PULMONARY METASTASES FROM RENAL CELL CARCINOMA: CLINICAL FEATURES AND THERAPEUTIC MANAGEMENT

Abstract

Renal cell carcinoma (RCC) is characterized by a high metastatic potential, with the lung representing the most frequent site of dissemination in patients with advanced disease. Pulmonary metastases play a central role in prognostic assessment and therapeutic decision-making. Over the past decade, major advances in immunotherapy and targeted therapies have profoundly transformed the management of metastatic RCC. This narrative review provides an overview of the biological behavior, clinical presentation, prognostic implications, and therapeutic management of pulmonary metastases from RCC. Available evidence suggests that pulmonary metastases exhibit distinct clinical characteristics, including enhanced sensitivity to immunotherapy-based combinations compared with other visceral metastatic sites. Immunotherapy–tyrosine kinase inhibitor combinations and dual immune checkpoint blockade now constitute the cornerstone of first-line treatment. In selected patients with lung-dominant oligometastatic disease, the integration of local treatment strategies such as pulmonary metastasectomy or stereotactic body radiotherapy may result in prolonged disease control. Multidisciplinary and individualized management remains essential to optimize clinical outcomes.

Keywords: Renal cell carcinoma; Pulmonary metastases; Immunotherapy; Targeted therapy; Oligometastatic disease.

1. Introduction

Renal cell carcinoma accounts for approximately 2–3% of all adult malignancies worldwide and represents the most common primary cancer of the kidney (1). Clear cell carcinoma is the predominant histological subtype. Despite curative-intent surgery for localized disease, a substantial proportion of patients will develop metastatic relapse during follow-up (2). The lung is the most frequent site of metastasis, observed in nearly half of patients with advanced disease (2). Pulmonary involvement significantly influences prognosis and therapeutic strategy, particularly in the era of immunotherapy-based treatments (3).

2. Biological and Clinical Characteristics of Pulmonary Metastases

Pulmonary metastases from RCC occur primarily through hematogenous dissemination via the renal vein and inferior vena cava (4). Radiological presentations include solitary or multiple pulmonary nodules and, less frequently, diffuse parenchymal involvement. Clinically, pulmonary metastases are often asymptomatic and detected incidentally during routine imaging (2). When present, symptoms may include cough, dyspnea, chest pain, or hemoptysis. RCC is characterized by an unpredictable clinical course, including the possibility of late metastatic recurrence many years after initial treatment (6).

3. Prognostic Implications

Prognostic evaluation in metastatic RCC is commonly based on the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria, which incorporate clinical and laboratory parameters (14). Patients are stratified into favorable, intermediate, and poor risk groups, guiding treatment decisions. Several studies have demonstrated that patients with lung-dominant metastatic disease have more favorable outcomes compared with those with liver or bone metastases, even in the immunotherapy era (4,5).

4. Systemic Treatment Strategies

The treatment landscape of metastatic RCC has evolved substantially with the introduction of immune checkpoint inhibitors. Dual immunotherapy with nivolumab plus ipilimumab has demonstrated durable overall survival benefit, particularly in patients with intermediate- and poor-risk disease (7). In addition, combinations of immunotherapy with tyrosine kinase inhibitors, such as pembrolizumab plus axitinib, nivolumab plus cabozantinib, and pembrolizumab plus lenvatinib, have shown high response rates and rapid tumor shrinkage (8–10). These regimens are particularly relevant for patients with pulmonary metastases requiring prompt disease control. Subsequent lines of therapy may include targeted agents depending on prior treatment exposure and disease kinetics (3).

A proposed therapeutic algorithm for the management of pulmonary metastatic renal cell carcinoma is presented in Figure 1.

5. Local Treatment of Oligometastatic Pulmonary Disease

The concept of oligometastatic disease has gained increasing interest in RCC (11). In selected patients with a limited number of lung metastases and controlled primary tumors, local treatment approaches such as pulmonary metastasectomy or stereotactic body radiotherapy

(SBRT) may offer prolonged disease control (12,13). Retrospective series have reported favorable long-term survival following complete resection of pulmonary metastases (15). SBRT provides an effective non-invasive alternative with high local control rates for pulmonary lesions (12).

6. Summary of Key Studies

The principal studies evaluating systemic and local treatment strategies in patients with pulmonary metastatic RCC are summarized in **Table 1** .

7. Discussion

Pulmonary metastases represent the most frequent metastatic manifestation of RCC and constitute a clinically distinct subgroup within metastatic disease. Compared with other visceral metastatic sites, lung involvement has consistently been associated with more favorable outcomes, including higher response rates to systemic therapies and prolonged survival (4,5). This observation suggests organ-specific tumor–host interactions that influence therapeutic sensitivity.

The introduction of immunotherapy has profoundly reshaped the management of metastatic RCC. Both dual immune checkpoint blockade and immunotherapy–tyrosine kinase inhibitor combinations have demonstrated robust efficacy, with particularly high response rates observed in pulmonary lesions (7–10). Subgroup analyses indicate that lung metastases often exhibit deeper and more durable responses than liver or bone metastases, which are commonly associated with poorer prognosis (4–6).

Several biological hypotheses may explain the favorable behavior of pulmonary metastases. The lung is a highly vascularized and immunologically active organ, potentially facilitating immune cell infiltration and antitumor immune responses (4). In addition, pulmonary metastases are frequently detected early through routine imaging, allowing timely therapeutic intervention. Although predictive biomarkers remain limited, these factors may collectively contribute to improved outcomes in lung-dominant disease (16).

The management of patients with pulmonary metastatic RCC should be individualized. Immunotherapy–tyrosine kinase inhibitor combinations are particularly suitable for patients requiring rapid tumor shrinkage, such as those with symptomatic disease or compromised respiratory function (8–10). Conversely, dual immunotherapy may offer durable disease control and treatment-free intervals in selected patients with limited tumor burden (7). The

concept of oligometastatic pulmonary disease further expands therapeutic options, as local treatments may achieve prolonged disease control when integrated with effective systemic therapy (11–13).

Despite these advances, several challenges remain. Most randomized trials were not designed to assess lung-specific outcomes as primary endpoints, limiting definitive conclusions. The optimal sequencing of therapies after progression on immunotherapy-based regimens remains uncertain, and evidence supporting local treatment strategies is largely retrospective (11,15). Furthermore, the absence of robust predictive biomarkers continues to limit personalized treatment selection (16).

8. Clinical Implications

Recognition of lung-dominant metastatic RCC is important in daily clinical practice. Pulmonary metastases often respond favorably to modern systemic therapies, and treatment discontinuation should be approached cautiously in cases of suspected pseudo-progression (17). Early multidisciplinary evaluation is recommended, particularly in patients with limited pulmonary disease who may be candidates for local therapies (11–13).

9. Management of Pulmonary Toxicities

Immune checkpoint inhibitors are associated with immune-related adverse events, including pneumonitis. Differentiating immune-related pneumonitis from disease progression or infection is critical, particularly in patients with pulmonary metastases (17). Prompt recognition and appropriate management, including treatment interruption and corticosteroid therapy when indicated, are essential to minimize morbidity while preserving oncologic outcomes.

10. Future Directions

Future research should focus on organ-specific endpoints in clinical trials, improved characterization of the pulmonary tumor microenvironment, and identification of predictive biomarkers of response (16). Advances in imaging, artificial intelligence–assisted radiological assessment, and novel therapeutic combinations may further refine the management of pulmonary metastatic RCC (18).

11. Limitations of This Review

This review is limited by its narrative design and the heterogeneity of available evidence. Many data supporting local treatment strategies are retrospective and subject to selection bias (11,15). Nevertheless, this review provides a comprehensive and clinically oriented synthesis of current evidence relevant to pulmonary metastatic RCC.

12. Conclusion

Pulmonary metastatic RCC is a common and clinically significant condition with favorable responsiveness to modern systemic therapies. Immunotherapy-based combinations have become the cornerstone of treatment and have significantly improved patient outcomes (7–10). Selected patients with lung-dominant oligometastatic disease may benefit from the integration of local therapies (11–13). Continued multidisciplinary collaboration and future research focusing on organ-specific outcomes are essential to further optimize management strategies.

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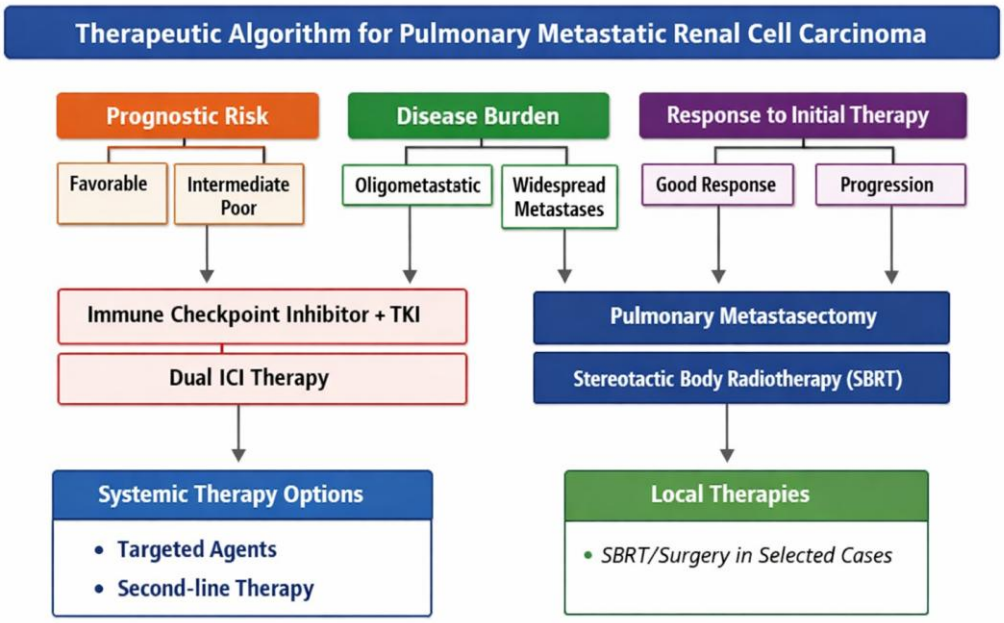

Figure 1. Therapeutic algorithm for the management of pulmonary metastatic renal cell carcinoma, integrating prognostic risk stratification, disease burden, and treatment response to guide systemic and local therapeutic strategies.

Ref.	Author (year)	Study design	Population	Treatment	Key lung-related findings
7	Motzer et al. (2018)	Phase III RCT	Metastatic RCC	Nivolumab + ipilimumab	Durable pulmonary responses and OS benefit
8	Rini et al. (2019)	Phase III RCT	Metastatic RCC	Pembrolizumab + axitinib	Rapid tumor shrinkage in lung lesions
9	Choueiri et al. (2021)	Phase III RCT	Metastatic RCC	Nivolumab + cabozantinib	Improved PFS and OS in lung-dominant disease
10	Motzer et al. (2021)	Phase III RCT	Metastatic RCC	Pembrolizumab + lenvatinib	High objective response rate in pulmonary

Ref.	Author (year)	Study design	Population	Treatment	Key lung-related findings
					metastases
6	Dabestani et al. (2014)	Systematic review	Metastatic RCC	Local therapies	Survival benefit in selected patients
15	Hofmann et al. (2005)	Retrospective cohort	RCC lung metastases	Metastasectomy	Five-year OS ≈ 45%
12	Tree et al. (2013)	Prospective series	Oligometastatic RCC	SBRT	Local control > 90%

Table 1. Major studies on pulmonary metastases from renal cell carcinoma