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Review

The Role of miRNA in the Management of Localized and Advanced Renal Masses, a Narrative Review of the Literature

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Abstract: Renal cell carcinoma (RCC) is the most common form of kidney cancer with 403,262 diagnoses and 170,000 deaths worldwide in 2018. Although partial or radical nephrectomy can be considered a successful treatment in early-stage or localized RCC, in advanced-stage disease, there is a high risk of metastasis or recurrence with a significantly poorer prognosis. Metastatic RCC is generally resistant to both chemotherapy and radiotherapy, and, despite several novel therapeutic agents, disease progression and mortality rates remain high. It is necessary to identify new diagnostic and therapeutic

strategies for the management of this cancer. Knowledge of microRNA (miRNA) has consistently increased in the last year. miRNAs play an important role in several biological processes, such as cell proliferation, differentiation, and cell death. Due to this, miRNAs have been identified as an important key in different diseases, especially in cancer, and several studies show miRNAs as attractive tools and targets for novel therapeutic approaches. Recently several miRNAs (including miR-22, miR-203, miR-301 and miR-193a-3p) have been linked to dysregulated molecular pathways involved with the proliferation of cancerous cells and resistance to therapeutic agents. In the present study, recent data from studies assessing the application of miRNAs as biomarkers, therapeutic targets, or modulators of response to treatment modalities in RCC patients are analyzed.

Keywords: renal cell carcinoma; miRNA; metastatic; cancer; biomarker

1. Introduction

Kidney cancer represents 2% of the global cases of cancers worldwide [1]. Among kidney cancer histotypes, renal cell carcinoma (RCC) is the most common form (80% of all cases), with 403,262 diagnoses and 170,000 deaths throughout the world in 2018 [2]. In their life, approximately 1 in 69 men and 1 in 116 women will be diagnosed with RCC [3]. Kidney cancer shows a heterogeneous clinical presentation, from small, localized tumors to aggressive metastatic diseases. RCC treatment depends on tumor stage and grade and the overall health status of the patients. Surgery represents the standard treatment for localized RCC, while cytoreductive nephrectomy and systemic treatments (targeted therapies and immunotherapeutic agents) represent the standard of care for patients presenting metastatic RCC (mRCC). Recent evidence suggested that stereotactic body radiotherapy (SBRT) may represent a new option in the treatment of primary local RCC and oligometastatic RCC [4]. Although RCC is curable by surgery, about 20% of patients have metastases and experience disease recurrence during follow-up [5]. Micro-RNAs (miRNA, miR) are 19 to 22 nucleotide-long endogenous small noncoding RNAs involved in different biological functions regulating more of 60% of human protein-coding genes related to cell growth, apoptosis, differentiation, and proliferation [6]. MiRNAs act also as tumor suppressors or oncogenes and can regulate several gene transcripts as well as the expression of other miRNAs. In particular, they are involved in cell proliferation and death, migration, epithelial–mesenchymal transition, tumor invasion and metastasis. MiRNAs can influence angiogenesis, energy metabolism and immune system activation and recruitment, as shown in Figure 1, MiRNAs can bind to a specific sequence at the 3′ or 5′ untranslated region (UTR) of their target genes or messenger RNA (mRNAs) or other coding sequences as well as promoter regions. Indeed, the miRNA interaction with 3′ and 5′ UTR induces the repression and transcription, respectively, of genes [6] (Figure 2) translational repression and mRNA deadenylation and decapping. The interaction with 5′ UTR and coding regions silences gene expression, while miRNA interaction with the promoter region induces transcription. In the last decades, several studies highlighted the role of miRNA in several human cancers, including lymphoma, glioblastoma, hepatocellular, breast, lung, colon–rectal, prostate and thyroid [7,8]. Due to this role and their profiling expression as markers of tumor origin, miRNAs could play an important role in the diagnosis, treatment, and prognosis of RCC, particularly thanks to their profile of expression. Therefore, this review offers an updated overview of the current knowledge about miRNAs as biomarkers, therapeutic targets, or modulators of response to treatment in RCC patients.

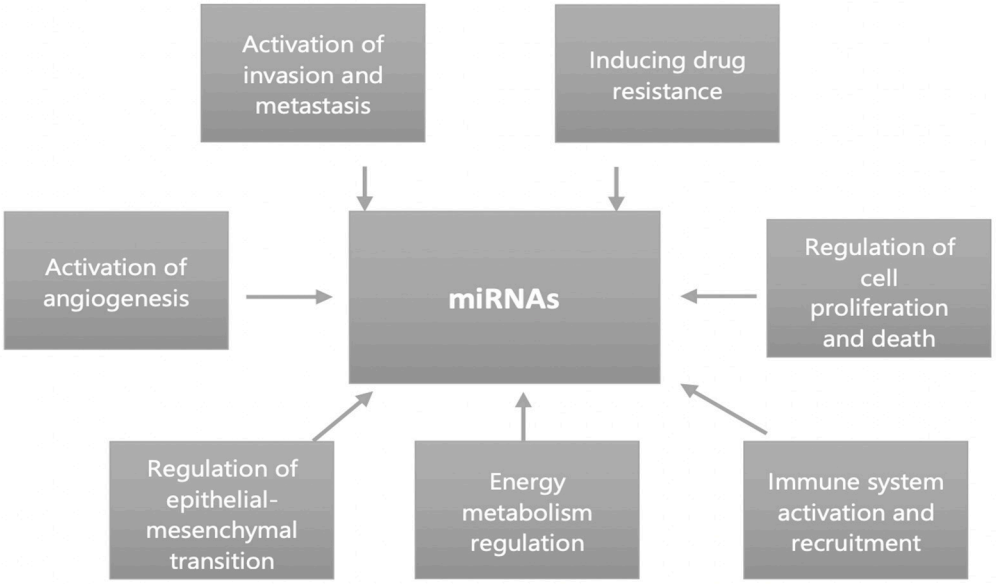

Figure 1. Cellular mechanisms regulated by miRNAs.

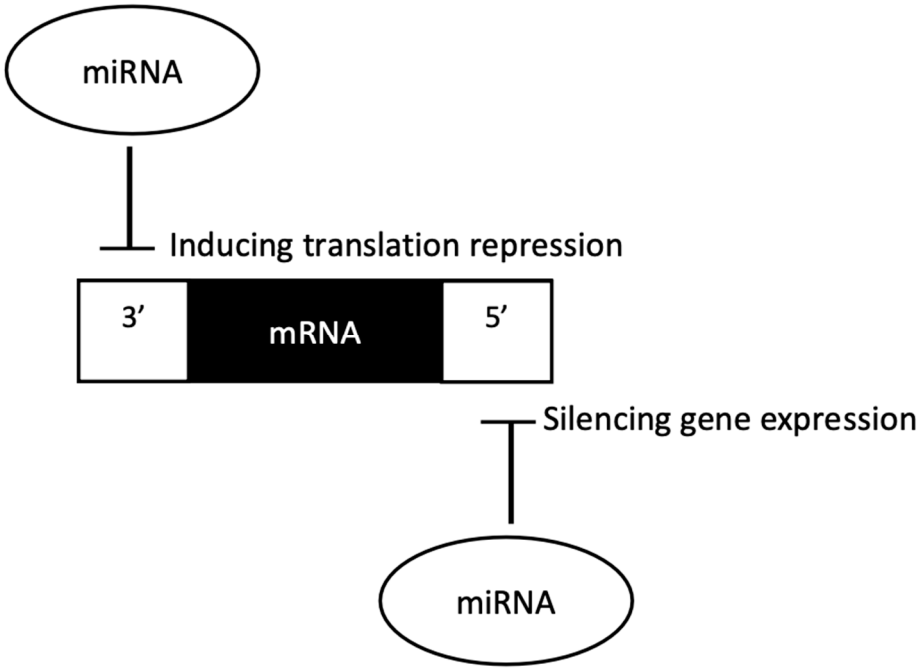

Figure 2. miRNAs regulation activity.

2. Materials and Methods

We conducted a narrative review of the most relevant articles in the Medline (US National Library of Medicine, Bethesda, MD, USA), Scopus (Elsevier, Amsterdam, The Netherlands), and Web of Science Core Collection (Thomson Reuters, Toronto, ON, Canada) databases. We included articles from January 2016 to August 2022. The following terms were combined to capture relevant publications: "miRNA" OR "non-coding RNA", OR "small RNA" AND "Kidney Cancer" OR "Local Renal Cell Carcinoma" OR "Advanced Renal Cell carcinoma". Only papers published in English and available in full text were included in the analysis. References lists in relevant articles and reviews were also screened for additional studies. Case reports, conference abstracts, editorial comments, and letters to the editor were excluded. According to the predefined type of review, the results were qualitatively described, as reported in the primary studies, without quantitative

synthesis. Two authors reviewed the records separately and individually to select relevant publications, with any discrepancies resolved by a third author. The search identified 297 articles. After the removal of duplicates, 196 articles were included. After screening based on title and abstract, 78 articles were selected for full-text screening, of which 20 articles could be included based on the criteria outlined above.

3. miRNA Isolation

The clinical implementation of cellular miRNAs as biomarkers for cancer diagnosis, prognosis and treatment relies on the possibility of isolating selected nucleotides from tissue samples and different biofluids [9]. Several commercial platforms for total nuclear and cytoplasmic RNA extraction and amplification through RT-qPCR from renal cancer tissue are routinely used, with comparative research outlining the need to optimize and standardize such platforms to the selected sample of interest in mammalian tissues [10]. Stable cell-free miRNA was isolated from plasma, serum and urine, with promising implications of poor invasion capability in the sample collection. Dias et al. described a protocol for the extraction of 9 selected miRNAs from circulating exosomes in human fresh plasma collected from patients affected by localized and metastatic ccRCC [11]. In brief, exosomes were harvested via sequential ultracentrifugation of the supernatant with visual confirmation on transmission electron microscopy and then utilized in RT-qPCR of the targeted nucleotide sequences. A similar protocol was presented by He et al. in a study investigating the role of exosomal miR-31-5p in the induction of resistance to sorafenib [12]. Assessment of the exosomal miRNA of the RCC microenvironment was recently shown to be relevant, as pro-tumorigenic miRNAs were found in exosomes related to the cross-talk between cancer cells and polarized M2 macrophages [13–15]. miRNAs directly secreted into the plasma by RCC tumor or stromal cells have also been proven to be stable in humans and were reliably isolated via RT-qPCR of a centrifuged miRNA phase [16–18]. Serum represents another ideal biofluid for miRNA isolation in RCC, with numerous protocols describing the isolation of multiple miRNA targets via RT-qPCR of human serum, showing the reliability of the biofluid as a substrate for the design of diagnostic panels [19–23]. Techniques for the isolation of exosomal miRNA from the serum of patients affected by ccRCC have also been presented, including the use of antibody-conjugated magnetic beads for exosome extraction [24,25]. Moreover, miRNAs extraction from urine samples was described and successfully used in a high-volume analysis by Outeiro-Pinho et al. to assess the downregulation via promoter hypermethylation of the oncosuppressor miR-30a-5p in ccRCC [26]. Protocols of miRNAs extraction from urine based on commercially available kits, spectrometry for purity assessment and subsequent RT-qPCR have been presented in studies assessing the role of miRNAs panels as biomarkers of RCC presence [27,28].

4. Localized RCC

4.1. Diagnosis

MiRNAs may support the diagnosis of localized RCC and improve the ability to discriminate cancer subtypes from benign lesions, possibly avoiding unnecessary treatment of undefined neoplasms (Table 1). Huang et al. compared miRNA expression profiles between 11 renal tumors and identified 48 miRNAs specific for ccRCC (i.e., miR-27a, miR-221, miR-34a, miR-103, miR143, miR-15a, miR-16, miR-17-5p, and miR-24), 9 specific miRNAs for non-tumor samples, and 33 detected in both groups with different degrees of expression [29]. Fridman et al. suggested that miR-210 and miR-221 could be employed to distinguish among clear cell/papillary and oncocytoma/chromophobe subtypes, miR-200c and miR-139-5p to differentiate oncocytoma from chromophobe and miR-31/miR-126 to discriminate clear cells from papillary tumors, with a 93% concordance with pathological specimens [30]. Petillo et al. found that miR-424 and miR-203 are overexpressed in clear-cell RCC and chromophobe, and under-expressed in papillary RCC and oncocytoma, while miR-20, miR-200b, miR-197, miR-320, and miR-186 are consistently under-expressed in oncocytoma and overexpressed in chromophobe RCC [31]. Juan et al. isolated 35 miRNAs

from 28 samples of ccRCC and observed that the downregulation of miR-135a, miR-136, miR-154, miR-337, miR-377 and miR-411 could be used as indirect proof for chromosome deletions linked to ccRCC [32]. Finally, Dias et al. analyzed miRNAs in plasma liquid biopsy from patients with ccRCC before and after surgery, finding that miR-25-3p, miR-126-5p, miR-200c-3p, and miR301a-3p decrease after surgery, while miR-1293 increases, suggesting a role of this miRNA as a biomarker to promptly identify recurrence [11].

4.2. Prognosis

MiRNAs can be used to predict the prognosis of certain tumor types. Petillo et al. established the role of the analysis of miR-32, miR-342, miR-130a and miR-30c-2 expression as a tool to identify groups of ccRCC with different prognoses [30]. Ge et al. identified 13 miRNAs (miR-223, miR-365–2, miR-21, miR-18a, miR-183, miR-335, miR-149, miR-9–2, miR-365–1, miR-130b, miR-9–1, miR-625, and miR-146b) associated with higher tumor recurrence rates [33], while Zhao et al. showed that the under expression of miR-497 was associated with worse tumor stage and higher histological grading [34]. Huang et al. found that three miRNAs (miR-21-5p, miR-223-3p, and miR-365a-3p) correlated with worse survival and higher recurrence rates in ccRCC [35]. These findings could be used, in the future, to develop new predictive models to tailor a patient-specific follow-up on the basis of individualized risk classes.

4.3. Treatment

The development of miRNA-based therapeutic strategies is still in its early phases. Signaling pathways involving several miRNAs have been identified as potential targets for the development of new drugs. One example is constituted by miR-1260b, consistently overexpressed in ccRCC, that has been proven to be inhibited by genistein, a flavonoid found in soy [36]. One major limitation to this new therapeutic approach is the vast number of miRNAs that can regulate a single gene, as proven by Sekino et al. [37]. Several phytocompounds are involved in miRNAs regulation and may affect cancer biology [38], resveratrol binds miRNA-33a and miRNA-122 and increases their levels; resveratrol also regulates the expression of miRNA-17 and suppresses their level through c-Myc; (−)-epigallocatechin-3-gallate decreases levels of miRNA-33a and miRNA-122; curcumin downregulates miRNA-21, which regulates the pathway of PTEN [39]. Quercetin downregulates miRNA-103a-3p, miRNA-125b, and miRNA-1202 [40]. Sulforaphan increases the expression of miR-124, which regulates the IL-6 receptor [41]. Considering RCC biologic link to hypoxia and angiogenesis, several pathways have been investigated. MiR-210, miR-29b, miR-142-43p and miR-424-5p, which are pro-angiogenic miRNAs overexpressed under hypoxic conditions, could be targeted by antiangiogenic treatment [42]. Finally, miR-26, was confirmed to inhibit the coronin-3 pathway, involved in the migration and invasion of RCC, and therefore could serve as a potential therapeutic target for miRNA-based therapy [43].

5. Locally Advanced and Metastatic RCC

5.1. Diagnosis

About 20% of patients with newly diagnosed RCC harbor metastases [44]. Those patients are treated with systemic therapy with or without cytoreductive nephrectomy, according to current guidelines [45]. Before deciding upon systemic treatment, a tumor biopsy is usually performed. In addition, liquid biopsy could potentially represent a valid tool to maximally personalize treatment patterns by analyzing different biomarkers, such as miRNA. [46]. For example, the levels of miR-122-5p are correlated with RCC metastasis and grade, and the levels of miR-206 are correlated with pT-stage and metastasis [47]. Similarly, levels of mir-27a-3p are correlated with advanced clinical stages for ccRCC patients [48]. Intriguingly, plasma from metastatic RCC (mRCC) patients exhibits higher levels of miR-301a-3p and lower levels of miR-1293 in comparison with localized RCC counterparts [11].

As a consequence, specific mi-RNA signatures might help clinicians to identify mRCC patients in combination with imaging modalities.

5.2. Prognosis

Despite recent advances, mRCC patients have poor prognosis with a median survival of 20 months, approximately [49]. The prognosis of these patients is usually stratified based on several risk scores (i.e., MSKCC, IMDC, and Leibovich score) [45]. Nonetheless, all of them rely on clinical information and laboratory tests without including biomarkers. Consequently, miRNAs might be adopted to refine risk stratification of mRCC. Under such premises, Heinzelman et al. identified a 4-miRNA score (miR-30a-3p/-30c-5p/-139-5p/-144-5p) exhibiting higher predictive capability for metastasis- free and overall survival than clinicopathological parameters, as well as the Leibovich score [50]. Similarly, other studies reported that levels of miR-1293 and miR-301-3p were associated with overall survival in mRCC patients [11] or that miR-452-5p levels were associated with a poor prognosis in mRCC patients [51]. Taken together, further studies should validate risk scores including miRNA signatures to better profile the prognosis of RCC patients.

5.3. Treatment

Sunitinib is routinely used as first-line therapy for mRCC. However, 10–20% of mRCC patients are inherently refractory to sunitinib [52]. In this regard, some studies investigated the role of miRNA as a potential biomarker of treatment response. For example, Kovacova et al. observed that miR-376b-3p is associated with response to sunitinib and allows to identify long-term responders (progression-free survival over 12 months), with a sensitivity and a specificity of 83 and 67%, respectively [17]. Similarly, miR-9-5p is also a marker of the therapeutic effect of sunitinib in RCC [53]. Moreover, Gamez-Pozo et al. found that miR-192, miR-193-3p and miR501-3p can identify poor responders to TKI therapy [54]. Recently, immune-checkpoint inhibitors have gained popularity in RCC due to data on survival benefits. Specifically, nivolumab significantly improved the median overall survival of mRCC patients, which led to its regulatory approval in both the EU and the USA. Concurrently, biomarkers to clearly identify patients, who might benefit most from immune-checkpoint inhibitors (anti-PD-1/anti PD-L1) are not available yet [55]. A recent study demonstrated that the expression of miRNAs, including miR-22/24/99a/194/214/335/339/708 can be used to predict which patients are likely to have a long-lasting response to nivolumab treatment [56]. In the upcoming years, clinicians might rely on specific miRNA signatures to characterize resistance and/or sensitivity to either immune-checkpoint inhibitors or TKIs.

Table 1. The expression of mi-RNA in renal cell cancer. RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitors. cc: clear cell; p: papillary; ch: chromophobe.

miRNA	Detection Site	Expression	Gene Target	Biological Functions	Role	Clinical Function
miR-25 [11]	plasma	↑ or ↓	PTEN, BCL2L11	Enhance cell migration and increase expression of N-cadherin and Slug	Prognosis	Under-expression after surgery
miR-126 [11]	RCC tissue, plasma	↓	SLC7A5, SERPINE1, VEGF	Decrease cell migration, Limits mTOR pathway	Diagnosis	High levels in pRCC Reduction after surgery

Table 1. *Cont.*

miRNA	Detection Site	Expression	Gene Target	Biological Functions	Role	Clinical Function
miR-200 [11]	RCC tissue, plasma	↑	VEGFA, PTEN, TIMP2	Promote cell proliferation	Diagnosis	High levels in chRCC and low in oncocytoma Under-expression after surgery
miR301 [11]	plasma	↑	TIMP2, PTEN BCL2L11	Promote cell proliferation	Diagnosis and Prognosis	Overexpression associated with metastatic risk and poor prognosis Downregulation after surgery
miR-1293 [11]	Plasma	-	-	-	Diagnosis and Prognosis	Overexpression after surgery Under-expression in metastatic patients Poor prognosis and metastatic risk
miR-376 [17]	RCC tissue	-	-	-	Therapy	Overexpression in RCC of patients with primary resistance versus long-term response to Sunitinib
miR-15 [29]	RCC tissue	↓	DMTF1	Tumor suppressor by activating the transcription of ARF	Diagnosis	
miR-16 [29]	RCC tissue	↑	SRPR_HUMAN	Guarantees the correct targeting of the proteins to the endoplasmic reticulum membrane	Diagnosis	
miR-27a [29]	RCC tissue	↑	Cadherin-5	Favors angiogenesis	Diagnosis	Positive association with advanced clinical stage and metastatic risk

Table 1. *Cont.*

miRNA	Detection Site	Expression	Gene Target	Biological Functions	Role	Clinical Function
miR-17 [29]	RCC tissue	↓	E2F1	Tumor suppressor protein with a crucial role in the control of cell cycle	Diagnosis	
miR-103 [29]	RCC tissure	↓	FBXW11	Prevent cell cycle progression	Diagnosis	
miR-34a [29]	RCC tissure	↑	DLL1	Promotes cell to cell communication	Diagnosis	
miR143 [29]	RCC tissue	↑	MAPK7	Promotes mitotic activity	Diagnosis	
miR-31 [30]	RCC tissure	↑	YAP1	Promotes the transcription of cyclin D1	Diagnosis	High levels in pRCC
miR-210 [30]	RCC tissue	↑	ISCU 1/2	Promotes the synthesis and maturation of protein for cell cycle progression	Diagnosis	High levels in p- and ccRCC
miR-221 [30]	RCC tissue	↑	KIT	Promote cell proliferation, migration, invasion and inhibit apoptosis	Diagnosis	High concentration in oncocytoma and chRCC
miR-30 [31]	RCC tissue, urine, and serum	↓ (c) and ↑ (a)	GRP78, Beclin-1, ITGA4, NRP2	Promotes cell growth	Prognosis	(c) Downregulation-poor prognosis (a) Upregulation-metastatic disease
miR-32 [31]	RCC tissue	-	-	-	Prognosis	Positive association with poor outcome
miR-186 [31]	RCC tissue	↓	SENP1	Inhibit cell proliferation, invasion and induce apoptosis, decrease level of p-IkBa and p-p65	Diagnosis and Prognosis	High levels in oncocytoma and low in chRCC
miR-197 [31]	RCC tissue	-	-	-	Diagnosis and Prognosis	High concentration in chRCC and low in oncocytoma

Table 1. *Cont.*

miRNA	Detection Site	Expression	Gene Target	Biological Functions	Role	Clinical Function
miR-203 [31]	RCC tissue	↓	p63	Decrease tumor growth, metastasis and increase the expression of E-cadherin, PTEN, p21 and p27	Diagnosis and Prognosis	Overexpression in ch- and ccRCC and under-expression in papillary RCC and oncocytoma
miR-424 [31]	RCC tissue	↑	WEE1	Limit cell cycle	Prognosis	High levels in clear cell RCC
miR-320 [31]	RCC tissue	↓	CFL2	Reduce tumor growth	Diagnosis	Low levels in chRCC and high in oncocytoma
miR-135a [32]	RCC tissue	↓	RASSF1A	Inhibit proliferation	Diagnosis	Downregulation in ccRCC
miR-154 [32]	RCC tissue	-	-	-	Diagnosis	Downregulation in ccRCC
miR-377 [32]	RCC tissue	-	-	-	Diagnosis	Downregulation in ccRCC
miR-411 [32]	RCC tissue	-	-	-	Diagnosis	Downregulation in ccRCC
miR-337 [32]	RCC tissue	-	-	-	Diagnosis	Downregulation in ccRCC
miR-130a [33]	RCC tissue	↑	PTEN/PI3K/AK	Cell proliferation	Prognosis	Under-expression in poor prognosis
miR-9 [33]	RCC tissue	↑	VEGF, E-cadherin, PRDM1	Angiogenesis, cell proliferation	Prognosis and Therapy	High levels predict recurrence rate
miR-18a [33]	RCC tissue				Prognosis	High levels predict recurrence rate
miR-149 [33]	RCC tissue	↑	FOXM1	Inhibit cell migration, invasion and proliferation	Prognosis	Positive association with higher recurrence rate
miR-183 [33]	RCC tissue	-	-	-	Prognosis	Positive association with higher recurrence rate
miR-21 [33]	RCC tissue	↑	PTEN, PDCD4, PIK3R1, TIMP3	Increase cell proliferation, invasion, migration and reduce apoptosis	Prognosis	Association of these mi-RNAs with worse survival and higher recurrence rates
miR-146 [33]	RCC tissue	-	-	-	Prognosis	Positive association with higher recurrence rate

Table 1. *Cont.*

miRNA	Detection Site	Expression	Gene Target	Biological Functions	Role	Clinical Function
miR-335 [33]	RCC tissue	-	-	-	Prognosis	Positive association with higher recurrence rate
miR-625 [33]	RCC tissue	-	-	-	Prognosis	Positive association with higher recurrence rate
miR-497 [34]	RCC tissues	↓	PDL1	Inhibit cell proliferation, migration and increase apoptosis	Prognosis	Under-expression associated with worse tumor stage and higher histological grade in clear cell RCC
miR-223 [35]	RCC tissue	↑	HMGCS1	-	Prognosis	Positive association with higher recurrence rate and worse survival and in ccRCC
miR-365 [35]	RCC tissue	↑	HMGCS1		Prognosis	Direct correlation with worse survival and higher recurrence rates
miR-1260b [36]	RCC tissue	↓	Wnt	Promote cell proliferation	Therapy	High concentration in RCC tissue Genistein promoted its downregula-tion
miR-26 [43]	RCC tissue	↓	Coronin-3	inhibiting the migration and invasion	Therapy	Overexpression inhibits RCC in cell growth and metastasis via down-regulating coronin-3
miR-139 [45]	RCC tissue	↑	TGFβ, Wnt, Rho,	Promotes cell proliferation	Diagnosis and Prognosis	High concentration in oncocytoma and low in chRCC Positive association with metastatic risk

Table 1. *Cont.*

miRNA	Detection Site	Expression	Gene Target	Biological Functions	Role	Clinical Function
miR-144 [45]	RCC tissue	↑	MAP3K8	Suppress cell proliferation, migration and invasion	Diagnosis and Prognosis	Positive association with metastatic risk
miR-206 [47]	RCC tissue	-	-	-	Diagnosis	Direct correlation with higher pT-stage and metastasis risk
miR-452 [51]	RCC tissue	↓	SMAD4	Suppresses RCC progression targeting various gene	Prognosis	Poor prognosis in mRCC patients Sunitinib reduces its expression
miR-192 [54]	Serum	-	-	-	Therapy	High concentration in poor responder patients to TKI therapy
miR-193 [54]	Serum	↑	ST3GalIV	Promote cell proliferation, invasion, migration and inhibit apoptosis, improve expression of PI3k and p-Akt	Therapy	High concentration in poor responder patients to TKI therapy
miR501 [54]	Serum	-	-	-	Therapy	High levels in poor responder patients to TKI therapy

6. miRNA Role in Clinical Practice and Future Perspective

Despite the promising data, miRNAs' performance as diagnosis and prognosis markers remains unclear. Several studies have been published in the last few years regarding the utility of miRNAs in diagnosis and prognosis. Regarding diagnosis, Gottardo et al. reported that miR-27, -28, -185, and let-7f-2 are overexpressed considerably in RCC specimens ($p < 0.05$) in comparison to a healthy kidney [57]. Nakada et al. reported that 37 miRNAs were significantly under-expressed in conventional RCC, while the other 6 were overexpressed; miRNA 141 and miRNA-200 were especially down-regulated [58]. Mytsyk et al. also compared the expression of miRNA-15a in the urine of healthy renal parenchyma/benign tumors and RCC patients, and they found that it was upregulated in the second case ($p < 0.01$) [59]. Liang et al. explored the potential in diagnosis and prognosis of three miRNA signatures: miR-21, miR-584, and miR-155 [60]. They showed a sensitivity of 98.3% and a specificity of 97.2% of these miRNAs in discriminating RCC from normal controls. Wulfken et al. reported that miRNA-1233 was increased in RCC patients, showing a sensitivity of 77.4% and specificity of 37.6%, as a diagnostic biomarker of RCC [61]. Regarding prognosis, Xu et al. identified nine miRNAs that strongly correlated with RCC prognosis ($p < 0.01$); in particular, they show high expression in patients with

a poor prognosis [62]. Zhao et al. showed that miR-187 expression was downregulated in ccRCC specimens, decreased with advancing tumor grade and stage, and high levels correlated with survival after surgery [63]. The upregulation of miR-21 seems to be associated with the cancer-specific survival of ccRCC patients [64]. Fritz et al. showed that the ratio of miR-21 to miR-10B correlates independently with survival ($p = 0.012$) and the TNM stage [65]. Vergho et al. reported that in ccRCC patients, miR-21, miR-126, and miRNA-221 could independently predict cancer-related death [66]. Fu et al. reported miRNA-125 as an independent adverse prognostic factor for recurrence and survival in RCC patients [67]. However, several investigations, including a higher number of patients, different stages and histologic subtypes or grades of differentiation of RCC, are required for the implementation of the current knowledge into clinical practice.

After the discovery of miRNA, a high volume of reports outlined their various roles in tumor pathogenesis, clinical progression, and therapeutic management, according to the target gene. Although small renal masses are detected accidentally by abdominal imaging, a diagnosis of metastatic RCC occurs in about one-third of patients [68]; therefore, novel strategies to support early diagnosis are necessary. In this contest, miRNAs can be considered a valid option. According to Ning et al., MiRNAs may be a diagnostic biomarker given their higher blood levels in RCC patients than in healthy volunteers; such levels were also shown to decrease during the postoperative period, therefore constituting a useful tool for monitoring therapeutic outcomes [69]. A renal cancer diagnosis is mainly confirmed through a computed tomography given its high sensitivity and specificity [45], although it determines exposure to ionizing radiations. Considering the lower incidence of RCC compared to colorectal or breast cancer, a screening program for the population is not provided by national healthcare systems, and mi-RNAs measurement for the prevention of RCC is not recommended. A future perspective may be represented by the assessment of the blood concentration of these biomarkers in patients with a greater diathesis to develop renal cancer. Indeed, patients with chronic kidney disease could benefit from the miRNAs used as a biomarker for the surveillance strategy [70]. MiRNAs may also contribute to the analysis of the prognosis of the disease, distinguishing between a confined tumor and a metastatic one, improving disease-free and overall survival [71]. As reported by Dias et al., the removal of localized ccRCCs is also associated with specific patterns of miRNA levels [32]. Consequently, a possible future indication could be in patients with known RCC undergoing medical therapy or surgery, alongside imaging to improve the quality of follow-up, as proposed for microsatellite analysis in urothelial cancer [72]. As previously reported, miRNAs play a central role in tumor pathogenesis, thus providing new targets for future cancer therapy.

Currently, chemotherapy offers higher survival for patients with advanced disease, although a complete response does not occur [73]. Furthermore, immunotherapy based on VEGF causes several side effects, such as neutropenia, thrombocytopenia, diarrhea, pneumonitis, and hypertension [74]. Several tumor-suppressing miRNAs have been identified as agents responsible for ccRCC growth, targeting several cell-cycle-related genes [75,76]. However, there are currently no in-vivo studies that can confirm the ex-vivo results. Therefore, future insights are needed to evaluate the potential of miRNAs in therapeutic management.

7. Conclusions

In conclusion, several pieces of evidence suggest miRNAs to be a promising and non-invasive biomarker in RCC. They demonstrate high stability and specificity. Nowadays, there is an imperious need for faster ways to detect and to treat different tumors. Since miRNAs are traceable in circulation and urine samples of patients, they could represent a good candidate in the diagnosis, subtype classification, screening of chemo- or radio-resistance, prognosis, and recurrence of RCC. Although miRNAs play a pivotal role in different aspects of RCC biology and development, none of them are still used in the clinical setting. Further larger-scale studies and clinical trials are necessary to better assess the mode

of action and regulatory mechanism. MiRNAs could also serve to develop personalized patient profiles, and to support targeted therapeutic interventions in the future.

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