Cytoreductive nephrectomy for metastatic renal cell carcinoma, the ultimate urologic 'Choosing Wisely' campaign: a narrative review

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Abstract: In the early 2000s, cytoreductive nephrectomy in addition to systemic cytokines became standard of care for treating metastatic renal cell carcinoma. Since that time, the development of novel systemic targeted therapies and immuno-oncologic agents have challenged the utility of cytoreductive nephrectomy in clinical practice. In 2019, the controversial CARMENA study was published, providing the first level one evidence suggesting that cytoreductive nephrectomy combined with targeted therapy yielded no survival advantage over targeted therapy alone in intermediate and poor risk metastatic renal cell carcinoma patients. Later that year, the SURTIME trial demonstrated that patients undergoing targeted therapy with delayed nephrectomy maintained a survival advantage over those that underwent upfront cytoreductive nephrectomy followed by targeted therapy. Both of these studies underscored the importance of patient selection and timing of cytoreductive nephrectomy and systemic therapy. As new immuno-oncologic agents are trialed, particularly in combination, the role of cytoreductive nephrectomy will continue to be questioned. In this narrative review, we discuss the evolution of the role of cytoreductive nephrectomy in treating metastatic renal cell carcinoma through the context of the ever-changing landscape of targeted therapies and immuno-oncologic agents. We assess the evidence for cytoreductive nephrectomy with respect to patient factors, timing of surgery, and combination with other therapies.

Keywords: Metastatic renal cell carcinoma (mRCC); cytoreductive nephrectomy; immunotherapy; immuno-oncology

Introduction

Renal cell carcinoma is the 8th most common cancer in the United States with an overall 5-year survival rate of 75% (1,2). In the United States, 16% of patients initially present with metastatic renal cell carcinoma (mRCC) (3), and of these patients, approximately 12% survive five years (2).

Cytoreductive nephrectomy (CN) is not offered as a curative surgery, but it can palliate hematuria, symptoms from neoplastic syndromes, or pain (4), and has been shown to prolong survival in the setting of systemic cytokines (5). Although CN has been reported to result in rare complete responses (6), it is frequently performed as an adjunct to systemic targeted therapy (TT) or immuno-oncology (IO) agents. The proposed mechanism of action of CN rests on

the principle that RCC produces cytokines that interfere with host defenses. By removing a large percentage of the tumor burden, anti-neoplastic immune function is restored (7).

In this narrative review, we discuss how the role of CN has evolved alongside the development of TT, IO, and TT/IO combinations. We assess how to best utilize CN in contemporary practice with respect to timing of surgery and the use of systemic therapy, highlighting current clinical trials. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2343).

Methods

Using PubMed, Google Scholar, and Wiley Online Library, we performed a non-systematic review of articles between January 1993 and September 2020. Search terms included combinations of the following terms: "metastatic renal cell carcinoma", "cytoreductive nephrectomy", "systemic therapy", "targeted therapy", and "immunotherapy". Articles selected were required to be original articles published in English. News articles, editorials, and unpublished works were excluded.

Information on clinical trials was collected from www.clinicaltrials.gov, which was accessed in April 2020. Trials were selected by using combinations of the search terms "renal cell carcinoma", "systemic therapy", and "cytoreductive nephrectomy". Trials were classified as completed (*Table 1*) if their status was listed as "completed" on www.clinicaltrials.gov. Trials were classified as ongoing (*Table 2*) if their status was listed as "active", "recruiting", "active, not yet recruiting", "active, not recruiting", or "suspended". Trials were excluded if they were listed as "terminated" or "withdrawn".

Current guidelines for CN

According to the National Comprehensive Cancer Network (NCCN), select patients with resectable mRCC should be offered CN (19). Candidates should have good performance status (ECOG <2), good prognostic features, and no brain metastases. Patients experiencing symptoms caused by their renal cancer, such as hematuria, may also be offered CN.

In light of results from the SURTIME and CARMENA trials, the European Association of Urology (EAU) updated their guidelines in 2018 for CN (16,17,20). The EAU now recommends performing immediate CN in patients with good performance status not requiring systemic therapy. For intermediate-risk patients with asymptomatic synchronous primary tumors, sunitinib should be offered as initial treatment, whereas CN as initial treatment is contraindicated; delayed CN can be offered in patients with a limited metastatic burden. Poor risk patients should never be offered CN, as supported by both retrospective and prospective studies (20).

Surgical considerations for CN

CN can be a complex operation associated with significant morbidity and mortality (21,22). In a retrospective multi-institutional analysis of 736 patients with mRCC undergoing CN, 10.9% of patients experienced intraoperative complications, the most common of which included bleeding (36%), splenic laceration (19%), and vascular injury (16%). Predictors of intraoperative complications included performing a thrombectomy or adjacent organ removal. 217 patients (29.5%) experienced postoperative complications, 6.1% of which were considered high grade (Clavien Dindo ≥3). Most common complications were vascular (30%), infectious (19%), and cardiopulmonary (17%). Estimated blood loss (OR 2.93; 95% CI: 1.20–7.15; P=0.02) and surgeon CN case volume (OR 0.13; 95% CI: 0.03–0.59; P=0.009) were identified as significant predictors of high grade complications (22).

Another study retrospectively evaluating 294 patients who underwent CN between 1990 and 2009 demonstrated a 12% early overall and 5% early major (Clavien Dindo ≥3) complication rate. The most common complications included wound infection (3%), acute renal failure (3%), pulmonary embolism (2%), and deep venous thrombosis (2%). Three deaths (1%) were reported in the immediate 30-day postoperative period. While most patients did not experience complications, 61% of patients pre-determined to be candidates for systemic therapy did not receive it within 60 days of surgery (21).

Traditionally performed via an open approach, data on outcomes associated with minimally-invasive CN are sparse. Primary renal tumors in patients with mRCC may have adverse features such as IVC thrombi, significant bulky adenopathy, or invasion into local structures, making surgery technically challenging. A 2016 multi-institutional study reported on 120 patients across three high volume centers who underwent either laparoscopic (96.6%) or robotic (3.4%) CN between 2001 and 2013. 28 patients (23.3%) had postoperative classifications, nearly 30% of

Table 1 Select completed clinical trials investigating CN + systemic therapy (last update: April 2020)

Trial number/ trial name	Trial phase	Target patient enrollment (n)	Patients enrolled (n)	Histology	Drug(s)	Treatment sequence	Comparator arm	Primary endpoint	mRCC only?	Key results
NCT01107509	NA	Not reported	20	CC	Everolimus	evero CN maintenance evero	NA	Tumor and met radiographic response	Yes	None reported
NCT01404104	NA	Not reported	11	All	Temsirolimus	temsiro →CN	NA	Tumor and met radiographic response	≥T2, either N+ and/or M1 permitted	None reported
NCT01892930	NA	Not reported	16	All	Stereotactic body radiation therapy	SBRT→CN or partial Nx	NA	Feasibility of nephrectomy	Yes	87.5% of patients underwent Nx after SBRT, and there were no post-surgical complications; 1- and 2-year OS rates 71 and 48%, respectively (8)
NCT01525017	1	Not reported	12	All	Ilixadencel	ilixa →CN	NA	AE, change in vital signs and lab parameters	Yes	No adverse events; 0 pts with objective response; 2 patients who received adjuvant sunitinib had objective response (9)
NCT01982097/ SANE	2	Not reported	61	All	Sorafenib	soraf →CN →maintenance soraf	NA	1° tumor size reduction, residual disease response rate	Yes	None reported
NCT00480389	2	30	19	CC	Sorafenib	soraf →CN →maintenance soraf	NA	1° pathologic response, TTP, AE	Yes	None reported
NCT01715935/ NEORAD	2	Not reported	25	CC	Everolimus	evero →CN→ maintenance ev	NA	objective clinical benefit	Locally advanced permitted	For mRCC patients: no change in tumor size pre-op; PFS was 18% at 12 months; no surgery-related AEs (10)
NCT02432846/ MERECA	2	Not reported	88	CC	Ilixadencel, sunitinib	ilixa →CN →suni	CN → suni	OS	Yes	Improved ORR in ilixa/suni arm (42.2% vs. 24%); no ilixa-related AEs; OS not reached yet (11)

Table 1 (*continued*)

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Trial number/ trial name	Trial phase	Target patient enrollment (n)	Patients enrolled (n)	Histology	Drug(s)	Treatment sequence	Comparator arm	Primary endpoint	mRCC only?	Key results
NCT01024205/ SuMR	2	Not reported	43	CC	Sunitinib	suni →CN →suni	NA	Clinical benefit ≥70%	Yes	For MSKCC intermediate risk: improved OS for VEGFR-TKI + deferred CN vs. upfront CN + TKI + VEGFR-TKI (33 vs. 22.8 months, HR 0.72; 95% CI 0.52-0.996) *data pooled from SuMR, PANTHER, SURTIME, and N06SUN (12)
EudraCT 2006- 006491-38/ N06SUN	2	22–40	22	CC	Sunitinib	suni →CN	NA	Primary tumor ORR	Yes	Mean size reduction in 1° tumor: 9.5%; 31.8% with partial response after induction suni→13.6% had complete response after CN; patients with metastatic growth after suni unlikely to benefit from CN (13)
NCT01512186/ PANTHER	2	95	104	CC	Pazopanib	azo →CN pazo	NA	Tumor and met radiographic response	Yes	Mean size reduction in 1° tumor: 14.4%; overall mean OS 22.7 months (95% CI, 14.3–not estimable); mean MSKCC poor risk OS 5.7 months (95% CI, 2.6-10.8) (14)
SWOG-8949	3	244	246	All	IFNα-2b	CN→IFNα-2b	IFNα-2b alone	OS	Yes	Improved OS in CN + IFNα-2b arm (11.1 vs. 8.1 months, P=0.05) (5)
EORTC-3047	3	80	85	CC	IFNα-2b	CN→IFNα-2b	IFNα-2b alone	TTP, OS	Yes	Improved TTP and OS in CN + IFNα-2b arm (17 vs. 7 months, HR 0.54; 95% CI: 0.31–0.94) (15)
NCT00930033/ CARMENA	3	576	450	CC	Sunitinib	CN → suni	suni alone	OS	Yes	No difference in OS between suni alone vs. CN + suni (18.4 vs. 13.9 months, HR 0.89; 95% CI: 0.71–1.10) (16)

Table 1 (*continued*)

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Trial number/ trial name	Trial phase	Target patient enrollment (n)	Patients enrolled (n)	Histology	Drug(s)	Treatment sequence	Comparator arm	Primary endpoint	mRCC only?	Key results
NCT01099423/ SURTIME	3	458	99	CC	Sunitinib	CN → suni	suni CN suni	Overall PFS	Yes	Improved OS in suni + delayed CN (32.4 vs. 15.0 months, HR 0.57; 95% CI: 0.34–0.95; P=0.03); poor accrual (17)
NCT00930345/ PREINSUT	4	100	33	CC	Sunitinib	CN → suni	suni →CN →suni	Prognostic value of biomarkers and imaging	Yes	Median OS 12.4 months but longer in patients who responded to suni (28.8 vs. 11.1 months; P=0.003); biomarkers associated with OS: SDF-1, sVEGFR1; biomarker associated with PFS: VEGFR2 (18)

CN, cytoreductive nephrectomy; mRCC, metastatic renal cell carcinoma; CC, clear cell; evero, everolimus; temsiro, temsirolimus; SBRT, stereotactic body radiation therapy; Nx, nephrectomy; ilixa, ilixadencel; soraf, sorafenib; suni, sunitinib; IFNα-2b, interferon-alpha-2b; AE, adverse events; 1°, primary; TTP, time to progression; OS, overall survival; ORR, objective response rate; PFS, progression free survival; MSKCC, Memorial Sloan Kettering Cancer Center; VEGFR, vascular endothelial growth factor receptor; TKI, tyrosine kinase inhibitor; HR, hazard ratio; CI, confidence intervals; sVEGFR, soluble vascular endothelial growth factor receptor; SDF-1, stromal cell-derived factor-1.

which were considered major (Clavien Dindo ≥3). 4 patients (3.3%) required conversion to open surgery (23). At this time, no randomized control trials have investigated how minimally invasive approaches compare with open CN.

The cytokine period

CN became standard of care for the treatment of mRCC after the publication of two landmark studies in 2001. In SWOG-8949, patients with mRCC were randomly assigned to receive CN with the cytokine interferon alfa-2b (IFNα-2b) or IFNα-2b alone. Those undergoing the combined regimen of CN and cytokines demonstrated improved overall survival (OS) compared to cytokines alone (11.1 vs. 8.1 months, P=0.05) (5). In EORTC-3047, Mickisch *et al.* randomized mRCC patients to receive CN with IFNα-2b or IFNα-2b alone. Patients in the CN plus cytokine arm also demonstrated increased OS (17 vs. 7 months, HR 0.54; 95% CI: 0.31–0.94) as well as increased time to progression (15) (*Table 1*). Both studies demonstrated a perioperative mortality rate under 1% (5,15). Pooled analysis of the SWOG and EORTC data showed that median survival was significantly greater for CN and IFNα-2b vs. IFNα-2b alone (13.6 vs. 7.8 months, HR 0.69; 95% CI: 0.55–0.87, P=0.002), irrespective of site of metastases and performance status (24). These results demonstrated that CN was a safe, life-prolonging treatment option for patients with mRCC who were treated with systemic cytokines (5,15,24).

The targeted therapy period

As the understanding of tumor biology improved (25), TT was brought to bear on mRCC in the early 2000s. The number of agents in this class rapidly expanded and now includes drugs targeting vascular endothelial growth factor (VEGF) and its receptor (VEGFR) including [sunitinib, sorafenib, axitinib, pazopanib, cabozantinib, bevacizumab (with IFNα)], mTOR inhibitors (temsirolimus, everolimus), and combination therapy (lenvatinib plus everolimus). Multiple randomized trials demonstrated the superiority of these therapies over traditional cytokines (3). However, the majority of patients in these studies had already undergone CN; therefore, it was not possible to determine the relative benefit of CN for patients being treated with TT.

There are several retrospective cohort studies that demonstrated a benefit to CN among patients treated with TT, although all suffered from significant selection bias

Table 2 Select ongoing clinical trials investigating CN + systemic therapy (last update: April 2020)

Trial number/ trial name	Trial phase	Target enrollment	Histology	Drug(s)	Treatment sequence	Comparator arm	Primary Endpoint	Status	mRCC only?	Trial Start Date
NCT02210117	1	105	CC	Nivolumab, bevacizumab, ipilimumab	nivo →CN →maintenance nivo	1) nivo/bev →maintenance nivo →CN; 2) nivo/ipi →CN →maintenance nivo	AE	Active, not recruiting	Yes	Nov 2014
NCT02595918	1	29	CC	Nivolumab	nivo →CN	NA	Feasibility of no delay of treatment	Recruiting	High risk disease permitted if met free recurrence predicted to be ≤80% in first 12 years after Nx	May 2016
NCT03473730	1	30	CC component	Daratumumab	dara →CN →maintenance dara	NA	AE	Recruiting	Yes	May 2018
NCT03324373	1	15	CC	Lenvatinib, everolimus	lenva/evero →CN	NA	AE, surgical complications	Suspended	Yes	Mar 2019
NCT04322955/ Cyto-KIK	2	48	CC component	Cabozantinib, nivolumab	nivo/cabo →CN (cabo stopped 21 days before)→maintenance nivo/cabo	nivo/cabo →CN (cabo stopped 14 days before)→maintenance nivo/cabo	complete response rate	Recruiting	Yes	Mar 2020
NCT00715442	2	50	CC	Sunitinib	suni →CN	NA	TTP, AE	Active, not recruiting	Yes	Jun 2008
NCT02446860/ ADAPTeR	2	29	CC	Nivolumab	nivo →CN→maintenance nivo	NA	AE	Recruiting	Yes	May 2015
NCT03494816/ NAXIVA	2	20	CC	Axitinib	axi→CN	NA	Improvement in Mayo classification	Recruiting	≥T3NanyMany	Dec 2017
NCT03055013/ PROSPER RCC	3	805	All	Nivolumab	nivo →CN→maintenance nivo	Partial/radical Nx alone	RFS	Recruiting	≥T2NXM0, TanyN+ M0, or oligometastatic that can be rendered M1 NED; ≤3 metastases; permitted metastatic sites: lung, adrenal, nodes, pancreas, soft tissue or skin	Feb 2017
NCT03977571/ NORDIC-SUN	3	400	All	Nivolumab, ipilimumab	nivo/ipi →CN →maintenance nivo	nivo/ipi→maintenance nivo	OS	Active, not yet recruiting	Yes	Sep 2019

CN, cytoreductive nephrectomy; mRCC, metastatic renal cell carcinoma; CC, clear cell; nivo, nivolumab; bev, bevacizumab; ipi, ipilimumab; dara, daratumumab; lenva, lenvatinib; evero, everolimus; cabo, cabozantinib; suni, sunitinib; axi, axitinib; AE, adverse events; Nx, nephrectomy; TTP, time to progression; RFS, recurrence-free survival; OS, overall survival; NED, no evidence of disease.

as patients who were offered CN were generally healthier than those not offered CN. Choueiri *et al.* examined the role of CN in a retrospective review of 314 patients with mRCC treated VEGF-inhibitors. The 201 patients that had undergone CN were generally younger and had better performance status than those who did not undergo CN. On multivariate analysis, the CN group had improved OS compared with the VEGF-inhibitor alone group (HR 0.68; 95% CI: 0.46–0.99; P=0.04) (26). Moreover, favorable and intermediate risk patients demonstrated an OS advantage, which was not demonstrated in patients in the poor risk group (26,27). In a larger retrospective study surveying the National Cancer Database (NCDB), patients with mRCC who received TT were identified and grouped into those who did and did not receive CN. Those who received CN were generally younger, had lower tumor stage, and no nodal disease. The CN group had increased OS compared with the non-surgical group (17.1 *vs.* 7.7 months; P<0.001) and lower risk of mortality by any cause (HR 0.45; 95% CI: 0.40–0.50; P<0.001) (28). While these and other studies support the use of CN in the setting of TT, the survival advantage from CN was lost in patients with poor risk disease (3,26,28). These findings highlighted the need for randomized studies of CN with use of TT (26,27).

Patient selection for CN

Disease risk stratification for patients with mRCC is critical for assigning prognosis, systemic therapy, and selection for CN. The Memorial Sloan Kettering Cancer Center (MSKCC)/Motzer and International Metastatic Database Consortium (IMDC)/Heng criteria are two models that use clinical characteristics to categorize mRCC patients into favorable, intermediate, and poor risk groups which correlate with OS (29-31). Developed for use in the cytokine era, the MSKCC score combines serum hemoglobin, calcium, and LDH, time from diagnosis to systemic therapy, and performance status (31). Similarly, the IMDC score takes into account serum hemoglobin and calcium, performance status, and time to receipt of systemic therapy but adds serum platelets and neutrophils (30). The IMDC model was specifically developed and validated for prognostication in patients with mRCC treated with TT (bevacizumab plus IFNα, sorafenib, and sunitinib) (30,32). Additional serum laboratory tests such as C-reactive protein, albumin, and neutrophil-lymphocyte ration (NLR) may predict OS as well. It is important to note that pre-surgical prognostic grouping can change postoperatively, as

some lab values may normalize after CN (4).

Retrospective studies have identified additional independent predictive factors to help select patients for CN, although many of these likely reflect unmeasured surgeon selection criteria as the factors generally reflect better patient health (4). Well-established prognostic factors for patients who will not benefit from CN include older age, poor performance status, high burden of metastatic disease (particularly metastases to bone, brain, or liver), primary tumor invasion of adjacent organs, and sarcomatoid features (4,7,33,34). Most recently, McIntosh *et al.* analyzed 608 mRCC patients who underwent CN at a single institution and identified five novel preoperative risk factors correlating with OS which included clinical T4 disease, retroperitoneal and supradiaphragmatic lymphadenopathy, hypoalbuminemia, and elevated lactate dehydrogenase as well as four previously reported risk factors such as systemic symptoms at diagnosis, bone metastasis, anemia, and neutrophil to lymphocyte ratio ≥4 (35). The group detected a significant difference in median OS between those who had one, two, and three of the reported risk factors [58.9 months (95% CI: 44.3–66.6 months) *vs.* 30.6 months (95% CI: 27.0–35.0 months) *vs.* 19.3 months (95% CI: 13.92.6–2 months)], respectively (P<0.0001) (35). They found that patients with adverse pathological features and poor risk disease tended to have a higher number of risk factors. These findings further illustrate the importance of using a risk-adapted approach in patient selection for CN (34,35).

Patient symptoms are another important aspect of selection for CN. 66% of patients with mRCC display symptoms with the most common being gross hematuria or flank pain from local tumor invasion, pain from bone metastasis, and dyspnea from lung metastasis (36). To assess the tradeoff between morbidity of surgery and improvement in symptoms, Larcher *et al.* reported on 317 patients with symptomatic mRCC treated with CN between 1988 and 2019. They found that after CN, 43% and 71% reported complete resolution or improvement in any symptoms related to their metastatic disease, respectively. With respect to local signs and symptoms, 91% and 95% demonstrated resolution and improvement, respectively. While the overall and major (Clavien Dindo ≥3) complication rates were 37% and 10%, respectively, the authors concluded that patients undergoing CN largely had a beneficial or mixed (symptom improvement/resolution with complication or no improvement/resolution without complication) response. IMDC risk group was not predictive of complication risk (36).

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In 2018, the CARMENA trial (NCT00930033) provided the first level one evidence about the role of CN in the setting of TT. In this non-inferiority study, 450 patients with MSKCC intermediate and poor risk clear cell mRCC were randomized to receive either CN followed by sunitinib or sunitinib alone. In the sunitinib only group, 17% ultimately required a CN, whereas in the CN-sunitinib group nearly 18% never received systemic therapy. After a median follow-up of 50.9 months, OS with sunitinib alone was non-inferior to CN followed by sunitinib [18.4 *vs.* 13.9 months (HR 0.89; 95% CI: 0.71–1.10)] (16) (*Table 1*). These results corroborate prior reports that poor risk patients do not typically achieve survival benefit from CN (4), although for the first time, the use of CN in intermediate risk patients was less certain.

While this study introduced a potential paradigm shift in the use of CN, the conclusions must be placed into context. Over 40% of patients in each arm had poor risk features, and OS was worse than contemporary studies (37), calling into question the external validity of the results. Also, the slow accrual of this study begets the possibility of recruitment bias, as healthier patients with fewer metastases may have chosen not to enroll (38). Arora *et al.* demonstrated that the CARMENA population might not necessarily be reflective of a general mRCC population by comparing CARMENA patients with NCDB patients who underwent CN and applying CARMENA inclusion criteria to the NCDB cohort. They found that the CARMENA cohort had lower OS, as well as more sites of metastasis and higher rates of metastases to the lymph node, lung, and bone compared to the NCDB cohort (20,38). Ultimately, providers should use caution when applying the findings from CARMENA to their everyday practice and understand that the importance of judicious patient selection cannot be overstated. Continued efforts should be directed at the development of improved predictive models that consider both patient symptoms and risk factors, identifying reliable biomarkers (39,40), and conducting larger randomized studies with higher proportions of good and intermediate risk patient populations undergoing CN.

Sequence of CN and TT

In those who are deemed candidates for CN, significant controversy exists over the sequence of performing surgery and initiating TT. Some argue for initial CN, as decreasing tumor burden limits the number of tumor clones that can develop and spread. Alternatively, initial CN may delay the receipt of systemic therapy, permitting unrestricted metastatic growth (20).

To address the sequence of initiating CN and TT, a retrospective cohort study using the Surveillance, Epidemiology, and End Results (SEER) registry from 2006 to 2011 compared 190 mRCC patients treated with initial CN and subsequent TT to 347 patients receiving initial TT, 28 of whom underwent delayed CN (41). When adjusted for clinical and pathologic factors, those treated with initial CN had a 5.8-month OS improvement compared to patients receiving TT (HR 0.50; 95% CI: 0.38–0.65) (41).

In another retrospective study, Bhindi *et al.* identified patients who underwent either initial CN (n=6,731) or TT (n=8,337) in the NCDB from 2006-2013 (42). Nearly half of those receiving initial CN went on to receive TT, while only 4.9% of those receiving initial TT underwent CN within 6 months. OS was 16.5 *vs.* 9.2 months for patients undergoing upfront CN *vs.* initial targeted therapy, respectively, (HR 0.61; 95% CI: 0.59–0.64; P<0.001). The authors concluded that upfront CN held a survival advantage over initial TT, as more patients had the opportunity to receive multimodal therapy (42).

In contrast to these results, a recent retrospective study of the IMDC database compared patients with mRCC who underwent CN followed by sunitinib (n=805), sunitinib followed by deferred CN (n=85), or sunitinib alone (n=805). The authors observed that deferred CN patients had an OS advantage (HR 0.45; 95% CI: 0.33–0.60; P<0.001) over the other groups. When comparing all patients who underwent CN, the OS advantage for deferred over upfront CN remained (HR 0.52; 95% CI: 0.39–0.70; P<0.001). Notably, only a fraction of patients included in the analysis were classified as poor risk (43). The mixed results from these studies highlight the limitations of retrospective cohort studies in guiding surgical selection. Patients who initially started on TT may have had poorer prognostic features prohibiting their surgical candidacy, underscored by the fact that only a minority underwent CN after TT in both studies favoring upfront CN (41,42). However, carefully selected patients who are healthy enough to undergo a CN may live significantly longer if TT is employed first (43).

SURTIME (NCT01099423), the first prospective data regarding the optimal sequence for TT and CN, was published in 2019. In this phase 3 trial, patients were randomized to receive upfront CN followed by sunitinib (n=50) or sunitinib followed by CN if patients had not progressed on therapy (n=49). Due to poor accrual, enrollment ended early, although intention-to-treat analysis

revealed a median OS of 32.4 *vs.* 15.0 months, for the delayed and initial CN arms, respectively (HR 0.57; 95% CI: 0.34–0.95; P=.03) (17) (*Table 1*). While underpowered, SURTIME suggested that receiving systemic TT prior to CN was beneficial, as it may aid in controlling metastatic disease. Furthermore, administration of preoperative TT may guide in patient selection for CN, as patients who progress on TT may not benefit from CN (7). Future prospective studies with larger cohorts are needed to further clarify the proper sequence of TT and CN.

CN and active surveillance

In some patients with mRCC, the growth of metastases is indolent. Several groups have utilized active surveillance (AS), or treatment delay (TD) with TT, in highly select patients with low-volume mRCC to avoid inherent toxicity and costs associated with systemic treatment (1). In a prospective phase 2 trial, 48 patients with asymptomatic, TT-naïve mRCC underwent radiographic surveillance until TT was deemed necessary by their providers. Of this cohort, 98% had already undergone nephrectomy, but the rate of primary nephrectomy *vs.* CN was not stated. Median time to progression was 9.4 months (95% CI: 7.4–13.4), and median AS time was 14.9 months (95% CI: 10.6–25.0 months). Prognostic factors associated with longer periods of AS included fewer sites of metastasis and fewer IMDC risk factors. Interestingly, patient anxiety, depression, and quality of life (QoL) scores did not change during the AS period (44).

In a subsequent retrospective review of the NCDB, Woldu *et al.* examined mRCC patients who underwent delayed treatment with TT after CN. Median TD was 2.1 months, and the majority of patients began TT within 4 months after CN. TD was not independently predictive of OS (1). More recently, Iacovelli *et al.* reported data from 16 Italian hospitals on 635 patients with mRCC who were deemed eligible for TT, but opted for AS. Of those who were metastatic at diagnosis, 68.7% had undergone CN. Median OS was 27.7 months (95% CI: 24.8–30.5), and median progression free survival (PFS) was 11.1 months (95% CI: 9.9–12.3) among all patients. TD was 8 weeks for the CN patients compared to 5.3 weeks for those who underwent nephrectomy for initially localized disease (P=0.001). However, TD after CN did not affect OS (45). Taken together, these studies provide evidence that AS may be a safe initial treatment strategy in some carefully selected mRCC patients and does not necessitate and tradeoff between survival and QoL (1,44,45).

The immune checkpoint inhibitor period and future directions

Systemic IO agents for mRCC are being rapidly introduced, and immune checkpoint inhibitors (ICIs) (46) targeting programed cell death 1 protein (PD-1) (nivolumab, pembrolizumab), programed death-ligand 1 (PD-L1) (avelumab), and CTLA-4 (ipilimumab) have been shown to be superior as first-line therapy for many patients with mRCC (19). In the phase 3 trial Checkmate-214 (NCT02231749), patients with untreated advanced RCC were risk-stratified using IMDC criteria and randomized to receive either sunitinib (n=546) or nivolumab/ipilimumab (n=550). 80% of the nivolumab/ipilimumab and 76% of the sunitinib group had a previous nephrectomy. Among patients with intermediate and poor risk RCC, the 18-month OS for nivolumab/ipilimumab *vs.* sunitinib was 75% *vs.* 60%, respectively (HR 0.63; 99.8% CI: 0.44–0.89; P<0.001). The nivolumab/ipilimumab group had a higher objective and complete response rate than the sunitinib group (37). The open-label phase 3 trial KEYNOTE-426 (NCT02853331) similarly randomized patients with treatment naïve advanced RCC to receive either pembrolizumab with axitinib (n=432) or sunitinib (n=429). Across all IMDC risk groups, patients in the pembrolizumab/axitinib arm exhibited improved OS (HR 0.53; 95% CI: 0.38–0.74; P<0.0001) than the sunitinib group (37). In JAVELIN Renal 101 (NCT02684006), advanced RCC patients were randomized to receive avelumab plus axitinib (n= 442) or sunitinib alone (n=444). The median PFS in the overall population was 13.8 *vs.* 8.4 months (HR 0.69; 95% CI: 0.56–0.84; P<0.001) for the avelumab/axitinib *vs.* sunitinib groups, respectively, with remarkably similar results for the subset of patients with PD-L1 positive tumors. Notably, over 99% of patients in both groups experienced adverse events (47). The promising results from these trials led to the approval of these combination therapies for advanced RCC, although toxicities must be taken into account when selecting patients for treatment.

As systemic therapies for mRCC rapidly evolve, the role of CN requires ongoing reevaluation. In a retrospective study using the NCDB, Singla *et al.* analyzed 391 patients who received either CN and IO (n=221) or IO alone (n=170). They observed that patients who underwent CN and IO had lower pT stage, tumor grade and size, and
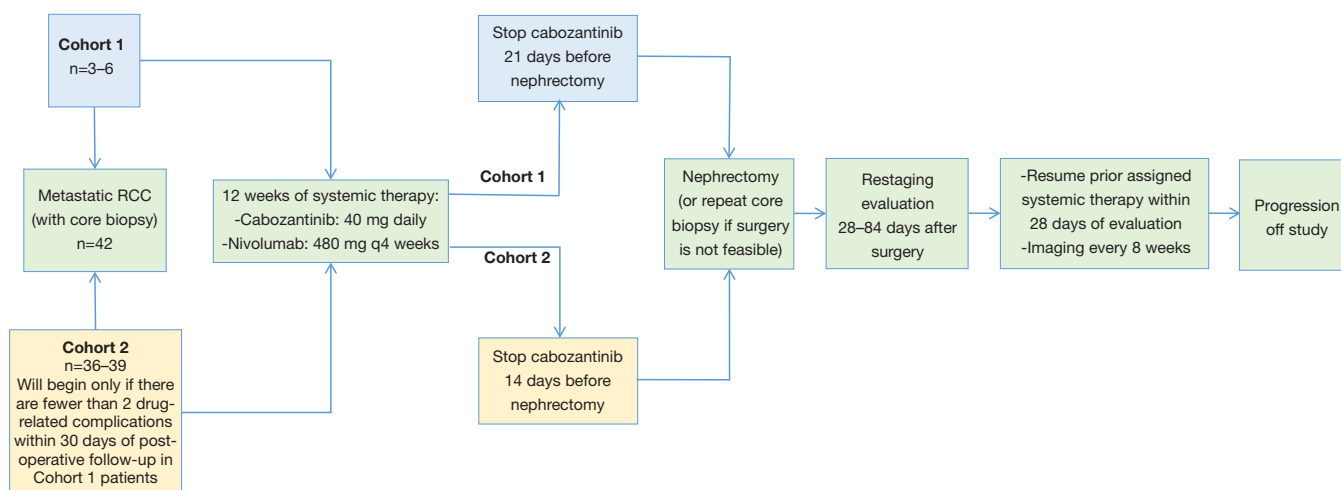
Figure 1 Schematic of Cyto-KIK Trial (NCT04322).

rates of lymphovascular invasion compared to the IO alone group. After a median follow-up of 14.7 months, the CN and IO group demonstrated superior OS compared to those receiving IO alone (not reached *vs.* 11.6 months; HR 0.23; P<0.001). Again, patients selected for CN may have had more favorable patient and tumor characteristics that contributed to their superior outcomes (48). Therefore, clinical trials are required to investigate the role of CN in the setting of IO therapy, as well as the sequencing of CN and IO systemic therapy (*Table 2*).

Compelling preclinical data in other solid tumors suggests a beneficial role for neoadjuvant IO prior to cytoreductive surgery. In a study of glioblastoma patients randomized to neoadjuvant or adjuvant pembrolizumab, the neoadjuvant group had significantly improved OS (13.7 *vs.* 7.5 months; HR 0.39; 95% CI: 0.17–0.94; P=0.04) (49). In patients with metastatic melanoma, the OpACIN study demonstrated that those treated with ipilimumab/nivolumab prior to surgery had an improved pathological response rate and relapse free survival (80% *vs.* 60%) than those who received adjuvant IO therapy (50,51). While the mechanisms underlying the clinical benefits of neoadjuvant IO are not fully understood, it is postulated that neoadjuvant IOs cause dying tumor cells to release tumor-specific antigens, which may prime the immune system by enhancing T cell proliferation and amplifying the anti-tumor response (49,51,52).

The combination of studies showing a benefit for neoadjuvant IO in others solid tumors and recent literature demonstrating improved OS with deferred CN supports the need for a clinical trial examining neoadjuvant IO

and deferred CN. The Cyto-KIK trial (NCT04322955) is a phase 2 multi-center trial investigating the impact of neoadjuvant nivolumab and cabozantinib (a VEGFR inhibitor) followed by CN and continued systemic therapy. The primary clinical endpoint is complete response rate with secondary endpoints including OS, PFS, primary tumor size reduction, toxicity, and surgical complications. Moreover, the investigators intend to use pre-treatment RCC tissue samples to identify biomarkers indicating response to TT and IO. The trial opened in 2020 with a target enrollment of 48 patients (*Figure 1*) (53).

Summary

CN is a rapidly changing treatment option for patients with mRCC. Before offering CN, clinicians should carefully select patients using pre-operative patient risk stratification tools; they should counsel patients on risk of surgery as well as benefits, including possible increased survival and symptomatic improvement. Moreover, some patients can be offered systemic therapies, but the optimal timing with surgery is still an active area of research.

This narrative review has inherent limitations as it is non-systematic. As with all non-systematic reviews, there is a possibility for bias, as the evidence provided has not been systematically evaluated. However, our intention is to provide a comprehensive overview on various aspects of CN, place its evolution into historical context, and highlight up-and-coming research. Additionally, most of the studies cited were retrospective in nature, as there is still a paucity

of level one evidence detailing the precise clinical role of CN. Randomized clinical trials will be critical for further understanding how to best use CN in practice.

Conclusions

The role of CN has evolved as the landscape of systemic therapy for mRCC has changed. While receipt of immediate TT has become standard for many patients, CN remains an important treatment option in carefully selected patients with good or intermediate risk mRCC. Because many questions remain regarding the optimal systemic therapy regimen and timing of surgery, patients interested in CN should be encouraged to do so as part of a clinical trial.

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Footnote

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