Review

Renal Cell Tumors: Uncovering the Biomarker Potential of ncRNAs

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Abstract: Renal cell tumors (RCT) remain as one of the most common and lethal urological tumors worldwide. Discrimination between (1) benign and malignant disease, (2) indolent and aggressive tumors, and (3) patient responsiveness to a specific therapy is of major clinical importance, allowing for a more efficient patient management. Nonetheless, currently available tools provide limited information and novel strategies are needed. Over the years, a putative role of non-coding RNAs (ncRNAs) as disease biomarkers has gained relevance and is now one of the most prolific fields in biological sciences. Herein, we extensively sought the most significant reports on ncRNAs as potential RCTs’ diagnostic, prognostic, predictive, and monitoring biomarkers. We could conclude that ncRNAs, either alone or in combination with currently used clinical and pathological parameters, might represent key elements to improve patient management, potentiating the implementation of precision medicine. Nevertheless, most ncRNA biomarkers require large-scale validation studies, prior to clinical implementation.

Keywords: Renal cell tumors; renal cell carcinoma; biomarkers; liquid biopsies; diagnosis; prognosis; non-coding RNAs; miRNA; lncRNA

1. Renal Cell Tumors

Renal cell tumors (RCT) rank 16th among the most common neoplasms in adults, representing more than 400,000 new cases yearly (2.2% of all cancer diagnosis) in both genders, with a mortality rate of 2.4/100,000, worldwide [1]. RCTs are a heterogenous group of tumors, spanning from benign to overtly malignant behavior and being highly diverse at the molecular, genomic/epigenomic, morphological, and clinical level [2]. Benign renal tumors correspond to 10–13% of all RCT, being oncocytomas the most prevalent, whereas clear cell renal cell carcinomas (ccRCC) are the most common and one of the most aggressive malignant RCT subtypes (70–75% of all cases), followed by papillary renal cell carcinomas (pRCC, 10–15%) and chromophobe renal cell carcinomas (chRCC, 5–10%) [3]. Since these four types of RCT represent the vast majority of renal tumors, they will represent the main focus of this review. Although, in recent years, mortality rate has dropped, incidence has increased, mainly due to incidental detection. Indeed, more than 50% of RCTs are incidentally detected after nonspecific musculoskeletal or gastrointestinal complaints entailing abdominal imaging [4]. Visible
and/or palpable manifestations, such as flank pain, hematuria, and abdominal mass are infrequent, only observed in a small number of cases, and are mostly associated with advanced disease [5]. Thus, physical examination does not allow for early diagnosis of RCT. Presently, partial or radical nephrectomy is the main curative treatment available since these tumors are notably resistant to both radio- and chemotherapy [6]. However, cases of complete curative treatment have been reported with interleukin-2 (IL-2) and nivolumab-based therapy [7,8]. The clinical benefit of adjuvant interferon-alpha (IFN-α) and IL-2, heat shock protein-peptide complex-96 (HSPPC-96, Vitespen®), girentuximab, or vascular endothelial growth factor receptor/tyrosine kinase inhibitor (VEGFR/TKI) for high-risk RCT patients remains unclear, as results of published randomized trials are conflicting [9–14]. Furthermore, 30 to 35% of the cases are diagnosed with locally invasive or distant disease, and 20 to 40% of the patients without metastasis at the time of diagnosis will develop metastatic dissemination during the disease course [15]. For metastatic renal cell carcinoma (mRCC), VEGFR/TKI antiangiogenic drugs, such as pazopanib, sunitinib, or cabozantinib, have been shown to improve disease control [16–18]. In patients where antiangiogenic agents are inefficient, the use of mammalian target of rapamycin (mTOR) pathway inhibitors, such as everolimus and temsirolimus, has shown favorable results [19]. Lastly, a new wave of immunotherapy-based approach is arising and, nivolumab, a programmed cell death 1 (PD-1) blocking antibody, and atezolizumab, a programmed cell death-ligand 1 (PD-L1) blocking antibody, have also demonstrated promising results by increasing mRCC overall survival (OS) [20,21]. According to the American Cancer Society, patients with localized disease present a five-year survival rate above 75%, whereas for mRCC patients it decreases to less than 15%. Poor prognosis of advanced RCC can be explained by a wide variety of factors, with the acquired resistance to targeted therapies the main one [22]. Currently, no adequate tools for the screening or early diagnosis of RCT are available. Furthermore, prognostication is mainly based on clinical stage and metastatic dissemination, and therapy efficacy is rather poor. Thus, the development and clinical implementation of more robust, reliable, and cost-effective biomarkers capable of RCTs’ early-stage detection and/or prediction of disease progression and therapy response is mandatory. To tackle these limitations, tumor-related genetic and/or epigenetic alterations may be used as biomarkers [23], ultimately improving patient survival and quality of life, while reducing healthcare costs through avoidance of futile therapeutic interventions.

2. Epigenetics

Epigenetics, firstly termed by Conrad Waddington in 1942, refers to mitotically and/or meiotically heritable and reversible changes in gene expression, which do not alter primary nucleotide sequence [24]. Epigenetic regulation involves four major types of modifications: DNA methylation, histone modifications/variants, chromatin remodeling complexes, and non-coding RNAs (ncRNAs) [23,24]. The first three control chromatin architecture, regulating gene expression (Figure 1). The transcriptional outcome of DNA methylation is genome location-dependent, since gene promoter DNA methylation leads to transcription repression, while gene body DNA methylation is associated with transcription activation. Histone-tail methylation is residue-specific, often leading to repressive marks and increased chromatin condensation, while acetylation results in activation marks and looser chromatin architecture [23]. Abnormalities in the normal function of the epigenetic machinery have been linked to several human conditions, including cancer [23]. Epigenetic deregulation often occurs early in tumorigenesis leading to a switch in the normal epigenetic patterns and accumulates during disease progression [25]. It is acknowledged that some of these epigenetic alterations might occur prior to the emergence of the malignant phenotype, thus constituting a valuable marker for cancer screening. From a technical point of view, methodologies available to detect those epigenetic marks are sensitive and robust, enabling easy measurement across individuals and with high-throughput screening potential [26].
After thorough analysis, 143 original articles were enrolled in the final version of this review. Proteins (1–2%). Thus, most RNAs are, indeed, ncRNAs, devoid of protein-coding potential [27]. For many years, ncRNAs were thought to be “transcriptional trash”. However, this perception has recently changed, and the pivotal roles of ncRNAs in major biological processes, such as imprinting, cell cycle, pluripotency, and gene expression regulation, are now widely acknowledged [28–30]. Based on the functional RNA molecule’s size, ncRNAs are further categorized into small non-coding RNAs (sncRNAs) and long non-coding RNAs (lncRNAs) post-transcriptionally regulate gene expression, both in the nucleus and cytoplasm. 

Global increase in RCT incidence over the last decades and the concerns regarding the most suitable follow-up and treatment for each patient demand reliable biomarkers amenable to clinical use. Herein, we aimed to critically review and highlight the most scientifically relevant and clinically promising studies concerning ncRNA-based biomarkers for RCT detection, prognostication, prediction of response to therapy, and patient monitoring.

3. Evidence Acquisition

Bibliography was selected after a PubMed search up to 19 April 2020 using the keywords: Non-coding RNA, biomarkers, and renal cell tumor, which resulted in the analysis of more than 400 manuscripts. All articles’ references were also examined for potentially useful studies. Furthermore, relevant articles were selected based on the following criteria: Written in English, the main topic is non-coding RNA, biomarkers, and renal cell carcinoma. Original reports were chosen based on the detail of analysis, mechanistic support of data, novelty, and potential clinical usefulness of the findings. After thorough analysis, 143 original articles were enrolled in the final version of this review.

4. Non-Coding RNAs (ncRNAs)

Although most of the genome is transcribed into RNAs, only a small percentage encodes for proteins (1–2%). Thus, most RNAs are, indeed, ncRNAs, devoid of protein-coding potential [27]. For many years, ncRNAs were thought to be “transcriptional trash”. However, this perception has recently changed, and the pivotal roles of ncRNAs in major biological processes, such as imprinting, cell cycle, pluripotency, and gene expression regulation, are now widely acknowledged [28–30]. Based
on the functional RNA molecule’s size, ncRNAs are further categorized into small non-coding RNAs (sncRNAs) if smaller than 200 base pairs in length [31,32] or long non-coding RNAs (lncRNAs) [33,34].

4.1. Small Non-Coding RNAs (sncRNAs)

The classification of sncRNAs as epigenetic mechanism of gene expression control remains controversial. Several studies have pointed that sncRNAs’ mechanism of action is post-transcriptional and should not be thus classified as epigenetic regulators, whereas others have a contrasting view. Nevertheless, this subclass of ncRNAs is biologically relevant. MicroRNAs (miRNAs) are the most well studied of these small molecules [35]. This class of small ncRNAs are 18–25 nucleotides in length [24] and regulate gene expression through RNA interference (RNAi) [23]. In the human genome, miRNAs are encoded by individual genes or clusters of few to several hundred different miRNAs genes [36]. The latter are then transcribed as polycistronic transcripts, which are ultimately processed into the individual mature miRNAs. In most cases, miRNAs are encoded by introns of non-coding or coding genes, but they can also be encoded by exonic regions [37]. Following transcription by RNA polymerase II, the primary miRNA (pri-miRNA) undergoes several steps of maturation, catalyzed by type III ribonucleases (RNases). First, in the nucleus, the Drosha complex cleaves the pri-miRNA, leading to the formation of the precursor miRNA (pre-miRNA). Then, after pre-miRNA transport to the cytoplasm, Dicer complex cleaves the molecule, generating a miRNA duplex, which is loaded into the pre-miRNA-inducing silencing complex (pre-miRISC), where the stable 5’ end strand—guide strand—is selected, generating the mature miRISC complex, whereas the other strand—passenger strand—is rapidly degraded [38]. Together with GW182 family of proteins, miRISC binds to mRNA targets by base complementarity and, ultimately, leads to gene silencing. Another type of sncRNAs are the P-element Induced Wimpy testis (PIWI)-interacting RNAs (piRNAs). First discovered in the beginning of the 21st century [39], these 21–35 nucleotide-long molecules are involved in viral infection response, transposable elements silencing, and regulation of gene expression by (1) leading PIWI proteins to cleave target RNA, (2) promoting heterochromatin assembly, and (3) inducing DNA methylation [40,41]. One of the main features that distinguishes miRNAs from piRNAs is that the latter have single-strand RNA precursors and its processing requires PIWI proteins of the Argonaute/PIWI family, but does not need DICER complex [42]. Small interfering RNAs (SiRNAs) are also classified as sncRNAs [31], but this review solely focused on miRNAs and piRNAs, as these are the most well studied.

4.1.1. MiRNAs and piRNAs in RCTs

Deregulated miRNA expression in cancer was first reported in the early 2000s by Calin and colleagues [43]. Since then, various studies have demonstrated differential miRNA expression profiles in benign and malignant neoplasms compared to healthy individuals. Dysregulation of miRNA expression occurs in various steps of tumorigenesis and in several tumor models [23], including RCT [24,44]. MiRNAs possess the ability to target several mRNAs, and one mRNA might be targeted by many miRNAs [45]. Depending on the target, miRNAs are classified as tumor suppressor miRNAs (TSmiRs) or as oncogenic miRNAs (oncomiRs). TSmiRs are usually downregulated in cancer and act through transcriptional repression of oncogenes, whereas oncomiRs are normally upregulated, and act by targeting tumor suppressor genes, leading to mRNA decay and/or degradation [46]. Nonetheless, several reports have demonstrated that, depending on the cellular context and the tumor type, the same miRNA may exhibit oncogenic or tumor suppressor activity, such as let-7g, which is downregulated in lung cancer and upregulated in colorectal cancer [47,48].

Concerning piRNAs, most are not complementary to putative target mRNAs, indicating that piRNAs may be involved in epigenetic regulation rather than post-transcriptional regulation, controlling a variety of biological processes and being also implicated in cancer development [49]. Several studies aimed to disclose their biological role in different cancer types [50], including RCC [51–53]. However,
the specific molecular mechanism underlying piRNAs’ deregulation in carcinogenesis is still poorly understood, and further investigation is needed.

Due to their tissue and cellular-specific functions and expression, the potential use of sncRNAs as diagnostic, prognostic, predictive, and monitoring cancer biomarkers has been extensively studied in the recent years. Here, we highlighted the most promising findings in RCT, both in tissue and liquid biopsies.

4.1.2. SncRNAs as Diagnostic Biomarkers

Tissue-Based Samples

The increasing number of asymptomatic, incidentally detected renal masses constitutes a major clinical challenge, considering the need to define the potential threat to the life of the patient. Whether a biopsy is mandatory or not remains controversial, considering that histopathological and/or cytopathological assessment may not provide a definitive diagnosis in a sizeable proportion of cases. Thus, the ability of sncRNAs to discriminate between normal and benign/malignant tissue has been investigated. Wotschofsky and co-workers [54] measured the differential expression of several miRNAs in a series of 111 ccRCC and matched normal tissue (MNT) using quantitative real-time PCR (RT-qPCR). The combination of miR-141, miR-155, and miR-184 identified malignancy with 95% sensitivity, 100% specificity, corresponding to an area under curve (AUC) of 0.990 [54]. In another study, miR-141 or miR-200b levels discriminated RCC from normal renal tissue (NRT) with 99.2% sensitivity, 100% specificity, and an AUC of 0.991. Furthermore, the same panel distinguished ccRCC, pRCC, or chRCC from benign renal tumors with 85.6% sensitivity, 100% specificity, and an AUC of 0.914 [55]. In 2015, Busch and colleagues [51] reported that piR-30924, piR-57125, and piR-38756 were differentially expressed in ccRCC compared to NRT and the combination of these piRNAs identified malignant disease with 91% sensitivity, 86% specificity, and an AUC of 0.910. Notably, the combination of the duo piR-30924 and piR-57125 distinguished metastatic-ccRCC (mccRCC) from non-metastatic ccRCC (non-mccRCC) with 73.0 sensitivity, 74.0 specificity, and an AUC of 0.760 [51]. Several other studies have been published since, and are summarized in Table 1. Because tissue biopsies are seldom performed and might not represent the entire lesion, these biomarkers might assist in the correct classification of the tumor. Moreover, this is an invasive procedure, which submits patients to stress and pain, eventually associated with increased risk of metastization, especially in ccRCC. Hence, discovery and validation of non-invasive screening/diagnosis biomarkers, capable of accurately identifying the nature of renal masses, is urgently needed.
Table 1. Summary of proposed diagnostic biomarkers for Renal Cell Tumors (RCT) in tissue.

| Year | Diagnostic Biomarker | Biological Source | Number of Cases/Controls | Diagnostic Performance | Reference |
|------|---------------------|-------------------|--------------------------|------------------------|-----------|
|      |                     |                   |                          | Sensitivity (%) | Specificity (%) | AUC | |
| 2009 | miR-200c            | Tissue            | 72 ccRCC; 72 MNT         | n.a.                | n.a.              | 0.970 | [56] |
| 2010 | miR-200c            | Tissue            | 13 chRCC; 21 oncocyotomas | n.a.                | n.a.              | 0.880 | [57] |
| 2012 | miR-21              | Tissue            | 71 ccRCC & 18 pRCC; 10 chRCC & 8 oncocyotomas | 83.0              | 90.0              | 0.886 | [58] |
| 2013 | 3 miR panel         | Tissue            | 111 ccRCC; 111 MNT       | 95.0                | 100.0             | 0.990 | [54] |
| 2013 | miR-210 + let-7c    | Tissue            | 16 pRCC type I; 17 pRCC type II | n.a.                | n.a.              | 0.919 | [59] |
| 2013 | miR-200b            | Tissue            | 90 RCC; 30 oncocyotomas  | 96.7                | 90.0              | 0.914 | [55] |
| 2014 | miR-3667            | Tissue            | 24 ccRCC; 40 NRT         | n.a.                | n.a.              | 0.847 | [60] |
| 2014 | miR-141             | Tissue            | 68 ccRCC; 68 MNT         | 86.8                | 97.1              | 0.930 | [61] |
| 2014 | miR-129-3p          | Tissue            | 69 ccRCC; 69 MNT         | 75.9                | 62.1              | 0.735 | [62] |
| 2014 | 5 miR panel         | Tissue            | 32 ccRCC; 16 NRT         | 100.0              | 100.0             | 1.000 | [63] |
| 2015 | 3 piRNA panel       | Tissue            | 106 ccRCC; 77 NRT        | 91.0                | 86.0              | 0.910 | [51] |
| 2016 | miR-145             | Tissue            | 44 RCC; 44 MNT           | n.a.                | 0.616             | 0.62 | [64] |
| 2016 | miR-141             | Tissue            | 27 ccRCC; 27 MNT         | n.a.                | n.a.              | 0.912 | [65] |
| 2016 | piR-823             | Tissue            | 153 RCC; 121 MNT         | n.a.                | n.a.              | 0.795 | [53] |
| 2017 | 4 miR panel         | Tissue            | 48 ccRCC; 50 benign renal tumors | 91.7              | 94.0              | 0.992 | [66] |
| 2017 | miR-34a             | Tissue            | 85 RCC; 85 MNT           | n.a.                | n.a.              | 0.854 | [67] |
| 2017 | miR-200c            | Tissue            | 19 chRCC; 11 oncocyotomas | 84.0              | 82.0              | 0.820 | [68] |
| 2017 | miR-200c            | Tissue            | 30 ccRCC; 30 MNT         | n.a.                | n.a.              | 0.860 | [69] |
| 2017 | miR-720             | Tissue            | 30 RCC; 30 NRT           | 80.0                | 100.0             | 0.905 | [70] |
| 2018 | miR-203             | Tissue            | 53 ccRCC; 53 MNT         | n.a.                | n.a.              | 0.944 | [71] |
| 2018 | miR-182-5p          | Tissue            | 24 ccRCC; 24 MNT         | n.a.                | n.a.              | 0.954 | [72] |
| 2018 | miR-224/miR-141     | Tissue            | 68 ccRCC; 68 MNT         | 97.1                | 98.5              | 0.990 | [73] |
| 2018 | miR-452-5p          | Tissue            | 20 RCC; 20 MNT           | n.a.                | n.a.              | 0.919 | [74] |
| 2019 | piR-34536           | Tissue            | 118 ccRCC; 75 NRT        | 78.0                | 78.1              | 0.815 | [75] |

MNT—matched normal tissue; NRT—normal renal tissue; RCC—renal cell carcinoma; ccRCC—clear cell renal cell carcinoma; pRCC—papillary renal cell carcinoma; chRCC—chromophobe renal cell carcinoma; n.a.—not available.
Liquid Biopsies

Recently, detection and characterization of circulating sncRNAs might represent a promising non-invasive technique to identify RCT [76]. SncRNAs are highly stable and abundant in plasma, serum, and other body fluids, being released from damaged or apoptotic normal cells, as well as from tumor cells. Numerous reports have proposed several RCT biomarkers in liquid biopsies. Serum samples were firstly used in a study by Wulfken and colleagues [77], which demonstrated that serum miR-1233 expression levels discriminated cancer patients from asymptomatic controls (AC) with 77.4% sensitivity and 37.6% specificity. The limited performance of this marker compared to tissue-based studies might be explained by technical limitations. Since then, methodology has improved, and miR-210 expression levels were found to discriminate ccRCC and AC in serum samples with 81.0% sensitivity and 79.4% specificity [78]. Recently, miR-1233 and miR-210 levels, in serum and in exosomes, discriminated ccRCC from healthy controls with 81.0/70.0% sensitivity and 76.0/62.2% specificity, respectively, with exosome-derived samples showing a better biomarker performance [79]. Moreover, plasma samples have also been tested. Specifically, miR-21 and miR-106a isolated from plasma (30 ccRCC and 30 AC) disclosed the ability to identify renal malignancy with 77.3% sensitivity and 96.4% specificity for the former miR and 86.7% sensitivity and 70.0% specificity for the latter [80]. Subsequently, Lou and colleagues [81] showed that miR-144-3p detected RCT with 87.1% sensitivity and 83.0% specificity. Notably, miR-144-3p was also able to distinguish ccRCC from benign mesenchymal tumors (angiomyolipomas) with 75.0% sensitivity and 71.7% specificity [81]. Finally, diagnostic biomarkers have also been tested in urine samples. In 2016, Butz and colleagues [82] reported that miR-126-3p and miR-34b-5p, isolated from urine exosomes, could discriminate ccRCC from healthy controls with 77.5% sensitivity and 72.4% specificity. Remarkably, both miRs also distinguished benign lesions from normal with 75.0% sensitivity and 82.8% [82]. Additionally, urinary miR-15a expression levels, evaluated in 67 RCT patients and 15 AC, detected malignancy with 98.1% sensitivity and 100% specificity [83]. A summary of these and other studies is depicted in Table 2.
### Table 2. Overview of different proposed diagnostic biomarkers for RCT in liquid biopsies.

| Year | Diagnostic Biomarker | Biological Source | Number of Cases/Controls | Diagnostic Performance | Reference |
|------|----------------------|-------------------|--------------------------|------------------------|-----------|
|      |                      |                   |                          | Sensitivity (%) | Specificity (%) | AUC      |          |
| 2011 | miR-1233             | Serum             | 84 RCC; 93 AC            | 77.4                  | 37.6           | 0.588    | [77]     |
| 2012 | miR-378 + miR-451    | Serum             | 90 RCC; 35 AC            | 81.0                  | 83.0           | 0.860    | [84]     |
| 2013 | miR-210              | Serum             | 68 ccRCC; 42 AC          | 81.0                  | 79.4           | 0.874    | [78]     |
| 2014 | miR-210              | Serum             | 34 ccRCC; 23 AC          | 65.0                  | 83.0           | 0.770    | [85]     |
| 2015 | miR-221              | Plasma            | 43 RCC; 34 AC            | 72.5                  | 33.3           | 0.696    | [86]     |
| 2015 | 5 miR panel          | Serum             | 76 stage I ccRCC; 107 AC | 80.0                  | 71.0           | 0.807    | [87]     |
| 2016 | miR-126-3p + miR-486-5p | Urine exosomes  | 24 benign renal tumors; 33 AC | 75.0                 | 87.5           | 0.850    | [82]     |
| 2016 | priR-823             | Serum             | 178 RCC; 101 AC          | n.a.                  | n.a.           | 0.626    | [53]     |
| 2016 | miR-144-3p           | Plasma            | 106 ccRCC; 123 AC        | 87.1                  | 83.0           | 0.910    | [81]     |
| 2017 | miR-21               | Plasma            | 30 ccRCC; 30 AC          | 77.3                  | 96.4           | 0.865    | [80]     |
| 2017 | miR-210              | Urine             | 75 ccRCC; 45 AC          | 57.8                  | 80.0           | 0.760    | [89]     |
| 2017 | Let-7a               | Urine             | 69 ccRCC; 36 AC          | 71.0                  | 81.0           | 0.831    | [90]     |
| 2017 | miR-451              | Plasma            | 94 ccRCC; 100 AC         | n.a.                  | n.a.           | 0.640    | [91]     |
| 2018 | miR-1233             | Serum exosomes    | 80 ccRCC; 82 AC          | 81.0                  | 76.0           | 0.820    | [79]     |
| 2018 | miR-15a              | Urine             | 67 RCT; 15 AC            | 98.1                  | 100            | 0.955    | [83]     |
| 2018 | miR-210 × miR-224    | Plasma            | 66 ccRCC; 67 AC          | 92.5                  | 45.5           | 0.659    | [73]     |
| 2018 | miR-210              | Serum exosomes    | 45 ccRCC; 30 AC          | 82.5                  | 80.0           | 0.878    | [92]     |
| 2019 | miR-508-3p & miR-885-5p | Serum            | 85 ccRCC; 35 AC          | n.a.                  | n.a.           | 0.900    | [93]     |
| 2020 | miR-432-5p           | Urine             | 44 ccRCC-SRM; 27 oncocytomas | n.a.              | n.a.           | 0.710    | [94]     |
| 2020 | miR-30a-5p            | Urine             | 171 ccRCC; 85 AC         | 63.0                  | 67.0           | 0.670    | [95]     |

RCC—renal cell carcinoma; ccRCC—clear cell renal cell carcinoma; RCT—renal cell tumor; ccRCC-SRM—clear cell renal cell carcinoma-small renal mass; AC—asymptomatic controls; me—promoter methylation; n.a.—not available.
4.1.3. SncRNAs as Prognostic Biomarkers

Tissue-Based Samples

Several sncRNAs have also been proposed as predictors of disease progression and outcome. Currently, RCT prognosis is mainly based on clinical stage and other clinical parameters at diagnosis. Nonetheless, specific sncRNAs might complement the currently used clinicopathological parameters, to improve patient management. In 2013, Wang and colleagues [96] reported that RCC patients disclosing higher miR-100 expression levels endured significantly shorter overall survival (OS), multiplying by a factor of three the risk of death comparing to those with low expression. Likewise, increased miR-630 expression levels independently predicted shorter OS, in multivariable analysis [97]. Importantly, sncRNAs have shown promise as predictors of disease-progression. Samaan and colleagues [98] divided their 258 ccRCC patient cohort into either miR-210 positive or negative expression groups. The first group of patients displayed markedly reduced disease-free survival (DFS) (hazard ratio (HR): 1.91; 95% confidence interval (CI): 1.10–3.310) compared to the negative expression group [98]. The same trend was observed in two subsequent studies, in which higher miR-210 expression associated with worse survival [99,100], whereas in another study increased miR-210 expression levels in ccRCC tissue associated with better survival [101]. Thus, multicentric studies with larger cohorts are needed to unveil the exact prognostic value of miR-210. Furthermore, high miR-27a-3p expression levels associated with shorter progression-free survival (PFS) [102], whereas low miR-155 expression entailed 5-fold increase risk to die from the disease. Notably, both miR-27a-3p and miR-155 expression levels were independent predictors of cancer-specific survival (CSS) in advanced ccRCC (stages III and IV) [103]. Table 3 summarizes these and other relevant findings concerning the prognostic value of miRNAs in RCC.
| Year | Prognostic Variable | Prognostic Biomarker | Biological Source | Number of Cases | Poor Prognosis | Prognostic Performance |
|------|---------------------|----------------------|-------------------|----------------|---------------|------------------------|
|      |                     |                      |                   |                |               | HR 95% CI              |
| 2010 | RFS                 | miR-9-3              | Tissue            | 59 ccRCC       | High methylation | 5.850 1.300–26.35     |
| 2012 | CSS                 | 4 miR panel          | Tissue            | 68 ccRCC       | High risk       | 8.800 * 2.620–29.58 *  |
| 2012 | DFS                 | miR-21               | Tissue            | 87 RCC         | Positive expression | 2.150 * 1.160–3.980 * |
| 2013 | RFS                 | miR-124-3            | Tissue            | 80 ccRCC       | High methylation | 9.370 2.680–32.80     |
| 2013 | DFS                 | miR-514              | Tissue            | 87 ccRCC       | Low expression   | 0.250 0.080–0.750     |
| 2013 | OS                  | miR-210              | Tissue            | 46 ccRCC       | Low expression   | 3.010 1.390–6.510     |
| 2013 | CSS                 | miR-486              | Tissue            | 46 RCC         | High expression   | 4.330 1.450–18.71     |
| 2013 | OS                  | miR-100              | Tissue            | 96 RCC         | High expression   | 3.600 1.800–5.200     |
| 2013 | CSS                 | miR-155              | Tissue            | 137 ccRCC      | Low expression   | 5.490 2.400–12.52     |
| 2014 | DFS                 | miR-21 & miR-126     | Tissue            | 103 ccRCC      | High risk        | 19.37 4.060–92.44     |
| 2014 | OS                  | miR-630              | Tissue            | 92 ccRCC       | High expression   | 3.021 2.074–5.726     |
| 2014 | DSS                 | miR-21/miR-10b       | Tissue            | 105 ccRCC      | High ratio       | 2.624 1.201–5.736     |
| 2014 | DFS                 | miR-129-3p           | Tissue            | 48 ccRCC       | Low expression   | 3.119 1.060–9.175     |
| 2014 | RFS                 | miR-125b             | Tissue            | 200 ccRCC      | High expression   | 3.931 1.213–12.74     |
| 2015 | OS                  | miR-497              | Tissue            | 86 ccRCC       | Low expression   | 2.583 1.691–6.361     |
| 2015 | DFS                 | miR-210              | Tissue            | 258 ccRCC      | Positive expression | 1.910 1.010–3.310   |
| 2015 | DFS                 | miR-126              | Tissue            | 260 ccRCC      | Negative expression | 0.300 * 0.180–0.500 * |
| 2015 | OS                  | miR-506              | Tissue            | 106 ccRCC      | Low expression   | 3.886 2.179–7.524     |
| 2015 | OS                  | miR-203              | Tissue            | 90 ccRCC       | Low expression   | 3.071 1.719–6.374     |
| 2015 | CSS                 | miR-21               | Tissue            | 45 RCC         | High expression   | 6.460 1.350–30.94     |
| 2015 | CSS                 | piR-43607            | Tissue            | 68 ccRCC       | High expression   | 1.240 * 1.082–1.445 * |
| 2015 | OS                  | miR-124-3p           | Tissue            | 62 ccRCC       | Low expression   | 2.600 * 1.069–7.262 * |
| 2015 | RFS                 | piR-38756            | Tissue            | 72 ccRCC       | High expression   | 3.150 1.960–9.320     |
| 2015 | PFS                 | miR-27a-3p           | Tissue            | 140 ccRCC      | High expression   | 2.710 1.230–6.420     |
| 2016 | DFS                 | miR-194              | Tissue            | 234 ccRCC      | Negative expression | 0.520 0.270–0.980 |
| 2016 | DFS                 | miR-19a              | Tissue            | 197 ccRCC      | High expression   | 2.410 1.217–4.773     |
| 2016 | PFS                 | miR-222-3p           | Tissue            | 74 ccRCC       | High expression   | 2.020 1.510–2.710     |
### Table 3. Cont.

| Year | Prognostic Variable | Prognostic Biomarker | Biological Source | Number of Cases | Poor Prognosis | Prognostic Performance | Reference |
|------|---------------------|----------------------|-------------------|----------------|----------------|------------------------|-----------|
| 2017 | CSS                 | miR-223-3p          | Tissue            | 78 ccRCC       | High expression | 3.510 1.600–7.690      | [66]      |
| 2017 | DFS                 | miR-10b             | Tissue            | 246 ccRCC      | Negative expression | 0.470 * 0.280–0.790 *   | [120]     |
| 2017 | OS                  | miR-766-3p          | Tissue            | 75 RCC         | Low expression   | 2.700 1.310–5.530       | [121]     |
| 2018 | OS                  | miR-566             | Tissue            | 42 ccRCC       | High expression  | 0.060 0.005–0.769       | [122]     |
| 2018 | OS                  | miR-18-5p           | Tissue            | 42 RCC         | High expression  | 0.175 0.032–0.953       | [123]     |
| 2018 | OS                  | miR-663a            | Tissue            | 42 ccRCC       | High expression  | 5.132 1.039–25.350      | [124]     |
| 2018 | OS                  | miR-572             | Tissue            | 42 RCC         | High expression  | 0.174 0.034–0.878       | [125]     |
| 2018 | RFS                 | miR-155-5p & miR-210-3p | Tissue            | 205 ccRCC      | High risk       | 2.700 1.280–5.680       | [100]     |
| 2018 | OS                  | miR-452-5p          | Tissue            | 102 RCC        | High expression  | 1.580 1.070–2.310       | [74]      |
| 2019 | OS                  | miR-23a-5p          | Tissue            | 118 RCC        | High expression  | 3.270 1.552–6.893       | [126]     |
| 2019 | OS                  | miR-183-5p          | Tissue            | 284 ccRCC      | High expression  | 0.550 0.364–0.832       | [127]     |
| 2019 | OS                  | miR-3133            | Tissue            | 135 ccRCC      | Low expression   | 2.802 1.391–5.646       | [128]     |
| 2019 | OS                  | miR-221-5p          | Tissue            | 196 ccRCC      | High expression  | 0.550 0.326–0.926       | [129]     |
| 2019 | PFS                 | piR-51810           | Tissue            | 118 ccRCC      | Low expression   | 0.431 0.190–0.975       | [75]      |
| 2019 | OS                  | miR-142-3p          | Tissue            | 284 RCC        | High expression  | 0.529 0.347–0.796       | [130]     |
| 2019 | OS                  | miR-106b-5p         | Tissue            | 284 ccRCC      | High expression  | 0.496 0.237–0.752       | [131]     |
| 2019 | MFS                 | 4 miR panel         | Tissue            | 83 ccRCC       | High risk        | 12.402 3.586–42.893     | [132]     |
| 2020 | DFS                 | miR-30a-5p<sup>nu</sup> | Tissue            | 227 ccRCC      | High methylation | 5.174 1.228–21.808      | [95]      |

*—univariable analysis; HR—hazard ratio; 95% CI—95% confidence interval; OS—overall survival; DFS—disease-free survival; PFS—progression-free survival; MFS—metastasis-free survival; CSS—cancer-specific survival; RFS—recurrence-free survival.
Liquid Biopsies

Studies on sncRNAs as potential biomarkers for RCC progression and/or disease outcome in liquid biopsies are rather scarce. Let–7i–5p low expression in exosomes from plasma of 65 mRCC patients associated with shorter OS [133]. Fujii and colleagues [134] showed that higher plasma-derived exosomal miR–224 expression levels negatively associated with shorter OS, CSS, and recurrence-free survival (RFS). A subsequent analysis of 67 ccRCC serum samples demonstrated that increased miR–206 and miR–122–5p expression associated with increased risk of disease progression and mortality, although, in multivariable analysis, only miR–206 retained independent value as predictor of PFS [135]. Finally, Dias and colleagues reported that higher miR–210, miR–221, and miR–1233 plasma levels associated with shorter CSS [99]. Detailed information of all relevant studies may be found in Table 4.

4.1.4. SncRNAs as Predictive Biomarkers of Response to Therapy

Tissue-Based Samples

Uncertainties concerning efficacy and deleterious side effects of RCC therapy negatively impact patient management [136–138]. Ideally, each patient should be prescribed the therapy most likely to specifically target and eliminate neoplastic cells, which sets the basis for precision medicine [139]. Considering their involvement in critical metabolic pathways, it is unsurprising that sncRNAs have been implicated in cancer therapy resistance [140–142]. Furthermore, sncRNAs have been proposed as predictors of response to therapy in RCC. Indeed, miR–141 expression levels were shown to predict response to sunitinib, as patients with low levels disclosed a significantly worse response [143]. In a different study, lower expression levels of both miR–155 (a well-known oncomiR) and miR–484 (with biological role yet to be fully understood) associated with increased time to progression (TTP) in a series of 63 mRCC patients (44 responders and 19 non-responders) treated with sunitinib [144]. Recently, Go and colleagues demonstrated that miR–421 was highly expressed in RCC tissues from patients who did not respond to VEGFR–TKI [145]. Table 5 provides additional information on the most relevant studies concerning the predictive value of sncRNAs in RCC.
| Year | Predictive Biomarker | Biological Source | Number of Cases/Cell Lines | Type of Therapy | Main Findings | Reference |
|------|---------------------|-------------------|---------------------------|----------------|--------------|-----------|
| 2012 | multi–miR panels    | Whole blood       | 38 ccRCC                  | Targeted therapy | Several miRs ⇒ prolonged or poor response to sunitinib | [146]     |
| 2013 | miR–141             | Tissue/in vitro   | 20 ccRCC                  | Targeted Therapy | ↓ miR–141 ⇒ poor response to sunitinib | [143]     |
| 2013 | miR–381             | In vitro          | 786–O                     | Chemotherapy     | MiR–381 + 5–FU ⇒ lower proliferation, and ↑ 5–FU efficacy | [147]     |
| 2014 | miR–942             | Tissue/in vitro   | 20 RCC & Caki–2           | Targeted Therapy | MIR–942 ⇒ sunitinib resistance ⇒ ↓ TTP & OS | [148]     |
| 2014 | miR–200c            | In vitro          | HEK293, SN12C, ACHN, 786–O & Caki–1 | Targeted Therapy | Mimic miR–200c ⇒ sensitivity to therapy with TKI | [149]     |
| 2015 | miR–27b             | In vitro/in vivo  | ACHN, 769–P, 786–O & Caki–1 | Chemotherapy     | Overexpressing miR–27b ⇒ sensitizes RCC cells to a variety of anti-cancer drugs, such as doxorubicin | [150]     |
| 2015 | miR–30a             | Tissue/in vivo    | 10 ccRCC & A498 + 786–O  | Targeted Therapy | Exogenously expression of miR–30a ⇒ ↑ sorafenib treatment efficacy | [151]     |
| 2015 | miR–200c            | In vitro          | Caki–1, Caki–2, A498, ACHN, 786–O & 769–P | Chemotherapy | ↓ miR–200c ⇒ resistance to docetaxel | [152]     |
| Year | Predictive Biomarker         | Biological Source | Number of Cases/Cell Lines | Type of Therapy | Main Findings                                      | Reference |
|------|-------------------------------|-------------------|-----------------------------|-----------------|---------------------------------------------------|-----------|
| 2015 | miR–155 & miR–484            | Tissue            | 63 RCC                      | Targeted Therapy | ↓ of both miRs ⇒ better response to sunitinib ⇒ ↑ TTP | [144]     |
| 2015 | miR–124                      | In vitro          | Caki–2                      | Chemotherapy     | ↓ miR–124 ⇒ resistance to doxorubicin and vinblastine | [153]     |
| 2015 | miR–221 & miR–222            | Tissue/in vivo    | 30 ccRCC & 786–O + ACHN     | Targeted Therapy | ↑ of both miRs ⇒ poor response to sunitinib therapy | [154]     |
| 2016 | miR–99b–5p                   | Tissue            | 40 ccRCC                    | Targeted Therapy | MiR–605 ⇒ ↓ after vorinostato and bevacizumab therapy in responders | [155]     |
| 2017 | miR–99b–5p                   | Serum             | 36 ccRCC                    | Targeted Therapy | ↑ of these miRs ⇒ long–term sunitinib response     | [156]     |
| 2017 | miR–144–3p                   | In vitro/in vivo  | 786–O & SN12–PM6 + Nude mice | Targeted Therapy | ↑ miR–144–3p ⇒ ↓ ARID1A and resistance to sunitinib | [157]     |
| 2017 | miR–451                      | In vitro          | ACHN & GRC–1                | Chemotherapy     | MiR–451 knockdown ⇒ ↑ sensitivity to adriamycin therapy | [158]     |
| 2018 | miR–942 & miR–133            | Tissue            | 56 RCC                      | Targeted Therapy | Both miRs ⇒ discriminate between sunitinib responders and non–responders | [159]     |
| 2019 | miR–421                      | Tissue            | 101 MRCC                    | Targeted Therapy | ↑ miR–421 in TKI non–responders                    | [160]     |
| 2019 | miR–376b–3p                  | Tissue            | 132 ccRCC                   | Targeted Therapy | ↓ miR–376b–3p in sunitinib poor responders          | [161]     |
| 2020 | miR–31–5p                    | Exosomes from plasma/in vitro/in vivo | 40 PD MRCC + 786–O + BALB/c nude mice | Targeted Therapy | ↑ miR–31–5p in PD vs non–PD patients’ plasma samples treated with sorafenib | [162]     |

RCC—renal cell carcinoma; ccRCC—clear cell renal cell carcinoma; 5–FU—5–fluorouracil; TTP—time to progression; OS—overall survival; PFS—progression-free survival; TKI—tyrosine kinase inhibitors; mRCC—metastatic renal cell carcinoma; PD—progressive disease; non-PD—non-progressive disease; ↓—downregulation; ↑—upregulation.
Liquid Biopsies

One of the main drawbacks of tissue-based studies is the inability to capture the dynamic nature of sncRNAs’ expression along time, either during disease progression or due to therapeutic intervention. The usage of liquid biopsies might circumvent this limitation, since it allows sample collection at several time points, i.e., prior to, during, and after treatment, enabling patient monitoring. In 2012, Gámez–Pozo and colleagues analyzed the expression of 287 miRs in 38 whole blood samples from patients with advanced RCC treated with sunitinib and constructed multiple models of poor and prolonged response to this TKI. Notably, miR–410, miR–1181, and miR–424 downregulation was associated with prolonged response, whereas low miR–192, miR–193a–3p, and miR–501–3p levels associated with limited response [146]. Additionally, serum miR–605 levels in mccRCC patients treated with vorinostat and bevacizumab were exclusively reduced in the responders’ group, comparing to the disease progression group [156]. Additional studies are summarized in Table 5.

In Vitro Studies

Several studies have been performed in RCC in vitro models in the pursuit of both predictive biomarkers and insights on therapy-resistance mechanisms. Although in vitro models do not fully mimic biological conditions, they allow for the discovery of potential sncRNA-based biomarkers, which may be subsequently validated in clinical samples. Gao and colleagues [149] reported that transfecting mimic miR–200c into ccRCC cell lines resistant to imatinib and sorafenib re-sensitized cells to therapy. Moreover, miR–200c was downregulated in RCC cell lines, whereas one of its targets, CYP1B1, was overexpressed. Remarkably, increased CYP1B1 levels were associated with docetaxel resistance [152]. Additionally, miR–101 downregulation in ccRCC cell lines associated with high UHRF1 (a miR–101 target) levels and, ultimately, to sunitinib resistance [163]. Detailed information on these and other studies can be found in Table 5.

4.2. LncRNAs

As previously mentioned, LncRNAs are a class of ncRNAs with more than 200 base pairs in length [33,34]. These molecules can be further categorized into different groups, depending on their genome location, sequence, morphology, structure, and functional features [164,165]. Most LncRNAs are synthesized by the same biogenesis machinery as mRNAs and endure post-transcriptional modifications, such as 5’ terminal methylguanosine cap (5’ cap), are often spliced in a canonical manner, and some are 3’ polyadenylated [165]. LncRNAs have a fine-tuned regulation by transcription factors and typically display a tissue-specific expression profile [164]. Functionally, LncRNAs have been implicated in a multitude of biological processes, such as nuclear organization through nucleosome remodeling [166], gene-to-gene interactions [167], and as regulators of miRNA expression [168], thus prompting the hypothesis that LncRNAs’ differential expression might be associated with human disease. Indeed, several pathological conditions display aberrant LncRNAs’ expression profile [169], including cancer [170].

4.2.1. LncRNAs in RCT

LncRNAs have been the focus of several research studies aiming at the discovery of novel biomarkers and understanding the biological mechanisms through which they influence the genesis and progression of RCT [171–173]. Compared to their protein-coding counterparts, LncRNAs are considerably less expressed, which might constitute a major pitfall for their use in clinical practice, since robust detection is quite challenging [174]. Nonetheless, the study of these molecules should be promoted, as technological advances might overcome the present limitations. Herein, we highlighted the most relevant studies reporting LncRNAs as potential diagnostic, prognostic, predictive, and monitoring biomarkers in RCT, both in tissue and liquid biopsies.
4.2.2. LncRNAs as Diagnostic Biomarkers

Tissue-Based Samples

Contrarily to snRNAs, published data concerning lncRNAs as RCT diagnostic biomarkers are limited. Over two decades ago, Thrash–Bingham and colleagues [175] reported, for the first time, that lncRNA expression was dissimilar among RCC subtypes. Using semiquantitative PCR, a marked increased expression of lncRNA antisense Hypoxia Inducible Factor (aHIF) in ccRCC, comparatively to pRCC, was disclosed [175]. Technology has evolved and these results were subsequently validated in 2011, when Bertozzi and colleagues [176] detected a differential expression of lncRNA aHIF between RCC and MNT, as well as between non-pRCC and pRCC tissue samples. In another study, comprising 102 ccRCC and 50 NRT, lncRNA CYP4A22–2/3 discriminated ccRCC from NRT with an AUC of 0.790 [177]. In 2016, the expression of lncRNA UC009YBY.1 and lncRNA ENST00000514034 was assessed in a set of 70 ccRCC and 70 MNT by Ren and colleagues [178]. These authors reported that the two lncRNAs could identify RCC tissue with 54.29% sensitivity and 82.86% specificity for the former, and 60.00% sensitivity and 67.14% specificity for the latter [178]. Finally, a recent study reported that lncRNA HOX Transcript Antisense RNA (HOTAIR) might also constitute a ccRCC diagnostic biomarker, disclosing an AUC of 0.9230 [71]. Table 6 summarizes the complete information on relevant published studies reporting lncRNAs as potential RCC diagnostic biomarkers.

| Year | Diagnostic Biomarker | Biological Source | Number of Cases/Controls | Diagnostic Performance | Reference |
|------|----------------------|-------------------|--------------------------|------------------------|-----------|
| 1999 | aHIF | Tissue | 10 ccRCC; 7 pRCC | n.a. | n.a. | n.a. | [175] |
| 2011 | aHIF | Tissue | 26 RCC; 26 MNT | n.a. | n.a. | n.a. | [176] |
| 2014 | AK096725 | Tissue | 70 RCC; 70 MNT | n.a. | n.a. | n.a. | [179] |
| 2015 | TTC34–3 | Tissue | 55 ccRCC; 52 MNT | n.a. | n.a. | 0.990 | [180] |
| 2015 | CYP4A22–2/3 | Tissue | 102 ccRCC; 50 NRT | n.a. | n.a. | 0.790 | [177] |
| 2016 | TRIM52–AS1 | Tissue | 60 RCC; 60 MNT | n.a. | n.a. | n.a. | [181] |
| 2016 | UCA1 | Tissue | 46 RCC; 46 MNT | n.a. | n.a. | n.a. | [182] |
| 2016 | UC009YBY.1 | Tissue | 70 RCC; 70 MNT | 54.3 | 82.9 | 0.700 | [178] |
| 2018 | HOXAIR | Tissue | 24 ccRCC; 24 MNT | n.a. | n.a. | 0.923 | [70] |
| 2016 | 5 lncRNA panel | Serum | 24 ccRCC; 27 AC | 79.2 | 88.9 | 0.900 | [183] |
| 2018 | GIHCG | Serum | 31 Stage I ccRCC; 46 AC | 80.7 | 84.8 | 0.886 | [184] |

MNT—matched normal tissue; NRT—renal normal tissue; RCC—renal cell carcinoma; ccRCC—clear cell renal cell carcinoma; pRCC—papillary renal cell carcinoma; AC—asymptomatic controls; n.a.—not available.

Liquid Biopsies

Based on our literature search, only two relevant studies evaluating the potential of lncRNAs as RCC diagnostic biomarkers in liquid biopsies were found. Wu and colleagues [183] assessed the expression of five lncRNAs (lncRNA–low expression in tumor (LET), Plasmacytoma Variant Translocation 1 (PVT1), Promoter Of CDKN1A Antisense DNA Damage Activated RNA (PANDAR), Phosphatase and Tensin Homolog Pseudogene 1 (PTENP1), and long intergenic non-protein coding RNA 963 (linc00963)) in two sets of ccRCC and AC serum samples. When combined in a panel, these biomarkers identified malignancy with 79.2% sensitivity and 88.9% specificity in the training set (24 ccRCC and 27 AC) and with 67.6% sensitivity and 91.4% specificity in the testing set (37 ccRCC and 35 AC) [183]. Subsequently, serum expression of lncRNA GIHCG was assessed in a set of 46 ccRCC and 46 AC samples. GIHCG expression discriminated ccRCC from healthy donors with 87.0% sensitivity and 84.8% specificity. Remarkably, it could also distinguish early-stage ccRCC from AC (31 stage
I ccRCC vs. 46 ACs) with 80.7% sensitivity and 84.8% specificity [184]. The complete information concerning these studies is provided in Table 6, together with tissue-based studies.

4.2.3. LncRNAs as Prognostic Biomarkers

Tissue-Based Samples

As for snRNAs, several reports on the potential of lncRNAs as RCC prognostic biomarkers in tissue samples have been published. In a series of 102 ccRCC, Ellinger and colleagues [177] showed that patients disclosing low lncRNA Zinc-Finger protein 180-2 (ZNF180-2) expression endured significantly shorter OS. Notably, lower expression of this lncRNA also correlated with shorter CSS and PFS [177]. In another study, expression levels of lncRNA regulator of Akt Signaling Associated With HCC And RCC (lncARSR) were assessed in a set of 205 ccRCC tissues from patients subdivided into high- and low-expression groups. Patients with lncARSR–high expression displayed significantly shorter RFS, doubling the risk of recurrence comparatively to the lncARSR–low expression group [185]. Furthermore, Bao and colleagues [186] reported that lncRNA PVT1 could serve as independent prognostic biomarker in ccRCC. Indeed, patients with high lncRNA PVT1 expression depicted 1.5 and 3.5 times higher risk of death or recurrence, respectively, compared to patients with low lncRNA PVT1 expression [186]. Recently, in a series of tissues from 204 ccRCC patients, Wang and colleagues [187] found that high lncRNA EGFR-antisense RNA 1 (EGFR–AS1) expression levels increased two-fold the risk of death. Table 7 depicts the complete information on these and other relevant studies assessing the potential of lncRNAs for RCC prognostication.
Table 7. LncRNAs as potential prognostic biomarkers in RCC tissues.

| Year | Prognostic Variable | Prognostic Biomarker | Biological Source | Number of Cases | Poor Prognosis | Prognostic Performance | Reference |
|------|---------------------|----------------------|-------------------|-----------------|----------------|-------------------------|-----------|
| 2014 | OS                  | CADM1–AS1            | Tissue            | 64 ccRCC        | Low expression | 0.211 | 0.088–0.504 | [188] |
| 2014 | OS                  | SPRY4–IT1            | Tissue            | 98 ccRCC        | High expression | 3.375 | 1.824–7.391 | [189] |
| 2015 | OS                  | NBAT–1               | Tissue            | 98 ccRCC        | Low expression | 3.701 | 1.261–9.784 | [190] |
| 2015 | OS                  | MALAT1               | Tissue            | 106 ccRCC       | High expression | 3.086 | 1.813–7.025 | [191] |
| 2015 | OS                  | H19                  | Tissue            | 92 ccRCC        | High expression | 3.894 | 1.872–8.014 | [192] |
| 2015 | PFS                 | ZNF180–2             | Tissue            | 102 ccRCC       | Low expression | 0.803 | 0.699–0.922 | [177] |
| 2016 | OS                  | Linc00152            | Tissue            | 77 ccRCC        | High expression | 2.577 | 1.233–5.387 | [193] |
| 2016 | RFS                 | IncARSR              | Tissue            | 205 ccRCC       | High expression | 2.023 | 1.213–3.375 | [185] |
| 2017 | OS                  | TUG1                 | Tissue            | 203 ccRCC       | High expression | 2.337 | 1.451–6.673 | [194] |
| 2017 | OS                  | TCL6                 | Tissue            | 71 ccRCC        | Low expression | 0.130 | 0.020–0.680 | [195] |
| 2017 | OS                  | SLINKY               | Tissue            | 100 ccRCC       | High expression | 8.440 | 1.770–40.23 | [196] |
| 2017 | OS                  | PANDAR               | Tissue            | 62 ccRCC        | High expression | 1.130 | 0.980–5.120 | [197] |
| 2017 | OS                  | MRCCAT1              | Tissue            | 68 ccRCC        | High expression | 2.306 | 1.003–2.849 | [198] |
| 2017 | OS                  | PVT1                 | Tissue            | 50 ccRCC        | High expression | 1.494 | 1.081–2.063 | [199] |
| 2017 | DFS                 | MF12–AS1             | Tissue            | 167 ccRCC       | Positive expression | 4.240 | 2.070–8.700 | [200] |
| 2017 | DFS                 | PVT1                 | Tissue            | 129 ccRCC       | High expression | 3.553 | 1.515–8.329 | [186] |
| 2018 | OS                  | ENSG00000241684      | Tissue            | 61 ccRCC        | Low expression | 5.378 | 2.084–13.88 | [201] |
| 2018 | OS                  | LUCAT1               | Tissue            | 64 ccRCC        | High expression | 3.650 | 1.356–9.826 | [202] |
| 2018 | OS                  | CRNDE                | Tissue            | 112 ccRCC       | High expression | 2.023 | 1.039–3.468 | [203] |
| 2019 | OS                  | EGFR–AS1             | Tissue            | 204 RCC         | High expression | 2.204 | 1.145–4.241 | [187] |
| 2016 | PFS                 | IncARSR              | Plasma            | 71 ccRCC        | High expression | n.a. | n.a. | [204] |
| 2018 | OS                  | GHCG                 | Serum             | 46 ccRCC        | High expression | n.a. | n.a. | [184] |

HR—hazard ratio; 95% CI—95% confidence interval; OS—overall survival; DFS—disease-free survival; PFS—progression-free survival; RFS—recurrence-free survival; RCC—renal cell carcinoma; ccRCC—clear cell renal cell carcinoma; n.a.—not available.
Liquid Biopsies

After literature revision, only two studies reporting on the potential of lncRNAs for RCC’s prognostication in liquid biopsies were found. Qu and colleagues [204] assessed the expression of lncARSR in 71 ccRCC plasma samples and verified that higher expression levels were associated with worse PFS. In the other study, serum samples from 46 ccRCC patients were analyzed and increased GIHCG expression levels associated with lower OS [184]. However, both studies lack biomarker prognostic performance analysis, preventing a more robust evaluation of the potential of lncRNAs assessed in liquid biopsies. Table 7 provides the complete information on these two studies.

4.2.4. LncRNAs as Predictive Biomarkers of Response to Therapy

Considering the limited number of studies assessing the ability of lncRNAs to predict response to therapy in RCC, we decided not to subdivide this section according to sample source. Qu and colleagues analyzed 71 plasma samples from ccRCC patients treated with sunitinib, in which high lncARSR expression levels were found in patients with progressive disease and poor response [204]. In another study, lncRNA Sorafenib Resistance in Renal Cell Carcinoma Associated (lncSRLR) expression was determined in tissue samples from 53 ccRCC patients treated with sorafenib. Patients with poor or no response to sorafenib therapy showed significantly higher expression levels of that lncRNA, which correlated with shorter PFS. In vitro studies revealed that lncSRLR knockdown in sorafenib-resistant RCC cell lines resulted in increased sensitivity to the treatment [205]. Furthermore, studies on RCC cell lines demonstrated a potential positive feedback loop between sunitinib and lncRNA Suppressing Androgen Receptor in Renal Cell Carcinoma (SARCC). Upon treatment with this TKI, lncRNA SARCC expression levels increased, leading to decreased resistance to sunitinib therapy [206]. Finally, a recent study reported that patients with poor response to sorafenib therapy displayed lower lncRNA Growth arrest-specific 5 (GAS5) expression levels. In vitro and in vivo experiments disclosed that overexpression of lncRNA GAS5 resulted in increased sensitivity to sorafenib [207]. Complete information on these studies is summarized in Table 8.

5. Conclusions

In summary, the data presented herein clearly support the feasibility of using ncRNAs as RCT biomarkers, both in tissue and liquid biopsies. Importantly, liquid biopsy-based samples are easily collected, minimally invasive, and may help to overcome the limitations of tissue biopsies. Further studies on ncRNAs should focus on technical and clinical validation, preferably using large-scale multicenter cohorts, allowing to determine whether these novel biomarkers may improve the clinical management of RCT patients. Finally, Figure 2 summarizes and illustrates the most promising
ncRNAs for RCTs’ detection, diagnosis, prognostication, and prediction to therapy response included in this review.

![Figure 2](image_url)

**Figure 2.** Summary of the most promising biomarker candidates for RCT. (A) Several ncRNAs have been proposed as ancillary tools for distinguishing tumor growth from normal tissue. Arrows represent each ncRNA expression level in RCT, comparing to normal samples (“red”—upregulated; “green”—downregulated). (B) Besides the potential use of ncRNAs to detect tumorigenesis, some were reported as capable to differentiate both malignant from benign lesions, and benign from asymptomatic conditions. The arrows represent ncRNA expression level (upper) in RCC, comparing to normal samples (“red”—upregulated; “green”—downregulated). (C) The potential of ncRNAs to stratify high-risk patients has been highly studied in recent years. The arrows represent each ncRNA expression level in patients displaying worse survival, comparing to those with better survival (“red”—upregulated; “green”—downregulated). (D) Lastly, ncRNA expression level has been proposed as potential predictor of therapy response. The arrows show the biological status of each ncRNA for a better response to therapy (“red”—upregulated; “green”—downregulated).

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**References**

1. Bray, F.; Ferlay, J.; Soerjomataram, I.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424. [CrossRef] [PubMed]
2. Maher, E.R. Genomics and epigenomics of renal cell carcinoma. Semin. Cancer Biol. 2013, 23, 10–17. [CrossRef] [PubMed]
3. Moch, H.; Cubilla, A.L.; Humphrey, P.A.; Reuter, V.E.; Ulbright, T.M. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours. Eur. Urol. 2016, 70, 93–105. [CrossRef] [PubMed]
4. Capitanio, U.; Bensalah, K.; Bex, A.; Boorjian, S.A.; Bray, F.; Coleman, J.; Gore, J.L.; Sun, M.; Wood, C.; Russo, P. Epidemiology of Renal Cell Carcinoma. *Eur. Urol.* 2019, 75, 638–648. [CrossRef] [PubMed]

5. Patard, J.-J.; Leray, E.; Rodriguez, A.; Rioux-Leclercq, N.; Guille, F.; Lobel, B. Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur. Urol.* 2003, 44, 226–232. [CrossRef]

6. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Daibestani, S.; Fernández-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyn, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur. Urol.* 2019, 75, 799–810. [CrossRef]

7. Rosenberg, S.A. Interleukin 2 for patients with renal cancer. *Nat. Clin. Pract. Oncol.* 2007, 4, 497. [CrossRef]

8. Rosenberg, J.; Milam, J.; Johnson, D.; et al. A randomized trial of interferon alfa-2a versus placebo in patients with advanced renal cell carcinoma. *Proc. Natl. Acad. Sci. U. S. A.* 1994, 91, 1043–1046. [CrossRef] [PubMed]

9. Rosenberg, S.A.;车根, J.; et al. A phase III trial of interleukin-2 therapy in patients with metastatic renal cell carcinoma: The 1979–1988 experience. *J. Clin. Oncol.* 2012, 30, 1303–1308. [CrossRef] [PubMed]

10. Rosenberg, S.; et al. Interleukin-2 therapy in renal cell carcinoma. *J. Urol.* 2000, 164, 97–102. [CrossRef] [PubMed]

11. Capitanio, U.; Bensalah, K.; Bex, A.; Boorjian, S.A.; Bray, F.; Coleman, J.; Gore, J.L.; Sun, M.; Wood, C.; Russo, P. Epidemiology of Renal Cell Carcinoma. *Eur. Urol.* 2019, 75, 74–84. [CrossRef] [PubMed]

12. Patard, J.-J.; Leray, E.; Rodriguez, A.; Rioux-Leclercq, N.; Guille, F.; Lobel, B. Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur. Urol.* 2003, 44, 226–232. [CrossRef]

13. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Daibestani, S.; Fernández-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyn, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur. Urol.* 2019, 75, 799–810. [CrossRef]

14. Rosenberg, S.A. Interleukin 2 for patients with renal cancer. *Nat. Clin. Pract. Oncol.* 2007, 4, 497. [CrossRef]

15. Capitanio, U.; Bensalah, K.; Bex, A.; Boorjian, S.A.; Bray, F.; Coleman, J.; Gore, J.L.; Sun, M.; Wood, C.; Russo, P. Epidemiology of Renal Cell Carcinoma. *Eur. Urol.* 2019, 75, 74–84. [CrossRef] [PubMed]

16. Patard, J.-J.; Leray, E.; Rodriguez, A.; Rioux-Leclercq, N.; Guille, F.; Lobel, B. Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur. Urol.* 2003, 44, 226–232. [CrossRef]

17. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Daibestani, S.; Fernández-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyn, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur. Urol.* 2019, 75, 799–810. [CrossRef]

18. Rosenberg, S.A. Interleukin 2 for patients with renal cancer. *Nat. Clin. Pract. Oncol.* 2007, 4, 497. [CrossRef]

19. Capitanio, U.; Bensalah, K.; Bex, A.; Boorjian, S.A.; Bray, F.; Coleman, J.; Gore, J.L.; Sun, M.; Wood, C.; Russo, P. Epidemiology of Renal Cell Carcinoma. *Eur. Urol.* 2019, 75, 74–84. [CrossRef] [PubMed]

20. Patard, J.-J.; Leray, E.; Rodriguez, A.; Rioux-Leclercq, N.; Guille, F.; Lobel, B. Correlation between symptom graduation, tumor characteristics and survival in renal cell carcinoma. *Eur. Urol.* 2003, 44, 226–232. [CrossRef]

21. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Daibestani, S.; Fernández-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyn, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. *Eur. Urol.* 2019, 75, 799–810. [CrossRef]

22. Rosenberg, S.A. Interleukin 2 for patients with renal cancer. *Nat. Clin. Pract. Oncol.* 2007, 4, 497. [CrossRef]

23. Capitanio, U.; Bensalah, K.; Bex, A.; Boorjian, S.A.; Bray, F.; Coleman, J.; Gore, J.L.; Sun, M.; Wood, C.; Russo, P. Epidemiology of Renal Cell Carcinoma. *Eur. Urol.* 2019, 75, 74–84. [CrossRef] [PubMed]
24. Henrique, R.; Luís, A.S.; Jerónimo, C. The Epigenetics of Renal Cell Tumors: From Biology to Biomarkers. *Front. Genet.* 2012, 3, 94. [CrossRef] [PubMed]

25. Morris, M.R.; Latif, F. The epigenetic landscape of renal cancer. *Nat. Rev. Nephrol.* 2016, 13, 47–60. [CrossRef]

26. Jerónimo, C.; Henrique, R. Epigenetic biomarkers in urological tumors: A systematic review. *Cancer Lett.* 2014, 342, 264–274. [CrossRef]

27. Beermann, J.; Piccoli, M.-T.; Viereck, J.; Thum, T. Non-coding RNAs in Development and Disease: Background, Mechanisms, and Therapeutic Approaches. *Physiol. Rev.* 2016, 96, 1297–1325. [CrossRef]

28. Geisler, S.; Coller, J. RNA in unexpected places: Long non-coding RNA functions in diverse cellular contexts. *Nat. Rev. Mol. Cell Biol.* 2013, 14, 699–712. [CrossRef]

29. Berezikov, E. Evolution of microRNA diversity and regulation in animals. *Nat. Rev. Genet.* 2011, 12, 846–860. [CrossRef]

30. Vidigal, J.A.; Ventura, A. The biological functions of miRNAs: Lessons from in vivo studies. *Trends Cell Biol.* 2014, 25, 137–147. [CrossRef]

31. Kim, V.N.; Han, J.; Siomi, M.C. Biogenesis of small RNAs in animals. *Nat. Rev. Mol. Cell Biol.* 2009, 10, 126–139. [CrossRef]

32. Czech, B.; Hannon, G. Small RNA sorting: Matchmaking for Argonautes. *Nat. Rev. Genet.* 2010, 12, 19–31. [CrossRef]

33. Mercer, T.R.; Dinger, M.E.; Mattick, J.W. Long non-coding RNAs: Insights into functions. *Nat. Rev. Genet.* 2009, 10, 155–159. [CrossRef] [PubMed]

34. Quinn, J.J.; Chang, H.Y. Unique features of long non-coding RNA biogenesis and function. *Nat. Rev. Genet.* 2015, 17, 47–62. [CrossRef] [PubMed]

35. Grimaldi, A.; Zarone, M.R.; Irace, C.; Zappavigna, S.; Lombardi, A.; Kawasaki, H.; Caraglia, M.; Misso, G. Non-coding RNAs as a new dawn in tumor diagnosis. *Semin. Cell Dev. Biol.* 2018, 78, 37–50. [CrossRef] [PubMed]

36. Treiber, T.; Treiber, N.; Meister, G. Publisher Correction: Regulation of microRNA biogenesis and its crosstalk with other cellular pathways. *Nat. Rev. Mol. Cell Biol.* 2019, 20, 321. [CrossRef] [PubMed]

37. Ha, M.; Kim, V.N. Regulation of microRNA biogenesis. *Nat. Rev. Mol. Cell Biol.* 2014, 15, 509–524. [CrossRef] [PubMed]

38. O’Brien, J.; Hayder, H.; Zayed, Y.; Peng, C. Overview of MicroRNA Biogenesis, Mechanisms of Actions, and Circulation. *Front. Endocrinol.* 2018, 9, 402. [CrossRef] [PubMed]

39. Aravin, A.A.; Naumova, N.M.; Tulin, A.V.; Vagin, V.V.; Rozovsky, Y.M.; Gvozdev, V. Double-stranded RNA-mediated silencing of genomic tandem repeats and transposable elements in the D. melanogaster germline. *Curr. Biol.* 2001, 11, 1017–1027. [CrossRef] [PubMed]

40. Vagin, V.V.; Sigova, A.; Li, C.; Gvozdev, V.; Seitz, H.; Zamore, P.D. A Distinct Small RNA Pathway Silences Selfish Genetic Elements in the Germline. *Science* 2006, 313, 320–324. [CrossRef] [PubMed]

41. Girard, A.; Sachidanandam, R.; Hannon, G.; Carmell, M.A. A germline-specific class of small RNAs binds mammalian Piwi proteins. *Nature* 2006, 442, 199–202. [CrossRef] [PubMed]

42. Ozata, D.M.; Gainetdinov, I.; Zoch, A.; O’Carroll, D.; Zamore, P.D. PIWI-interacting RNAs: Small RNAs with big functions. *Nat. Rev. Genet.* 2018, 20, 89–108. [CrossRef] [PubMed]

43. Calin, G.A.; Dumitru, C.D.; Shimizu, M.; Bichi, R.; Zupo, S.; Noch, E.; Aldler, H.; Rattan, S.; Keating, M.; Rai, K.; et al. Frequent deletions and down-regulation of micro–RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc. Natl. Acad. Sci. USA* 2002, 99, 15524–15529. [CrossRef] [PubMed]

44. The Cancer Genome Atlas Research Network; Cancer Genome Atlas Research Network Comprehensive molecular characterization of clear cell renal cell carcinoma. *Nature* 2013, 499, 43–49. [CrossRef] [PubMed]

45. Lin, S.; Gregory, R.I. MicroRNA biogenesis pathways in cancer. *Nat. Rev. Cancer* 2015, 15, 321–333. [CrossRef]

46. Guil, S.; Esteller, M. DNA methylomes, histone codes and miRNAs: Tying it all together. *Int. J. Biochem. Cell Biol.* 2009, 41, 87–95. [CrossRef]

47. Takamizawa, J.; Chamoto, K.; Tsuji, T.; Funamoto, H.; Kosaka, A.; Matsuzaka, J.; Sato, T.; Konishi, H.; Fujio, K.; Yamamoto, K.; et al. Reduced Expression of the let-7 MicroRNAs in Human Lung Cancers in Association with Shortened Postoperative Survival. *Cancer Res.* 2004, 64, 3753–3756. [CrossRef]

48. Nakajima, G.; Hayashi, K.; Xi, Y.; Kudo, K.; Uchida, K.; Takasaki, K.; Yamamoto, M.; Ju, J. Non–coding MicroRNAs hsa–let–7g and hsa–miR–181b are Associated with Chemoresponse to S–I in Colon Cancer. *Cancer Genom. Proteom.* 2006, 3, 317–324.
49. Cheng, Y.; Wang, Q.; Jiang, W.; Bian, Y.; Zhou, Y.; Gou, A.; Zhang, W.; Fu, K.; Shi, W. Emerging roles of piRNAs in cancer: Challenges and prospects. *Aging* 2019, 11, 9932–9946. [CrossRef]

50. Yu, Y.; Xiao, J.; Hann, S.S. The emerging roles of PIWI-interacting RNA in human cancers. *Cancer Manag. Res.* 2019, 11, 5895–5909. [CrossRef]

51. Busch, J.; Ralla, B.; Jung, M.; Wotschowsky, Z.; Trujillo-Arribas, E.; Schwabe, P.; Kilic, E.; Fendler, A.; Jung, K. Piwi-interacting RNAs as novel prognostic markers in clear cell renal cell carcinomas. *J. Exp. Clin. Cancer Res.* 2015, 34, 61. [CrossRef] [PubMed]

52. Li, Y.; Wu, X.; Gao, H.; Jin, J.M.; Li, A.X.; Kim, Y.S.; Pal, S.K.; Nelson, R.A.; Lau, C.M.; Guo, C.; et al. Piwi-Interacting RNAs (piRNAs) Are Dysregulated in Renal Cancer Carcinoma and Associated with Tumor Metastasis and Cancer-Specific Survival. *Mol. Med.* 2015, 21, 381–388. [CrossRef] [PubMed]

53. Iliev, R.; Fedorko, M.; Machackova, T.; Mlcochova, H.; Svoboda, M.; Pacik, D.; Dolezel, J.; Stanik, M.; Capoor, M.N. Expression Levels of PIWI-interacting RNA, piR-823, Are Deregulated in Tumor Tissue, Blood Serum and Urine of Patients with Renal Cell Carcinoma. *Anticancer. Res.* 2016, 36, 6419–6424. [CrossRef] [PubMed]

54. Wotschofsky, Z.; Busch, J.; Kempkensteffen, C.; Weikert, S.; Schaser, K.D.; Melcher, I.; Kilic, E.; Miller, K.; Kristiansen, G.; et al. Diagnostic and prognostic potential of differentially expressed miRNAs between metastatic and non-metastatic renal cancer cells at the time of nephrectomy. *Clin. Chim. Acta* 2013, 416, 5–10. [CrossRef]

55. Silva-Santos, R.M.; Costa-Pinheiro, P.; Luis, A.; Antunes, L.; Lobo, F.; Oliveira, J.; Henrique, R.; Jeronimo, C. MicroRNA profile: A promising ancillary tool for accurate renal cell tumour diagnosis. *Br. J. Cancer* 2013, 109, 2646–2653. [CrossRef]

56. Jung, M.; Mollenkopf, H.-J.; Grimm, C.H.; Wagner, I.; Albrecht, M.; Waller, T.; Pilarsky, C.; Johannsen, M.; Stephan, C.; Lehrach, H.; et al. MicroRNA profiling of clear cell renal cell cancer identifies a robust signature to define renal malignancy. *J. Cell. Mol. Med.* 2009, 13, 3918–3928. [CrossRef]

57. Fridman, E.; Dotan, Z.; Barshack, I.; Ben David, M.; Dov, A.; Tabak, S.; Zion, O.; Benjamin, S.; Benjamin, H.; Kuker, H.; et al. Accurate Molecular Classification of Renal Tumors Using MicroRNA Expression. *J. Mol. Diagn.* 2010, 12, 687–696. [CrossRef]

58. Faragalla, H.; Yousef, Y.M.; Scorilas, A.; Khalil, B.; White, N.M.; Mejia-Guerrero, S.; Khella, H.; Jewett, M.A.; Evans, A.; Lichner, Z.; et al. The Clinical Utility of miR-21 as a Diagnostic and Prognostic Marker for Renal Cell Carcinoma. *J. Mol. Diagn.* 2012, 14, 385–392. [CrossRef]

59. Wach, S.; Nolte, E.; Theil, A.; Stöhr, C.; Rau, T.T.; Hartmann, A.; Ekici, A.; Keck, B.; Taubert, H.; Waldek, B. MicroRNA profiles classify papillary renal cell carcinoma subtypes. *Br. J. Cancer* 2013, 109, 714–722. [CrossRef]

60. Zaravinos, A.; Lambrou, G.I.; Mourmouras, N.; Katayfogiots, P.; Papagregoriou, G.; Giannikou, K.; Delakas, D.; Deltas, C. New miRNA Profiles Accurately Distinguish Renal Cell Carcinomas and Upper Tract Urothelial Carcinomas from the Normal Kidney. *PLoS ONE* 2014, 9, e91646. [CrossRef]

61. Chen, X.; Wang, X.; Ruan, A.; Han, W.; Zhao, Y.; Lu, X.; Xiao, P.; Shi, H.; Wang, R.; Chen, L.; et al. miR-141 Is a Key Regulator of Renal Cell Carcinoma Proliferation and Metastasis by Controlling EphA2 Expression. *Clin. Cancer Res.* 2014, 20, 2617–2630. [CrossRef] [PubMed]

62. Chen, X.; Ruan, A.; Wang, X.; Han, W.; Wang, R.; Lou, N.; Ruan, H.; Qu, B.; Yang, H.; Zhang, X. miR–129–3p, as a diagnostic and prognostic biomarker for renal cell carcinoma, attenuates cell migration and invasion via downregulating multiple metastasis–related genes. *J. Cancer Res. Clin. Oncol.* 2014, 140, 1295–1304. [CrossRef] [PubMed]

63. Vergho, D.; Knetz, S.; Kalogirou, C.; Burger, M.; Krebs, M.; Rosenwald, A.; Spahn, M.; Löser, A.; Kocot, A.; Riedmüller, H.; et al. Impact of miR-21, miR-126 and miR-221 as Prognostic Factors of Clear Cell Renal Cell Carcinoma with Tumor Thrombus of the Inferior Vena Cava. *PLoS ONE* 2014, 9, e109877. [CrossRef] [PubMed]

64. Papadopoulos, E.I.; Petraki, C.; Gregorakis, A.; Fragoulis, E.G.; Scorilas, A. Clinical evaluation of microRNA-145 expression in renal cell carcinoma: A promising molecular marker for discriminating and staging the clear cell histological subtype. *Boil. Chem.* 2016, 397, 529–539. [CrossRef]

65. Liep, J.; Kilic, E.; Meyer, H.A.; Busch, J.; Jung, K.; Rabien, A. Cooperative Effect of miR–141–3p and miR–145–5p in the Regulation of Targets in Clear Cell Renal Cell Carcinoma. *PLoS ONE* 2016, 11, e0157801. [CrossRef] [PubMed]

66. Kovalik, C.G.; Palmer, D.A.; Sullivan, T.B.; Teebagy, P.A.; Dugan, J.M.; Libertino, J.A.; Burks, E.J.; Canes, D.; Rieger-Christ, K.M. Profiling microRNA from nephrectomy and biopsy specimens: Predictors of progression and survival in clear cell renal cell carcinoma. *BJU Int.* 2017, 120, 428–440. [CrossRef]
67. Toraih, E.A.; Ibrahim, A.T.; Fawzy, M.S.; Hussein, M.H.; Al-Qahtani, S.A.M.; Shaalan, A.A.M. MicroRNA-34a: A Key Regulator in the Hallmarks of Renal Cell Carcinoma. *Oxidative Med. Cell. Longev.* 2017, 2017, 1–21. [CrossRef]

68. Di Meo, A.; Saleeb, R.; Wala, S.J.; Khella, H.W.; Ding, Q.; Zhai, H.; Krishan, K.; Krizova, A.; Gabril, M.; Evans, A.; et al. A miRNA-based classification of renal cell carcinoma subtypes by PCR and in situ hybridization. *Oncotarget* 2017, 9, 2092–2104. [CrossRef]

69. Yadav, S.; Khandelwal, M.; Seth, A.; Saini, A.; Dogra, P.N.; Sharma, A. Serum microRNA Expression Profiling: Potential Diagnostic Implications of a Panel of Serum microRNAs for Clear Cell Renal Cell Cancer. *Urology* 2017, 104, 64–69. [CrossRef]

70. Bhat, N.S.; Colden, M.; Dar, A.A.; Saini, S.; Arora, P.; Shahryari, V.; Yamamura, S.; Tanaka, Y.; Kato, T.; Majid, S.; et al. MicroRNA–770 Regulates E-cadherin–alphaE-catenin Complex and Promotes Renal Cell Carcinoma. *Mol. Cancer Ther.* 2018, 17, 2840–2848. [CrossRef]

71. Dasgupta, P.; Kulkarni, P.; Majid, S.; Shahryari, V.; Hashimoto, Y.; Bhat, N.S.; Shiina, M.; Deng, G.; Saini, S.; Tabatabai, Z.L.; et al. MicroRNA-203 Inhibits Long Noncoding RNA HOTAIR and Regulates Tumorigenesis through Epithelial-to-mesenchymal Transition Pathway in Renal Cell Carcinoma. *Mol. Cancer Ther.* 2018, 17, 1061–1069. [CrossRef] [PubMed]

72. Kulkarni, P.; Dasgupta, P.; Bhat, N.S.; Shahryari, V.; Shiina, M.; Hashimoto, Y.; Majid, S.; Deng, G.; Saini, S.; Tabatabai, Z.L.; et al. Elevated miR–182–5p Associates with Renal Cancer Cell Mitotic Arrest through Diminished MALAT-1 Expression. *Mol. Cancer Res.* 2018, 16, 1750–1760. [CrossRef] [PubMed]

73. Chen, X.; Lou, N.; Ruan, A.; Qiu, B.; Yan, Y.; Wang, X.; Du, Q.; Ruan, H.; Han, W.; Wei, H.; et al. miR–224/miR–141 ratio as a novel diagnostic biomarker in renal cell carcinoma. *Oncol. Lett.* 2018, 16, 1666–1674. [CrossRef] [PubMed]

74. Zhai, W.; Li, S.; Zhan, J.; Chen, Y.; Ma, J.; Kong, W.; Gong, D.; Zheng, J.; Xue, W.; Xu, Y. Sunitinib–suppressed miR–452–5p facilitates renal cancer cell invasion and metastasis through modulating SMAD4/SMAD7 signals. *Mol. Cancer* 2018, 17, 157. [CrossRef] [PubMed]

75. Zhao, C.; Tolkach, Y.; Schmidt, D.; Toma, M.; Muders, M.H.; Kristiansen, G.; Müller, S.C.; Ellinger, J. Mitochondrial PIWI-interacting RNAs are novel biomarkers for clear cell renal cell carcinoma. *World J. Urol.* 2018, 37, 1639–1647. [CrossRef]

76. Li, J.; Chen, C.; Shi, Z. The biological roles and clinical implications of microRNAs in clear cell renal cell carcinoma. *J. Cell. Physiol.* 2017, 233, 4458–4465. [CrossRef]

77. Wulfken, L.M.; Moritz, R.; Ohlmann, C.; Holdenrieder, S.; Jung, V.; Becker, F.; Herrmann, E.; Walgenbach-Brüning, G.; Von Ruecker, A.; Müller, S.C.; et al. MicroRNAs in Renal Cell Carcinoma: Diagnostic Implications of serum miR-1233 Levels. *PLoS ONE* 2011, 6, e25787. [CrossRef]

78. Zhao, A.; Li, G.; Péoc’h, M.; Genin, C.; Gigante, M. Serum miR-210 as a novel biomarker for molecular diagnosis of clear cell renal cell carcinoma. *Exp. Mol. Pathol.* 2013, 94, 115–120. [CrossRef]

79. Zhang, W.; Ni, M.; Su, Y.; Wang, H.; Zhu, S.; Zhao, A.; Li, G. MicroRNAs in Serum Exosomes as Potential Biomarkers in Clear-cell Renal Cell Carcinoma. *Eur. Urol. Focus* 2018, 4, 412–419. [CrossRef]

80. Tusong, H.; Maolakuerban, N.; Guan, J.; Rexiati, M.; Wang, W.-G.; Azhati, B.; Nuerrula, Y.; Wang, Y.-J. Functional analysis of serum microRNAs miR-21 and miR-106a in renal cell carcinoma. *Cancer Biomark.* 2017, 18, 79–85. [CrossRef]

81. Lou, N.; Ruan, A.-M.; Qiu, B.; Bao, L.; Xu, Y.-C.; Zhao, Y.; Sun, R.-L.; Zhang, S.-T.; Xu, G.-H.; Ruan, H.-L.; et al. miR–144–3p as a novel plasma diagnostic biomarker for clear cell renal cell carcinoma. *Urol. Oncol.* 2017, 35, 36.e7. [CrossRef] [PubMed]

82. Butz, H.; Nofech-Mozes, R.; Ding, Q.; Khella, H.W.; Szabó, P.M.; Jewett, M.; Finelli, A.; Lee, J.; Ordon, M.; Stewart, R.; et al. Exosomal MicroRNAs Are Diagnostic Biomarkers and Can Mediate Cell–Cell Communication in Renal Cell Carcinoma. *Eur. Urol. Focus* 2016, 2, 210–218. [CrossRef] [PubMed]

83. Mytsyk, Y.; Dosenko, V.; Borys, Y.; Kucher, A.; Gazdikova, K.; Büsselberg, D.; Caprnda, M.; Kruzliak, P.; Farrow, A.A.; Lubov, M. MicroRNA-15a expression measured in urine samples as a potential biomarker of renal cell carcinoma. *Int. Urol. Nephrol.* 2018, 50, 851–859. [CrossRef] [PubMed]

84. Redova, M.; Poprach, A.; Nekvindova, J.; Iliev, R.; Radova, L.; Lakomy, R.; Svoboda, M.; Vyzula, R.; Slaby, O. Circulating miR-378 and miR-451 in serum are potential biomarkers for renal cell carcinoma. *J. Transl. Med.* 2012, 10, 55. [CrossRef]
85. Iwamoto, H.; Kanda, Y.; Sejima, T.; Osaki, M.; Okada, F.; Takenaka, A. Serum miR-210 as a potential biomarker of early clear cell renal cell carcinoma. *Int. J. Oncol.* 2013, 44, 53–58. [CrossRef]

86. Teixeira, A.L.; Ferreira, M.; Silva, J.; Gomes, M.; Dias, F.; Santos, J.I.; Maurício, J.; Lobo, F.; Medeiros, R. Higher circulating expression levels of miR-221 associated with poor overall survival in renal cell carcinoma patients. *Tumor Biol.* 2013, 35, 4057–4066. [CrossRef]

87. Wang, C.; Hu, J.; Lu, M.; Gu, H.; Zhou, X.; Chen, X.; Zen, K.; Zhang, C.-Y.; Zhang, T.; Ge, J.; et al. A panel of five serum miRNAs as a potential diagnostic tool for early-stage renal cell carcinoma. *Sci. Rep.* 2015, 5, 7610. [CrossRef]

88. Fedorko, M.; Staník, M.; Iliev, R.; Rédová-Lojová, M.; Machacková, T.; Svoboda, M.; Pacík, D.; Dolezel, J.; Slabý, O. Combination of MiR-378 and MiR-210 Serum Levels Enables Sensitive Detection of Renal Cell Carcinoma. *Int. J. Mol. Sci.* 2015, 16, 23382–23389. [CrossRef]

89. Li, G.; Zhao, A.; Péoch, M.; Cottier, M.; Mottet, N. Detection of urinary cell-free miR-210 as a potential tool of liquid biopsy for clear cell renal cell carcinoma. *Urol. Oncol. Semin. Orig. Investig.* 2017, 35, 294–299. [CrossRef]

90. Fedorko, M.; Jurácek, J.; Staník, M.; Svoboda, M.; Poprach, A.; Buchler, T.; Pacík, D.; Dolezel, J.; Slabý, O. Detection of let-7 miRNAs in urine supernatant as potential diagnostic approach in non-metastatic clear-cell renal cell carcinoma. *Biochem. Med.* 2017, 27, 411–417. [CrossRef]

91. Chanudet, E.; Wozniak, M.B.; Bouaoun, L.; Byrnes, G.B.; Mukeria, A.; Zaridze, D.G.; Brennan, P.; Muller, D.C.; Sceolo, G. Large-scale genome-wide screening of circulating microRNAs in clear cell renal cell carcinoma reveals specific signatures in late-stage disease. *Int. J. Cancer* 2017, 141, 1730–1740. [CrossRef] [PubMed]

92. Wang, X.; Wang, T.; Chen, C.; Wu, Z.; Bui, P.; Li, S.; Chen, B.; Liu, R.; Zhang, K.; Li, W.; et al. Serum exosomal miR-210 as a potential biomarker for clear cell renal cell carcinoma. *J. Biochem.* 2018, 120, 1492–1502. [CrossRef] [PubMed]

93. Liu, S.; Deng, X.; Zhang, J. Identification of dysregulated serum miR–508–3p and miR–885–5p as potential diagnostic biomarkers of clear cell renal carcinoma. *Mol. Med. Rep.* 2019, 20, 5075–5083. [CrossRef] [PubMed]

94. Di Meo, A.; Brown, M.D.; Finelli, A.; Jewett, M.A.; Diamandis, E.P.; Mac-Way, F. Prognostic urinary miRNAs for assessment of small renal masses. *Clin. Biochem.* 2019, 75, 15–22. [CrossRef]

95. Outeiro–Pinho, G.; Barros-Silva, D.; Aznar, E.; Sousa, A.-I.; Vieira-Coimbra, M.; Oliveira, J.; Gonçalves, C.S.; Costa, B.M.; Junker, K.; Henrique, R.; et al. MicroRNA–30a–5p(me): A novel diagnostic and prognostic biomarker for clear cell renal cell carcinoma in tissue and urine samples. *J. Exp. Clin. Cancer Res.* 2020, 39, 98. [CrossRef]

96. Wang, G.; Chen, L.; Meng, J.; Chen, M.; Zhuang, L.; Zhang, L. Overexpression of microRNA-100 predicts an unfavorable prognosis in renal cell carcinoma. *Int. J. Urol.* 2013, 20, 373–379. [CrossRef]

97. Zhao, J.-J.; Chen, P.-J.; Duan, R.-Q.; Li, K.-J.; Wang, Y.-Z.; Li, Y. Up-regulation of miR-630 in clear cell renal cancer regulates ISCU and correlates with good prognosis. *Br. J. Cancer* 2013, 108, 1133–1142. [CrossRef] [PubMed]

98. Samaan, S.; Khella, H.W.; Girgis, A.; Scorilas, A.; Lianidou, E.; Gabril, M.; Krylov, S.N.; Jewett, M.; Ólafsdóttir, J.; et al. Serum miR-210 as a potential biomarker for clear cell renal cell carcinoma. *Int. Urol. Nephrol.* 2017, 49, 468–477. [CrossRef] [PubMed]

99. Wang, X.; Wang, T.; Chen, C.; Wu, Z.; Bai, P.; Li, S.; Chen, B.; Liu, R.; Zhang, K.; Li, W.; et al. A panel of miR-27a-3p as an independent predictive factor for recurrence in clear cell renal cell carcinoma. *Int. J. Clin. Exp. Pathol.* 2015, 8, 4057–4066. [CrossRef]

100. Chanudet, E.; Wozniak, M.B.; Bouaoun, L.; Byrnes, G.B.; Mukeria, A.; Zaridze, D.G.; Brennan, P.; Muller, D.C.; Sceolo, G. Large-scale genome-wide screening of circulating microRNAs in clear cell renal cell carcinoma reveals specific signatures in late-stage disease. *Int. J. Cancer* 2017, 141, 1730–1740. [CrossRef] [PubMed]

101. McCormick, R.I.; Blick, C.; Teixeira, A.L.; Ferreira, M.; Adem, B.; Bastos, N.; Vieira, J.; Fernandes, M.; Sequeira, M.I.; Mauricio, J.; Lobo, F.; et al. Plasmatic miR-210, miR-221 and miR-1233 profile: Potential liquid biopsies candidates for clear cell renal cell carcinoma. *Clin. Biochem.* 2017, 50, 589–594. [CrossRef]

102. Nakata, W.; Uemura, M.; Sato, M.; Fujita, K.; Jingushi, K.; Ueda, Y.; Kitae, K.; Tsujikawa, K.; Nonomura, N.; Oue, N.; et al. Detection of let-7 miRNAs in urine supernatant as potential diagnostic approach in non-metastatic clear-cell renal cell carcinoma. *Int. J. Cancer* 2017, 141, 1730–1740. [CrossRef] [PubMed]

103. Shinmei, S.; Sakamoto, N.; Goto, K.; Sentani, K.; Anami, K.; Hayashi, T.; Teishima, J.; Matsubara, A.; Oue, N.; Kitadai, Y.; et al. MicroRNA-155 is a predictive marker for survival in patients with clear cell renal cell carcinoma. *Int. J. Urol.* 2012, 20, 468–477. [CrossRef] [PubMed]
104. Hildebrandt, M.A.T.; Gu, J.; Lin, J.; Ye, Y.; Tan, W.; Tamboli, P.; Wood, C.G.; Wu, X. Hsa-miR-9 methylation status is associated with cancer development and metastatic recurrence in patients with clear cell renal cell carcinoma. *Oncogene* 2010, 29, 5724–5728. [CrossRef]

105. Wu, X.; Weng, L.; Li, X.; Guo, C.; Pal, S.K.; Jin, J.M.; Li, Y.; Nelson, R.A.; Mu, B.; Onami, S.H.; et al. Identification of a 4-microRNA Signature for Clear Cell Renal Cell Carcinoma Metastasis and Prognosis. *PLoS ONE* 2012, 7, e35661. [CrossRef]

106. Gebauer, K.; Peters, I.; Dubrowinskaja, N.; Hennenlotter, J.; Abbas, M.; Scherer, R.; Tezval, H.; Merseburger, A.S.; Stenzl, A.; A Kuczyk, M.; et al. Hsa-mir–124–3 CpG island methylation is associated with advanced tumours and disease recurrence of patients with clear cell renal cell carcinoma. *Br. J. Cancer* 2013, 108, 131–138. [CrossRef]

107. Goto, K.; Oue, N.; Shinmei, S.; Sentani, K.; Sakamoto, N.; Naito, Y.; Hayashi, T.; Teishima, J.; Matsubara, A.; Yasui, W. Expression of miR-486 is a potential prognostic factor after nephrectomy in advanced renal cell carcinoma. *Mol. Clin. Oncol.* 2012, 1, 235–240. [CrossRef]

108. Vergho, D.C.; Kneitz, S.; Rosenwald, A.; Scherer, C.; Spahn, M.; Burger, M.; Riedmiller, H.; Kneitz, B. Combination of expression levels of miR-21 and miR-126 is associated with cancer-specific survival in clear-cell renal cell carcinoma. *BMC Cancer* 2014, 14, 25. [CrossRef]

109. Fritz, H.K.; Lindgren, D.; Ljungberg, B.; Axelson, H.; Dahlbäck, B. The miR(21/10b) ratio as a prognostic marker in clear cell renal cell carcinoma. *Eur. J. Cancer* 2014, 50, 1758–1765. [CrossRef]

110. Hu, Q.; Liu, Z.; Pan, D.; Zhang, W.; Xu, L.; Zhu, Y.; Liu, H.; Xu, J. Tumor miR-125b predicts recurrence and survival of patients with clear-cell renal cell carcinoma after surgical resection. *Cancer Sci.* 2014, 105, 1427–1434. [CrossRef]

111. Zhao, X.; Zhao, Z.; Xu, W.; Hou, J.; Du, X. Down-regulation of miR-497 is associated with poor prognosis in renal cancer. *Int. J. Clin. Exp. Pathol.* 2015, 8, 758–764. [PubMed]

112. Khella, H.W.; Scorilas, A.; Mozes, R.; Mirham, L.; Lianidou, E.; Krylov, S.N.; Lee, J.Y.; Ordon, M.; Stewart, R.; Jewett, M.A.; et al. Low Expression of miR-126 Is a Prognostic Marker for Metastatic Clear Renal Cell Carcinoma. *Am. J. Pathol.* 2015, 185, 693–703. [CrossRef] [PubMed]

113. Yang, F.-Q.; Zhang, H.-M.; Chen, S.-J.; Yan, Y.; Zheng, J.-H. MiR–506 is down–regulated in clear cell renal cell carcinoma and inhibits cell growth and metastasis via targeting FLOT. *PLoS ONE* 2015, 10, e0120258.

114. Xu, M.; Gu, M.; Zhang, K.; Zhou, J.; Wang, Z.; Da, J. miR-203 inhibition of renal cancer cell proliferation, migration and invasion by targeting of FGFR. *Diagn. Pathol.* 2015, 10, 24. [CrossRef]

115. Tang, K.; Xu, H. Prognostic value of meta-signature miRNAs in renal cell carcinoma: An integrated miRNA expression profiling analysis. *Sci. Rep.* 2015, 5, 10272. [CrossRef]

116. Butz, H.; Szabó, P.M.; Khella, H.W.; Nofech-Mozes, R.; Patócs, A.; Mac-Way, F. miRNA-target network reveals miR-124aa as a key miRNA contributing to clear renal cell carcinoma aggressive behaviour by targeting CAV1 and FLOT. *Oncotarget* 2015, 6, 12543–12557. [CrossRef]

117. Nofech-Mozes, R.; Khella, H.W.Z.; Scorilas, A.; Youssef, L.; Krylov, S.N.; Lianidou, E.; Sidiropoulos, K.G.; Gabri, M.; Evans, A.; Mac-Way, F. MicroRNA-194 is a Marker for Good Prognosis in Clear Cell Renal Cell Carcinoma. *Cancer Med.* 2016, 5, 656–664. [CrossRef]

118. Ma, Q.; Peng, Z.; Wang, L.; Li, Y.; Wang, K.; Zheng, J.; Liang, Z.; Liu, T. miR-19a correlates with poor prognosis of clear cell renal cell carcinoma patients via promoting cell proliferation and suppressing PTEN/SMAD4 expression. *Int. J. Oncol.* 2016, 49, 2589–2599. [CrossRef]

119. García-Donías, J.; Beuselinck, B.; Ingłada-Pérez, L.; Castro, O.G.; Schöffski, P.; Wozniak, A.; Bechter, O.; Apellániz-Ruiz, M.; Leandro-García, I.J.; Esteban, E.; et al. Deep sequencing reveals microRNAs predictive of antiangiogenic drug response. *JCI Insight* 2016, 1, e86051. [CrossRef]

120. Khella, H.W.Z.; Daniel, N.; Youssef, L.; Scorilas, A.; Nofech-Mozes, R.; Mirham, L.; Krylov, S.N.; Liandeau, E.; Krizova, A.; Finelli, A.; et al. miR-10b is a prognostic marker in clear cell renal cell carcinoma. *J. Clin. Pathol.* 2017, 70, 854–859. [CrossRef]

121. Chen, C.; Xue, S.; Zhang, J.; Chen, W.; Gong, D.; Zheng, J.; Ma, J.; Xue, W.; Chen, Y.; Zhai, W.; et al. DNA-methylation-mediated repression of miR-766-3p promotes cell proliferation via targeting SF2 expression in renal cell carcinoma. *Int. J. Cancer* 2017, 141, 1867–1878. [CrossRef] [PubMed]

122. Pan, X.; Quan, J.; Li, Z.; Zhao, L.; Zhou, L.; Jinling, X.; Weijie, X.; Guan, X.; Li, H.; Yang, S.; et al. miR-566 functions as an oncogene and a potential biomarker for prognosis in renal cell carcinoma. *Biomed. Pharmacother.* 2018, 102, 718–727. [CrossRef] [PubMed]
123. Zhou, L.; Li, Z.; Pan, X.; Lai, Y.; Quan, J.; Zhao, L.; Xu, J.; Xu, W.; Guan, X.; Li, H.; et al. Identification of miR-18a-5p as an oncogene and prognostic biomarker in RCC. *Am. J. Transl. Res.* 2018, 10, 1874–1886. [PubMed]

124. Zhou, L.; Pan, X.; Li, Z.; Chen, P.; Quan, J.; Lin, C.; Lai, Y.; Xu, J.; Xu, W.; Guan, X.; et al. Oncogenic miR-663a is associated with cellular function and poor prognosis in renal cell carcinoma. *Biomed. Pharmacother.* 2018, 105, 1155–1163. [CrossRef]

125. Pan, X.; Li, Z.; Zhao, L.; Quan, J.; Zhou, L.; Xu, J.; Xu, W.; Guan, X.; Li, H.; Yang, S.; et al. microRNA-572 functions as an oncogene and a potential biomarker for renal cell carcinoma prognosis. *Onco. Rep.* 2018, 40, 3092–3101. [CrossRef]

126. Quan, J.; Pan, X.; Li, Y.; Hu, Y.; Tao, L.; Li, Z.; Zhao, L.; Wang, J.; Li, H.; Lai, Y.; et al. MiR-23a-3p acts as an oncogene and potential prognostic biomarker by targeting PNRC2 in RCC. *Biomed. Pharmacother.* 2019, 110, 656–666. [CrossRef]

127. Li, H.; Pan, X.; Gui, Y.; Quan, J.; Li, Z.; Zhao, L.; Guan, X.; Xu, J.; Xu, W.; Lai, Y. Upregulation of miR-183–5p predicts worse survival in patients with renal cell cancer after surgery. *Cancer Biomark.* 2019, 24, 153–158. [CrossRef]

128. Chen, X. Expression of microRNA-3133 correlates with the prognosis in patients with clear renal cell carcinoma. *Medicine* 2019, 98, e16008. [CrossRef]

129. Liu, S.; Wang, Y.; Li, W.; Yu, S.; Wen, Z.; Chen, Z.; Lin, F. miR–221–5p acts as an oncogene and predicts worse survival in patients of renal cell cancer. *Biomed. Pharmacother.* 2019, 119, 109406. [CrossRef]

130. Peng, X.; Pan, X.; Liu, K.; Zhang, C.; Zhao, L.; Li, H.; Guan, X.; Xu, W.; Xu, J.; Zhang, F.; et al. miR–142–3p as a novel biomarker for predicting poor prognosis in renal cell carcinoma patients after surgery. *Int. J. Biol. Markers* 2019, 34, 302–308. [CrossRef]

131. Liu, K.; Pan, X.; Peng, X.; Zhang, C.; Li, H.; Guan, X.; Xu, W.; Xu, J.; Zhao, L.; Wang, T.; et al. Associations of high expression of miR-106b-5p detected from FFPE sample with poor prognosis of RCC patients. *Pathol. Res. Pract.* 2019, 215, 152391. [CrossRef] [PubMed]

132. Heinzelmann, J.; Arndt, M.; Pleyers, R.; Fehlmann, T.; Hoelters, S.; Zeuschner, P.; Pryalukhin, A.; Schaeffeler, E.; Bohle, R.M.; et al. 4-miRNA Score Predicts the Individual Metastatic Risk of Renal Cell Carcinoma Patients. *Ann. Surg. Oncol.* 2019, 26, 3765–3773. [CrossRef] [PubMed]

133. Du, M.; Giridhar, K.V.; Tian, Y.; Tschannen, M.R.; Zhu, J.; Huang, C.-C.; Kilari, D.; Kohli, M.; Wang, L. Plasma exosomal miRNAs-based prognosis in metastatic kidney cancer. *Oncotarget* 2017, 8, 63703–63714. [CrossRef]

134. Fuji, N.; Hirata, H.; Ueno, K.; Mori, J.; Oka, S.; Shimizu, K.; Kawai, Y.; Inoue, R.; Yamamoto, Y.; Matsumoto, H.; et al. Extracellular miR-224 as a prognostic marker for clear cell renal cell carcinoma. *Oncotarget* 2017, 8, 109877–109888. [CrossRef] [PubMed]

135. Heinemann, F.G.; Tolkach, Y.; Deng, M.; Schmidt, D.; Kristiansen, G.; Müller, S.; Ellinger, J. Serum miR–122–5p and miR–206 expression: Non–invasive prognostic biomarkers for renal cell carcinoma. *Clin. Epigenetics* 2018, 10, 11. [CrossRef]

136. Schwandt, A.; Wood, L.S.; Rini, B.; Dreicer, R. Management of side effects associated with sunitinib therapy for patients with renal cell carcinoma. *Oncotargets Ther.* 2009, 2, 51–61.

137. Eisen, T.; Sternberg, C.N.; Robert, C.; Mulders, P.; Pyle, L.; Zbinden, S.; Izzedine, H.; Escudier, B. Targeted Therapies for Renal Cell Carcinoma: Review of Adverse Event Management Strategies. *J. Natl. Cancer Inst.* 2012, 104, 93–113. [CrossRef]

138. Makhov, P.; Joshi, S.; Ghatalia, P.; Kutikov, A.; Uzzo, R.; Kolenko, V.M. Resistance to Systemic Therapies in Clear Cell Renal Cell Carcinoma: Mechanisms and Management Strategies. *Mol. Cancer Ther.* 2018, 17, 1355–1364. [CrossRef]

139. Institute, N.C. Precision Medicine in Cancer Treatment. 3 October 2017. Available online: https://www.cancer.gov/about-cancer/treatment/types/precision-medicine (accessed on 1 April 2020).

140. Corrà, F.; Agnoletto, C.; Minotti, L.; Baldassari, F.; Volinia, S. The Network of Non-coding RNAs in Cancer Drug Resistance. *Front. Oncol.* 2018, 8, 327. [CrossRef]

141. Wang, W.-T.; Han, C.; Sun, Y.-M.; Chen, T.-Q.; Chen, Y.-Q. Noncoding RNAs in cancer therapy resistance and targeted drug development. *J. Hematol. Oncol.* 2019, 12, 55. [CrossRef]

142. Zhang, X.; Xie, K.; Zhou, H.; Wu, Y.; Li, C.; Liu, Y.; Liu, Z.; Xu, Q.; Liu, S.; Xiao, D.; et al. Role of non-coding RNAs and RNA modifiers in cancer therapy resistance. *Mol. Cancer* 2020, 19, 1–26. [CrossRef] [PubMed]
143. Berkers, J.; Govaere, O.; Wolter, P.; Beuselinck, B.; Schöffski, P.; Van Kempen, L.C.; Albersen, M.; Oord, J.V.D.; Roskams, T.; Swinnen, J.; et al. A Possible Role for MicroRNA-141 Down-Regulation in Sunitinib Resistant Metastatic Clear Cell Renal Cell Carcinoma Through Induction of Epithelial-to-Mesenchymal Transition and Hypoxia Resistance. *J. Urol.* 2013, 189, 1930–1938. [CrossRef] [PubMed]

144. Merhautová, J.; Hezova, R.; Poprach, A.; Kovarikova, A.; Radova, L.; Svoboda, M.; Vyza, R.; Demlova, R.; Slaby, O. miR-155 and miR-484 Are Associated with Time to Progression in Metastatic Renal Cell Carcinoma Treated with Sunitinib. *BioMed Res. Int.* 2015, 2015, 1–5. [CrossRef] [PubMed]

145. Go, H.; Kang, M.J.; Kim, P.-J.; Lee, J.-L.; Park, J.Y.; Park, J.-M.; Ro, J.Y.; Cho, Y.M. Development of Response Classifier for Vascular Endothelial Growth Factor Receptor (VEGFR)-Tyrosine Kinase Inhibitor (TKI) in Metastatic Renal Cell Carcinoma. *Pathol. Oncol. Res.* 2017, 25, 51–58. [CrossRef]

146. Gámez-Pozo, A.; Antón-Aparicio, L.M.; Bayona, C.; Borrega, P.; Sancho, M.I.G.; García-Dominguez, R.; De Portugal, T.; Ramos-Vázquez, M.; Pérez-Carrion, R.; Bolós, M.V.; et al. MicroRNA Expression Profiling of Peripheral Blood Samples Predicts Resistance to First-line Sunitinib in Advanced Renal Cell Carcinoma Patients. *Neoplasia* 2012, 14, 1144–1152. [CrossRef]

147. Chen, B.; Duan, L.; Yin, G.; Tan, J.; Jiang, X. miR-381, a novel intrinsic WEE1 inhibitor, sensitizes renal cancer cells to 5-FU by up-regulation of Cdc2 activities in 786-O. *J. Chemotherapy.* 2013, 25, 229–238. [CrossRef]

148. Prior, C.; Perez-Gracia, J.L.; Garcia-Dominguez, N.; Lianidou, E.; et al. miR–221 and miR–145 are differentially expressed in metastatic renal cell carcinoma. *J. Pathol. Oncol.* 2015, 6, 23–31. [CrossRef] [PubMed]

149. Gao, C.; Peng, F.H.; Peng, L.K. MiR-200c sensitizes clear-cell renal cell carcinoma cells to sorafenib and imatinib by targeting heme oxygenase-1. *Neoplasma* 2014, 61, 680–689. [CrossRef]

150. Mu, W.; Hu, C.; Zhang, H.; Qu, Z.; Cen, J.; Qu, Z.; Li, C.; Ren, H.; Li, Y.; He, X.; et al. miR-27b synergizes with anticancer drugs via p53 activation and CYP1B1 suppression. *Cell Res.* 2015, 25, 477–495. [CrossRef]

151. Zheng, B.; Zhu, H.; Gu, D.; Pan, X.; Qian, L.; Xue, B.; Yang, D.; Zhou, J.; Shan, Y. MiRNA-30a-mediated autophagy inhibition sensitizes renal cell carcinoma cells to sorafenib. *Biochem. Biophys. Res. Commun.* 2015, 459, 234–239. [CrossRef]

152. Chang, I.; Mitsui, Y.; Fukuhara, S.; Gill, A.; Wong, D.K.; Yamamura, S.; Shahryari, V.; Tabatabai, Z.L.; Dahlia, R.; Shin, D.M.; et al. Loss of miR-200c up-regulates CYP1B1 and confers docetaxel resistance in renal cell carcinoma. *Oncotarget* 2015, 6, 7774–7787. [CrossRef] [PubMed]

153. Long, Q.-Z.; Du, Y.-F.; Liu, X.-G.; Li, X.; He, D.-L. miR-124 represses FZD5 to attenuate P-glycoprotein-mediated chemo-resistance in renal cell carcinoma. *Tumor Biol.* 2015, 36, 7017–7026. [CrossRef] [PubMed]

154. Khella, H.W.Z.; Butz, H.; Ding, Q.; Rotondo, F.; Evans, K.R.; Kupchak, P.; Dharsee, M.; Latif, A.; Suárez, C.; Castellano, D.; Del Alba, A.G.; Lozano, M.D.; et al. Identification of Tissue microRNAs Predictive of Sunitinib Activity in Patients with Metastatic Renal Cell Carcinoma. *PloS ONE* 2014, 9, e86263. [CrossRef]

155. Lukamowicz-Rajska, M.; Mittmann, C.; Prummer, M.; Zhong, Q.; Bedke, J.; Hennenlotter, J.; Stenzl, A.; Mischo, A.; Bihr, S.; Schmidinger, M.; et al. MiR-98b-5p expression and response to tyrosine kinase inhibitor treatment in clear cell renal carcinoma patients. *Oncotarget* 2016, 7, 78433–78447. [CrossRef] [PubMed]

156. Pili, R.; Liu, G.; Chintala, S.; Verheul, H.; Rehman, S.; Attwood, K.; Lodge, M.A.; Wahl, R.; Martin, J.I.; Miles, K.M.; et al. Combination of the histone deacetylase inhibitor vorinostat with bevacizumab in patients with clear-cell renal cell carcinoma: A multicentre, single-arm phase I/II clinical trial. *Br. J. Cancer* 2017, 116, 874–883. [CrossRef] [PubMed]

157. Puente, J.; Lainez, N.; Dueñas, M.; Méndez-Vidal, M.J.; Esteban, E.; Castellano, D.; Martinez-Fernández, M.; Basterretxea, L.; Juan-Fita, M.J.; Antón, L.; et al. Novel potential predictive markers of sunitinib outcomes in long-term responders versus primary refractory patients with metastatic clear–cell renal cell carcinoma. *Oncotarget* 2017, 8, 30410–30421. [CrossRef]

158. Xiao, W.; Lou, N.; Ruan, H.; Bao, L.; Xiong, Z.; Yuan, C.; Tong, J.; Xu, G.; Zhou, Y.; Qu, Y.; et al. Mir-144-3p Promotes Cell Proliferation, Metastasis, Sunitinib Resistance in Clear Cell Renal Cell Carcinoma by Downregulating ARID1A. *Cell. Physiol. Biochem.* 2017, 43, 2420–2433. [CrossRef]

159. Sun, X.; Lou, L.; Zhong, K.; Wan, L. MicroRNA-451 regulates chemo-resistance in renal cell carcinoma by targeting ATF-2 gene. *Exp. Biol. Med.* 2017, 242, 1299–1305. [CrossRef]

160. Kovacova, J.; Juracek, J.; Poprach, A.; Büchler, T.; Kopecký, J.; Fiala, O.; Svoboda, M.; Capoor, M.N. Candidate MicroRNA Biomarkers of Therapeutic Response to Sunitinib in Metastatic Renal Cell Carcinoma: A Validation Study in Patients with Extremely Good and Poor Response. *Anticancer Res.* 2018, 38, 2961–2965. [CrossRef]
161. Kovacova, J.; Juracek, J.; Poprach, A.; Kopecky, J.; Fiala, O.; Svboda, M.; Fabian, P.; Radova, L.; Brabec, P.; Buchler, T.; et al. MiR-376b-3p Is Associated With Long-term Response to Sunitinib in Metastatic Renal Cell Carcinoma Patients. Cancer Genom. Proteom. 2019, 16, 353–359. [CrossRef] [PubMed]

162. He, J.; He, J.; Min, L.; He, Y.; Guan, H.; Wang, J.; Peng, X. Extracellular vesicles transmitted miR–31–5p promotes sorafenib resistance by targeting MLH1 in renal cell carcinoma. Int. J. Cancer 2020, 146, 1052–1063. [CrossRef] [PubMed]

163. Goto, Y.; Kurozumi, A.; Nohata, N.; Kojima, S.; Matsushita, R.; Yoshino, H.; Yamazaki, K.; Ishida, Y.; Ichikawa, T.; Naya, Y.; et al. The microRNA signature of patients with sunitinib failure: Regulation of UHRF1 pathways by microRNA-101 in renal cell carcinoma. Oncotarget 2016, 7, 59070–59086. [CrossRef] [PubMed]

164. Prensner, J.; Chinnaiyan, A.M. The emergence of lncRNAs in cancer biology. Cancer Discov. 2011, 1, 391–407. [CrossRef] [PubMed]

165. Wang, C.; Wang, L.; Ding, Y.; Lu, X.; Zhang, G.; Yang, J.; Zheng, H.; Wang, H.; Jiang, Y.; Xu, L. LncRNA Structural Characteristics in Epigenetic Regulation. Int. J. Mol. Sci. 2017, 18, 2659. [CrossRef]

166. Zhao, Z.; Dammert, M.A.; Grummt, I.; Bierhoff, H. IncRNA-Induced Nucleosome Repositioning Reinforces Transcriptional Repression of rRNA Genes upon Hypotonic Stress. Cell Rep. 2016, 14, 1876–1882. [CrossRef]

167. Ma, W.; Ay, F.; Lee, C.; Gülsoy, G.; Deng, X.; Cook, S.; Hesson, J.; Cavanaugh, C.; Ware, C.B.; Krümm, A.; et al. Fine-scale chromatin interaction maps reveal the cis-regulatory landscape of human lncRNA genes. Nat. Methods 2014, 12, 71–78. [CrossRef]

168. Hansen, T.B.; Jensen, T.I.; Clausen, B.H.; Bramsen, J.B.; Finsen, B.R.; Damgaard, C.K.; Kjems, J. Natural RNA circles function as efficient microRNA sponges. Nature 2013, 495, 384–388. [CrossRef]

169. Distefano, J.K. The Emerging Role of Long Noncoding RNAs in Human Disease. Metab. Pathw. Eng. 2018, 1706, 91–110. [CrossRef]

170. Huarte, M. The emerging role of IncRNAs in cancer. Nat. Med. 2015, 21, 1253–1261. [CrossRef]

171. Song, S.; Wu, Z.; Wang, C.; Liu, B.; Ye, X.; Chen, J.; Yang, Q.; Ye, H.; Xu, B.; Wang, L. RCCRT1 is Correlated With Prognosis and Promotes Cell Migration and Invasion in Renal Cell Carcinoma. Urology 2014, 84, 730.e1. [CrossRef]

172. Wang, Y.; Liu, J.; Bai, H.; Deng, Y.; Lv, P.; Wu, S. Long intergenic non-coding RNA 00152 promotes renal cell carcinoma progression by epigenetically suppressing P16 and negatively regulates miR-205. Am. J. Cancer Res. 2017, 7, 312–322. [PubMed]

173. Xue, D.; Wang, H.; Chen, Y.; Shen, D.; Lu, J.; Wang, M.; Zebibula, A.; Xu, L.; Wu, H.; Li, G.; et al. Circ–AKT3 inhibits clear cell renal cell carcinoma metastasis via altering miR–296–3p/E–cadherin signals. Mol. Cancer 2019, 18, 151. [CrossRef] [PubMed]

174. Mattick, J.W.; Rinn, J. Discovery and annotation of long noncoding RNAs. Nat. Struct. Mol. Biol. 2015, 22, 5–7. [CrossRef] [PubMed]

175. Thrash-Bingham, C.A.; Tartof, K.D. aHIF: A Natural Antisense Transcript Overexpressed in Human Renal Cancer and During Hypoxia. J. Natl. Cancer Inst. 1999, 91, 143–151. [CrossRef] [PubMed]

176. Bertozzi, D.; Iurlaro, R.; Sordet, O.; Marinello, J.; Zaffaroni, N.; Capranico, G. Characterization of novel antisense HIF-1α transcripts in human cancers. Cell Cycle 2011, 10, 3189–3197. [CrossRef]

177. Ellinger, J.; Alam, J.; Rothenburg, J.; Deng, M.; Schmidt, D.; Syring, I.; Miersch, H.; Perner, S.; Müller, S.C. The long non–coding RNA Inc–ZNF180–2 is a prognostic biomarker in patients with clear cell renal cell carcinoma. Am. J. Cancer Res. 2015, 5, 2799–2807. [CrossRef]

178. Ren, X.; Lan, T.; Chen, Y.; Shao, Z.; Yang, C.; Peng, J. IncRNA uc009yby.1 promotes renal cell proliferation and is associated with poor survival in patients with clear cell renal cell carcinomas. Oncol. Lett. 2016, 12, 1929–1934. [CrossRef]

179. Qin, C.; Han, Z.; Qian, J.; Bao, M.; Li, P.; Ju, X.; Zhang, S.; Zhang, L.; Li, S.; Cao, Q.; et al. Expression Pattern of Long Non-Coding RNAs in Renal Cell Carcinoma Revealed by Microarray. PLoS ONE 2014, 9, e99372. [CrossRef]

180. Blondeau, J.J.; Deng, M.; Syring, I.; Schröder, S.; Schmidt, D.; Perner, S.; Müller, S.C.; Ellinger, J. Identification of novel long non-coding RNAs in clear cell renal cell carcinoma. Clin. Epigenetics 2015, 7, 10. [CrossRef]

181. Liu, Z.; Zhang, C.; Xia, S.-Y.; Xi, Y.-C.; Yan, H.-Y. Downregulation of long non-coding RNA TRIM52-AS1 functions as a tumor suppressor in renal cell carcinoma. Mol. Med. Rep. 2016, 13, 3206–3212. [CrossRef]

182. Li, Y.; Li, Y.; Chen, D.; Yu, Z.; Ni, L.; Mao, X.; Gui, Y.; Lai, Y.; Wang, T.; Jin, L.; et al. Identification of long-non coding RNA UCA1 as an oncogene in renal cell carcinoma. Mol. Med. Rep. 2016, 13, 3326–3334. [CrossRef] [PubMed]
183. Wu, Y.; Wang, Y.-Q.; Weng, W.-W.; Zhang, Q.-Y.; Yang, X.-Q.; Gan, H.-L.; Yang, Y.-S.; Zhang, P.-P.; Sun, M.-H.; Xu, M.-D.; et al. A serum-circulating long non-coding RNA signature can discriminate between patients with clear cell renal cell carcinoma and healthy controls. *Oncogenesis* 2016, 5, e192. [CrossRef] [PubMed]

184. He, Z.-H.; Qin, X.-H.; Zhang, X.-L.; Yi, J.-W.; Han, J.-Y. Long noncoding RNA GIHCG is a potential diagnostic and prognostic biomarker and therapeutic target for renal cell carcinoma. *Eur. Rev. Med. Pharmacol. Sci.* 2018, 22, 46–54. [PubMed]

185. Qu, L.; Wu, Z.; Li, Y.; Xu, Z.; Liu, B.; Liu, F.; Bao, Y.; Wu, D.; Liu, J.; Wang, A.; et al. A feed-forward loop between IncARSR and YAP activity promotes expansion of renal tumour-initiating cells. *Nat. Commun.* 2016, 7, 12692. [CrossRef]

186. Bao, X.; Duan, J.; Yan, Y.; Ma, X.; Zhang, Y.; Wang, H.; Ni, D.; Wu, S.; Peng, C.; Fan, Y.; et al. Upregulation of long noncoding RNA PVT1 predicts unfavorable prognosis in patients with clear cell renal cell carcinoma. *Cancer Biomark.* 2017, 21, 55–63. [CrossRef] [PubMed]

187. Wang, A.; Bao, Y.; Wu, Z.; Zhao, T.; Wang, D.; Shi, J.; Liu, B.; Sun, S.; Yang, F.; Wang, L.; et al. Long noncoding RNA EGFR-AS1 promotes cell growth and metastasis via affecting HuR mediated mRNA stability of EGFR in renal cancer. *Cell Death Dis.* 2019, 10, 1–14. [CrossRef]

188. Yao, J.; Chen, Y.; Wang, Y.; Liu, S.; Yuan, X.; Pan, F.; Geng, P. Decreased expression of a novel lncRNA CADM1-AS1 is associated with poor prognosis in patients with clear cell renal cell carcinomas. *Int. J. Clin. Exp. Pathol.* 2014, 7, 2758–2767.

189. Zhang, H.-M.; Yang, F.-Q.; Yan, Y.; Che, J.-P.; Zheng, J.-H. High expression of long non-coding RNA SPRY4-IT1 predicts poor prognosis of clear cell renal cell carcinoma. *Int. J. Clin. Exp. Pathol.* 2014, 7, 5801–5809.

190. Xue, S.; Li, Q.-W.; Che, J.-F.; Guo, Y.; Yang, F.-Q.; Zheng, J.-H. Decreased expression of long non-coding RNA NBAT-1 is associated with poor prognosis in patients with clear cell renal cell carcinoma. *Int. J. Clin. Exp. Pathol.* 2015, 8, 3765–3774.

191. Zhang, H.-M.; Yang, F.-Q.; Chen, S.-J.; Che, J.; Zheng, J.-H. Upregulation of long non-coding RNA MALAT1 correlates with tumor progression and poor prognosis in clear cell renal cell carcinoma. *Tumor Biol.* 2014, 36, 2947–2955. [CrossRef]

192. Wang, L.; Cai, Y.; Zhao, X.; Jia, X.; Zhang, J.; Liu, J.; Zhen, H.; Wang, T.; Tang, X.; Liu, Y.; et al. Down-regulated long non-coding RNA H19 inhibits carcinogenesis of renal cell carcinoma. *Neoplasma* 2015, 62, 412–418. [CrossRef]

193. Wu, Y.; Tan, C.; Weng, W.-W.; Deng, Y.; Zhang, Q.-Y.; Yang, X.-Q.; Gan, H.-L.; Wang, T.; Zhang, P.-P.; Xu, M.-D.; et al. Long non-coding RNA Linc00152 is a positive prognostic factor for and demonstrates malignant biological behavior in clear cell renal cell carcinoma. *Am. J. Cancer Res.* 2016, 6, 285–299. [PubMed]

194. Wang, P.-Q.; Wu, Y.-X.; Zhong, X.-D.; Liu, B.; Qiao, G. Prognostic significance of overexpressed long non-coding RNA TUG1 in patients with clear cell renal cell carcinoma. *Eur. Rev. Med. Pharmacol. Sci.* 2017, 21, 82–86. [PubMed]

195. Su, H.; Sun, T.; Wang, H.; Shi, G.; Zhang, H.; Sun, F.-K.; Ye, D. Decreased TCL6 expression is associated with poor prognosis in patients with clear cell renal cell carcinoma. *Oncotarget* 2016, 8, 5789–5799. [CrossRef] [PubMed]

196. Gong, X.; Siprashvili, Z.; Emina, O.; Shen, Z.; Sato, Y.; Kume, H.; Homma, Y.; Ogawa, S.; Khavari, P.A.; Pollack, J.R.; et al. Novel lincRNA SLINKY is a prognostic biomarker in kidney cancer. *Oncotarget* 2017, 8, 18657–18669. [CrossRef] [PubMed]

197. Xu, Y.; Tong, Y.; Zhu, J.; Lei, Z.; Wan, L.; Zhu, X.; Ye, F.; Xie, L. An increase in long non-coding RNA PANDAR is associated with poor prognosis in clear cell renal carcinoma. *BMC Cancer* 2017, 17, 373. [CrossRef]

198. Li, J.-K.; Chen, C.; Liu, J.-Y.; Shi, J.-Z.; Liu, S.-P.; Liu, B.; Wu, D.-S.; Fang, Z.-Y.; Bao, Y.; Jiang, M.-M.; et al. Long noncoding RNA MRCCAT1 promotes metastasis of clear cell renal cell carcinoma via inhibiting NPR3 and activating p38-MAPK signaling. *Mol. Cancer* 2017, 16, 111. [CrossRef]

199. Yang, T.; Zhou, H.; Liu, P.; Yan, L.; Yao, W.; Chen, K.; Zeng, J.; Li, H.; Hu, J.; Xu, H.; et al. lncRNA PVT1 and its splicing variant function as competing endogenous RNA to regulate clear cell renal cell carcinoma progression. *Oncotarget* 2017, 8, 85353–85367. [CrossRef]

200. Flippot, R.; Mouawad, R.; Spanel, J.-P.; Rouprêt, M.; Compérat, E.; Bitker, M.-O.; Parra, J.; Vaessen, C.; Allanic, F.; Manach, Q.; et al. Expression of long non-coding RNA MFII2-AS1 is a strong predictor of recurrence in sporadic localized clear-cell renal cell carcinoma. *Sci. Rep.* 2017, 7, 1–9. [CrossRef]
201. Su, H.; Wang, H.; Shi, G.-H.; Zhang, H.; Sun, F.; Ye, D. Downregulation of long non-coding RNA ENSG00000241684 is associated with poor prognosis in advanced clear cell renal cell carcinoma. Eur. J. Surg. Oncol. 2018, 44, 840–846. [CrossRef]

202. Wang, L.-N.; Zhu, X.-Q.; Song, X.-S.; Xu, Y. Long noncoding RNA lung cancer associated transcript 1 promotes proliferation and invasion of clear cell renal cell carcinoma cells by negatively regulating miR–495–3p. J. Cell. Biochem. 2018, 119, 7599–7609. [CrossRef]

203. Ding, C.; Han, F.; Xiang, H.; Xia, X.; Wang, Y.; Dou, M.; Zheng, J.; Li, Y.; Xue, W.; Ding, X.; et al. LncRNA CRNDE is a biomarker for clinical progression and poor prognosis in clear cell renal cell carcinoma. J. Cell. Biochem. 2018, 119, 10406–10414. [CrossRef] [PubMed]

204. Qu, L.; Ding, J.; Chen, C.; Wu, Z.; Liu, B.; Gao, Y.; Chen, W.; Liu, F.; Sun, W.; Li, X.-F.; et al. Exosome-Transmitted lncARSR Promotes Sunitinib Resistance in Renal Cancer by Acting as a Competing Endogenous RNA. Cancer Cell 2016, 29, 653–668. [CrossRef] [PubMed]

205. Xu, Z.; Yang, F.; Wei, D.; Liu, B.; Chen, C.; Bao, Y.; Wu, Z.; Wu, D.; Tan, H.; Li, J.; et al. Long noncoding RNA–SRLR elicits intrinsic sorafenib resistance via evoking IL–6/STAT3 axis in renal cell carcinoma. Oncogene 2017, 36, 1965–1977. [CrossRef] [PubMed]

206. Zhai, W.; Sun, Y.; Guo, C.; Hu, G.; Wang, M.; Zheng, J.; Lin, W.; Huang, Q.; Li, G.; Zheng, J.; et al. LncRNA–SARCC suppresses renal cell carcinoma (RCC) progression via altering the androgen receptor(AR)/miRNA–143–3p signals. Cell Death Differ. 2017, 24, 1502–1517. [CrossRef] [PubMed]

207. Liu, L.; Pang, X.; Shang, W.; Xie, H.; Feng, Y.; Feng, G. Long non–coding RNA GAS5 sensitizes renal cell carcinoma to sorafenib via miR–21/SOX5 pathway. Cell Cycle 2019, 18, 257–263. [CrossRef] [PubMed]