Cancer Causes & Control (2021) 32:675–680
https://doi.org/10.1007/s10552-021-01435-z

REVIEW ARTICLE

Association between cytoreductive nephrectomy and survival among patients with metastatic renal cell carcinoma receiving modern therapies: a systematic review and meta-analysis examining effect modification according to systemic therapy approach

Mary E. Hall[1] · Bimal Bhindi[2,3] · Amy N. Luckenbaugh[1] · Aaron A. Laviana[1] · Kelvin A. Moses[1] · Raj Satkunasivam[4,5] · Brian Rini[6] · Zachary Klaassen[7,8] · Christopher J. D. Wallis[1]

Received: 23 December 2020 / Accepted: 13 April 2021 / Published online: 8 May 2021

Abstract

Purpose Cytoreductive nephrectomy (CN) has played a role in treatment of metastatic renal cell carcinoma (mRCC) since trials demonstrated a survival benefit in patients receiving CN with interferon. With the publication of CARMENA, it became clear that the value of CN may depend on the co-therapy administered. We sought to assess the benefit of CN in the era of modern immunotherapy (IO).

Methods We performed a systematic review to identify studies assessing CN in patients receiving TT or IO. We extracted multivariable-adjusted hazard ratios for the association between CN and overall survival (OS) and performed random effects meta-analysis. We tested for effect modification by systemic therapy approach on the association between CN and OS by pooling the difference in logHR associated with CN for patients treated with TT versus IO.

Results We identified three comparisons assessing CN in patients receiving TT or IO. Pooled analysis indicated improved survival with CN in both the TT (2 cohorts, pooled HR: 0.52, 95% CI 0.46–0.59; $I^2 = 80\%$) and IO era (2 cohorts; pooled HR: 0.28, 95% CI 0.16–0.49; $I^2 = 21\%$), with a stronger association in the IO era ($p = 0.01$; $I^2 = 0\%$).

Conclusion In observational datasets, we observed a larger survival benefit to CN in patients treated with IO-based regimens versus those treated with TT-based regimens. While the role of CN for patients receiving TT has recently been questioned, this suggests that the results of CARMENA do not necessarily preclude a benefit to CN when combined with IO-based regimens.

Keywords Kidney cancer · Renal cell carcinoma · Cytoreductive nephrectomy · Immunotherapy

Introduction

Cytoreductive nephrectomy (CN) has played a key role in the management of patients with metastatic renal cell carcinoma (mRCC) since randomized trials demonstrated significant improvement in survival (6-months in pooled analyses [1]) for patients treated with CN and interferon alpha-2b versus interferon alpha-2b alone. Registry-based studies demonstrating a survival benefit to CN further supported this practice in patients receiving targeted-therapy (TT) [2, 3]. However, with publication of the CARMENA trial, which failed to demonstrate a benefit for CN among patients receiving sunitinib [4], it became clear the apparent value of CN may depend, in part, on the systemic therapy that patients received. An updated analysis of CARMENA found that CN may retain benefit among patients with intermediate-risk disease with a single risk factor [5], consistent with previous observational studies [2, 3].

Recently, a number of immune checkpoint inhibitor-based regimens have demonstrated superiority to sunitinib [6] and have become standard of care. Among patients receiving first line immunotherapy (IO) regimens, the benefit of CN remains unclear.

Presently available data assessing CN among patients receiving IO are limited to observational data. Given discrepancies between observational studies and CARMENA, selection biases may explain the observed benefit of CN in observational data. We postulated that these biases would be

✉ Christopher J. D. Wallis
wallis.cjd@gmail.com

Extended author information available on the last page of the article

consistent in analyses of CN when performed using the same dataset. Thus, to assess whether the results of CARMENA (in patients receiving TT) may be extrapolated to those receiving IO, we sought to quantitatively assess whether the results of observational studies assessing CN in patients receiving TT differed from those receiving IO.

Methods and analysis

Our search was designed and performed with the assistance of a medical librarian, and this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [7]. On 10 April 2020, we searched PubMed and conference proceedings of relevant medical societies (American Society of Clinical Oncology, ASCO; European Society of Medical Oncology, ESMO; American Urologic Association, AUA; and European Association of Urology, EAU) to identify observational cohort studies assessing the effect of CN in patients receiving either TT or IO using a combination of MeSH terms and free text for metastatic renal cell carcinoma, cytoreductive nephrectomy, targeted therapy, tyrosine kinase inhibitor, immunotherapy, and checkpoint inhibitor. No limits were applied with respect to publication year or language. We subsequently limited included studies to those where we were able to identify analyses of the effect of CN in patients receiving TT and IO from the same dataset (whether in the same manuscript or not), based on the assumption that selection biases and residual confounders were likely to be more similar within rather than across datasets. We repeated this literature review in EMBASE and found no further unique results. Two authors (M.E.H. and C.J.D.W.) independently performed abstract review and data abstraction. We identified two comparisons assessing CN in patients receiving TT or IO in the National Cancer Database (NCDB) and one from the International Metastatic RCC Database Consortium (IMDC). For each study, we extracted multivariable-adjusted hazard ratios for the association between CN and overall survival (OS).

We used random-effects models in order to account for the clinical heterogeneity inherent in the data. To examine differences in OS between patients receiving TT and those receiving IO while accounting for database-level correlation, we calculated the difference in log hazard ratio (logHR) associated with CN observed among patients receiving TT and those receiving IO, for each dataset (NCDB and IMDC). We then used random-effects meta-analysis to assess whether this difference in logHR differed from the null using the $\chi 2$ test and quantified heterogeneity by I^2 values (which "describes the percentage of total variation across studies that is due to heterogeneity rather than chance" [8]). All reported P values are two-sided, and $p = 0.05$ was used to indicate statistical significance.

Results

Among 280 results, we identified three relevant studies: two reported comparisons of CN with systemic therapy and systemic therapy alone using the National Cancer Database (NCDB) (one each among patients receiving TT- and IO-based systemic therapy) and one abstract utilizing the International Metastatic RCC Database Consortium (IMDC; Table 1, Fig. 1) [9–11].

Pooled results from these studies demonstrated a significant benefit for CN and systemic therapy versus systemic therapy alone in both patients receiving TT (pooled HR: 0.52, 95% CI 0.46–0.59; $I^2 = 80\%$) and receiving IO (pooled HR: 0.28, 95% CI 0.16–0.49; $I^2 = 21\%$). Pooled analysis accounting for dataset-level correlations demonstrated evidence of statistically significant effect modification ($p = 0.01$, $I^2 = 0\%$), with a greater benefit of CN in patients receiving IO. When assessed individually among each dataset, there was evidence of effect modification in patients identified in the NCDB ($p = 0.02$) but not the IMDC ($p = 0.35$, Fig. 2).

Discussion

In this pooled analysis of two observational datasets, we found a survival benefit to CN in patients treated with both TT- and with IO-based systemic therapy. Given the lack of benefit to cytoreductive surgery demonstrated among patients receiving sunitinib in the CARMENA trial, selection biases likely account for much of the benefit observed. Previous systematic reviews have been published which examine the benefit of CN in the TT era across all available data, and suggested notable differences in outcomes based on factors such as performance status, metastatic burden, and timing of therapy [2]. Rather than attempting to replicate these analyses, we recognized that lack of a large body of randomized evidence within this sphere allows for introduction of bias and sheds a light on the need for additional investigation as available therapies evolve, providing the impetus for our study. Notably, we observed a significantly stronger associated effect with CN on survival among patients who received IO-based systemic therapy versus those receiving TT. Thus, these hypothesis-generating data suggest the potential that CN may provide a greater survival benefit when combined with IO utilizing checkpoint inhibitors than with TT.

There are several potential explanations which may contribute to our observed results. First, there may be evolving selection biases with an increasingly select subset

Table 1 Characteristics of included studies

	TT cohort				IO cohort			
	Hanna 2016		IMDC 2020		Singla 2020		IMDC 2020	
Sample size (N)	15,390		4,202		391		437	
Age, mean (years)	63 (median)		61.9		60		61.4	
Gender (%)								
Male	68.6		NR		73.4		NR	
Female	31.4				26.6			
Race (%)								
White	80.1		NR		84.1		NR	
Black	9.9				5.4			
Hispanic	6.4				7.7			
Other	3.6				2.8			
CCI (%)								
0	73.0		NR		77.7		NR	
1	20.2				17.4			
2	6.8				4.8			
Clinical T stage (%)								
T0	0		NR		1.8		NR	
T1	20.3				18.4			
T2	12.6				29.9			
T3	21.4				29.9			
T4	10.4				6.9			
Unknown	35.3				14.1			
Clinical N stage (%)								
N0	43.7		NR		60.8		NR	
N1	33.2				27.8			
Unknown	23.1				10.5			
Histology (%)								
Clear cell	79.1		82.3				81.4	
Papillary	4.0							
Chromophobe	0.6							
Collecting duct	0.7							
Sarcomatoid	5.3				5.7			
Other	10.3							
Intervention (%)								
Received CN	35		63		57		56	
Systemic therapy	65		37		43		44	
Follow up, median	NR		42.0 mo		14.7 mo		14.1 mo	
Median OS (mo)	CN	No CN	CN	No CN	CN	No CN	CN	No CN
	17.1	7.7	26.5	10.3	Not reached	11.6	53.6	21.4
Multivariable HR (95% CI)	0.49 (0.46–0.52)		0.56 (0.51–0.62)		0.22 (0.11–0.42)		0.39 (0.19–0.83)	

NR: not recorded

of patients with mRCC undergoing CN, driven by the results of CARMENA, which would make the association between CN and survival in those receiving IO appear spuriously stronger. However, in the studies utilized in this analysis, CN was performed in 35% of patients in the TT-era [10] and 57% of patients in the IO-era [11], arguing against this explanation.

Alternatively, the observed difference may be due to differing biologic activity of the agents, timing of CN, and different synergies between CN and the co-administered systemic therapy. CN previously demonstrated survival benefit in patients receiving immunotherapy with interferon-α [1]. Thus, it is plausible that CN may have more of a synergistic benefit when combined with modern immunotherapeutic

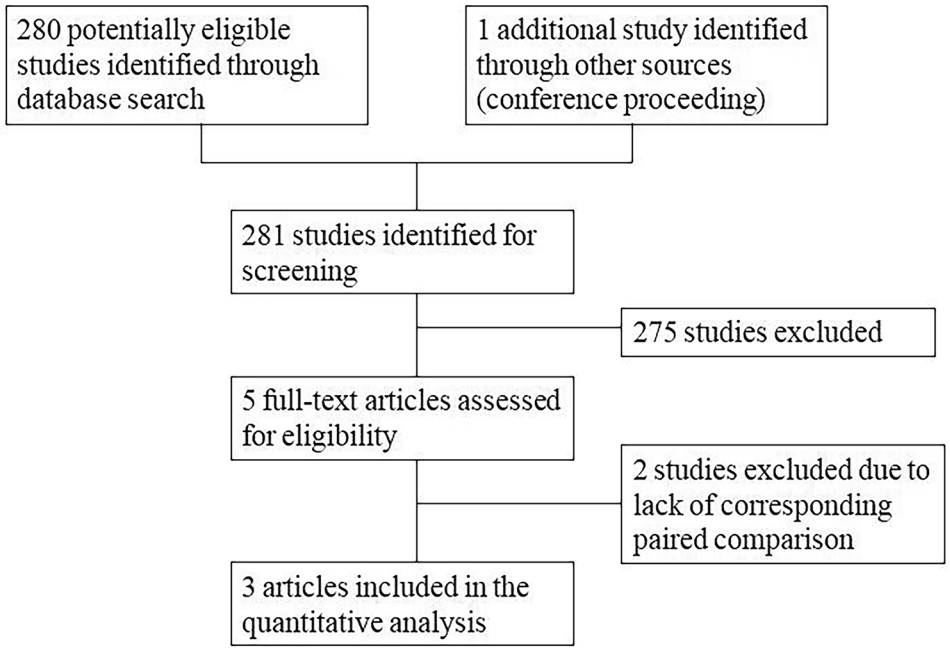

Fig. 1 PRISMA diagram

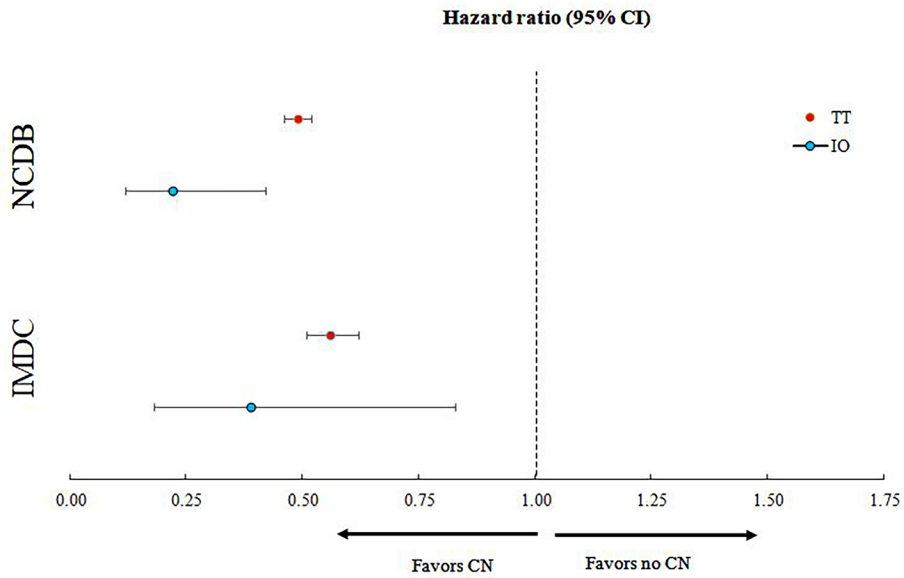

Fig. 2 Forest plot of studies comparing cytoreductive nephrectomy plus systemic therapy with systemic therapy alone stratified by database (NCDB versus IMDC) and treatment type (targeted therapy versus checkpoint inhibitor)

approaches utilizing checkpoint inhibitors versus when combined with TT; for example, by surgically removing a pool of regulatory T-cells which are inhibitory to the anti-tumor response [12]. Notably, stratified meta-analysis within datasets demonstrated a significant difference based on systemic therapy only in the NCDB dataset. This may reflect differences in the patients captured (a more generalizable sample in the NCDB) or more expert care in the centers of excellence contributing to IMDC.

We recognize that this analysis has several limitations. First, we used aggregate data. Second, there are limited data among patients receiving IO, due to the relatively short duration of time that IO therapies have been used in mRCC in addition to the rapid evolution of these therapies. Third, the retrospective nature of the data utilized introduces the risk of selection bias (due to confounding by indication among patients who receive cytoreductive nephrectomy in these analyses), and unmeasured confounding is also likely to contribute. However, as explained previously, by analyzing within rather than across datasets, we sought to minimize the effect of this on our conclusions. Fourth, the increasing utilization of combination IO and TT regimens, rather

than IO-only treatments may limit the generalizability of the question of CN in patients receiving IO therapy. Finally, the timing of CN in relation to systemic therapy cannot be ignored. The SURTIME trial, published following the CARMENA results, observed improved overall survival in patients receiving delayed CN after sunitinib treatment, rather than upfront. Although there may be biologic differences with the newer IO agents, as previously discussed, we cannot dismiss the importance of timing in relation to systemic therapy [13]. In the study by Singla et al. among patients in the NCDB database, of the 221 patients who underwent CN, 89% underwent upfront CN while the remaining 11% underwent delayed CN after receipt of IO. Hanna et al. noted similar proportions of patients undergoing upfront versus delayed CN in the TT era (88.4% and 11.6%, respectively), and noted improved overall survival in the delayed group. For the purposes of our study, the IMDC data on timing of CN was not available which limits our ability to interpret these results as a whole. Additional consideration should be given to this factor in future trials examining the benefit of CN in the IO era.

Conclusions

This analysis provides hypothesis-generating data to suggest that CN may potentially provide a greater survival benefit when combined with IO utilizing checkpoint inhibitors than with TT. Although there are limitations of observational data, this analysis implies that the results of CARMENA may not preclude a benefit of CN when combined with IO-based regimens. As such, the results of specific trials directly evaluating the role of CN when combined with IO-based regimens (including NORDIC-SUN [14] and SWOG-1931 [15]) should be examined closely before drawing definitive conclusions. Importantly, these trials are intentionally designed to optimize patient selection by evaluating IO response prior to surgery. While awaiting these results, patients potentially eligible for CN should ideally be discussed in a multidisciplinary setting to optimize patient selection.

Author contributions Conception and design: Christopher Wallis, Mary Hall; Acquisition of data: Christopher Wallis, Mary Hall; Analysis and interpretation of data: Christopher Wallis, Mary Hall, Bhimal Bhindi, Amy Luckenbaugh, Aaron Laviana, Kelvin Moses, Zachary Klassen, Brian Rini, Raj Satkunasivam; Drafting of the manuscript: Christopher Wallis, Mary Hall; Critical revision of the manuscript for important intellectual content: Christopher Wallis, Mary Hall, Bhimal Bhindi, Amy Luckenbaugh, Aaron Laviana, Kelvin Moses, Zachary Klassen, Brian Rini, Raj Satkunasivam; Statistical Analysis: Christopher Wallis.

Funding None.

Data availability Publicly available data.

Declarations

Conflict of interest Brian Rini—Research Funding to Institution: Pfizer, Merck, GNE/Roche, Peloton, Aveo, Astra-Zeneca, BMS; Consulting: BMS, Pfizer, GNE/Roche, Aveo, Novartis, Synthorx, Peloton, Compugen, Merck, Corvus, Surface Oncology, 3DMedicines, Arravive, Alkermes; Stock: PTC Therapeutics.

References

1. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED (2004) Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. J Urol 171(3):1071–1076. https://doi.org/10.1097/01.ju.0000110610.61545.ae
2. Bhindi B et al (2019) Systematic review of the role of cytoreductive nephrectomy in the targeted therapy era and beyond: an individualized approach to metastatic renal cell carcinoma. Eur Urol 75(1):111–128. https://doi.org/10.1016/j.eururo.2018.09.016
3. Larcher A et al (2019) Individualised indications for cytoreductive nephrectomy: which criteria define the optimal candidates? Eur Urol Oncol 2(4):365–378. https://doi.org/10.1016/j.euo.2019.04.007
4. Mejean A et al (2018) Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. N Engl J Med 379(5):417–427. https://doi.org/10.1056/NEJMoa1803675
5. Mejean A et al (2019) Cytoreductive nephrectomy (CN) in metastatic renal cancer (mRCC): update on carmena trial with focus on intermediate IMDC-risk population. J Clin Oncol 37(15 suppl):4508. https://doi.org/10.1200/JCO.2019.37.15_suppl.4508
6. Hahn AW et al (2019) First-line treatment of metastatic renal cell carcinoma: a systematic review and network meta-analysis. Eur Urol Oncol 2(6):708–715. https://doi.org/10.1016/j.euo.2019.09.002
7. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 62(10):1006–1012. https://doi.org/10.1016/j.jclinepi.2009.06.005
8. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ 327(7414):557–560. https://doi.org/10.1136/bmj.327.7414.557
9. Bakouny Z et al (2020) "Cytoreductive nephrectomy for metastatic renal cell carcinoma treated with immune checkpoint inhibitors or targeted therapy—a propensity score based analysis." Presented at the at genitourinary cancers symposium, San Francisco
10. Hanna N et al (2016) Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a national cancer data base study. J Clin Oncol 34(27):3267–3275. https://doi.org/10.1200/JCO.2016.66.7931
11. Singla N et al (2020) Improved survival after cytoreductive nephrectomy for metastatic renal cell carcinoma in the contemporary immunotherapy era: an analysis of the national cancer database. Urol Oncol. https://doi.org/10.1016/j.urolonc.2020.02.029
12. Taube JM et al (2012) Colocalization of inflammatory response with B7–h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med 4(127):127ra37. https://doi.org/10.1126/scitranslmed.3003689
13. Bex A et al (2019) Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized

clinical trial. JAMA Oncol 5(2):164–170. https://doi.org/10.1001/jamaoncol.2018.5543
14. Donskov F, Hospital AU, Aarhus UO (2020) Deferred cytoreductive nephrectomy in synchronous metastatic renal cell carcinoma: the NORDIC-SUN-Trial. ed: https://ClinicalTrials.gov/show/NCT03977571. Accessed 7 Mar 2021
15. Group SO, Institute NC (2020) Comparing the outcome of immunotherapy-based drug combination therapy with or without surgery to remove the kidney in metastatic kidney cancer, the PROBE Trial. ed: https://ClinicalTrials.gov/show/NCT04510597. Accessed 7 Mar 2021

Authors and Affiliations

Mary E. Hall[1] · Bimal Bhindi[2,3] · Amy N. Luckenbaugh[1] · Aaron A. Laviana[1] · Kelvin A. Moses[1] · Raj Satkunasivam[4,5] · Brian Rini[6] · Zachary Klaassen[7,8] · Christopher J. D. Wallis[1]

Mary E. Hall
mary.e.hall.1@vumc.org

Bimal Bhindi
bimal.bhindi@ahs.ca

Amy N. Luckenbaugh
amy.n.luckenbaugh@vumc.org

Aaron A. Laviana
aaron.a.laviana@vumc.org

Kelvin A. Moses
kelvin.a.moses@vumc.org

Raj Satkunasivam
raj.satkunasivam@gmail.com

Brian Rini
brian.rini@vumc.org

Zachary Klaassen
zklaassen19@gmail.com

[1] Department of Urology, Vanderbilt University Medical Center, A1302 Medical Center North, Nashville, TN 37232-2765, USA

[2] Section of Urology, Department of Surgery, University of Calgary, Calgary, AB, Canada

[3] Southern Alberta Institute of Urology, Calgary, AB, Canada

[4] Department of Urology, Houston Methodist Hospital, Houston, TX, USA

[5] Center for Outcomes Research, Houston Methodist Hospital, Houston, TX, USA

[6] Department of Medical Oncology, Vanderbilt University Medical Center, Nashville, TN, USA

[7] Division of Urology, Medical College of Georgia At Augusta University, Augusta, GA, USA

[8] Georgia Cancer Center, Augusta, GA, USA