THERAPEUTIC ADVANCES in
Medical Oncology

Review

Should we be afraid of radiotherapy for hemorrhagic brain metastases? A narrative review

Ther Adv Med Oncol

2024, Vol. 16: 1–11

DOI: 10.1177/17588359241289203

Aleksandra Łupicka*, Weronika Kowalczyk*, Bartosz Cyman and Mateusz Spałek

***Abstract*:** Brain metastases (BM) are the most common intracranial malignancies. They are responsible for death as well as impairment of quality of life and cognitive function. In some cases, BMs can cause intracranial hemorrhage, which is not only responsible for the acute onset of either a new focal neurological deficit or worsening of a preexisting focal deficit but also poses a new challenge in treatment planning and clinical management. The aim of this study was to evaluate the available treatment modalities and their efficacy in hemorrhagic brain metastases (HBMs) with special attention to radiotherapy. In this review, we searched PubMed, BMJ, NCBI, Springer, BMC Cancer, Cochrane, and Google Scholar for articles containing data on the diagnosis and treatment of patients with HBMs, excluding the pediatric population. Treatment strategies consist of neurosurgery, whole brain radiotherapy, and stereotactic techniques (fractionated stereotactic radiosurgery (fSRS)/stereotactic radiosurgery (SRS)). Although the optimal treatment strategy for HBMs has not been established, we found no convincing evidence that radiotherapy, especially fSRS/SRS, is contraindicated in HBMs. We concluded that fSRS/SRS is a promising option for patients with HBM, particularly when surgical intervention poses risks.

Keywords: brain metastases, fractionated radiotherapy, Gamma Knife, hemorrhagic brain metastases, radiotherapy, stereotactic radiosurgery

Received: 28 February 2024; revised manuscript accepted: 18 September 2024.

Introduction

Brain metastases (BMs) can adversely affect quality of life and cognitive function, often leading to death. They occur in 20%–40% of cancer patients and are the most common form of intracranial malignancy.[1] Treatment options for BMs have been mainly palliative and have historically included surgery plus whole brain radiotherapy (WBRT) or WBRT alone. Modern surgical techniques and stereotactic radiosurgery (SRS) or fractionated stereotactic radiosurgery (fSRS) significantly improve the outcomes of focal BM treatment, even in multiple lesions.[2]

However, in some clinical scenarios, BMs can cause intracranial hemorrhage (ICH) with serious consequences such as hematoma expansion, perihematomal edema (PHE) with increased intracranial pressure, intraventricular extension of hemorrhage with hydrocephalus, seizures, venous thrombotic events, hyperglycemia, increased blood pressure, fever, and infection.[3] Hemorrhage in BMs is frequently reported and may cause the acute onset of either a new focal neurological deficit or worsening of preexisting focal deficits, often associated with a deterioration in the level of consciousness. Hemorrhagic brain metastases (HBMs) also pose challenges in treatment planning and present a poorly understood area of clinical management. Despite the availability of modern systemic treatments, sudden deterioration in performance status can lead to discontinuation of potentially effective therapy.

Correspondence to:
Mateusz Spałek
The Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Wilhelma Konrada Roentgena 5, Warsaw 02-781, Poland
mateusz.spalek@nio.gov.pl

Aleksandra Łupicka
Weronika Kowalczyk
Bartosz Cyman
The Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw, Warsaw, Poland

*These authors contributed equally

HBMs manifest as multiple lesions with large edema and irregular shape.[4] On imaging, blood products are observed, either as a clear blood-fluid level or suggested by magnetic resonance imaging (MRI) sequencing on precontrast T1 sequences, even when no blood-fluid level is visible.[5] From a clinical perspective, the distinction between actively bleeding HBMs and those with previous but inactive bleeding is crucial. Actively bleeding HBMs appear as hyperdense (bright) areas on computed tomography (CT) scans and hyperintense (bright) areas on T1-weighted MRI images, indicating fresh blood. In contrast, inactive bleeding shows older, hypodense (darker) areas on CT and may appear darker or more variable on MRI, reflecting resolved or organized blood. Active bleeding may also show new or expanding hemorrhagic regions on follow-up imaging, while inactive bleeding remains stable or decreases in size over time.[6] Recognition of fresh hemorrhage requires immediate action, such as surgery, to minimize further brain damage. Identification of previously hemorrhagic but stabilized lesions can influence long-term patient management strategies, considering potential complications and rehabilitation. Accurate differentiation of these conditions is critical to providing appropriate medical care and achieving optimal therapeutic outcomes.

Nevertheless, the optimal strategy of treatment for HBMs is not established. In the case of a single HBM, the method of choice is surgery. In multiple or inoperable HBMs, radiation oncologists are reluctant to use fSRS/SRS.[7] As a result, the predominant treatment remains WBRT or best supportive care, even though it is not the optimal treatment.

The aim of this study was to present the diagnostic possibilities, treatment methods, and optimal regimens of HBMs. Furthermore, we want to find out if there is any evidence that prohibits the use of fSRS/SRS in HBMs.

Methods

Our narrative review is conducted on research from PubMed, Cochrane, and Google Scholar. We analyzed all articles that include data about diagnostics and treatment of patients with HBMs, except pediatric studies, in the English language. We included comments, reviews, and preclinical and clinical studies discussing the issues regarding HBMs published before December 1, 2023. We included the articles that provided any results or concepts regarding HBMs. We allowed analysis of cross-suggestions. A strategy employing two keywords to search the databases included "hemorrhage" and "hemorrhagic disorders" and "brain metastases" as necessary phrases. The selection of articles was performed by consensus among all authors.

Etiology

The incidence of HBMs varies with tumor histology and may occur in as many as 35.7% of BMs.[8] In patients with intracranial neoplasms, the incidence of spontaneous intracerebral hemorrhage is approximately 2.5% and varies from 1.4% to 10%.[9] Compared to gliomas, BMs have a higher incidence of intracerebral hemorrhage (14% vs 0.8%). Certain types of neoplasms, such as melanoma, renal cell carcinoma, choriocarcinoma, and thyroid carcinoma, are known to have a higher likelihood of spontaneous bleeding. For melanoma metastases, the incidence in affected patients ranges from 29% to 50%.[10] In adenocarcinoma and anaplastic carcinoma BMs, bleeding occurs in only 2.9% and 4.7% of cases, respectively.[8]

In general, approximately 20% of BMs may show signs of recent hemorrhage on neuroimaging, such as MRI or CT, within 15 days. One of the studies reported that patients with pretreatment intratumoral hemorrhage had a shorter survival of 2.1 months compared to patients with nonhemorrhagic BMs who had a survival of 6.8 months.[11] The risk of local failure is increased by larger treatment volumes and the presence of hemorrhage. The study found that patients with pretreatment radiographic evidence of HBMs had worse local control. One possible explanation is that hemorrhagic tumors are inherently larger and tumor volume increases the risk of local failure, as observed in previous studies. However, hemorrhagic status was also shown to have a greater impact on local control than tumor volume alone.[10] Alternatively, the presence of blood products may make it difficult to accurately define tumor margins for treatment planning.[12] This may explain their higher rate of local failure, which may be due to the combination of increased tumor size and radiographic features that make treatment planning difficult.[10]

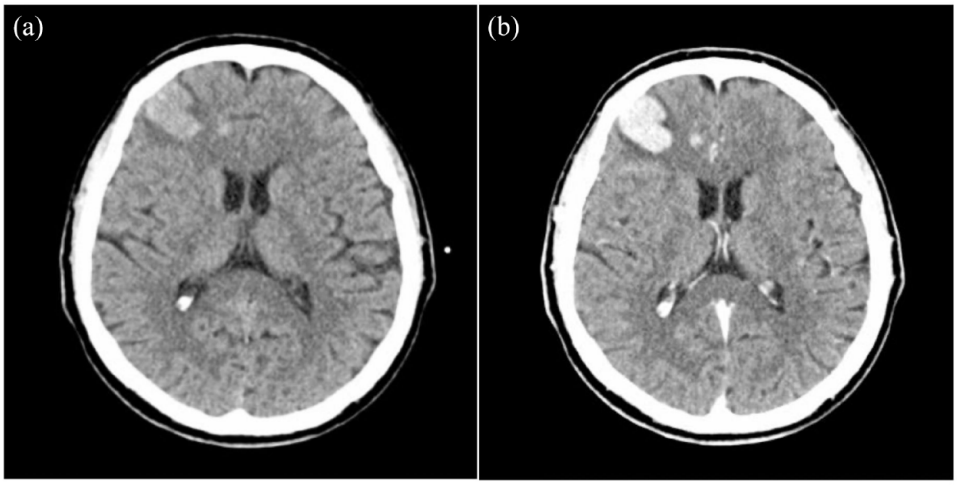

Figure 1. Presentation of hemorrhagic brain metastases in a 62-year-old patient with melanoma. (a) Non-contrast-enhanced computed tomography shows an area of hemorrhage in the subcortical region of the right frontal lobe with perihematomal edema and suspicion of small hemorrhage medially. (b) Contrast-enhanced computed tomography reveals more areas suspicious of malignancy and abnormal vascularity.

In addition, exceptional case reports have been described in the literature in which HBMs may mimic cavernous angioma.[9] Two such cases have been reported in patients with metastatic melanoma.[13] Another type of vascular brain anomaly is the association of a cerebral arteriovenous malformation with an intracranial metastasis or in the case of a cerebral arteriovenous fistula.[14]

Etiopathology

The causes of large hemorrhages in brain tumors are not fully understood. Based on pathological observations of our cases and other studies, it appears that the mechanism may be related to the proliferation of vascular endothelial cells, leading to the occlusion of blood vessels.[15] In addition, poorly formed vessels within the tumor may become distorted and easily rupture and bleed. Tumor blood vessels are disorganized and lack normal hierarchical structure, with defective endothelial junctions and absent smooth muscle, leading to increased fragility.[16,17] This structural compromise results in a leaky vasculature that is prone to rupture, causing bleeding within the tumor and contributing to its complex microenvironment.[18] Vascular necrosis, which causes a loss of vascular support, may also contribute to bleeding. Tumor invasion of vessel walls and increased venous pressure are associated with increased intracranial pressure. Theoretically, radiotherapy may be a contributing factor as well.[19]

Diagnosis of HBMs

Brain hemorrhage resulting from metastases is primarily diagnosed with two imaging techniques, namely CT and MRI. Given that HBMs account for a relatively modest proportion of intracerebral hemorrhage, it is of great clinical importance to accurately distinguish the nature of bleeding between other, more frequent causes like primary ICH or primary hemorrhagic brain tumors.

Computed tomography

To increase the efficiency of distinguishing HBMs from other types of ICH it is imperative to recognize the features of tumor-related hemorrhage, which can be discerned through CT examination. These include taking into consideration contrast enhancement, density value traits, PHE, location of bleeding, or selection of CT technique (Figure 1).

Non-contrast-enhanced computed tomography is perceived as a gold standard of imaging when a brain hemorrhage is suspected.[20] If there is a suspicion of secondary ICH, contrast-enhanced CT should be considered. There are some features that may indicate the presence of metastases:

- peripheral enhancement around hematoma, including areas distant from the bleeding—these are the consequences of anomalous vascular conditions prior to hemorrhage,

- irregular enhancement,
- thick rim enhancement,
- definite mass enhancement.

Another important issue is density value traits. It is proven that tumorous ICHs have significantly lower some of histogram parameters of ICH attenuation (25th and 5th percentile value) compared to non-tumorous ICHs.[20] However, these cannot be used to differentiate HBM from primary brain tumors—in such cases, clinical factors and patient history also have to be taken into account to make a correct diagnosis.

Moreover, PHE is a factor that plays a role in HBM diagnosis. There is some data originating from retrospective studies suggesting that neoplastic PHE is characterized by higher PHE volume, higher PHE volume/total hemorrhage volume ratio, and higher relative PHE volume adjusted for density (which is calculated with relative PHE/ICH density formula).[21] Relative PHE with a cut-off of >0.5 is an indicator of a tumorous ICH, but an independent cohort study is needed to confirm the findings. In addition, the atypical location of hemorrhage may be an indication of HBM, especially subcortical areas or areas adjacent to dural membranes, tentorium, major cerebral veins, or sinuses.[22]

Finally, the proper choice of CT technique enables a more accurate diagnosis of HBM. There is some proof that with the usage of dual-energy computed tomography (DECT) the differentiation between the enhanced portion of a tumor from an underlying hematoma becomes more straightforward as DECT allows to distinguish hematoma and iodine, both being present in the area of HBM.[20] Melanoma metastases may also appear hyperdense on CT in the absence of hemorrhage due to melanotic pigment.

Magnetic resonance imaging. A vast variety of sequences in MRI enable to improve the capacity to diagnose HBM.[23] It is known that there are some signal intensity patterns that can help to distinguish tumorous ICH from pure bleeding.

Typical MRI sequences used to detect HBM include contrast-enhanced T1-weighted imaging (CE T1WI) and T2*-weighed imaging (T2*WI). CE T1WI is used to highlight the areas of abnormal blood supply and enhance the presence of contrast in tissues, which together allow HBM detection.[24] In T2*WI areas suspected of HBM, associated with the accumulation of hemosiderin and deoxyhemoglobin, manifest as areas with reduced signal intensity. These changes are typically attributed to blood stagnation and the presence of chronic micro-hemorrhages. Another sequence sensitive to blood product detection is susceptibility-weighted imaging, which usage is reported to increase the likelihood of HBM diagnosis.

MR perfusion also plays a role in the detection of malignant lesions being an underlying cause of brain hemorrhage.[25] Higher values of relative cerebral blood flow and relative cerebral blood volume combined with peripheral linear enhancement presence may significantly contribute to the correct diagnosis of HBM, although no differentiation between brain metastases and primary brain tumors is known within mentioned parameters.

Treatment options

BMs are typically managed through a combination of treatment modalities, such as surgery, WBRT, and fSRS/SRS. Systemic treatments like chemotherapy or targeted therapy may also be used, often in combination with corticosteroids. However, there are no standards or recommendations regarding the optimal management of patients with HBMs.[7]

Neurosurgery. Surgery remains the treatment of choice for countable HBMs.[26] According to the American Society for Radiation Oncology, surgical resection is recommended for patients who are expected to survive at least 3 months and have brain lesions larger than 3–4 cm.[27] It is important to note that surgical resection is only recommended for patients who can safely undergo the procedure.[28]

Boissonneau et al.[9] proposed a detailed approach for the neurosurgical management of patients with HBMs and conducted a thorough review of the literature on this topic. According to their recommendations, patients without a clear oncologic history and with suspected HBMs should undergo immediate surgical intervention and pathologic analysis of the removed tissue to confirm the diagnosis. For patients with a known oncologic history and a life expectancy of more than 3 months, they suggest performing a cranial bone biopsy for epidural hematomas and a dura mater biopsy for subdural hematomas.[9] En bloc resection is

recommended when feasible. In cases where the patient's life expectancy is less than 3 months, the focus should shift to providing optimal supportive care rather than pursuing aggressive surgical intervention.[9] Additionally, Boissonneau et al.[9] highlights that in patients with difficult-to-resect lesions, especially those without a cancer diagnosis, obtaining a diagnosis from a different site may be beneficial for guiding treatment decisions. In addition, in patients with HBMs, neurosurgeons should consider the functional prognosis before deciding on surgery.[29] The surgical approach should take into account the functional anatomy of the human brain white matter pathway, with the goal of performing a minimal cortectomy and accessing the brain metastasis and clot through an intraparenchymal "safe" corridor. The shortest route to the clot through the brain is not always the best option because it may damage important eloquent subcortical pathways.

Radiotherapy. Radiotherapy remains a mainstay of treatment for BMs. However, radiotherapy techniques have evolved significantly over the past 30 years. The development of stereotactic techniques, namely fSRS and SRS, has allowed for very high local efficacy and reduced toxicity compared to WBRT, which has historically been used in patients with multiple BMs.[30–33] Nevertheless, WBRT is still a valuable option for selected patients with BMs who cannot undergo fSRS/SRS or are not receiving systemic treatment active in the CNS.

SRS should be used when feasible because of the reduction in cognitive impairment compared to WBRT. In the case of a higher number of BMs or a large total irradiated volume, fSRS is a viable alternative. Historically, fSRS/SRS were used in a limited number of BMs but current data allow their use even in more than 10 lesions.[2] Available technologies enabled simultaneous irradiation of multiple lesions without any loss in accuracy.[34] However, in clinical practice, many radiation oncologists do not use fSRS/SRS in HBMs. The first reason could be the fear of local failure due to the presence of blood within the target volume. Unpredictable changes in volume and density within the tumor may affect dose distribution or even proper dose delivery to the planned target volume. In addition, target delineation in HBM is challenging due to unclear tumor boundaries. Finally, there is concern that fSRS/SRS increases the risk of the next ICH.

Unfortunately, there is still very little data available on the role of fSRS/SRS in HBMs. We have found eight major studies that are fully or partially related to this topic. The summary is provided in Table 1. The first study assessed the impact of SRS on the risk of bleeding in patients with malignant melanoma BMs.[35] It analyzed 358 melanoma BMs in 110 patients using serial MRI scans to compare the incidence of bleeding before and after SRS treatment. The results showed no significant change in bleeding rates after SRS, although patients with prior bleeding had a higher risk of subsequent bleeding. Overall survival was higher in patients with a single metastasis, and local control rates were affected by bleeding both before and after SRS. The study concluded that SRS does not significantly alter the risk of bleeding but emphasized the importance of recognizing bleeding at follow-up to avoid misinterpreting it as treatment failure. The next study evaluated the impact of Gamma Knife SRS (GKS) on survival in patients with BMs from malignant melanoma, focusing on factors affecting survival, including bleeding before and after GKS.[12] Data from 59 patients with 208 brain metastases treated between 1998 and 2007 were analyzed to identify factors affecting survival. The results showed better survival for patients with a single metastasis, no pre-GKS bleeding, and a total tumor volume of less than 4 cm^3. Post-GKS bleeding did not independently affect survival, in contrast to pre-GKS bleeding. The study concluded that tumor burden and pre-GKS hemorrhage status significantly influence survival outcomes in patients with melanoma BMs treated with GKS, without increasing post-treatment bleeding rates. Therefore, the authors suggested that SRS does not contribute to the risk of bleeding in these patients.

The bi-institutional German study evaluated the risk of ICH in patients with BMs treated with SRS while receiving anticoagulant therapy (ACT).[36] Forty-one patients with 97 BMs were followed for a median of 8.2 months and the incidence of ICH was assessed by imaging. The cumulative incidence of bleeding at 6, 12, and 18 months was low, and none of the ICH events resulted in neurological deficits or required intervention. BMs with prior bleeding events or from malignant melanoma were more likely to bleed after SRS. The study concludes that the risk of ICH in patients receiving ACT and undergoing SRS for BM is not clinically significant, although certain factors may increase the risk of bleeding.

Table 1. Summary of articles.

Title	Study type	Number of patients (lesions)	Outcome measures
Ghia et al.[35]	Retrospective cohort	110 (358)	Local control: lower for HBMs pre-radiosurgery (51.7% vs 64.9%, $p = 0.03$) or post-radiosurgery (32.7% vs 67.8%, $p < 0.001$)
Redmond et al.[12]	Retrospective cohort	59 (208)	Overall survival: better in patients with non-HBMs pre-radiosurgery hemorrhage ($p = 0.004$)
Ehret et al.[36]	Retrospective cohort	41 (97)	Post-radiosurgery bleeding risk: brain metastases with previous bleeding events and malignant melanoma metastases presented more frequently demonstrate intracranial hemorrhage after radiosurgery ($p = 0.02$, $p = 0.01$).
Mathieu et al.[11]	Retrospective cohort	244 (754)	Local control after radiosurgery: significantly worse in hemorrhagic brain metastasis (univariate $p = 0.0005$, multivariate $p = 0.002$, hazard rate ratio 2.528).
Suzuki et al.[37]	Retrospective cohort	54 (131)	Characteristics of HBMs: no rebleeding into tumors that were hemorrhagic before treatment was noted after radiosurgery, and the mean tumor volume in hemorrhagic tumors was significantly greater than in nonhemorrhagic tumors both before and after radiosurgery ($p < 0.01$ and $p < 0.005$, respectively), local response and control rates were good whether intratumor hemorrhage occurred.
Bauer-Nilsen et al.[10]	Retrospective cohort	134 (936)	6-Months local control: worse in hemorrhagic metastases than in nonhemorrhagic metastases (43% vs 83%, $p < 0.001$).
Lesueur et al.[7]	Clinical trial protocol	Not applicable	Not applicable.

HBM, hemorrhagic brain metastases.

Another study evaluated the efficacy of SRS in treating BMs from malignant melanoma in 244 patients, treating 754 tumors.[11] With a median survival of 5.3 months post-SRS and 7.8 months from diagnosis of BMs, the research identified controlled systemic disease, a single BM, and a high Karnofsky performance score as factors associated with improved survival. Local tumor control was maintained in 86.2% of cases, but new BMs occurred in 41.7% of patients. Predictors of local failure included larger tumor volume and prior bleeding, while multiple lesions and lack of systemic immunotherapy were associated with the development of new metastases. The study concludes that SRS is a safe and effective option for the treatment of melanoma BMs, with certain clinical characteristics indicating better outcomes.

The Japan study examined the incidence and characteristics of spontaneous hemorrhage in 54 patients with 131 BMs following linear accelerator SRS.[37] Prior to SRS, 7.4% of metastases had hemorrhage, which increased to 18.5% after treatment. Hemorrhages were observed only in treated tumors and not in newly developed metastases. Symptomatic bleeding occurred in three cases, often within 1 month of SRS, with varying changes in tumor size at the time of bleeding. Factors associated with a higher likelihood of bleeding after SRS included being female, having a larger pretreatment tumor volume, and receiving treatment with a higher number of isocenters or a higher maximum dose. Nevertheless, the rate of hemorrhage after SRS was not significantly different between patients with and without pretreatment hemorrhages. The study concludes that aggressive SRS for larger BMs may lead to better local control, but also increases the risk of early post-treatment bleeding. On the other hand, local response and control rates were good regardless of the occurrence of intratumoral hemorrhage, either before or after SRS.

Bauer-Nilsen et al.[10] study analyzed the outcomes of SRS in 134 patients with 936 melanoma BMs,

focusing on the difference in local control, toxicity, and survival between hemorrhagic and solid tumors. Patients with HBMs had significantly worse local tumor control at 6 months post-SRS compared to patients with solid metastases. Overall survival rates for all patients were 42%, 31%, and 12% at 12, 24, and 72 months, respectively, after initial SRS. The study found no significant difference in toxicity between the two groups, but factors such as prior WBRT, chemotherapy, margin dose, and radiographic features of melanin deposition or clear hemorrhage were significant predictors of local tumor progression. The results suggest that HBMs have worse local control outcomes after SRS, emphasizing the importance of early intervention.

We found one prospective study protocol regarding the use of fSRS for HBMs.[7] The STEREO-HBM study is a multicenter phase II trial designed to evaluate the safety and efficacy of fSRS for patients with HBMs. Patients with up to three brain metastases will receive 30 Gy in three fractions over 1 week, with a focus on patients with at least one HBM. The trial's primary endpoints include the rate of bleeding complications at 4 months post-fSRS and the rate of local control at 6 months, using multimodal MRI to monitor intra-tumoral hemorrhagic events. This research seeks to fill the gap in clinical guidance for the treatment of HBMs, a topic that has been limited in research and characterized by hesitancy among radiation oncologists due to fear of exacerbating bleeding risks. The results of this study could significantly impact the standard of care for the treatment of HBMs by providing evidence-based recommendations for the use of fSRS.

Upon reviewing the results of various studies, it is evident that HBMs generally have a poorer prognosis compared to non-HBMs. Studies consistently indicate that SRS may be less effective in controlling local tumors in HBMs due to the complications associated with bleeding. For instance, local control rates tend to be lower in HBMs, and the risk of subsequent bleeding remains a concern.

Challenging issues with HBMs

Anticoagulant therapy. Patients suffering from cancer are at risk of various comorbidities that may require therapeutic ACT. Moreover, the coagulation status can be affected by various factors, including chemotherapy or bone marrow invasion that can induce thrombocytopenia, liver metastases that can affect coagulation factors, and targeted therapies, such as tyrosine-kinase inhibitors, which have been associated with an increased frequency of fatal ICH in patients with BMs. Around 20% of patients with BMs develop venous thromboembolism.[38] The decision to prescribe therapeutic anticoagulation in this population is challenging due to limited published evidence regarding its safety. In an article in Blood, Donato et al.[38] reported that ACT, specifically with enoxaparin, does not increase the risk of ICH in patients with BMs, challenging concerns about anticoagulation in this high-risk population. Their matched, retrospective cohort study, which included sophisticated statistical analysis and a blinded review of radiographic imaging, showed no significant difference in the cumulative incidence of ICH between patients treated with enoxaparin and controls. Despite the high baseline risk of ICH in patients with BMs, particularly those with renal cell carcinoma or melanoma, the study found that ACT did not increase this risk. This study fills a critical knowledge gap due to the limited inclusion of patients with brain metastases in randomized anticoagulation trials and provides valuable evidence from a well-designed retrospective study. The findings suggest a broader fulcrum for balancing the risks of anticoagulation in cancer patients with brain metastases and support the use of low-molecular-weight heparin in the management of venous thromboembolism in this patient population. This retrospective cohort study of 293 cancer patients with brain metastases, comparing 104 patients treated with therapeutic doses of enoxaparin with 189 controls, found no significant difference in the risk of ICH between the two groups at 1 year. ICH was classified into trace, measurable, and significant categories, with similar cumulative incidences observed across these categories in both the enoxaparin and control cohorts. However, the study identified a fourfold higher risk of ICH in patients with melanoma or renal cell carcinoma compared to patients with lung cancer, a risk not affected by enoxaparin use. Overall survival was comparable between the enoxaparin and control groups. The results suggest that therapeutic anticoagulation with enoxaparin does not increase the risk of ICH in patients with brain metastases. Another article suggests that the use of anticoagulation is considered safe for low-molecular-weight heparin and factor Xa inhibitors.[9]

Targeted therapies. Inhibitors of angiogenesis, such as bevacizumab, a monoclonal antibody targeting the vascular endothelial growth factor (VEGF) frequently used in renal cancer, may induce coagulopathy and increase the risk of hemorrhage. The risk of spontaneous tumor hemorrhage associated with bevacizumab administration remains a topic of discussion, although clinical trial data suggest the risk is low. One meta-analysis evaluated the potential risk of ICH associated with the administration of bevacizumab in patients with BMs.[39] The study analyzed eight studies with a total of 8713 patients. The results showed that the inclusion of bevacizumab in treatment regimens for patients with BMs did not significantly increase the risk of ICH compared to patients who did not receive bevacizumab, with an odds ratio of 1.20 and a 95% confidence interval ranging from 0.69 to 2.09 ($p = 0.53$). Despite the consistent results in retrospective study subgroups, the analysis of prospective studies was inconclusive. Overall, this meta-analysis suggests that bevacizumab treatment in solid tumor patients with BM does not significantly increase the risk of ICH.

VEGF is crucial for surgical wound healing, and using bevacizumab before and after surgery can heighten the risk of wound-healing issues. Given that bevacizumab has a half-life of about 3 weeks (20 days), it is recommended that patients wait at least 6–8 weeks after stopping bevacizumab before undergoing surgery. One study showed that bevacizumab did not increase the risk of severe bleeding in cancer patients who received anticoagulation.[40] It also does not seem to raise the incidence of ICH beyond its natural occurrence in gliomas or brain metastases and is not contraindicated for malignant brain tumors.[41]

Tyrosine-kinase inhibitors, such as sunitinib, sorafenib, or erlotinib may also pose a risk of bleeding. However, continuous daily dosing of sunitinib in patients with brain metastases was found to be safe and manageable, with no observed increase in the risk of ICH.[42] Another study demonstrated the penetration of the blood–brain barrier by sorafenib and erlotinib is limited.[43]

Authors' comments and recommendations

In this narrative review, we have provided a broad overview of the diagnostic issues and management of HBMs. The information presented in this narrative review is primarily based on a combination of literature review and the authors' expertise. Importantly, we found no evidence to prohibit the use of fSRS/SRS in HBMs due to the higher risk of significant complications or lack of efficacy. Clinical studies on this topic with limited sample sizes are available but scarce. Indeed, one study suggested worse local control of melanoma HBMs treated with SRS as compared to melanoma nonhemorrhagic BMs.[10] However, the local control after fSRS/SRS is still good and superior to local control after WBRT.[11] The influence of fSRS/SRS on the risk of post-treatment bleeding is not clear but we can say that its occurrence is not related to worse local control.[37] ACT should be introduced if clinically appropriate regardless of the presence of BMs. Optimal management of HBMs requires multidisciplinary review and, in some cases, discussion in a multidisciplinary tumor board. The summary of recommendations is presented in Figure 2.

It is important to acknowledge certain limitations associated with this narrative review. First, it may be susceptible to publication bias, particularly in the research and development field, where negative outcomes are often underreported, leading to an overrepresentation of positive outcomes. In addition, the level of evidence generated by the majority of published studies of HBMs in oncology remains low. Further research on this topic is warranted, particularly about the dissemination of findings that may have led to unfavorable results.

Conclusion

We can formulate several conclusions that could be valuable in clinical practice. First, a multidisciplinary approach involving a team of neurosurgeons, radiation oncologists, medical oncologists, radiologists, and other healthcare professionals is essential for establishing an optimal regimen of treatment. Second, fSRS/SRS may be a valuable option for patients with HBMs if the bleeding BMs cannot be safely removed. The reviewed studies suggest that while SRS is a promising option for the treatment of brain metastases, its efficacy in HBMs is somewhat compromised by the risks associated with bleeding. The findings underscore the need for careful patient selection and the potential benefits of combining SRS with other treatment modalities to improve outcomes in patients with HBMs. Further research on this topic is warranted.

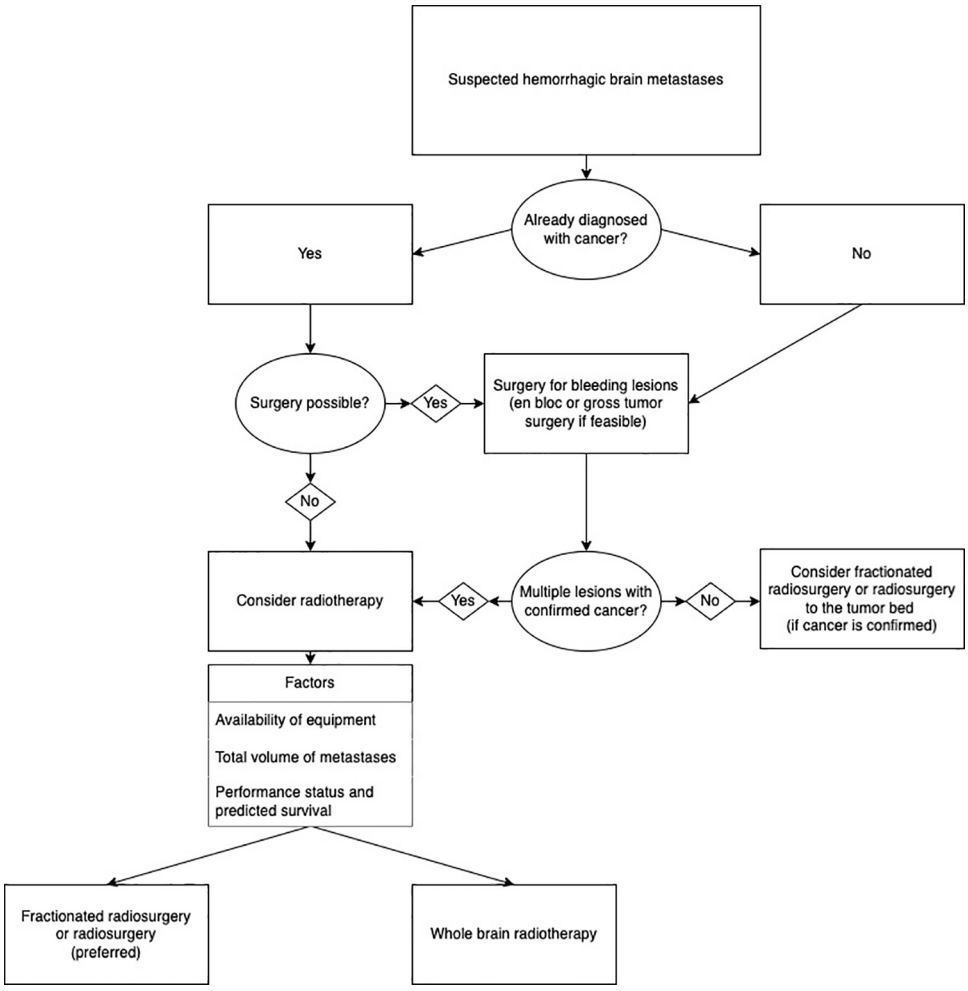

Figure 2. Management of hemorrhagic brain metastases: authors' recommendations.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Aleksandra Łupicka: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing – original draft.

Weronika Kowalczyk: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing – original draft.

Bartosz Cyman: Data curation; Formal analysis; Investigation; Methodology; Resources; Visualization; Writing – original draft.

Mateusz Spałek: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The processing charges cost was covered by the Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland. The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The data analyzed for this study can be found within the manuscript.

ORCID iD

Mateusz Spałek https://orcid.org/0000-0002-3960-7673

References

1. Soffietti R, Rudā R and Mutani R. Management of brain metastases. *J Neurol* 2002; 249: 1357–1369.
2. Yamamoto M, Higuchi Y, Sato Y, et al. Stereotactic radiosurgery for patients with 10 or more brain metastases. *Prog Neurol Surg* 2019; 34: 110–124.
3. Balami JS and Buchan AM. Complications of intracerebral haemorrhage. *Lancet Neurol* 2012; 11: 101–118.
4. Ma R, Fang S-K, Hou S, et al. Suspected brain metastasis from lung cancer mimicking intracerebral hemorrhage: a case report. *Medicine* 2018; 97: e0106.
5. Bordia R, Zhong H, Lee J, et al. Melanoma brain metastases: correlation of imaging features with genomic markers and patient survival. *J Neurooncol* 2017; 131: 341–348.
6. Jain A, Malhotra A and Payabvash S. Imaging of spontaneous intracerebral hemorrhage. *Neuroimaging Clin N Am* 2021; 31: 193–203.
7. Lesueur P, Kao W, Leconte A, et al. Stereotactic radiotherapy on brain metastases with recent hemorrhagic signal: STEREO-HBM, a two-step phase 2 trial. *BMC Cancer* 2020; 20: 147.
8. Kondziolka D, Bernstein M, Resch L, et al. Significance of hemorrhage into brain tumors: clinicopathological study. *J Neurosurg* 1987; 67: 852–857.
9. Boissonneau S, Graillon T, Rolland A, et al. Management of patients suffering from hemorrhagic intracranial metastases: propositions to help the neurosurgeon in emergency situations based on a literature review. *Neurochirurgie* 2021; 67: 369–374.
10. Bauer-Nilsen K, Trifiletti DM, Chatrath A, et al. Stereotactic radiosurgery for brain metastases from malignant melanoma and the impact of hemorrhagic metastases. *J Neurooncol* 2018; 140: 83–88.
11. Mathieu D, Kondziolka D, Cooper PB, et al. Gamma knife radiosurgery in the management of malignant melanoma brain metastases. *Neurosurgery* 2007; 60: 471–481; discussion 481–482.
12. Redmond AJ, Diluna ML, Hebert R, et al. Gamma knife surgery for the treatment of melanoma metastases: the effect of intratumoral hemorrhage on survival. *J Neurosurg* 2008; 109(Suppl.): 99–105.
13. Lu AY, Patel AR, Kuzmik GA, et al. Brainstem melanomas presenting as a cavernous malformation. *Neurochirurgie* 2014; 60: 184–187.
14. Morollón N, Arrese I, Zamora T, et al. Histology of a cerebral hemorrhage: AVM as a seat of a metastatic choriocarcinoma. *Neurocirugía* 2015; 26: 143–146.
15. Kim SS, Lee S, Park M, et al. Associated factors of spontaneous hemorrhage in brain metastases in patients with lung adenocarcinoma. *Cancers* 2023; 15: 619.
16. Cheng SY, Nagane M, Huang HS, et al. Intracerebral tumor-associated hemorrhage caused by overexpression of the vascular endothelial growth factor isoforms VEGF121 and VEGF165 but not VEGF189. *Proc Natl Acad Sci U S A* 1997; 94: 12081–12087.
17. Liwnicz BH, Wu SZ and Tew JM. The relationship between the capillary structure and hemorrhage in gliomas. *J Neurosurg* 1987; 66: 536–541.
18. Lin Q, Choyke PL and Sato N. Visualizing vasculature and its response to therapy in the tumor microenvironment. *Theranostics* 2023; 13: 5223–5246.
19. Fujita K and Matsumoto S. [Intracerebral hemorrhage in brain tumors (author's transl)]. *No Shinkei Geka* 1980; 8: 929–934.
20. Kim SJ, Lim HK, Lee HY, et al. Dual-energy CT in the evaluation of intracerebral hemorrhage of unknown origin: differentiation between tumor bleeding and pure hemorrhage. *Am J Neuroradiol* 2012; 33: 865–872.
21. Nawabi J, Hanning U, Broocks G, et al. Neoplastic and non-neoplastic causes of acute intracerebral hemorrhage on CT. *Clin Neuroradiol* 2020; 30: 271–278.
22. Schrader B, Barth H, Lang EW, et al. Spontaneous intracranial haematomas caused by neoplasms. *Acta Neurochir* (*Wien*) 2000; 142: 979–985.
23. Destian S, Sze G, Krol G, et al. MR imaging of hemorrhagic intracranial neoplasms. *Am J Roentgenol* 1989; 152: 137–144.

24. Zhang W, Ma X-X, Ji Y-M, et al. Haemorrhage detection in brain metastases of lung cancer patients using magnetic resonance imaging. *J Int Med Res* 2009; 37: 1139–1144.
25. Shankar JJS and Sinha N. Diagnosing neoplastic hematoma: role of MR perfusion. *Clin Neuroradiol* 2019; 29: 263–268.
26. Yoo H, Jung E, Gwak HS, et al. Surgical outcomes of hemorrhagic metastatic brain tumors. *Cancer Res Treat* 2011; 43: 102–107.
27. Gondi V, Bauman G, Bradfield L, et al. Radiation therapy for brain metastases: an ASTRO clinical practice guideline. *Pract Radiat Oncol* 2022; 12: 265–282.
28. Enrique G-V, Irving S, Ricardo B-I, et al. Diagnosis and management of brain metastases: an updated review from a radiation oncology perspective. *J Cancer Metastasis Treat* 2019; 5: 54.
29. Voets NL, Bartsch A and Plaha P. Brain white matter fibre tracts: a review of functional neuro-oncological relevance. *J Neurol Neurosurg Psychiatry* 2017; 88: 1017–1025.
30. Shinde A, Akhavan D, Sedrak M, et al. Shifting paradigms: whole brain radiation therapy versus stereotactic radiosurgery for brain metastases. *CNS Oncol* 2019; 8: CNS27.
31. Cohen-Inbar O and Sheehan JP. The role of stereotactic radiosurgery and whole brain radiation therapy as primary treatment in the treatment of patients with brain oligometastases—a systematic review. *J Radiosurg SBRT* 2016; 4: 79–88.
32. McCalla A, Upadhyay R, Perlow HK, et al. WBRT is associated with higher rates of hematologic toxicity than stereotactic radiosurgery in brain metastasis patients. *Int J Radiat Oncol Biol Phys* 2023; 117: e137–e138.
33. Yoo KH, Park DJ, Choi JH, et al. Optimizing the synergy between stereotactic radiosurgery and immunotherapy for brain metastases. *Front Oncol* 2023; 13: 1223599.
34. Meeks SL, Mercado CE, Popple RA, et al. Practical considerations for single isocenter LINAC radiosurgery of multiple brain metastases. *Pract Radiat Oncol* 2022; 12: 195–199.
35. Ghia AJ, Tward JD, Anker CJ, et al. Radiosurgery for melanoma brain metastases: the impact of hemorrhage on local control. *J Radiosurg SBRT* 2014; 3: 43–50.
36. Ehret F, Kaul D, Mose L, et al. Intracranial hemorrhage in patients with anticoagulant therapy undergoing stereotactic radiosurgery for brain metastases: a bi-institutional analysis. *Cancers* 2022; 14: 465.
37. Suzuki H, Toyoda S, Muramatsu M, et al. Spontaneous haemorrhage into metastatic brain tumours after stereotactic radiosurgery using a linear accelerator. *J Neurol Neurosurg Psychiatry* 2003; 74: 908–912.
38. Donato J, Campigotto F, Uhlmann EJ, et al. Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study. *Blood* 2015; 126: 494–499.
39. Yang L, Chen C-J, Guo X-L, et al. Bevacizumab and risk of intracranial hemorrhage in patients with brain metastases: a meta-analysis. *J Neurooncol* 2018; 137: 49–56.
40. Leighl NB, Bennouna J, Yi J, et al. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study. *Br J Cancer* 2011; 104: 413–418.
41. Narita Y. Drug review: safety and efficacy of bevacizumab for glioblastoma and other brain tumors. *Jpn J Clin Oncol* 2013; 43: 587–595.
42. Novello S, Camps C, Grossi F, et al. Phase II study of sunitinib in patients with non-small cell lung cancer and irradiated brain metastases. *J Thorac Oncol* 2011; 6: 1260–1266.
43. Chen H, Kuhn J, Lamborn KR, et al. Phase I/II study of sorafenib in combination with erlotinib for recurrent glioblastoma as part of a 3-arm sequential accrual clinical trial: NABTC 05-02. *Neurooncol Adv* 2020; 2: vdaa124.