuvant radiotherapy can still be beneficial. This case series shows that hemorrhagic lesions do not seem to have frequent local recurrences that are truly melanotic.

CONCLUSION

In this series, it appears that melanoma patients who present with a suspected hemorrhagic brain metastasis that instead shows no viable tumor cells may be managed with close observation rather than immediate adjuvant radiation. Here, only one patient experienced a local lesion recurrence that proved to be melanoma. Clinicians should be aware of this low risk of recurrence as the incidence of melanoma continues to rise worldwide.

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