Metástasis Cerebrales Hemorrágicas en la Neurooncología Moderna: Riesgo Hemostático, Toma De Decisiones Quirúrgicas y Estrategias Terapéuticas Integradas

Hemorrhagic Brain Metastases in Modern Neuro-Oncology: Hemostatic Risk, Surgical Decision-Making, and Integrated Therapeutic Strategies

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RESUMEN

Las metástasis cerebrales hemorrágicas representan un desafío importante para la neurooncología contemporánea debido a su asociación con deterioro neurológico agudo, hipertensión

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IECCMEXICO Review

intracraneal, discapacidad funcional y decisiones terapéuticas complejas. Su comportamiento clínico está determinado por la histología del tumor primario, las alteraciones vasculares, las características de las lesiones metastásicas, los trastornos de la coagulación y los tratamientos oncológicos previos. El objetivo de esta revisión narrativa fue analizar críticamente los factores relacionados con el sangrado intracraneal, las indicaciones neuroquirúrgicas y las estrategias de tratamiento multimodal en adultos con metástasis cerebrales hemorrágicas. Se examinó literatura científica internacional, incluyendo cohortes observacionales, ensayos clínicos aleatorizados y guías multidisciplinarias, mediante un enfoque descriptivo e integrador que incorporó contribuciones latinoamericanas. La evidencia revisada identificó al melanoma, el carcinoma de células renales y el carcinoma tiroideo como neoplasias con una considerable predisposición hemorrágica. El tamaño tumoral y los antecedentes de sangrado se asociaron con diferencias en la presentación hemorrágica y el control local de la enfermedad. Los estudios observacionales sobre anticoagulación terapéutica no demostraron un incremento uniforme del riesgo de hemorragia intracraneal, aunque persisten limitaciones importantes en pacientes con sangrado activo. La resección neuroquirúrgica ofrece beneficios establecidos en pacientes seleccionados con metástasis cerebrales, particularmente en el control local y los resultados neurológicos, pero la evidencia específica sobre lesiones hemorrágicas continúa siendo limitada. La radiocirugía estereotáctica constituye una alternativa relevante de tratamiento local, aunque las metástasis hemorrágicas pueden presentar menor control tumoral que las no hemorrágicas. La inmunoterapia y las terapias dirigidas han ampliado las posibilidades terapéuticas; sin embargo, su integración óptima en situaciones de hemorragia aguda permanece incierta. En conjunto, los hallazgos destacan que la presencia de hemorragia no debe constituir el único criterio para seleccionar el tratamiento. Resulta fundamental una evaluación multidisciplinaria individualizada que incorpore la gravedad neurológica, la biología tumoral, el riesgo hematológico y el pronóstico oncológico. Se requieren investigaciones prospectivas multicéntricas para establecer criterios estandarizados de estratificación del riesgo y optimizar la secuencia terapéutica.

PALABRAS CLAVE

metástasis cerebrales hemorrágicas, hemorragia intracraneal, neurocirugía, neurooncología, radiocirugía estereotáctica, anticoagulación, riesgo hemorrágico, tratamiento oncológico multimodal, metástasis encefálicas, hematología

ABSTRACT

Hemorrhagic brain metastases represent a major challenge in contemporary neuro-oncology due to their association with acute neurological deterioration, intracranial hypertension, functional impairment, and complex therapeutic decision-making. Their clinical behavior is influenced by primary tumor histology, vascular abnormalities, metastatic lesion characteristics, coagulation disturbances, and previous oncological treatments. This narrative review aimed to critically examine the determinants of intracranial bleeding, neurosurgical indications, and multimodal treatment strategies in adults with hemorrhagic brain metastases. Relevant international scientific literature, including observational cohorts, randomized clinical trials, and multidisciplinary guidelines, was analyzed through a descriptive and integrative approach, incorporating contributions from Latin America. The reviewed evidence identified melanoma, renal cell carcinoma, and thyroid carcinoma as malignancies with substantial hemorrhagic susceptibility. Tumor dimensions and pre-existing bleeding were associated with differences in hemorrhagic presentation and local disease control. Observational studies evaluating therapeutic anticoagulation did not demonstrate a uniform increase in intracranial bleeding, although important limitations remain in patients with active hemorrhage. Neurosurgical resection provides established benefits in selected patients with brain metastases, particularly regarding local control and neurological outcomes, but evidence specifically addressing hemorrhagic lesions remains limited. Stereotactic radiosurgery offers an important local treatment option, although hemorrhagic metastases may exhibit inferior local control compared with nonhemorrhagic lesions. Immunotherapy and molecularly targeted treatments have expanded therapeutic possibilities, yet their optimal integration in acute hemorrhagic presentations remains uncertain. Overall, the findings emphasize that hemorrhagic status alone should not determine treatment selection. Individualized multidisciplinary assessment incorporating neurological severity, tumor biology, hematological risk, and systemic

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oncological prognosis is essential. Further prospective multicenter investigations are necessary to establish standardized risk stratification and optimize therapeutic sequencing.

KEYWORDS

hemorrhagic brain metastases, intracranial hemorrhage, neurosurgery, neuro-oncology, stereotactic radiosurgery, anticoagulation, hemorrhagic risk, multimodal cancer treatment, cerebral metastases, hematology

INTRODUCCIÓN

Brain metastases represent one of the most significant neurological complications of systemic cancer, frequently contributing to neurological deterioration, functional disability, and reduced survival. Among their clinical presentations, hemorrhagic brain metastases constitute a particularly challenging condition because intracranial bleeding may precipitate acute neurological deficits, increased intracranial pressure, seizures, and life-threatening deterioration. Their management requires the integration of neurosurgical assessment, hematological evaluation, and oncological treatment within an individualized therapeutic framework. Despite advances in neuroimaging, surgical techniques, stereotactic radiosurgery, and systemic therapies, uncertainty persists regarding the optimal management of patients presenting with hemorrhagic metastatic lesions (Vogelbaum et al., 2022; Roth et al., 2021).

The occurrence of intracranial hemorrhage in metastatic disease is influenced by several factors, including primary tumor histology, abnormal tumor vascularization, lesion size, previous treatments, and alterations in hemostasis. Metastases originating from melanoma and renal cell carcinoma exhibit a particularly high propensity for spontaneous bleeding, although hemorrhagic complications may also arise from other malignancies. The disruption of the blood–brain barrier, vascular fragility, tumor-associated angiogenesis, and intratumoral necrosis contribute to the complex pathophysiology of metastatic hemorrhage. Furthermore, thrombocytopenia, coagulation abnormalities, and therapeutic anticoagulation may complicate clinical assessment and treatment selection. Donato et al. (2015) demonstrated that intracranial bleeding risk in patients with brain metastases varies considerably according to tumor characteristics, emphasizing the importance of distinguishing underlying biological susceptibility from treatment-related hemorrhagic risk.

Neurosurgical decision-making becomes especially relevant when hemorrhagic lesions produce substantial mass effect, progressive neurological deficits, obstructive hydrocephalus, or intracranial hypertension. Surgical resection may provide immediate decompression, pathological confirmation, and local tumor control; however, its potential benefits must be balanced against anatomical accessibility, operative risk, neurological status, extracranial disease burden, and expected survival. The landmark trial conducted by Patchell et al. (1990) established the therapeutic relevance of surgical resection in selected patients with solitary brain metastases, whereas subsequent research demonstrated the importance of postoperative radiation therapy in reducing intracranial recurrence (Patchell et al., 1998). Nevertheless, these findings cannot be directly generalized to all hemorrhagic presentations, particularly those involving multiple metastatic lesions, extensive hematomas, or patients with significant systemic deterioration.

Radiotherapy represents another fundamental component of intracranial metastatic disease management. Stereotactic radiosurgery has become an established treatment for appropriately selected patients, offering targeted irradiation while limiting exposure of surrounding brain tissue. However, pre-existing intratumoral hemorrhage may influence lesion delineation, treatment planning, radiological interpretation, and subsequent local control. Studies involving melanoma brain metastases have reported associations between hemorrhagic presentation and unfavorable local treatment outcomes, although the relationship between radiosurgery and subsequent bleeding remains incompletely understood (Ghia et al., 2014; Bauer-Nilsen et al., 2018). More recent investigations have examined hemorrhagic complications following stereotactic treatment in patients receiving contemporary systemic therapies, highlighting the need for careful patient selection and longitudinal imaging surveillance (Jablonska et al., 2023; Zoga et al., 2022).

From a hematological perspective, the coexistence of metastatic intracranial disease and thromboembolic complications introduces additional therapeutic challenges. Patients with advanced malignancies frequently develop venous thromboembolism requiring anticoagulation, yet intracranial metastatic lesions raise concerns regarding potentially catastrophic bleeding. Available evidence suggests that anticoagulation-related risk should not be

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IECCMEXICO Review

considered uniform across all patients with brain metastases. Instead, treatment decisions should account for tumor histology, previous intracranial hemorrhage, platelet count, coagulation status, thrombotic severity, and individual neurological risk (Leader et al., 2020; Hamulyák et al., 2024). Recent multinational evidence has further emphasized the importance of individualized anticoagulant selection and structured risk assessment rather than indiscriminate therapeutic exclusion (Hamulyák et al., 2025).

Simultaneously, advances in immunotherapy and molecularly targeted treatments have expanded therapeutic possibilities for patients with intracranial metastatic disease. Immune checkpoint inhibitors have demonstrated clinically meaningful intracranial activity in selected patients with melanoma brain metastases, contributing to a broader shift toward combining local and systemic treatment strategies (Long et al., 2018). Nevertheless, patients with active intracranial hemorrhage, major neurological symptoms, or urgent surgical indications remain insufficiently represented in several pivotal oncological studies. Consequently, the optimal sequence of surgical intervention, stereotactic irradiation, and systemic therapy remains an important unresolved clinical question. Contemporary multidisciplinary guidelines emphasize individualized treatment planning, although recommendations specifically addressing hemorrhagic metastases remain limited by heterogeneous study populations and the predominance of retrospective evidence (Gondi et al., 2022; Vogelbaum et al., 2022).

These challenges acquire additional relevance in international healthcare settings, where access to advanced neuroimaging, specialized neurosurgical services, stereotactic irradiation, and modern systemic therapies may differ considerably. Latin American clinical experience contributes important regional perspectives on intracranial metastatic disease management, particularly regarding radiosurgical treatment implementation, institutional resources, and clinical decision-making (Santos et al., 2015; Rojas-López et al., 2026). Incorporating evidence from diverse healthcare environments is therefore necessary to identify therapeutic principles that remain applicable beyond highly specialized centers.

The present narrative review aims to critically examine the biological and clinical determinants of hemorrhage in brain metastases, the factors guiding neurosurgical intervention, and the integration of radiotherapeutic and systemic oncological strategies. Particular attention is directed toward the relationship between tumor-specific hemorrhagic susceptibility, neurological severity, hematological abnormalities, and therapeutic selection. The central research question is how bleeding risk and clinical presentation should influence the choice and sequencing of neurosurgical, radiotherapeutic, and systemic treatments in patients with hemorrhagic brain metastases. To address this question, the review integrates relevant clinical studies, observational cohorts, randomized trials, and international practice guidelines, including evidence from Latin American settings. By examining these complementary dimensions, the article seeks to identify clinically meaningful decision factors, highlight persistent evidence gaps, and provide a structured foundation for multidisciplinary management and future research.

DESARROLLO

Hemorrhagic brain metastases represent a complex clinical entity in which malignant intracranial dissemination is accompanied by vascular disruption and bleeding within or around metastatic lesions. Unlike nonhemorrhagic metastases, these lesions may produce abrupt neurological deterioration, complicate radiological assessment, and require urgent therapeutic decisions. Their clinical behavior is determined not only by the extent of intracranial disease but also by the biological characteristics of the primary malignancy, the severity of hemorrhage, and the patient's systemic condition. Consequently, effective management requires coordinated interpretation of oncological, neurological, neurosurgical, and hematological findings (Roth et al., 2021; Vogelbaum et al., 2022).

Biological Mechanisms and Hemorrhagic Susceptibility

The pathophysiology of hemorrhagic brain metastases involves abnormal tumor angiogenesis, disruption of vascular architecture, endothelial instability, and progressive invasion of surrounding cerebral tissue. Neoplastic blood vessels frequently exhibit structural abnormalities that compromise vascular integrity, increasing susceptibility to spontaneous rupture. Rapid tumor proliferation, regional hypoxia, and intratumoral necrosis may further contribute to bleeding, particularly in highly vascular metastatic lesions.

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IECCMEXICO Review

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IECCMEXICO Review

Primary tumor histology constitutes an important determinant of hemorrhagic susceptibility. Melanoma and renal cell carcinoma are particularly associated with spontaneous intracranial hemorrhage, reflecting their vascular characteristics and biological aggressiveness. However, hemorrhagic metastases may also occur in patients with lung cancer, breast cancer, thyroid carcinoma, and other solid malignancies. The frequency and clinical consequences of bleeding vary among histological subtypes, making tumor-specific evaluation essential when estimating neurological risk (Donato et al., 2015; Łupicka et al., 2024).

Intratumoral hemorrhage may occur spontaneously or in association with therapeutic interventions, although the presence of bleeding after treatment does not necessarily establish a causal relationship. This distinction is especially relevant in patients receiving stereotactic irradiation, targeted therapies, or immunotherapy. Tumor progression, treatment-associated necrosis, and pre-existing vascular fragility may overlap, requiring longitudinal imaging and careful assessment of clinical circumstances (Zoga et al., 2022).

Clinical Presentation and Neurological Assessment

The clinical manifestations of hemorrhagic brain metastases range from incidental radiological findings to acute neurological emergencies. Headache, seizures, focal motor deficits, cognitive disturbances, altered consciousness, and signs of increased intracranial pressure may occur according to lesion location, hemorrhage volume, associated edema, and mass effect. Rapid clinical deterioration may indicate expanding hemorrhage, ventricular obstruction, or impending cerebral herniation.

Neurological evaluation should establish the patient's level of consciousness, focal neurological deficits, functional status, and evidence of intracranial hypertension. Computed tomography is particularly useful in the acute setting because it rapidly identifies intracranial blood, mass effect, midline displacement, and hydrocephalus. Contrast-enhanced magnetic resonance imaging subsequently provides more detailed characterization of metastatic burden, anatomical relationships, hemorrhagic components, and associated parenchymal abnormalities.

Nevertheless, hemorrhage may obscure underlying tumor boundaries and complicate the distinction between viable neoplastic tissue, hematoma, edema, and treatment-related changes. Serial imaging is therefore important when initial studies do not adequately characterize the lesion. Clinical and radiological findings must be interpreted together rather than relying exclusively on hemorrhage dimensions or tumor size (Roth et al., 2021; Vogelbaum et al., 2022).

Hematological Determinants of Intracranial Bleeding

Hematological abnormalities substantially influence the management of hemorrhagic metastatic lesions. Thrombocytopenia, coagulation disorders, anticoagulant exposure, and cancer-associated hemostatic disturbances may modify bleeding severity and therapeutic safety. At the same time, malignancy is strongly associated with venous thromboembolism, creating situations in which the prevention of potentially fatal thrombotic complications must be balanced against intracranial hemorrhagic risk.

Observational research suggests that therapeutic anticoagulation does not uniformly increase intracranial bleeding risk across all patients with brain metastases. Donato et al. (2015) examined intracranial hemorrhage in patients receiving therapeutic enoxaparin and highlighted the importance of tumor-specific bleeding susceptibility. Similarly, Leader et al. (2020) evaluated direct oral anticoagulants in patients with brain metastases, contributing evidence relevant to anticoagulant selection.

More recent analyses have reinforced the need to consider previous intracranial bleeding, histological diagnosis, platelet abnormalities, thrombotic severity, and radiological stability before initiating or resuming anticoagulant therapy (Hamulyák et al., 2024; Hamulyák et al., 2025). However, findings from retrospective cohorts should not be interpreted as demonstrating equivalent safety for every anticoagulation strategy, particularly in patients with active or expanding intracranial hemorrhage.

Neurosurgical Decision-Making and Operative Considerations

Neurosurgical treatment occupies a central position in the management of selected patients with hemorrhagic brain metastases. The principal indications for considering surgical intervention include significant mass effect, progressive

neurological deterioration, symptomatic lesions with substantial hematoma formation, obstructive hydrocephalus, and the need for histopathological confirmation when diagnosis remains uncertain.

Surgery may accomplish several therapeutic objectives simultaneously, including decompression of intracranial structures, evacuation of symptomatic hematoma, removal of metastatic tissue, and acquisition of diagnostic specimens. Nevertheless, treatment selection must account for lesion accessibility, proximity to eloquent cerebral regions, multiplicity of metastatic disease, functional status, systemic disease control, and perioperative bleeding risk.

The randomized investigations conducted by Patchell et al. (1990, 1998) established important principles supporting surgical management and postoperative irradiation in selected patients with brain metastases. Although these studies were not specifically designed to investigate hemorrhagic lesions, their findings remain relevant to the broader therapeutic framework.

In hemorrhagic metastases, the urgency of decompression must be balanced against the potential neurological consequences of surgery and the overall oncological prognosis. Patients presenting with rapidly declining consciousness or severe compressive effects may require emergency assessment, whereas neurologically stable individuals may benefit from multidisciplinary evaluation before definitive treatment selection (Vogelbaum et al., 2022).

Radiotherapy and Local Intracranial Control

Stereotactic radiosurgery has become an important treatment option for patients with limited intracranial metastatic disease, particularly when lesions are relatively small, anatomically suitable, and do not require urgent decompression. Its principal advantage is the delivery of highly conformal radiation doses to metastatic targets while reducing unnecessary irradiation of surrounding brain tissue.

However, hemorrhagic metastases introduce additional challenges related to target delineation, changes in lesion volume, the interpretation of post-treatment imaging, and local tumor control. Ghia et al. (2014) and Bauer-Nilsen et al. (2018) reported clinically relevant associations between hemorrhagic melanoma metastases and treatment outcomes following radiosurgery.

Subsequent research has examined the relationship between stereotactic irradiation, intralesional hemorrhage, and radiation necrosis. Jablonska et al. (2023) emphasized the clinical relevance of symptomatic hemorrhage in patients treated for melanoma brain metastases, while McKenzie et al. (2022) explored post-treatment bleeding in relation to radiosurgical fractionation.

These findings indicate that hemorrhagic presentation should be considered during radiotherapeutic planning, although it should not automatically exclude patients from stereotactic treatment. Selection must account for neurological stability, lesion dimensions, hemorrhage characteristics, previous interventions, and the anticipated therapeutic benefit. Contemporary clinical guidelines support individualized use of stereotactic radiosurgery, fractionated stereotactic radiotherapy, postoperative radiation, and whole-brain radiotherapy according to the extent and characteristics of intracranial disease (Gondi et al., 2022).

Systemic Oncological Treatment and Multimodal Integration

The development of immune checkpoint inhibitors and molecularly targeted agents has substantially expanded treatment opportunities for patients with brain metastases. In selected malignancies, these therapies demonstrate intracranial antitumor activity and may contribute to prolonged disease control when combined with appropriate local treatment.

In melanoma, combinations involving nivolumab and ipilimumab have demonstrated intracranial responses in selected populations, supporting the incorporation of immunotherapy into multidisciplinary treatment strategies (Long et al., 2018). Nevertheless, the applicability of these findings to patients with active hemorrhage, substantial neurological symptoms, or urgent surgical requirements remains limited.

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IECCMEXICO Review

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IECCMEXICO Review

The sequence of systemic and local therapies represents an important clinical consideration. Patients with significant neurological compromise may require stabilization or local intervention before systemic treatment, whereas selected neurologically stable patients may be candidates for systemic therapy as part of an integrated approach. Treatment planning should therefore consider the molecular characteristics of the primary tumor, previous therapeutic exposure, extracranial disease activity, neurological function, and expected treatment-related complications.

Rather than viewing surgery, irradiation, and systemic treatment as competing alternatives, contemporary management increasingly emphasizes their complementary roles. The central challenge is identifying which intervention provides the greatest immediate neurological benefit while preserving opportunities for sustained oncological control (Vogelbaum et al., 2022; Roth et al., 2021).

International Evidence and Latin American Perspectives

The management of hemorrhagic brain metastases is influenced by institutional resources, specialized personnel, technological availability, and access to contemporary oncological treatments. Differences in healthcare infrastructure may affect the timing of diagnostic imaging, neurosurgical evaluation, stereotactic treatment, and systemic therapy.

Latin American studies contribute valuable perspectives regarding radiotherapeutic management and the implementation of intracranial metastatic disease treatment in regional healthcare systems. Research conducted in Brazil has evaluated factors associated with local control after radiosurgery, while a multi-institutional Latin American survey has examined regional practices in the treatment of multiple brain metastases (Santos et al., 2015; Rojas-López et al., 2026).

Although these investigations are not exclusively focused on hemorrhagic lesions, they provide relevant context for understanding the practical application of international recommendations. Greater regional representation in prospective studies would help clarify how differences in healthcare resources, treatment accessibility, and patient characteristics influence outcomes in hemorrhagic metastatic disease.

Overall, the available literature supports a multidisciplinary and risk-adapted approach to hemorrhagic brain metastases. Nevertheless, substantial uncertainty persists regarding the prediction of clinically significant bleeding, optimal timing of surgical intervention, safety of anticoagulation, selection of radiotherapeutic strategies, and integration of systemic oncological treatment. These unresolved issues justify further investigation and provide the conceptual foundation for the present review.

OBJETIVO GENERAL Y OBJETIVOS ESPECÍFICOS

General Objective

To critically analyze the biological, neurological, hematological, and oncological factors associated with hemorrhagic brain metastases through a comprehensive narrative review of international scientific literature, with particular emphasis on bleeding risk stratification, neurosurgical decision-making, and multimodal treatment strategies, in order to establish an evidence-informed framework that supports individualized clinical assessment and multidisciplinary therapeutic planning.

Specific Objectives

Cognitive Domain: Knowledge, Understanding, Application, Analysis, Evaluation, and Creation

- **Identify** the principal biological mechanisms, primary tumor characteristics, and hematological abnormalities associated with intracranial hemorrhage in patients with brain metastases.

- **Explain** the pathophysiological relationships between abnormal tumor vascularization, endothelial instability, intratumoral necrosis, coagulation disturbances, and hemorrhagic complications.

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IECCMEXICO Review

- **Apply** established neurological, radiological, and oncological assessment criteria to theoretical clinical scenarios involving hemorrhagic metastatic lesions.

- **Analyze** the factors influencing neurosurgical decision-making, including neurological deterioration, hematoma characteristics, mass effect, anatomical accessibility, functional status, and extracranial disease burden.

- **Evaluate** the available evidence regarding surgical resection, stereotactic radiosurgery, fractionated radiotherapy, anticoagulation, immunotherapy, and molecularly targeted treatments.

- **Develop** an integrated conceptual framework for multidisciplinary therapeutic decision-making based on hemorrhagic risk, neurological severity, tumor biology, and anticipated oncological outcomes.

Psychomotor Domain: Procedural Interpretation and Clinical Skill Development

Within the educational scope of this literature review, psychomotor objectives emphasize the development of procedural competencies through structured clinical exercises rather than direct interventions involving patients.

- **Demonstrate** the sequential interpretation of standardized neuroimaging examples to recognize hemorrhagic lesions, cerebral edema, mass effect, and findings associated with neurological emergencies.

- **Organize** clinical information using structured assessment instruments that integrate neurological findings, hematological parameters, imaging characteristics, and oncological history.

- **Perform**, within simulated educational exercises, the sequential steps of a multidisciplinary assessment algorithm for selecting potential neurosurgical and nonsurgical treatment pathways.

Affective Domain: Professional Judgment, Ethical Awareness, and Multidisciplinary Collaboration

- **Recognize** the importance of patient safety, neurological preservation, and individualized treatment decisions when evaluating patients with hemorrhagic brain metastases.

- **Value** interdisciplinary collaboration among neurosurgery, oncology, hematology, radiation oncology, neuroradiology, and supportive care professionals.

- **Integrate** ethical considerations, patient preferences, functional prognosis, and quality-of-life outcomes into the critical appraisal of therapeutic alternatives.

- **Promote** evidence-informed clinical reasoning that acknowledges scientific uncertainty, avoids unnecessary interventions, and supports equitable access to specialized cancer care across diverse healthcare settings.

OBJETO DE ESTUDIO

The object of study of this narrative review is the clinical, biological, and therapeutic complexity of hemorrhagic brain metastases, with particular emphasis on the mechanisms underlying intracranial bleeding, the factors influencing neurosurgical decision-making, and the integration of multimodal oncological treatments. These metastatic lesions constitute a distinctive manifestation of intracranial malignancy in which tumor-related vascular abnormalities and hemorrhagic complications interact with neurological function, systemic cancer progression, and therapeutic interventions (Roth et al., 2021; Vogelbaum et al., 2022).

The population of interest comprises adult patients with brain metastases originating from extracranial solid malignancies, particularly melanoma, renal cell carcinoma, lung cancer, breast cancer, and other neoplasms associated with intracranial metastatic dissemination. Special attention is directed toward patients presenting with spontaneous intratumoral hemorrhage, hemorrhagic transformation of previously identified metastatic lesions, or bleeding complications occurring during oncological treatment. The review also considers patients with concomitant hematological abnormalities, cancer-associated thrombosis, or exposure to anticoagulant therapies, given their potential influence on intracranial bleeding risk (Donato et al., 2015; Hamulyák et al., 2024).

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Revista IECCMEXICO

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IECCMEXICO Review

From a biological perspective, the phenomenon under investigation encompasses the relationships between tumor angiogenesis, vascular fragility, endothelial disruption, intratumoral necrosis, coagulation abnormalities, and hemorrhagic susceptibility. These mechanisms are examined alongside tumor histology and treatment-related factors to understand differences in bleeding patterns and clinical outcomes. Previous investigations involving hemorrhagic melanoma metastases provide relevant evidence regarding the association between intracranial bleeding and subsequent local disease control (Ghia et al., 2014; Bauer-Nilsen et al., 2018).

From a clinical perspective, the object of study includes neurological manifestations, neuroimaging characteristics, hemorrhage severity, functional status, and the presence of complications requiring urgent intervention. Particular emphasis is placed on identifying the circumstances under which intracranial bleeding modifies therapeutic priorities, especially when surgical decompression must be considered in relation to stereotactic irradiation or systemic oncological treatment.

The therapeutic dimension encompasses surgical resection, hematoma evacuation, stereotactic radiosurgery, fractionated radiotherapy, systemic immunotherapy, molecularly targeted agents, and individualized anticoagulation strategies. These interventions are evaluated in relation to neurological stabilization, local tumor control, treatment-associated complications, and preservation of functional independence. Their integration is considered within contemporary multidisciplinary recommendations and the available evidence regarding intracranial metastatic disease (Gondi et al., 2022; Leader et al., 2020; Vogelbaum et al., 2022).

The principal analytical dimensions of the study are:

- **Hemorrhagic risk:** Tumor histology, vascular characteristics, coagulation abnormalities, previous bleeding, and treatment-associated factors.
- **Neurological severity:** Clinical deterioration, lesion location, hematoma characteristics, cerebral edema, mass effect, and intracranial hypertension.
- **Neurosurgical decision-making:** Indications for intervention, surgical accessibility, neurological prognosis, operative risks, and potential therapeutic benefits.
- **Multimodal oncological management:** Selection and sequencing of radiotherapy, systemic treatment, and surgical interventions.
- **Clinical outcomes:** Intracranial hemorrhage recurrence, local tumor control, neurological function, treatment complications, overall survival, and quality of life.

The geographical scope is international, incorporating evidence from North America, Europe, Asia, and Latin America. Particular consideration is given to Latin American scientific contributions and the potential influence of regional healthcare resources on the implementation of specialized neurological and oncological treatments.

As a narrative review, the study does not involve direct patient recruitment, collection of individual clinical records, or experimental interventions. Its unit of analysis consists of published scientific evidence, including clinical studies, observational cohorts, therapeutic trials, systematic reviews, and professional guidelines. The purpose is to synthesize existing knowledge, examine areas of clinical uncertainty, and identify factors that may support individualized management.

Ultimately, the object of study is not limited to the presence of hemorrhage within metastatic brain lesions but extends to the interaction between bleeding susceptibility, neurological urgency, and oncological treatment opportunities. Understanding these relationships is essential for developing an integrated perspective on hemorrhagic brain metastases and identifying priorities for future clinical research.

METODOLOGÍA

Study Design and Methodological Approach

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Revista IECCMEXICO

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IECCMEXICO Review

This study was structured as a narrative literature review with a descriptive, analytical, and integrative approach, aimed at examining the biological mechanisms, clinical implications, and therapeutic challenges associated with hemorrhagic brain metastases. The methodological framework was based on the **scientific method**, incorporating systematic identification of relevant literature, critical assessment of published evidence, comparative analysis, and qualitative synthesis of findings.

A narrative review design was selected because hemorrhagic brain metastases involve heterogeneous clinical presentations, primary tumor histologies, therapeutic interventions, and outcome measures. This approach permits the integration of findings from observational studies, clinical trials, systematic reviews, and international guidelines while identifying areas of agreement, uncertainty, and insufficient evidence.

The investigation was organized around three principal analytical domains: intracranial bleeding risk, neurosurgical decision-making, and multimodal oncological management. These domains were defined according to the clinical complexity of hemorrhagic metastatic lesions and their relevance to contemporary multidisciplinary practice (Roth et al., 2021; Vogelbaum et al., 2022).

Research Question and Scientific Framework

The central research question was formulated as follows:

How do tumor-related hemorrhagic risk factors, neurological severity, and hematological characteristics influence neurosurgical decision-making and the selection of multimodal oncological treatments in adult patients with hemorrhagic brain metastases?

The review adopted the Population, Concept, and Context (PCC) framework to organize its scope.

- **Population:** Adult patients with brain metastases arising from extracranial solid malignancies.
- **Concept:** Intracranial hemorrhage, bleeding susceptibility, surgical indications, hematological complications, and multimodal therapeutic strategies.
- **Context:** Neurosurgical, neuro-oncological, hematological, and radiation oncology settings at an international level, including Latin American healthcare environments.

The working hypothesis guiding the analytical synthesis was that the management of hemorrhagic brain metastases requires an integrated assessment of tumor histology, hemorrhage characteristics, neurological stability, coagulation status, and oncological prognosis, rather than reliance on any isolated clinical or radiological parameter. This hypothesis was used as a conceptual proposition for literature analysis, not as a hypothesis subjected to experimental statistical testing.

Sources of Information and Literature Search Strategy

The literature search framework prioritized biomedical publications indexed in PubMed/MEDLINE and Scopus, complemented by relevant articles from peer-reviewed journals and clinical practice guidelines issued by recognized international scientific organizations.

The search strategy was designed around combinations of controlled vocabulary and free-text terms addressing the principal research domains. The following Boolean expression was established as a reproducible core search strategy:

("brain metastases" OR "cerebral metastases" OR "intracranial metastases") AND (hemorrhage OR haemorrhage OR bleeding OR hemorrhagic) AND (neurosurgery OR surgical resection OR stereotactic radiosurgery OR radiotherapy OR anticoagulation OR immunotherapy)

Additional targeted searches were defined using terms such as *melanoma brain metastases, renal cell carcinoma, intracranial hemorrhage risk, therapeutic anticoagulation, hematoma evacuation, local tumor control,* and *multimodal treatment*.

To incorporate Latin American contributions, geographical descriptors including *Latin America, Brazil, Mexico,* and *Argentina* were considered in supplementary searches.

The bibliographic scope included foundational investigations and contemporary publications relevant to the evolution of therapeutic practice. Particular emphasis was placed on evidence published between 2015 and 2026, while earlier landmark studies were retained when necessary to explain established neurosurgical principles.

For reproducibility, the final search record should document database-specific queries, execution dates, applied filters, and the number of retrieved records. The search framework described here does not establish that an exhaustive systematic search or formal study-screening process was performed.

Eligibility Criteria

The eligibility framework was established to prioritize publications directly related to hemorrhagic brain metastases and clinically relevant evidence concerning their management.

Inclusion criteria

- Peer-reviewed scientific publications addressing brain metastases, intracranial hemorrhage, or related therapeutic complications.
- Original observational studies, randomized clinical trials, systematic reviews, narrative reviews, and evidence-based clinical guidelines.
- Studies examining hemorrhagic risk factors, neurosurgical treatment, radiation therapy, anticoagulation, or systemic oncological interventions.
- Publications involving adult patients with metastatic intracranial disease.
- Articles available in English or Spanish.
- International and Latin American publications providing relevant biological, clinical, or therapeutic information.

Exclusion criteria

- Publications exclusively addressing primary intracranial tumors without relevant implications for brain metastases.
- Studies concerning non-neoplastic intracranial hemorrhage without a meaningful relationship to metastatic cancer.
- Non-peer-reviewed opinion pieces lacking identifiable scientific support.
- Duplicate publications reporting substantially overlapping evidence without additional analytical value.
- Studies with insufficient methodological or clinical information to support meaningful interpretation.

Studies involving nonhemorrhagic brain metastases were eligible when they provided essential comparative evidence regarding surgery, radiotherapy, or systemic treatment. Their findings were distinguished from evidence specifically derived from hemorrhagic metastatic populations.

Data Extraction and Organization

A standardized evidence-extraction framework was defined to facilitate consistent examination of selected publications. The principal variables included author and year, geographical setting, study design, population characteristics, primary tumor histology, hemorrhagic presentation, therapeutic interventions, and reported clinical outcomes.

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO
Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Additional information of interest included neurological deterioration, intracranial bleeding recurrence, local tumor control, radiation-related complications, anticoagulant exposure, overall survival, and functional outcomes.

The extracted information was organized into thematic categories corresponding to the principal objectives of the review. This classification was intended to facilitate comparisons across different study designs while preserving distinctions between direct evidence on hemorrhagic lesions and broader evidence concerning brain metastases.

Critical Appraisal of Scientific Evidence

The methodological assessment focused on study design, population representativeness, clinical relevance, potential sources of bias, and consistency of reported outcomes.

Randomized trials were considered particularly informative when evaluating therapeutic effectiveness in the populations they studied, whereas retrospective cohorts were examined with attention to confounding, patient selection, and differences in baseline hemorrhagic risk. Clinical guidelines were assessed in relation to the strength and applicability of their recommendations.

Special consideration was given to the limitations of extrapolating findings from nonhemorrhagic metastatic populations to patients presenting with active intracranial bleeding. Similarly, associations between therapeutic interventions and subsequent hemorrhage were not interpreted as proof of causation without adequate supporting evidence.

Because this was a narrative review, no quantitative meta-analysis, pooled effect estimates, or formal certainty-of-evidence grading was undertaken.

Data Synthesis and Interpretation

The evidence was integrated through a qualitative thematic synthesis structured around three major clinical domains.

The first domain examined hemorrhagic susceptibility, including primary tumor histology, vascular abnormalities, previous intracranial bleeding, coagulation disorders, and anticoagulant exposure.

The second domain evaluated neurosurgical decision-making, emphasizing neurological severity, mass effect, anatomical accessibility, surgical objectives, and operative considerations.

The third domain explored multimodal oncological management, including stereotactic irradiation, postoperative radiotherapy, systemic immunotherapy, molecularly targeted agents, and treatment sequencing.

Comparative interpretation emphasized clinically relevant agreements and discrepancies across the selected literature. Findings were considered within the limitations of their original study populations, and unresolved questions were identified as priorities for future investigation.

Ethical Considerations and Methodological Limitations

The review was designed around previously published scientific literature and did not involve direct patient contact, experimental procedures, or access to identifiable individual health records. Consequently, no new clinical interventions or patient-level data collection were required.

The principal methodological limitations arise from the narrative design, heterogeneity of underlying studies, and the relative scarcity of prospective investigations specifically focused on hemorrhagic brain metastases. Additional limitations include variation in definitions of intracranial hemorrhage, differences in radiological assessment, and potential selection bias in retrospective treatment cohorts.

FASES DEL DESARROLLO

Identification and Delimitation of the Research Problem

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IECCMEXICO Review

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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

The initial phase involved defining the clinical problem represented by hemorrhagic brain metastases and identifying the principal uncertainties surrounding their management. Particular attention was directed toward the coexistence of intracranial bleeding, neurological deterioration, tumor-related vascular abnormalities, and the therapeutic complexity of advanced systemic malignancies.

The research problem was delimited to three interconnected dimensions: hemorrhagic susceptibility, neurosurgical decision-making, and multimodal oncological treatment. These dimensions were selected because they represent critical determinants of neurological outcomes and therapeutic planning.

Existing clinical guidelines recognize the importance of multidisciplinary management in patients with brain metastases; however, recommendations specifically addressing hemorrhagic presentations remain comparatively limited (Roth et al., 2021; Vogelbaum et al., 2022).

Formulation of the Research Question and Working Hypothesis

Following the identification of the problem, the central research question was formulated to examine how bleeding risk, neurological severity, and hematological characteristics influence treatment selection in patients with hemorrhagic brain metastases.

A conceptual working hypothesis was established: optimal therapeutic decision-making depends on the integration of tumor-specific hemorrhagic susceptibility, radiological characteristics, neurological status, systemic disease burden, and available treatment modalities.

This proposition was informed by investigations reporting differences in intracranial hemorrhagic risk according to primary tumor histology and by studies examining the relationship between bleeding and local treatment outcomes (Donato et al., 2015; Bauer-Nilsen et al., 2018).

Because the investigation follows a narrative review design, this hypothesis serves as an organizing framework for evidence interpretation rather than a proposition requiring experimental confirmation.

Identification and Selection of Scientific Evidence

The literature identification phase was structured around searches in biomedical databases, particularly PubMed/MEDLINE and Scopus, using combinations of terms related to brain metastases, intracranial hemorrhage, neurosurgery, stereotactic irradiation, anticoagulation, and systemic cancer treatment.

The predefined eligibility criteria prioritize original clinical investigations, observational cohorts, randomized trials, scientific reviews, and international practice guidelines.

Evidence was categorized according to its relevance to hemorrhagic susceptibility, neurological complications, treatment selection, and clinical outcomes. Foundational publications were considered alongside recent investigations to contextualize the evolution of neurosurgical and oncological management.

The search and selection framework also incorporates Latin American contributions, recognizing the importance of regional clinical experience and differences in access to specialized treatments (Santos et al., 2015; Rojas-López et al., 2026).

The proposed process requires documentation of search dates, database-specific strategies, retrieved records, and reasons for exclusion to support methodological transparency.

Classification and Critical Examination of Evidence

The analytical phase was designed to distinguish the principal biological, clinical, and therapeutic findings reported in the selected literature.

Evidence concerning hemorrhagic susceptibility was classified according to tumor histology, vascular characteristics, previous intracranial bleeding, hematological abnormalities, and treatment-related factors. Studies addressing

anticoagulation were evaluated separately to distinguish baseline tumor-associated bleeding susceptibility from the potential effects of antithrombotic therapies (Leader et al., 2020; Hamulyák et al., 2025).

Neurosurgical evidence was examined according to clinical presentation, indications for resection, neurological severity, lesion accessibility, and anticipated operative benefits. Historical randomized investigations provided an important foundation for understanding the role of surgical resection and postoperative irradiation, although their applicability to actively hemorrhagic metastases requires careful interpretation (Patchell et al., 1990; Patchell et al., 1998).

Studies involving stereotactic radiosurgery were assessed with particular attention to hemorrhagic presentation, local control, post-treatment bleeding, and radiation-associated complications (Ghia et al., 2014; Jablonska et al., 2023).

This phase also incorporated an assessment of methodological limitations, including retrospective study design, heterogeneous patient populations, confounding variables, and differences in outcome definitions.

Comparative Analysis of Therapeutic Strategies

The comparative phase focused on examining the clinical circumstances in which neurosurgical intervention, radiotherapy, or systemic treatment may offer the greatest therapeutic benefit.

Surgical management was considered in relation to symptomatic mass effect, neurological deterioration, hematoma formation, and the potential need for immediate intracranial decompression.

Radiotherapeutic strategies were examined according to lesion characteristics, neurological stability, expected local control, and treatment-associated complications. Particular consideration was given to the uncertainty surrounding stereotactic irradiation of previously hemorrhagic metastatic lesions (Łupicka et al., 2024).

Systemic treatment strategies were evaluated according to primary malignancy, intracranial activity, previous treatments, and the potential integration of immunotherapy or targeted agents with local interventions. Evidence from melanoma brain metastases provided an important reference for examining the role of immune checkpoint inhibition (Long et al., 2018).

The comparative approach did not assume that a single therapeutic modality is universally superior. Instead, it emphasized the identification of clinical factors that may favor particular treatment sequences in different neurological and oncological circumstances.

Integration and Qualitative Synthesis

The synthesis phase was structured to consolidate findings from the three principal research domains into an integrated interpretation of hemorrhagic brain metastasis management.

The analysis examined how tumor-specific bleeding susceptibility interacts with neurological severity, hematological characteristics, anatomical considerations, and systemic cancer prognosis.

Areas of agreement between studies were distinguished from findings characterized by uncertainty or conflicting evidence. Particular emphasis was placed on avoiding direct extrapolation from populations with nonhemorrhagic brain metastases when evaluating interventions in patients with active intracranial bleeding.

The synthesis was also intended to identify clinically relevant decision points, including the need for urgent decompression, suitability for stereotactic treatment, anticoagulation considerations, and selection of systemic therapies.

Rather than generating new quantitative estimates, this phase supports the development of a structured clinical interpretation grounded in published evidence and contemporary multidisciplinary recommendations (Gondi et al., 2022; Vogelbaum et al., 2022).

Identification of Knowledge Gaps and Research Priorities

Edición 5, Año 3, Número 2, 2026
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IECCMEXICO Review

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Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

The final analytical phase focused on recognizing limitations in the current evidence and identifying priorities for future investigation.

Important unresolved questions include the development of validated hemorrhagic risk prediction models, the optimal timing of surgical intervention, the safety of anticoagulation following intracranial bleeding, and the comparative effectiveness of radiotherapeutic strategies in hemorrhagic metastatic lesions.

Additional uncertainties concern the sequencing of immunotherapy, targeted treatment, and local intracranial interventions, particularly among patients with symptomatic hemorrhage or substantial neurological impairment.

The limited representation of Latin American populations in prospective neuro-oncological investigations further supports the need for multicenter research addressing regional treatment accessibility, patient characteristics, and clinical outcomes.

These knowledge gaps are relevant to the development of more precise and equitable multidisciplinary treatment strategies.

Interpretation and Formulation of Conclusions

The concluding phase of the scientific method involves integrating the reviewed evidence to formulate conclusions aligned with the initial research question and stated objectives.

The interpretative framework considers the extent to which available studies support individualized assessment of hemorrhagic risk, neurological urgency, neurosurgical indications, and multimodal oncological treatment.

Conclusions should distinguish established clinical recommendations from findings supported primarily by observational evidence. They should also recognize the limitations of narrative synthesis and avoid attributing causality to associations that have not been adequately tested.

RESULTADOS Y DISCUSIÓN

Figure 1.

Hemorrhagic Risk According to Primary Tumor Histology

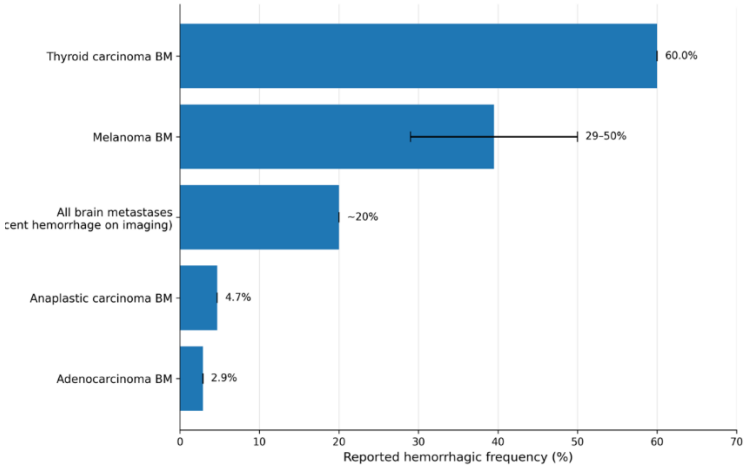


Figure 1 shows a marked variation in the reported frequency of hemorrhage among brain metastases according to the underlying primary tumor histology. The highest value represented in the figure corresponds to **thyroid carcinoma brain metastases**, in which hemorrhage was identified in **60%** of cases in the series reported by Kim et al. (2021). Although thyroid cancer is a relatively uncommon primary source of brain metastases, this finding is relevant because

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IECCMEXICO Review

it reinforces the concept that some tumor types have a disproportionately high bleeding tendency once intracranial dissemination occurs. This observation is clinically important because hemorrhage may complicate radiological interpretation, increase symptom burden, and influence the urgency of neurosurgical and oncological decision-making.

The second highest category shown is **melanoma brain metastases**, with a reported hemorrhagic frequency ranging from **29% to 50%**. This range is consistent with the literature summarized by Łupicka et al. (2024), who emphasized that melanoma metastases are among the lesions most strongly associated with spontaneous intracranial bleeding. In practical terms, this finding supports the recognition of melanoma as one of the principal histologies to be considered when evaluating patients with suspected hemorrhagic metastatic lesions. The broad range also suggests variability across cohorts, which may reflect differences in imaging criteria, patient selection, lesion burden, previous treatment exposure, and timing of hemorrhage assessment.

At the overall population level, the figure includes the estimate that approximately **20% of all brain metastases** may exhibit signs of recent hemorrhage on neuroimaging, as summarized by Łupicka et al. (2024). This intermediate proportion highlights that hemorrhage is not a rare incidental phenomenon in metastatic intracranial disease. Rather, it is a relatively frequent radiological and clinical event that deserves systematic consideration in the initial work-up and follow-up of patients with brain metastases. The presence of hemorrhage may alter symptom presentation, worsen edema and mass effect, and complicate differentiation between tumor progression and treatment-related change.

By contrast, the lowest frequencies in the figure correspond to **anaplastic carcinoma brain metastases** and **adenocarcinoma brain metastases**, with reported values of **4.7%** and **2.9%**, respectively, as cited in the narrative synthesis by Łupicka et al. (2024). These lower proportions illustrate that hemorrhagic behavior is not uniform across metastatic histologies. This variation supports the notion that bleeding risk is biologically mediated rather than merely a nonspecific consequence of intracranial tumor presence. Tumor vascular structure, angiogenic activity, endothelial fragility, and necrotic change likely contribute to these differences, which in turn may have implications for risk stratification and surveillance.

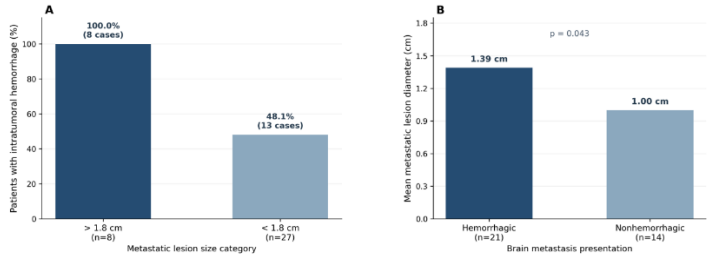
From an analytical standpoint, the figure supports three relevant observations. First, **hemorrhagic risk is histology-dependent**, with certain tumors showing a distinctly higher tendency toward bleeding. Second, **high-risk histologies such as melanoma and thyroid carcinoma should be interpreted with heightened clinical vigilance**, especially when patients present with acute neurological symptoms, seizures, sudden focal deficits, or unexplained radiological changes. Third, **the overall burden of hemorrhage in brain metastases is sufficiently substantial to justify its inclusion as a central variable in multidisciplinary assessment**, particularly when surgery, anticoagulation, or stereotactic irradiation are being considered.

It is also important to interpret the figure cautiously. The values shown derive from **different studies with heterogeneous populations and methods**, which means they should be read as comparative descriptive evidence rather than directly comparable pooled statistics. For example, the 60% estimate for thyroid carcinoma metastases comes from a single institutional series, whereas the melanoma data are expressed as a range across multiple studies. Similarly, the estimate of approximately 20% for all brain metastases refers to recent hemorrhage identified on neuroimaging, which may not be equivalent to clinically symptomatic hemorrhage. Therefore, the figure is best understood as a visual summary of the pattern of hemorrhagic susceptibility reported in the literature, not as a definitive ranking based on uniform methodology.

Even with these limitations, the overall message remains clear: **hemorrhage in brain metastases is not randomly distributed across tumor types**. Instead, it is strongly influenced by primary tumor biology, and this has direct implications for diagnosis, monitoring, and treatment planning. In the context of this review, Figure 1 provides a useful foundation for the subsequent analysis of clinical presentation, anticoagulation-related concerns, neurosurgical decision-making, and multimodal treatment selection.

Figure 2.

Relationship Between Metastatic Lesion Size and Intracranial Hemorrhage



The results presented in Figure 2 demonstrate an association between metastatic lesion size and the occurrence of intratumoral hemorrhage in patients with brain metastases originating from thyroid carcinoma. The two complementary analyses reveal differences in hemorrhagic frequency according to lesion dimensions, as well as measurable variation in mean tumor diameter between hemorrhagic and nonhemorrhagic presentations. These observations provide quantitative evidence of the relationship between anatomical tumor characteristics and hemorrhagic manifestations within this specific metastatic population (Kim et al., 2021).

Panel A illustrates the distribution of intratumoral hemorrhage according to metastatic lesion size. Among patients with lesions larger than 1.8 cm, hemorrhage was identified in **100% of cases (8/8)**. In contrast, among patients with lesions smaller than 1.8 cm, hemorrhage occurred in **48.1% (13/27)**. This represents a descriptive difference of approximately 51.9 percentage points between the two size categories. The findings demonstrate that all patients classified within the larger-lesion group exhibited radiological evidence of bleeding, whereas hemorrhage was present in fewer than half of those within the smaller-lesion group (Kim et al., 2021).

The distribution also demonstrates that hemorrhage was not restricted to the largest metastatic lesions. Despite the substantial difference between categories, 13 patients with lesions smaller than 1.8 cm exhibited intratumoral bleeding. Therefore, the observed relationship between lesion size and hemorrhagic presentation does not indicate that smaller metastases are uniformly nonhemorrhagic. Rather, the findings reveal variability in bleeding occurrence across the examined dimensions, with a greater observed frequency among larger lesions.

Panel B presents the differences in mean metastatic lesion diameter between hemorrhagic and nonhemorrhagic groups. Hemorrhagic metastases exhibited a mean diameter of **1.39 cm**, compared with **1.00 cm** among nonhemorrhagic lesions. The absolute difference was 0.39 cm, corresponding to a 39% greater mean diameter in the hemorrhagic group relative to the nonhemorrhagic group. The original investigation reported a statistically significant difference between these measurements ($p = .043$), providing additional support for the association between larger metastatic dimensions and hemorrhagic presentation within the analyzed population (Kim et al., 2021).

The original study also reported differences in lesion diameter variability. Hemorrhagic metastases demonstrated a mean diameter of 1.39 ± 0.82 cm, whereas nonhemorrhagic metastases measured 1.00 ± 0.44 cm. The larger standard deviation observed among hemorrhagic lesions indicates greater dispersion in tumor dimensions within that group. Nevertheless, the overlap in lesion sizes between groups indicates that tumor diameter alone does not fully distinguish hemorrhagic from nonhemorrhagic metastatic disease.

The clinical and radiological characteristics of the underlying population provide additional context for these findings. Kim et al. (2021) reported neurological symptoms in 54.29% of patients, extracranial metastatic disease in 94.29%, peritumoral edema in 73.53%, and intratumoral hemorrhage in 60%. These findings describe a population characterized by substantial systemic disease burden and frequent intracranial radiological abnormalities. However, the reported frequencies represent different clinical dimensions and cannot be interpreted as demonstrating direct relationships between individual symptoms, edema, and hemorrhagic status.

Regarding anatomical distribution, supratentorial involvement was identified in 51.43% of patients, while combined supratentorial and infratentorial involvement was observed in 45.71%. Isolated infratentorial disease was comparatively uncommon. The study further examined lesion location in relation to hemorrhagic presentation, identifying differences among anatomical subgroups, although these comparisons involved relatively small numbers of patients (Kim et al., 2021).

Edición 5, Año 3, Número 2, 2026
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Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

The reported findings are consistent with the broader observation that hemorrhagic brain metastases exhibit heterogeneous structural and radiological characteristics. Łupicka et al. (2024) described variation in hemorrhagic presentation according to primary tumor histology and emphasized differences in tumor volume and radiological appearance across the available studies. Their review also documented methodological variability among investigations, particularly in the identification and classification of hemorrhagic lesions.

An important distinction concerns the relationship between lesion dimensions and the radiological detection of hemorrhage. In the original cohort, intratumoral bleeding was identified using magnetic resonance imaging characteristics, including susceptibility-sensitive sequences. Consequently, the reported frequencies represent imaging-defined hemorrhage rather than exclusively symptomatic or clinically severe intracranial bleeding. This distinction is relevant when comparing the findings with investigations that measure acute neurological deterioration, hematoma expansion, or hemorrhage requiring neurosurgical intervention.

The results should also be interpreted in relation to the sample size and study design. The cohort included 35 patients, of whom 21 presented with hemorrhagic brain metastases and 14 had nonhemorrhagic lesions. Although the difference in mean lesion diameter reached statistical significance, the findings originated from a retrospective investigation involving a single primary malignancy. Furthermore, the size threshold of 1.8 cm was identified through a classification and regression tree analysis within the original dataset. Accordingly, this threshold should be understood as a study-specific finding rather than a universally validated cutoff for predicting intracranial bleeding.

Figure 3.

Intracranial Hemorrhage in Patients Receiving Therapeutic Anticoagulation

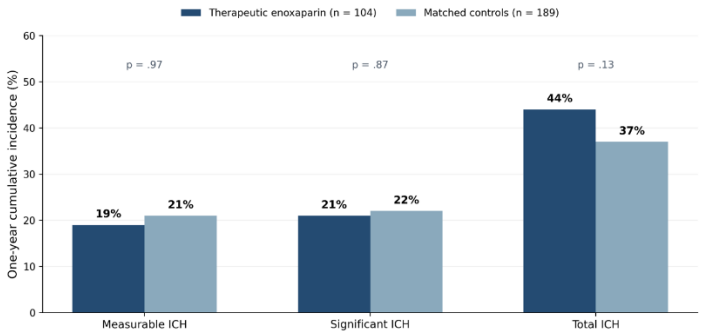


Figure 3 illustrates the relationship between therapeutic anticoagulation and intracranial hemorrhage among patients with brain metastases, based on the comparative findings reported by Donato et al. (2015). The analysis includes three hemorrhagic outcome categories—measurable, significant, and total intracranial hemorrhage—and compares their cumulative incidence over a one-year observation period between patients receiving therapeutic enoxaparin and matched controls without therapeutic anticoagulation. Across the examined outcomes, the original investigation did not identify statistically significant differences between treatment groups, although the absolute frequencies varied according to the hemorrhage category.

The study included 293 patients with metastatic intracranial disease, comprising 104 individuals who received therapeutic enoxaparin and 189 matched controls. Intracranial hemorrhages were identified through radiological assessment and classified according to predefined characteristics. The investigators used competing-risk methods to estimate cumulative incidence, accounting for mortality during follow-up. This statistical approach was particularly relevant because patients with brain metastases may die before experiencing or undergoing evaluation for a hemorrhagic event (Donato et al., 2015).

The first comparison concerns **measurable intracranial hemorrhage**, which occurred with a one-year cumulative incidence of 19% in the enoxaparin group and 21% in the control group. The absolute difference between groups was

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

two percentage points, with a slightly lower observed incidence among anticoagulated patients. The original statistical analysis demonstrated no significant difference (p = .97), with a reported hazard ratio of 1.02 and a 90% confidence interval of 0.66–1.59. These results indicate that the observed incidence of measurable bleeding was comparable between groups within the examined population. However, the confidence interval does not exclude every clinically meaningful difference in risk (Donato et al., 2015).

The second comparison addresses **significant intracranial hemorrhage**, an outcome defined according to bleeding volume, neurological symptoms, or the requirement for surgical intervention. The cumulative incidence was 21% among patients receiving therapeutic enoxaparin and 22% among controls. The absolute difference was one percentage point, and the comparison was not statistically significant (p = .87). This similarity was also observed when the investigators examined the distribution of hemorrhage severity, although individual clinical presentations varied.

Further examination of significant hemorrhagic events demonstrated that most were associated with neurological symptoms. Donato et al. (2015) reported symptomatic presentations in 87.5% of significant hemorrhages within the enoxaparin group and 94.7% within the control group. Neurosurgical intervention was required in six patients from each group among those experiencing significant hemorrhage, representing 25% and 15.8% of the respective significant-hemorrhage cases. The comparison did not reach statistical significance (p = .51). These additional findings provide descriptive information regarding the clinical severity of intracranial hemorrhagic events, beyond their cumulative incidence.

The third comparison evaluates **total intracranial hemorrhage**, encompassing the broader radiologically identified bleeding events included in the study classification. The one-year cumulative incidence was 44% in the enoxaparin group and 37% in the control group. This represents an absolute difference of seven percentage points, with a numerically higher incidence among patients receiving therapeutic anticoagulation. Nevertheless, the difference was not statistically significant (p = .13). Unlike the first two comparisons, the total hemorrhage category demonstrated a greater separation between groups, although the study did not establish a statistically significant association between enoxaparin exposure and increased overall intracranial bleeding.

Importantly, the three outcomes shown in Figure 3 represent different classifications of hemorrhagic events rather than independent groups of patients. Consequently, the percentages cannot be added together or interpreted as mutually exclusive frequencies. The distinction between measurable hemorrhage, significant hemorrhage, and total hemorrhage is essential for understanding the original analysis, particularly because clinically consequential bleeding may be distinguished from smaller radiologically detected events.

Beyond the overall cohort, the original investigation examined intracranial hemorrhage according to primary malignancy. Among patients with non-small cell lung cancer, the one-year cumulative incidence of measurable hemorrhage was 12% in the enoxaparin group and 16% among controls. Significant hemorrhage occurred at cumulative incidences of 15% and 19%, respectively. Neither comparison demonstrated a statistically significant difference between anticoagulated and non-anticoagulated patients (Donato et al., 2015).

A different hemorrhagic profile was observed among patients with melanoma or renal cell carcinoma. In this combined subgroup, measurable intracranial hemorrhage exhibited cumulative incidences of 42% among enoxaparin-treated patients and 52% among controls. Significant hemorrhage occurred at corresponding incidences of 35% and 34%. Although these frequencies were substantially higher than those observed in patients with lung cancer, anticoagulation exposure was not associated with a statistically significant difference in hemorrhagic incidence within the subgroup.

The multivariable analysis reported by Donato et al. (2015) further identified an approximately fourfold higher hazard of measurable intracranial hemorrhage in patients with melanoma or renal cell carcinoma compared with those with lung cancer, with an adjusted hazard ratio of 3.98 (90% CI: 2.41–6.57; p < .001). This finding provides additional quantitative evidence of differences in hemorrhagic susceptibility according to underlying tumor histology. The relationship between primary malignancy and bleeding was therefore distinguishable from the comparison of anticoagulation exposure within the study population.

The investigators also evaluated overall survival, reporting median values of 8.4 months among enoxaparin-treated patients and 9.7 months among controls. The survival comparison did not demonstrate a statistically significant

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

difference in the primary analysis (p = .65). However, the authors explored potential time-related selection bias in additional analyses, an important consideration when interpreting observational comparisons in which anticoagulant treatment may begin after the diagnosis of brain metastases.

The results presented in Figure 3 are consistent with the broader hematological literature addressing anticoagulation in patients with intracranial metastatic disease. Leader et al. (2020) evaluated intracranial bleeding among patients with brain metastases receiving direct oral anticoagulants or low-molecular-weight heparin, while Hamulyák et al. (2024) reviewed the complexities of balancing hemorrhagic and thrombotic risks in this population. These publications provide additional context, although their study designs, anticoagulant exposures, and bleeding definitions differ from those of Donato et al. (2015).

Several methodological considerations accompany the interpretation of these findings. First, the investigation was retrospective, and treatment allocation was not randomized. Second, the primary malignancies and baseline bleeding susceptibilities were heterogeneous. Third, the absence of statistically significant differences does not establish therapeutic equivalence or prove the absence of anticoagulation-associated risk in every patient subgroup. Finally, the reported findings cannot be directly extrapolated to patients with active, expanding, or recently destabilized intracranial hemorrhage, for whom the available evidence remains more limited.

Figure 4.

Neurosurgical Management and Clinical Outcomes in Patients With Brain Metastases

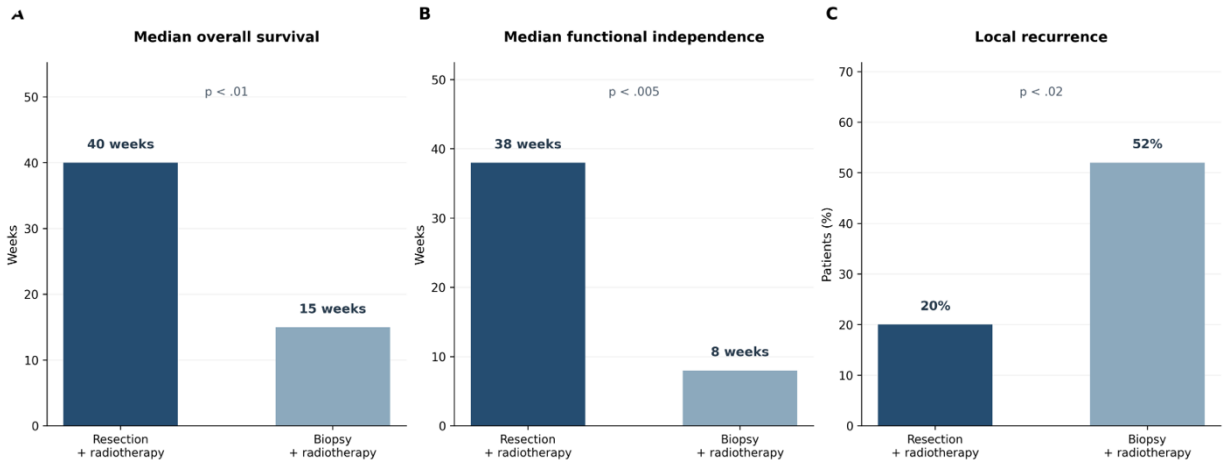


Figure 4 presents three complementary clinical outcomes associated with neurosurgical management of solitary brain metastases: overall survival, preservation of functional independence, and recurrence at the original metastatic site. The findings originate from the randomized clinical trial conducted by Patchell et al. (1990), which included 48 patients assigned to surgical resection followed by radiotherapy or needle biopsy followed by radiotherapy without resection. The comparison provides quantitative evidence regarding the role of neurosurgical intervention in selected patients with intracranial metastatic disease.

Panel A demonstrates differences in median overall survival between the two therapeutic groups. Patients undergoing surgical resection followed by radiotherapy achieved a median survival of 40 weeks, whereas those receiving radiotherapy without tumor resection demonstrated a median survival of 15 weeks. The absolute difference was 25 weeks, corresponding to an approximately 2.7-fold longer median survival in the surgically treated group. The original survival analysis identified a statistically significant difference between treatment strategies ($p < .01$), indicating that the observed separation in survival outcomes was unlikely to be explained solely by random variation within the study population (Patchell et al., 1990).

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

The reported survival difference was accompanied by variations in neurological mortality. Patchell et al. (1990) documented a median time to death from neurological causes of 62 weeks in the surgical group compared with 26 weeks among patients receiving radiotherapy without resection. The corresponding survival distributions differed significantly ($p < .0009$). These findings provided additional information concerning neurological outcomes and the course of intracranial disease, extending beyond overall survival alone.

Panel B illustrates the duration of functional independence, an outcome reflecting the period during which patients maintained sufficient neurological function to perform everyday activities independently. The median duration of functional independence was 38 weeks among patients undergoing surgical resection and postoperative radiotherapy, compared with 8 weeks among those receiving radiotherapy without resection. The absolute difference of 30 weeks represented an approximately 4.8-fold longer period of functional independence in the surgical group. This comparison was statistically significant ($p < .005$), demonstrating substantial differences in the duration of preserved functional capacity between the two treatment strategies (Patchell et al., 1990).

The magnitude of this difference is particularly relevant when examining the clinical burden of intracranial metastatic disease. Neurological impairment associated with brain metastases may involve motor dysfunction, cognitive disturbances, language impairment, seizures, or reduced mobility. However, the functional independence outcome represented in Figure 4 was determined using the original study's assessment framework and should not be interpreted as a direct measurement of each individual neurological symptom. Instead, it describes the overall duration of maintained functional capacity within the trial population.

Panel C demonstrates differences in local tumor recurrence. Recurrence at the original metastatic site was documented in 20% of surgically treated patients, corresponding to 5 of 25 individuals. In contrast, recurrence occurred in 52% of patients receiving radiotherapy without resection, corresponding to 12 of 23 individuals. The absolute difference between groups was approximately 32 percentage points, and the comparison was statistically significant ($p < .02$). These findings indicate that surgical resection followed by radiotherapy was associated with a lower observed frequency of recurrence at the original metastatic site (Patchell et al., 1990).

The original investigation distinguished recurrence at the treated metastatic site from the development of additional distant intracranial or leptomeningeal disease. This distinction is essential because local control and intracranial disease progression represent separate clinical outcomes. While the surgical group demonstrated a lower rate of recurrence at the original lesion, the occurrence of distant brain or leptomeningeal metastases did not differ significantly between treatment groups. Patchell et al. (1990) reported these events in 20% of patients undergoing surgery and 13% of those receiving radiotherapy without resection ($p = .52$).

The three outcomes presented in Figure 4 therefore describe different dimensions of disease management. Overall survival provides information regarding the duration of life following treatment, functional independence reflects the maintenance of neurological capacity, and local recurrence describes disease control at the original metastatic site. Although these measures are clinically related, they represent distinct endpoints and should not be interpreted interchangeably.

A further consideration concerns the characteristics of the study population. The investigation evaluated patients with a single brain metastasis who were considered eligible for the assigned interventions. Consequently, the results reflect outcomes in a selected population rather than the entire spectrum of patients with metastatic intracranial disease. Individuals with extensive systemic disease, multiple metastatic lesions, substantial functional impairment, or anatomically inaccessible tumors may exhibit different treatment outcomes.

The applicability of these findings to hemorrhagic brain metastases requires additional clarification. The Patchell et al. (1990) trial was not specifically designed to evaluate patients presenting with active intracranial hemorrhage, expanding hematomas, or acute neurological deterioration secondary to metastatic bleeding. Therefore, the survival and recurrence differences shown in Figure 4 cannot be directly attributed to the surgical management of hemorrhagic lesions.

Nevertheless, the trial provides foundational evidence regarding neurosurgical treatment of brain metastases. Contemporary guidelines identify surgery as a treatment consideration in selected patients, particularly those with large

lesions producing mass effect or requiring pathological diagnosis. The ASCO-SNO-ASTRO guideline also emphasizes that surgical benefit depends on patient selection, intracranial disease characteristics, and the overall clinical context (Vogelbaum et al., 2022).

The distinction between historical and contemporary radiotherapeutic approaches must also be maintained. The Patchell et al. (1990) trial employed whole-brain radiotherapy, whereas current management increasingly incorporates stereotactic radiosurgery and more selective postoperative radiation techniques. Consequently, the observed comparison should not be interpreted as demonstrating superiority of surgery over every contemporary nonsurgical treatment strategy.

The findings reported by Patchell et al. (1998) further expanded the evidence regarding postoperative intracranial disease management by investigating the effects of radiation therapy following complete surgical resection. Although this subsequent trial addressed a different comparison, it contributed additional evidence concerning local recurrence and postoperative treatment strategies.

Figure 5.

Hemorrhagic Status and Local Tumor Control Following Stereotactic Radiosurgery

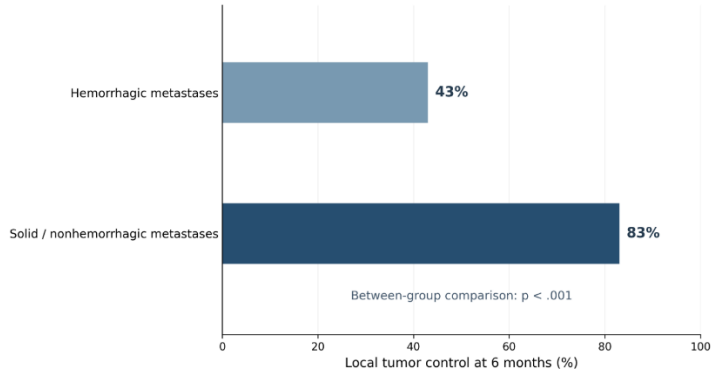


Figure 5 demonstrates a substantial difference in local tumor control following stereotactic radiosurgery between hemorrhagic and nonhemorrhagic melanoma brain metastases. The analysis is based on the retrospective investigation conducted by Bauer-Nilsen et al. (2018), which evaluated 134 patients harboring a total of 936 intracranial metastatic lesions treated with stereotactic radiosurgery. The results provide quantitative evidence of an association between pretreatment hemorrhagic characteristics and subsequent local oncological outcomes.

At six months following radiosurgical treatment, **local tumor control was achieved in 43% of hemorrhagic metastases**, compared with **83% of solid melanoma metastases**. This represents an absolute difference of 40 percentage points between the two groups. Expressed as a descriptive ratio, the observed local control percentage among hemorrhagic lesions was approximately 52% of that reported among nonhemorrhagic lesions. The original investigators identified a statistically significant difference between groups ($p < .001$), indicating a strong association between hemorrhagic presentation and reduced local tumor control within the examined cohort (Bauer-Nilsen et al., 2018).

The magnitude of this difference is particularly notable because both groups received stereotactic radiosurgery, allowing comparison according to radiological lesion characteristics within a common therapeutic modality. Nevertheless, the retrospective design does not establish that hemorrhage itself directly caused reduced treatment effectiveness. Differences in lesion dimensions, tumor biology, treatment exposure, and other clinical characteristics may have contributed to the observed outcomes.

The original study further examined factors associated with local tumor progression through multivariable analysis. Radiographic evidence of clear intratumoral hemorrhage was associated with a higher hazard of local progression,

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO
Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

with a reported hazard ratio of **2.20 (p < .001)**. Radiographic characteristics consistent with melanin deposition were also associated with local progression, with a hazard ratio of **3.73 (p < .001)**. These findings indicate that specific pretreatment imaging characteristics were associated with different probabilities of subsequent local tumor failure, even after accounting for additional variables incorporated into the statistical model (Bauer-Nilsen et al., 2018).

Additional treatment-related factors were identified in the multivariable analysis. Previous whole-brain radiotherapy was associated with a higher hazard of local progression (HR = 1.62; p = .003), whereas previous chemotherapy demonstrated a hazard ratio of 0.69 (p = .011). The prescribed marginal radiation dose was also associated with local progression, with a hazard ratio of 0.88 (p < .001). These findings describe associations observed within the original dataset; they should not be interpreted as isolated causal effects of individual treatments.

An important observation concerns the distinction between local tumor control and treatment-associated toxicity. Although hemorrhagic metastases demonstrated substantially lower local control at six months, Bauer-Nilsen et al. (2018) did not identify a statistically significant difference in toxicity between hemorrhagic and solid lesions. Therefore, reduced local control did not correspond to a demonstrated increase in overall treatment toxicity within the reported analysis.

Complementary evidence was provided by Ghia et al. (2014), who evaluated 110 patients with 358 melanoma brain metastases treated with stereotactic radiosurgery. Hemorrhage was documented before treatment in **83 of 358 lesions (23.2%)**, whereas post-treatment hemorrhage was observed in **73 of 358 lesions (20.4%)**. The comparison did not demonstrate a statistically significant difference in hemorrhage frequency before and after radiosurgery (p = .362). These findings provide an additional perspective on the relationship between radiosurgical treatment and intratumoral bleeding, although the two assessments do not constitute a randomized comparison of treatment-associated hemorrhagic risk.

The same investigation identified previous hemorrhage as a factor associated with subsequent hemorrhagic events. This finding distinguishes the influence of pre-existing lesion characteristics from the overall comparison of hemorrhage frequencies before and after treatment. Accordingly, the presence of hemorrhage before radiosurgery and the occurrence of new hemorrhage after treatment represent related but separate analytical outcomes (Ghia et al., 2014).

More recent evidence has expanded the examination of hemorrhagic complications following stereotactic treatment. Jablonska et al. (2023) investigated melanoma brain metastases treated with stereotactic radiosurgery and evaluated symptomatic intralesional hemorrhage alongside radiation necrosis. Their investigation identified hemorrhage as an important post-treatment outcome requiring assessment independently from radiation-associated tissue injury.

Similarly, McKenzie et al. (2022) examined radiosurgical fractionation and the occurrence of post-treatment hemorrhage in melanoma brain metastases, contributing additional evidence regarding treatment characteristics and subsequent bleeding events. Differences in study populations, radiation techniques, clinical endpoints, and follow-up periods limit direct numerical comparisons between these investigations and the findings presented in Figure 5.

The population evaluated by Bauer-Nilsen et al. (2018) also exhibited substantial variation in long-term survival. Overall survival following the first stereotactic radiosurgery treatment was reported as **42% at 12 months, 31% at 24 months, and 12% at 72 months**. These estimates describe survival across the overall study population and should not be interpreted as survival rates specific to the hemorrhagic subgroup.

This distinction is important because local tumor control and overall survival measure different clinical outcomes. Local control describes the behavior of treated intracranial lesions, whereas overall survival is influenced by multiple factors, including extracranial disease progression, systemic treatment response, neurological complications, and general patient condition.

The broader evidence summarized by Łupicka et al. (2024) also identifies hemorrhagic presentation as a relevant characteristic in studies examining radiosurgical outcomes. Their review describes differences in local control among hemorrhagic and nonhemorrhagic metastases while acknowledging the heterogeneity and predominantly retrospective nature of the available evidence.

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO
Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Several methodological limitations should be considered when interpreting Figure 5. First, the comparison was derived from an observational cohort rather than a randomized trial. Second, the findings specifically concern melanoma brain metastases and cannot automatically be generalized to lesions originating from renal cell carcinoma, lung cancer, breast cancer, or other primary malignancies. Third, the reported local control percentages were determined using the original study's radiological evaluation and follow-up framework.

Additionally, the analysis combined information from multiple metastatic lesions within a smaller number of patients. Because several lesions may occur in the same individual, lesion-level observations are not necessarily statistically independent. The interpretation of outcomes should therefore respect the analytical methods and unit of observation employed by the original investigators.

DISCUSIÓN

The management of hemorrhagic brain metastases represents a complex intersection between neuro-oncology, neurosurgery, hematology, and radiation oncology. The findings examined in this narrative review demonstrate that intracranial hemorrhage is not a uniform manifestation of metastatic disease but rather a heterogeneous complication influenced by primary tumor histology, vascular characteristics, metastatic lesion dimensions, coagulation abnormalities, and previous therapeutic interventions. Although substantial progress has been achieved in the treatment of brain metastases, the available evidence continues to reveal important limitations in the prediction of hemorrhagic events, selection of surgical candidates, and integration of local and systemic oncological treatments. These uncertainties are particularly relevant because patients with active intracranial bleeding are frequently underrepresented in prospective therapeutic investigations (Roth et al., 2021; Vogelbaum et al., 2022; Łupicka et al., 2024).

One of the most relevant findings concerns the relationship between primary tumor histology and hemorrhagic susceptibility. The reviewed literature consistently identifies melanoma and renal cell carcinoma among the malignancies most strongly associated with intracranial bleeding. In addition, metastatic thyroid carcinoma demonstrates considerable hemorrhagic potential, as illustrated by the retrospective findings of Kim et al. (2021), in which 60% of patients with thyroid brain metastases exhibited intratumoral hemorrhage. Melanoma metastases have demonstrated hemorrhagic frequencies ranging from approximately 29% to 50% across published investigations, reinforcing the importance of tumor-specific biological characteristics (Łupicka et al., 2024). However, the differences in study populations, imaging protocols, and hemorrhage definitions prevent direct interpretation of these estimates as a definitive hierarchy of bleeding risk across all metastatic histologies.

From a pathophysiological perspective, differences in hemorrhagic susceptibility are consistent with the heterogeneous vascular behavior of metastatic tumors. Abnormal angiogenesis, endothelial instability, intratumoral necrosis, and disruption of vascular integrity may contribute to hemorrhagic manifestations. Nevertheless, the relative contribution of these processes remains incompletely characterized, particularly because most clinical investigations evaluate radiological and therapeutic outcomes rather than directly quantifying tumor vascular abnormalities. Consequently, the association between histology and hemorrhage should be understood as a clinically relevant biological relationship whose underlying mechanisms require further investigation.

The relationship between metastatic lesion size and hemorrhage introduces an additional dimension of clinical heterogeneity. Kim et al. (2021) reported a greater mean lesion diameter among hemorrhagic thyroid brain metastases than among nonhemorrhagic lesions, with a statistically significant difference between groups. Furthermore, all patients within the subgroup exhibiting lesions larger than 1.8 cm demonstrated intratumoral hemorrhage, whereas bleeding was also identified among patients with smaller lesions. These findings suggest that tumor dimensions may contribute to hemorrhagic susceptibility without independently determining whether bleeding will occur. Importantly, the limited sample size and histology-specific nature of the investigation prevent the proposed size threshold from being applied universally to other metastatic populations.

This distinction becomes particularly important when interpreting the relationship between structural tumor characteristics and neurological severity. Large metastatic lesions may produce extensive edema or mass effect even in the absence of substantial hemorrhage, whereas smaller lesions located within anatomically sensitive regions may

cause pronounced neurological manifestations following relatively limited bleeding. Therefore, lesion diameter, hemorrhage volume, anatomical location, and neurological function represent complementary rather than interchangeable clinical variables. Contemporary multidisciplinary recommendations emphasize the integration of these characteristics when evaluating intracranial metastatic disease, although specific risk models for hemorrhagic lesions remain insufficiently validated (Roth et al., 2021; Vogelbaum et al., 2022).

The findings concerning anticoagulation provide an important perspective on the interaction between cancer-associated thrombosis and intracranial hemorrhage. Malignancy creates a prothrombotic environment, and patients with metastatic cancer frequently require anticoagulant treatment for venous thromboembolism. Nevertheless, the presence of intracranial metastases introduces concern regarding potentially severe hemorrhagic complications. Donato et al. (2015) demonstrated that therapeutic enoxaparin was not associated with a statistically significant increase in measurable or significant intracranial hemorrhage compared with matched controls. At one year, measurable hemorrhage occurred at cumulative incidences of 19% and 21%, respectively, while significant hemorrhage occurred at incidences of 21% and 22%.

These findings challenge the assumption that all patients with brain metastases necessarily experience a substantial additional hemorrhagic risk following therapeutic anticoagulation. However, the observational nature of the evidence is critical to its interpretation. Treatment decisions were not randomized, and patients with particular clinical characteristics may have been more or less likely to receive anticoagulation. Furthermore, the absence of statistical significance does not establish therapeutic equivalence or demonstrate safety in patients with active, expanding, or recently unstable intracranial hemorrhage.

Additional investigations have explored anticoagulant treatment beyond low-molecular-weight heparin. Leader et al. (2020) examined intracranial hemorrhage among patients with brain metastases receiving direct oral anticoagulants or low-molecular-weight heparin, contributing evidence concerning the comparative safety of different anticoagulant strategies. More recent research has emphasized the need to consider primary tumor histology, previous hemorrhage, platelet abnormalities, and the severity of thromboembolic disease when interpreting bleeding risk (Hamulyák et al., 2024; Hamulyák et al., 2025). Collectively, these findings support the relevance of individualized hematological assessment while highlighting the limited prospective evidence available for patients with hemorrhagic metastatic lesions.

Neurosurgical decision-making constitutes another central element of the reviewed evidence. The historical randomized investigation by Patchell et al. (1990) demonstrated improvements in overall survival, functional independence, and local tumor control among selected patients undergoing surgical resection followed by radiotherapy compared with radiotherapy without resection. The substantial differences observed between groups established an important foundation for the role of surgery in the management of solitary brain metastases.

Nevertheless, the applicability of these findings to hemorrhagic metastatic disease requires careful consideration. The original trial did not specifically evaluate patients presenting with active intracranial hemorrhage, severe hematoma-related mass effect, or acute deterioration requiring emergency decompression. Furthermore, the study population consisted of selected patients with solitary metastatic lesions treated using radiotherapeutic strategies that differ from many contemporary approaches. Consequently, these results provide evidence for the broader value of neurosurgical intervention but do not independently establish the optimal surgical indications or outcomes in hemorrhagic metastases.

In the setting of hemorrhagic brain metastases, the therapeutic objectives of surgery may extend beyond oncological resection to include hematoma evacuation, reduction of intracranial pressure, and stabilization of neurological function. These additional objectives distinguish hemorrhagic lesions from metastatic tumors treated exclusively for local disease control. However, the potential benefits of intervention must be considered alongside operative bleeding risk, anatomical accessibility, functional prognosis, systemic disease burden, and the likelihood of meaningful neurological recovery. Vogelbaum et al. (2022) emphasize that patients with large intracranial lesions producing mass effect may be more likely to benefit from surgery, whereas those with extensive uncontrolled systemic disease or multiple asymptomatic metastases may derive more limited benefit.

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO
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IECCMEXICO Review

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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

The relationship between surgery and postoperative radiotherapy also deserves consideration. Patchell et al. (1998) demonstrated that postoperative whole-brain radiotherapy reduced intracranial recurrence following complete resection of a solitary brain metastasis. However, contemporary practice increasingly incorporates stereotactic radiation techniques that offer more localized treatment. This evolution limits the direct applicability of historical radiotherapy comparisons to modern therapeutic sequencing, particularly in patients whose hemorrhagic lesions have undergone urgent decompression or partial surgical removal.

The radiotherapeutic findings represent one of the most relevant areas of uncertainty identified in this review. Bauer-Nilsen et al. (2018) reported substantially lower six-month local tumor control among hemorrhagic melanoma brain metastases compared with nonhemorrhagic lesions following stereotactic radiosurgery, with corresponding rates of 43% and 83%. The observed difference remained clinically notable and was supported by multivariable analyses associating pretreatment hemorrhagic characteristics with subsequent local progression. These findings indicate that hemorrhagic presentation may be an important marker of treatment outcome.

However, several alternative explanations must be considered. Hemorrhagic lesions may differ from nonhemorrhagic metastases in tumor dimensions, vascular characteristics, biological aggressiveness, and pretreatment disease status. Blood products may also complicate radiological target definition or the distinction between viable tumor tissue and hemorrhagic components. Therefore, the relationship between hemorrhage and reduced local control cannot necessarily be interpreted as a direct biological reduction in radiosensitivity.

Additional evidence from Ghia et al. (2014) suggests that stereotactic radiosurgery does not invariably increase the frequency of intracranial hemorrhage compared with pretreatment observations. Nevertheless, previous hemorrhage was associated with subsequent bleeding, indicating that baseline lesion characteristics remain relevant when evaluating post-treatment outcomes. The available findings therefore distinguish two separate questions: whether hemorrhagic metastases demonstrate different local control rates after irradiation, and whether irradiation itself increases the probability of subsequent hemorrhage. These questions involve different endpoints and should not be considered equivalent.

More recent investigations have addressed post-radiosurgical hemorrhage, fractionation strategies, and radiation-related complications. McKenzie et al. (2022) evaluated hemorrhagic outcomes following stereotactic treatment of melanoma brain metastases, while Jablonska et al. (2023) examined symptomatic intralesional hemorrhage in relation to other post-treatment complications. Although these studies contribute important information, differences in treatment protocols, lesion characteristics, imaging surveillance, and outcome definitions limit direct comparisons. Łupicka et al. (2024) concluded that the available evidence does not establish hemorrhagic presentation as an absolute contraindication to stereotactic radiosurgery, although the evidence base remains limited.

The integration of systemic oncological therapies introduces an additional challenge, particularly because the effectiveness of immunotherapy and targeted agents varies according to tumor biology, neurological symptoms, and previous treatment exposure. Long et al. (2018) demonstrated meaningful intracranial activity with nivolumab and ipilimumab in selected patients with melanoma brain metastases, supporting the expanding role of systemic treatment in intracranial disease management. However, evidence from patients with asymptomatic or neurologically stable metastatic lesions cannot necessarily be extrapolated to those presenting with acute hemorrhage, substantial cerebral edema, or urgent neurosurgical indications.

This distinction is supported by subsequent investigations examining immunotherapy outcomes according to neurological presentation. In the CheckMate 204 study, intracranial clinical benefit was substantially greater among asymptomatic patients than among those presenting with neurological symptoms or requiring corticosteroids. These findings indicate that baseline neurological status is an important variable when interpreting systemic treatment outcomes, although symptom severity and corticosteroid exposure may be associated with additional differences in disease burden and prognosis. Importantly, these cohorts were not designed to isolate the effect of active intracranial hemorrhage on immunotherapy effectiveness.

The sequencing of neurosurgical intervention, radiotherapy, and systemic therapy therefore remains one of the principal unresolved issues in hemorrhagic brain metastasis management. Patients with severe neurological

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

compromise may require immediate stabilization and local intervention, whereas neurologically stable individuals may undergo more extensive multidisciplinary assessment before definitive treatment selection. The optimal therapeutic sequence is also influenced by extracranial disease activity, the molecular characteristics of the primary malignancy, anticipated systemic treatment response, and individual functional prognosis. Although contemporary guidelines emphasize multidisciplinary treatment planning, direct comparative evidence specifically addressing different therapeutic sequences in hemorrhagic metastatic populations remains limited (Vogelbaum et al., 2022; Roth et al., 2021).

An additional consideration concerns the interpretation of radiological outcomes following multimodal treatment. Hemorrhage, tumor progression, radiation necrosis, and treatment-associated inflammatory changes may produce overlapping imaging findings. This diagnostic complexity may affect estimates of local control, particularly in retrospective studies using different imaging protocols and follow-up intervals. Consequently, standardized radiological definitions and consistent outcome assessment procedures are important methodological priorities for future studies investigating hemorrhagic metastatic lesions.

The international applicability of the reviewed evidence also warrants discussion. Much of the available research originates from specialized neuro-oncological centers with access to advanced neuroimaging, dedicated neurosurgical services, stereotactic irradiation, and contemporary systemic cancer treatments. However, these resources are not uniformly available across healthcare systems. Latin American investigations, including the Brazilian experience reported by Santos et al. (2015) and the regional radiosurgery survey conducted by Rojas-López et al. (2026), provide relevant information concerning regional treatment practices and the implementation of specialized intracranial therapies. Although these studies do not specifically establish treatment outcomes for hemorrhagic metastases, they contribute to understanding the broader context in which multidisciplinary management strategies are applied.

Differences in healthcare infrastructure may influence diagnostic delays, referral pathways, access to surgical intervention, availability of radiation treatment, and continuity of oncological follow-up. These circumstances may affect the feasibility of implementing recommendations derived from highly specialized institutions. Nevertheless, the reviewed evidence does not permit quantitative conclusions regarding regional differences in hemorrhagic complications or survival. Dedicated multicenter studies involving Latin American populations would be necessary to determine whether treatment accessibility and institutional resources are independently associated with outcomes in hemorrhagic brain metastases.

Several limitations of the present review should be acknowledged. First, the narrative methodology permits integration of heterogeneous evidence but does not provide the quantitative precision of a formal meta-analysis. Second, many investigations specifically examining hemorrhagic brain metastases are retrospective, increasing susceptibility to selection bias, confounding, and incomplete outcome assessment. Third, the clinical definitions of hemorrhage vary across studies, ranging from radiologically detectable blood products to symptomatic intracranial bleeding requiring intervention. These differences complicate comparisons and limit the interpretation of reported hemorrhagic frequencies.

Furthermore, several foundational studies included in the review were conducted before the widespread adoption of contemporary stereotactic techniques, molecularly targeted therapies, and immune checkpoint inhibitors. Although these investigations remain relevant to the historical development of treatment principles, their findings may not fully represent current therapeutic outcomes. Similarly, evidence derived from nonhemorrhagic metastatic populations cannot be assumed to apply directly to patients with active bleeding, particularly when evaluating surgical urgency, anticoagulation safety, or systemic treatment effectiveness.

A further limitation concerns the distinction between descriptive associations and causal relationships. The observation that hemorrhagic lesions demonstrate lower local control following stereotactic radiosurgery does not prove that hemorrhage directly reduces radiosensitivity. Likewise, the absence of statistically significant differences in intracranial bleeding between anticoagulated and non-anticoagulated groups does not establish equivalent safety in all clinical circumstances. These distinctions are essential for maintaining an appropriate interpretation of observational evidence.

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO

Edition 5, Year 3, Number 2, 2026
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IECCMEXICO Review

Future investigations should prioritize prospective multicenter cohorts incorporating standardized definitions of intracranial hemorrhage, detailed tumor histology, baseline neurological status, coagulation parameters, lesion characteristics, and treatment exposure. Comparative studies evaluating surgical intervention, stereotactic radiotherapy, and systemic treatments in well-defined hemorrhagic populations would also improve understanding of therapeutic effectiveness and safety. Particular attention should be directed toward the development of validated hemorrhagic risk prediction tools and the evaluation of anticoagulation strategies following recent intracranial bleeding.

The incorporation of patient-centered outcomes represents another important research priority. Overall survival and radiological local control remain essential measures of therapeutic effectiveness, but they do not fully characterize neurological recovery, preservation of independence, cognitive function, or quality of life. Future research would benefit from integrating these outcomes into longitudinal assessments, particularly when evaluating patients who experience acute neurological deterioration or undergo urgent surgical intervention.

Taken together, the reviewed evidence demonstrates that hemorrhagic brain metastases cannot be adequately understood through a single clinical variable or therapeutic perspective. Primary tumor histology and lesion characteristics influence hemorrhagic susceptibility, neurological severity determines the urgency of assessment, hematological abnormalities complicate treatment selection, and oncological prognosis shapes the potential benefits of intervention. The available studies support the relevance of multidisciplinary evaluation while revealing persistent uncertainty regarding optimal treatment sequencing and comparative effectiveness.

CONCLUSIÓN

Hemorrhagic brain metastases represent a clinically complex manifestation of advanced systemic malignancy, characterized by the interaction of tumor-specific vascular abnormalities, intracranial bleeding, neurological deterioration, and therapeutic challenges. The findings synthesized in this narrative review demonstrate that hemorrhagic susceptibility varies considerably according to primary tumor histology, metastatic lesion characteristics, and associated hematological conditions. Melanoma, renal cell carcinoma, and thyroid carcinoma exhibit particularly relevant hemorrhagic tendencies, emphasizing the importance of incorporating tumor biology into individualized clinical assessment.

Neurosurgical management remains an essential therapeutic consideration, particularly in patients presenting with significant mass effect, progressive neurological deterioration, or symptomatic intracranial hemorrhage. Although surgical resection has demonstrated benefits in selected populations with brain metastases, the applicability of historical evidence to actively hemorrhagic lesions remains limited. Consequently, surgical decisions must integrate neurological urgency, anatomical accessibility, functional status, systemic disease burden, and anticipated treatment outcomes.

The reviewed evidence also highlights the complexity of anticoagulation in patients with metastatic intracranial disease. Available observational studies suggest that therapeutic anticoagulation does not uniformly increase intracranial hemorrhage risk; however, bleeding susceptibility differs substantially among tumor histologies and clinical circumstances. Individualized hematological evaluation is therefore necessary, particularly when thromboembolic complications coexist with previous or active intracranial bleeding.

Stereotactic radiosurgery and systemic oncological therapies have expanded treatment opportunities for patients with brain metastases. Nevertheless, hemorrhagic lesions may demonstrate reduced local tumor control following radiosurgical treatment, while the evidence regarding post-treatment bleeding and optimal therapeutic sequencing remains incomplete. Immunotherapy and molecularly targeted treatments offer additional possibilities for selected patients, although their effectiveness and safety in the presence of acute hemorrhagic complications require further investigation.

The integration of neurosurgery, radiation oncology, medical oncology, hematology, and neuroradiology emerges as a fundamental component of comprehensive management. Treatment selection should consider not only intracranial

disease control and overall survival but also neurological recovery, preservation of functional independence, quality of life, and patient preferences. These considerations are particularly important in healthcare environments where access to specialized interventions may be limited.

Despite advances in neuro-oncological treatment, the current evidence remains constrained by retrospective study designs, heterogeneous definitions of hemorrhage, variable patient populations, and the limited availability of prospective comparative investigations. Future research should prioritize standardized hemorrhagic risk assessment, validated prognostic models, comparative evaluation of therapeutic strategies, and multicenter collaboration, including greater participation from Latin American institutions.

In conclusion, **the optimal management of hemorrhagic brain metastases cannot be determined by hemorrhagic status alone**. Rather, it requires an individualized, evidence-informed approach that integrates tumor biology, neurological severity, hematological risk, and oncological prognosis. Strengthening the scientific evidence supporting these decisions will be essential for improving treatment selection, reducing preventable complications, and promoting better neurological and oncological outcomes.

Edición 5, Año 3, Número 2, 2026
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Revista IECCMEXICO
Edition 5, Year 3, Number 2, 2026
E-ISSN: 3061-8045, P-ISSN: 3061-8517
IECCMEXICO Review

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