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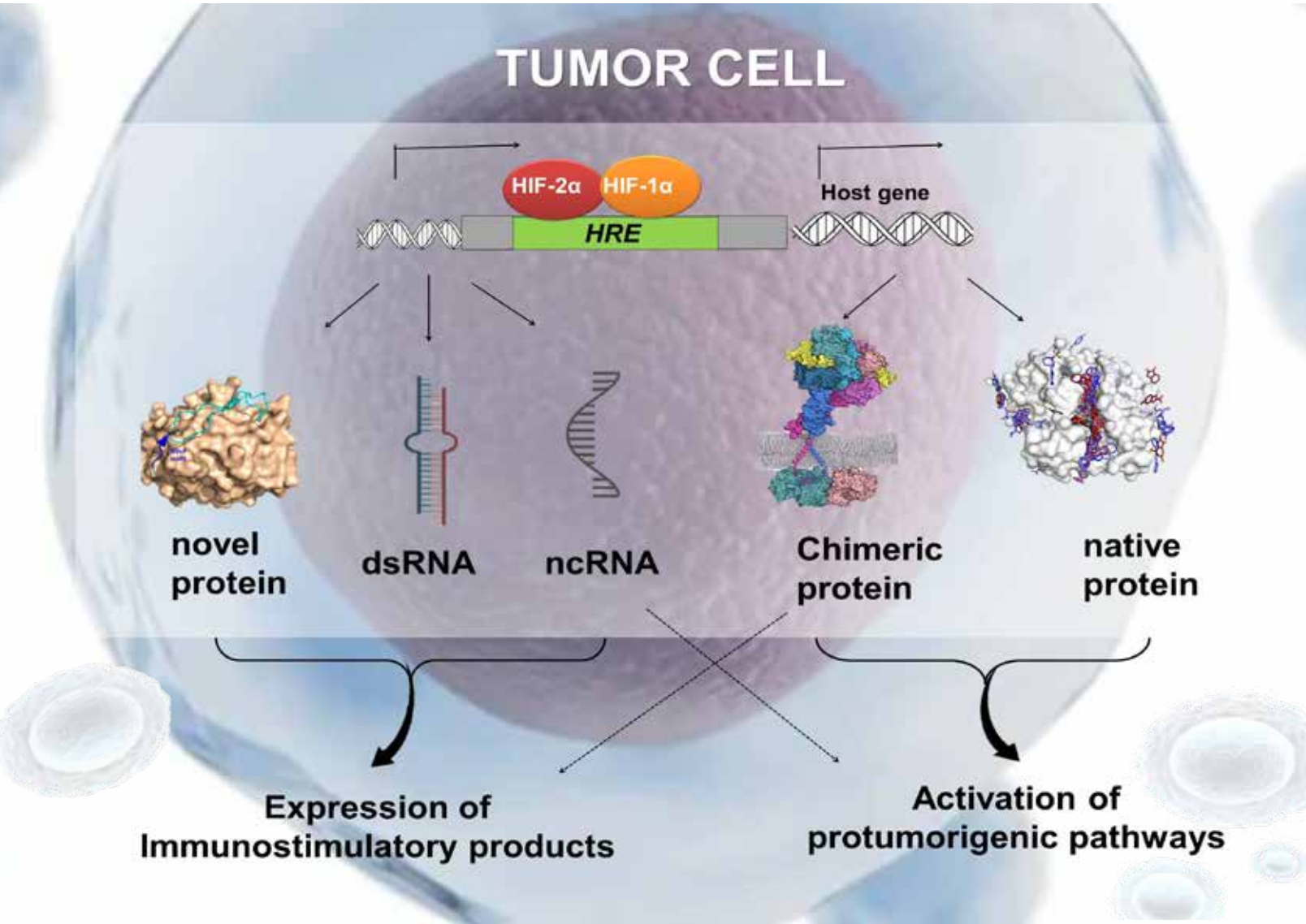

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

Artist rendering; for illustration purposes only.

In RCC, <u>all</u> T3 tumors are characterized by their invasiveness.[1]
These tumors extend into structures within or adjacent to the kidney system, including the renal fat, the renal vein, the vena cava, or the pelvicalyceal system.[1,a]

Patients with more invasive tumors are at a higher risk of their cancer returning.[2]
Identify patients in your practice who have T3 tumors so you can take appropriate action following nephrectomy.

How will you manage your next patient with an invasive T3 tumor?

*T3 tumors do not extend beyond Gerota's fascia or into the ipsilateral adrenal gland.[1]
RCC = renal cell carcinoma.

References: 1. Edge SB, Greene FL, Byrd DR, et al, eds. Kidney. In: *AJCC Cancer Staging Manual*. 8th ed. Springer International Publishing; 2017:739–748. **2.** Sundaram M, Song Y, Rogerio JW, et al. Clinical and economic burdens of recurrence following nephrectomy for intermediate high- or high-risk renal cell carcinoma: a retrospective analysis of Surveillance, Epidemiology, and End Results-Medicare data. *J Manag Care Spec Pharm*. 2022;28(10):1149–1160. doi:10.18553/jmcp.2022.22133.

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ABOUT THE COVER
A graphic illustration for proposed mechanism of the association between ICI response and hERV expression. In tumor cells, expression of solo-LTRs possibly induces activation of pro-tumorigenic pathways. In the setting of ICI, authors hypothesize that neoantigens promote a more robust immune cell response, allowing for improved response to ICI.

KCJ CONTENTS

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KCJ ORIGINAL REVIEW OPEN ACCESS

Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma – Current Concepts and Contentions in the Era of Immune Checkpoint Inhibitors

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ABSTRACT

Cytoreductive nephrectomy (CN), or the removal of the primary kidney tumor in the setting of metastatic disease, plays a critical role in the treatment of metastatic renal cell carcinoma (mRCC). The benefits of CN, are multifactorial including alleviating symptoms but also eliminating cells potentially prone to future metastasis, and potentially extending a patient's survival. As innovations in mRCC treatment continue to emerge, the importance and timing of CN in patient care remains the subject of ongoing debate in the scientific community. With advancements in modern therapies and the introduction of immune checkpoint inhibitors (ICI), the optimal integration of CN in mRCC management becomes even more important to investigate. This manuscript reviews the key literature related to CN and critically evaluates data that investigated CN efficacy. Furthermore, this article summarizes data to help identify ideal candidates for CN, and explores options for integrating CN within the contemporary systemic therapy landscape.

KEYWORDS

Cytoreductive nephrectomy, Immune Checkpoint Inhibitors, Renal Cell Carcinoma, Patient Selection.

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INTRODUCTION

Renal cell carcinoma will affect about 82,000 people in the U.S. in 2023. Unfortunately, around 30% of the individuals who present with RCC will have metastatic disease either within their regional lymph nodes or at distant sites at the time of their presentation[1,2]. While the majority of patients with metastatic RCC are not curable, there has been a consistent improvement in the overall survival of patients who develop mRCC over the last two decades[3]. Much of this improvement has come from a deeper understanding of RCC tumor biology, and the host immune response within the tumor microenvironment[4]. One of the most important advancements in mRCC management has been the development of immune checkpoint inhibitor therapy[5-9], which has led to a substantial improvement in survival for mRCC patients compared to single agent tyrosine kinase inhibitor (TKI) therapies. As a result, standard first line therapies for mRCC are combinations of ICI/ICI or ICI/TKI therapies.

While there have been significant improvements in the survival of patients with mRCC due to advancements in systemic therapy, surgery continues to remain a critical component of the management of a subset of patients with mRCC. CN has been used throughout the history

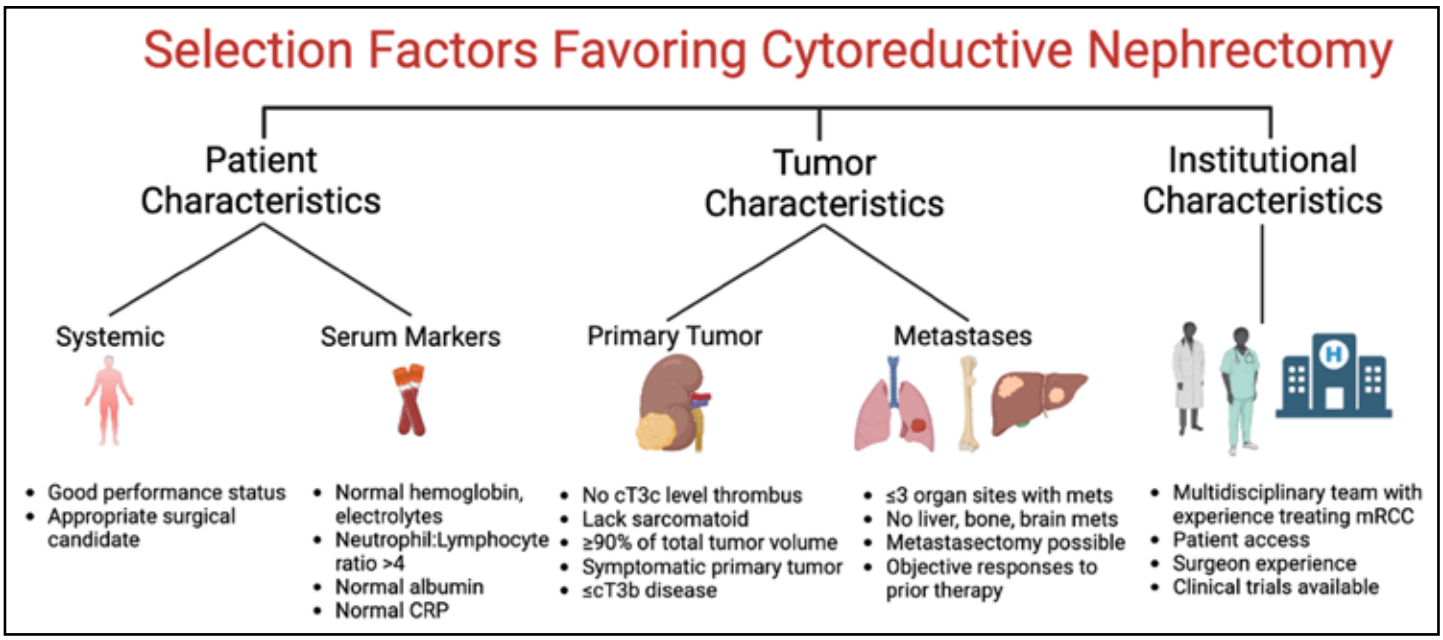

FIGURE 1. . Selection factors favoring cytoreductive nephrectomy. Multiple factors must be considered when deciding on candidacy for cytoreductive nephrectomy. This figure highlights the variables that have been shown to impact outcomes following cytoreductive nephrectomy. CRP = C-reactive protein, mRCC = metastatic renal cell carcinoma.

of mRCC management, but became standard of care in 2001 based on the results of two randomized trials[10-12]. Cytoreductive nephrectomy is defined as the removal of the primary renal mass in the setting of synchronous metastatic disease[13]. This can either occur prior to the receipt of any systemic therapy (termed "upfront" CN) or after systemic therapy has been delivered (termed "deferred" CN). There are multiple reasons that CN is performed: 1) to remove tumor that harbors cells capable of metastasizing or are resistant to therapy, 2) to palliate symptoms such as pain, gross hematuria, early satiety, which thereby improves the patient quality of life, and 3) to extend patient survival. Despite these indications, the role of CN has become controversial due to publication of a randomized trial in 2018 that demonstrated non-inferior outcomes for CN combined with sunitinib compared to sunitinib alone[14]. This clinical trial was controversial and had significant limitations, which reduced the impact of the findings in the context of modern mRCC management. The goal of this review is to concisely summarize the historical context of CN leading up to the current era of ICI therapy, including a critical analysis of the controversies surrounding CN and how CN can best be incorporated into the management of patients with mRCC.

CYTOREDUCTIVE NEPHRECTOMY – A BRIEF HISTORY

Prior to the implementation of effective systemic therapies, CN was used sparingly and was considered more for symptomatic purposes. Spontaneous regression of metastatic disease after patients received CN was reported but exceptionally rare[15]. Cytoreductive nephrectomy became a standard of care after the publication of two clinical trials in 2001: SWOG 8949 and EORTC 30947[10,12]. The two trials had similar study designs and randomized patients to either IFN-α alone or upfront CN followed by IFN-α. A combined analysis of these trials demonstrated an overall survival benefit favoring the CN arm (13.6 months vs 7.8 months, P=0.001)[11]. While these data are older, and IFN-α is significantly less effective than modern ICI therapy, the data from these trials provide a unique view of the benefit of CN. When these trials were conducted, there were no approved second line systemic therapy options available. Therefore, the survival data from these trials is less influenced by subsequent

STUDY	Treatment arm	% with Prior Nephrectomy
Motzer et al *NEJM* 2007 (17)	Sunitinib	91%
Escudier et al *NEJM* 2007 (18)	Sorafenib	94%
Motzer et al *Lancet* 2008 (77)	Everolimus	96%
Rini et al *JCO* 2008 (78)	Bevacizumab + IFN	85%
Sternberg et al *JCO* 2010 (79)	Pazopanib	89%
Motzer et al *NEJM* 2013 (80)	Pazopanib	82%
Motzer et al *NEJM* 2015 (81)	Nivolumab	89%
Choueiri et al *NEJM* 2015 (82)	Cabozantinib	85%
Motzer et al *NEJM* 2018 (83)	Nivolumab + Ipilimumab	82%
Motzer et al *NEJM* 2019 (84)	Avelumab + Axitinib	80%
Rini et al *NEJM* 2019 (6)	Pembrolizumab + Axitinib	83%
Rini et al *Lancet* 2019 (9)	Atezolizumab + Bevacizumab	74%
Choueiri et al *NEJM* 2021 (8)	Nivolumab + Cabozantinib	69%
Motzer et al *NEJM* 2021 (85)	Lenvatinib + Pembrolizumab	74%
Choueiri et al *NEJM* 2023 (86)	Cabozantinib + Nivolumab + Ipilimumab	65%

TABLE 1. Percent of patients who received a prior nephrectomy in phase III trials for metastatic RCC

Randomized Trial	Median Overall Survival in Sunitinib Arm
Mejean et al. *NEJM*. 2018 (CARMENA trial) (14)	18.4
Powles et al. *Lancet Oncol*. 2020 (21)	Not Reached
Motzer et al. *Cancer*. 2022 (20)	38
Rini et al. *Lancet*. 2019 (9)	34.9
Motzer et al. *NEJM*. 2014 (87)	29.1
Motzer et al. *NEJM*. 2007 (17)	26.4

TABLE 2. Median overall survival of patients randomized to sunitinib treatment in the CARMENA trial compared to other phase III randomized trials for metastatic renal cell carcinoma. CN=cytoreductive nephrectomy

therapies that patients might have pursued outside the trial setting. This offers a clearer understanding of the impact of CN on overall survival, devoid of the effects created by different second line therapies on patient survival. These data demonstrate a significant benefit for appropriately selected patients undergoing CN.

The cytokine era of systemic therapy (prior to 2006) consisted of IFN-α and IL-2, both of which had limited efficacy and high toxicity[16].After the cytokine era of systemic therapy, TKI therapy became standard of care starting with sorafenib and sunitinib therapy, after two phase III trials in 2007 demonstrated benefit of these agents over IFN-α[17,18]. In 2015, nivolumab (an anti-PD1 antibody that activates exhausted CD8+ T cells) became the first FDA approved ICI therapy for the treatment of mRCC, bringing about the ICI therapy era of mRCC management[19]. Since that time, multiple phase III trials have demonstrated the ability of ICI therapy to extend patient survival in the setting of mRCC. For example, the phase III trial CheckMate 214 published extended follow-up showing a median overall survival of 56 months for patients treated with nivolumab plus ipilimumab, and the KEYNOTE-426 trial demonstrated a median overall survival of 46 months among patients treated with pembrolizumab plus axitinib[20,21]. These results are nearly two fold higher than the median overall survival of patients receiving sunitinib, which was 26 months upon the trial's final analysis[22]. Thus, there has been a clear improvement in the survival of patients with mRCC being treated in clinical trials with modern ICI therapies.

It is important to note that all of the phase III trials investigating modern systemic therapies for mRCC included a large proportion of patients that had received a prior nephrectomy (either prior to metastatic progression or at the time of synchronous metastatic disease) (TABLE 1). Thus, the survival benefits of all modern systemic therapies for mRCC have to be interpreted knowing that most patients had their primary tumors removed prior to systemic therapy administration. In truth, randomized clinical trial data for systemic therapies in mRCC do not exist in the absence of surgery, which is a key reason that surgery is considered part of the multidisciplinary care of mRCC.

CONTROVERSIES REGARDING CYTOREDUCTIVE NEPHRECTOMY

The most recent catalyst for CN controversy was publication of the results of the CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) clinical trial[14], randomized 1:1 mRCC patients treated with upfront CN followed by sunitinib versus sunitinib alone. This was designed as a non-inferiority trial with overall survival as the primary endpoint and statistically powered to include 576 patients. The trial was published in 2018 and demonstrated non-inferior survival outcomes in the systemic therapy alone arm vs CN plus systemic therapy arm (18.4 vs 13.9 months, respectively). The results and trial design sparked immediate debate in the literature and at scientific conferences.

Despite providing the first randomized clinical trial data in two decades, the CARMENA study had significant limitations. First, the trial enrolled extremely slowly and did not reach its accrual goal. Two planned interim analyses (after 152 and 304 deaths) were performed and both concluded that the trial should continue. However, immediately after the second interim analysis, the sponsor closed the trial because of poor accrual. At the time of publication, the trial was able to enroll 450 patients across 79 centers over 8 years, significantly short of enrollment goal of 576 patients. In both study cohorts, there was significant contamination from not receiving the primary treatment or receiving other secondary treatments, which could bias the outcomes.

The trial was analyzed according to the intention-to-treat principle, but patients were frequently managed differently than their designated trial arm protocol. Seven percent of patients in the surgical arm did not receive a CN and 18% of patients did not receive subsequent sunitinib therapy and 5% did not get sunitinib. In both groups, about half of patients received additional lines of systemic therapies after sunitinib. One of the strongest criticisms of this study was the enrichment of the study cohort for poor risk patients with high volume metastatic disease. In CARMENA, the median patient had 2 sites of metastatic disease with 14 cm of overall tumor burden with 8.8 cm primary tumors. Nearly half (44%) of patients enrolled in the CN arm had poor risk disease according to the Memorial Sloan Kettering Cancer Center (MSKCC) mRCC risk classification. Multiple prior retrospective studies have demonstrated that poor risk patients with high volume disease outside of the kidney are least likely to derive a survival benefit from CN and should be counseled against upfront surgery. Evaluation of the CARMENA patients and known predictors of poor outcomes after CN demonstrate a high-risk patient population enrolled in the study to receive CN. The MD Anderson Cancer Center investigators published preoperative predictors of worse overall survival after CN[23]. These predictors included node positive disease (N+), bone metastases, and high stage disease (clinical T4 disease). The CARMENA patients included 35% with N+ disease and 36% with bone metastases. Additionally, 70% within the surgery arm had cT3-T4 disease compared to only 51% within the sunitinib only arm. The selection of high-risk patients for inclusion in this trial is further supported by the fact that the median overall survival in the sunitinib arm is much lower than the median survival in the sunitinib arm from other modern

phase III randomized trials (TABLE 2). A post hoc analysis of the CARMENA trial demonstrated that patients with one IMDC risk factor had significantly longer OS in comparison to those with two or more IMDC risk factors[24]. Lastly, it should be noted that systemic therapy options evolved considerably during the eight-year study and when the trial results were published, sunitinib was no longer used for first line therapy for mRCC patients, further limiting the applicability of the results to modern clinical practice. Strong conclusions from the CARMENA trial should be that appropriate patient selection is critical for successful outcomes[25].

Treatment Era	Study	Study type	Number undergoing CN	Number without CN	Median Follow-up (months)	Median OS for CN Patients (months)	HR OS (95% CI)
ICI ERA	Bakouny et al 2023 (74)	Observational	234	203	12	54	0.61 (0.41-0.90)
	Hahn et al 2023 (88)	Observational (Sarcomatoid mRCC only)	118	39	33.9	30.1	0.98 (0.65-1.47)
	Singla et al 2020 (89)	Observational	221	170	14.7	Not reached	0.23 (0.15-0.37)
TKI ERA	Chakiryan et al 2022 (90)	Observational	5005	7761	36	NR	0.49 (0.47-0.51)
	Marchioni et al 2019 (50)	Observational	575	276	9	10	0.38 (0.30-0.47)
	Mejean et al 2018 (14)	Prospective RCT	226	224	50.9	13.9	1.13 (0.91-1.40) †
	Klatte et al 2018 (29)	Observational	97	164	14.6	25.6	0.63 (0.46-0.84)
	Patel et al 2017 (30)	Observational	289	773	52	NR	0.53 (0.24-1.15)
	de Groot et al 2016 (32)	Observational	73	73	NR	17.9	0.61 (0.41-0.92)
	Hanna et al 2016 (33)	Observational	5374	10,016	NR	17.1	0.49 (0.46-0.52)
	Heng et al 2014 (35)	Observational	982	676	39.1	20.6	0.60 (0.52-0.69)
	Abern et al 2014 (36)	Observational	2629	4514	13	NR	0.40 (0.37-0.43)
	Conti et al 2014 (37)	Observational	6915	13,189	12	15	0.41 (0.39-0.43)
	Choueiri et al 2011 (38)	Observational	201	113	16.3	19.8	0.68 (0.46-0.99)
	You et al 2011 (91)	Observational	45	33	8.2	21.6	0.53 (0.24-1.15)

TABLE 3. Studies investigating the survival associations with cytoreductive nephrectomy by treatment era. *CN = cytoreductive nephrectomy, OS = overall survival, HR = hazard ratio comparing patients receiving CN to those who did not receive CN, ICI = immune checkpoint inhibitor, TKI = tyrosine kinase inhibitor, NR = Not reported*
†HR reported as patients who did not undergo CN compared to patients who did undergo CN

Another question that was attempted to be investigated with a randomized clinical trial is optimal timing of CN (before or after systemic therapy). The SURTIME trial (Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients with Metastatic Kidney Cancer) investigated the timing of CN and sunitinib therapy[26]. Patients were randomized to either upfront CN followed by sunitinib or sunitinib therapy followed by deferred CN. Like CARMENA, SURTIME had difficulty enrolling patients and only 99 patients were recruited to the trial before it was closed. In the intention to treat population, the 28-week progression free rate (PFR) was 42% compared to 43% in the upfront versus deferred CN patients (P=0.61) and the median overall survival was 15 months versus 32.4 months in the upfront versus deferred CN patients (P=0.03)[26]. The trial indicated no significant improvement in the 28-week PFR with a possible survival benefit for deferred CN but results are difficult to interpret with small patient numbers. As a response to poor enrollment, 28-week PFR became a revised primary endpoint. Additionally, within the deferred CN arm, 29% of patients did not undergo surgery while 92% of patients in the upfront CN received surgery. The trial was not powered to detect an overall survival benefit and the survival analysis was exploratory. A per-protocol analysis ultimately did not demonstrate a significant overall survival difference between the two arms. Lastly, sunitinib as first line therapy is no longer clinically applicable to modern management of mRCC. In summary, the SURTIME trial suggested minimal difference in endpoints with different timing of CN but did not definitively answer the question.

The CARMENA and SURTIME trials fueled significant controversy regarding the utility and timing of CN in the management of patients with mRCC. Following the publication of these trials, the European Association of Urology (EAU) guidelines regarding CN were modified and recommended poor risk patients (based on MSKCC risk criteria) should not undergo CN and intermediate and poor risk patients should receive systemic therapy first before CN is considered[27]. The findings of these clinical trials, however, need to be balanced with the large number of observational data that suggest a continued survival benefit for patients receiving CN (TABLE 3)[28-38]. The conflicting evidence between randomized trials and observational studies likely resides in surgical selection bias. The appropriate selection of patients for CN is critical to successful outcomes, and this concept is reflected in many modern guideline recommendations (TABLE 4).

PATIENT SELECTION FOR CYTOREDUCTIVE NEPHRECTOMY – CHOOSING WISELY

There are no standardized selection factors for identifying ideal patients for CN. Multiple different prognostic and predictive variables have been identified, all of which have been investigated in observational studies. In general, variables that predict survival outcomes following CN fall into three major categories: institutional associated variables, patient associated variables, and tumor

GUIDELINE COMMITTEE	GUIDELINE RECOMMENDATIONS
2022 European Association of Urology (63)	1. Do not perform CN in MSKCC poor-risk patients. 2. Do not perform immediate CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy. 3. Start systemic therapy without CN in intermediate-risk patients who have an asymptomatic synchronous primary tumor and require systemic therapy. 4. Discuss delayed CN with patients who derive clinical benefit from systemic therapy. 5. Perform immediate CN in patients with good performance status who do not require systemic therapy. 6. Perform immediate CN in patients with oligometastases when complete local treatment of the metastases can be achieved
2022 National Comprehensive Cancer Network (69)	1. CN before systemic therapy is recommended in select patients with a potentially surgically resectable primary mass. 2. Patients with metastatic disease who present with hematuria or other symptoms related to the primary tumor should be offered palliative nephrectomy if they are surgical candidates. 3. Patients with surgically resectable primary RCC and oligometastatic sites may be candidates for nephrectomy and surgical metastasectomy or ablation for patients who are not metastasectomy candidates. 4. Patients who have undergone a nephrectomy and later develop oligometastatic recurrence also have the option of metastasectomy, radiation, or ablation.
2022 American Society of Clinical Oncology (92)	1. Select patients with metastatic clear cell RCC may be offered cytoreductive nephrectomy. Select patients include those with optimally one IMDC risk factor who can have a significant majority of their tumor burden removed at the time of surgery
American Urological Association	No guideline recommendations

TABLE 4. Guideline recommendations regarding cytoreductive nephrectomy from different guideline committees. CN = cytoreductive nephrectomy, MSKCC = Memorial Sloan Kettering Cancer Center, IMDC = International Metastatic RCC Database Consortium

associated variables. Within each of these categories, multiple variables have been identified that help to select ideal candidates for CN (FIGURE 1).

Tumor Characteristics

Certain characteristics of the primary and metastatic tumors are significantly associated with outcomes following CN. Patients are thought to be more likely to benefit from CN if the primary tumor accounts for the majority of total tumor burden within the patient[39, 40]. One study demonstrated that when assessing both metastatic and primary tumors, if the volume of the primary tumor comprises more than 90% of the total tumor burden, patients are likely to experience improved cancer-specific survival following CN[40].

Also, primary tumors with a tumor thrombus pose a unique challenge in the metastatic setting. Tumors that invade the inferior vena cava can progress rapidly toward the right atrium and cause significant symptoms such as leg swelling, fatigue, weight loss, liver failure and ultimately death. Up to 50% of patients with tumor thrombi can have metastatic disease. Abel *et al.* demonstrated that compared to tumor thrombi that only invade the renal vein (i.e., level 0), tumor thrombi that have advanced above the diaphragm (level IV) have significantly reduced overall survival (median 22 vs 9 months, respectively)[41]. Conversely, tumor thrombi that are still below the diaphragm but above the renal vein did not have significantly worse survival than level 0 thrombi (20 vs 22 months, respectively)[41]. Thus, patients with tumor thrombi invading the IVC should still be considered for CN by experienced surgeons.

The number and location of metastases should also be considered when identifying CN candidates. A greater number of different metastatic sites is associated with inferior outcomes following CN and certain locations portend more aggressive disease[42-45]. Patients with lung, pancreas, thyroid, or adrenal metastases tend to have a more indolent pattern of progression and may be better suited for upfront CN, while patients with liver or brain metastases tend to have worse overall survival and more rapid disease progression and may benefit from upfront systemic therapy followed by deferred CN in those who respond or demonstrate disease stability[42-44]. Metastasectomy should also be considered particularly for patients with oligometastatic disease in surgically resectable locations. Patients undergoing complete metastasectomy with CN (either at the same time or in a delayed fashion) have superior cancer-specific survival; however, patients undergoing metastasectomy typically are highly selected for excellent performance status and more indolent tumor biology[46, 47]. If surgical extirpation is not an option, metastasis directed therapy can be achieved in some circumstances using either ablative technology[48]. or stereotactic body radiotherapy (SBRT). A phase 2 trial by Tang *et al.* recently reported treating 30 patients with ≤5 metastatic tumors with SBRT to all metastatic sites. Median progression-free survival was 22.7 months and authors concluded that SBRT may delay systemic therapy initiation or facilitate breaks from systemic therapy among patients with oligometastatic RCC[49].

Additional tumor related characteristics that should be considered when deciding on CN are tumor associated symptoms, tumor histology, and sarcomatoid dedifferentiation. Patients may present with a symptomatic primary tumor with pain, gross hematuria, or paraneoplastic syndromes. In these situations, CN should be considered for appropriate surgical candidates to palliate symptoms and improve patient quality of life. Regarding non-clear cell histology, outcomes following CN are less well defined, but in general similar principles apply to patient selection and observational studies have demonstrated a survival benefit for patients receiving CN even with non-clear cell histologies.[50, 51]. Tumors harboring sarcomatoid dedifferentiation are particularly aggressive. Prior to ICI therapy, patients with metastatic sarcomatoid RCC often had rapid disease progression and short median overall survival, and observational studies of CN for patients with metastatic sarcomatoid disease showed worse survival compared to patients without sarcomatoid disease[52]. Sarcomatoid disease appears uniquely responsive to ICI therapy, however, and patients with sarcomatoid disease have experienced impressive responses with ICI therapy compared to older systemic therapy

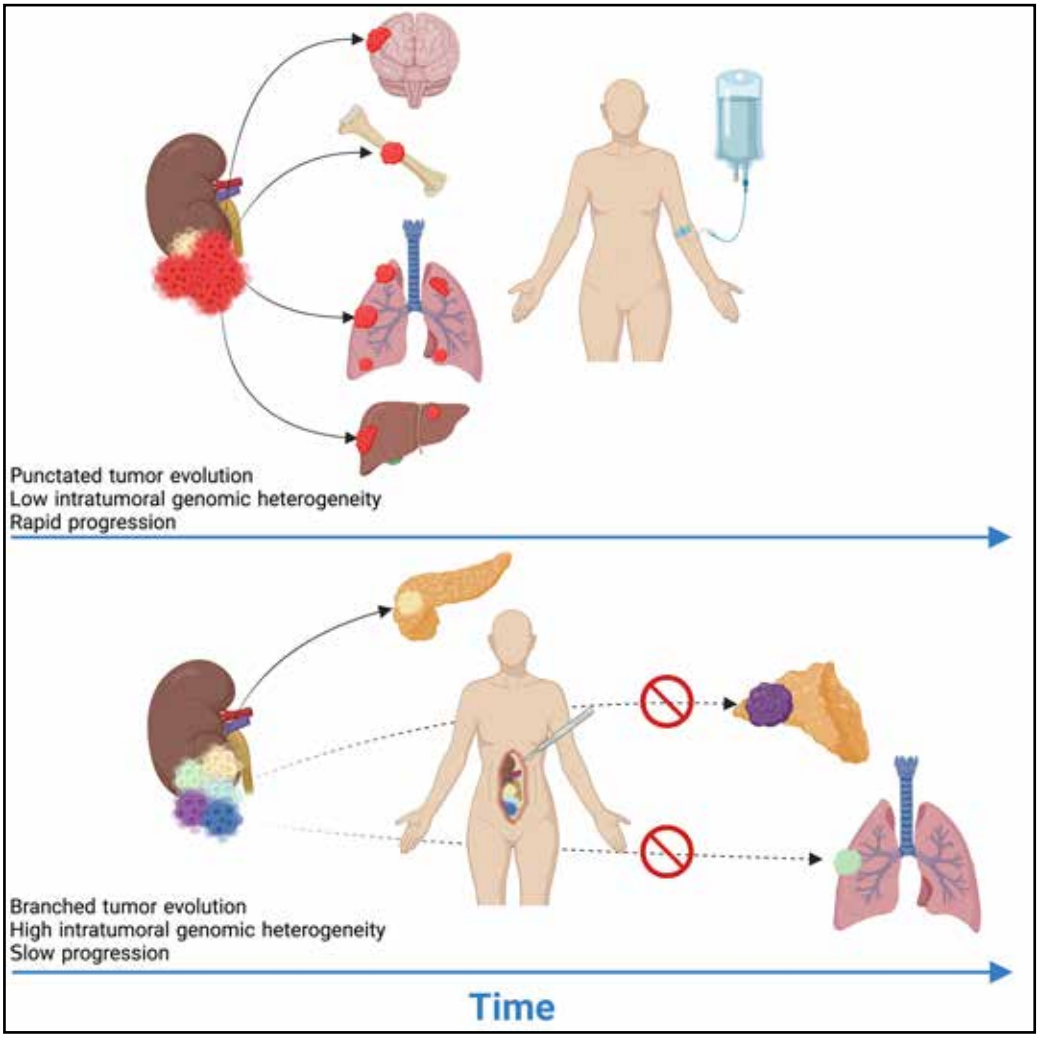

FIGURE 2 | Renal cell carcinoma tumor evolution and management overtime. Two different evolutionary patterns are represented in the figure. In the top panel, the renal cell carcinoma tumor evolution consists of a largely monoclonal cell population that acquired early, aggressive genetic change (e.g., BAP1 mutation) resulting in a genetically homogenous tumor cell population (indicated by the primarily red color cells making up the primary tumor). This results in rapid, widespread metastatic development, and these patients are often better suited for upfront systemic therapy. The bottom panel reveals a branched tumor evolution in which a genetically heterogenous tumor contains multiple different clonal populations. These tumors typically metastasize slowly and in an oligometastatic fashion with different metastatic tumors derived from different clonal populations within the primary tumor (represented by the different colored cells in the primary tumor). Cytoreductive nephrectomy is ideally suited for these patients by removing clonal populations of cells that potentially have future metastatic potential to different sites.

agents. The KEYNOTE-426 trial evaluating pembrolizumab+axitinib and the CheckMate 214 trial evaluating nivolumab+ipilimumab both demonstrated improved disease response among sarcomatoid tumors compared to the sunitinib control arm[5,6]. Thus, patients with sarcomatoid dedifferentiation and mRCC should be considered for upfront ICI/ICI or ICI+TKI therapy and later treated with surgery if there has been significant response to systemic therapy and a residual primary tumor. One challenge with sarcomatoid dedifferentiation is that clinicians frequently do not know if the tumor harbors sarcomatoid dedifferentiation at presentation or prior to offering surgery as it is not reliably detected on imaging or biopsy and is mainly determined after nephrectomy has been performed.

Among patients with borderline unfavorable tumor characteristics, some propose using upfront systemic therapy as a "litmus test" to determine whether or not the patient will progress even in the setting of systemic therapy. If a patient progresses, they are unlikely to benefit from surgical intervention. However, if a patient has a durable response to therapy, they may be more likely to benefit from surgery. In these situations, CN can be considered in the deferred setting. This is particularly relevant in the ICI therapy era, where significant responses to ICI/ICI and ICI/TKI therapy have been observed.

Patient Characteristics

One of the fundamental challenges faced by clinicians is determining the fitness of patients preoperatively and estimating a patient's individual risk of morbidity and mortality for a complex operation such as CN. Various measures of performance status have been used to estimate these risks including the Eastern cooperative group performance status scale[53], Karnofsky performance status[54], and Charlson comorbidity index[55]. While each of these measures can give a general idea of the patient level of fitness and comorbidity, none were specifically designed to measure a patient's risk of morbidity from CN or their subsequent survival following CN. In general, patients with poor performance status are felt to be higher-risk candidates for CN and favored to receive initial systemic therapy. Patient performance status is dynamic, however, and may improve after receiving systemic therapy making them eligible for CN after initial systemic therapy. This demonstrates the importance of a multidisciplinary approach to mRCC patient management when determining surgical eligibility, which should be considered not only during the initial evaluation of the patient but throughout a patient's disease course.

Other serum-based markers have been identified as predictive of patient outcomes. The presence of preoperative anemia, hypercalcemia, and hypoalbuminemia have been associated with worse survival following CN[56, 57]. Markers of systemic inflammation such as the elevated neutrophil lymphocyte ratio and

elevated C-reactive protein have also been associated with worse survival outcomes following CN[58-60]. While each of these variables may incrementally better inform selection of patients for CN, none has been routinely incorporated into patient selection and most require further external validation. Additionally, the majority of these markers were evaluated in the TKI therapy era, and require further study in the setting of modern ICI therapy.

Prognostic scores

Various prognostic scores have also been developed that incorporate many of the previously described variables. Two frequently used prognostic scoring systems are the Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria and the International Metastatic RCC Database Consortium risk criteria[61, 62]. The MSKCC and IMDC risk criteria are similarly designed but incorporate different prognostic variables that predict survival outcomes for patients with mRCC. Currently, the IMDC risk criteria are more frequently utilized as they were more recently developed in the TKI therapy era. Each variable in the IMDC risk criteria is assigned 1 point and the variables included are neutrophilia, thrombocytopenia, anemia, hypercalcemia, Karnofsky performance status <80, and time from diagnosis to systemic therapy of <1 year. Patients with mRCC are categorized into favorable (0 risk factors), intermediate (1-2 risk factors) and poor (≥3 risk factors) risk groups. The EAU guidelines recommend that intermediate and poor risk patients should receive systemic therapy first and poor risk patients do not benefit from CN[63] The limitation of using these risk stratifications to make decisions regarding CN is that they were not designed specifically to address survival outcomes following CN. Also, the risk classifications are often dynamic and may change during the disease course. A patient may initially present with poor risk disease (due to lab abnormalities such as anemia, hypercalcemia, and neutrophilia) but these may improve after receipt of systemic therapy or CN[64, 65].

In order to address these limitations, prognostic scoring systems have been developed specifically in CN patient populations to help identify appropriate candidates for CN[23, 66] Updating their prior prognostic classification system[66], the MD Anderson Cancer Center group recently evaluated a modern cohort of CN patients and identified 9 predictors of worse overall survival following CN[23]. The advantage of this study is that it incorporates variables that can be obtained preoperatively to risk stratify patients and was designed specifically in a CN patient population. Similarly, a study using the European registry for metastatic RCC (REMARCC) developed a scoring system to predict overall survival following upfront CN. The study incorporated BMI, metastatic location (lung, liver, bone), number of metastatic sites, and performance status into their model for predicting survival[67]. Both studies require further external validation and given the time periods within which patients were included, it is unlikely that many patients received ICI therapy during the course of their mRCC treatment, highlighting the need for prospective registries of mRCC patients receiving CN to identify predictors of favorable outcomes.

The medical system impact on cytoreductive nephrectomy

Another critical aspect of outcomes following CN is the system in which the patient is treated. Management of patients with mRCC is nuanced and complex, requiring coordination between multiple disciplines. Patients with mRCC interact with oncologists (including urologic, medical and radiation), pathologists, radiologists, interventional radiologists, anesthesiologists, nursing staff (in the clinic, infusion centers, inpatient units, research coordinators, and operating room), medical technologists (in the operating room and clinics), phlebotomists, billing and insurance staff, fellows, residents, and medical students to name only a few. Coordination of these components requires a system designed to and experienced in delivering care to patients with mRCC. Poor access to centers such as these may limit the ability for a patient to receive CN and negatively impact the survival outcomes of patients following CN. Cytoreductive nephrectomy has been shown to be more frequently performed at academic institutions and among the privately insured[30]. Higher hospital volume is also independently associated with improved mortality following CN[68]. Thus, patient access to systems that routinely manage mRCC and a thoughtful multidisciplinary discussion of these complex cases is critical for favorable outcomes.

CYTOREDUCTIVE NEPHRECTOMY IN THE ERA OF IMMUNE CHECKPOINT INHIBITORS

Since nivolumab approval in 2015, there has been rapid incorporation of ICI therapy into the management of mRCC, and ICI/ICI or ICI/TKI combinations are now first line therapy[69]. The improvements in response rates to modern systemic therapy again begs the question if there is still a role for CN. Given ICI therapy's relatively recent approval, very few studies have addressed the impact of CN on survival outcomes in the setting of ICI therapy and those that have are often small sample sizes with limited follow-up[70-73]. Cytoreductive nephrectomy following ICI therapy does appear safe and feasible. One of the largest multi-institutional studies by Shapiro et al. demonstrated that among 75 patients undergoing deferred CN following ICI therapy, the high-grade complication rate was only 3% with no 90-day mortalities. Additionally, 48% of patients were able to enter a period of surveillance following their CN, delaying further systemic therapy.(71) Thus, patients being treated with CN at experienced centers face low morbidity rates even compared to historic CN series[57].

Regarding survival outcomes, a recent study by Bakouny *et al* used the IMDC database to evaluate the impact of upfront CN (N=234) vs no CN (N=203) on survival outcomes among patients treated with ICI therapy. Multivariable analysis demonstrated upfront CN was associated with significantly improved overall survival compared to no CN among patients treated with ICI therapy (HR 0.61, 95% CI 0.41-0.9, P=0.013)[74]. These studies again appear to confirm that among appropriately selected patients, CN is safe and associated with improved survival.

CYTOREDUCTIVE NEPHRECTOMY FUTURE DIRECTIONS

As we gain a deeper understanding of RCC tumor biology, we may begin to better select patients for CN based on tumor biology. The TRACERx studies have demonstrated that tumors harboring BAP1 mutations are associated with rapid tumor progression and low intratumoral genomic heterogeneity. These patients may not derive a survival benefit from CN compared to tumors harboring primarily PBRM1 mutations without BAP1 mutations, which are associated with slow progression and high intratumoral genomic heterogeneity (FIGURE 2)[75]. The Memorial Sloan Kettering group also demonstrated that BAP1 mutations negatively affected OS among patients undergoing CN, while SETD2 and KDM5C mutations were associated with reduced risk of death[76]. Additional explorations into the tumor and immune microenvironments may help identify predictive biomarkers associated with patient survival following CN[4].

Clinical trials investigating CN are currently being conducted. Active trials include PROBE (NCT04510597), NORDIC-SUN (NCT03977571), and Cyto-KIK (NCT04322955). While these trials will provide insight on the role of CN in the deferred setting, there are currently no large trials investigating the use of upfront CN, which is utilized in healthy patients with minimal metastatic disease. Prior studies including CARMENA and SURTIME have demonstrated the difficulties accruing to CN specific trials, thus other mechanisms for studying CN in a robust and generalizable manner are necessary to supplement clinical trials. An additional robust method for studying CN in the future will be multi-institutional prospective registries to investigate CN outcomes, particularly in the upfront setting. While not randomized, prospective registry data can still provide important insight into CN practice patterns, perioperative morbidity, and survival outcomes, particularly in the rapidly changing treatment landscape of mRCC.

An additional unexplored area of research is the study of patient reported outcomes and quality of life following CN using validated HRQoL instruments used in most studies of systemic therapy. One of the primary proposed benefits of CN is that it improves patient symptoms and quality of life, but evidence to support this hypothesis is absent. Additionally, it is critical to involve multidisciplinary care across the patient's journey of treatment. Future studies to address these issues must be conducted.

CONCLUSION

Cytoreductive nephrectomy remains a critically important component of the multidisciplinary approach to management of patients with mRCC. A large body of evidence supports the use of CN in appropriately selected patients. Patients with good performance status and limited metastatic burden are ideal candidates for CN. The use and timing of CN will continue to evolve as our understanding of RCC tumor biology advances and systemic therapies continue to improve.

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CONFLICTS OF INTEREST

None

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KCJ ORIGINAL REVIEW

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Current perspective on the impact of endogenous retroviruses in clear cell renal cell carcinoma

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ABSTRACT

Human endogenous retroviruses (hERVs) have emerged as a mechanism for tumor development and progression in clear cell renal cell carcinoma (ccRCC). Increased expression of various hERVs has been reported in ccRCC with associated activation of anti-tumor immune responses. Retrospective analysis of hERV expression in human ccRCC tumor tissue suggests hERV expression may be associated with improved response to immune checkpoint inhibitors. However, the use of expression to predict response is limited by our ability to annotate and detect hERV expression. This review discusses the biology of hERVs, their role in ccRCC, and the possible impact on ccRCC response to immunotherapy.

KEYWORDS

Renal Cell Carcinoma, Endogenous Retroviruses, Immunotherapy

INTRODUCTION

Kidney cancer is the eighth most common cancer among both sexes in the United States and is estimated to cause 14,890 deaths in 2023[1]. Clear cell renal cell carcinoma (ccRCC) is the most common histologic type of kidney cancer, comprising up to 85% of RCC. ccRCC is characterized by the loss or mutation of the von Hippel-Lindau gene, resulting in constitutive activation of hypoxia-inducible factors (HIF) and upregulation of downstream signaling pathways, including vascular endothelial growth factor (VEGF). Other commonly mutated genes in ccRCC include those that encode chromatin-modifying enzymes, such as SETD2, PBRM1, and BAP-1, and PIK3CA. Over the past 20 years, the treatment paradigm for ccRCC has substantially changed with improved understanding of the underlying tumor biology. However, a mainstay in systemic therapies for ccRCC has been immunotherapy with a relative lack of understanding of the biologic drivers of response and resistance in ccRCC.

Historically, ccRCC has been considered responsive to immunotherapy with interferon-alfa and high-dose interleukin-2 as standard treatments[2,3]. More recently, ccRCC has demonstrated significant response to immune checkpoint inhibitors (ICI), but activity is only observed in a subset of tumors. A proposed mechanism of ICI response in other tumors is high tumor mutational burden (TMB) leading to increased tumor-associated antigens. In melanoma, increased TMB is associated with significantly improved long-term benefit[4]. However, ccRCC demonstrates a lower TMB than other cancers that respond to ICI. For example, melanoma typically has 10-400 mutations per megabase[4], while ccRCC demonstrates an average of 1.1 mutations / Mb[5–7]. Since ccRCC has lower TMB, alternative mechanisms of immunogenicity have been evaluated and expression of human endogenous retroviruses (hERVs) have been identified as a possible biomarker of response.

Over the past couple of decades, hERVs have been increasingly recognized as upregulated in human cancers[8–16]. Additionally, hERV products have been shown to elicit antitumor immune response in both renal cell carcinoma and other tumor types[17–22]. Recent studies highlight the significant role that hERVs may play not only in the development and progression of ccRCC, but also the response to immunotherapy[15,23–25]. In this review, we focus on the biology of hERVs, their identified roles in RCC, and how hERVs may impact response to immunotherapy in ccRCC.

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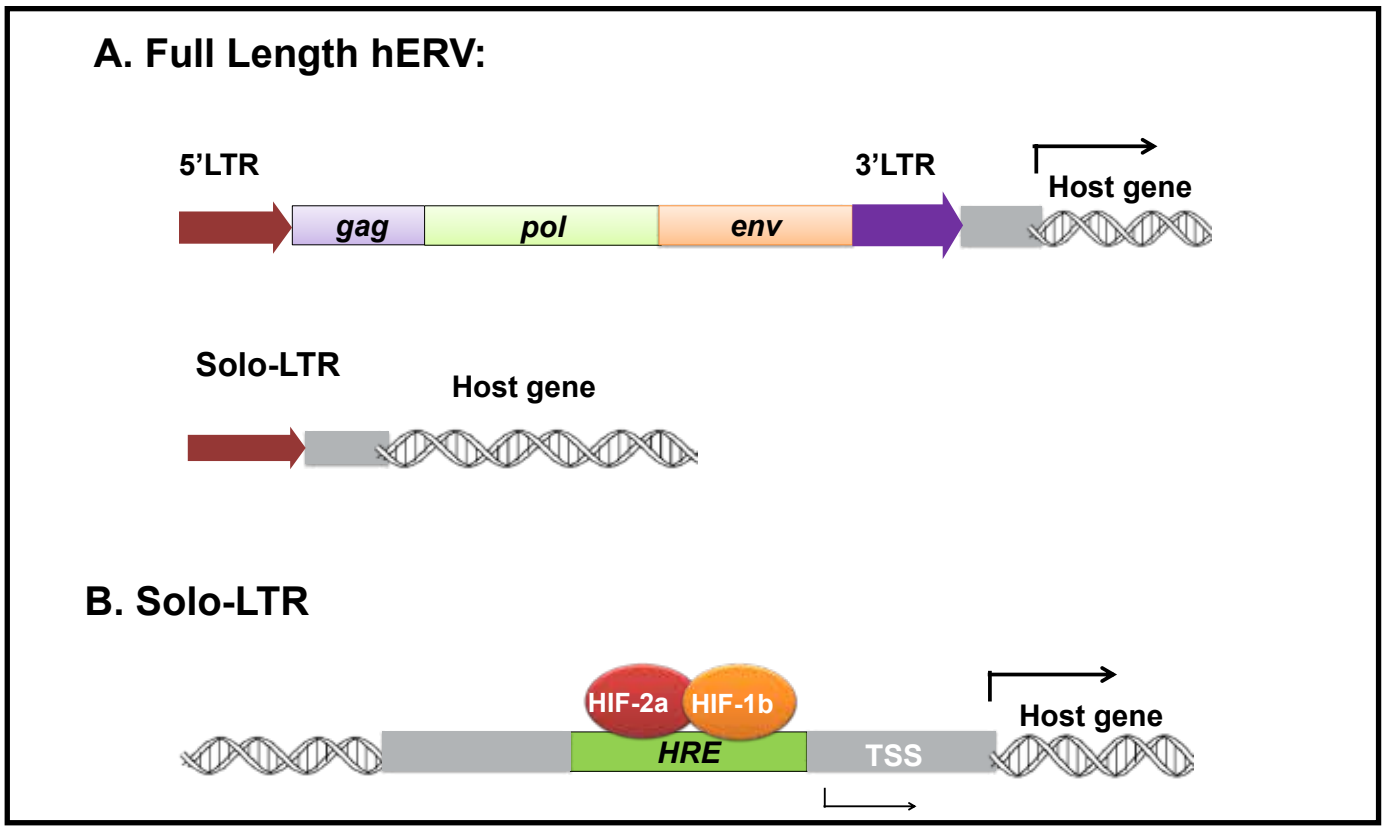

FIGURE 1 | The structure of hERVs retains gene regulatory elements, such as hypoxia response elements (HREs). **A.** Full-length hERVs consist of gag, pol, env, and 5′ and 3′ LTRs. Solo-LTRs lose gag, pol, and env, retaining an LTR and the included gene regulatory elements. **B.** Regulatory elements retained in solo-LTRs, such as hypoxia response elements (HRE) or transcriptional start sites (TSS), can be bound by transcription factors, such as hypoxia inducible factor (HIF), to promote expression of both hERVs and regulated genes.

The biology of endogenous retroviruses

Human endogenous retroviruses (hERVs) are endogenous viral components present in the human genome which originated as retroviruses millions of years ago and were incorporated into the genome of germ line cells. hERVs form the majority of long terminal repeats (LTRs) and comprise about 8% of the human genome26. While hERVs are defective in viral replication and typically lose the ability to encode proteins, they contribute to regulation of the human genome by acting as promoters, enhancers, repressors, poly-A signals, and alternative splice sites for human genes[19]. hERVs are typically silenced in normal somatic tissues19, but hERV expression has been reported as increased in a variety of cancers[8–14], including ccRCC[15,17,18], autoimmune disease, and neurological disorders[27–30].

Over 50 families of hERVs have been identified and are categorized into classes I-III[26]. For example, HERV-E and HERV-H are class I, while HERV-K is a class II hERV[26]. The structure of each individual hERV typically contains gag, pol, and env components, which are flanked on the 5' and 3' ends by two gene regulatory sequences, long terminal repeats (LTR)[26]. While most of the hERVs in the human genome lose coding ability, a few hERVs retain the ability to encode functional proteins, such as HERV-K and HERV-W[31,32]. Loss of hERV coding ability can be due to non-allelic homologous recombination between the 3' and 5' LTRs, resulting in solo-LTRs and loss of the gag, pol, and env components[33,34]. Within the human genome, hERVs typically exist in the solo-LTR form and maintain gene regulatory function through the presence of transcriptional regulatory motifs[34,35] (FIGURE 1). However, some hERVs, such as those in the ERVK family, do preserve a functional gag gene or open-reading frame for the pol and env genes[36].

hERVs may promote tumorigenesis through a variety of mechanisms. First, expression of hERVs can activate tumor-promoting signaling pathways, including the RAS-ERK and Wnt/β-catenin pathways[8,37,38], which promote cell proliferation and transformation. Second, the hERV envelope protein, syncytin-2, has been shown to have immunosuppressive properties[39]. However, hERV expression also promotes the detection of tumors by the immune system. Immunotherapy research in other tumor types has demonstrated that a subset of HERV-K and HERV-H proviruses express immune-stimulating antigens on tumor cells, which can then be recognized and killed by cytotoxic T-cells[20,22].

Endogenous retroviruses in clear cell renal cell carcinoma

Over the past two decades, hERV expression has been strongly implicated in the development and progression of ccRCC and is associated with clinical outcomes. First, multiple hERVs demonstrate increased expression in ccRCC, including HERV-E[16,18], HHLA2[40], and HERVERI[41]. Interestingly, expression of HERV-E in ccRCC appears to be interrelated to the underlying tumor biology. HERV-E expression levels correlate with HIF-2α levels and HERV-E expression was abrogated by introduction of normal VHL or HIF-2α knock-down[16]. Additionally, HIF-2α can act as a transcriptional factor for HERV-E by binding a HIF response element (HRE) located in the proviral 5' long terminal repeat (LTR)[16]. Cherkasova *et al.*, also demonstrated that this LTR was hypermethylated in normal tissues, preventing hERV expression, and hypomethylated in HERV-E expressing ccRCC tumors[16], allowing for increased expression. In a separate study, Siebenthall *et al* identified HIF-binding to other LTR sites genome-wide which correlated with gene expression changes in RCC, including HIF binding at an HRE in an hERV LTR located upstream of the stem cell transcription factor POU5F1 (OCT4), resulting in increased POU5F1 expression levels[42].

Increased hERV expression is also associated with PBRM1 loss in primary human ccRCC tumors[41]. PBRM1 is the second most frequently mutated gene in ccRCC5 and encodes a member of the PBAF (polybromo BRG1 associated factor) SWI/SNF chromatin remodeling complex[43,44]. This SWI/SNF complex regulates nucleosome positioning and gene expression[43,44]. We utilized the UMRC2 kidney cancer cell line to confirm that *in vitro* silencing of PBRM1, HIF1, and HIF2 resulted in increased expression of hERVs in a HIF1 and HIF2 dependent manner[41]. We also identified a specific family of hERVs, the HERVERI superfamily, that are enriched in PBRM1-regulated hERVs[41]. Therefore, expression of the HERVERI superfamily is dependent upon loss of function mutations in two genes that are highly specific to ccRCC, VHL and PBRM1, and may explain its unique association with this cancer.

Furthermore, the expression of hERVs in ccRCC is immunogenic, activating T-cell responses. First, in a study utilizing TCGA datasets from 18 tumor types, Rooney *et al.* identified that high immune cytolytic activity in ccRCC is associated with elevated expression of the HERV-E loci, ERVE-4[45]. Additionally, Cherkasova *et al.* demonstrated that proteins predicted to encode the HERV-E envelope protein (HLA-A*0201-restricted

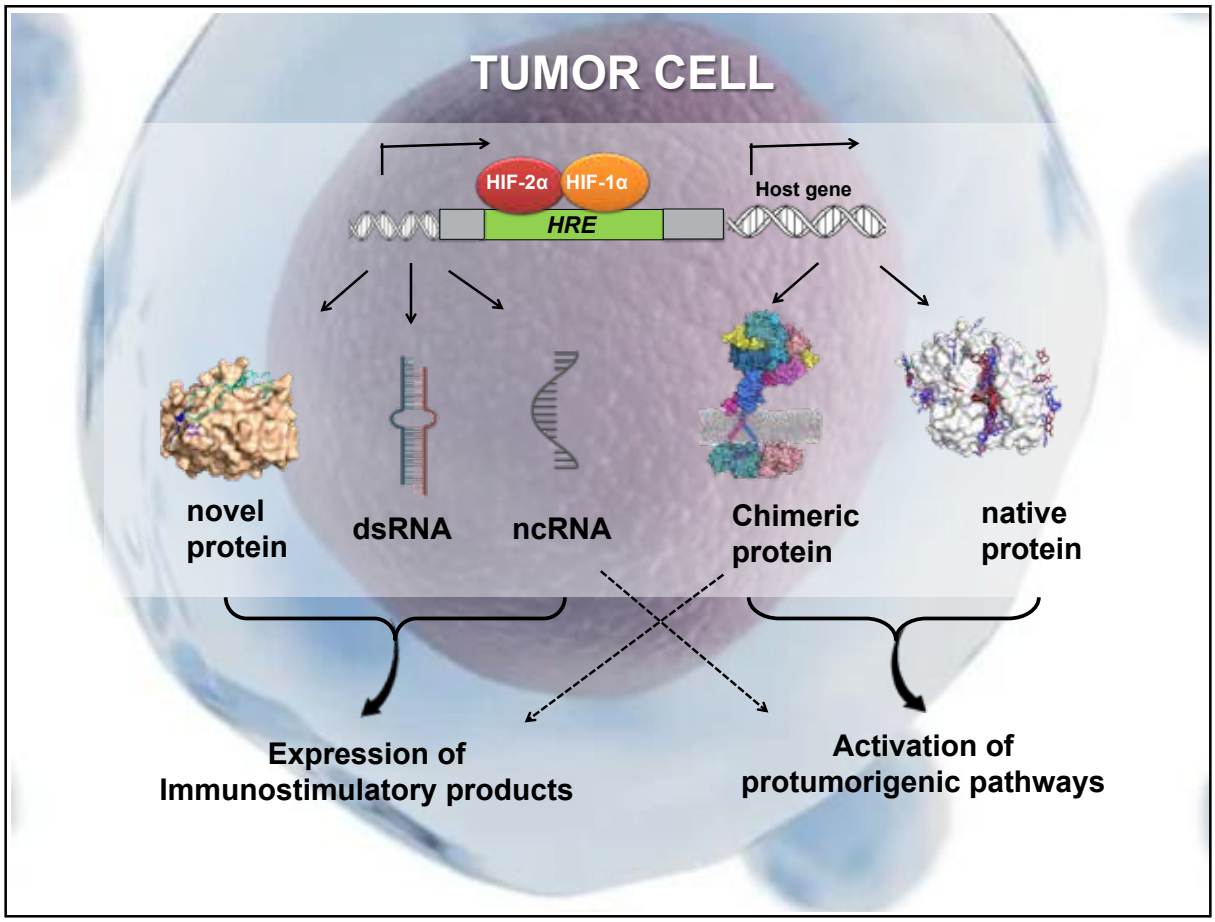

FIGURE 2: Proposed mechanism of the association between ICI response and hERV expression. In tumor cells, expression of solo-LTRs is proposed to result in the expression of RNA (including non-coding RNA (ncRNA) or double-stranded RNA (dsRNA)) or provirus-derived proteins which act as tumor-specific antigens which can induce tumor-specific immune cell responses or activation of pro-tumorigenic pathways. In the setting of ICI, we hypothesize that neoantigens promote a more robust immune cell response, allowing for improved response to ICI.

peptides) are expressed in ccRCC tumors and are immunogenic in vitro[17]. Furthermore, in a patient demonstrating regression of renal cell carcinoma after receiving an allogeneic hematopoietic stem cell transplant, a CD8+ T-cell clone recognizing a HERV-E antigen was isolated[18], suggesting tumor-specific T-cell reactivity in response to HERV-E expression. These results indicate that hERV- based antigens could act as targets for possible T-cell derived immunotherapy in ccRCC.

Finally, the expression of hERVs in ccRCC is associated with patient clinical outcomes. Human endogenous retrovirus-H long terminal repeat-associating protein 2 (HHLA2) demonstrates increased expression in ccRCC compared to normal kidney tissue at both RNA and protein levels[40] and HHLA2 expression was associated with poor overall survival[40]. Additionally, in a study utilizing the TCGA (The Cancer Genome Atlas) pan-cancer dataset, mean hERV expression in ccRCC was significantly negatively prognostic for overall survival and, when comparing Kaplan Meier curves for the upper versus lower 50th percentile mean hERV expression, ccRCC was one of only five tumor types that demonstrated significant separation of survival curves[15]. Of these five tumor types, ccRCC demonstrated the most significant association, with higher hERV expression associated with significantly shorter overall survival[15]. Further work in this dataset identified possible hERV signaling through the RIG-I-like pathway and B-cell activation and patients with both higher expression of B-cell receptor-associated signatures and down-regulation of RIG-I-like signatures demonstrated significantly shorter overall survival[15].

The impact of ERVs on response to immunotherapy in RCC

The introduction of immune checkpoint inhibitors (ICI) for the treatment of ccRCC has significantly improved patient outcomes. However, significant responses are only observed in a subset of patients and much work has focused on identifying predictive biomarkers. Given the immunogenicity of hERV expression discussed above, studies have utilized patient samples from ICI clinical trials to assess the association between hERV expression and tumor response to ICI.

In 24 metastatic ccRCC tumors treated with single-agent PD-1/PD-L1 blockade, ICI responders demonstrated significantly higher expression of ERV3-2 than non-responders[23]. Using the TCGA KIRC dataset, this study also demonstrated that high expression of twenty hERVs that were identified as potentially immunogenic was associated with increased immune infiltration, checkpoint pathway upregulation, and a higher CD8+ T-cell proportion in tumor infiltrating leukocytes compared to low hERV expression[23]. By performing qRT-PCR on tumor samples from CheckMate010, Pignon *et al.* also evaluated the association between 4 hERVs (pan-ERVE4, pan-ERV3.2, hERV4700 GAG, and hERV4700 ENV) and response to nivolumab[24]. Using a cutoff of the 25th percentile, high levels of hERV4700 ENV were associated with significantly longer median progression free survival and higher overall response rates[24]. Similarly, using tumor samples from CheckMate 025, Ficial *et al.* identified that in ccRCC tumors treated with nivolumab, higher hERV-E RNA expression levels were associated with increased durable response rate and longer progression-free survival[25]. Additionally, in the previously mentioned TCGA pan-cancer dataset, a transcriptional signature indicating anti-PD1 responsiveness (IPRES_aPD1_responder) demonstrated positive association with hERV expression in 79.2% of significantly associated hERVs in all tumor types[15]. Within ccRCC specifically, higher expression of hERV 4700 was associated with response to anti-PD1 therapy[15]. When combined, these studies suggest that high hERV expression may identify patients who might respond to ICI. FIGURE 2 illustrates a proposed mechanism for this improved response in the setting of hERV expression.

However, when Braun *et al.*, subsequently pooled data from CheckMate009, CheckMate010, and CheckMate025, they did not identify a robust association between hERV expression and response to immunotherapy. In this study, they first validated RNA-seq-based expression of hERV using qRT-PCR and demonstrated that RNA-sequencing did not reliably quantify ERV3-2 expression. However, they did identify a weak association between ERV2282 and ERV3382 expression with response and overall survival and progression free survival. However, when divided into high and low expression levels, the significant association with PFS and OS did not persist[46].

Additionally, using tissue from the ADAPTeR trial, in which patients with metastatic ccRCC were treated with nivolumab, Au *et al* concluded that ccRCC-specific hERV expression did not directly correlate with response to anti-PD-1 treatment[47]. Specifically, they performed RNA-sequencing on a total of 60 tumor samples from 14 patients and annotated hERVs using a previously built "complete custom repeat region annotation"[48]. Even when accounting for annotation discrepancies between prior analyses, the hERVs previously identified as associated with cytotoxic T-cell presence, ccRCC response to ICI, or providing antigens were not differentially expressed between ICI responders and non-responders or associated with ICI response in this study[47]. However, 10 different hERV annotations were significantly associated with ICI response but demonstrated a mix of restriction to responders versus non-responders, demonstrating a different pattern of hERV association with ICI response than observed in the above studies[47]. Based on

these results and data indicating that hERVs previously reported as upregulated in ccRCC may be expressed on immune cells, Au *et al* suggest that hERV expression in ccRCC may reflect tumor purity and the diverse cellular composition of ccRCC tumors[47].

As described above, PBRM1 loss is associated with increased expression of hERVs in primary ccRCC human tumors and additional work has evaluated the interplay between PBRM1 mutation, hERV expression, and ICI response. First, previous work has evaluated predictors of ICI response in ccRCC and variably identified PBRM1 mutations as a predictive biomarker[46,49–53]. While studies identified an association between PBRM1 loss of function mutations and second-line, single-agent ICI response[46,49,50,53], additional groups evaluating PBRM1 mutations and ICI response in first-line treatment with combination VEGF inhibitor and ICI did not identify an association[51,52]. Additional work by Liu *et al* highlights the role that HIF plays in this response since PBRM1 deficient, HIF axis-intact cells show ICI resistance[54]. This study utilized VHL and PBRM1 wild-type RENCA cells, which are murine-derived RCC cells from a BALB/c background, in which PBRM1 knockout was achieved using CRISPR/Cas9 technology[54]. When introduced into mice subcutaneously, both PBRM1 wild-type and knockout cells established tumors and PBRM1 knockout tumors showed worse survival than control tumors following treatment with PD-1 antibody[54]. Further evaluation of how the concurrent loss of PBRM1 and VHL impact ICI response is needed.

In addition to using hERV expression as a predictive biomarker for ICI response, future directions can also explore alternative approaches to exploiting the biology of hERVs. First, as hERVs are immunogenic, they may have the capacity to serve as vaccine targets. Indeed, in a mouse model with tumors formed from murine renal carcinoma cells (Renca) altered to express the HERV-K Gag proteins, mice vaccinated using a recombinant virus expressing the HERV-K Gag protein demonstrated reduced tumor growth and reduction in pulmonary tumor nodules[55]. Similar results were observed when mice with tumors expressing HERV-K Env proteins were vaccinated against the HERV-K Env protein[56]. Second, it may also be possible to manipulate the expression of hERVs to increase response to immunotherapy. For example, kidney cancer cell lines and primary cells that were treated with a DNA hypomethylating agent, decitabine, demonstrated increased expression of transposable elements, LINE1, and ERVs ERV3-2 and ERV4700, which were associated with immune infiltration and ICI response on bioinformatic analysis[57]. Finally, work investigating the impact of treating HLA-A*11:01 positive patients with metastatic ccRCC with HERV-E TCR transduced CD8+ and CD34+ enriched T-cells is ongoing (NCT03354390) and remains a promising option for exploiting hERV expression to more effectively treat ccRCC.

CONCLUSIONS

A subset of ccRCC tumors demonstrate increased expression of human endogenous retroviruses, endogenous viral components which have been incorporated into the human genome. ccRCC expression of hERVs seems to be interrelated to its distinct underlying tumor biology, with hERV expression levels related to both the VHL-HIF pathway and PBRM1 loss. Furthermore, the expression of hERVs in ccRCC is immunogenic, resulting in activation of tumor-specific T-cell responses in vitro and *in vivo*, and studies in mouse models highlight the potential for hERVs to act as vaccine targets. While higher hERV expression is associated with worse overall survival in ccRCC, data evaluating the association between hERV expression and response to ICI is conflicting. While single study reports identified encouraging associations with improved patient outcomes, only weak associations were observed when studies were combined, possibly reflecting differences in intratumoral heterogeneity and the tumor microenvironment. As such, additional knowledge of the mechanisms and pathways by which HERVs impact ccRCC tumorigenesis and therapeutic response is needed for optimal therapeutic development and continued improvements in patient outcomes.

FUTURE DIRECTIONS

Further investigation of the impact of human ERVs on the pathogenesis and progression of ccRCC will allow for improved understanding of the role ERVs play in response to therapies. Additionally, utilizing tissue from clinical trials assessing response to combination immunotherapy or prior to receiving systemic therapy may shed light on the seeming discrepancies in the association of hERV expression and ICI response. Finally, a broader understanding of the biology of hERV in ccRCC is necessary, including 1) characterizing the expression of hERVs in ccRCC tumor cells versus the tumor microenvironment; 2) elucidating the key downstream signaling pathways activated by hERVs and the interplay with VHL loss and chromatin modifying enzymes, and 3) identifying additional tumor-specific antigens. Further knowledge of the key cell types, antigens, and signaling pathways impacted by hERVs will allow further development of synergistic therapies and optimization of first-line treatments for individual patients.

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KCJ ORIGINAL REVIEW

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An Opportunity to Study Mechanisms of Palliative Care by Integrating into Management of The Treatment of Renal Cancer Carcinoma

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ABSTRACT

Achieving patient-centered care requires helping patients understand their illness, eliciting patient values, and developing a collaborative care plan with input from patient and physician. Combining existing models in communication skills and shared decision making provides a road map for accomplishing these tasks in delivering patient-centered care. In this article, we highlight the importance of patient understanding of their prognosis as a key step in delivering patient-centered care. We then review literature suggesting that both patient and patient's physicians' emotions play an inhibitory role in accurate formulation and communication of prognosis by physicians and accurate incorporation of this information by patients. We postulate that the finding of benefit of early integration of palliative care (PC) in improving patient-centered outcomes may be addressing these inhibitory factors. Key skills of empathic communication by a PC team that is focused on addressing patient emotions may facilitate better understanding of prognosis and thus improved patient-centered decision leading to improved patient centered outcomes. Finally, we propose advances treatment of renal cell carcinoma makes it an ideal disease that can inform this hypothesis of how integration of PC works. Specifically, we propose that the curability potential in metastatic RCC, amplifies challenges associated with patient prognostic understanding and decision making. Studying which discipline – primary oncology team or palliative care team – can help patients achieve more accurate prognostic understanding leading to more patient centered choices and improved patient-centered care.

KEYWORDS

Palliative Care, Renal Cell Carcinoma, Kidney Cancer

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INTRODUCTION

> ***"The secret of the care of the patient is caring for the patient."***
>
> \- Francis Peabody, 1921

Early integration of palliative care (PC) has been advocated in routine oncological care in the past decade based on studies showing improvement in patient symptoms, quality of life and survival[1-7]. Despite these recommendations, retrospective review of inpatient and outpatient data shows that most patients do not receive palliative care services as recommended by the guidelines, including patients with kidney cancer [8-10]. At the same time, the mechanism by which improvement in patient centered outcomes including survival are achieved by integration is not clear.

In the United States, an estimated 79,000 new cases and about 14,000 deaths due to kidney and renal pelvis cancer are projected to occur in 2022 alone[11]. Over 90% of kidney cancer cases are due to renal cell carcinoma (RCC). About 30% of patients initially present with metastatic RCC and another third of patients will have cancer recurrence with distant metastases after extirpative surgery[12,13]. With recent advances in immunotherapy, the landscape for treatment and outcome of RCC has changed ushering in multitude of challenges and opportunities[14]. Here, we focus on one of these challenges, providing accurate prognostic understanding, and the representative opportunity it represents to study the mechanism of palliative care interventions. Advances in treatment has led to additional prognostic uncertainty of "*can I be cured*?" to the existing prognostic uncertainty of "how long do I have, doctor?" By integrating palliative care into routine RCC care, we propose to study which discipline in the multidisciplinary team can help patients achieve more accurate prognostic understanding, leading to improved decision making and, patient outcomes.

Importance of accurate prognostic understanding

Studies of early palliative care integration demonstrated survival benefits in patients receiving early integration of palliative care[5, 15]. In one study, at the time of the early integration of PC in metastatic lung cancer, disease was deemed incurable, and yet at baseline, 32% of patients expected that their metastatic disease was curable, and 69% reported that elimination of all cancer was a reasonable goal

of treatment. With integration of monthly palliative care visits, a greater percentage of patients in the early palliative care arm were noted to have cultivated an accurate understanding of prognosis (82.5% vs. 59.6%). Furthermore, the authors found that patients having an accurate understanding of disease prognosis and undergoing palliative care treatment were least likely to opt for aggressive and standard of care intravenous chemotherapy treatment within 60 days of death[15]. The study reported survival benefits in patients with early palliative are arm. It also showed that those with more accurate improved prognostic understanding chose less chemotherapy[5,15]. Thus, improved, and accurate illness and prognostic understanding and decisions based on accurate prognostic understanding likely play a role in patient outcomes which aligns with our goals of patient-centered care and shared decision making (SDM).

Model for Conveying Accurate Prognostic Understanding – Communication Skills and Shared Decision Making

We can view the importance of accurate prognostic understanding in a larger context of patient-centered care. Institute of Medicine defined patient-centered care as "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions"[16]. Thus, physicians must accomplish at least two major tasks to provide patient-centered care, 1) to elicit and understand the patient's preferences, needs, and values and 2) to develop a collaborative plan with the patient that respects and honors their preferences, needs, and values.

There are two separate models that accomplish these two goals. A communication skills (CS) model, SPIKES, that provides a roadmap for building rapport, eliciting patient preferences, needs and values by using skills such as active listening, reflection, and empathic communication[17]. A shared decision making model allows for the development and implementation of a collaborative plan with input and collaboration from patients and physicians[18]. SDM ensures that among the various treatment choices, patient preferences and values are guiding the decision. Together, communication skills and shared decision making provide specific tasks for physicians and patients to complete to achieve optimal patient-centered care.

These two tasks can be modeled in a combined CS and SDM models into one as shown in Figure 1. In this combined model, when a patient and a physician come together to make a decision, the SDM model acknowledges that they both bring their own worldview to the discussion. These worl`dviews are shaped by individual background, lived experiences, knowledge, and emotions[18]. These worldviews shape the perceptions of the conversation between a patient and a physician, and the decisions are made based on these perceptions. These perceptions are what can be assessed by physicians when listening to a patient's story initially as they build a rapport with the patient and family. The language and vocabulary used by the patient can provide a window into that patient's perspectives that will help or impede future decision making. In addition, the physician needs to elicit patient preferences and values along with their hopes and fears by listening and asking direct questions. Physician uses principles of empathic communication throughout the conversation and over the long term relationship including use of open-ended and guided closed-ended questions[17].

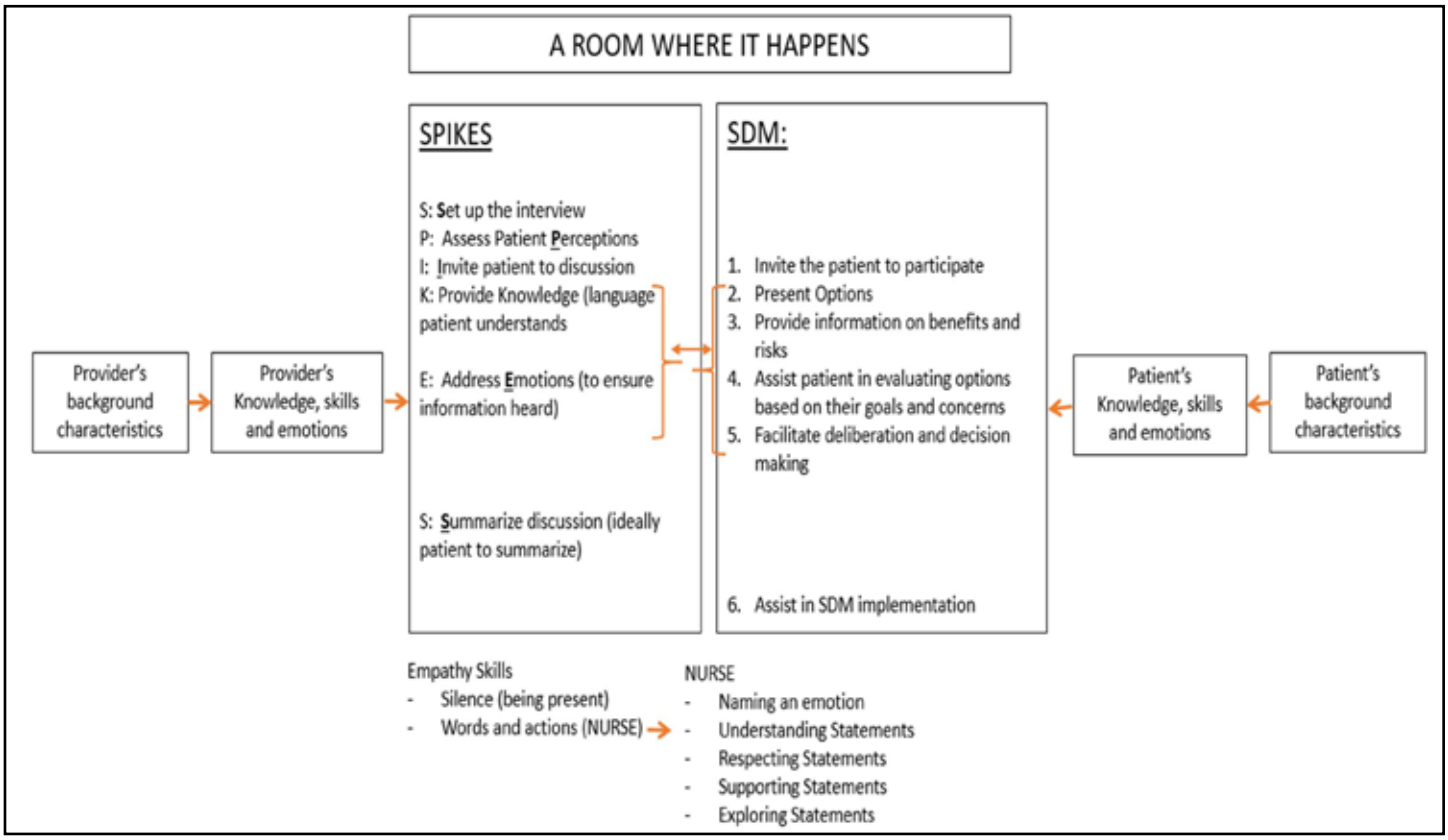

FIGURE 1. The room where it happens: Visualization of Patient Centered Care (Adapted with permission from Kane et al., 2014).

Once the physician has had a good understanding of the disease and patient goals and preferences, they can invite the patient to start the decision-making process for therapies. The process includes reviewing options for therapies in a stepwise and iterative manner. For each therapy choice, risk and benefits are explained and understood and how they impact patient preferences and goals are highlighted. Given this can be emotionally challenging and cognitively overwhelming conversation, the physician needs to conduct the conversation with great empathy, including using the non-verbal skills of silence and reflective listening and verbal skills to ensure patients hear and understand what is said. Examples of these verbal skills include: Naming an emotion (N), Understanding statements (U), Respecting statements (R), Supporting statements (S) and Exploring statements (E) or commonly referred to as NURSE acronym[19].

Although shown in Figure 1 as a series of steps, providing information is likely to be an iterative process with multiple pauses, iterations, and restart of the conversation to ensure that the patient understands their disease, their treatment goals, and their potential treatment options including risks and benefits of each of these options. The physician uses patient's own words and language to increase the odds that the patient hears and understands what is being said. This iterative process allows the physician to guide the discussion with the patient and families, while eliciting and refining patient values and preferences. Finally, once all the discussions have occurred and they can be a collaborative agreement on best treatment option and specific next steps. The physician can ask the patient to summarize the patient's understanding to ensure all have mutual understanding of the discussion and the collaborative plan.

Patient and Physician Emotions Are Key Intermediaries to prognostic understanding

As shown above, to achieve a patient-centered decision, the physician first must understand the patient worldview including their goals, values, and preferences, and then provide information that is heard and understood by the patient. The information can include prognostic information. After obtaining a mutual understanding, the physician then needs to help the patient make decisions that are aligned with that patient's goals. The key to this complex process is the fundamental of CS, empathic communication as shown in Figure 1.

Both patient and provider emotions play a key role in what and how information is conveyed and what was heard during the above conversation. If the conversation or patient understanding is suboptimal, it may lead to patients making choices incongruent to their values and preferences. The challenge thus is both patient and physician emotions.

For example, two separate studies showed potential impact of physician emotions on formulating and communicating prognosis. In one study, a longer the physicians had known the patient, more likely the physician would err in their prognostication [20]. In a different study, what physicians told the researchers about prognosis (formulated prognosis) was and what they told patients (communicated prognosis) differed by more than 20% and both were significantly inaccurate (for example, communicated 90 days survival estimate when actual was 26 days)[20, 21]. Thus, both conscious and unconscious optimism, possibly from provider emotions, plays a role in formulation and communication of inaccurate prognosis[21].

Similarly, patients' emotions and world view may impact what they hear and how they make decisions. Aim of phase 1 studies is to assess for dose limiting toxicities and optimal dose for future research and involve first in human drug or combination of drugs. Review of informed consents have shown that there is almost never a promise of direct benefit to subjects, rarely mention cure, and usually communicate seriousness and unpredictability of risk[22].

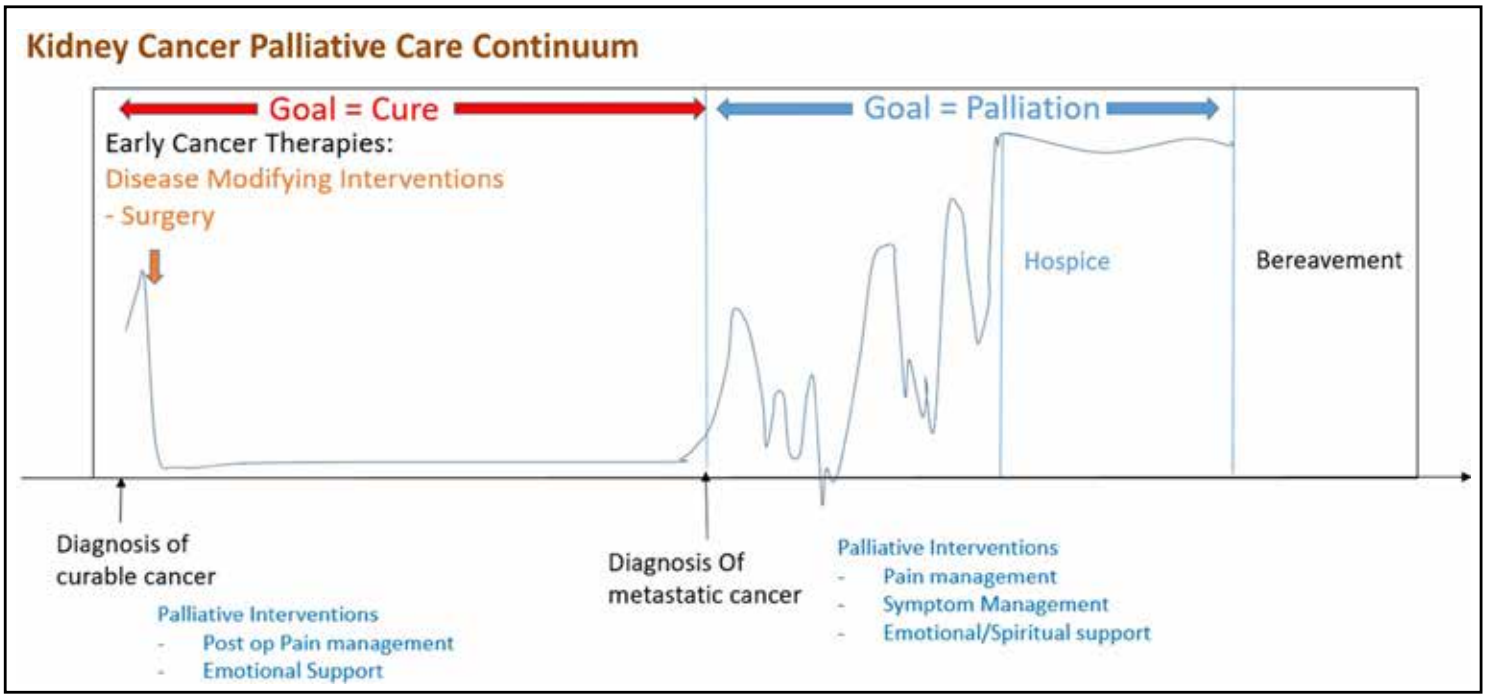

FIGURE 2. Model of palliative interventions in curative and palliative setting for kidney cancer

Despite their consent, patients participating in these trials reported a different perception and that provides insights into how patients perceive and make decisions. In a large multi-centered study of one hundred-sixty-three patients participating in phase 1 studies showed that 75% of patients felt the pressure to participate because their cancer was growing and similar percentage of patients reported feeling somewhat or very anxious when they were not receiving some sort of anti-cancer therapies [23]. More interestingly, only 3% of participants reported they personally were very or somewhat unlikely to benefit from participating in the phase 1 study even though 60% of them estimated that others were unlikely to benefit[23].

In a different study of patients being evaluated for phase 1 studies showed that those patients who enrolled in the phase 1 study reported higher likelihood of response to therapy compared to patients that did not enroll or physicians who had consulted with them[24]. Thus, patients perceive and process information thru the lens of their emotions and worldview which may lead to more inaccurate expectations of benefit of therapy.

Thus, physician and patient emotions can prevent accurate prognostication and communication of the prognosis by the physician and can lead to patients making decisions without accurately understanding of their prognosis and its implications on their therapy options and likely outcomes. Thus, a decision made with inaccurate information can lead to flawed and ultimately poor decisions such as continuing ineffective therapies or taking therapies that are unlikely to benefit and may even be counterintuitive to their stated goals.

Integration of Palliative Care in RCC and Exploration of Mechanism of action of Palliative care

Palliative care is specialized medical care delivered by a multidisciplinary team of physicians, nurses, social workers, and other specialists addressing multiple domains of care.[25, 26]. Palliative care team focuses on symptom management as well as provides expert communications with patients and caregivers. The expert communication, as shown in the Figure 1, involves addressing emotions with empathy. When symptom management and expert communication are provided by the primary oncology team, it is called "primary palliative care" and when using a subspecialty team, it is called "subspecialty palliative care"[27]. Post-operative pain by the urologist; prevention and treatment of side effects of medical therapies by the medical oncologists; radiation to alleviate pain from bone metastasis by the radiation oncologists are all examples of delivery of primary palliative care delivered by the oncology team. In addition to these symptoms, one or more of the primary teams can discuss treatment goals and address patient emotional and spiritual needs. When needed, these primary teams can consult with subspecialists to help them manage patient's symptoms or communications, it would be considered specialist palliative care. Using this definition, we can conclude that palliative interventions start concurrently with curative treatments, continue alongside palliative intent therapies, until a point where focus changes to providing comfort, eventually transitions to hospice (Figure 2).

All the challenges to SDM listed above with inaccurate prognosis, communication, and patient perceptions have been studied prior to advances in oncologic therapies such as immunotherapy. Immunotherapy, and specifically immune checkpoint inhibitor (ICI) therapy, has changed the landscape of management of RCC. Prior to the advances in immunotherapy, the answer to the question "can I be cured" when presenting with metastatic disease was "no" with confidence ad now, it is much more nuanced. Recent phase III studies with combination of immunotherapies show that even with metastatic disease, up to 7-16% patients can have long-term complete remission and may be even cured[28-31]. This creates a further challenge and an opportunity in communicating prognosis to achieve patient centered decision using SDM.

This challenge of difficulty in communicating 'curability' highlighted in a study of patients with advanced lung cancer and genitourinary (GU) malignancies receiving immunotherapy[32, 33]. Approximately 20-95% of patients had an inaccurate understanding of their curability and had increased anxiety compared to those with an accurate understanding of their cancer[34].

Considering the challenge of prognostic uncertainty caused by improved RCC outcomes and the observation that palliative care integration has been shown to both improve prognostic understanding and contribute to the making of more patient-centered decisions, RCC is an ideal disease in which to study how palliative care improves patient survival.

There is already pilot data of integration of palliative care into routine RCC care in the immunotherapy era[27]. We hypothesize that using the model for decision making above and understanding how the above tasks are completed, we may be able to understand the mechanism by which integration of palliative care enhances patient outcomes. We further hypothesize that the advances in RCC treatment in the past decade with increased uncertainty makes it an ideal disease to study and elucidate these mechanisms that can then be utilized in other diseases.

Mechanisms include improved patient prognostic understanding via improved management of patient emotions and communication. As studies have showed that the longer an oncologist knows a patient, accurate prognostication becomes more difficult, and it becomes even harder to communicate this prognosis accurately, an independent palliative team may have less emotional burden to facilitate an honest conversation[20, 21]. A separate team that is focused solely on patient symptoms including emotional symptoms, also allows patients increased opportunities to feel "cared for," as was highlighted by Dr. Peabody, without getting chemotherapy and scans.

We hypothesize that potential mechanisms of the benefits from palliative care may include:

- Improved illness communication, through improved physician understanding of patient worldview and management of patient emotions
- Improved prognostic understanding leading to improved shared decision making

Patients with RCC undergoing concurrent oncological and palliative care can be assessed along with each team for how information is conveyed and heard by the patient. While both the primary oncology team providing palliative care can be skilled, the context of the conversations with patients who are focused on cancer and therapies may preclude accurate exchange of information due to the emotional

reactions from both patients and the primary team. Having a subspecialty palliative care team with expertise in symptom management and communication skills may allow patients and the PC team to have discussions in a non-cancer treatment context, which may facilitate better information incorporation and even improved decision making.

By evaluating how information on diagnosis, staging and treatment goals are discussed, how patient understands them and how the discussion of prognosis is conducted, and decision made to start, continue, change, or stop cancer directed therapies will allow us to understand the role primary oncology and palliative care team plays in improving patient understanding and decision making.

An improved mechanistic understanding of how palliative care team impacts patient outcomes may help guide future implementation and research. Understanding whether the primary team, due to its relationship with the patient, is likely to be handicapped in an objective discussion may facilitate better identification of when and how to integrate palliative care. Understanding which factors predict which patients view and relate to primary team and the palliative care teams different may also provide better insights into which patients need early palliative care integration to optimize patient-centered care.

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KCJ EDITORIAL PERSPECTIVE

OPEN ACCESS

HIF Pathway Inhibition hold much promise and Point Toward an expanding RCC Armamentarium

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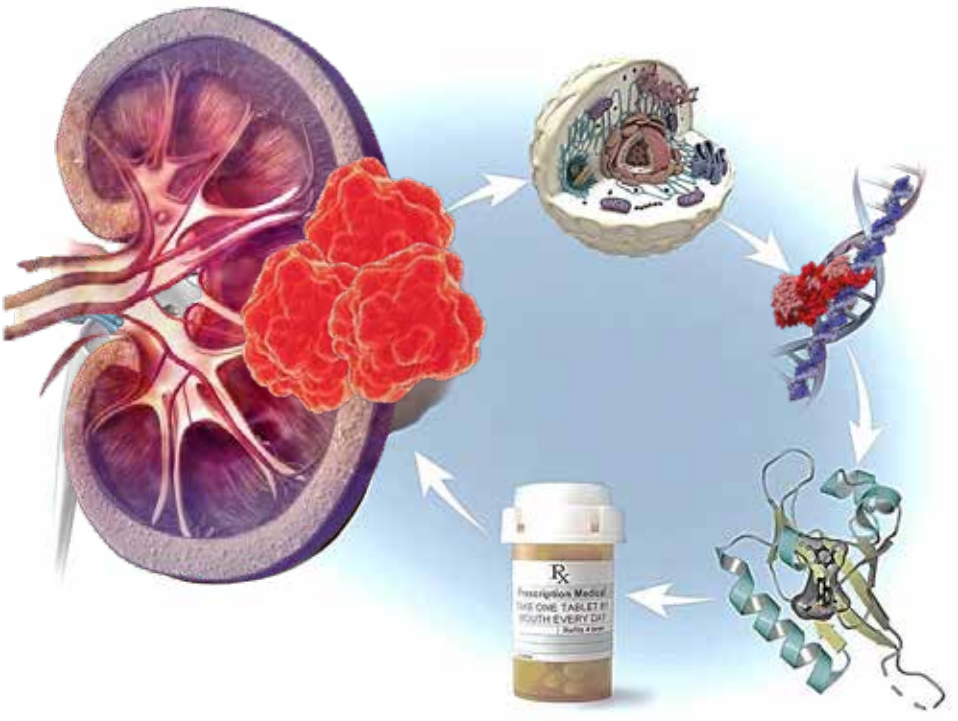
The journey of Belzutifan towards the goal of getting its FDA approval for patients with refractory renal cell carcinoma has reached another milestone[1]. The FDA has granted priority review to the supplemental new drug application (sNDA) for belzutifan. The sNDA seeks approval for the indication of patients with previously treated advanced renal cell carcinoma following immune checkpoint and anti-angiogenic therapies. The interim findings from LITESPARK-005(NCT04195750) demonstrates that the treatment with belzutifan led to a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared with everolimus in adult patients with advanced renal cell carcinoma whose disease progressed following PD-1/PD-L1 and VEGF tyrosine kinase inhibitor (TKI) treatments[2].

The current study results add to a growing body of early phase trial results that suggest meaningful clinical benefits from HIF2 pathway inhibition in patients with RCC. "*This is not only the first new mechanism to demonstrate potential in advanced RCC in recent years but also the first phase III trial to show positive results in advanced RCC following these therapies*", says Marjorie Green, MD, senior vice president at Merck Research Laboratories, in a press release[1]. "*Patients with advanced RCC face low survival rates, and for those whose cancer progresses following PD-1/L1 and VEGF-TKI therapies, there is a need for new treatment options that can reduce their risk of disease progression or death.*"

This registrational study where patients with treatment-refractory clear cell RCC were randomized between belzutifan and everolimus was conducted with the goal of obtaining approval for belzutifan in the refractory disease setting. "*Based on the data on the phase 1b/2 study we conducted in patients with previously treated advanced RCC, it became clear belzutifan is an active drug*[3,4]," Eric Jonasch, MD, professor in the department of genitourinary medical oncology, division of cancer medicine, at The University of Texas MD Anderson Cancer Center in Houston, TX. The safety portion of the analysis showed that belzutifan's profile was consistent with that shown in prior studies as there were no



new safety signals with either treatment compared with previously reported safety outcomes with the treatments. However, the shortcoming of this study is improvement in overall survival (OS) did not reach statistical significance despite statistically significant improvement demonstrated in another secondary end point, objective response rate (ORR). OS will be tested again at a subsequent analysis.

The impact of recent LITESPARK-005 findings on securing the belzutifan's niche including how far up in the treatment algorithm it could move, remains to be seen. As expected, the investigators are already exploring whether survival outcomes with longer follow-up will confirm the promising initial clinical activity of the combination in this setting. Advanced phase trials are testing belzutifan plus lenvatinib versus cabozantinib in the treatment refractory setting [NCT04586231], and the addition of belzutifan to lenvatinib and pembrolizumab as frontline therapy [NCT04736706] are ongoing. LITESPARK-005 is 1 of 4 late-stage trials evaluating belzutifan in RCC. Similarly, we are keeping a close eye on belzutifan's prospects as part of second-line (LITESPARK-011), treatment-naïve (LITESPARK-012) and adjuvant therapy (LITESPARK-022; belzutifan plus pembrolizumab; NCT05239728) in advanced RCC setting. Currently, there is a lot of excitement around belzutifan. It is going to be interesting to see where that agent ends up panning out in RCC.

In this issue, Shapiro and colleagues critically evaluate the efficacy of cytoreductive nephrectomy and explore options for integrating CN within the contemporary systemic therapy landscape. Gessner and colleagues summarizes the biology of hERVs, their identified role in ccRCC, and and how hERVs may impact response to immunotherapy in ccRCC. In other review piece, Patel *et al* proposes that early integration of palliative care into routine RCC care can help improved decision making and patient outcomes.

Happy fall season 2023!

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https://doi.org/10.52733/KCJ21n3-mi

AI model reveals kidney tumor features, potential for treatment response prediction

A team of Dana-Farber researchers have utilized artificial intelligence (AI) models to assess the clinical features of kidney cancer tumor samples to predict how tumors may respond to immune therapy. This finding was published in *Cell Reports Medicine*.

Using their AI-based tool, the team examined pathology slides of tumors from patients who were part of the CheckMate 025 randomized phase III clinical trial, which tested treatment with an ICI or an mTOR inhibitor in patients with ccRCC who had previously been treated with standard therapy.

"We wanted to know what a tumor that responds to immunotherapy looks like," says first author Jackson Nyman, Ph.D. "Is there anything in the pathology slide that might give us clues about what is different about the tumors?"

The AI model can predict that tumor microheterogeneity and immune infiltration were associated with improved overall survival among patients taking immune checkpoint inhibitors. The tumors that responded to ICIs had both higher levels of tumor microheterogeneity and denser infiltration of lymphocytes in high-grade regions.

"This is an example of the growing convergence of AI and cancer biology," says co-senior author Eliezer Van Allen, MD, Chief of the Division of Population Sciences at Dana-Farber. "It represents a major opportunity to measure key features of the tumor and its immune microenvironment at the same time. These measures could help drive not only biological discovery but also potentially guide cancer care."

Next, the Dana-Farber team plans to assess the deep learning tool in an ongoing clinical trial using combination immunotherapy in patients with ccRCC. The team also plans to explore whether these visual clues in pathology slides are related to molecular features of the tumor, such as alterations in genes.

REFERENCE: Eliezer M. Van Allen, Spatially aware deep learning reveals tumor heterogeneity patterns that encode distinct kidney cancer states, Cell Reports Medicine (2023). DOI: 10.1016/j.xcrm.2023.101189.

Researchers decipher the genetic code of rare form of kidney cancer

The genetic code of a rare form of kidney cancer, called reninoma, has been studied for the first time. The recent finding published by researchers at the Wellcome Sanger Institute, Great Ormond Street Hospital and The Royal Free Hospital in Nature Communications, also revealed that a new drug target could serve as an alternative treatment if surgery is not recommended.

There are around 100 cases of reninoma reported to date worldwide, and it is amongst the rarest of tumors in humans. Although it can usually be cured with surgery, it can cause severe hypertension or it can spread and develop into metastases. There are no existing medical treatments for reninoma and management involves surgery alone. Until now, it had been unknown what genetic error causes reninoma.

In the new study, a collaboration between the Wellcome Sanger Institute and Great Ormond Street Hospital and The Royal Free Hospital, funded by The Little Princess Trust, researchers found that there is a specific error in the genetic code of a known cancer gene, NOTCH1, that is behind the development of this rare cancer.

The team examined two cancer samples from a young adult and a child with advanced genomic techniques, known as whole genome and single nuclear sequencing. Their findings suggest that the use of existing drugs targeting this specific gene is a possible solution to treating reninoma for patients where surgery is not a viable option.

"Our work aims to fill that gap. This is the first time that we have identified the drivers for reninoma and we hope that our work continues to pave the way towards new therapies for childhood cancers." said Taryn Treger, first author of the study and The Little Princess Trust Fellow at the Wellcome Sanger Institute

Dr Tanzina Chowdhury, co-lead author of the study, at Great Ormond Street Hospital, said: "Rare kidney cancers known as reninomas do not respond to conventional anti-cancer therapies. The only known treatment at the moment is surgery. Our study shows that, actually, there is a specific and well-studied gene that drives this rare cancer. If we use already known drugs that affect this gene, we might be able to treat it without the need for an invasive technique such as surgery."

REFERENCE: Treger, T. D., et al. (2023). Targetable NOTCH1 rearrangements in reninoma. Nature Communications. doi.org/10.1038/s41467-023-41118-8.

Genetic variants help uncover potential new treatment pathway in kidney cancer

Investigators at UCLA Jonsson Comprehensive Cancer Center have found that inhibition of the purine salvage pathway in hereditary leiomyomatosis and renal cell cancer (HLRCC) tumors reduced growth of the tumors in vivo, signaling a possible new treatment strategy for patients with kidney cancer, according to findings published in Cancer Discovery. The targeting of this pathway is based on the study findings that a number of genetic variants previously of unknown significance rely on the purine salvage pathway for growth, and they predispose patients to HLRCC, which increases the risk of developing aggressive kidney cancer.

The investigators assessed the activity and level of fumarate present among 74 variants of the fumarate hydratase gene that were previously of unknown significance. Among those, over half were found to be inactive and likely contributing to growth of the disease. Upon analysis, the investigators uncovered that an accumulation of fumarate due to fumarate hydratase deficiency disrupts pathways for cell growth, causing the cells to rely on the purine salvage pathway for proliferation instead.

“Based on these findings, not only can we now better characterize a lot of patients who have a variant and did not previously know if they really had an increased risk of kidney cancer, we can possibly repurpose this well-tolerated drug to be a rapidly translatable treatment strategy. And we are hoping this is something that we can repurpose quickly for those affected by these variants,” said senior author Heather Christofk, PhD.

When the investigators analyzed the response of cell cultures and mice to the use of 6-mercaptopurine, which targets the purine salvage pathway, they found that the drug led to a reduction in the number of nucleotides and tumor growth. “One way to stop tumor growth from occurring, is to potentially target this pathway. We found that these tumors rely on this alternative pathway, which

uses nutrients from the environment in order to synthesize nucleotides. Generating nucleotides is essential for the tumor cells to replicate and sustain growth," explained lead author Blake Wilde, MD.

The authors concluded, "These findings suggest pathogenicity of patient-associated FH variants and reveal purine salvage as a targetable vulnerability in FH-deficient tumors." The study was funded in part by the Kidney Cancer Association, National Cancer Institute, American Cancer Society and Driven to Cure.

REFERENCE: Wilde BR, Chakraborty N, Matulionis N, et al. FH variant pathogenicity promotes purine salvage pathway dependence in kidney cancer. Cancer Discov. DOI:10.1158/2159-8290.CD-22-0874

FDA Grants Fast Track designation to CAR-T Cell Therapy (IVS-3001) in RCC therapy

The U.S. Food and Drug Administration (FDA) has granted Fast Track designation to its revolutionary product, IVS-3001, a chimeric antigen receptor (CAR) T-cell therapy, for the treatment of patients with renal cell carcinoma. This significant milestone marks a crucial step forward in advancing cancer treatment options and improving patient outcomes.

IVS-3001 is a cutting-edge CAR-T cell immunotherapy that targets the rarely exploited immune checkpoint and tumor-specific antigen known as HLA-G. This molecule, typically expressed only during pregnancy, protects the fetus from the mother's immune system. However, in cancer, HLA-G can be utilized by tumors to create a protective microenvironment, evading the immune system, and promoting tumor growth. By targeting this mechanism, IVS-3001 aims to reinvigorate the body's natural defense to combat cancer effectively.

The Fast Track designation to IVS-3001 was based on the compelling data from the Investigational New Drug Application (IND) submission, and the potential for addressing the unmet need in patients with HLA-G positive locally advanced or metastatic clear cell renal cell carcinoma (RCC) who have failed or are intolerant to standard RCC therapies. The first-in-human, single-arm, open-label, phase 1/2a trial plans to investigate the safety, tolerability, pharmacokinetics, and clinical activity of IVS-3001 when given to patients with previously treated, locally advanced, or metastatic solid tumors which are HLA-G-positive.

"We are thrilled to receive the FDA's Fast Track designation for IVS-3001," said Dr. Jake Kushner, CEO of Invectys. "This recognition further validates the potential of our CAR-T cell therapy in revolutionizing cancer treatment for patients with solid tumors. The dedicated team at Invectys, as well as our partners, are committed to bringing this innovative therapy to the clinic and making a meaningful difference in the lives of cancer patients."

In the proposed study, IVS-3001 may be administered to up to 117 patients, with up to 24 treated in phase 1 dose-escalation portion, and up to 93 in phase 2a of the study.4 Those enrolled will be patients with histologically or pathologically confirmed locally advanced unresectable or metastatic HLA-G-positive select solid tumor malignancy who failed or intolerant to standard of care therapies known to confer clinical benefit per treating physician, measurable disease, life expectancy of >12 weeks, an ECOG performance status of 0 or 1, adequate venous access for apheresis, and adequate organ function.

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Olaparib shows promise in kidney cancer subtype

Data from an interim analysis of the phase 2 ORCHID trial (NCT03786796) presented during the 2023 Kidney Cancer Research Summit showed that single-agent olaparib (Lynparza) elicited responses in patients with renal cell carcinoma (RCC) that harbored BAP1 or other DNA repair (DDR) gene mutations.

Results shown that the patients who received olaparib (n = 11) achieved a disease control rate (DCR) of 18% with an objective response rate of 9% and stable disease (SD) rate of 18%. Genetic mutations included BAP1 (61.5%), ATM (15.4%), PALB2 (15.4%), BRCA1 (7.7%), BRCA2 (7.7%), and 1 patient had co-mutations of BAP1 and PALB2. Of 3 patients who experienced tumor reduction, 2 had BAP1 alterations.

The efficacy and safety demonstrated by olaparib (Lynparza) monotherapy in patients with renal cell carcinoma (RCC) harboring BAP1 or DNA damage repair (DDR) gene mutations in the phase 2 ORCHID trial (NCT03786796) could help inform current and future investigations of PARP inhibitor–based regimens in the RCC space. Treatment with the agent resulted in a disease control rate (DCR) of 18% in this population (n = 11). The objective response rate (ORR) achieved with olaparib was 9%, and the stable disease (SD) rate was 18%. Moreover, 27% of patients experienced tumor reduction, including 2 patients who had BAP1-mutated disease. One of those patients achieved a durable partial response (PR) to treatment, and the other experienced prolonged SD lasting for 10 months.

The ORCHID trial, which utilized a Simon's minimax 2 stage design, enrolled patients with advanced or metastatic RCC who previously received at least 1 prior line of systemic treatment and whose tumors harbored somatic or germline DDR gene alterations. To be eligible, patients were required to have an ECOG performance status of 0 or 1 and acceptable renal, hepatic, and hematologic function. Overall, olaparib monotherapy was found to be well tolerated, with limited grade 3 or higher adverse effects (AEs) observed. The most common treatment-related AEs reported in 2 or more of patients who received the agent included anemia (any grade, 69.2%; grade ≥3, 23.1%), diarrhea (30.8%; 0%), fatigue (30.8%; 0%), increased creatinine (23.1%; 0%), musculoskeletal pain (23.1%; 7.7%), nausea (23.1%; 7.7%), hyperkalemia (15.4%; 7.7%), and peripheral edema (15.4%; 0%). "The study met the prespecified end point for Simon stage 1 design, and in stage 2," lead study author Yasser Mohamed Ali Ged, MBBS, said.

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https://doi.org/10.52733/KCJ21n3-jc

Adjuvant Nivolumab Plus Ipilimumab Versus Placebo for Localized Renal Cell Carcinoma After Nephrectomy (CheckMate 914): A Double-Blind, Randomized, Phase 3 Trial

Motzer RJ et al. Target Oncol. 2023 Sep;18(5):639-641. doi: 10.1007/s11523-023-00987-1.

ABSTRACT: This is a summary of a research article reporting Part A of the CheckMate 914 study (NCT03138512; EudraCT 2016-004502-34). Following surgery to remove renal cell carcinoma (RCC), people with a high risk of the cancer returning received nivolumab plus ipilimumab (adjuvant therapy) or placebo to see if this risk was reduced. The results of this study showed that the risk of RCC returning or death was not changed with adjuvant nivolumab plus ipilimumab treatment compared with placebo. In addition, people treated with nivolumab plus ipilimumab had more side effects compared with people treated with placebo (89% versus 57%).

Interpretability of radiomics models is improved when using feature group selection strategies for predicting molecular and clinical targets in clear-cell renal cell carcinoma: insights from the TRACERx Renal study *Ortain MR et al. Cancer Imaging. 2023 Aug 14;23(1):76. doi: 10.1186/s40644-023-00594-3.*

METHODS: Contrast-enhanced CT scans from the first 101 patients recruited to the TRACERx Renal Cancer study (NCT03226886) were used to derive radiomics classification models to predict 20 molecular, histopathology and clinical target variables. Manual 3D segmentation was used in conjunction with automatic sub-segmentation to generate radiomics features from the core, rim, high and low enhancing sub-regions, and the whole tumour. Comparisons were made between two classification model pipelines: a Conventional pipeline reflecting common radiomics practice, and a Proposed pipeline including two novel feature selection steps designed to improve model interpretability. RESULTS: Classification performance was significant ($p < 0.05$, H0:AUROC = 0.5) for 11 of 20 targets using either pipeline and for these targets the AUROCs were within ± 0.05 for the two pipelines, except for one target where the Proposed pipeline performance increased by > 0.1. Five of these targets (necrosis on histology, presence of renal vein invasion, overall histological stage, linear evolutionary subtype and loss of 9p21.3 somatic alteration marker) had AUROC > 0.8. Models derived using the Proposed pipeline contained fewer feature groups than the Conventional pipeline, leading to more straightforward model interpretations without loss of performance. Sub-segmentations lead to improved performance and/or improved interpretability when predicting the presence of sarcomatoid differentiation and tumour stage.

CONCLUSIONS: Use of the Proposed pipeline, which includes the novel feature selection methods, leads to more interpretable models without compromising prediction performance.

Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial *Albiges L et al. Lancet Oncol. 2023 Aug;24(8):881-891. doi: 10.1016/S1470-2045(23)00276-0.*

METHODS: KEYNOTE-B61 is a single-arm, phase 2 trial being conducted at 48 sites (hospitals and cancer centres) in 14 countries (Australia, Canada, France, Hungary, Ireland, Italy, Poland, South Korea, Russia, Spain, Türkiye, Ukraine, the UK, and the USA). Adult patients (aged ≥18 years) with previously untreated stage IV non-clear-cell renal cell carcinoma and a Karnofsky performance status of 70% or higher were eligible for enrolment. All enrolled patients received pembrolizumab 400 mg intravenously every 6 weeks for up to 18 cycles (2 years) plus lenvatinib 20 mg orally once daily or until disease progression, unacceptable toxicity, or withdrawal; lenvatinib could be continued beyond 2 years. The primary endpoint was the proportion of patients with a confirmed objective response as per adjusted Response.

FINDINGS: Between Feb 23, 2021, and Jan 21, 2022, 215 patients were screened; 158 were enrolled and received treatment. Median age at baseline was 60 years (IQR 52-69), 112 (71%) of 158 patients were male, 46 (29%) were female, 128 (81%) were White, 12 (8%) were Asian, three (2%) were Black or African American, and 15 (9%) were missing data on race. As of data cutoff (Nov 7, 2022), median study follow-up was 14·9 months (IQR 11·1-17·4). 78 of 158 patients had a confirmed objective response (49%; 95% CI 41-57), including nine (6%) patients with a confirmed complete response and 69 (44%) with a confirmed partial response. Eight (5%) patients died due to adverse events, none of which was considered related to the treatment by the investigators (one each of cardiac failure, peritonitis, pneumonia, sepsis, cerebrovascular accident, suicide, pneumothorax, and pulmonary embolism).

INTERPRETATION: Pembrolizumab plus lenvatinib has durable antitumour activity in patients with previously untreated advanced non-clear-cell renal cell carcinoma, with a safety profile consistent with that of previous studies. Results from KEYNOTE-B61 support the use of pembrolizumab plus lenvatinib as a first-line treatment option for these patients.

Checkpoint Inhibitors in Combination With Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors: The CHEERS Phase 2 Randomized Clinical Trial

Spass M et al. JAMA Oncol. 2023 Sep 1;9(9):1205-1213. doi: 10.1001/jamaoncol.2023.2132.

INTERVENTIONS: Patients were randomized (1:1) to receive anti-PD-1/PD-1 ligand 1 ICIs alone as per standard

of care (control arm) or combined with stereotactic body radiotherapy 3 × 8 gray to a maximum of 3 lesions prior to the second or third ICI cycle, depending on the frequency of administration (experimental arm). Randomization was stratified according to tumor histologic findings and disease burden (3 and fewer or more than 3 cancer lesions).
RESULTS: Among 96 patients included in the analysis (mean age, 66 years; 76 [79%] female), 72 (75%) had more than 3 tumor lesions and 65 (68%) had received at least 1 previous line of systemic treatment at time of inclusion. Seven patients allocated to the experimental arm did not complete the study-prescribed radiotherapy course due to early disease progression (n = 5) or intercurrent illness (n = 2). With a median (range) follow-up of 12.5 (0.7-46.2) months, median PFS was 2.8 months in the control arm compared with 4.4 months in the experimental arm (hazard ratio, 0.95; 95% CI, 0.58-1.53; P = .82). Between the control and experimental arms, no improvement in median OS was observed (11.0 vs 14.3 months; hazard ratio, 0.82; 95% CI, 0.48-1.41; P = .47), and objective response rate was not statistically significantly different (22% vs 27%; P = .56), despite a local control rate of 75% in irradiated patients. Acute treatment-related toxic effects of any grade and grade 3 or higher occurred in 79% and 18% of patients in the control arm vs 78% and 18% in the experimental arm, respectively. No grade 5 adverse events occurred.
CONCLUSIONS AND RELEVANCE: This phase 2 randomized clinical trial demonstrated that while safe, adding subablative stereotactic radiotherapy of a limited number of metastatic lesions to ICI monotherapy failed to show improvement in PFS or OS.

Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial

Pal SK et al. Lancet. 2023 Jul 15;402(10397):185-195. doi: 10.1016/S0140-6736(23)00922-4.

FINDINGS: From July 28, 2020, to Dec 27, 2021, 692 patients were screened for eligibility, 522 of whom were assigned to receive atezolizumab-cabozantinib (263 patients) or cabozantinib (259 patients). 401 (77%) patients were male and 121 (23%) patients were female. At data cutoff (Jan 3, 2023), median follow-up was 15·2 months (IQR 10·7-19·3). 171 (65%) patients receiving atezolizumab-cabozantinib and 166 (64%) patients receiving cabozantinib had disease progression per central review or died. Median progression-free survival was 10·6 months (95% CI 9·8-12·3) with atezolizumab-cabozantinib and 10·8 months (10·0-12·5) with cabozantinib (hazard ratio [HR] for disease progression or death 1·03 [95% CI 0·83-1·28]; p=0·78). 89 (34%) patients in the atezolizumab-cabozantinib group and 87 (34%) in the cabozantinib group died. Median overall survival was 25·7 months (95% CI 21·5-not evaluable) with atezolizumab-cabozantinib and was not evaluable (21·1-not evaluable) with cabozantinib (HR for death 0·94 [95% CI 0·70-1·27]; p=0·69). Serious adverse events occurred in 126 (48%) of 262 patients treated with atezolizumab-cabozantinib and 84 (33%) of 256 patients treated with cabozantinib; adverse events leading to death occurred in 17 (6%) patients in the atezolizumab-cabozantinib group and nine (4%) in the cabozantinib group.

Association between age and efficacy of first-line immunotherapy-based combination therapies for mRCC: a meta-analysis

Yanagisawa T et al. Immunotherapy2023 Oct;15(15):1309-1322. doi: 10.2217/imt-2023-0039.

AIM: To compare the efficacy of first-line immune checkpoint inhibitor (ICI)-based combinations in metastatic renal cell carcinoma (mRCC) patients stratified by chronological age. Methods: According to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, hazard ratios for overall survival (OS) from randomized controlled trials were synthesized. Results: Five RCTs were eligible for meta-analyses. ICI-based combinations significantly improved OS compared with sunitinib alone, both in younger (<65 years) and older (≥65 years) patients, whereas the OS benefit was significantly better in younger patients (p = 0.007). ICI-based combinations did not improve OS in patients aged ≥75 years. Treatment rankings showed age-related differential recommendations regarding improved OS.
CONCLUSION: OS benefit from first-line ICI-based combinations was significantly greater in younger patients. Age-related differences could help enrich shared decision-making.of administration (experimental arm). Randomization was stratified according to tumor histologic findings and disease burden (3 and fewer or more than 3 cancer lesions).

Web-based nomogram and risk stratification system constructed for predicting the overall survival of older adults with primary kidney cancer after surgical resection

Jiang L et al. J Cancer Res Clin Oncol . 2023 Oct;149(13):11873-11889.

RESULTS: A total of 15,989 elderly KC patients undergoing surgery were included. All patients were randomly divided into training set (N = 11,193, 70%) and validation set (N = 4796, 30%). The nomogram produced C-indexes of 0.771 (95% CI 0.751-0.791) and 0.792 (95% CI 0.763-0.821) in the training and validation sets, respectively, indicating that the nomogram has excellent predictive accuracy. The ROC, AUC, and calibration curves also showed the same excellent results. In addition, DCA and time-dependent ROC showed that the nomogram outperformed the TNM staging system with better net clinical benefits and predictive efficacy.
CONCLUSIONS: Independent influencing factors for postoperative OS in elderly KC patients were sex, age, histological type, tumor size, grade, surgery, marriage, radiotherapy, and T-, N-, and M-stage. The web-based nomogram and risk stratification system could assist surgeons and patients in clinical decision-making.

KCJ Author Guidelines

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References

All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style. Example: Lewczuk J, Piszko P, Jagas J, et al. Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest. 2001;119:818-823.

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