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Review – Kidney Cancer

Systematic Review of the Role of Cytoreductive Nephrectomy in the Targeted Therapy Era and Beyond: An Individualized Approach to Metastatic Renal Cell Carcinoma

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Abstract

Context: The role of cytoreductive nephrectomy (CN) in the management of metastatic renal cell carcinoma (mRCC) in the targeted therapy (TT) era is controversial.
Objective: To assess if CN versus no CN is associated with improved overall survival (OS) in patients with mRCC treated in the TT era and beyond, characterize the morbidity of CN, identify prognostic and predictive factors, and evaluate outcomes following treatment sequencing.
Evidence acquisition: Medline, EMBASE, and Cochrane databases were searched from inception to June 4, 2018 for English-language clinical trials, cohort studies, and case-control studies evaluating patients with mRCC who underwent and those who did not undergo CN. The primary outcome was OS. Risk of bias was evaluated using the Cochrane Collaborative tools.
Evidence synthesis: We identified 63 reports on 56 studies. Risk of bias was considered moderate or serious for 50 studies. CN was associated with improved OS among patients with mRCC in 10 nonrandomized studies, while one randomized trial (CARMENA) found that OS with sunitinib alone was noninferior to that with CN followed by sunitinib. The risk of perioperative mortality and Clavien $\geq$3 complications ranged from 0% to 10.4% and from 3% to 29.4%, respectively, with no meaningful differences between upfront CN or CN after presurgical systemic therapy (ST). Notably, 12.9–30.4% of patients did not receive ST after CN. Factors most consistently prognostic of decreased OS were progression on presurgical ST, high C-reactive protein, high neutrophil-lymphocyte ratio, poor International Metastatic renal cell carcinoma Database Consortium (IMDC)/Memorial Sloan Kettering Cancer Center (MSKCC) risk classification, sarcomatoid dedifferentiation, and poor performance status. At the same time, good performance status and good/intermediate IMDC/MSKCC risk classification were most consistently predictive of OS benefit with CN. In a randomized trial investigating the sequence of CN and ST (SURTIME), an OS trend was observed with CN after a period of ST in patients without

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progression compared with upfront CN. However, the study was underpowered and results are exploratory.
Conclusions: Currently, ST should be prioritized in the management of patients with de novo mRCC who require medical therapy. CN maintains a role in patients with limited metastatic burden amenable to surveillance or metastasectomy, and may potentially be considered in patients with favorable response after initial ST or for symptom's palliation.
Patient summary: In the contemporary era, receiving systemic therapy is the priority in metastatic kidney cancer. Nephrectomy still has a role in patients with limited burden of metastases, well-selected patients based on established prognostic and predictive factors, and patients with a favorable response after initial systemic therapy.

1. Introduction

The role of cytoreductive nephrectomy (CN) was established during an era when metastatic renal cell carcinoma (mRCC) was treated with cytokines, and few such patients survived beyond 2 yr [1]. At that time, patients with their primary tumor in situ were particularly noted to have poor responses to cytokines [2–5]. Moreover, case reports noted regression of metastatic disease in patients who underwent CN [1,6]. CN was proposed to improve antitumor immune system response by reducing the burden of RCC that was producing factors interfering with T-cell function [7–10]. Based on these preclinical and clinical data, two randomized trials were performed, which demonstrated in a combined analysis a 31% decrease in the risk of mortality and significantly improved median overall survival (OS; 13.6 vs 7.8 mo) among patients with mRCC who underwent CN [11].

Shortly thereafter, targeted therapies (TTs) emerged and demonstrated superiority to previous standard cytokines, replacing these agents as standard of care for systemic therapy (ST) in mRCC [12–20]. Even though the progression-free survival (PFS) and/or OS benefit attributed to these agents has largely been established in study populations in which 75–100% of patients have had prior nephrectomy [12–16,19,21], the role of CN in mRCC has been questioned in the setting of these more effective systemic agents, given that some patients are unable to receive TT after CN due to perioperative complications or disease progression [2,5,11,22]. Indeed, utilization of CN has declined since the introduction of TT [23,24].

In order to better understand the role of CN in the TT era, our primary objective was to conduct a systematic review to assess whether CN versus no CN is associated with improved OS in patients with mRCC treated in the TT era. Our secondary objectives were to characterize the morbidity of CN, identify prognostic and predictive factors, and evaluate outcomes following treatment sequencing (see the Supplementary material, Appendix 1, for detailed list of primary [PRQs] and secondary [SRQs] research questions).

2. Evidence acquisition

2.1. Methods of systematic review

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting this systematic review [25].

2.2. Study eligibility criteria

Clinical trials, cohort studies, and case-control studies were considered for inclusion. Case reports and case series were excluded. Other publications such as studies not using human subjects, editorials, commentaries, review articles, and those not subject to peer review (ie, reports of data from Vital Statistics and dissertations or theses) were also excluded.

2.3. Information sources and search strategy

Medline and EMBASE databases were searched using the OvidSP platform, as well as the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews, for English-language studies indexed from database inception to June 4, 2018 without restrictions on publication year, by a professional librarian (the full search strategy is given in the Supplementary material, Appendix 2). Following literature search, all duplicates were excluded. References from review articles, commentaries, editorials, included studies, and conference publications of relevant medical societies were hand searched and cross referenced to ensure completeness. Conference abstracts were included when sufficient information could be obtained from corresponding authors.

Where there was more than one publication resulting from the same patient cohort, we aimed to select a single representative study, with preference for more contemporary publications, and publications with a larger number of patients and more reliable methods of exposure and outcome ascertainment. If different reports from the same study population provided complementary data that were relevant to our research questions, then both reports were included and considered as a single study.

2.4. Types of participants and exposure

We reviewed studies reporting on patients diagnosed with RCC that was metastatic at presentation, with patients who underwent and those who did not undergo CN, as determined by administrative and/or clinical health records. Additionally, for SRQ1 and SRQ2, studies including only patients who underwent CN were also reviewed. All studies were required to include patients treated in the TT era in order to focus on contemporary patients and outcomes, except for SRQ2 and SRQ3, where it was deemed important to identify all potential prognostic and predictive

factors even if they were reported prior to the introduction of TTs. CN could be performed at any point in time after mRCC diagnosis for all primary and secondary research questions, except for SRQ4, where the treatment sequencing was evaluated. Studies focusing on patients undergoing cytoreductive partial nephrectomy or ablative procedures were not included.

2.5. Outcome measures

The primary outcome for PRQ and SRQ2–SRQ4 was OS. For SRQ1, the outcomes of interest were the proportion experiencing perioperative mortality, any complication, any major (Clavien $\geq$3) complication, blood transfusion rate, median or mean length of hospital stay, median or mean time to ST after CN, and percent of patients not receiving ST after CN.

2.6. Study selection methods and data collection

One author (B.B.) performed study selection and all data abstraction including evaluation of study characteristics and outcome measures, with independent verification by all other coauthors. Disagreements were resolved by consensus. Titles and abstracts were used to screen for initial study inclusion. Full-text review was used where abstracts were insufficient to determine whether the study met inclusion or exclusion criteria.

Studies were considered relevant to the PRQ if they reported a hazard ratio (HR) estimate for the association between CN and OS. Risk adjustment was required for nonrandomized studies. Studies were considered relevant to SRQ1 if they reported the proportion of patients experiencing any of the perioperative outcomes of interest or reported median/mean length of stay or time to ST. Studies were considered relevant to SRQ2 if they reported an HR or Kaplan-Meier analysis for the association between one or more patient- or tumor-related pretreatment factors and OS. Prognostic factors were required to be independently associated with OS [26]. Studies were considered relevant to SRQ3 if they evaluated whether the treatment effect of CN on OS was different based on predictive factors using stratified survival analyses and/or interactions terms. A patient- or tumor-related factor was considered as predictive of benefit/harm associated with CN if the treatment effect of CN was different for patients with versus those without the factor [26]. Studies were considered relevant to SRQ4 if they compared OS between patients treated initially with CN versus those treated initially with TT.

2.7. Risk of bias assessment

Risk of bias assessment was performed by two authors (B.B. and R.J.M.) using the Cochrane Collaborative Risk of Bias tool for randomized trials [27] and the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies [28] (see the Supplementary material, Appendix 3).

2.8. Assessment of heterogeneity and reporting bias

We identified heterogeneity using the Q test, estimated it using the DerSimonian-Laird method, and quantified it using I^2 values [29]. We assessed publication bias for outcomes with $\geq$10 included studies using funnel plots.

2.9. Data synthesis and analysis

Study characteristics and outcomes were tabulated separately for each research question, and a narrative synthesis was performed. Forest plots were created using Review Manager 5.3 software (Cochrane Collaboration, 2014; The Nordic Cochrane Centre, Copenhagen, Denmark) to summarize outcome data for the PRQ. Clear-cell and non–clear-cell RCC were evaluated separately in subset analyses. Meta-analyses were not performed due to inherent clinical and methodological heterogeneity.

3. Evidence synthesis

3.1. Literature search

A total of 382 unique records were identified and screened, and 143 articles were selected for full-text review. After full-text review, 63 articles were included in the qualitative systematic review (Supplementary Fig. 1). The reasons why articles were excluded upon full-text review are summarized in Supplementary Table 1.

3.2. Impact of CN on OS

Thirteen reports on 11 studies were included in the analysis of the PRQ [24,30–40], including three articles evaluating the Surveillance, Epidemiology, and End Results (SEER) registry that were considered as a single study (Table 1) [24,39–41]. One study was a randomized trial [41]. The other 10 were population-based [24,32,36,39,40], multicenter (including one using a hospital-based national dataset) [30,31,33,34,37], or single-center [35,38] retrospective cohort studies. CN was administered before ST in five studies [30–32,35,38], and before or after ST in two studies [33,41], and the sequence was not specified in four studies. Sunitinib was the most common first-line systemic agent used [30–32,34,35,38,41].

In the risk of bias assessment (Supplementary Table 2), four studies in this analysis [31,37,38,41] were judged as having a moderate risk of bias, and seven studies [24,30,32–36,39,40] were judged as having a serious risk of bias. CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) [41] was closed before original endpoints at second interim analysis based on the results observed after International Metastatic renal cell carcinoma Database Consortium (IMDC) report and slow accrual. This trial was enriched with poor-risk patients who are not known to benefit from CN, although inclusion criteria required a performance status of 0–1 and eligibility for both CN and ST, therefore defining a clinically relevant

Table 1 – Studies evaluating association between cytoreductive nephrectomy and overall survival

First author (year)	Design	Country of origin, included years	Pre- versus post-TT introduction	Number of patients	Age distribution (yr)	First-line systemic agents used	CN-systemic therapy sequence	Median follow-up (mo)
Mejean (2018) [41]	Prospective randomized trial	France, Norway, England, Scotland, Sweden 2009–2017	Post-TT	*N* (total) = 450 *N* (CN) = 226 *N* (no CN) = 224	CN: median 63 (range 33–84) No CN: median 62 (range 30–87)	Sunitinib	CN before systemic therapy[a]	50.9 (range 0.0–86.6)
Choueiri (2011) [30]	Retrospective cohort, multicenter	Canada and USA, 2004–2008	Post-TT	*N* (total) = 314 *N* (CN) = 201 *N* (no CN) = 113	Age <60: *n* = 157 (50%) Age ≥60: *n* = 157 (50%)	Sunitinib (63%) Sorafenib (30%) Bevacizumab (7%)	CN before systemic therapy	16.3
Day (2016) [31]	Retrospective cohort, multicenter	Australia, 2006–2012	Post-TT	*N* (total) = 91 N (CN) = 46 N (no CN) = 45	CN: median 59.0 No CN: median 64.6	Sunitinib (74%) Pazopanib (4%) Everolimus (4%) Bevacizumab (2%) Interferon (2%) Temsirolimus (1%)	CN likely before systemic therapy[b]	87
de Groot (2016) [32]	Retrospective matched cohort, population based	The Netherlands, 2008–2010	Post-TT	*N* (total) = 146 *N* (CN) = 73 *N* (no CN) = 73	CN: median 62 (IQR 28, 77) No CN: median 64 (IQR 24, 89)	Sunitinib	CN before systemic therapy	NR[c]
Hanna (2016) [33]	Retrospective cohort, national hospital-based dataset	USA (NCDB), 2006–2013	Post-TT	*N* (total) = 15 390 *N* (CN) = 5374 N (no CN) = 10 016	Median 63 (IQR 55, 71)	NR	CN before or after systemic therapy	NR
Heng (2014) [34]	Retrospective cohort, multicenter	Canada, USA, Belgium, South Korea, Japan, Denmark, Greece, and Singapore; study years not specified	Post-TT	*N* (total) = 1658 *N* (CN) = 982 *N* (no CN) = 676	CN: median 59.3 (IQR 52.7, 67.4) No CN: median 59.9 (IQR 54.6, 70.0)	CN; no CN Sunitinib (67%; 79%) Sorafenib (20%; 8.6%) Axitinib (0.4%; 0.4%) Bevacizumab (4.0%; 1.5%) Temsirolimus (3.6%; 6.4%) Pazopanib (2.8%; 2.8%) Everolimus (1.0%; 1.0%) Other (0.7%; 0.3%)	NR	39.1 (IQR 36.0, 41.5)
Klatte (2018) [35]	Retrospective cohort, single center	UK, 2006–2017	Post-TT	*N* (total) = 261 *N* (CN) = 97 *N* (no CN) = 164	Mean 62.2 (SD 11.2)	Sunitinib (60.5%) Pazopanib (28.4%) Other (11.1%)	CN before systemic therapy	14.6 (IQR 7.1, 24.3)
Patel (2017) [36]	Retrospective cohort, population based	Australia, 2001–2009	Pre/post-TT	*N* (total) = 1062 *N* (CN) = 289 *N* (no CN) = 773	Age <50: 101 Age 50–59: 185 Age 60–69: 242 Age 70–79: 276 Age 80+: 258	NR	NR	52
Tatsugami (2015) [37]	Retrospective cohort, multicenter	Japan, 2001–2010	Pre/post-TT	*N* (total) = 330 *N* (CN) = 254 *N* (no CN) = 76	Median 63.5 (IQR 11, 87)	Cytokines (39.7%) Targeted therapy (38.9%) None (21.5%)	NR	NR
You (2011) [38]	Retrospective cohort, single center	South Korea, 2006–2009	Post-TT	*N* (total) = 78 *N* (CN) = 45 *N* (no CN) = 33	Median 59 (range 34–79)	Sunitinib (81%) Sorafenib (19%)	CN before systemic therapy	8.2

Table 1 (*Continued*)

First author (year)	Design	Country of origin, included years	Pre- versus post-TT introduction	Number of patients	Age distribution (yr)	First-line systemic agents used	CN-systemic therapy sequence	Median follow-up (mo)
Abern (2014) [39] [d]	Retrospective cohort, population based	USA (SEER), 2005–2009	Post-TT	*N* (total) = 7143 *N* (CN) = 2629 *N* (no CN) = 4514	CN: median 61 (IQR 53, 68) No CN: median 68 (IQR 59, 78)	NR	NR	13 (IQR 4, 28)
Conti (2014) [24] [d]	Retrospective cohort, population based	USA (SEER), 1993–2010	Pre/post-TT	*N* (total) = 20 104 *N* (CN) = 6915 *N* (no CN) = 13 189	CN: mean 60.8 (SD 11.3) No CN: mean 67.8 (SD 12.8)	NR	NR	12 (IQR 5, 30)
Marchioni (2017) [40] [d]	Retrospective cohort, population based	USA (SEER), 2001–2014	Pre/post-TT	*N* (total) = 851 *N* (CN) = 575 *N* (no CN) = 276	Median 62 (IQR 53, 71.5)	NR	NR	9 (IQR 4, 21)

CN = cytoreductive nephrectomy; IQR = interquartile range; NCDB = National Cancer Database; NR = not reported; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results; TT = targeted therapy.

[a] While patients were randomized to CN followed by sunitinib versus sunitinib alone, 17.0% of patients in the sunitinib-only arm received subsequent CN.

[b] All patients in the CN group had surgery within 3 mo of diagnosis of metastatic disease.

[c] Median follow-up was not reported, but it was stated that 207 of 220 patients from unmatched source cohort had died at the last follow-up.

[d] Three SEER articles were analyzed as a single study.

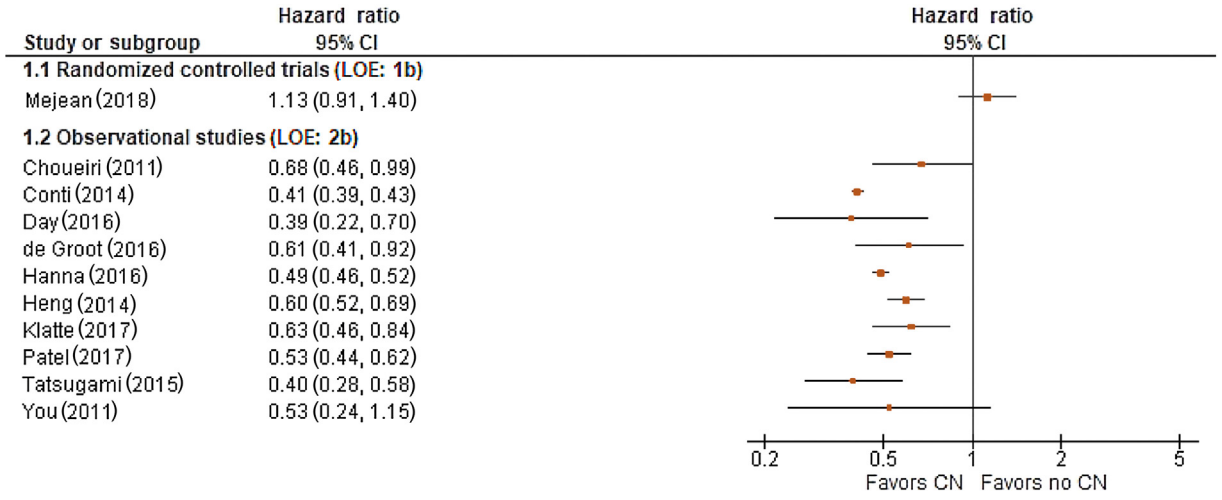
population for the question of the role of CN. It is unknown whether the study population was representative of patients believed to benefit most from CN study, given that CARMENA focused on patients who required upfront ST, automatically rendering all patients at least an intermediate risk, and did not enroll patients who were eligible for upfront surveillance or a delayed ST strategy [42]. There was also a significant crossover in the two arms as 17% of patients randomized to the sunitinib-alone arm underwent subsequent CN, while 7% of patients in the upfront CN arm did not undergo CN [41]. All observational studies were considered inferior to CARMENA in terms of level of evidence and risk of bias. The inability to account for unmeasured differences between CN and control groups led to all observational studies being considered as having at least a moderate risk of bias for the confounding domain. Common reasons for being considered as having a serious risk of bias were not adjusting for performance status, comorbidity, or Memorial Sloan Kettering Cancer Center (MSKCC) or IMDC risk scores [24,36,39,40], and including only patients who received ST [30,32–35], which does not account for patients who did not receive postoperative ST due to perioperative complications or disease progression [2,5,11,22]. In the funnel plot for observational studies, there was no clear evidence of publication bias (Supplementary Fig. 2).

The adjusted HR estimates for the association between CN and OS from all the observational studies including in the PRQ analysis are summarized in Figure 1A. The point estimates for all observational studies favor CN versus no CN (10 studies; HR estimates ranging from 0.39 to 0.68), with all but one study attaining statistical significance. Findings were generally similar for analyses on clear-cell RCC (four studies; HR estimates ranging from 0.36 to 0.64; Fig. 1B) and non–clear-cell RCC (three studies; HR estimates ranging from 0.38 to 0.61; Fig. 1C) subsets.

In contrast, the CARMENA trial [41] found that sunitinib alone was noninferior to CN followed by sunitinib for the primary outcome of OS in patients with de novo metastatic clear-cell RCC (median OS 18.4 vs 13.9 mo; HR = 0.89; 95% confidence interval [CI] 0.71–1.10; Fig. 1A). 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) subsets in this trial.

3.3. *Complications and delays to ST after CN*

The analysis for SRQ1 included 18 studies (Table 2) [22,30,41,43–57]. Two were prospective randomized trials [41,57], three were prospective nonrandomized single-arm trials [46–48], and the remainder were population based [43,51,55,56], multicenter [30,44,52], or single-center [22,45,49,50,53,54] retrospective cohort studies. Six studies reported on patients who underwent upfront CN [22,30,41,43–45], three studies evaluated patients undergoing presurgical ST followed by consideration for CN [46–48], and six studies reported on patients treated with both sequences [49–54,57]. There was notable variation between studies in the use of minimally invasive CN.



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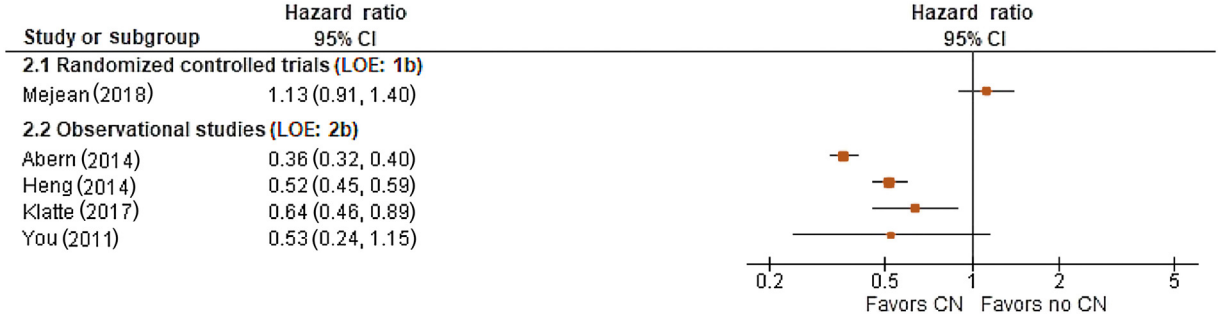

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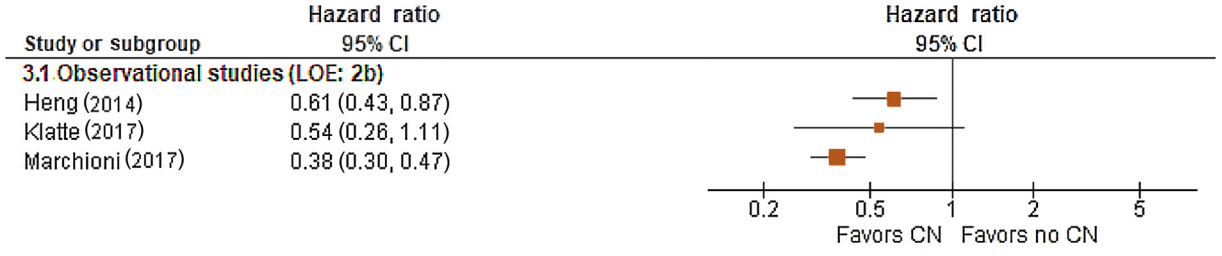

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Fig. 1 – Summary of studies evaluating the association between cytoreductive nephrectomy and overall survival in metastatic renal cell carcinoma. (A) All studies. (B) Clear-cell RCC subset. (C) Non–clear-cell RCC subset (observational only). The hazard ratio effect estimates are summarized here for each study evaluating the impact of CN on overall survival, categorized by whether it applies to metastatic renal cell carcinoma patients overall, clear-cell RCC subsets, or non-clear cell renal cell carcinoma subsets, as well as by level of evidence. The hazard ratio for no CN versus CN was reported as 0.89 (95% CI 0.71–1.10) in the paper by Mejean et al. [41], 1.90 (95% CI 1.61–2.25) in the paper by Patel et al. [36], and 1.9 (95% CI 0.9–4.3) in the paper by You et al. [38]. The presented hazard ratios in the figures are calculated as the inverse. CI = confidence interval; CN = cytoreductive nephrectomy; LOE = level of evidence; RCC = renal cell carcinoma.

Table 2 – Morbidity of cytoreductive nephrectomy

First author (year)	Design, county of origin, years	*N* (CN)	Age (yr)	CN-ST seq.	MIS (%)	Median LOS (d)	Periop mortality (%)	Any complication (%)	Clavien ≥3 complication (%)	Transfusion (%)	Time to ST after CN	Percent not getting ST after CN (%)[a]
Studies evaluating patients who underwent upfront CN												
Mejean (2018) [41]	Prospective randomized trial	226	63 (range 33–84)	Upfront CN	NR	NR	NR	NR	NR	NR	NR	17.7
Abdollah (2011) [43]	Retrospective cohort, population based, USA (Florida inpatient database), 1999–2008	1063	≤49: *n* = 125 50–59: *n* = 239 60–69: *n* = 345 70–79: *n* = 258	Upfront CN	9.1	5 (range 1–272)	In-hospital: 2.4%	In-hospital: 26.5%	NR	24.3	NR	NR
Blick (2010) [44]	Retrospective cohort, multicenter, UK, 2003–2007	25	Median 63 (range 30–85)	Upfront CN	92	3 (range 2.5–11)	0	12	4	12	NR	17[b]
Choueiri (2011) [30]	Retrospective cohort, multicenter, Canada and USA, 2004–2008	201	Median 60	Upfront CN	NR	NR	NR	NR	NR	NR	Median 5 mo (IQR 2, 17)	NR
Kutikov (2010) [22]	Retrospective cohort, single center, USA, 1990–2008	141	Median 60.5 (range 16–82)	Upfront CN	17.7	NR	5.7	NR	NR	NR	Median 2.5 mo (range 0.13–61.5)	25.8[c]
O'Malley (2011) [45]	Retrospective cohort, single center, USA, 2002–2010	65	Mean 61 (range 42–90)	Upfront CN	60	3 (IQR 2, 5)	2	48	8	26	4.4 mo (range 3.3–6.6)	26[d] (28% did not receive ST within 2 mo)
Studies evaluated patients who had CN performed after initial ST												
Jonasch (2009) [46]	Single-center prospective phase 2 trial, 2005–2008	52	Median 61 (range 35–83)	CN after ST: *n* = 42 Did not proceed to CN: *n* = 10	NR	5 (range 1–70)	5	NR	NR	NR	NR	NR
Powles (2011) [47]	Combined analysis of 2 prospective phase 2 trials, UK and the Netherlands, 2007–2009	47	Median 58.5 (range 37–78)	CN after ST: *n* = 47 Did not proceed to CN: *n* = 19	11[e]	NR	2	26	9	NR	21 d (range 14–82)[e]	NR[f]
Powles (2016) [48]	Prospective phase 2 trial, UK, 2008–2012	65	Median 64 (IQR 56, 71)	CN after ST: *n* = 65 Did not proceed to CN: *n* = 39	34	7 (IQR 5, 8)	1	22	3	NR	NR	NR[g]
Studies including both patients who had CN before and after ST												
Bex (2017) [57]	Prospective randomized trial	8[h]	Upfront CN: median 60 Deferred CN: median 58	Upfront CN: *n* = 46 CN after ST: *n*= 40	NR	NR	Within 30 d: 2%	Upfront CN: 43.5% Deferred CN: 27.5%	Upfront CN: 28.3% Deferred CN: 25.0%	NR	NR	13
Chapin (2011) [49]	Retrospective cohort, single center, USA, 2004–2010	173	Median 60.1 (range 20.9–80.0)	Upfront CN: *n* = 103 CN after ST: *n* = 70	17.9	6 (range 1–107)	Within 12 mo: 10.4%	Within 12 mo, overall: 57% Presurgical ST: 65.7% Upfront CN: 51.4%	Within 12 mo: 29.4%	NR	NR	NR
Gershman (2016) [50]	Retrospective cohort, single center, USA, 1990–2009	294	Median 60 (IQR 52, 68)	Upfront CN: *n* = 272 CN after ST: *n* = 22	6	6 (IQR 5, 7)	Within 30 d: 1%	Within 30 d: 12%	Within 30 d: 5%	51	Median 56 d	30.4[i] (61.6% did not receive ST within 60 d)

Table 2 (*Continued*)

First author (year)	Design, county of origin, years	*N* (CN)	Age (yr)	CN-ST seq.	MIS (%)	Median LOS (d)	Periop mortality (%)	Any complication (%)	Clavien ≥3 complication (%)	Transfusion (%)	Time to ST after CN	Percent not getting ST after CN (%)[a]
Jackson (2015) [51]	Retrospective, population based, UK, 2012	279	Median 62 (range 19–95)	Upfront CN: *n* = 239 CN after ST: *n* = 40	34	NR	1.8	22.6	8	24.1	NR	NR
Patel (2016) [52]	Retrospective cohort, two centers, USA, 2007–2014	48	Upfront CN: mean 59 (SD 14.9) CN after ST: mean 57 (SD 12.5)	Upfront CN: *n* = 27 CN after ST: *n* = 21	44	Upfront CN: 4.5 (IQR 3, 8) ST then CN: 7 (IQR 5, 11)	NR	Overall: 39.6% Upfront CN: 33.3% ST then CN: 47.6%	Overall: 12.5% Upfront CN: 0% ST then CN: 26.8%	NR	Median 1.4 mo (IQR 0.9, 2.4)	NR
Silberstein (2012) [53]	Retrospective cohort, single center, USA, 1989–2009	195	Median 62 (IQR 42, 69)	Upfront CN: *n*= 181 CN after ST: *n* = 14	6	NR	Within 56 d: 4.6%	Within 56 d: 36.9%	Within 56 d: 8.2%	NR	NR	41.5[j]
Westesson (2014) [54] [k]	Retrospective cohort, single center, USA, 1990–2007	76	Mean 62	Upfront CN: *n* = 71 CN after ST: *n* = 5	0	NR	Within 30 d: 7.9%	Within 30 d Intraoperative: 11.8% Postoperative: 37%	Within 30 d: 7.9%	92	NR	12.9[l]
CN-systemic therapy sequence unknown												
Sun (2012) [55]	Retrospective, population based, USA (NIS), 1998–2007	3300	Age <75: *n* = 2796 Age ≥75: *n* = 504	NR	NR	Age <75: 6 (IQR 4, 9) Age ≥75: 7 (IQR 5, 11)	In-hospital Overall: 2.3% Age <75: 1.9% Age ≥75: 4.8%	In-hospital Overall: 23.5% Age <75: 22.8% Age ≥75: 27.8%	NR	Overall: 22.8% Age <75: 21.5% Age ≥75: 29.8%	NR	NR
Takagi (2014) [56]	Retrospective, population based, Japan, 2007–2012	1074	Age <65: *n* = 495 Age 65–74: *n* = 369 Age ≥75: *n* = 210	NR	23	T1: 11 (IQR 9, 17) T2: 13 (IQR 9, 19) T3: 15 (IQR 10, 26) T4: 18 (IQR 11, 36)	3.4	11.5	NR	36.7	NR	NR

CN = cytoreductive nephrectomy; IQR = interquartile range; IVC = inferior vena cava; LOS = length of stay; MIS = minimally invasive surgery; NR = not reported; seq = sequence; SD = standard deviation; ST = systemic therapy.

[a] In order to understand how many patients were precluded from receiving ST due to undergoing CN, percentages not receiving ST after CN were calculated after excluding patients electing postoperative surveillance or metastasectomy only.

[b] Of 25 patients in this analysis, twos elected surveillance. Of 23 patients, four (17%) did not receive ST for unknown reasons, while 19 (83%) received ST.

[c] Of 141 patients in this analysis, nine elected surveillance. Of 132 patients, 34/(25.8%) did not receive ST, 13 (9.8%) had rapid disease progression, 10 (7.6%) refused ST, eight (6.1%) died perioperatively, and three (2.3%) did not get ST for unknown reasons. Meanwhile, 98 (74.2%) received systemic therapy.

[d] Of the 65 patients in the analysis, none elected surveillance. Seventeen (26%) patients did not receive ST and 18 (28%) were ineligible to start ST at 2 mo. Eight (12%) patients experienced rapidly progressive disease, six experienced surgically related delays (9%), two (3%) experienced both surgically related reasons and rapid progression, and two (3%) had metastatic progression that was treated surgically. Meanwhile, 48 (48/65; 74%) patients received ST.

[e] Obtained from earlier report on 52 patients who received upfront sunitinib and 37 patients who underwent CN [107].

[f] The authors reported in the reasons for not undergoing planned CN after upfront targeted therapy (29%), which included disease progression (18%), patient choice (8%), patient unfit for surgery (2%), and patient died of infection prior to surgery (2%).

[g] The authors reported in the reasons for not undergoing planned CN after upfront targeted therapy (37%), which included disease progression (12%), patient choice (9%), patient unfit for surgery (5%), and other (11%).

[h] SURTIME included 99 patients, with 50 patients randomized to immediate CN and 49 to deferred CN. Forty-six patients underwent CN in the immediate CN arm and 40 patients underwent CN in the deferred CN arm.

[i] Of 201 patients in this analysis, 89 elected initial surveillance. Of 112 patients, 34 (30.4%) did not receive ST. Within 60 d, 30 (26.8%) of 112 patients did not receive ST for disease-related reasons, 12 (10.7%) did not receive ST for surgery-related reasons, three (2.7%) died perioperatively, and 24 (21.4%) did not receive ST for other reasons. Meanwhile, 78 (69.6%) patients eventually received ST.

[j] While 81 (41.5%) did not receive ST, it is not reported how many of these patients underwent active surveillance with or without metastasectomy. Therefore, this value may be an overestimate.

[k] All patients in this study underwent CN with level II–IV IVC tumor thrombectomy.

[l] Of the 76 patients in this analysis, four elected surveillance, and no follow-up data were available for 10 patients. Of 62 patients, six (9.7%) died perioperatively and two (3.2%) died due to disease progression prior to receiving ST. Meanwhile, 54 of 62 (87.1%) patients received ST.

In the risk of bias assessment (Supplementary Table 2), six studies were considered to have a low risk of bias [45,46,50,53,56,57], six studies were considered to have a moderate risk of bias [22,41,47–49,51], and six nonrandomized studies were considered to have a serious risk of bias [30,43,44,52,54,55]. Reasons for classification as having a serious risk of bias were lack of risk adjustment of patients who received and those who did not receive presurgical ST [52], use of patient samples that are not representative of the broader population of patients undergoing CN [44,54], and capturing only in-hospital complications [43,55].

Peri- and postoperative outcomes are summarized in Table 2. Among studies reporting on perioperative mortality and/or complications [22,43–56], nine did not specify the timeframe during which events were evaluated [22,44–48,51,52,56], two evaluated in-hospital complications [43,55], and five evaluated complications within 30 d [50,54,57], 56 d [53], or 12 mo [49]. The risk of perioperative mortality, any complication, and any major (Clavien $\geq$3) complication ranged from 0% to 10.4%, 12% to 57%, and 3% to 29.4%, respectively.

Among studies evaluating upfront CN [22,30,43–45,57], the risk of perioperative mortality, any complication, and any major (Clavien $\geq$3) complication ranged from 0% to 5.7%, 12% to 48%, and 4% to 28.2%, respectively. Among studies reporting on patients who underwent CN after presurgical ST [46–48,57], the risk of perioperative mortality, any complication, and any major complication ranged from 1% to 5%, 22% to 27.5%, and 3% to 25%, respectively (varying time frames; see Table 2). Among three studies directly comparing adverse event risk between patients treated with upfront CN versus CN after presurgical ST [49,51,52], no significant differences were noted in the risks of perioperative mortality or complications, although Chapin et al. [49] found that presurgical ST was associated with an increased risk of wound complications, such as wound infection, superficial wound dehiscence, and possibly fascial dehiscence, although most patients treated with presurgical ST in this study had received bevacizumab. Older age [51,53], poor performance status [51,53], greater comorbidity [56], larger tumor size [51], radiographic evidence of a tumor thrombus [50], clinical stage T4 [56], and liver metastasis [50] were independent risk factors for complications in patients undergoing CN.

Eleven studies reported on receipt of ST after CN [22,30,41,44,45,47,50,52–54,57]. Excluding patients undergoing metastasectomy or elective surveillance for low-volume metastatic disease after CN, the percentage of patients not receiving ST after CN ranged from 12.9% to 30.4% among the seven studies reporting reasons for not receiving ST [22,41,44,45,50,54,57]. Silberstein et al. [53] reported that 41.5% of patients did not receive ST after CN, but did not distinguish patients electing surveillance for their metastases. The most common reasons for not receiving ST after CN were disease progression and postoperative complications [22,50,53]. Meanwhile, among studies of patients treated with upfront ST [46–48,57], 18–38% did not undergo planned CN after upfront ST, most often due to disease progression.

Among patients receiving ST, the median time from CN to ST ranged from 21 d to 5 mo [22,30,45,47,50,52]. It is unclear to what extent local protocols for waiting to start ST after CN influenced the timing of receipt of postoperative ST. Some studies defined timely receipt of ST as receiving ST at 60 d or 2 mo after CN [45,50,53]. In this regard, one study reported that 28% of patients did not receive ST within 2 mo [50], while another study reported that 61.6% did not receive ST within 60 d [45]. Clavien grade $\geq$2 postoperative complications were independently associated with the probability of not receiving ST within 60 d (odds ratio [OR] = 0.32; 95% CI 0.12–0.86; p = 0.024) [53].

3.4. *Prognostic factors for OS*

Characteristics of the 38 reports on 33 studies [24,31–33,35–37,46–48,58–85] included in the analysis for SRQ2 are summarized in Supplementary Table 3 (unless already summarized in Table 1). Three of these studies were prospective [46–48], while the remaining studies were retrospective. Fifteen reports evaluated patients with mRCC who underwent and who did not undergo CN [24,31–33,35–37,46–48,59,61,73,79,84], while 23 reports exclusively evaluated cohorts of patients who underwent CN [58,60,62–72,74–78,80–83,85].

Studies in this analysis were considered as having a moderate [31,37,46–48,58,60–66,68–70,73,75,77,79,81–83] or serious [24,32,33,35,36,59,67,71,72,74,76,78,80,84,85] risk of bias. Inadequate adjustment for confounding was the most common reason for classification of studies as having a serious risk of bias.

Independent preoperative patient- and tumor-related prognostic factors that were evaluated in two or more studies are summarized in Tables 3 and 4, respectively, while those evaluated only in one study are summarized in Supplementary Table 4. The factors most consistently found to be independently associated with OS were neutrophil-lymphocyte ratio (four of five studies; 80%), C-reactive protein (five of six studies; 83%), IMDC or MSKCC risk classification (seven of 10 studies; 70%), and tumor response to presurgical ST (three of three studies; 100%; Tables 3 and 4). Patient performance status (eight of 13 studies; 62%), comorbidity (three of five studies; 60%), serum lactate dehydrogenase (five of eight studies; 62%), number of metastases (seven of 13 studies; 54%), presence of liver metastasis (four of seven studies; 57%), tumor grade (seven of 13 studies; 54%), and sarcomatoid dedifferentiation (six of nine studies; 67%) were also independent prognostic factors in the majority of studies in which these were evaluated (Tables 3 and 4). However, it is worth noting that no factors have been demonstrated to have strong prognostic abilities. For example, in an external validation study, MSKCC and IMDC criteria were found to have c-indexes of 0.66 and 0.71, respectively [86].

3.5. *Factors predicting for OS benefit with CN*

Six studies were included in the analysis of SRQ3 [30,35,84,85,87,88], for which study characteristics have been presented in Table 1 and Supplementary Table 3.

Table 3 – Independent patient-related prognostic factors for patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma

First author (year)	Number of patients in analysis	Age	Sex	Marital status	Performance status	Comorbidity	BMI	Systemic symptoms	Symptomatic	Hemoglobin	Platelets	ANC	ALC	NLR	LDH	Serum Ca	CRP	Albumin	Serum creatinine	Serum alkaline phosphatase	IMDC/MSKCC classifications
Analyses of patients who underwent and who did not undergo CN																					
Aizer (2014) [59] [a]	5055	Y	N	Y	×	×	×	×	×	×	×	××	×	×	×	×	×	×	×	×	×
Conti (2014) [24] [a]	20 104	–	–	–	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Day (2016) [31]	91	×	×	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	×	×	×	Y
de Groot (2016) [32] [b]	143	×	×	×	Y	×	×	×	×	×	N	×	×	×	×	Y	×	×	×	×	×
Hanna (2016) [33]	15 390	Y	N	×	×	Y	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Jonasch (2009) [46]	50	×	×	×	×	×	×	×	×	×	×	×	×	×	Y	N	×	×	×	×	N
Ito (2012) [73] [c]	181	N	N	×	Y	×	×	×	×	N	×	×	×	×	N	N	Y	×	×	N	×
Klatte (2018) [35]	261	N	N	×	Y	×	×	×	×	N	Y					N	×	×	×	×	×
Ohno (2014) [79] [b]	73	N	N	×	Y	N	×	×	N	N		N	N	Y	N	N	N	×	×	×	×
Patel (2017) [36]	1062	Y	Y	N	×	Y	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Powles (2011) [47,106]	66	×	N	×	×	×	×	×	×	×	N	N	×	×	×	×	×	×	×	×	Y
Song (2016) [84]	74	Y	N	×	×	×	Y	×	×	N	×	×	×	×	Y	Y	×	×	×	×	×
Tatsugami (2015) [37] [d]	330	×	×	×	Y	×	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	Y
Analyses of patients who underwent CN																					
Abel (2017) [58] [c,e]	427	×	×	×	×	×	×	Y	×	N	N	N	N	×	Y	N	×	N	×	×	×
Baum (2016) [60]	64	N	N	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	×	×	×	×
Blute (2017) [62]	67	N	N	×	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	Y
Capitanio (2013) [63] [f]	242	×	×	×	×	×	×	×	×	Y	×	×	×	×	×	×	×	×	×	×	×
Carrasco (2014) [64]	505	×	×	×	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Corcoran (2015) [65]	246	N	×	×	N	N	×	N	N	N	×	×	×	×	×	×	×	Y	×	×	×
Culp (2010) [66] [g]	566	×	×	×	×	×	×	N	×	×	×	×	×	×	Y	×	×	Y	Y	N	×
Kassouf (2007) [75] [g]	606	N	×	×	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Margulis (2013) [77] [g]	601	×	×	×	–	×	×	×	×	N	N	N	×	×	–	N		–	N	–	N
Fajkovic (2016) [67]	613	×	×	×	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	×	×	×
Fukuda (2018) [68] [c,h]	170	N	N	×	Y	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	Y
Fukuda (2018) [69] [c,h]	152	Y	×	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	×	×	×	–
Ishihara (2017) [c,h]	118	–	–	×	×	×	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	–
Gu (2017) [70] [c,i]	184	N	N	×	×	×	×	×	×	Y	N	N	×	×	×	×	×	N	×	×	×
Gu (2017) [71] [c,i]	161	–	–	×	×	×	×	×	×	–	×	×	×	N	×	×	×	–	×	×	×
Kalogirou (2017) [74] [e]	146	×	×	×	×	Y	×	×	×	Y	×	×	×	×	×	×	Y	×	×	×	×
Lee (2017) [76]	244	N	×	×	×	×	N	×	×	×	×	×	×	×	×	×	×	×	×	×	Y
Pierorazio (2007) [80] [c]	55	N	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Sakai (2014) [81] [c]	164	N	N	×	×	×	×	×	×	×	×	×	×	×	×		Y	×	×	×	Y
Sharma (2015) [82]	93	N	×	×	N	×	N	×	×	×	×	×	×	×	×	×	×	N	×	×	N
Shuch (2008) [83] [c]	418	N	N	×	Y	×	×	×		N	×	×	×	×	×	×	×	×	×	×	×
You (2015) [85] [c]	96	N	N	×	Y	×	×	N	N	Y	N	Y	×	×	N	N	×	N	×	×	×
Positive studies/total studies (%)		5/20 (25)	1/15 (7)	1/2 (50)	8/13 (62)	3/5 (60)	1/3 (33)	1/4 (25)	0/2 (0)	4/12 (33)	1/7 (14)	1/6 (17)	0/2 (0)	4/5 (80)	5/8 (62)	2/9 (22)	5/6 (83)	2/6 (33)	1/2 (50)	0/2 (0)	7/10 (70)

AIC = Akaike information criteria; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; BIC = Bayesian information criteria; BMI = body-mass index; CN = cytoreductive nephrectomy; CRP = C-reactive protein; IMDC = International Metastatic renal cell carcinoma Database Consortium; IVC = inferior vena cava; LDH = lactate dehydrogenase; MSKCC = Memorial Sloan Kettering Cancer Center; NLR = neutrophil-lymphocyte ratio; OS = overall survival; RCC = renal cell carcinoma.

Factors found to be independent prognostic factors in a study are marked as "Y," while those found not to be independent prognostic factors are marked as "N" in the table. A dash indicates that a variable was evaluated but not counted, since a paper using the same study cohort also reported this finding (this was done to avoid double counting). A cross indicates that the variable was not evaluated. Only factors evaluated by at least two studies are shown in this table.

[a] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

[b] Stepwise selection process was used for variable selection for the multivariable model. Variables not included in the multivariable model for this reason were considered not to be independently associated with OS in this analysis.

[c] *p* values on univariate analysis were used to guide inclusion in the multivariable model.

[d] Only subset studied variables were included in the multivariable model. The variable selection process was unclear.

[e] Cohort of patients with metastatic RCC who underwent CN and IVC tumor thrombectomy.

[f] Variable selection for the multivariable model based on AIC or BIC.

[g] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

[h] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

[i] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

Table 4 – Independent tumor-related prognostic factors for patients undergoing cytoreductive nephrectomy for metastatic renal cell carcinoma

First author (year)	Number of patients in analysis	Tumor size	Tumor side	T stage	Thrombus level	LN metastasis	No. of metastases	Liver metastasis	Lung metastasis	Bone metastasis	Brain metastasis	Histology	Grade	Sarcomatoid dedifferentiation	Tumor response to presurgical ST	Fraction percent tumor removed
Analyses of patients with underwent and who did not undergo CN																
Aizer (2011) [59] [a]	5055	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	×
Conti (2014) [24]	20 104	Y	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Bex (2008) [61]	33	×	×	×	×	×	×	×	×	×	×	×	×	×	Y	×
Day (2016) [31]	91	×	×	×	×	×	×	×	×	×	×	Y	×	×	×	×
de Groot (2016) [32] [b]	143	×	×	×	×	×	×	Y	×	×	×	×	×	×	×	×
Ito (2012) [73]	181	N	×	×	×	×	Y	×	×	×	×	×	×	×	×	×
Klatte (2018) [35]	261	×	×	×	×	Y	×	Y	N	N	N	N	×	×	×	×
Ohno (2014) [79] [b]	73	N	×	N	×	N	×	×	N	×	×	×	×	×	×	×
Patel (2017) [36]	1062	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Powles (2011) [47,106]	66	×	×	×	×	×	N	×	×	×	×	×	Y		Y	×
Powles (2016) [48]	104	×	×	×	×	×	×	×	×	×	×	×	×	×	Y	×
Song (2016) [84]	74	×	×	N	×	×	Y	×	N	×	×	×	×	×	×	×
Tatsugami (2015) [37] [c]	330	×	××	Y	×	×	×	×	×	×	×	×	×	×	×	×
Analyses of patients who underwent CN																
Abel (2017) [58] [d,e]	427	×	×	×	Y	N	×	×	×	×	×	N	×	Y	×	×
Baum (2016) [60]	64	×	×	N	×	×	×	×	×	×	×	×	N	×	×	×
Blute (2017) [62]	67	N	×	×	×	×	×	×	×	×	×	×	N	×	×	N
Capitanio (2013) [63] [f]	242	Y	×	×	×	×	Y	×	×	×	×	×	×	N	×	×
Carrasco (2014) [64]	505	×	×	×	×	Y	Y	×	×	×	×	N	×	Y	×	×
Corcoran (2015) [65]	246	×	×	Y	×	N	Y	×	×	×	×	Y	Y	N	×	×
Culp (2010) [66]	566	×	×	Y	×	Y	N	Y	×	×	×	N	Y	Y	×	×
Kassouf (2007) [75] [g]	606	×	×	–	×	–	×	×	×	×	×	×	N	–	×	×
Margulis (2013) [77] [g]	601	×	×	×	×	×	–	×	×	×	×	×	×	×	×	×
Fukuda (2018) [68] [d,h]	170	N	×	N	×	×	N	Y	×	×	×	Y	×	Y	×	×
Fukuda (2018) [69] [d,h]	152	×	×	×	×	N	×	–	×	×	Y	–	×	–	×	×
Ishihara (2017) [72] [d,h]	118	×	×	–	×	N	–	N	×	×	×	N	N	×	×	×
Gu (2017) [70] [d,i]	184	N	N	×	×	×	N	×	×	×	×	N	Y	Y	×	×
Gu (2017) [71] [d,i]	161	–	–	N		N	–	×	×	×	×	Y	–	×	×	×
Kalogirou (2017) [74] [f]	146	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Lee (2017) [76]	244	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×
Nukui (2018) [78]	53	×	×	×	×	×	×	×	×	×	×	×	Y	×	×	×
Pierorazio (2007) [80] [d]	55	N	×	×	×	Y	N	×	×	×	×	×	Y	×	×	Y
Sakai (2014) [81] [c]	164	×	×	×	×	Y	×	N	N	N	N	N	N	N	×	×
Sharma (2015) [82]	93	N	×	×	×	×	Y	×	×	×	×	×	×	×	×	×
Shuch (2008) [83] [d]	418	N	×	N	×	N	Y	×	×	×	×	×	Y	Y	×	×
You (2015) [85] [d]	96	N	N	N	N	Y	N	N	×	N	N	×	×	×	×	×
Positive studies/total studies (%)		2/11 (18)	0/2 (0)	3/10 (30)	1/2 (50)	6/13 (46)	7/13 (54)	4/7 (57)	0/4 (0)	0/3 (0)	1/4 (25)	5/12 (42)	7/12 (58)	6/9 (67)	3/3 (100)	1/2 (50)

AIC = Akaike information criteria; BIC = Bayesian information criteria; CN = cytoreductive nephrectomy; IVC = inferior vena cava; LN = lymph node; OS = overall survival; RCC = renal cell carcinoma; ST = systemic therapy.
Factors found to be independent prognostic factors in a study are marked as "Y," while those found not to be independent prognostic factors are marked as "N" in the table. A dash indicates that a variable was evaluated but not counted, since a paper using the same study cohort also reported this finding (this was done to avoid double counting). A cross indicates that the variable was not evaluated. Only factors evaluated by at least two studies are shown in this table.

[a] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

[b] Stepwise selection process was used for variable selection for the multivariable model. Variables not included in the multivariable model for this reason were considered not to be independently associated with OS in this analysis.

[c] Only subset studied variables were included in the multivariable model. The variable selection process was unclear.

[d] *p* values on univariate analysis were used to guide inclusion in the multivariable model.

[e] Cohort of patients with metastatic RCC who underwent CN and IVC tumor thrombectomy.

[f] Variable selection for the multivariable model based on AIC or BIC.

[g] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

[h] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

[i] These articles reported on different prognostic factors from the same study cohort and were thus analyzed as a single study. As such, if both papers evaluated a prognostic factor and showed the same finding, this was counted only once.

Table 5 – Factors predicting overall survival benefit with cytoreductive nephrectomy

First author (year)	Analytic approach	Predictive factors identified	Results
Choueiri (2011) [30]	Stratified unadjusted KM analyses; stratified univariable models	IMDC risk group	Int. risk ($p = 0.004$): HR = 0.46 (95% CI 0.27–0.78) CN vs no CN: median OS 27.5 vs 13.1 mo Poor risk ($p = 0.06$): HR = 0.67 (95% CI 0.44–1.01) CN vs no CN: median OS 9.8 vs 5.8 mo
		Karnofsky performance status	KPS ≥80 ($p = 0.003$): HR = 0.51 (95% CI 0.33–0.80) CN vs no CN: median OS 23.9 vs 14.5 mo KPS <80 ($p = 0.08$): HR = 0.65 (95% CI 0.40–1.05) CN vs no CN: median OS 10.1 vs 6.0 mo
		Age	Age ≤75 ($p < 0.0001$): HR = 0.41 (95% CI 0.29–0.56) CN vs no CN: median OS 20.2 vs 9.3 mo Age >75 ($p = 0.62$): HR = 0.65 (95% CI 0.40–1.05) CN vs no CN: median OS 10.2 vs 9.4 mo
		Brain metastasis	No brain met ($p < 0.0001$): HR = 0.44 (95% CI 0.32–0.60) CN vs no CN: median OS 20.2 vs 9.4 mo Brain met ($p = 0.08$): HR = 0.36 (95% CI 0.12–1.12) CN vs no CN: median OS 12.8 mo vs NR
Fujikawa (1999) [87]	Stratified unadjusted KM analyses	C-reactive protein	CRP < 1.0 ng/ml ($p = 0.41$): CN vs no CN: median DSS 3.7 vs 2.5 yr CRP ≥1.0 ng/ml ($p = 0.005$): CN vs no CN: median DSS 1.9 vs 0.6 yr
Klatte (2018) [35] [a]	Stratified IPTW-adjusted Cox models with interaction terms	Gender	Female: HR = 0.34 (95% CI 0.19–0.60) Male: HR = 0.77 (95% CI 0.54–1.09) p-int = 0.03
		Karnofsky performance status	KPS ≥80: HR = 0.50 (95% CI 0.34–0.75) KPS <80: HR = 0.95 (95% CI 0.61–1.48) p-int = 0.06
		Thrombocytosis	Present: HR = 0.25 (95% CI 0.12–0.54) Absent: HR = 0.76 (95% CI 0.55–1.05) p-int = 0.01
Mathieu (2015) [88]	Stratified unadjusted KM analyses[b]	MSKCC risk score	Good or intermediate risk ($p = 0.02$): CN vs. no CN: median OS 42.4 vs 16.8 mo Poor risk ($p = 0.9$): CN vs no CN: median OS 5.2 vs 5.2 mo
		ECOG performance status	ECOG 0–1 ($p = 0.04$): CN vs no CN: median OS 43.3 vs 16.7 mo ECOG 2–3 ($p = 0.8$): CN vs no CN: median OS 12.6 vs 8.0 mo
Song (2016) [84]	Stratified unadjusted KM analyses	Number of risk factors (age ≤45, BMI <19 or >30, LDH >1.5 × ULN, serum Ca >10 mg/ml, number of mets ≥3)	0–2 Risk factors ($p = 0.042$): CN vs no CN: median OS 40.0 vs 23.2 mo 3–5 Risk factors ($p = 0.535$): CN vs no CN: median OS 6.7 vs 6.0 mo
You (2015) [85]	Stratified unadjusted KM analyses	Number of risk factors (KPS <80, Hb < LLN, ANC > ULN, stage cN2)	0–1 Risk factors ($p = 0.011$): CN vs no CN: median OS 29.9 vs 18.1 mo 2–4 Risk factors ($p = 0.544$): CN vs no CN: median OS 8.6 vs 8.2 mo

ANC = absolute neutrophil count; BMI = body mass index; CI = confidence interval; CN = cytoreductive nephrectomy; CRP = C-reactive protein; DSS = disease-specific survival; ECOG = Eastern Cooperative Oncology Group; Hb = hemoglobin; HR = hazard ratio; IMDC = International Metastatic renal cell carcinoma Database Consortium; IPTW = inverse probability of treatment weighting; KM = Kaplan-Meier; KPS = Karnofsky performance status; LDH = lactate dehydrogenase; LLN = lower limit of normal; met = metastasis; MSKCC = Memorial Sloan Kettering Cancer Center; NR = not reported; OS = overall survival; ULN = upper limit of normal.

[a] Klatte et al. [35] also evaluated the interaction terms for the following candidate predictors that were not significant: age (p-int = 0.32), lung metastasis (p-int = 0.78), bone metastasis (p-int = 0.40), liver metastasis (p-int = 0.82), nodal metastasis (p-int = 0.17), number of metastatic sites (p-int = 0.80), histologic subtype (p-int = 0.81), anemia (p-int = 0.47), neutrophilia (p-int = 0.56), and hypercalcemia (p-int = 0.18).

[b] Multivariable analyses were also reported to be performed to confirm an associated OS benefit in patients with good or intermediate MSKCC risk and in patients with good ECOG performance status. However, these results were not shown.

All six studies were considered to have a serious risk of bias [30,35,84,85,87,88]. Of note, five studies assessing factors predictive of OS benefit with CN relied on unadjusted analyses that did not account for potential confounders [30,84,85,87,88], while only one study used the preferred approach [89] of testing interaction terms in adjusted models (see Table 5) [35].

Good performance status [30,35,85,88] and good/intermediate IMDC/MSKCC risk classification [30,88] were the most commonly reported factors predictive of an OS benefit associated with CN versus no CN (Table 5). The remaining predictive factors are described in the Supplementary material (Appendix 5).

3.6. *Sequencing of CN and ST*

Six studies were included in the analysis of SRQ4 (Table 6) [33,57,90–93]. One study was a prospective randomized

Table 6 – Studies evaluating the sequencing of cytoreductive nephrectomy and targeted therapy

First author (year)	Design	Source population, included years	*N* (total]	Comparison	Age (yr)	Median follow-up (mo)	Primary findings on sequencing
Hanna (2016) [33] [a]	Retrospective cohort, national hospital-based dataset	USA (NCDB), 2006–2013	4223	CN followed by TT ($n = 3733$) versus TT followed by CN ($n = 490$)	Median 63 (IQR 55, 71)	NR	In an unadjusted KM analysis, 1-, 2-, and 3-yr OS rates were higher with TT followed by CN (log-rank $p < 0.001$): CN then TT: 61.2%, 37.8%, and 26.6% TT then CN: 73.3%, 48.1%, and 35.3%
MacLeod (2017) [91]	Retrospective cohort, population based	USA (SEER-Medicare), 2006–2011	537	CN then TT ($n = 190$) versus initial TT ± subsequent CN ($n = 347$)	Age 65–75: 55.9% Age >75: 44.1%	12 (IQR 5.2, 22)	Initial CN then TT associated with improved OS compared with initial TT ± subsequent CN (multivariable-adjusted HR 0.50, 95% CI 0.38–0.65, $p < 0.001$): Propensity score matching: OS advantage of 5.8 mo
Stroup (2013) [92]	Retrospective cohort, multicenter	USA, 2005–2009	35	CN followed by sunitinib ($n = 17$) versus sunitinib followed by CN ($n = 18$)	Initial CN: mean 57 (SD 17.1) Initial TT: mean 55 (SD 9.9)	Initial CN: 29.9 Initial TT: 25.4	In an unadjusted KM analysis, there was no significant difference in OS between CN followed by sunitinib versus sunitinib ± subsequent CN ($p = 0.579$)
Wood (2009) [93]	Retrospective cohort, single center	USA, 2005–2007	102	CN ± subsequent TT ($n = 58$) versus TT followed by CN ($n = 44$)	Median 58.3	11.4 (range 1.2–42.4)	In an unadjusted KM analysis, there was no significant difference in CSS between CN ± subsequent TT versus TT followed by CN (median CSS 31.0 vs 27.7 mo, $p = 0.697$)
Bhindi (2018) [90]	Retrospective cohort, national hospital-based dataset	USA (NCDB), 2006–2013	15 068	Initial CN ± subsequent TT ($n = 6731$) versus initial TT ± subsequent CN ($n = 8337$)	≤50: 16.3% 51–60: 30.7% 61–70: 31.6% >70: 21.4%	31 (IQR 19, 50)	In IPTW analysis, initial CN versus initial TT is associated with improved OS (median 16.5 vs 9.2 mo; HR = 0.61; 95% CI 0.59–0.64; $p < 0.001$). Initial CN patients were more likely to get multimodal therapy (ie, both CN and TT: 48.0% vs 4.7%)
Bex (2017) [57]	Multicenter Prospective randomized trial	The Netherlands, Canada, UK, Belgium, 2010–2016	99	Initial CN ± subsequent sunitinib ($n = 50$) versus initial sunitinib ± subsequent CN ($n = 49$)	Initial CN: median 60 Initial sunitinib: median 58	39.6 (IQR 33.6, 45.6)	In the ITT analysis, no difference in progression-free rate at 28 wk (immediate CN: 42.0% vs deferred CN: 42.9%; $p > 0.99$); improved OS with deferred CN (28 vs 35 deaths; HR = 0.57; 95% CI 0.34–0.95; $p = 0.032$)

CI = confidence interval; CN = cytoreductive nephrectomy; CSS = cancer-specific survival; HR = hazard ratio; IQR = interquartile range; ITT = intention to treat; KM = Kaplan-Meier; NCDB = National Cancer Database; NR = not reported; OS = overall survival; SD = standard deviation; SEER = Surveillance, Epidemiology, and End Results; TT = targeted therapy.

[a] Subset analysis in the manuscript.

trial [57], while the remainder were retrospective observational studies; one study was population based [91], two studies used a national hospital-based database [33,90], one study was a multicenter study [92], and one study evaluated a single-institution cohort [93].

Three studies were considered to have a moderate risk of bias [57,90,91], and three studies were considered to have a serious risk of bias [33,92,93], mainly due to the reliance on unadjusted analyses or the inability to completely adjust for differences between exposure groups. Immortal time bias and/or related selection bias was also a potential concern in the observational studies on sequencing (see the Supplementary material, Appendix 4). Owing to poor accrual, SURTIME was required to revise their accrual target from 458 to 98 patients and modified their primary endpoint from PFS to progression-free rate at 28 wk.

There was variability between studies regarding whether patients were included only if they received both treatments or whether patients were included regardless of whether they received the second treatment (TT after initial CN or CN after initial TT). Two studies compared the sequence of CN and TT among patients who received both modalities (Table 6) [33,92]. In unadjusted analyses, Hanna et al. [33] found that TT followed by CN was associated with improved OS, while Stroup et al. [92] found no significant difference in OS according to sequence. Wood et al. [93] compared patients who underwent TT followed by CN with those who underwent CN with or without subsequent TT, and found no difference in cancer-specific survival between groups. Meanwhile, MacLeod et al. [91] compared patients who underwent CN followed by TT with those undergoing initial TT with or without subsequent CN, while Bhindi et al. [90] compared initial treatment with CN, with or without subsequent TT, versus initial treatment with TT, with or without subsequent CN. Both studies found that initial treatment with CN was associated with improved survival. Notably, only 4.7–8.1% of patients from these two studies underwent CN after initial TT [90,91]. Bhindi et al. [90] also noted that patients who underwent deferred CN after initial TT had comparable OS to the initial CN group.

The only randomized trial on this topic, SURTIME, initially sought to compare median PFS between patients who underwent immediate CN and those who received immediate sunitinib with the plan for deferred CN (Table 6) [57]. There was no significant difference in progression-free rate at 28 wk (immediate CN: 21/50 events [42.0%] vs deferred CN: 21/49 events [42.9%]; $p > 0.99$). A difference in OS was noted in favor of deferred CN (28 vs 35 deaths; HR = 0.57; 95% CI 0.34–0.95; $p = 0.032$) in the intention-to-treat analysis, but there was no significant difference in the per-protocol analysis (HR = 0.71; 95% CI 0.40–1.24; $p = 0.225$).

4. Discussion

In the TT era, CARMENA [41] and SURTIME [57] have tempered the enthusiasm toward initial CN for mRCC, which was generated from retrospective data and pre-TT era randomized trials. Although CARMENA accrued slowly and was enriched with poor-risk patients who do not benefit from CN, it nonetheless represents the highest level of evidence to date on the topic and overcomes several of the unmeasured sources of bias impacting the nonrandomized retrospective literature that we cannot control. It remains unknown whether patients traditionally thought to benefit from CN, such as those with a limited metastatic burden, were actually included in CARMENA and how common is this patient phenotype. Thus, CN likely still has a role in the initial treatment in patients with good performance status and limited metastatic burden amenable to surveillance or metastasectomy, in patients requiring palliation, and in patients with a favorable response or stable disease after initial treatment with TT (Supplementary Fig. 3).

Prognostic and predictive factors have been described, but their ability to discriminate survival outcomes are likely to be moderate at best and are inadequate to be used as the sole method for identifying candidates for CN [86]. Poor performance status [30,35,85,88] and poor IMDC/MSKCC risk classification [30,88] were associated with a poor prognosis and were predictive of a lack of OS benefit with CN, while good performance status and good/intermediate IMDC/MSKCC risk classification were predictive of OS benefit with CN. While other prognostic factors have been identified, their ability to predict OS benefit or absence of OS benefit with CN remains to be formally demonstrated.

Among patients deemed suitable for CN, the initial treatment approach and optimal sequencing of CN and TT remain to be defined. Pending further data, individualized clinical decision making is warranted. Among patients without adverse IMDC/MSKCC risk factors, good performance status, and low-volume metastatic burden, initial CN may be reasonable, particularly if the remainder of the metastatic disease burden may be amenable to surveillance [94] or metastasis-directed therapy [95]. When feasible in appropriately selected patients, complete resection of metastatic disease is associated with markedly improved survival [95–97]. Moreover, metastasectomy may potentially allow patients to remain off ST and avoid the associated toxicities. Symptoms from the primary tumor, such as significant hematuria, may also be a reason for considering upfront CN. In contrast, in patients with poor IMDC/MSKCC risk disease, poor performance status, and large-volume metastatic burden, initial treatment with ST may be most appropriate. Moreover, brain metastases, spinal metastases, bone metastases associated with or at risk of pathological fracture, and other symptomatic metastases may need to be addressed with metastasis-directed therapy and/or ST prior to considering CN, particularly given that 13–30% of patients do not proceed to ST after upfront CN due to rapid disease progression or perioperative complications [22,44,45,50,54].

For patients in whom the optimal initial treatment approach is equivocal, initial treatment with TT may be a reasonable approach based on SURTIME [57] and prospective single-arm studies [46–48]. This approach may select out patients who are resistant to TT. Moreover, CN after initial TT appears to have comparable outcomes to upfront CN. However, the duration of TT prior to considering

subsequent CN and the criteria for considering CN in this setting remain to be defined. Additionally, with checkpoint inhibitors as a first-line management option in mRCC [21], further work is needed to determine whether these agents can be used in the same manner.

Ultimately, decision making for patients with mRCC is complex, and as such, these patients are ideally managed by experienced institutions and multidisciplinary teams, particularly given that a facility volume–related survival advantage has been demonstrated [98]. Indeed, it has been demonstrated that patients are more likely to receive upfront CN or CN after initial TT when treated at academic institutions [90]. Meanwhile, higher hospital volume has been shown to be associated with a lower risk of complications and failure to rescue after complications for patients undergoing CN [99].

It is paramount to acknowledge the limitations of the literature in the TT era. The role for CN in mRCC was established during an era when STs had limited efficacy [1] and needs to be reframed in the context of more effective ST options. Observational studies are susceptible to several forms of bias, including selection bias and unmeasured confounding. On the contrary, CARMENA focused on patients requiring ST and therefore may not have included the population of patients most likely to benefit from CN. Furthermore, the PFS and OS benefits attributed to modern ST have largely been established in study populations in which 75–100% of patients have had prior nephrectomy [12–16,19,21]. Therefore, it is unclear to what extent the efficacy of ST is reliant on the primary tumor being removed, and further work is still needed to refine the precise role of CN in mRCC. Finally, much of the literature focuses on clear-cell mRCC, and more work is needed to determine the optimal management of non–clear-cell mRCC. Given the limited efficacy of ST to date in non–clear-cell RCC, CN might have a greater role for this group of histologies.

Importantly, it is necessary to reassess the role of CN in the setting of checkpoint inhibitors now garnering first-line treatment status, especially in intermediate- and poor-risk patients [21,100,101]. It is known that RCC secretes soluble forms of PD-L1 that may interfere with immune response [102–105]. It remains to be determined whether cytoreduction (ie, reduction of immunosuppressive signals) may improve the efficacy of checkpoint inhibitors. Notably, in the Checkmate-214 pivotal study [41], the benefit of the dual checkpoint inhibition blockade over sunitinib was similar in patients with and without prior CN.

5. Conclusions

CARMENA and SURTIME have tempered enthusiasm toward the initial treatment of de novo mRCC with CN, which had been generated from retrospective data and pre-TT era randomized trials. ST should generally represent the priority for the management of mRCC in the TT era and beyond, as it is notable that 13–30% of patients do not proceed to ST after upfront CN due to rapid disease progression or complications. Upfront CN should not be standard management in patients with poor performance status, poor IMDC/MSKCC-risk patients, patients with other poor prognostic features, or intermediate IMDC/MSKCC-risk patients who require ST. Conversely, CN still has a role in the management of mRCC in patients with limited metastatic burden amenable to surveillance or metastasectomy, in patients requiring palliation, and potentially in patients with a favorable response or stable disease after initial ST. Improved risk stratification systems and/or biomarkers are needed. Multidisciplinary evaluation at high-volume centers may be helpful in allowing the consideration of different treatment approaches by experienced teams and enrollment into clinical trials.

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Analysis and interpretation of data: Bhindi, Abel, Albiges, Bensalah, Boorjian, Daneshmand, Karam, Mason, Powles, Bex.
Drafting of the manuscript: Bhindi.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.09.016.

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