



The Indonesian Journal of General Medicine

A Comprehensive Literature Review of Histopathology of Renal Cell Carcinoma

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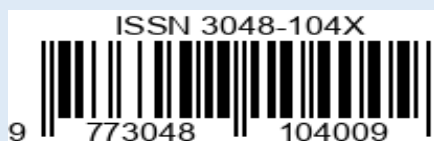
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Article History :

Received date : 2024/09/19
Revised date : 2024/10/02
Accepted date : 2024/11/17
Published date : 2024/12/22



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ABSTRACT

Background: The histopathology of renal cell carcinoma (RCC) encompasses a diverse array of subtypes, each characterized by distinct morphological and genetic features that have significant implications for clinical outcomes and treatment strategies. The evolution of our understanding of RCC has been reflected in a series of pivotal studies over the years, which have contributed to the molecular and histological classification of this malignancy. **Literature Review:** The exploration of ancillary techniques by (Pradhan et al., 2009) further enriched the discourse on RCC by emphasizing the significance of integrating histomorphology with molecular and cytogenetic analyses. This multifaceted approach is vital for improving diagnostic accuracy and tailoring treatment plans to individual patient needs ((Pradhan et al., 2009)). The comprehensive molecular characterization conducted by The Cancer Genome Atlas ((J. Ricketts et al., 2018)) revealed distinct genetic drivers associated with various RCC subtypes, emphasizing the importance of understanding these alterations for developing effective treatment strategies ((J. Ricketts et al., 2018)). Recent advancements in digital pathology, as discussed by (Zhu et al., 2020) and (Abu Haeyeh et al., 2022), highlight the potential of deep learning techniques to enhance diagnostic accuracy and streamline the classification of RCC subtypes, thus improving clinical outcomes ((Zhu et al., 2020); (Abu Haeyeh et al., 2022)). **Conclusion:** The analysis of papillary renal cell carcinoma by (S. Chawla et al., 2023) underscores the unique biological characteristics of this subtype and the challenges in advancing therapeutic strategies compared to clear cell RCC ((S. Chawla et al., 2023)). The literature collectively illustrates the dynamic and evolving nature of RCC histopathology, emphasizing the need for ongoing research to refine classification systems and enhance understanding of tumor biology, ultimately aiming to improve patient outcomes.

Keyword: Histopathology, Renal Cell Carcinoma

INTRODUCTION

The histopathology of renal cell carcinoma (RCC) encompasses a diverse array of subtypes, each characterized by distinct morphological and genetic features that have significant implications for clinical outcomes and treatment strategies. The evolution of our understanding of RCC has been reflected in a series of pivotal studies over the years, which have contributed to the molecular and histological classification of this malignancy.

In 2006, (N. Young et al., 2006) provided a foundational overview of RCC subtypes, emphasizing the distinct growth patterns and histological characteristics of papillary RCC, chromophobe RCC, and oncocytoma, among others. They highlighted the clinical significance of the World Health Organization (WHO) classification, particularly noting that clear cell RCC is associated with the highest rates of metastasis and mortality ((N. Young et al., 2006)). This early work set the stage for a more nuanced understanding of RCC's histopathological diversity.

(Suresh, 2007) expanded on this classification by detailing the histomorphological features of RCC, noting the removal of certain categories such as sarcomatoid RCC from the classification schema. This study emphasized the genetic underpinnings of RCC, recognizing it as a family of cancers arising from renal tubular epithelium, and underscored the importance of histological subtyping for prognosis and treatment ((Suresh, 2007)).

(Pradhan et al., 2009) further contributed to the discourse by exploring the role of ancillary techniques in the sub-typing of renal tumors. They noted that RCC constitutes a heterogeneous group with unique cytogenetic and chromosomal aberrations, which are critical for understanding the tumor's behavior and guiding treatment decisions ((Pradhan et al., 2009)).

The investigation into metastatic clear cell RCC was advanced by (Lee et al., 2013), who identified diverse histological features in metastatic cases compared to primary lesions. This work underscored the necessity of accurate

diagnosis in guiding treatment, particularly as advancements in therapies for advanced RCC were emerging ((Lee et al., 2013)).

(Fu et al., 2016) provided a comprehensive analysis of imaging characteristics across common RCC subtypes, revealing that subtype differentiation has critical implications for clinical decision-making. Their findings indicated that clear cell tumors often exhibit greater heterogeneity and poorer prognosis compared to papillary and chromophobe subtypes ((Fu et al., 2016)).

The Cancer Genome Atlas ((J. Ricketts et al., 2018)) conducted an extensive molecular characterization of RCC, identifying distinct genetic drivers and phenotypic features across major subtypes. This study highlighted the correlation between specific genetic alterations and survival outcomes, reinforcing the need for subtype-specific therapeutic strategies ((J. Ricketts et al., 2018)).

Recent advancements in digital pathology have been explored by (Zhu et al., 2020), who developed a deep neural network to assist in the

histological classification of RCC. Their work addressed the challenges of variability in manual classifications, demonstrating the potential of automated systems to enhance diagnostic accuracy ((Zhu et al., 2020)).

Building on this technological foundation, (Abu Haeyeh et al., 2022) presented a novel deep-learning framework aimed at classifying renal histopathology images. This study highlighted the importance of accurate histological assessment in determining prognosis and treatment pathways for various RCC subtypes ((Abu Haeyeh et al., 2022)).

Finally, (S. Chawla et al., 2023) focused on papillary renal cell carcinoma, discussing its unique biological characteristics and the lag in therapeutic advancements compared to clear cell RCC. Their analysis of clinical trials underscored the complexities inherent in treating this heterogeneous subtype ((S. Chawla et al., 2023)).

Together, these studies illustrate the dynamic landscape of RCC histopathology, where ongoing research continues to refine

classification systems and enhance our understanding of tumor biology, ultimately aiming to improve patient outcomes.

LITERATURE REVIEW

The article "Current Trends in the Molecular Classification of Renal Neoplasms" by (N. Young et al., 2006) provides a comprehensive overview of the histopathological features and classifications of various renal cell carcinoma (RCC) subtypes. The authors emphasize the complexity involved in diagnosing RCC due to the overlapping histological characteristics that can be present across different subtypes.

One of the key insights is the detailed description of papillary RCC, which is characterized as a circumscribed, encapsulated mass featuring a distinct papillary growth pattern. The authors categorize papillary RCC into two types: Type 1 and Type 2. Type 1 is noted for its papillae lined by a single layer of small tumor cells with scant cytoplasm, while Type 2 presents with higher nuclear grades and more pronounced cellular features, including eosinophilic cytoplasm and pseudostratified nuclei. This classification underscores the

importance of histological examination in differentiating between subtypes, which is critical for determining prognosis and treatment strategies.

The article further explores chromophobe RCC, which displays an alveolar or nested growth pattern with distinct cellular characteristics such as irregular nuclei and perinuclear halos. The authors also highlight the presence of oncocytoma, which is closely related to chromophobe carcinoma but is consistently benign. This differentiation is vital, as it informs clinical management and expectations regarding patient outcomes.

A significant challenge in the histopathological classification of RCC is the potential for sampling error, particularly in small tumor biopsies obtained from nephron-sparing procedures. The limited histologic information that can be acquired from such samples complicates diagnosis and may lead to misclassification. The authors effectively illustrate this point by discussing how all RCC subtypes can exhibit overlapping growth patterns

and cellular characteristics, which can lead to diagnostic ambiguities.

Moreover, the article discusses the aggressive nature of collecting duct carcinoma, which has the highest propensity for metastasis among renal epithelial tumors. In contrast, papillary and chromophobe RCC are described as relatively indolent, though they still possess the potential for metastasis or transformation into high-grade cancers. This information is crucial for clinicians in tailoring treatment approaches, particularly since systemic therapy for metastatic RCC with nonclear cell histology is not standardized.

The article "Histomorphological Characterization of Adult Renal Neoplasms" by (Suresh, 2007) provides a comprehensive overview of the histopathological classification of renal cell carcinoma (RCC). Suresh delineates the initial categorization of RCC into four primary histological types: clear cell, granular cell, tubulopapillary, and sarcomatoid. This classification underscores the complexity of RCC as a disease

entity, suggesting that it encompasses distinct subtypes, each characterized by unique genetic alterations.

A significant advancement discussed in the article is the recognition of sarcomatoid RCC not as a separate histological type but rather as a high-grade transformation that can occur in various RCC subtypes. This insight is crucial as it shifts the understanding of RCC's histopathology, emphasizing the dynamic nature of tumor progression and the potential for varying histological presentations within a single tumor type.

Furthermore, Suresh introduces the multilocular cystic variant of clear cell RCC, which is noted for its low recurrence and metastasis potential. This variant highlights the heterogeneity within clear cell RCC and suggests that not all histological types carry the same prognostic implications. The article also addresses the aggressive nature of collecting duct carcinoma, emphasizing its origin in the medullary collecting ducts and its propensity for early metastasis.

The article effectively illustrates the anatomical behavior of RCC, noting its typical cortical location and the tumor's capacity to invade surrounding structures, including the renal vein and potentially the right atrium. This anatomical understanding is critical for clinicians as it informs surgical approaches and prognostic evaluations.

Moreover, the article references the World Health Organization's (WHO) classification criteria, which provide a framework for the light microscopic features used in subtyping RCC. This standardization is essential for pathologists and oncologists in diagnosing and managing the disease effectively.

The article "Sub-typing of renal cell tumours; contribution of ancillary techniques" by (Pradhan et al., 2009) provides a comprehensive overview of renal cell carcinoma (RCC), which represents a significant portion of adult renal neoplasms. The authors emphasize the heterogeneity of adult renal epithelial neoplasms, highlighting the importance of

subtyping RCC for treatment, prognosis, and understanding its underlying biology. This classification is essential not only for clinical management but also for advancing research into the molecular and cytogenetic aspects of RCC.

The article outlines the historical context of RCC classification, noting the establishment of the Heidelberg classification in 1997, which was based on molecular and cytogenetic studies. This classification marked a pivotal shift in how renal tumors are categorized, moving away from purely morphological criteria to a more nuanced understanding that incorporates genetic and cellular origins. The authors further detail the World Health Organization's (WHO) classification, which includes various subtypes such as clear cell RCC, papillary RCC, and chromophobe RCC, among others. Each subtype is characterized by distinct histologic and immunohistochemical features, which are critical for accurate diagnosis and targeted therapies.

A critical evaluation of the material reveals that the authors

successfully underscore the necessity of ancillary techniques in the classification of renal tumors. By integrating histomorphology, immunohistochemistry, and ultrastructural studies, the study advocates for a multifaceted approach to diagnosis that can lead to improved management strategies. This is particularly relevant given the diverse clinical behaviors exhibited by different RCC subtypes. The emphasis on ancillary techniques also highlights the evolving nature of pathology, where traditional histopathological methods are increasingly complemented by advanced diagnostic tools that can provide deeper insights into tumor biology.

Moreover, the article points out the implications of accurate classification for patient outcomes, reinforcing the notion that tailored treatment approaches based on subtype classification can significantly impact prognosis. As RCC continues to be a leading cause of cancer-related mortality, the insights provided by (Pradhan et al., 2009) are crucial for clinicians and researchers alike, as they navigate the

complexities of renal tumor pathology.

The article titled "Histologic Variations and Immunohistochemical Features of Metastatic Clear Cell Renal Cell Carcinoma" by (Lee et al., 2013) provides a comprehensive examination of the histological characteristics and immunohistochemical profiles of metastatic clear cell renal cell carcinoma (CCRCC). The authors emphasize the significance of accurately diagnosing metastatic RCC and its specific subtype, especially in light of advancements in treatment options for advanced renal cell carcinoma.

In their investigation, the authors present a detailed analysis of various histological features observed in metastatic CCRCC compared to primary lesions. This comparative approach is crucial, as it highlights the potential morphological variations that may occur during the progression of the disease. The study underscores the importance of recognizing these histological differences, as they can have implications for prognosis and treatment strategies.

The article meticulously discusses the immunohistochemical features of metastatic CCRCC, which serve as valuable diagnostic tools. The authors explore how specific markers can aid in distinguishing metastatic CCRCC from other renal tumors and metastatic lesions from different origins. This aspect of their research is particularly relevant, as the accurate identification of the tumor subtype can significantly influence clinical management decisions.

One of the strengths of the study is its focus on the clinical relevance of histological and immunohistochemical variations. By correlating these features with clinical outcomes, the authors provide insights into how specific histological patterns may be associated with aggressive behavior or resistance to therapy. This information is critical for pathologists and oncologists alike, as it can guide treatment planning and patient counseling.

However, while the study presents valuable findings, it is essential to consider the limitations inherent in its design. The sample size

and selection criteria may affect the generalizability of the results. Additionally, the authors could have elaborated on the potential implications of their findings in the context of emerging treatment modalities, which would enhance the practical applicability of their research.

The article titled "Multimodality Imaging Characteristics of the Common Renal Cell Carcinoma Subtypes: An Analysis of 544 Pathologically Proven Tumors" by (Fu et al., 2016) provides a comprehensive examination of renal cell carcinoma (RCC), which constitutes a significant portion of malignant renal neoplasms in adults. The authors emphasize the critical nature of subtype differentiation in RCC, highlighting that clear cell, papillary, and chromophobe tumors account for the majority of cases, with clear cell RCC being the most prevalent subtype.

A key insight from the article is the association between the histological subtype of RCC and its clinical behavior and prognosis. Clear cell RCC, which represents

approximately 70% of cases, is noted for its poor prognosis, while papillary RCC and chromophobe RCC are associated with intermediate and favorable prognoses, respectively. This differentiation is crucial, as it can influence clinical decision-making and therapeutic strategies for patients. The authors effectively argue that understanding these distinctions can lead to better patient outcomes, underscoring the importance of accurate histopathological classification.

The article also provides detailed descriptions of the imaging characteristics associated with each subtype. Clear cell RCC is characterized by its hypervascular nature and potential for intratumoral heterogeneity, which may manifest as hemorrhage, necrosis, or cyst formation. In contrast, papillary RCC typically presents as homogeneous and hypovascular, while chromophobe RCC can display a homogeneous consistency despite being larger in size. Notably, the authors point out the emergence of specific imaging patterns, such as spoke-wheel enhancement and a central stellate scar in chromophobe

RCCs, which could aid in non-invasive diagnosis.

(Fu et al., 2016) utilize a substantial sample size of 544 pathologically proven tumors, which strengthens the validity of their findings. The integration of imaging findings with demographic and clinical parameters adds depth to the analysis and provides a holistic view of the disease. However, while the study presents valuable insights, it could benefit from a more thorough discussion on the implications of these imaging characteristics in guiding treatment decisions and predicting patient outcomes.

The article titled "The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma" by (J. Ricketts et al., 2018) provides an extensive analysis of renal cell carcinoma (RCC), emphasizing its heterogeneity and the distinct genetic and phenotypic features associated with its various subtypes. The authors meticulously evaluated 843 RCC samples across three primary histological subtypes: clear cell RCC, papillary RCC, and chromophobe RCC. This large-scale

genomic study is significant as it underscores the complexity of RCC, which is not a singular disease but a collection of histologically defined cancers with unique genetic drivers and clinical outcomes.

One of the key insights from the study is the identification of somatic alterations in critical genes such as BAP1, PBRM1, and PTEN, which were linked to subtype-specific survival outcomes. These findings highlight the importance of understanding the genetic landscape of RCC for developing targeted therapeutic strategies. Additionally, the article discusses the implications of altered metabolic pathways and their correlation with decreased survival rates, which is crucial for future research into metabolic interventions in RCC management.

The study also introduces the concept of a CpG island methylator phenotype (CIMP-RCC), which is characterized by a distinct early-onset disease profile and poor survival rates. This subtype is associated with mutations in the fumarate hydratase (FH) gene, indicating a potential pathway for targeted therapies.

Furthermore, the identification of a metabolically divergent (MD) chromophobe RCC subtype with a unique metabolic expression pattern linked to poor survival adds a new layer of complexity to the classification of RCC.

The authors effectively utilize comprehensive genomic analyses to delineate the immune-related Th2 gene expression signature, which correlates with decreased survival across all major histological subtypes. This finding emphasizes the role of the immune microenvironment in RCC and suggests avenues for immunotherapy that could enhance patient outcomes.

The article "Development and Evaluation of a Deep Neural Network for Histologic Classification of Renal Cell Carcinoma on Biopsy and Surgical Resection Slides" by (Zhu et al., 2020) presents a significant advancement in the histopathological classification of renal cell carcinoma (RCC) through the application of deep learning techniques. The authors emphasize the clinical importance of accurately classifying RCC subtypes, as these classifications have profound

implications for patient prognosis and treatment strategies.

One of the critical insights from the study is the acknowledgment of the challenges faced by pathologists in manually classifying RCC. The authors highlight the time-consuming nature of this task and the high rates of inter-observer and intra-observer variability that can compromise diagnostic accuracy. By introducing a convolutional neural network (CNN)-based model, the study aims to address these challenges by providing a more efficient, objective, and consistent evaluation of histopathology images.

The methodology employed in this research is robust, utilizing a dataset comprising 78 independent surgical resection slides and an additional 69 surgical resection RCC slides sourced from The Cancer Genome Atlas database. This diverse dataset enhances the generalizability of the model and reinforces the validity of the findings. The CNN model developed in this study demonstrates the capability to automatically process digitized histopathology images, effectively

learning to extract relevant cellular patterns associated with tumors. This automated approach not only streamlines the classification process but also reduces the potential for human error inherent in manual evaluations.

The results of the study indicate that the CNN-based model achieved a high level of accuracy in differentiating RCC from benign renal tumors and in classifying various RCC subtypes. This is a significant contribution to the field, as it suggests that deep learning can play a crucial role in enhancing diagnostic precision in histopathology. Moreover, the findings underscore the potential of computerized image analysis to support pathologists in making more informed decisions, thereby improving patient outcomes.

However, while the study showcases the promise of deep learning in histopathological classification, it is essential to consider the limitations and challenges that may arise in clinical practice. For instance, the implementation of such technology requires access to high-quality

digitized images and adequate computational resources, which may not be available in all healthcare settings. Additionally, further validation of the model in diverse clinical environments and across larger datasets would be necessary to establish its reliability and efficacy fully.

The article "Development and Evaluation of a Novel Deep-Learning-Based Framework for the Classification of Renal Histopathology Images" by (Abu Haeyeh et al., 2022) presents a comprehensive overview of renal cell carcinoma (RCC), highlighting its histopathological diversity and the advancements in diagnostic methodologies. The authors emphasize the importance of accurately classifying RCC subtypes, which are critical for determining prognosis and treatment strategies.

RCC is characterized by its various subtypes, primarily Clear cell RCC, Papillary RCC, and Chromophobe RCC, each exhibiting distinct histological features and clinical outcomes. Clear cell RCC, accounting for 70–90% of cases, is

noted for its poor prognosis, with a 5-year survival rate ranging from 50–69%. The article effectively delineates the morphological characteristics of each subtype, underscoring that Clear cell RCC contains lipid- and glycogen-rich clear cells, while Papillary RCC can be further divided into two subtypes based on histological appearance. Chromophobe RCC, although less prevalent (4–8%), is depicted as the least aggressive and possessing the best prognosis among the RCC subtypes.

The authors introduce a novel deep-learning framework designed to classify renal histopathology images, thus enhancing diagnostic accuracy. While the RC-CAD system demonstrates high accuracy in distinguishing Clear cell RCC from other subtypes, it is noted that the system's performance diminishes when analyzing smaller renal masses. This limitation is significant, as it highlights the challenges faced in the early detection of RCC, where microscopic images of H&E-stained slides remain the gold standard for diagnosis.

Moreover, the article critically addresses the role of imaging modalities in differentiating between RCC subtypes, suggesting that while technological advancements are promising, they cannot replace the definitive diagnosis provided by biopsy. The integration of deep learning into histopathological evaluation is a noteworthy contribution, as it may facilitate more efficient and accurate classification of RCC, potentially leading to improved patient outcomes.

The article "An Update on the Treatment of Papillary Renal Cell Carcinoma" by (S. Chawla et al., 2023) provides a comprehensive overview of papillary renal cell carcinoma (pRCC), highlighting its position as the second-most prevalent subtype of kidney cancer, accounting for approximately 15% of cases. The authors emphasize that, despite notable advancements in therapeutic strategies, progress in treating pRCC has not kept pace with that of clear cell renal cell carcinoma (ccRCC). This discrepancy is attributed to the heterogeneous nature of pRCC

subtypes, which complicates treatment approaches and outcomes.

The review delves into the distinct biological characteristics of pRCC, which are crucial for understanding its pathophysiology and potential treatment pathways. The authors note that the histological diversity within pRCC necessitates a tailored approach to therapy, as different subtypes may respond variably to standard treatments. This aspect underscores the importance of histopathological analysis in guiding clinical decisions and the development of personalized medicine strategies.

Furthermore, (S. Chawla et al., 2023) discuss recent clinical trials that have focused on histology and biology-based interventions. They highlight that these trials are pivotal in identifying specific biomarkers and therapeutic targets unique to pRCC. By emphasizing the need for histology-driven research, the authors advocate for a shift in clinical trial design that prioritizes the biological underpinnings of pRCC, which may lead to more effective treatment modalities.

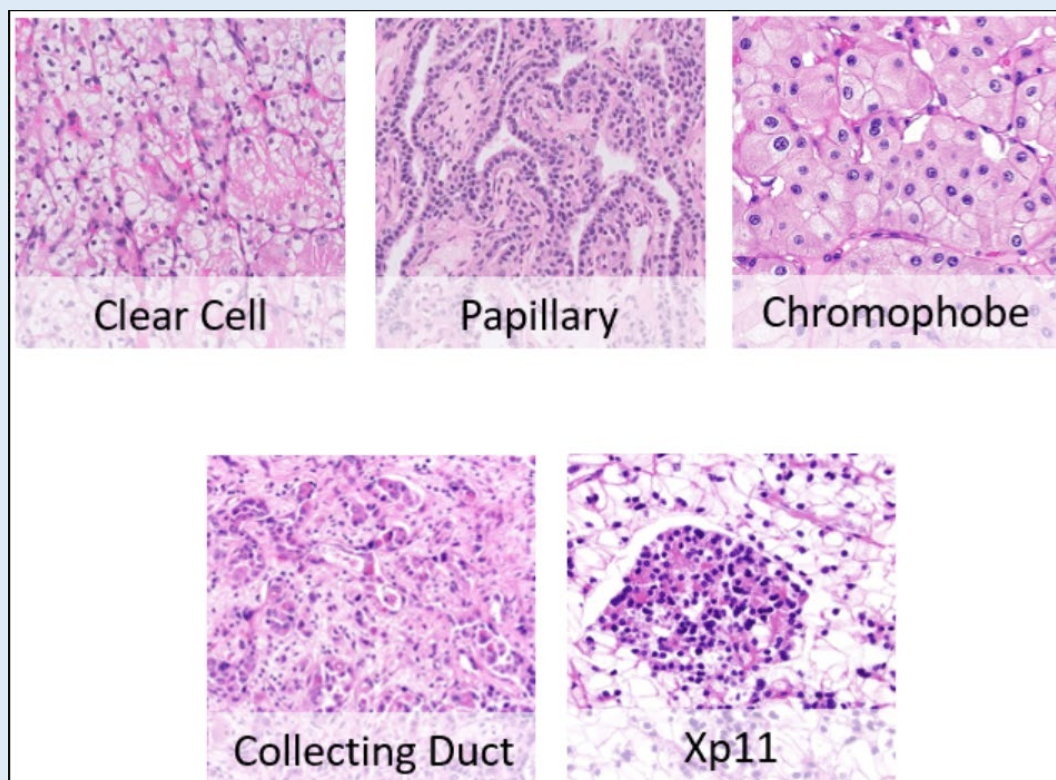


Figure 1. Histopathological features of subtype of renal cell carcinoma (RCC)

CONCLUSION

The literature on the histopathology of renal cell carcinoma (RCC) reveals a complex landscape characterized by diverse subtypes, each with unique morphological, genetic, and clinical implications. The foundational work by (N. Young et al., 2006) established key classifications of RCC subtypes, notably highlighting clear cell RCC's aggressive nature and its association with higher rates of metastasis and mortality. This early categorization underscored the importance of the World Health Organization (WHO)

classification in guiding clinical management ((N. Young et al., 2006)).

Subsequent studies, such as the one by (Suresh, 2007), expanded on these classifications by detailing the histomorphological features of RCC and advocating for a nuanced understanding of its genetic underpinnings. This work reinforced the necessity of histological subtyping not only for prognosis but also for the development of targeted treatment strategies ((Suresh, 2007)).

The exploration of ancillary techniques by (Pradhan et al., 2009) further enriched the discourse on RCC by emphasizing the significance of integrating histomorphology with molecular and cytogenetic analyses. This multifaceted approach is vital for improving diagnostic accuracy and tailoring treatment plans to individual patient needs ((Pradhan et al., 2009)).

The investigation into metastatic clear cell RCC by (Lee et al., 2013) highlighted the variations in histological features between primary and metastatic lesions, reinforcing the necessity for precise diagnostic techniques to guide treatment decisions ((Lee et al., 2013)). Additionally, (Fu et al., 2016) provided critical insights into the imaging characteristics of RCC subtypes, illustrating how these distinctions can influence clinical management and patient outcomes ((Fu et al., 2016)).

The comprehensive molecular characterization conducted by The Cancer Genome Atlas ((J. Ricketts et al., 2018)) revealed distinct genetic drivers associated with various RCC subtypes, emphasizing the

importance of understanding these alterations for developing effective treatment strategies ((J. Ricketts et al., 2018)). Recent advancements in digital pathology, as discussed by (Zhu et al., 2020) and (Abu Haeyeh et al., 2022), highlight the potential of deep learning techniques to enhance diagnostic accuracy and streamline the classification of RCC subtypes, thus improving clinical outcomes ((Zhu et al., 2020); (Abu Haeyeh et al., 2022)).

Lastly, the analysis of papillary renal cell carcinoma by (S. Chawla et al., 2023) underscores the unique biological characteristics of this subtype and the challenges in advancing therapeutic strategies compared to clear cell RCC ((S. Chawla et al., 2023)). The literature collectively illustrates the dynamic and evolving nature of RCC histopathology, emphasizing the need for ongoing research to refine classification systems and enhance understanding of tumor biology, ultimately aiming to improve patient outcomes.

DISCLOSURE STATEMENT

- Disclosure Statement : The authors have no conflicts of Interest to declare
- Funding Sources : None
- Acknowledgements : -
- Author Contribution : All authors discussed and contributed the final content for journal submission and publication

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