SAS Journal of Surgery
Abbreviated Key Title: SAS J Surg
ISSN 2454-5104
Journal homepage: https://www.saspublishers.com

OPEN ACCESS

Urology B

Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: Current Evidence and Clinical Decision-Making in the Era of Immune Checkpoint Inhibitors

Mohammed Amine ELAFARI[1]*, Ayoub MAMAD[1], Mohammed Amine BIBAT[1], Amine SAOULI[2], Pr Amine SLAOUI[1], Pr Tariq KARMOUNI[1], Pr Abdelatif KOUTANI[1], Pr Khalid ELKHADER[1]

[1]Urology B Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco
[2]Urology Department, Moulay Youssef Hospital, Rabat, Morocco

DOI: https://doi.org/10.36347/sasjs.2026.v12i08.002 | **Received:** 26.03.2026 | **Accepted:** 07.05.2026 | **Published:** 06.08.2026

***Corresponding author:** Mohammed Amine ELAFARI
Urology B Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco

Abstract **Review Article**

Cytoreductive nephrectomy (CN) has been a cornerstone of multimodal management of metastatic renal cell carcinoma (mRCC) since the cytokine era. However, the advent of targeted therapies and, more recently, immune checkpoint inhibitor (ICI)-based combination regimens has prompted a critical re-evaluation of its role, timing, and patient selection. The CARMENA trial demonstrated noninferiority of sunitinib alone compared with upfront CN followed by sunitinib, while the SURTIME trial suggested that deferred CN may be preferable to immediate surgery. In the ICI era, no prospective randomized data are yet available, but multiple large retrospective analyses and a pooled FDA analysis suggest a persistent survival benefit for CN in carefully selected patients. Current guidelines from the NCCN, EAU, and ASCO reflect this nuanced landscape, recommending individualized decision-making with emphasis on risk stratification, tumor burden, and response to initial systemic therapy. Ongoing phase III trials, NORDIC-SUN, PROBE (SWOG-1931), and SEVURO-CN, are expected to provide definitive evidence. This mini review synthesizes the current evidence and guideline recommendations to inform clinical practice.

Keywords: metastatic renal cell carcinoma, cytoreductive nephrectomy, immune checkpoint inhibitors, CARMENA trial, targeted therapy, overall survival.

1. INTRODUCTION

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies, with roughly 30% of patients presenting with metastatic disease at diagnosis [1]. Cytoreductive nephrectomy, the surgical removal of the primary renal tumor in the setting of distant metastases, was established as standard of care based on two landmark randomized controlled trials (SWOG 8949 and EORTC 30947) conducted in the interferon-alpha era, which demonstrated a combined median overall survival (OS) improvement of 5.8 months favoring CN plus interferon over interferon alone [2-3].

The treatment landscape for mRCC has undergone dramatic transformation over the past two decades, first with the introduction of VEGF receptor tyrosine kinase inhibitors (TKIs) and subsequently with ICI-based combination regimens. These advances have necessitated a reassessment of the role of CN within contemporary multimodal treatment strategies [4-5].

2. Evidence From the Targeted Therapy Era

2.1 The CARMENA Trial

The CARMENA (Cancer du Rein Métastatique Néphrectomie et Antiangiogéniques) trial was a phase III randomized study of 450 patients with intermediate- or poor-risk metastatic clear cell RCC, comparing upfront CN followed by sunitinib versus sunitinib alone [1,6]. The trial demonstrated that sunitinib alone was noninferior to CN plus sunitinib for OS (stratified HR for death, 0.89; 95% CI, 0.71–1.10; noninferiority margin ≤1.20), with median OS of 18.0 months for sunitinib alone versus 13.9 months in the CN plus sunitinib group [1]. Updated analysis with IMDC risk reclassification confirmed noninferiority (HR 0.97; 95% CI, 0.79–1.19), and notably, patients with two or more IMDC risk factors had significantly longer OS with sunitinib alone (31.2 vs. 17.6 months; HR 0.65; p = 0.03). However, patients with only one IMDC risk factor showed a nonsignificant trend favoring CN (31.4 vs. 25.2 months; HR 1.30; p = 0.2) [6].

Important limitations of CARMENA include broad inclusion criteria allowing enrollment of 43% MSKCC poor-risk patients, potential crossover effects (17% of patients in the sunitinib-alone arm underwent secondary CN), and the fact that the trial was conducted before the widespread adoption of ICI-based regimens [2,7].

2.2 The SURTIME Trial

The SURTIME trial, conducted by the EORTC, randomized 99 patients with synchronous metastatic clear cell RCC to immediate CN followed by sunitinib versus deferred CN after three cycles of sunitinib [2]. While the primary endpoint of progression-free rate at 28 weeks was not met, an exploratory OS analysis favored the deferred CN approach (median OS 32.4 vs. 15.0 months; HR 0.57; 95% CI, 0.34–0.95; p = 0.03) [2]. Critically, the landmark analysis demonstrated that patients whose disease progressed before planned surgery had poor outcomes regardless of treatment arm, supporting the concept that initial systemic therapy can serve as a selection tool to identify patients unlikely to benefit from CN [2].

A meta-analysis of individual patient data from 15 studies (3,990 patients) in the targeted therapy era demonstrated superior OS (HR 0.58; 95% CI, 0.54–0.62) and cancer-specific survival (HR 0.63; 95% CI, 0.53–0.75) favoring CN, with the benefit persisting in the upfront CN subgroup (HR 0.70; 95% CI, 0.63–0.78) [8]. However, an instrumental variable analysis designed to account for unmeasured confounding yielded an HR of 0.92, closely approximating the CARMENA result (HR 1.12), suggesting that conventional observational methods may overestimate the benefit of CN due to selection bias [7].

3. Evidence in the Immune Checkpoint Inhibitor Era

The introduction of ICI-based combination regimens, including nivolumab plus ipilimumab, pembrolizumab plus axitinib, pembrolizumab plus lenvatinib, nivolumab plus cabozantinib, and avelumab plus axitinib, has fundamentally changed the first-line treatment of mRCC, with objective response rates exceeding 55–71% [1,9]. This paradigm shift has raised the question of whether CN retains clinical relevance in the ICI era.

3.1 Retrospective Evidence

Multiple large retrospective studies have reported survival benefits associated with CN in patients receiving ICI-based therapy:

- An IMDC analysis of 4,639 patients found that upfront CN was associated with significantly improved OS in both ICI-treated (HR 0.61; 95% CI, 0.41–0.90) and targeted therapy-treated (HR 0.72; 95% CI, 0.67–0.78) cohorts, with no significant interaction between treatment modality and CN benefit (p = 0.6) [10].
- A TriNetX database analysis of 11,094 patients demonstrated that upfront CN was associated with improved OS in both TKI (HR 0.623; 95% CI, 0.56–0.694) and ICI (HR 0.688; 95% CI, 0.607–0.779) cohorts on multivariable analysis [11].
- A National Cancer Database analysis of 4,369 patients receiving ICIs found that CN was independently predictive of improved OS (HR 0.53; 95% CI, 0.41–0.68) [12].
- A multicenter study of 367 patients demonstrated a 67% reduction in all-cause mortality with CN plus ICI versus ICI alone (median OS 56.3 vs. 19.1 months; p 0.0001), with no significant difference between upfront and deferred CN [13].
- A SEER-based analysis of 6,030 patients reported a 71% reduction in all-cause mortality with CN (HR 0.29; 95% CI, 0.25–0.33), with five-year OS rates of 31.5% versus 3.6% [14].
- A recent TriNetX analysis of 5,960 patients receiving NCCN-recommended first-line ICI-TKI regimens showed consistent survival benefits across all four preferred regimens after propensity score matching (five-year OS: 57.7% vs. 45.0%; HR 1.56; 95% CI, 1.33–1.83) [15].

3.2 FDA Pooled Analysis

A US FDA pooled analysis of patient-level data from five trials of ICI plus antiangiogenic therapy included 981 patients with stage IV disease at initial diagnosis [16]. Patients who underwent CN before ICI therapy had significantly improved outcomes: median PFS 15 versus 11 months (adjusted HR 0.71; 95% CI, 0.59–0.85), median OS 46 versus 28 months (adjusted HR 0.63; 95% CI, 0.51–0.77), and objective response rate 60% versus 46%. The authors acknowledged that selection factors for CN may be prognostic and could not be fully controlled in this retrospective analysis [16].

3.3 A Narrative Review of the ICI Era

A 2026 narrative review identified 12 retrospective studies comparing outcomes in mRCC patients treated with ICI-based regimens with or without CN [17]. Six studies demonstrated a survival benefit for CN with HRs ranging from 0.19 to 0.63, a finding consistent within the upfront CN subgroup. However, the retrospective nature, selection bias, and immortal time bias inherent to these studies limit definitive conclusions [17].

3.4 Immunologic Rationale

RCC is recognized as an immunogenic tumor, characterized by spontaneous regression phenomena and immune cell infiltration [18]. Several biological rationales support the potential synergy between CN and ICI therapy: reduction of tumor burden may enhance anti-cancer immunity, the primary tumor may harbor immune-resistant clones that limit systemic ICI efficacy,

and broader antigen spread from the primary tumor may enhance ICI-mediated immune responses [17-19]. Immunogenomic analysis of patients undergoing consolidative CN after ICI therapy has identified distinct NK cell and T cell clonal expansions among long-term responders, with complete pathologic responses observed in a subset of patients [20].

4. Current Guideline Recommendations

4.1 NCCN Guidelines (v2.2026)

The NCCN Kidney Cancer Guidelines recommend that for stage IV mRCC with a potentially surgically resectable primary, treatment should be individualized based on symptoms and extent of metastatic disease [9]. Options include CN, systemic therapy (preferred in clear cell histology with poor-risk features), or clinical trial (category 2B) [9]. The General Principles of Management specify that candidates for CN prior to systemic therapy should generally have excellent performance status (ECOG PS 2) and no brain metastases, while patients with large-volume distant metastases or tumors with large sarcomatoid burdens should receive systemic therapy prior to CN [9].

4.2 EAU Guidelines

The EAU Guidelines, updated following the CARMENA trial, no longer recommend upfront CN in patients with intermediate- and poor-risk mRCC [21]. CN is reserved for patients with limited metastatic burden amenable to surveillance or metastasectomy, patients with favorable response after initial systemic therapy, and those requiring palliation of symptoms [22]. A systematic review informing the EAU position concluded that systemic therapy should be prioritized in de novo mRCC requiring medical therapy, with CN considered in well-selected patients based on established prognostic and predictive factors [22].

4.3 ASCO Guidelines

The ASCO Guideline for Management of Metastatic Clear Cell RCC recommends that CN should be considered for patients with one IMDC risk factor (intermediate-risk disease) [23]. Optimal candidates have the significant majority of tumor burden within the kidney, good ECOG performance status, and absence of brain, bone, or liver metastases [23]. IMDC poor-risk patients are likely to benefit more from immediate systemic therapy, although delayed CN can be considered with good response to systemic treatment [23]. CN is best performed by high-volume surgeons at high-volume centers as part of multidisciplinary consultation [23].

5. Patient Selection and Timing

Across guidelines and the available evidence, several factors consistently inform patient selection for CN:

- **Favorable candidates**: ECOG PS 0–1, IMDC favorable or intermediate risk (one risk factor), majority of tumor burden within the kidney, oligometastatic disease, absence of brain/bone/liver metastases, and durable response to initial systemic therapy [6,9,22-23].
- **Unfavorable candidates**: IMDC poor risk (≥2 risk factors), large-volume distant metastases, sarcomatoid differentiation, poor performance status, and progression on initial systemic therapy [2,6,9,22].

Regarding timing, the SURTIME trial provided the conceptual framework for using initial systemic therapy as a selection tool: patients who progress early are unlikely to benefit from CN, while those with stable or responding disease may derive surgical benefit [2]. This deferred approach has been endorsed by multiple expert panels and is being formally tested in ongoing trials [17,19,24].

Beyond its role as a selection tool, deferred CN provides a critical 'biological window' to observe tumor kinetics. This strategy effectively identifies patients with fulminant disease progression who are unlikely to derive any surgical benefit, thereby sparing them from the morbidity of an unnecessary procedure while prioritizing immediate systemic control.

The following table synthesizes the clinical, pathological, and therapeutic factors that currently guide the selection of optimal candidates for cytoreductive nephrectomy.

Table 1: Clinical Selection Criteria for Cytoreductive Nephrectomy in the ICI Era

Feature	Favorable Candidates (Consider CN)	Unfavorable Candidates (Systemic Therapy First)
	Performance Status	ECOG PS 0–1
Risk Stratification	IMDC Favorable or Intermediate (1 risk factor)	IMDC Poor Risk (≥2 risk factors)
Tumor Burden	Majority of burden in the kidney; Oligometastatic	High-volume distant metastases; Sarcomatoid features
Metastatic Sites	Absence of brain, bone, or liver metastases	Presence of CNS or visceral (liver/bone) involvement
Response to Therapy	Durable response or stable disease on initial systemic treatment	Primary progression on initial systemic therapy

6. Ongoing Prospective Trials

Three phase III randomized trials are currently evaluating the role of CN in the ICI era and are expected to provide definitive evidence:

- **NORDIC-SUN** (NCT03977571): A multicenter randomized trial comparing deferred CN versus no surgery in patients with synchronous mRCC receiving checkpoint immunotherapy, with OS as the primary endpoint and an integrated translational research program [24].
- **PROBE / SWOG-1931** (NCT04510597): A phase III trial randomizing patients 1:1 to CN versus continued systemic therapy after 10–14 weeks of ICI-based combination therapy, with OS as the primary endpoint. The study is powered to detect a 47% improvement in median survival (HR 0.68) with a sample size of 302 patients [19].
- **SEVURO-CN** (NCT05753839): A trial expected to elucidate the role of upfront CN in the ICI era [17].
- In addition to clinical outcomes, these contemporary trials are expected to explore molecular and genomic biomarkers. Such insights will be vital in moving beyond clinical risk scores (like IMDC) toward a more personalized approach, potentially identifying specific immune signatures that predict synergy between the primary tumor resection and ICI response.

7. CONCLUSIONS

The role of CN in mRCC has evolved substantially from the cytokine era through the targeted therapy era and into the current ICI era. While the CARMENA trial demonstrated that upfront CN is not beneficial for all patients, particularly those with intermediate- and poor-risk disease, accumulating retrospective evidence and a pooled FDA analysis suggest that CN retains a meaningful survival benefit in carefully selected patients receiving ICI-based therapy. Current guidelines from the NCCN, EAU, and ASCO uniformly emphasize individualized decision-making, risk stratification using IMDC criteria, and multidisciplinary evaluation. The deferred CN approach, using initial systemic therapy response as a selection tool, has emerged as a rational strategy. Results from the NORDIC-SUN, PROBE, and SEVURO-CN trials are eagerly awaited and will be critical in defining the optimal integration of CN within contemporary ICI-based treatment paradigms.

Declaration

Authors' contributions: All authors contributed to the conceptualization, data collection, and drafting of the manuscript.

Acknowledgement: None.

Funding details: There are no funding sources to be declared.

Conflicts of interest: The authors declare that they have no competing interests.

Data availability: Supporting material is available if further analysis is needed.

REFERENCES

1. Rose TL, Kim WY. Renal Cell Carcinoma: A Review. JAMA. 2024 ;332(12) :1001-1010. doi :10.1001/jama.2024.12848.
2. Bex A, Mulders P, Jewett M, *et al.,* Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib: The SURTIME Randomized Clinical Trial. JAMA Oncology. 2019 ;5(2):164-170. Doi :10.1001/jamaoncol.2018.5543.
3. Chiong E, Tay MH, Tan MH, *et al.,* Management of Kidney Cancer in Asia: Resource-Stratified Guidelines from the Asian Oncology Summit 2012. The Lancet Oncology. 2012 ;13(11) : e482-91. doi :10.1016/S1470-2045(12)70433-3.
4. Young M, Jackson-Spence F, Beltran L, *et al.,* Renal Cell Carcinoma. Lancet (London, England). 2024 ;404(10451):476-491. doi :10.1016/S0140-6736(24)00917-6.
5. Das A, Shapiro DD, Craig JK, Abel EJ. Understanding and Integrating Cytoreductive Nephrectomy with Immune Checkpoint Inhibitors in the Management of Metastatic RCC. Nature Reviews Urology. 2023;20(11):654-668. doi:10.1038/s41585-023-00776-5.
6. Méjean A, Ravaud A, Thezenas S, *et al.,* Sunitinib Alone or After Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Is There Still a Role for Cytoreductive Nephrectomy? European Urology. 2021 ;80(4) :417-424. doi: 10.1016/j.eururo.2021.06.009.
7. Chakiryan NH, Gore LR, Reich RR, *et al.,* Survival Outcomes Associated with Cytoreductive Nephrectomy in Patients with Metastatic Clear Cell Renal Cell Carcinoma. JAMA Network Open. 2022 ;5(5) : e2212347. doi :10.1001/jamanetworkopen.2022.12347.
8. Esagian S, Ziogas I, Kosmidis D, *et al.,* Long-term survival outcomes of cytoreductive nephrectomy combined with targeted therapy for metastatic renal cell carcinoma: A systematic review and individual patient data meta-analysis. J Clin Oncol. 2021 ;39(suppl 6 ; abstr 317). Doi : 10.1200/JCO.2021.39.6_suppl.317.
9. National Comprehensive Cancer Network. Kidney Cancer (Version 2.2026). Updated 2026-04-14.
10. Bakouny Z, El Zarif T, Dudani S, *et al.,* Upfront Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors or Targeted Therapy : An Observational Study from the International Metastatic Renal Cell

Carcinoma Database Consortium. European Urology. 2023 ;83(2) :145-151. doi: 10.1016/j.eururo.2022.10.004.
11. Lai GS, Li JR, Wang SS, *et al.,* Outcome Benefits of Upfront Cytoreductive Nephrectomy for Patients with Metastatic Renal Cell Carcinoma : An Analysis of the TriNetX Database. PloS One. 2024 ;19(3) : e0299102. doi: 10.1371/journal.pone.0299102.
12. Perimbeti S, Jiang C, Deng L, *et al.,* Impact of cytoreductive nephrectomy (CN) on survival in metastatic renal cell cancer (mRCC) treated with immune checkpoint inhibitors (ICI). Journal of Clinical Oncology. 2022 ;40(Suppl 6) :359. doi : 10.1200/JCO.2022.40.6_suppl.359.
13. Gross EE, Li M, Yin M, *et al.,* A Multicenter Study Assessing Survival in Patients with Metastatic Renal Cell Carcinoma Receiving Immune Checkpoint Inhibitor Therapy with and Without Cytoreductive Nephrectomy. Urologic Oncology. 2023 ;41(1) :51. e25-51. e31. doi: 10.1016/j.urolonc.2022.08.013.
14. Peng X, Duan L, Wu Q, *et al.,* Survival Benefits of Cytoreductive Nephrectomy in Patients with Metastatic Renal Cell Carcinoma : Evidence From a SEER-based Retrospective Cohort Study. PloS One. 2025 ;20(7) : e0318896. doi: 10.1371/journal.pone.0318896.
15. Manivasagam SS, Aminsharifi A, Raman JD. Revisiting Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma: Real-World Evidence of Survival Benefit with First-Line Immunotherapy and Targeted Therapy Regimens. Journal of Clinical Medicine. 2025 ;14(15):5543. Doi :10.3390/jcm14155543.
16. Fallah J, Gittleman H, Weinstock C, *et al.,* Cytoreductive Nephrectomy in the Era of Immune Checkpoint Inhibitors: A US Food and Drug Administration Pooled Analysis. Journal of the National Cancer Institute. 2024 ;116(7):1043-1050. doi :10.1093/jnci/djae066.
17. Flammia RS, Campi R, Bologna E, *et al.,* Cytoreductive Nephrectomy in the Era of Immune-Checkpoint Inhibitors : Back to the Future ? BJU International. 2026 ;137(5):763-769. doi :10.1111/bju.70168.
18. Hara T, Miyake H. The Role of Cytoreductive Nephrectomy in the Era of Immune Checkpoint Inhibitors: A Review of Current Evidence and Ongoing Trials. International Journal of Urology. 2025 ;32(1):7-14. Doi :10.1111/iju.15594.
19. Vaishampayan U, Tangen C, Tripathi A, *et al.,* SWOG S1931 (PROBE): Phase III randomized trial of immune checkpoint inhibitor (ICI) combination regimen with or without cytoreductive nephrectomy (CN) in advanced renal cancer. Journal of Clinical Oncology. 2022;40(Suppl 6): TPS402. doi: 10.1200/JCO.2022.40.6_suppl.TPS402.
20. Reese S, Jiang H, Kuo F, *et al.,* Clinical and immunogenomic outcomes of consolidative cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with immune checkpoint blockade. Journal of Clinical Oncology. 2023 ;41(Suppl 6):720. doi: 10.1200/JCO.2023.41.6_suppl.720.
21. Dahm P, Ergun O, Uhlig A, *et al.,* Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma. The Cochrane Database of Systematic Reviews. 2024;6:CD013773. doi: 10.1002/14651858.CD013773.pub2.
22. Bhindi B, Abel EJ, Albiges L, *et al.,* Systematic Review of the Role of Cytoreductive Nephrectomy in the Targeted Therapy Era and Beyond : An Individualized Approach to Metastatic Renal Cell Carcinoma. European Urology. 2019 ;75(1):111-128. doi: 10.1016/j.eururo.2018.09.016.
23. Singer EA, Rumble RB, Van Veldhuizen PJ. Management of Metastatic Clear Cell Renal Cell Carcinoma: ASCO Guideline Q&A. JCO Oncology Practice. 2023 ;19(3):127-131. doi :10.1200/OP.22.00660.
24. Iisager L, Ahrenfeldt J, Donskov F, *et al.,* Multicenter Randomized Trial of Deferred Cytoreductive Nephrectomy in Synchronous Metastatic Renal Cell Carcinoma Receiving Checkpoint Inhibitors : The NORDIC-SUN-Trial. BMC Cancer. 2024 ;24(1):260. doi:10.1186/s12885-024-11987-3.