The Role of Surgery in Metastatic Renal Cell Carcinoma in 2024

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ABSTRACT: Renal cell carcinoma (RCC) is the most common solid tumour of the kidney and accounts for 3% of all cancers. While immune checkpoint inhibitor (ICI)-based combination therapies have emerged as the first-line treatment for metastatic renal cell carcinoma (mRCC), the role of surgery has become more controversial. This review summarizes the evidence, current role and future directions for surgery in mRCC management. The survival benefits of cytoreductive nephrectomy (CN) shown in the interferon era have encountered increasing disputes in the tyrosine-kinase inhibitor (TKI) and ICI eras. Undoubtedly, several systematic reviews based on retrospective data have supported the survival benefits of CN. Nevertheless, 2 prospective trials, CARMENA and SURTIME, proved that sunitinib as the upfront therapy resulted in noninferior survival outcomes compared with immediate CN. The safety of CN does have solid ground in the current literature. Several studies suggested that preoperative systemic therapy did not seem to aggravate perioperative complications or mortality rates, in experienced centres. Meticulous patient selection is the rule of thumb in the modern management of mRCC patients. The limitations of the existing prognostication models, however, must be acknowledged. Clinicians should adopt a multidisciplinary and holistic approach and contemplate all patient, disease, surgeon and socio-economical factors, before deciding who should go for surgery. The advent of metastasis-directed therapy (MDT) and survival benefits of adjuvant pembrolizumab shown in the oligometastatic subgroup, where complete metastasectomy could be achieved (M1 NED), calls for more comparative studies against upfront ICI combinations. In summary, CN brings survival benefits to well-selected good-to-intermediate-risk mRCC patients. Individualized and multidisciplinary care is pivotal.

KEYWORDS: Combination immunotherapy, immunotherapy, oligometastatic disease, stereotactic radiosurgery, radiation therapy (radiotherapy), surgery, metastasis

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Introduction

Renal cell carcinoma (RCC) is the most common solid tumour of the kidney and accounts for 3% of all cancers.[1] Every year, more than 430 000 people are diagnosed with kidney tumours globally, and approximately 179 000 people die from kidney tumours.[2] An updated epidemiological study, using the GLOBOCAN database, suggested that the incidence of kidney cancer is rising globally, particularly for European countries and younger populations aged 50 or below.[3] Therefore, kidney cancer undoubtedly represents an enormous health issue in modern uro-oncology practice.

The terminology of metastatic renal cell carcinoma (mRCC) actually encompasses de novo (ie, RCC which presents with metastases in the first place), oligometastatic (typically defined as 5 or fewer sites of metastases,[4] albeit in the absence of a global consensus) and oligoprogressive disease (ie, any new-onset metastasis that happens after treatment for initial localized disease). According to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, the median overall survival (OS) of mRCC patients can be highly variable, ranging from 43 months for favourable risk patients to less than 8 months for poor-risk patients.[5]

The advent of combination therapies based on immune checkpoint inhibitors (ICIs) has revolutionized the treatment landscape for mRCC and improved their survival compared with the tyrosine-kinase inhibitor (TKI) era.[6] However, this brings about 2 important clinical questions. This first one is whether there is still a role for surgery in the contemporary mRCC management, amid the breakthrough in systemic therapy. Second, if so, how we should choose the best patients to receive systemic therapy versus surgery remains a myth.

In this review, we would elucidate the role of surgery and address the evidence and controversies in the contemporary management of mRCC.

Cytoreductive Nephrectomy in the Interferon Era

The high immunogenicity and hypervascularity of RCC has rendered the disease resistant to conventional chemotherapy.[7,8] The systemic therapies for mRCC have been evolving over the past 2 decades from interferons and TKIs, to ICI-based combinations.[6,9] Consequently, on top of palliating local symptoms, the survival benefits of cytoreductive nephrectomy (CN) in

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mRCC ought to be considered separately in the different eras of systemic therapy.

In the interferon era, the survival benefit of CN in selected mRCC patients was indisputable. Flanigan et al reported, in their randomized controlled trial (RCT) of 241 mRCC patients, that CN followed by interferon alpha-2b (IFN) resulted in longer OS, compared with IFN-2b alone (median OS 11.1 months vs 8.1 months, $P = .05$). Furthermore, such a benefit was shown to be independent of performance status, metastatic sites and the presence or absence of a measurable metastatic lesion.[10] In a combined analysis of 2 prospective randomized trials (N = 331) using the same protocol, the CN-plus-IFN arm also outperformed the IFN arm in median OS (13.6 months vs 7.8 months, $P = .002$).[11]

Cytoreductive Nephrectomy in the Targeted Therapy Era

With the advent of vascular endothelial growth factor (VEGF)-targeted therapy (TT), the role of CN in mRCC management has become more controversial, despite improved survival and response rates compared with IFN.[12-14]

Several retrospective studies have supported CN in the TKI era. From a retrospective study based on the IMDC data, the median OS of mRCC patients with CN versus without CN was 20.6 versus 9.5 months ($P < .0001$). The hazard ratio (HR) of mortality was 0.60 (95% confidence interval, 0.52-0.69; $P < .0001$).[15] The patients with estimated survival of fewer than 12 months or 4 or more IMDC prognostic factors were found not to benefit from CN. Similarly, according to a systematic review of 10 non-randomized studies by Bhindi et al, CN was associated with improved OS among patients with mRCC.[16] However, such findings from retrospective studies were bound to be subjected to selection bias, because patients with better premorbid and performance status, together with lower metastatic burdens, were more likely to have received CN.

Nevertheless, the alleged survival benefit of CN in the TKI era does not appear to be reproducible in prospective settings. CARMENA and SURTIME are 2 landmark prospective studies in this aspect. The CARMENA trial was a prospective noninferiority randomized trial including 450 mRCC patients of intermediate-to-poor risk by the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model. It demonstrated that sunitinib alone resulted in noninferior OS versus CN followed by sunitinib (18.4 months vs 13.9 months).[17] This trial is criticized for its poor accrual rates, contamination with high metastasis burden (42% of total tumour volume), poor-risk patient in 57% and nonpulmonary metastasis in 72%. An updated post hoc analysis of the CARMENA trial showed that sunitinib monotherapy continued to result in noninferior OS, but CN may still be beneficial to patients with 1 IMDC risk score and lung-only metastases.[18] SURTIME was another RCT that randomized 99 patients to either upfront CN followed by 4 cycles of sunitinib, or to 3 cycles of sunitinib followed by CN and 2 adjuvant cycles of sunitinib. In short, the deferred surgery group had better median OS compared with the upfront surgery group (32.4 months vs 15 months; HR = 0.57; 95% CI = 0.34-0.95).[19] While these findings are not completely against surgery for mRCC, caution must be exercised in interpreting the results. This trial was underpowered due to its poor accrual and high metastatic burden with 89% patients having at least 2 metastatic sites.

Cytoreductive Nephrectomy in the ICI Era

As of now, despite the paucity of prospective data, retrospective data still cast an affirmative vote for CN in the ICI era. In 2022, Bakouny et al reported a retrospective analysis of 4639 patients from the prospectively maintained IMDC cohort, which compared survival outcomes of CN versus no CN in mRCC patients who received upfront ICI or TT. The key findings on multivariable analyses were that patients receiving CN had significantly longer OS than those not, no matter in the TT-treated or ICI-treated populations (HR = 0.72, $P < .001$; HR = 0.61, $P = .013$, respectively).[20]

Similarly, an American multi-centre retrospective cohort study by Gross et al reported longer OS for CN versus no CN in 367 mRCC patients treated with ICI at any point in their disease course. A 67% reduction in risk of all-cause mortality was found on multivariate analyses.[21]

On the contrary, the criticisms that upfront CN might limit the use of systemic therapy should not be understated. We should be cautious that around 20% of the patients treated with CN in the CARMENA and SURTIME trials did not receive systemic therapy, because of complications or deconditioning after surgery.[18,19] Likewise, the European Urology review by Bakouny et al did not include the subgroup of patients who did not receive systemic therapy after CN, raising concerns about its selection bias.[20]

Cytoreductive Nephrectomy in Nonclear-cell RCC (nccRCC)

Contrary to conventional wisdom about the favourable prognosis of localized nccRCC (namely, papillary RCC and chromophobe RCC) compared with localized ccRCC treated with surgery,[22] there have been reports that metastatic nccRCC patients tend to have shorter survival compared with their metastatic ccRCC counterparts.[23,24] There are considerable differences in their response to systemic therapies and hence their different first-line systemic therapies.[6]

Amid the rarity of prospective studies, the role of CN in nccRCC can only be evaluated using retrospective studies. According to the studies by Marchioni et al[25] and Luzzago et al,[26] both using data from the Surveillance, Epidemiology and End Results (SEER) registry before 2015, the combination of CN and systemic therapy was associated with improved OS, compared with systemic therapy alone. However, we must be vigilant in acknowledging that the use of most ICI combinations was popularized after 2015, and that ICI has been yielding encouraging initial results in metastatic nccRCC [27,28].

Moreover, while the European Association of Urology (EAU) guidelines still recommend sunitinib as the first-line therapy for metastatic nccRCC other than the papillary subtype (pRCC),[6] agents including pembrolizumab, cabozantinib and savolitinib have shown promising results over sunitinib for metastatic pRCC.[26,29,30] Therefore, it is imperative for further studies to evaluate the role of CN in nccRCC.

Considerations in Patient Selection

Given all the conflicting evidence, it is pivotal for practicing urologists and oncologists to identify the ideal candidates for CN. Patient selection is where patient factors, disease factors and surgeon factors all come into play.

Currently, the MSKCC and IMDC models are prevalently used to prognosticate mRCC patients. For instance, the EAU guidelines recommend that immediate CN be offered to patients with good performance status who do not require systemic therapy, and to patients with oligometastases where complete metastasis-directed therapy (MDT) can be achieved. In addition, delayed CN should be considered for good responders to systemic therapy. On the contrary, CN is not recommended for MSKCC poor-risk patients or intermediate-risk patients who have an asymptomatic synchronous tumour and require systemic therapy.[6]

There are several limitations to such an approach of model-based prognostication. First, these models were derived from TKI and interferon data before the popularization of ICI. Second, there was no consideration for the volume, sites and numbers of metastases, which were shown to have prognostic significance.[24] Besides, the disease entities of oligometastatic and oligoprogressive RCC would not have any bearing in changing management, when indeed the development of MDT and adjuvant therapy after metastatectomy has been blossoming, as we would discuss in the following section.

Abel et al proposed a 7-item SCREEN score (3 or more metastatic sites, total metastatic tumour burden ⩾5 cm, bone metastasis, systemic symptoms, low serum haemoglobin, low serum albumin and neutrophil/lymphocyte ratio ⩾4), which was derived from their 914 mRCC patients treated with upfront CN. It was found to outperform the IMDC model in the predicting accuracy of first-year mortality (receiver operating characteristic [ROC] curves 0.76 for SCREEN versus 0.55 for IMDC).[31]

There are also studies suggesting that the use of multidisciplinary team discussion involving urologists, radiologists, oncologists, radiotherapists, pathologists and specialist nurses may improve survival outcomes for mRCC patients.[32]

In this regard, the development of better prognostication methods and adoption of coordinated multidisciplinary care are high in order, to make the best personalized clinical decisions for mRCC patients.

Safety of Cytoreductive Nephrectomy

Similar to any major surgeries, the benefits must be weighed against the risks, and CN is no exception. To surgeons, there have been natural concerns about desmoplastic reactions that may arise from presurgical systemic therapy, and increase perioperative morbidities. Specific to CN, whether or not systemic therapy is administered before operation would have affect the complication rates is also an intriguing question.

Chapin et al found, from their cohort of 173 CN patients, that presurgical systemic therapy was not predictive of increased Clavien-Dindo ⩾3 complications, although it did predict more wound complications, compared with the immediate CN group.[33]

This finding was echoed by De Bruijn et al who reported, from the SURTIME data, that the postoperative Clavien-Dindo ⩾3 adverse events, 30-day readmission and in-hospital mortality rates were 6.5%, 13% and 4.3% in the upfront surgery arm; and 2.5%, 7.5% and 2.5% in the deferred arm, respectively. The authors concluded that the post-CN complication profiles were not different, regardless of the sequence of surgery and sunitinib therapy.[34]

When it comes to post-ICI CN, a study by Shapiro et al showed that 4% had intraoperative complications, 25% had 90-day postoperative complications, 3% had Clavien⩾3 complications, and none had 90-day mortality.[35]

Overall, the contemporary complication profiles for CN appear acceptable both in the treatment-naïve and postsystemic therapy settings.

The Concept of Metastasectomy for RCC (and Subsequent Adjuvant Therapy)

Apart from attacking the primary tumour, surgery, radiotherapy and/or ablation can be effective methods to control confined sites of metastases. This principle is known as MDT. Unlike oligometastatic prostate cancer where there have been established definitions and treatment recommendations,[6] the term 'oligometastatic RCC' is not universally defined yet. Most authors accept that it refers to 5 or fewer metastatic sites.

A systematic review conducted by Dabestani et al included 16 comparative studies investigating the role of surgery or radiotherapy in mRCC patients.[36] It concluded that complete MDT by surgery or radiotherapy improved survival and local symptom relief, compared with incomplete or no MDT, although the risks of bias and confounding factors were high in all the studies.

Another systematic review by Guevelou et al showed that stereotactic ablative radiotherapy (SABR) achieved high local control rates >90% for synchronous or metachronous mRCC, delayed systemic therapy by 9 months and improved response rates to systemic therapy from 17% to 56%, although there was no clear OS benefit.[37]

Moreover, the KEYNOTE 564 trial represents the only positive study for adjuvant pembrolizumab to manifest disease-free-survival (DFS) benefits in their initial release (HR for recurrence or death = 0.68; 95% CI = 0.53 to 0.87; P = .002), and even OS benefit (38% lower risk of death) from its updates at the 2024 ASCO Genitourinary Cancers Symposium, for

Table 1. Key studies of CN in ICI era.

PUBLICATION	NATURE OF STUDY	TREATMENT ARMS	POPULATION	KEY RESULTS
CARMENA 2021	RCT	Sunitinib vs CN followed by sunitinib	N = 450 intermediate-to-high MSKCC risk mRCC	Noninferior OS (18.4 mo vs 13.9 mo)
SURTIME 2019	RCT	Deferred surgery (sunitinib followed by CN and adjuvant sunitinib) vs upfront CN followed by sunitinib	N = 99 clear-cell mRCC with resectable primary tumour and ⩽3 surgical risk factors	Noninferior OS (32.4 mo vs 15 mo)
Bakouny et al[20]	Retrospective study	CN vs no CN among mRCC who received upfront ICI or TT	N = 4639 IMDC database	Improved OS for CN subgroup, for both ICI and TT use (HR = 0.72 and 0.61, respectively)
Gross et al[21]	Retrospective study	CN + ICI vs no CN + ICI	N = 367 mRCC treated with ICI at any point	Relative risk reduction in all-cause mortality by 67%
Meagher et al[39]	Retrospective study	Upfront CN followed systemic therapy (TKI or ICI) vs systemic therapy followed by CN cancer-specific survival	N = 189 REMARRC database	Worse cancer-specific survival (CSS) (HR = 2.04) and OS (HR = 1.49)

patients at high risk of recurrence after nephrectomy for ccRCC. The authors defined high risk of recurrence as tumour stage 2 with nuclear grade 4 or sarcomatoid differentiation, tumour stage 3 or higher, regional lymph-node metastasis or stage M1 with no evidence of disease (M1 NED).

Notably, the trial actually included 5.8% patients with M1 NED who were rendered disease-free by both CN and complete metastasectomy. The DFS benefit for this subgroup (HR for recurrence or death = 0.29; 95% confidence interval = 0.12-0.69) was more prominent than that for the M0 subgroup (HR = 0.74; 95% CI = 0.57-0.96).[38] Despite the small sample size, this is the best existing evidence and is thought-provoking for future development of a treatment bundle of CN, complete metastasectomy, followed by adjuvant Pembrolizumab, to optimize the outcomes for selected oligometastatic RCC patients.

Sequence of Treatment

With the blossoming options of surgical and systemic therapies in mRCC, a pivotal clinical question will be what the optimal sequence of treatment is. A recent multi-centre retrospective study based on CN patients from the REMARCC (Registry of Metastatic RCC) database concluded that among the 189 patients (148 TKI + CN, 41 IO + CN), systemic therapy after CN was associated with worse cancer-specific survival (HR = 2.04; $P < .001$), as well as worse OS (HR = 1.49; $P = .039$) on multivariable analyses. Moreover, their ICI subgroup analysis stratified by CN timing proved that delayed CN after ICI led to better 5-year OS (50% vs 30%; $P = .042$) and CSS (90% vs 30%, $P = .019$), but such findings did not hold true after TKI use.[39]

In the absence of prospective trials on the sequence between ICI and CN, retrospective data appeared to incline towards upfront ICI, to achieve better oncological outcomes. Table 1 summarized the key findings of selected up-to-date studies.

Future Directions

There are currently knowledge gaps in the prognostication, treatment sequence, patient selection for CN and MDT in the contemporary management of mRCC, where ICI-based combinations are the first-line therapies. Genetics and biomarkers are possible new gadgets for use, although concrete clinical benefits must first be shown.[40] Uro-oncologists and researchers should aim at defining oligometastatic RCC, and refining prognostication and possibly decision-making models for mRCC patients.

As of now, there are 2 ongoing phase 3 clinical trials. The NORDIC-SUN trial (NCT03977571) aims to compare nivolumab/ipilimumab with or without CN, whereas the PROBE trial (NCT04510597) aims to compare standard-of-care systemic therapy with or without surgery. Both trials would have OS as the primary endpoint. The CYTO-KIK trial (NCT04322955) is a phase 2 trial investigating the effect of upfront cabozantinib and nivolumab on the oncological outcomes of subsequent CN. Their results would be eagerly awaited.

Another direction worth exploring would be the comparison between upfront ICI combination therapies and CN plus complete MDT followed by adjuvant Pembrolizumab. It is hoped that through concerted research efforts, we can optimize the treatment pathways and patient selection for mRCC patients in the foreseeable future.

Limitations

Our review is limited by its nonsystematic search strategy, and the selection and publication biases resulting from the selected retrospective studies.

Conclusions

For mRCC, CN can potentially optimize survival outcomes, but case selection and timing of surgery are crucial. Upfront CN

is no longer considered the standard of care for unselected intermediate and all poor-risk mRCC patients. In addition, a deferred CN approach is generally favoured to maximize chance of receiving systemic therapy and to select patients who may benefit most from surgery. In patients with oligometastatic disease, nephrectomy with MDT can be offered (to achieve M1 NED), followed by adjuvant pembrolizumab. ICI has revolutionized the management of mRCC, and the role of CN in the ICI era will be unveiled in years through clinical trials.

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REFERENCES
1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer*. 2018;103:356-387. doi:10.1016/j.ejca.2018.07.005
2. Bukavina L, Bensalah K, Bray F, et al. Epidemiology of renal cell carcinoma: 2022 update. *Eur Urol*. 2022;82:529-542. doi:10.1016/j.eururo.2022.08.019
3. Huang J, Leung DK, Chan EO, et al. A global trend analysis of kidney cancer incidence and mortality and their associations with smoking, alcohol consumption, and metabolic syndrome. *Eur Urol Focus*. 2022;8:200-209. doi:10.1016/j.euf.2020.12.020
4. All S, Garant A, Hannan R. Stereotactic ablative radiation (SAbR) for oligometastatic RCC. *Semin Radiat Oncol*. 2021;31:227-234. doi:10.1016/j.semradonc.2021.02.002
5. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141-148. doi:10.1016/S1470-2045(12)70559-4
6. Ljungberg B, Albiges L, Abu-Ghanem Y, et al. European association of urology guidelines on renal cell carcinoma: the 2022 update. *Eur Urol*. 2022;82(4):399-410. doi:10.1016/j.eururo.2022.03.006
7. Lapeyre-Prost A, Terme M, Pernot S, et al. Immunomodulatory activity of VEGF in cancer. *Int Rev Cell Mol Biol*. 2017;330:295-342. doi:10.1016/bs.ircmb.2016.09.007
8. Papaccio F, Della Corte CM, Viscardi G, et al. HGF/MET and the immune system: relevance for cancer immunotherapy. *Int J Mol Sci*. 2018;19:3595. doi:10.3390/ijms19113595
9. Bossé D, Ong M. Evolution in upfront treatment strategies for metastatic RCC. *Nat Rev Urol*. 2020;17:73-74. doi:10.1038/s41585-019-0271-6
10. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med*. 2001;345:1655-1659. doi:10.1056/NEJMoa003013
11. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol*. 2004;171:1071-1076. doi:10.1097/01.ju.0000110610.61545.ae
12. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115-124. doi:10.1056/NEJMoa065044
13. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068. doi:10.1200/JCO.2009.23.9764
14. Choueiri TK, Halabi S, Sanford BL, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the Alliance A031203 CABOSUN Trial [published correction appears in J Clin Oncol. 2017;35(32):3736] [published correction appears in J Clin Oncol. 2018;36(5):521]. *J Clin Oncol*. 2017;35:591-597. doi:10.1200/JCO.2016.70.7398
15. Heng DY, Wells JC, Rini BI, et al. Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol*. 2014;66:704-710. doi:10.1016/j.eururo.2014.05.034
16. 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. *Eur Urol*. 2019;75:111-128. doi:10.1016/j.eururo.2018.09.016
17. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med*. 2018;379:417-427. doi:10.1056/NEJMoa1803675
18. 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? *Eur Urol*. 2021;80:417-424. doi:10.1016/j.eururo.2021.06.009
19. 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 [published correction appears in JAMA Oncol. 2019;5(2):271]. *JAMA Oncol*. 2019;5:164-170. doi:10.1001/jamaoncol.2018.5543
20. 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. *Eur Urol*. 2023;83:145-151. doi:10.1016/j.eururo.2022.10.004
21. 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. *Urol Oncol*. 2023;41:51.e25-51.e31. doi:10.1016/j.urolonc.2022.08.013
22. Abu-Ghanem Y, Powles T, Capitanio U, et al. The impact of histological subtype on the incidence, timing, and patterns of recurrence in patients with renal cell carcinoma after surgery-results from RECUR Consortium. *Eur Urol Oncol*. 2021;4:473-482. doi:10.1016/j.euo.2020.09.005
23. Kroeger N, Xie W, Lee JL, et al. Metastatic non-clear cell renal cell carcinoma treated with targeted therapy agents: characterization of survival outcome and application of the International mRCC Database Consortium criteria. *Cancer*. 2013;119:2999-3006. doi:10.1002/cncr.28151
24. Dudani S, de Velasco G, Wells JC, et al. Evaluation of clear cell, papillary, and chromophobe renal cell carcinoma metastasis sites and association with survival. *JAMA Netw Open*. 2021;4:e2021869. doi:10.1001/jamanetworkopen.2020.21869
25. Lee CH, Voss MH, Carlo MI, et al. Phase II trial of cabozantinib plus nivolumab in patients with non-clear-cell renal cell carcinoma and genomic correlates. *J Clin Oncol*. 2022;40:2333-2341. doi:10.1200/JCO.21.01944
26. McDermott DF, Lee JL, Ziobro M, et al. Open-label, single-arm, phase II study of pembrolizumab monotherapy as first-line therapy in patients with advanced non-clear cell renal cell carcinoma. *J Clin Oncol*. 2021;39:1029-1039. doi:10.1200/JCO.20.02365
27. Marchioni M, Bandini M, Preisser F, et al. Survival after cytoreductive nephrectomy in metastatic non-clear cell renal cell carcinoma patients: a population-based study. *Eur Urol Focus*. 2019;5:488-496. doi:10.1016/j.euf.2017.11.012
28. Luzzago S, Palumbo C, Rosiello G, et al. Association between systemic therapy and/or cytoreductive nephrectomy and survival in contemporary metastatic non-clear cell renal cell carcinoma patients. *Eur Urol Focus*. 2021;7:598-607. doi:10.1016/j.euf.2020.04.009

29. Pal SK, Tangen C, Thompson IM Jr, et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet*. 2021;397:695-703. doi:10.1016/S0140-6736(21)00152-5
30. Choueiri TK, Heng DYC, Lee JL, et al. Efficacy of savolitinib vs sunitinib in patients with MET-driven papillary renal cell carcinoma: the SAVOIR phase 3 randomized clinical trial [published correction appears in JAMA Oncol. 2020;6(9):1473]. *JAMA Oncol*. 2020;6:1247-1255. doi:10.1001/jamaoncol.2020.2218
31. Abel EJ, Master VA, Spiess PE, et al. The Selection for Cytoreductive Nephrectomy (SCREEN) score: improving surgical risk stratification by integrating common radiographic features. *Eur Urol Oncol*. 2024;7:266-274. doi:10.1016/j.euo.2023.06.008
32. Zeng Y, Zhu S, Wang Z, et al. Multidisciplinary team (MDT) discussion improves overall survival outcomes for metastatic renal cell carcinoma patients. *J Multidiscip Healthc*. 2023;16:503-513. doi:10.2147/JMDH.S393457
33. Chapin BF, Delacroix SE Jr, Culp SH, et al. Safety of presurgical targeted therapy in the setting of metastatic renal cell carcinoma. *Eur Urol*. 2011;60:964-971. doi:10.1016/j.eururo.2011.05.032
34. De Bruijn RE, Mulders P, Jewett MA, et al. Surgical safety of cytoreductive nephrectomy following sunitinib: results from the Multicentre, Randomised Controlled Trial of Immediate Versus Deferred Nephrectomy (SURTIME). *Eur Urol*. 2019;76:437-440. doi:10.1016/j.eururo.2019.06.006
35. Shapiro DD, Karam JA, Zemp L, et al. Cytoreductive nephrectomy following immune checkpoint inhibitor therapy is safe and facilitates treatment-free intervals. *Eur Urol Open Sci*. 2023;50:43-46. doi:10.1016/j.euros.2023.01.016
36. Dabestani S, Marconi L, Hofmann F, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. *Lancet Oncol*. 2014;15:e549-e561. doi:10.1016/S1470-2045(14)70235-9
37. Le Guevelou J, Sargos P, Siva S, et al. The emerging role of extracranial stereotactic ablative radiotherapy for metastatic renal cell carcinoma: a systematic review. *Eur Urol Focus*. 2023;9:114-124. doi:10.1016/j.euf.2022.08.016
38. Choueiri TK, Tomczak P, Park SH, et al. Adjuvant pembrolizumab after nephrectomy in renal-cell carcinoma. *N Engl J Med*. 2021;385:683-694. doi:10.1056/NEJMoa2106391
39. Meagher MF, Minervini A, Mir MC, et al. Does the timing of cytoreductive nephrectomy impact outcomes? Analysis of REMARCC registry data for patients receiving tyrosine kinase inhibitor versus immune checkpoint inhibitor therapy. *Eur Urol Open Sci*. 2024;63:71-80. doi:10.1016/j.euros.2024.02.001
40. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. *World J Urol*. 2018;36:1943-1952. doi:10.1007/s00345-018-2309-4