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Kidney cancer metastasis to the brain; a narrative review study

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ABSTRACT

Brain metastasis (BM) from renal cell carcinoma (RCC) represent a significant clinical challenge, associated with high morbidity and poor prognosis. The advent of targeted therapies and immune checkpoint inhibitors (ICIs) has transformed the management of metastatic RCC (mRCC), yet patients with brain metastasis remain underrepresented in clinical trials, and optimal management strategies are still evolving. The findings indicated that brain metastasis occur in approximately 5–15% of patients with mRCC, with clear cell histology and the presence of extracranial metastases as key risk factors. The pathophysiology involves complex molecular mechanisms, including hematogenous dissemination and genetic alterations. Clinical presentation is often symptomatic, with headaches, focal deficits, and seizures, but a substantial proportion of cases are detected incidentally. Magnetic resonance imaging (MRI) remains the gold standard for diagnosis, though screening is typically reserved for symptomatic or high-risk patients. Treatment is multimodal: surgery and stereotactic radiosurgery (SRS) are mainstays for local control, while systemic therapies, particularly cabozantinib and ICI-based regimens, have shown promising intracranial activity. Prognosis remains guarded, with median survival after BM diagnosis ranging from 10 to 18 months, but outcomes have improved in the ICI era. In conclusion, the management of RCC brain metastases requires a multidisciplinary, individualized approach. Advances in systemic and local therapies have improved survival, but significant challenges remain, including the risk of intracranial hemorrhage and the need for better screening and surveillance strategies. Ongoing research into molecular mechanisms and novel therapeutics holds promise for further progress in this high-risk population.

Implication for health policy/practice/research/medical education:

Brain metastasis (BM) from renal cell carcinoma (RCC) remain a challenging complication marked by high morbidity and historically limited survival, though outcomes have improved with advances in surgery, radiotherapy, and modern systemic therapies such as cabozantinib and immune checkpoint inhibitors (ICIs). Optimal care relies on early detection, timely local treatment for symptomatic or limited disease, and thoughtful integration of effective systemic agents. Important gaps persist, including the need for improved surveillance, better management of complications like intracranial hemorrhage, and greater inclusion of these patients in clinical trials.

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Introduction

Renal cell carcinoma (RCC) is the most common primary malignancy of the kidney, accounting for approximately 3–5% of all adult cancers (1–3). The global incidence of RCC has been rising, with over 80,000 new cases and more than 14,000 deaths estimated in the United States in 2024 alone (1,4). While localized RCC is often curable with surgical resection, most patients present with or eventually develop metastatic disease (mRCC) (1,5,6). Among the various sites of RCC metastasis, the brain is particularly

ominous, conferring significant morbidity and a historically poor prognosis (7). Brain metastasis (BM) from RCC occur in approximately 5%–25% of patients with mRCC, though the true incidence may be underestimated due to limited screening of asymptomatic individuals (8,9). The clinical management of RCC-BM is complicated by the tumor's relative resistance to conventional radiotherapy, the blood-brain barrier's limitation on drug delivery, and the high risk of intracranial hemorrhage (10,11). The therapeutic landscape has evolved dramatically in the

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past two decades, with the introduction of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) improving systemic disease control and, by extension, survival outcomes for many patients; however, patients with BM are often excluded from pivotal clinical trials, resulting in a paucity of high-level evidence to guide management in this subgroup (12). This narrative review aims to provide a comprehensive synthesis of current knowledge on RCC brain metastases, including epidemiology, pathophysiology, clinical presentation, diagnostic strategies, treatment modalities, prognosis, and emerging therapies.

Search strategy

A comprehensive literature search was performed across major scientific databases, including PubMed, Scopus, Web of Science, the Cochrane Library, and the Google Scholar search engine, to identify peer-reviewed English-language studies published up to January 2026 that addressed brain metastases arising from RCC. The search strategy incorporated the terms (“renal cell carcinoma” OR “kidney cancer” OR “RCC”) AND (“brain metastases” OR “cerebral metastases” OR “intracranial metastases”), with filters applied for English-language publications, human studies, and article types such as reviews, clinical trials, observational studies, case series, meta-analyses, and clinical guidelines. No lower date limit was imposed, while the upper limit was set at January 31, 2026. Reference lists of key articles were manually screened to identify additional relevant studies, and retracted or non-peer-reviewed materials were excluded to ensure the reliability of the evidence base.

Epidemiology

The incidence of brain metastases in RCC varies across studies, reflecting differences in patient populations, diagnostic practices, and definitions of synchronous versus metachronous metastases. Large population-based analyses and institutional cohorts estimate that BM develops in approximately 5–25% of patients with mRCC (8,9). In a recent analysis of the TriNetX Oncology database, among 14,650 patients with RCC, 730 (5.0%) developed BM, with the majority (65.8%) presenting metachronously (i.e., more than two months after RCC diagnosis) (9). Other studies report higher rates, particularly in cohorts enriched for advanced disease or with systematic brain imaging, with incidences up to 28.4% (12). Clear cell RCC (ccRCC) is the predominant histologic subtype associated with BM, accounting for over 75% of cases (1). Non-clear cell subtypes, such as papillary and chromophobe RCC, have a lower propensity for brain involvement (3% and 2%, respectively). Risk factors for BM include younger age, larger primary

tumor size, sarcomatoid differentiation, lymph node involvement, and the presence of lung or bone metastases (12,13). The timing of BM development is clinically relevant. Synchronous BM (diagnosed within two months of RCC diagnosis) is less common but portends a worse prognosis compared to metachronous BM; however, survival after BM diagnosis does not significantly differ between synchronous and metachronous cases once BM are established (9). Advances in systemic therapies have extended the survival of mRCC patients, potentially increasing the cumulative incidence of BM as patients live longer (12). This trend underscores the importance of vigilant surveillance and tailored management strategies for this high-risk population.

Pathophysiology

The metastatic cascade leading to RCC brain involvement is multifactorial, involving tumor-intrinsic properties, host microenvironment, and molecular alterations. Hematogenous dissemination is the primary route, with tumor cells entering the venous circulation, traversing the pulmonary capillary bed, and ultimately seeding the cerebral vasculature. The “cava-type” pathway, involving the inferior vena cava and right heart, is implicated in up to 75% of cases (1). At the molecular level, several genetic and epigenetic alterations drive RCC metastasis. In ccRCC, loss of chromosome 3p and mutations in the von Hippel–Lindau (VHL) tumor suppressor gene are foundational events, leading to dysregulation of hypoxia-inducible factors (HIFs) and promotion of angiogenesis (1,14). Additional mutations in PBRM1, BAP1, SETD2, and genes involved in the PI3K/AKT/mTOR pathway further contribute to tumor progression and metastatic potential. In papillary RCC, MET gene alterations are prominent, while chromophobe RCC is characterized by distinct chromosomal losses (1). The brain microenvironment poses unique challenges for metastatic colonization. The blood-brain barrier restricts the entry of many systemic agents and immune cells, while the brain’s rich vascular network and unique stromal components may facilitate tumor cell survival and growth (1,15). RCC-BM are often highly vascular, predisposing to intratumoral hemorrhage and peritumoral edema (10). Emerging evidence highlights the role of tumor microenvironment, immune modulation, and metabolic reprogramming in facilitating BM. Tumor-associated macrophages, hypoxic conditions, and altered angiogenic signaling contribute to the establishment and progression of BM (1). Understanding these mechanisms is critical for the development of targeted therapies and biomarkers.

Clinical presentation

Clinical presentation of RCC brain metastases is highly

variable, influenced by the size, number, and location of metastatic lesions as well as the extent of associated edema or hemorrhage, but most patients develop neurologic symptoms (16). Headache and seizure are common, reported in most cases, typically resulting from increased intracranial pressure or mass effect (17,8). Many individuals experience focal neurologic deficits, including focal weakness or paralysis, aphasia, or sensory disturbances (18). A significant proportion of BM are detected incidentally during imaging for other indications, particularly in the era of improved systemic disease control and increased use of brain MRI (magnetic resonance imaging). In a multicenter cohort, a few of the mRCC patients screened for clinical trial eligibility were found to have asymptomatic BM. Notably, patients with asymptomatic BM detected on screening had better survival outcomes than those diagnosed after symptom onset (12). Intracranial hemorrhage is a notable complication that may present acutely with headache, neurologic deterioration, or even sudden death; the risk is heightened in patients receiving anticoagulation or anti-angiogenic therapies (10).

Diagnosis

Imaging modalities

Using MRI with contrast is the gold standard for detecting and characterizing brain metastases, offering superior sensitivity and specificity compared to computed tomography (CT). MRI is particularly adept at identifying small, multifocal, or posterior fossa lesions, as well as distinguishing BM from other intracranial pathologies. The CT scan may be used in emergent settings or when MRI is contraindicated, but its sensitivity for small or non-hemorrhagic lesions is limited (19,20). Advanced imaging techniques, such as diffusion-weighted imaging (DWI), perfusion MRI, and positron emission tomography (PET), may provide additional information regarding lesion biology and treatment response (1).

Screening and surveillance

Current guidelines, including those from the National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU), recommend brain imaging for RCC patients only if neurologic symptoms are present or if clinically indicated by high-risk features (e.g., multiple extracranial metastases, clear cell histology, or lung involvement) (21). Routine screening of asymptomatic patients is not universally endorsed, though emerging evidence suggests that early detection via screening MRI may improve outcomes; in a recent cohort study, patients with BM detected on screening MRI had significantly smaller lesions and longer overall survival compared to those diagnosed after symptom onset (median overall

survival [OS] 86.7 versus 27.9 months) (12). These findings support consideration of screening in selected high-risk populations, though the optimal frequency and cost-effectiveness remain to be determined.

Emerging diagnostic tools

Liquid biopsy approaches, including circulating tumor DNA (ctDNA), circulating tumor cells, and exosomal biomarkers, are under investigation for their potential to detect and monitor BM non-invasively (1). While promising, these techniques are not yet standard of care.

Treatment modalities

Surgery

- Indications and outcomes: Surgical resection is generally reserved for patients with a limited number of accessible BM, particularly those causing significant mass effect, hemorrhage, or neurologic symptoms (22). Gross total resection can provide rapid symptom relief, reduce intracranial pressure, and facilitate histopathologic diagnosis. In selected patients, surgery is associated with improved local control and survival, especially when combined with adjuvant radiotherapy (23).
- Evidence: In a multi-institutional series, neurosurgical resection was performed in 23 of 24 patients with RCC-BM, resulting in improved Karnofsky Performance Status (KPS) in 62.5% of cases and prolonged survival in those with single BM, prior nephrectomy, or systemic therapy (24). A retrospective cohort demonstrated that the addition of surgery to radiotherapy and systemic therapy conferred a median OS of 21.7 months, compared to 12.3 months with radiotherapy plus systemic therapy and 2.0 months with systemic therapy alone (20-22).
- Complications: Surgical risks include infection, hemorrhage, neurologic deficits, and perioperative morbidity. Intracranial hemorrhage is a particular concern in RCC-BM due to its hypervascularity (10).

Radiotherapy

- Principles: Stereotactic radiosurgery (SRS) delivers high-dose, focused radiation to discrete intracranial targets, sparing surrounding normal tissue. It is the preferred modality for patients with a limited number (typically ≤ 4) of small-to-moderate-sized BM, including those not amenable to surgery (23).

- Efficacy: SRS achieves local control rates of 75–97% in RCC BM, despite the tumor's relative radioresistance to conventional fractionated radiotherapy (23). In a cohort of 43 patients treated with single-fraction gamma knife radiosurgery (sf-GKRS), 12- and 18-month local control rates were 97% and 90%, respectively, with a median OS of 15.7 months (25).
- Combination with systemic therapy: The integration of SRS with TKIs or ICIs may enhance efficacy via synergistic mechanisms, though the optimal sequencing and safety profile are under investigation (23).
- Toxicity: Adverse radiation effects (ARE), including radionecrosis and peritumoral edema, occur in up to 42% of patients but are seldom symptomatic. Risk factors include larger tumor volume, high radiation dose, and pre-existing edema. The use of corticosteroids and low serum albumin is associated with worse outcomes (25).
- Whole-brain radiotherapy (WBRT): WBRT is generally reserved for patients with multiple (>4) or diffuse BM not amenable to focal therapies, or as salvage therapy for widespread intracranial progression; its use has declined due to neurocognitive toxicity and the superior local control achieved with SRS. Median OS with WBRT alone is typically 3–7 months (23).

Systemic therapy

- Agents and mechanisms: TKIs targeting vascular endothelial growth factor receptor (VEGFR) (e.g., sunitinib, sorafenib, pazopanib, axitinib, cabozantinib) have revolutionized mRCC management. Their efficacy in BM is influenced by BBB penetration and tumor biology (26).
- Efficacy: Early-generation TKIs (sunitinib, sorafenib) demonstrated limited intracranial activity, with low objective response rates and short progression-free survival in BM cohorts. In contrast, cabozantinib, a multi-kinase inhibitor targeting VEGFR, MET, and AXL, has shown robust intracranial responses. In a multicenter retrospective study of 88 patients with RCC BM, cabozantinib achieved intracranial response rates of 47–55% and a median OS of 15–16 months, with an acceptable safety profile (27).
- Combination with radiotherapy: TKIs may potentiate the effects of SRS, improving local control and survival without significantly increasing toxicity (23). However, concurrent use may elevate the risk of radiation necrosis, particularly with VEGFR inhibitors (25).

- mTOR Inhibitors: Agents such as everolimus and temsirolimus have demonstrated safety in patients with RCC BM, particularly those previously treated with anti-angiogenic therapies or radiotherapy. Their intracranial efficacy is modest, and they are typically reserved for later-line therapy (26).
- Agents and rationale: ICIs targeting PD-1 (nivolumab, pembrolizumab), PD-L1 (avelumab, atezolizumab), and CTLA-4 (ipilimumab) have become the standard of care in mRCC. Their activity in BM is supported by the immunogenic microenvironment of RCC and the presence of tumor-infiltrating lymphocytes (12).
- Combination strategies: The combination of ICIs with TKIs (e.g., nivolumab plus cabozantinib) has demonstrated improved systemic and intracranial outcomes in mRCC, though dedicated BM cohorts are limited (12).

Prognosis

Brain metastases from RCC are associated with a poor prognosis, though outcomes have improved in the era of targeted and immune therapies. Median OS after BM diagnosis ranges from 10 to 18 months, with 1-year survival rates of 40–60% (9,28). Prognostic factors influencing survival include:

Performance status (KPS/ECOG): The most robust predictor; KPS <80 is associated with worse outcomes (23).

Number of BM: Solitary or oligometastatic disease confers a better prognosis than multiple BM (12).

Extracranial disease burden: Absence of extracranial metastases is favorable, though its independent prognostic value is debated (25).

Timing of brain metastasis: Synchronous BM at RCC diagnosis portends poorer survival than metachronous BM, though survival after BM diagnosis is similar (9).

Treatment modality: Aggressive local therapy (surgery/SRS) and receipt of systemic therapy (especially ICIs or cabozantinib) are associated with improved survival (29). Notably, patients with BM detected on screening MRI have significantly better outcomes than those diagnosed after symptom onset, highlighting the potential benefit of early detection (12). Intracranial hemorrhage remains a significant cause of morbidity and mortality, with a 1-year cumulative incidence of 15–35% in RCC BM patients, particularly those receiving anticoagulation or anti-angiogenic therapy (10).

Conclusion

Brain metastases from RCC represent a formidable clinical challenge, associated with significant morbidity

and historically poor prognosis. Advances in surgical, radiotherapeutic, and systemic therapies, particularly the advent of cabozantinib and ICI—have improved survival and quality of life for many patients. Early detection, aggressive local therapy for symptomatic or oligometastatic disease, and integration of effective systemic agents are key components of optimal management. Despite progress, substantial gaps remain, including the need for better screening and surveillance strategies, management of complications such as intracranial hemorrhage, and inclusion of BM patients in clinical trials. Ongoing research into the molecular mechanisms of metastasis, novel therapeutics, and personalized approaches holds promise for further advances. Multidisciplinary collaboration and individualized care remain the cornerstones of effective management for RCC patients with brain metastases.

Authors' contribution

Conceptualization: Farzaneh Futuhi and Zahra Sahraei.

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Visualization: Zahra Sahraei.

Writing—original draft: All authors.

Writing—review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized [Grammarly](#) and [Copilot](#) to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the accuracy and content of the publication.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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