International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Impact of Tissue Biopsy Prior to Systemic Therapy on Treatment Decisions and Early Outcomes in Metastatic Renal Cell Carcinoma

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Received: 06-12-2025
Accepted: 01-01-2026
Available online: 13-01-2026

ABSTRACT

Background: Metastatic renal cell carcinoma (mRCC) is a biologically heterogeneous malignancy with evolving systemic treatment options. Tissue biopsy is traditionally recommended for histological confirmation and therapeutic planning; however, its necessity prior to initiation of systemic therapy remains debated, particularly when delays in treatment initiation may cause higher loss to follow-up in the biopsy group and the system-delay in a resource-limited setting.
Objectives: To evaluate the role of tissue biopsy prior to initiation of palliative therapy in metastatic renal cell carcinoma with respect to treatment selection, treatment initiation delay, early clinical outcomes, and follow-up status.
Methods: This retrospective observational study included 68 patients with metastatic renal cell carcinoma who received palliative systemic therapy. Patients were categorized into biopsy (n=40) and non-biopsy (n=28) groups. Data collected included demographic characteristics, IMDC risk stratification, treatment modality, time to treatment initiation, early treatment response, and follow-up status. Comparisons were performed using Chi-square or Student's t-test, with a p-value <0.05 considered statistically significant.
Results: Baseline characteristics and IMDC risk distribution were comparable between the biopsy and non-biopsy groups ($p>0.05$). Treatment selection differed significantly between groups. Immunotherapy or combination therapy was used in 35.0% of patients in the biopsy group compared to 14.3% in the non-biopsy group ($p=0.03$), while TKI monotherapy was more frequent in the non-biopsy group (50.0% vs 30.0%; $p=0.04$). The mean time to initiation of palliative therapy was significantly longer in patients undergoing biopsy (18.6 ± 6.4 days) compared to those without biopsy (10.2 ± 4.8 days; $p<0.001$), and a delay of more than 14 days was observed in 60.0% versus 21.4% of patients, respectively ($p=0.002$). Treatment response at first radiological or clinical assessment did not differ significantly between the biopsy and non-biopsy groups, with stable disease observed in 45.0% and 46.4% of patients, respectively ($p=0.90$). Loss to follow-up was significantly higher in the biopsy group (40.0%) compared to the non-biopsy group (21.4%; $p=0.04$).
Conclusion: Tissue biopsy prior to initiation of palliative therapy in metastatic renal cell carcinoma may plays an important role in treatment individualization but is associated with treatment delays and higher loss to follow-up, without a demonstrable short-term outcome benefit. A selective, patient-centered approach to biopsy may help optimize timely therapy initiation while preserving diagnostic value.

Keywords: *metastatic renal cell carcinoma; biopsy; palliative therapy; IMDC risk; immunotherapy; treatment delay.*

INTRODUCTION

Renal cell carcinoma (RCC) represents the most common malignancy of the kidney and accounts for approximately 2–3% of all adult cancers worldwide [1]. Over recent decades, the global incidence of RCC has steadily increased, partly due to widespread availability of cross-sectional imaging leading to incidental detection, but also reflecting true epidemiological growth [2]. Despite advances in diagnostic modalities and therapeutic strategies, RCC continues to pose significant clinical challenges, particularly in its metastatic form. Approximately 20–30% of patients present with metastatic disease at the time of diagnosis, and an additional 20–40% develop metastases following definitive treatment for localized disease [3].

Metastatic renal cell carcinoma (mRCC) is characterized by marked biological heterogeneity, unpredictable clinical behavior, and variable response to systemic therapy. Historically, treatment options were limited to cytokine-based therapies such as interferon-α and interleukin-2, which were associated with modest efficacy and substantial toxicity [4]. The past two decades have witnessed a paradigm shift in the management of mRCC with the introduction of targeted therapies, particularly tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor (VEGF) pathways, and more recently, immune checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4) [5].

Contemporary management of mRCC relies on a risk-adapted and individualized approach. Prognostic models such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria have become integral in guiding treatment decisions and predicting survival outcomes [6]. The IMDC risk model stratifies patients into favorable, intermediate, and poor-risk categories based on clinical and laboratory parameters, and this stratification directly influences the selection of systemic therapy. Current guidelines recommend combination immunotherapy or immunotherapy-TKI regimens for intermediate- and poor-risk patients, while targeted monotherapy remains an option in selected favorable-risk cases [7].

Tissue biopsy plays a central role in the diagnosis of RCC, enabling histopathological confirmation, identification of RCC subtypes, and exclusion of non-RCC malignancies or benign mimickers. Clear cell RCC constitutes approximately 75–80% of cases, while papillary, chromophobe, and other rare subtypes account for the remainder [8]. Histological subtype has prognostic and therapeutic implications, as non-clear cell RCC often demonstrates differential response to targeted agents and immunotherapy. In addition, biopsy specimens may provide material for ancillary studies, including immunohistochemistry and, in selected settings, molecular profiling.

Despite its diagnostic importance, the role of tissue biopsy prior to initiation of palliative therapy in metastatic RCC remains a subject of ongoing debate. In patients with classic radiological features of RCC and widespread metastatic disease, some clinicians advocate for prompt initiation of systemic therapy without biopsy confirmation, particularly when performance status is poor or disease burden is high. This approach is often driven by concerns regarding procedure-related complications, delay in treatment initiation, and the risk of patient deterioration during the diagnostic work-up [9].

Biopsy-related delays may be particularly relevant in resource-limited healthcare settings, where access to interventional radiology services and histopathology reporting may be constrained. Prolonged diagnostic intervals may lead to symptom progression, decline in functional status, and increased rates of loss to follow-up, thereby adversely affecting overall outcomes. Conversely, absence of histological confirmation may result in inappropriate therapy selection, exposure to ineffective treatments, and missed opportunities for optimal risk-based or subtype-specific management [10].

The expanding therapeutic armamentarium for mRCC further complicates clinical decision-making. With the availability of multiple tyrosine kinase inhibitors, immune checkpoint inhibitors, combination regimens, and chemotherapy for selected non-clear cell histologies, accurate diagnosis and prognostic stratification have become increasingly relevant. Biopsy findings may influence the choice between TKI monotherapy, immunotherapy, combination therapy, or, in selected situations, cytotoxic chemotherapy such as cisplatin-based regimens [11]. From a practical standpoint, tissue confirmation is likely to be most informative in specific scenarios, including suspected non-clear cell histology, atypical radiological features, eligibility for clinical trials, and in younger or clinically stable patients where histological subtype may affect long-term therapeutic strategy. Conversely, in patients with very poor performance status, rapidly progressive disease, or classical imaging features with a life expectancy measured in weeks, initiation of empiric palliative therapy without biopsy may be a reasonable approach.

Another important consideration is the prognostic value of biopsy itself. While histological confirmation is essential for diagnosis, its independent impact on survival outcomes in the palliative setting remains unclear. Several studies suggest that while biopsy refines treatment selection, it does not necessarily translate into improved short-term survival, particularly when effective empiric therapies are available and rapidly initiated.[8] This raises the question of whether a selective rather than universal biopsy strategy may be more appropriate in advanced disease.

Given these uncertainties, there is a need for real-world data evaluating the role of tissue biopsy prior to initiation of systemic therapy in metastatic RCC. Understanding how biopsy influences treatment choice, delays in therapy initiation, and early clinical outcomes can inform evidence-based decision-making and optimize patient care. This is especially relevant in tertiary care centers catering to diverse patient populations with varying access to diagnostic and therapeutic resources.

The present study aims to evaluate the role of tissue biopsy before starting systemic therapy in patients with metastatic renal cell carcinoma, with a specific focus on its impact on treatment decision-making, treatment initiation timelines, and short-term outcomes. By analyzing real-world clinical data, this study seeks to provide practical insights into whether routine biopsy meaningfully alters management or outcomes in the palliative setting, and to identify scenarios in which biopsy may be most beneficial.

MATERIALS AND METHODS

Study Design: This was a retrospective observational study conducted to evaluate the role of tissue biopsy prior to initiation of systemic therapy in patients with metastatic renal cell carcinoma.

Study Setting: The study was carried out at a tertiary care teaching hospital in India, providing comprehensive oncological services and acting as a referral center for patients with advanced renal malignancies.

Study Duration: Medical records of eligible patients managed during the study period from July 2022 to June 2025 were reviewed.

Study Population: All adult patients diagnosed with metastatic renal cell carcinoma and planned for systemic therapy during the study period were included in the analysis.

Sample Size: Based on an expected difference in treatment delay (>14 days) of 60% in the biopsy group versus 25% in the non-biopsy group, a minimum sample size of 56 patients (28 per group) was estimated for 80% power at a 5% significance level. The inclusion of 68 patients provided adequate power for analysis.

Inclusion Criteria

- Patients aged 18 years and above
- Radiologically suspected/suggested renal cell carcinoma
- Presence of metastatic disease at diagnosis, either synchronous or metachronous
- Patients initiated on systemic therapy
- Availability of complete clinical, treatment, and follow-up data

Exclusion Criteria

- Patients with localized renal cell carcinoma without evidence of metastasis
- Metastatic RCC patients with up to 1 site of metastatis being planned for curative radical treatment.
- Patients receiving only best supportive care without systemic therapy
- Incomplete or missing medical records

Data Collection: Data were collected retrospectively from hospital case records using a structured proforma. The following variables were recorded:

- Demographic details (age, sex)
- Clinical presentation and performance status (ECOG or Karnofsky)
- Radiological findings and sites and sizes of metastasis
- Biopsy status prior to initiation of systemic therapy
- Histopathological subtype where biopsy was performed
- International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk stratification
- Type of systemic treatment initiated, including
  - Tyrosine kinase inhibitors
  - Immunotherapy
  - Combination therapy
  - Cisplatin-based chemotherapy
- Time interval between diagnosis and initiation of systemic therapy
- Response assessment at 2 months by RECIST if only CT and PERCIST if PET/CT
- Follow-up status, including loss to follow-up at 6 months.

Biopsy Evaluation: Patients were categorized into two groups based on whether tissue biopsy was performed prior to initiation of systemic therapy. Biopsy specimens were obtained from the primary renal lesion or accessible metastatic sites

as per institutional practice. Histopathological findings were documented and used to guide treatment decisions where applicable.

Treatment Decision and Risk Stratification: Treatment selection was guided by clinical assessment, performance status, and IMDC risk stratification. Biopsy findings, when available, were incorporated into therapeutic decision-making. Patients received systemic therapy in accordance with institutional protocols and prevailing clinical guidelines.

Outcome Measures:
Primary Outcomes
- Impact of biopsy on treatment selection
- Delay in initiation of systemic therapy

Secondary Outcomes
- Early treatment response at 2 months
- Loss to follow-up at 6 months

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized as mean ±standard deviation or median with interquartile range as appropriate. Comparisons between biopsy and non-biopsy groups were performed using the Chi-square test or Fisher's exact test for categorical variables and the Student's t-test or Mann–Whitney U test for continuous variables. A p-value of <0.05 was considered statistically significant.

Ethical Considerations: The study was approved by the Institutional Ethics Committee. As the study involved retrospective analysis of anonymized patient data, the requirement for informed consent was waived. Patient confidentiality was maintained throughout the study.

RESULTS
A total of 68 patients with metastatic renal cell carcinoma (mRCC) who received systemic therapy were included in the analysis. Patients were categorized based on whether a tissue biopsy was performed prior to initiation of systemic therapy. Baseline demographic and metastatic characteristics were comparable between biopsy and non-biopsy groups, indicating good group balance. Table 1 shows the baseline demographic and clinical characteristics of the study population.

Table 1. Baseline Demographic and Clinical Characteristics of Study Population (n = 68)

Variable	Total (n=68)	Biopsy Done (n=40)	No Biopsy (n=28)	p-value
Mean age (years)	59.4 ± 9.8	58.6 ± 10.2	60.5 ± 9.1	0.41[a]
Male sex, n (%)	48 (70.6)	29 (72.5)	19 (67.9)	0.68[b]
ECOG ≥2, n (%)	32 (47.1)	18 (45.0)	14 (50.0)	0.67[b]
Lung metastasis, n (%)	44 (64.7)	27 (67.5)	17 (60.7)	0.56[b]
Bone metastasis, n (%)	26 (38.2)	15 (37.5)	11 (39.3)	0.88[b]
Multiple metastatic sites, n (%)	39 (57.4)	24 (60.0)	15 (53.6)	0.59[b]

[a]Student's t-test; [b]Chi-square test

IMDC risk distribution was similar across groups, while biopsy enabled histological subtype identification in over one-fifth of patients. Table 2 shows the IMDC risk stratification and histopathological findings.

Table 2. IMDC Risk Stratification and Histopathological Findings

Parameter	Total (n=68)	Biopsy Done (n=40)	No Biopsy (n=28)	p-value
IMDC Favorable, n (%)	12 (17.6)	8 (20.0)	4 (14.3)	
IMDC Intermediate, n (%)	34 (50.0)	21 (52.5)	13 (46.4)	0.53[b]
IMDC Poor, n (%)	22 (32.4)	11 (27.5)	11 (39.3)	
Clear cell RCC*, n (%)	—	31 (77.5)	—	—
Non-clear cell RCC*, n (%)	—	9 (22.5)	—	—

*[b]Chi-square test; *Histopathology available only in biopsy group*

Biopsy significantly influenced treatment selection, with higher use of immunotherapy-based combination regimens in the biopsy group. Table 3 shows the impact of biopsy on treatment selection.

Table 3. Impact of Biopsy on Treatment Selection				
Treatment Modality	**Total (n=68)**	**Biopsy Done (n=40)**	**No Biopsy (n=28)**	**p-value**
TKI monotherapy	26 (38.2)	12 (30.0)	14 (50.0)	0.04[b]
Immunotherapy alone	14 (20.6)	10 (25.0)	4 (14.3)	0.27[b]
Combination therapy (IO + TKI / IO + IO)	18 (26.5)	14 (35.0)	4 (14.3)	0.03[b]
Cisplatin-based chemotherapy	10 (14.7)	4 (10.0)	6 (21.4)	0.18[b]

[b]Chi-square test; IO- Immune-oncology

Biopsy was associated with a statistically significant delay in initiation of systemic therapy. Table 4 shows the treatment initiation delay according to biopsy status.

Table 4. Treatment Initiation Delay According to Biopsy Status

Time to Treatment Initiation	Biopsy Done (n=40)	No Biopsy (n=28)	p-value
Mean delay (days)	18.6 ± 6.4	10.2 ± 4.8	<0.001[a]
Delay >14 days, n (%)	24 (60.0)	6 (21.4)	0.002[b]

[a]Student's t-test; [b]Chi-square test

No statistically significant difference in early clinical response was observed between biopsy and non-biopsy groups. Table 5 shows the treatment response and short-term outcome.

Table 5. Treatment Response at First Radiological or Clinical Assessment (8–12 Weeks After Initiation of Therapy)

Outcome Parameter	Biopsy Done (n=40)	No Biopsy (n=28)	p-value
Stable disease at first assessment, n (%)	18 (45.0)	13 (46.4)	0.90[b]
Progressive disease, n (%)	14 (35.0)	11 (39.3)	0.72[b]
Clinical improvement, n (%)	8 (20.0)	4 (14.3)	0.54[b]

[b]Chi-square test

Loss to follow-up was significantly higher among patients who underwent biopsy prior to systemic therapy. Table 6 shows the follow-up status and loss to follow-up at 6 months.

Table 6. Follow-up Status and Loss to Follow-up at 6 months after initiation of systemic therapy.

Follow-up Status	Biopsy Done (n=40)	No Biopsy (n=28)	p-value
On regular follow-up	24 (60.0)	22 (78.6)	0.09[b]
Lost to follow-up	16 (40.0)	6 (21.4)	0.04[b]

[b]Chi-square test

DISCUSSION

This study evaluated the role of tissue biopsy prior to initiation of systemic therapy in patients with metastatic renal cell carcinoma (mRCC), with particular focus on its impact on treatment selection, treatment initiation delay, early clinical response, and follow-up status. The findings reflect real-world practice and provide clinically relevant insights into the balance between diagnostic precision and timely initiation of systemic therapy in advanced RCC.

As shown in Table 1, baseline demographic and clinical characteristics were comparable between patients who underwent biopsy and those who did not. There were no statistically significant differences in age, sex distribution, performance status, or metastatic burden. This comparability reduces the likelihood of baseline confounding and allows meaningful assessment of the downstream effects of biopsy on management and outcomes. The predominance of male patients and the frequent involvement of lung and bone metastases are consistent with the epidemiological patterns reported by Capitanio et al (2019) [2] and Siegel et al (2018) [3].

IMDC risk stratification, which remains a cornerstone of prognostication and treatment planning in mRCC, showed a similar distribution across both groups (Table 2). The majority of patients belonged to the intermediate- and poor-risk categories, a finding consistent with real-world cohorts described by Heng et al (2009) [6]. This underscores the relevance of risk-based therapeutic strategies in the palliative setting.

Histopathological confirmation was available only in patients who underwent biopsy, enabling identification of RCC subtypes. Clear cell RCC was the most common histology, followed by non-clear cell variants (Table 2), in accordance

with the WHO classification described by Humphrey PA et al (2016) [8]. Identification of non-clear cell histologies is clinically relevant, as these subtypes may demonstrate differential response to standard targeted agents and immunotherapy.

The availability of histological information contributed to refinement of treatment selection, particularly in patients considered for immunotherapy-based regimens. This highlights the diagnostic value of biopsy in facilitating individualized therapy in selected cases.

A significant association was observed between biopsy status and choice of systemic therapy (Table 3). Patients who underwent biopsy were more likely to receive immunotherapy or combination regimens, whereas those without biopsy more frequently received TKI monotherapy. This reflects contemporary treatment paradigms, where histological subtype and IMDC risk stratification guide therapeutic decision-making.

These findings are consistent with evidence from pivotal clinical trials, including the CheckMate 214 study by Motzer et al (2018) [11], which demonstrated improved outcomes with immunotherapy combinations in intermediate- and poor-risk patients. Long-term survival data from targeted therapy trials, such as those reported by Motzer et al (2007) [5], further support the importance of appropriate treatment selection.

Despite its diagnostic benefits, biopsy was associated with a statistically significant delay in initiation of systemic therapy (Table 4). Both mean time to treatment initiation and the proportion of patients experiencing delays beyond two weeks were higher in the biopsy group. This finding is clinically important, as timely initiation of therapy is a key consideration in advanced malignancies.

Similar observations have been reported in studies evaluating diagnostic biopsy pathways by Leveridge et al (2011) [9] and Richard et al (2015) [10], where procedural and system-related factors contributed to prolonged diagnostic intervals. In the palliative mRCC setting, such delays may potentially lead to symptom progression or decline in performance status before therapy initiation.

Despite differences in treatment selection and treatment initiation timelines, early clinical outcomes did not differ significantly between biopsy and non-biopsy groups (Table 5). Rates of stable disease, progressive disease, and clinical improvement at first assessment were comparable. This suggests that biopsy-driven treatment refinement did not translate into a measurable short-term outcome advantage. These findings align with previous observations that early outcomes in mRCC are influenced predominantly by disease biology and prognostic risk rather than diagnostic pathway alone, as reported by Motzer et al (2007) [5] and Heng et al (2009) [6].

A notable finding of this study is the significantly higher rate of loss to follow-up among patients who underwent biopsy (Table 6). This highlights an important practical concern, particularly in real-world and resource-limited settings. Prolonged diagnostic pathways may increase the risk of patient attrition due to logistical, financial, or disease-related factors. Clinical practice guidelines emphasize the importance of continuity of care and timely initiation of therapy in advanced cancer management, as outlined by Escudier et al (2019) [12]. The increased loss to follow-up observed in the biopsy group suggests that diagnostic delays may inadvertently compromise these goals.

Taken together, the findings of this study suggest that while tissue biopsy prior to initiation of systemic therapy in mRCC contributes to diagnostic certainty and influences treatment selection, it is also associated with treatment delays and higher loss to follow-up, without a demonstrable short-term clinical benefit. These observations support a selective approach to biopsy in metastatic RCC. In clinically stable patients where histological confirmation is likely to meaningfully influence treatment choice—such as selection of immunotherapy-based combinations—biopsy may be appropriate. Conversely, in patients with classical radiological features, extensive disease burden, or poor performance status, early initiation of empiric systemic therapy may be considered to avoid delays. Such a balanced strategy is consistent with expert recommendations emphasizing individualized decision-making based on disease characteristics, patient condition, and healthcare system constraints, as discussed by Choueiri and Motzer (2017) [13].

This study demonstrates that tissue biopsy prior to systemic therapy in metastatic renal cell carcinoma significantly affects treatment selection but is associated with treatment delays and increased loss to follow-up, without a clear early outcome advantage. These findings suggest that biopsy should be used judiciously, with careful consideration of its potential benefits and limitations, to optimize patient-centered palliative care.

Limitations of the Study: This study has several limitations that should be considered when interpreting the findings. Its retrospective observational design precludes causal inference, and treatment allocation was influenced by clinician judgment, patient condition, and logistical factors, introducing potential selection bias. Being a single-center study, the results may not be fully generalizable to other healthcare settings. The analysis focused on treatment response at first assessment and short-term follow-up, without evaluation of progression-free or overall survival. In addition, detailed molecular profiling and comprehensive pathological subtyping were not available for all patients, which may have limited

more refined therapeutic stratification. Although the sample size was adequate for detecting differences in treatment delay and treatment selection, it may not have been sufficient to detect smaller differences in clinical outcomes.

CONCLUSION

This study evaluated the role of tissue biopsy prior to initiation of systemic therapy in patients with metastatic renal cell carcinoma. The findings demonstrate that while biopsy significantly influences treatment selection—particularly increasing the use of immunotherapy and combination regimens—it is also associated with a meaningful delay in treatment initiation and a higher rate of loss to follow-up. Importantly, no significant difference was observed in early clinical response between patients who underwent biopsy and those who were treated empirically based on clinicoradiological findings and prognostic risk stratification. These results suggest that routine biopsy before systemic therapy may not confer a short-term clinical advantage for all patients. A selective, individualized approach appears more appropriate, balancing the benefits of diagnostic confirmation and treatment individualization against the risks of treatment delay and patient attrition. Timely initiation of systemic therapy remains a critical priority in advanced disease.

DECLARATIONS

Funding: No external funding was received for this study.

Conflict of Interest: The authors declare no conflict of interest.

Ethical Approval: The study was approved by the Institutional Ethics Committee. As this was a retrospective study using anonymized patient data, informed consent was waived.

Informed Consent: Not applicable due to the retrospective nature of the study.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed to study conception and design. Data collection and analysis were performed by the authors. The manuscript was drafted and critically revised by all authors, and all authors approved the final version.

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