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Brief Correspondence – Guidelines

Updated European Association of Urology Guidelines for Cytoreductive Nephrectomy in Patients with Synchronous Metastatic Clear-cell Renal Cell Carcinoma

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Abstract

Cytoreductive nephrectomy (CN) has been the standard of care in patients with metastatic clear-cell renal cancer who present with the tumour in place. The CARMENA trial compared systemic therapy alone with CN followed by systemic therapy. This article outlines the new guidelines based on these data.
Patient summary: The CARMENA trial demonstrates that immediate cytoreductive nephrectomy should no longer be considered the standard of care in patients diagnosed with intermediate and poor risk metastatic renal cell carcinoma when medical treatment is required. However, the psychological burden poor risk patients experience hearing that removal of their primary tumour will not be beneficial, should be carefully considered.

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Cytoreductive nephrectomy (CN) followed by cytokine therapy was established as the standard of care in patients with synchronous metastatic disease and a renal tumour at presentation (primary metastatic renal cell carcinoma [mRCC]) 17 yr ago. Data from two randomised trials showed a significant survival advantage for this approach. Survival at this time was short with a median overall survival (OS) of 13.6 mo in the CN arms [1]. These poor outcomes were a reflection of the lack of effective systemic therapies in the cytokine era. Outcomes for renal cancer have been stratified into three prognostic groups to facilitate prognostication and treatment choice [2]. Patients presenting with primary mRCC are almost exclusively in the intermediate- or poor-risk categories.

The vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), such as sunitinib, have changed outcomes in this disease. Recent survival data suggest median OS of between 25–30 mo in metastatic clear-cell histologies [3]. Retrospective data regarding the role of CN in the VEGFR-TKI era is difficult to interpret due to inherent biases [4]. On one hand, removal of large tumour bulk within the kidney may reduce the potential for new aggressive biological clones to develop and drive [5]. On the other hand, immediate CN results in a significant delay in starting systemic therapy, which fails to address the ultimately fatal metastatic disease, allowing it to progress unchecked [6].

CARMENA (Cancer du Rein Métastatique Nephrectomie et Antiangiogéniques), a randomised, controlled, phase III non-inferiority trial, was designed to answer the question of whether CN is still necessary in the VEGFR-TKI era [7]. The data have implications for the management of primary mRCC; therefore, the European Association of Urology Renal Cell Cancer Guidelines Panel updated their recommendations for CN.

Prior to the publication of CARMENA, previous single-arm and randomised phase II work has explored the role of CN in this setting [8–10]. These studies have focused on a period of VEGFR-TKI (usually 8–12 wk) followed by CN. Results demonstrated that the subgroup of poor-risk patients had poor outcomes irrespective of CN, whereas intermediate-risk patients who respond to therapy and underwent CN showed impressive outcomes. The most significant data are from the SURTIME randomised phase II trial (Table 1) [10]. SURTIME explored three cycles of sunitinib prior to CN as an alternative approach to immediate CN followed by sunitinib.

Initially planned as phase III, the study accrued poorly and closed after 5.7 yr as phase II. The trial had strict eligibility criteria and included only the best surgical

Table 1 – Comparison between CARMENA and SURTIME

	CARMENA	SURTIME
Total numbers	450	99
Sponsor	APHP	EORTC
Intervention	Immediate CN plus sunitinib versus sunitinib alone	Immediate CN plus sunitinib versus 3 mo sunitinib followed by CN plus sunitinib
Trial design	Randomised phase III, non-inferiority 576 patients or 456 events needed to demonstrate non-inferiority	Randomised phase III, superiority 458 patients or 380 events needed to demonstrate superiority
		Downsized to 98 patients to demonstrate superiority of progression-free rate at 28 wk
Study population and key-inclusion criteria	Patients with synchronous clear-cell mRCC and an asymptomatic primary tumour in place	Patients with synchronous clear-cell mRCC and an asymptomatic primary tumour in place
	PS 0-1	PS 0-1
		No more than 3 of 7 preoperative unfavourable surgical factors
Primary endpoint	OS in the ITT population	Progression-free rate at 28 wk in the ITT analysis
Secondary endpoint	PFS in the ITT analysis	OS in the ITT analysis
	OS in per-protocol analysis	PFS and OS in the per-protocol analysis
Median tumour burden by RECIST 1.1 (mm)	142 (23–399)	162 (45–419)
Median primary tumour size	88 (6–200)	94.5 (13–200)
Median age (range), yr	63 (33–84)	59 (39–78)
MSKCC risk score (%)		
Intermediate	256 (47)	87 (89)
Poor	193 (43)	12 (11)
PS		
0	252 (54)	67 (67.7)
1	198 (46)	33 (32.3)
Median number of metastatic sites (range)	2 (1–5)	2 (1–4)
Allocated to immediate CN	226	50
Allocated to sunitinib alone (CARMENA) or sunitinib followed by CN (SURTIME)	224	49
Overall survival (median) in the ITT analyses		
CN followed by sunitinib	13.9 mo (95% CI:11.8–18.3)	15.0 mo (95% CI: 9.3–29.5)
Experimental arm	18.4 mo (95% CI: 14.7–23.0)	32.4 mo (95% CI: 14.5–65.3)

CARMENA = Cancer du Rein Métastatique Nephrectomie et Antiangiogéniques; CI = confidence interval; CN = cytoreductive nephrectomy; EORTC = European Organisation for Research and Treatment of Cancer; ITT = intention-to-treat; mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan-Kettering Cancer Center; OS = overall survival; PS = performance status; PFS = progression-free survival; RECIST = Response Evaluation Criteria In Solid Tumours; SURTIME = Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer; WHO = World Health Organization.

candidates based on seven preoperative factors predicting outcome after CN [11]. While the primary endpoint exploring progression-free survival was not met, the intention-to-treat (ITT) hazard ratio (HR) of OS, a secondary endpoint, of deferred versus immediate CN was 0.57 (95% confidence interval [CI]: 0.34–0.95, $p = 0.032$), with a median OS of 32.4 (95% CI: 14.5–65.3) and 15.0 mo (95% CI: 9.3–29.5), respectively. Although the study was underpowered, and OS exploratory, these data support the hypothesis that delaying systemic therapy for immediate CN may be problematic for patients whose progressive disease will critically advance without treatment.

CARMENA explored immediate CN followed by sunitinib versus sunitinib alone and showed that sunitinib alone was not inferior to CN followed by sunitinib with regard to OS [7]. The trial included patients with clear-cell mRCC of intermediate- and poor-Memorial Sloan Kettering Cancer Center (MSKCC) risk (Table 1). The study did not reach the full accrual of the planned 576 patients. Based on the advice from the Independent Data Monitoring Commission, the trial steering committee closed the study with 450 patients included. In an ITT analysis, median OS with CN was 13.9 mo versus 18.4 mo with sunitinib alone (HR = 0.89; 95% CI: 0.71–1.10). Therefore, the study succeeded in demonstrating that systemic therapy alone was not inferior to CN followed by systemic therapy. Indeed, the data appears to favour the systemic therapy alone arm. In an exploratory subgroup analysis, the median OS was 19.0 mo with CN and 23.4 mo with sunitinib alone (HR = 0.92; 95% CI: 0.60–1.24) for MSKCC intermediate-risk patients and 10.2 mo and 13.3 mo for MSKCC poor-risk patients, respectively (HR = 0.86; 95% CI: 0.62–1.17). Consistent with the ITT analysis, two per-protocol analyses accounting for patients in the CN arm who did either not undergo surgery ($n = 16$) or did not receive sunitinib ($n = 40$), and patients in the sunitinib only arm, who did not receive the study drug ($n = 11$) demonstrated non-inferiority (HR = 0.87; 95% CI: 0.69–1.1 and HR = 0.98; 95% CI: 0.77–1.25). Of note, 38 patients in the sunitinib only arm (17%) required secondary CN due to acute symptoms or for complete or near-complete response.

Both the studies need cautious interpretation. CARMENA, despite its larger study population size, did not reach the full accrual required for a statistical design using a one-sided alpha to demonstrate non-inferiority which may have an impact on the robustness of the results. In addition, CARMENA did not use validated prognostic factors to select patients. The main eligibility criteria for inclusion required only clear-cell primary mRCC and an ECOG 0-1 performance status (PS). Consequently, the trial included a high percentage of poor-risk patients (44% and 41% in the immediate CN and sunitinib alone arms, respectively). Previous data have suggested that poor-risk patients derive no benefit from CN [12]. This raises the possibility of patient selection, where individuals with good prognostic factors were not taking part, opting for alternative treatment regimens instead. Whether or not there was genuine equipoise around the CN question is therefore debatable. However, given that patients had to be PS 0-1 and eligible for surgery and systemic therapy to enter the trial, CARMENA captured a clinically fit, relevant population. Furthermore, the median OS of the upfront CN arm of CARMENA (13.9 mo) was very similar to the OS in the respective arm of SURTIME. Removing the poor-risk subgroup from the final analysis would further decrease the power of the trial. Both the poor- and intermediate-risk subgroup analyses were unplanned.

SURTIME was also underpowered due to poor accrual, which was in part a consequence of very stringent inclusion criteria to select only the most favourable candidates for CN [11]. Although the trial included predominantly MSKCC intermediate-risk patients, the sample size did not allow us to draw definite conclusions. In addition, OS was a secondary endpoint, reducing statistical robustness for this endpoint.

Nevertheless, the consequences of the CARMENA trial are significant and clinically meaningful. Immediate CN should no longer be considered the standard of care in intermediate- and poor-risk mRCC patients when medical treatment is required. Immediate CN is associated with morbidity and mortality and there is no subgroup in which this approach is superior. CARMENA clearly demonstrates that MSKCC poor-risk patients derive no benefit from CN and are potentially harmed by a surgical intervention. This confirms the previous retrospective data [12]. However, assessment of the psychological burden that a poor-risk patient experiences on hearing that the removal of their primary tumour will not be beneficial should be carefully considered.

Together, the subgroup analyses of the MSKCC intermediate-risk group in CARMENA and SURTIME with predominantly MSKCC intermediate-risk patients provide evidence that immediate CN should not be performed in MSKCC intermediate-risk patients requiring sunitinib or an equivalent VEGFR-TKI. The OS in the immediate CN arms of both trials was numerically shorter than that for patients starting with sunitinib, although not statistically significant.

The question remains whether or not MSKCC intermediate-risk patients with mRCC receiving immediate sunitinib benefit from deferred CN in the absence of disease progression. The survival benefit in SURTIME for patients with deferred CN was 17.4 mo and represents a clinically meaningful OS trend in favour of this approach over upfront CN. Unfortunately, the study was underpowered to provide a definite answer. Of note, 38 patients in CARMENA required CN in the sunitinib only arm either because of local symptoms or because of an opportunity to cease systemic therapy after CN. This occurred after a median of 11.1 mo from randomisation, suggesting that approximately 30% of patients surviving the first 7–12 mo may require a secondary nephrectomy with this approach. Taken together, the course of disease in patients receiving immediate sunitinib in both trials provides weak evidence that performing deferred CN at 3 mo or later in patients who do not progress on VEGFR-TKI therapy may be attractive.

Finally, two other clinical scenarios should be considered. Both CARMENA and SURTIME included only patients who were judged to require systemic therapy with sunitinib (metastasis accounted for 42% of total tumour volume). Therefore, these trials do not answer the question of CN in patients with low-volume metastatic disease, a good

Table 2 – Recommendations for patients with primary mRCC requiring systemic therapy with VEGRFR-TKI

Recommendation 1	Strength
Do not perform CN in MSKCC poor-risk patients.	Strong
Recommendation 2	**Strength**
Do not perform *immediate* CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Recommendation 3	**Strength**
Start sunitinib without CN in MSKCC intermediate-risk patients who have an asymptomatic synchronous primary tumour and require systemic therapy with VEGFR-TKI.	Weak
Recommendation 4	**Strength**
Discuss delayed CN in MSKCC intermediate-risk patients under VEGFR-TKI therapy who derive long-term sustained benefit and/or minimal residual metastatic burden.	Weak
Recommendation 5	**Strength**
Perform immediate CN in patients with good performance who do not require systemic therapy.	Weak

CN = cytoreductive nephrectomy; mRCC = metastatic renal cell carcinoma; MSKCC = Memorial Sloan-Kettering Cancer Center; VEGFR-TKI = vascular endothelial growth factor receptor tyrosine kinase inhibitors.

performance, favourable, and intermediate risk who do not require treatment with VEGFR-TKI but may be observed instead. In these cases, immediate CN retains its role as prospective single-arm studies have shown that patients can be observed and the time to targeted therapy can be substantial [13].

Furthermore, superiority of nivolumab and ipilimumab over sunitinib has led to a paradigm change in the first-line treatment for intermediate- and poor-risk patients [14]. This changes the first-line therapy for the patients entered into CARMENA and SURTIME. In the pivotal CheckMate 214 trial, 187 mRCC patients were included with their primary tumour in place demonstrating a survival benefit with immune checkpoint inhibition. Therefore, the role and sequence of CN in the era of immunotherapy needs to be reinvestigated.

Consequently, the panel has made the following recommendations for patients with primary mRCC requiring systemic therapy with VEGRFR-TKI (Table 2), based on consensus methods using a modified Delphi survey (see Supplementary material 1–3).

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Study concept and design: Bex, Powles, Ljungberg.
Acquisition of data: Bex, Powles.
Analysis and interpretation of data: Bex, Powles, Ljungberg, Albiges, Bensalah, Giles, Hora, Kuczyk, Lam, Marconi, Merseburger, Staehler, Volpe.
Drafting of the manuscript: Bex.
Critical revision of the manuscript for important intellectual content: Albiges, Bensalah, Giles, Hora, Kuczyk, Lam, Marconi, Merseburger, Staehler, Volpe, Hofmann, Dabestani, Tahbaz, Fernández-Pello, Abu-Ghanem.
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Professor Dr. Axel Bex has received company speaker honoraria from Pfizer, participated in trials for Pfizer Europe, participated in advisory boards for GlaxoSmithKline and Novartis, is a company consultant for Pfizer and Novartis, and has received grants/research support from Pfizer.
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Professor Dr. Börje Ljungberg has received company speaker honoraria from GlaxoSmithKline, Roche, Pfizer, and Novartis, has participated in trials for GlaxoSmithKline, Medivation, Pfizer, and Janssen R&D, and has been on advisory boards for Pfizer and GlaxoSmithKline.
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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.2018.08.008.

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