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REVIEW

Cytoreductive nephrectomy for synchronous metastatic renal cell carcinoma. Is there enough evidence?

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Summary *Objective: To assess the role of Cytoreductive Nephrectomy for synchronous metastatic Renal Cell Carcinoma patients in the Systemic Therapy era and beyond regarding the Overall Survival, the optimal sequence between Systemic Therapy and Cytoreductive Nephrectomy and prognostic factors.*

Methods: The systematic review was conducted in accordance with the PRISMA guidelines. Bibliographic search was performed in Medline (PubMed), ClinicalTrials.gov, and Cochrane Library-Cochrane Central Register of Controlled Trials (CENTRAL). Studies included were those indexed from 2005 in an attempt to limit those conducted in the cytokine era. Risk of bias assessment was performed by two authors (K.S and T.L) using the Cochrane Collaborative Risk of Bias tool for randomized trials, the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies.

Results: Cytoreductive nephrectomy was associated with improved overall survival in all but one of the observational studies. While in all of these studies the unvariable analysis showed improved overall survival in favor of the cytoreductive nephrectomy group in some studies the subgroup analysis showed no benefit. Regarding the optimal sequence, deferred cytoreductive nephrectomy demonstrated better results in more studies than upfront cytoreductive nephrectomy but a advantage was not clearly certain. In the analysis of possible prognostic factors for overall survival with cytoreductive nephrectomy, most common prognostic factors found were age (in 8 studies), tumor histology (in 7 studies), number of metastasis (in 6 studies), and T stage.

Conclusions: Cytoreductive nephrectomy can still play an important role in wisely selected patients, although the role of cytoreductive nephrectomy in the new immunotherapy era needs to be defined.

KEY WORDS: *Cytoreductive nephrectomy; Metastatic renal cell carcinoma; Systemic therapy; Immune check point inhibitors.*

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INTRODUCTION

During the last two decades, the role of *cytoreductive nephrectomy* (CN) in the treatment of synchronous *metastatic renal cell carcinoma* (mRCC) has been reevaluated many times according to the newly discovered different oncological therapies. In the cytokine era, due to lack of significant effectiveness of medical therapies, CN was considered the standard of treatment justified by two randomized phase 3 trials (SWOG 8949, EORTC30947) (1, 2). Both trials showed an overall survival (OS) benefit of CN followed by *interferon-alpha* (IFN-a) 2b versus interferon alone (1-3). Since 2005, *systemic therapies* (ST), such as *vascular endothelial growth factor receptors* (VEGFR)-*tyrosine kinase inhibitors* (TKI) and *mammalian target of rapamycin* (mTOR) inhibitors, replaced cytokines as they have been proven superior to cytokines (4, 5). CN was evaluated, regarding possible advantages on OS in mRCC patients treated with ST, through multiple retrospective studies. The CARMENA trial (6) and the SURTIME trial (7), are the only *randomized controlled trials* (RCT) investigating the role of CN in the ST era. These two studies reduced the enthusiasm on upfront CN and opened a discussion about which patients treated with ST could benefit more by CN. Furthermore, new therapeutic agents such as *immune check point inhibitors* (ICI), presented as superior to TKI in recent studies (8-10). These controversial observations prompted us to conduct a systematic review in order to examine the role of CN for synchronous mRCC patients in the ST era and beyond regarding the *overall survival* (OS), the optimal sequence between ST and CN and prognostic factors.

METHODS

The systematic review was conducted in accordance with the PRISMA guidelines (*Preferred Reporting Items for Systematic Reviews and Meta-Analysis*) (11).

Bibliographic search was performed in Medline (PubMed), ClinicalTrials.gov, and Cochrane Library-Cochrane Central Register of Controlled Trials (CENTRAL). Studies included were those indexed from 2005 in an attempt to limit those conducted in the cytokine era. The last search date was March 14, 2022.

The following medical subject heading terms were used in combination with Boolean operators (AND, OR, NOT): ("*cytoreductive nephrectomy*") AND ("*targeted therapy*" OR "*systemic therapy*" OR "*immune oncology [IO]*" OR immunotherapy OR "*immune checkpoint inhibitor**" OR "*immunooncology*") NOT (Review[Publication Type]) NOT (Meta-analysis[Publication Type]) NOT (Systematic review[Publication Type]).

Two independent reviewers (K.S, T.L) screened all articles retrieved by the initial search. All disagreements were

No conflict of interest declared.

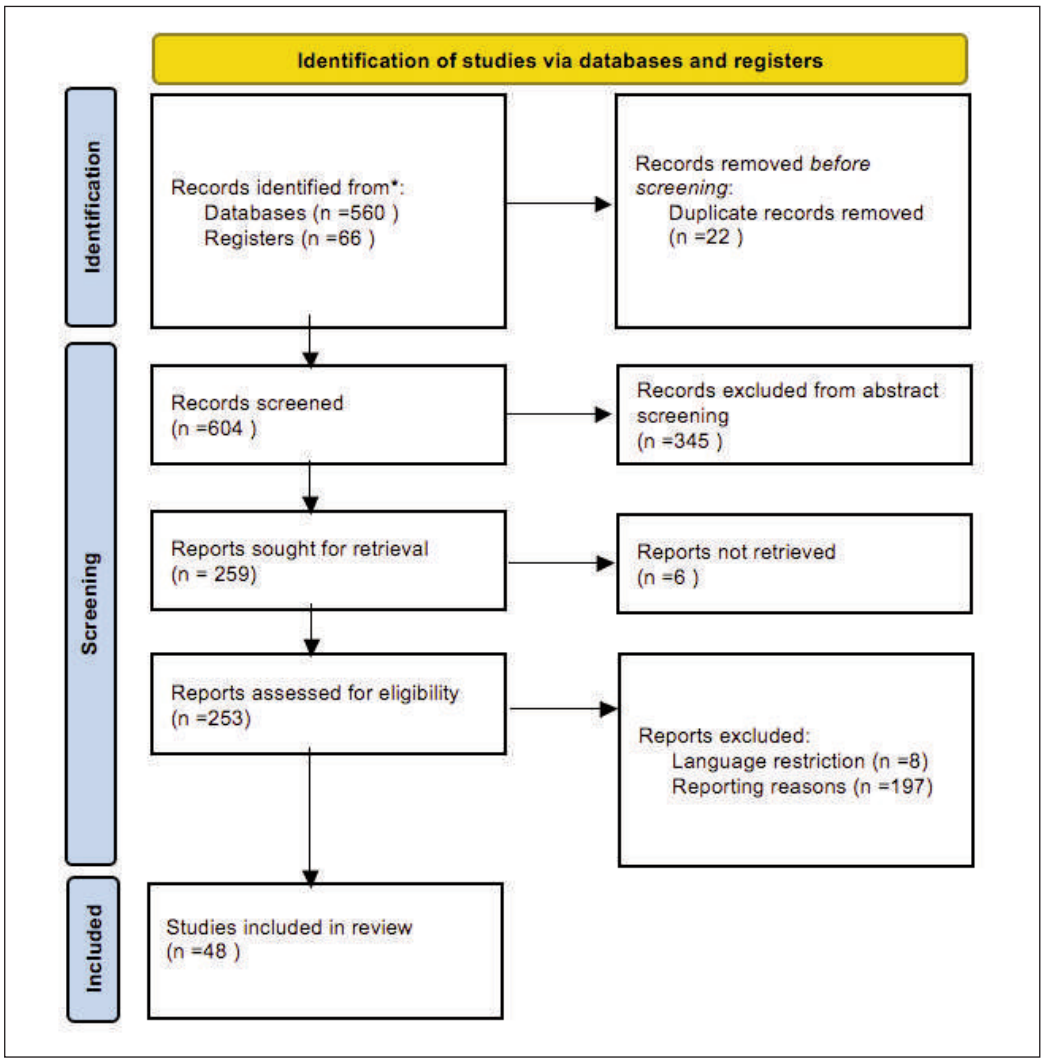

Figure 1.
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only.

resolved with discussion, and final decision was reached by consensus with a third reviewer (M.I.). Reference lists were systematically searched for relevant articles in a snowball procedure.
An ethical approval is not required because this study is a review of the existing international literature.

Study criteria
Clinical trials, cohort studies, and case-control studies were considered for inclusion (Figure 1).
Excluded studies met ≥ 1 of the following criteria: (1) irrelevant to the subject studies, (2) studies published in a non-English language, (3) case reports, case series including less than 10 patients, systematic reviews and meta-analyses, and (4) editorials, perspectives, and letters to the editors, (5) studies including only drugs from cytokine era (studies excluded are summarized in **Supplementary Table 1**).

Types of participants and exposure
Patients diagnosed with synchronous mRCC, who underwent CN. Studies with patients undergoing partial nephrectomy, ablative procedures or nephrectomy for palliative reasons were not included. Primary research question was the effect of CN in the OS. Secondary questions were the optimal sequence between systemic therapies and CN, and possible prognostic factors.

Risk of bias assessment
Risk of bias assessment was performed by two authors (K.S and T.L) using the Cochrane Collaborative Risk of Bias tool for randomized trials (12), the Cochrane Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies (13) (Table 1). Most common reasons for the studies evaluating the relationship between CN and OS to be classified as having moderate or serious risk of bias were the unmeasured differences between CN and control groups and the inadequate adjustment for confounding factors. The inability to adjust for differences between groups was also found in the studies assessing the prognostic factors and the role of sequence between ST and CN. Moreover, the studies assessing the sequence between ST and CN also demonstrated selection bias.

Results

Cytoreductive nephrectomy and overall survivor
Thirty studies were included in the analysis of the rela-

Table 1.
Risk of bias assessment for non-randomized studies.

First author (year)	Confounding	Participant selection	Intervention classification	Deviation from inteended treatment	Missing data	Outcome measurement	Selected reporrting	Overall bias
Day (2016)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
de Groot (2016)	Moderate	Serious	Low	Low	Moderate	Low	Low	Serious
Hanna (2016)	Moderate	Serious	Low	Low	Moderate	Low	Low	Serious
Heng (2014)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Klatte (2018)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Patel (2017)	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious
Tatsugami (2015)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
You (2011)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Abern (2014)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Conti (2014)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Marchioni (2019)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Patel (2017)	Serious	Moderate	Low	Low	Moderate	Moderate	Low	Serious
Aizer (2014)	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Song (2016)	Serious	Serious	Low	Low	Low	Low	Low	Serious
Abel (2017)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Corcoran (2014)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Culp (2010)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Culp (2014)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Kalogirou (2017)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Sakai (2014)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Sharma (2015)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
You (2015)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
MacLeod (2017)	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Stroup (2013)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Wood (2009)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Luzaggo (2021)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Singla (2020)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Palumbo (2020)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Choi (2018)	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Janish (2020)	Moderate	Serious	Low	Low	Moderate	Low	Moderate	Serious
Alnimer (2021)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Vaishampayan (2019)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Graham (2019)	Moderate	Serious	Low	Low	Low	Moderate	Low	Serious
You (2014)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Zhao (2019)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Poprach (2020)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Bakouny (2020)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Dragomir (2021)	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Ljungberg (2020)	Serious	Serious	Low	Low	Low	Low	Low	Serious
Mcintosh (2020)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Rosiello (2019)	Serious	Serious	Low	Low	Low	Low	Low	Serious
Teishima (2018)	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Adashek (2021)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Bhindi (2020)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
De Bruijn (2020)	Serious	Serious	Low	Low	Low	Low	Low	Serious
Uprety (2018)	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Risk of bias assessment for randomized studies.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinded outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Bex (2017)	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Mejean (2018)	Low	Low	Low	Low	Low	Low	Moderate	Moderate

tionship between CN and OS (14-42, 65) (Table 2). All of the studies except for one (41), which was a prospective randomized trial, were retrospective cohort studies.
Ten of them were from the *Surveillance*, *Epidemiology*, and *End Results* (SEER) database, 4 from *International Metastatic RCC Database Consortium* (IMDC), two from *National Cancer Database* (NCDB) and the rest were single or multi-center studies. Most common systemic agent used was sunitinib (Table 1), while there were three studies (2, 40, 42) comparing CN with the use of ICIs. These studies are of great importance, as they are the first retrospective studies on the role of CN in the immunotherapy era and demonstrated an OS benefit in patients treated with ICI plus CN compared to ICI alone (HR 0.23-0.39,

Table 2.
Studies evaluating the association between CN and OS.

Study	Number of patients	Systemic agents used	CN-systemic therapy sequence	Median OS (CN *vs* no CN) OS HR (95% CI)	Supplementary info for the study
Conti (2014) (14), Retrospective cohort, USA (SEER) 1993-2010	N (total) = 20104 N (CN) = 6915 N (no CN) = 13819	NR	NR	15 *vs* 4, HR 0.41 (95% CI 0.37-0.55)	Non-clear cell renal cell carcinoma studied
Aizer (2014) (15), Retrospective cohort, USA (SEER) 2000-2009	N (total) = 591 N (CN) = 384 N (no CN) = 207	NR	NR	14 *vs* 6, HR 0.45 (95% CI 0.39-0.43)	Cytokines + ST
Abern (2014) (16), Retrospective cohort, USA (SEER) 2005-2009	N (total) = 7143 N (CN) = 2629 N (no CN) = 4514	NR	NR	HR 0.33 (95% CI 0.31-0.36)	Median OS in months: NR
Vaishampayan (2019) (17), Retrospective cohort, USA (SEER) 2010-2016	N (total) = 18422 N (CN)= 7660 N (no CN) =10762	NR	NR	18 *vs* 3, HR 0.39 (95% CI 0.30-0.33)	-
Zhao (2019) (18), Retrospective cohort, USA (SEER) 2010-2014	N (total) = 1113 N (CN) = 618 N (no CN) = 415	NR	NR	26 *vs* 9, HR 0.40 (95% CI 0.35-0.47)	-
Marchioni (2019) (19), Retrospective cohort, USA (SEER) 2001-2014	N (total) = 851 N (CN) = 575 N (no CN) = 276	NR	NR	HR 0.38 (95% CI 0.30-0.47)	Median OS in months: NR Non-clear Cell Renal Cell Carcinoma studied
Palumbo (2020) (20), Retrospective cohort, USA (SEER) 2010-2015	N (total) = 2241 N (CN) = 1168 N (no CN) = 1073	NR	NR	28 *vs* 12, HR 0.49 (95% CI 0.41-0.58)	-
Luzzago (2021) (21), Retrospective cohort, USA (SEER) 2006-2015	N (total) = 1573 N (no-treatment) = 350 N (ST alone) = 387 N (CN) = 396 N (CN+ST) = 440	NR	CN before ST	No treatment = 3 ST alone = 7 CN = 9 CN+ST = 13 HR = NR	Non-clear cell renal cell carcinoma studied
Alnimer (2021) (22), Retrospective cohort, USA (SEER) 2010-2016	N (total) = 5483 N (CN) = 2991 N (no CN) = 2483	NR	NR	24 *vs* 6, HR 0.33 (95% CI 0.28-0.40)	-
Hanna (2016) (23), Retrospective cohort, USA (NCDB) 2006-2013	N (total) = 15390 N (CN) = 5374 N (no CN) = 10016	NR	CN before or after ST	17.1 *vs* 7.7, HR 0.49 (95% CI 0.46-0.52)	-
Singla (2020) (24), Retrospective cohort, USA (NCDB) 2015-2016	N (total) = 391 N (CN) = 221 N (no CN) = 170		Upfront CN = 197, ST before CN = 24	No CN = 11.6 HR 0.23 (95% CI 0.15-0.37)	Median OS was not reached in the CN group. Patients were treated with immune checkpoint inhibitors
Choi (2018) (25), Retrospective cohort, Korea (Single center) 2005-2015	N (total) = 294 N (CN) = 109 N (no CN) = 105	Sunitinib (52.4%) Pazopanib (26.2%) Sorafenib (10.9%) Temsirolimus (4.4%)	ST before CN	29 *vs* 11, HR 0.40 (95% CI 0.28-0.58)	-
Janish (2020) (26), Retrospective cohort, Germany (Single center) 2000-2016	N (total) = 262 N (CN) = 104 N (no CN) = 158	Sunitinib (66%) Sorafenib (20%) Pazopanib (10%)	CN before ST	27 months for the CN group	No difference in OS between the two groups P > 0.05
You (2011) (27), Retrospective cohort, Korea (Single center) 2006-2009	N (total) = 78 N (CN) = 45 N (no CN) = 33	Sunitinib (81%) Sorafenib (19%)	CN before ST	21.6 *vs* 13.9, HR 0.53 (95% CI 0.24-1.15)	-
Graham (2019) (28), Retrospective cohort, international (IMDC) 2005-2017	N (total) = 353 N (CN) = 244 N (no CN) = 109	Sunitinib (54%) Temsirolimus (23%) Pazopanib (11%) Sorafenib (2.8%)	CN before ST	16.3 *vs* 8.6, HR 0.62 (95% CI 0.45-0.85)	Metastatic Papillary Renal Cell Carcinoma studied
Klatte (2017) (29), Retrospective cohort, UK (Single center), 2006-2017	N (total) = 261 N (CN) = 97 N (no CN) = 164	Sunitinib (60.5%) Pazopanib (28.4%) cabozantinib or Nivolumab (8.4%) other (34.5%)	CN before ST	Unadjusted: 25.6 *vs* 12.4, HR 0.46 (95% CI 0.34-0.62) IPTW-adjusted: 20.9 *vs* 12.6, HR 0.63 (95% CI 0.46-0.84)	-
You (2014) (30), Retrospective cohort, Korea (Single center) 2006-2012	N (total) = 171 N (CN) = 96 N (no CN) = 75	Sunitinib (70%), Sorafenib(19%), Pazopanib (4%), Temsirolimus (7%)	CN before ST	19.9 *vs* 11.7 HR: NR	-
Tatsugami (2015) (31), Retrospective cohort, Japan (multicenter) 2001-2015	N (total) = 330 N (CN) = 254 N (no CN) = 76	NR	NR	27.4 *vs* 10.3, HR 0.40 (95% CI 0.29-0.57) Subgroup analysis for patients receiving only ST: 30.9 *vs* 15.5, HR 0.48 (95% CI 0.28-0.90)	Mixed population of approximately half patients receiving Cytokines and half receiving Systemic Therapy

Day (2016) (32), Retrospective cohort, Australia (multicenter) 2006-2012	N (total) = 91 N (CN) = 46 N (no CN) = 45	Sunitinib (74%) Pazopanib (4%) Everolimus (4%) Bevacizumab (2%) Interferon (2%) Temsirolimus (1%)	CN before ST	23 *vs* 10.9, HR 0.33 (95% CI 0.20-0.55)	-
Choueiri (2011) (33), Retrospective cohort, Canada and USA (multicenter) 2004-2008	N (total) = 314 N (CN) = 201 N (no CN) = 113	Sunitinib (63%) Sorafenib (30%) Bevacizumab (7%)	CN before ST	19.8 *vs* 9.4, HR 0.68 (95% CI 0.46-0.99)	-
Heng (2014) (34), Retrospective cohort, international (IMDC), years not specified	N (total) = 1658 N (CN) = 982 N (no CN) = 676	CN; no CN Sunitinib (67%; 79%) Sorafenib (20%; 8.6%) Axitinib (0.4%; 0.4%) Bevacizumab (4%; 1.5%) Temsirolimus (3.6%; 6.4%) Pazopanib (2.8%; 2.8%) Everolimus (1%; 1%) Other (0.7%; 0.3%)	NR	20.6 *vs* 9.6, HR 0.60 (95% CI 0.52-0.69)	-
De Groot (2016) (35), Retrospective population based matched cohort, The Netherlands 2008-2010	N (total) = 146 N (CN) = 73 N (no CN) = 73	Sunitinib	CN before ST	17.9 *vs* 8.8, HR 0.61 (95% CI 0.41-0.92)	-
Poprach (2020) (36), Retrospective cohort, Czech Republic (National registry) 2007-2018	N (total) = 730 N (CN) = 458 N (no CN) = 272	Sunitinib (78.8%) Pazopanib (21.2%)	CN before ST	27.2 *vs* 14.2, HR 0.55 (95% CI 0.45-0.68)	-
Song (2016) (37), Retrospective cohort, China (single center) 2006-2014	N (total) = 74 N (CN) = 51 N (no CN) = 23	Sunitinib (44.6%) Sorafenib (29.7%) Famitinib (18.9%) Pazopanib (6.7%)	CN before ST	32.2 *vs* 23 HR: NR	-
Bhindi (2020) (38), Retrospective cohort, IMDC 2006-2018	N (total) = 1541 N (CN+Sunitinib) = 805 N (no CN) = 651 N (Sunitinib+dCN) = 85	Sunitinib	CN before or after ST	CN+sunitinib *vs* sunitinib *vs* sunitinib+dCN 19 *vs* 10 *vs* 46 Upfront CN+sunitinib *vs* sunitinib HR 0.89 (95% CI 0.71-1.1) Sunitinib+dCN *vs* sunitinib HR 0.89 (95% CI 0.71-1.1) Sunitinib+dCN *vs* Upfront CN +sunitinib HR 0.52 (95% CI 0.39-0.70)	Comparative analyses of upfront CN+ sunitinib *vs* sunitinib+ dCN *vs* sunitinib
Patel (2017) (39), Retrospective cohort, Australia 2001-2009	N (total) = 1062 N (CN) = 289 N (no CN) = 773	NR	NR	HR 1.90 (95% CI 1.61-2.25)	OS in months NR Includes cytokine era
Dragomir (2021) (40), Retrospective cohort, Canada (multicenter) 2011-2020	N (total) = 788 N (CN) = 80 N (CN+ST) = 383 N (ST+CN) = 73 N (ST only) = 282	Sunitinib (51.1%) Pazopanib (16.8%) Ipilimumab/ Nivolumab (13.8%) other (18.9%)	CN before or after ST	CN+ST *vs* ST 36 *vs* 18, HR 0.65 (95% CI 0.52-0.82) ST+CN *vs* ST 48 *vs* 18, HR 0.41 (95% CI 0.28-0.60) CN (only) *vs* ST (only) 24 *vs* 18, HR 0.75 (95% CI 0.48-1.17) CN+ST *vs* ST+CN 36 *vs* 48, HR 0.66 (95% CI 0.42-1.04)	One of few studies including patients treated with ICI
Mejean (2018) (41), Prospective Randomized trial, France, Norway, England, Scotland, Sweden 2009-2017	N (total) = 450 N (CN) = 226 N (no CN) = 224	Sunitinib	CN before or after ST	13.9 *vs* 18.4, HR 0.89 (95% CI 0.71-1.1)	17% of patients in the sunitinib-only arm received subsequent CN
Bakouny (2020) (42) Retrospective cohort, international (IMDC) 2009-2019	N (total) = 4054 N (TT only) = 1386 N (CN+TT) = 2470 N (CN+ICI) = 143 N (ICI only) = 282	NR	CN before or after ST	CN+ ICI *vs* ICI 53.6 *vs* 21.4, HR = 0.44 (95% CI 0.30-0.64) CN+ TT *vs* TT 26.5 *vs* 10.3, HR = 0.48 (95% CI 0.45-0.52)	One of few studies including patients treated with ICI
Uprety (2018) (65), Retrospective cohort, USA (SEER) 2006-2012	N (total) = 3376 N (CN) = 1110 N (no CN) = 2266	NR	NR	18 *vs* 4	

CN = Cytoreductive nephrectomy; dCN = Deferred CN; OS = Overall survival; HR = hazard ratio; ST = Systemic therapy; NR = Not reported; CI = Confidence interval; SEER = Surveillance, Epidemiology, and End Results; NCDB = National Cancer Database; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

with 95% CI 0.15-0.37 and 0.19-0.83). Regarding the sequence of CN and ST, CN was administered before ST in 12 studies (21, 26-30, 32, 33, 35-37), before or after in 5 (23, 38, 40-42), after in one study (25) while sequence was not specified in the rest.

CN was associated with improved OS in all but one of the observational studies (26), with HRs ranging from 0.23 to 1.90 (Table 1). In all of these studies (14-25, 27-42) the univariable analysis showed improved OS in favor of the CN group although in some studies subgroup analysis

showed no benefit (33, 34). *Choueiri et al.* (33) stratified patients according to the IMDC prognostic factors and demonstrated that poor-risk patients had no significant benefit in OS (HR 0.67 95% CI 0.44-1.01, p = 0.06). Also, *Heng et al.* (34), in a similar subgroup analysis showed absence of OS benefit for poor risk patients (OS 6 *vs* 5.4 months, p > 0.1).

The CARMENA trial (41), the only prospective trial in this review, compared sunitinib plus CN versus sunitinib alone in mRCC patients and showed for the first time the non-inferiority of systemic therapy compared to upfront CN plus sunitinib, with OS 18.4 months *vs* 13.9 months (HR 0.89 95% CI 0.71-1.1). Results were similar in the intermediate risk (HR 0.92 95% CI 0.68-1.24) and poor-risk (HR 0.86 95% CI 0.62-1.17) patients. However, the study has some serious limitations. In the sunitinib alone arm, 17% of the patients underwent subsequent CN and 7% of patients in the CN plus sunitinib arm did not receive surgery. The study also included only poor-risk *Memorial Sloan Kettering Cancer Center* (MSKCC) and intermediate-risk MSKCC patients that have been shown before not to benefit from CN (33, 34).

Sequencing of cytoreductive nephrectomy and systemic therapies

Ten studies were included in the analysis of the sequencing of CN and ST (Table 3). Nine studies were retrospective cohorts (23, 38, 40, 43-48), and one was a prospec-

Table 3.
Studies evaluating the sequencing of CN and ST.

Study	Number of patients	Comparison	Findings
Wood (2009) (43), Retrospective cohort, USA (single center) 2005-2007	N (total) = 102 N (CN+TT) = 58 N (TT+CN) = 44	CN followed by TT *versus* TT followed by CN	Unadjusted KM analysis revealed similar median CSS. 31 *vs* 27.7 mo, p = 0.697
Stroup (2013) (44), Retrospective cohort, USA (multi center) 2005-2009	N (total) = 35 N (CN+Sunitinib) = 17 N (Sunitinib+ CN) = 18	CN followed by Sunitinib *versus* Sunitinib followed by CN	Unadjusted KM analysis revealed no difference in OS p = 0.579
Hanna (2016) (23), Retrospective cohort, USA (NCDB) 2006-2013	N (total) = 4223 N (CN+TT) = 3733 N (TT+CN) = 490	CN followed by TT *versus* TT followed by CN	Unadjusted KM analysis revealed, 1-, 2-, and 3-year OS rates were: 61.2%, 37.8%, 26.6% for CN+TT patients *versus* 73.3%, 48.1%, 35.3% for TT+CN patients log-rank p < 0.001
Macleod (2017) (45), Retrospective cohort, USA (SEER) 2006-2011	N (total) = 537 N (CN+TT) = 190 N (TT+CN) = 347	CN followed by TT *versus* TT followed by CN	Median OS of CN+TT *vs* TT+CN: 17.4 *vs* 9.2 months HR 0.50 (95% CI 0.38-0.65) In propensity score matching: 5.8 months advantage for immediate CN
Bex (2018) (7), Prospective RCT, The Netherlands, Canada, UK, Belgium 2010-2016	N (total) = 99 N (CN+Sunitinib) = 50 N (Sunitinib+ CN) = 49	CN followed by Sunitinib *versus* Sunitinib followed by CN	In the ITT population, no difference in PFR at 28 weeks (CN+Sunit. 42% *vs* Sunit.+CN 43% p = 0.61) Median OS of CN+Sunit. *vs* Sunit.+CN: 15 *vs* 32.4 months HR 0.57 (95% CI 0.34-0.95) p = 0.032 In the PPP the OS was greater in deferred CN but not statistically significant p = 0.23
Bhindi (2018) (46), Retrospective cohort, USA (NCDB) 2006-2013	N (total) = 15068 N (CN+TT) = 6731 N (TT+CN) = 8337	CN followed by TT *versus* TT followed by CN	In IPTW analysis, median OS of CN+TT *vs* TT+CN: 16.5 *vs* 9.2 months HR 0.61 (95% CI 0.59-0.64) p < 0.001
Bhindi (2020) (38), Retrospective cohort, USA (IMDC) 2006-2018	N (total) = 1541 N (CN+Sunitinib) = 805 N (no CN) = 651 N (Sunitinib+dCN) = 85	CN followed by Sunitinib *versus* Sunitinib followed by CN	Median OS of CN+Sunitinib *vs* Sunitinib+deferred CN: 19 *vs* 46 months HR 0.52 (95% CI 0.39–0.70) p < 0.001
Kapoor (2019) (47), Retrospective cohort, Canada (single center) 2009-2016	N (total) = 54 N (CN+TT) = 32 N (TT+CN) = 22	CN followed by TT *versus* TT followed by CN	Median OS of CN+TT *vs* TT+CN: 30.7 *vs* 36.9 months When stratified by number of metastatic sites (< 3 *vs* ≥ 3 sites) median OS was significantly longer in the upfront TT group with ≥ 3 metastasis sites: 33 *vs*. 12.1 months HR 4.65 (95% CI 1.18–18.39) p = 0.03 In intermediate-risk patients, upfront TT group had longer OS: 70.5 *vs*. 30.7 months HR 3.25 (95% CI 1.16–9.08) p = 0.03
De Bruijn (2020) (48), Retrospective analysis, Pooled data from prospective trials 2006-2016	N (total) = 338 N (CN+TT) = 149 N (TT+CN) = 189	CN followed by TT *versus* TT followed by CN	In unselected for risk group Median OS of CN+TT *vs* TT+CN: 18.4 *vs* 24.3 months HR 0.78 (95% CI 0.59–1.04) p = 0.09 In intermediate-risk group Median OS of CN+TT *vs* TT+CN: 22.8 *vs* 33 months HR 0.72 (95% CI 0.52–0.99) p = 0.047
Dragomir (2021) (40), Retrospective cohort, Canada (multicenter) 2011-2020	N (total) = 788 N (CN) = 80 N (CN+ST) = 383 N (ST+CN) = 73 N (ST only) = 282	CN followed by ST *versus* ST followed by CN ST includes TT or immune check point inhibitors	Median OS of CN+ST *vs* ST+CN: 36 *vs* 48 months HR 0.66 (95% CI 0.42–1.04)

CN = Cytoreductive nephrectomy; OS = Overall survival; CSS = Cancer specific survival,; HR = Hazard ratio; ST = Systemic therapy; TT = Ttargeted therapy; CI = Confidence interval; KM = Kaplan Meier; ITT = Intention to treat; PPP = Per protocol population; SEER = Surveillance, Epidemiology, and End Results; NCDB = National Cancer Database; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.

Figure 2.
Prognostic factors.

tive *randomized controlled trial* (RCT) (7). Out of retrospective studies, two were population based (45, 38), three studies used a national hospital-based database (46, 23, 40), two were from a single institution (43, 47), one study was multicenter (44) and one study pooled data from 4 prospective trials (48).

In two studies (45, 46), CN prior to ST found to have an advantage in OS. *Macleod et al.* (45) showed that median OS of immediate CN was 17.4 months vs 9.2 in the deferred CN group, with HR 0.50 (95% CI 0.38-0.65). An advantage of 5.8 months for the immediate CN group was also found in propensity score matching. There was no survival benefit regarding the sequencing of CN and ST in three studies (40, 43, 44). Unadjusted *Kaplan Meier* (KM) analyses from both *Wood et al.* and *Stroup et al.* did not reveal a benefit in survival in neither the upfront nor the differed CN group ($p = 0.697$ and $p = 0.579$ respectively). In the only prospective RCT from *Bex et al.* (7) median OS in the deferred CN group was greater than in the immediate one in the intention to treat population (32.4 *vs* 15 months, HR 0.57; 95% CI 0.34-0.95, $p = 0.032$) but not in the per protocol population (HR 0.71; 95% CI 0.40-1.24, $p = 0.23$). Similar results with advantage of deferred CN were reported in four more studies (23, 38, 47, 48). Interestingly, *Bhindi et al.* (38, 46), in two studies reported contradictory results for the role of deferred CN. When initial treatment with CN, with or without subsequent *targeted therapy* (TT) was compared to initial treatment with TT, with or without subsequent CN in a sample population pooled from *National Cancer Data Base* (NCDB) (46), Authors found an OS benefit for the first group (HR 0.61; 95% CI 0.59-0.64, $p < 0.001$). However, in a more recent study (38), a retrospective cohort with data from *International mRCC Database Consortium* (IMDC), comparison of CN followed by Sunitinib *versus* Sunitinib followed by CN, favored the latter (HR 0.52; 95% CI 0.39-0.70, $p < 0.001$). Another study of notable mention comes from *Dragomir et al.* (40), as it is the only one that included in the ST arm patients who were also treated with ICI. This study also favors deferred than initial CN (HR 0.66; 95% CI 0.42-1.04).

Prognostic factors for OS with CN

Twenty-four studies were included in the analysis of possible prognostic factors for OS with CN. In Figure 2 independent prognostic factors are demonstrated with green color, those found not to be independent prognostic factors are demonstrated with red, while those not assessed are the ones in the white cells.

Most common prognostic factors found in the analysis were age (in 8 studies) (15, 18, 23, 27, 30, 39, 52, 53, 57), tumor histology (in 7 studies) (15, 18, 26, 27, 32, 51-53), number of metastasis (in 6 studies) (18, 30, 45, 51, 55, 60), and T stage (in 6 studies) (18, 31, 51-53, 57, 58). Other factors were, sarcomatoid histology, IMDC or MSKCC classification, systemic symptoms, lymphadenopathy, hemoglobin and albumin level, levels of serum calcium or creatinine or platelets, *C-reactive protein* (CRP) level, absolute neutrophil count and neutrophil-lymphocyte ratio, bone metastasis, lymph node metastasis, visceral metastasis or liver metastasis, tumor grade, sex, *body mass index* (BMI), marital status, race, level of thrombus, if existing, and other comorbidities. From the factors mentioned above, those associated with poor overall survival after CN are high T stage and number of metastasis, sarcomatoid histology, bone metastasis, lymph node metastasis, visceral metastasis or liver metastasis, thrombus level above the diaphragm, existing comorbidities, presence of systemic symptoms, poor IMDC or MSKCC classification, unmarried status, poor

performance status, hemoglobin level less than the lower limit of normal, LDH level above the upper limit of normal and a neutrophile/lymphocyte ratio ≥ 4. Female gender, thrombocytosis, CRP level ≥ 1 ng/ml, good performance status, and good/intermediate IMDC or MSKCC classification were considered having an OS benefit.

Discussion

Treatment of synchronous mRCC has faced many changes in recent years, due to the ongoing development of new drugs, making the therapeutic choice a complex task. The two well-known RCTs that were published regarding the role of CN in mRCC patients, CARMENA and SURTIME, changed what we thought to be the standard of care. The role of CN was deeply questioned, and systemic therapies were found to be more effective. Results from SURTIME and CARMENA (6, 7) demonstrated an absence of benefit in immediate CN, while deferred CN showed an OS benefit in intermediate risk patients. However, their results should be interpreted with caution as both CARMENA and SURTIME, are found to have certain pitfalls. For instance, in CARMENA there was a significant crossover with 17% of patients in the sunitinib alone arm undergoing subsequent CN, and 7% of patients in the CN plus sunitinib arm not receiving surgery. SURTIME on the other hand, suffered from poor accrual, changing the primary endpoint from *progression free survival* (PFS) to *progression free rate* (PFR). A discordance was also found, between the intention to treat and per protocol population, OS outcome. For that reason, the selection of patients who might benefit from CN is of great importance. In our review, most of the studies evaluating the effect of CN in OS showed a benefit of CN (14-25, 27-42). Although most of these studies are retrospective and observational, their results cannot be overlooked. In three studies that used ICIs (2, 40, 42), CN demonstrated an OS benefit. Given the absence of prospective studies with patients treated with ICIs, these results underline the importance of CN in the mRCC treatment.

Prognostic factors have been described, with age, tumor histology, number of metastasis and T stage being the most common. There are also two prognostic models allowing patient risk stratification: MSKCC and IMDC risk scores (34, 63). These models stratify patients in favor, intermediate and poor risk categories, using *performance status* (PS), time from diagnosis to treatment, hemoglobin concentration, calcium level and lactate dehydrogenase level as criteria. According to current evidence, poor MSKCC/IMDC risk patients do not seem to benefit from upfront CN (33, 34) while other patients such as those with good risk prognosis and good PS seem to benefit the most from CN. It should be noted however, that MSKCC/IMDC prognostic scores were originally designed to predict OS in patients with mRCC, and not the OS benefit associated with CN (65). That shows the need for new validated prognostic models. Among patients that were found to benefit from CN, the optimal sequence between CN and TT is not yet well established, as was also documented in our review.

Deferred CN demonstrated better results, in more studies than upfront CN (7, 23, 38, 47, 48) but a certain advantage was not clear.

Despite the new insights into the treatment of mRCC patients that CARMENA and SURTIME provided, TKIs are not anymore considered the standard of care as ICIs have been established as first-line therapy in mRCC patients. Three randomized trials: The CheckMate-214 (nivolumab plus ipilimumab *vs* sunitinib), KEYNOTE-426 (pembrolizumab plus axitinib vs sunitinib), and JAVELIN Renal 101 (avelumab plus axitinib vs sunitinib) demonstrated the superiority of ICIs in the treatment of mRCC whereas sunitinib and other VEGFR-TKI monotherapies are reserved for those who cannot tolerate ICI combination or have no access to these drugs(9-11). What we already know from CARMENA and SURTIME has to be re-evaluated. *Singla et al.* (24) in the first retrospective analysis of the role of CN in the immunotherapy era, demonstrated an OS benefit for those patients treated with ICI plus CN compared to ICI alone (HR 0.23; 95% CI 0.15-0.37). In this regard, further data from high level of evidence studies are required in order to define the role of CN in the modern *immune oncology* (IO) era. Currently there are two RCTs underway, to guide us to that. The PROBE trial (NCT04510597) will evaluate the combination of CN followed by IO or TKI+ IO compared to no CN. The NORDIC-SUN trial (NCT03977571) will evaluate the role of deferred CN in patients receiving combination IO.

We acknowledge that the present study had several limitations. The major limitations were the retrospective nature of the studies included and the small number of studies having ICIs as the main agent used. The retrospective nature could have resulted in selection bias in performance of CN. Moreover, many studies come from an era when systemic therapies were not well established.

Conclusions

The role of CN on mRCC treatment remains a controversial issue. Data from most recent studies have questioned the benefit from CN, shifting the first line treatment from surgical to medical. CN can still play an important role in wisely selected patients, although the role of CN in the new immunotherapy era still needs to be defined.

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