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ARTICLE

Too good for CARMENA: criteria associated with long systemic therapy free intervals post cytoreductive nephrectomy for metastatic clear cell renal cell carcinoma

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ABSTRACT

Purpose: The prospective CARMENA trial surprisingly suggested that patients with upfront metastatic clear-cell renal cell carcinoma (m-ccRCC) would not benefit from cytoreductive nephrectomy (CN). We aimed to identify the m-ccRCC patient subpopulation who would benefit from the continued use of CN.

Methods: We performed a retrospective cohort study on upfront m-ccRCC patients and identified three subgroups: patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) only without CN (TKI ONLY), patients undergoing CN immediately followed within 6 months by VEGFR-TKIs (CN > TKI) and patients undergoing CN followed by a considerable therapy-free interval of at least 6 months (CN > AS). Kaplan-Meier survival analysis and Cox proportional hazards regression models were used to compare outcomes and investigate predictive factors.

Results: We included 119 patients. Overall survival was 17, 13 and 56 months for the CN > TKI, TKI only and CN > AS subgroups, respectively ($p < 0.0001$). Oligometastatic disease (HR = 0.33, 95% CI = 0.21–0.54, $p < 0.0001$), lung as only metastatic site (HR = 0.48, 95% CI = 0.31–0.76, $p = 0.001$) and having ≤ 2 evaluable International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (HR = 0.56, 95% CI = 0.32–0.98, $p = 0.04$) were predictive for systemic therapy free survival after diagnosis.

Conclusions: The CARMENA results only apply for m-ccRCC patients in immediate need for systemic therapy, but not for patients in whom a period of AS can be expected after CN. Patients in whom systemic therapy most likely can be deferred and who are likely to benefit from CN have oligometastatic disease, only present in the lung and few (≤2) evaluable IMDC criteria.

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Introduction

Worldwide, renal cell carcinoma (RCC) is the 6th most frequently diagnosed malignancy for men and the 10th in women, accounting for 3% of all malignancies and 90% of solid kidney tumors. Up to 17% of newly diagnosed cases are metastatic at presentation and up to another one third of cases treated with curative intent will eventually develop metastases [1,2].

Cytoreductive nephrectomy (CN) has been the gold standard in the treatment of upfront metastatic RCC (mRCC). Two prospective randomized controlled trials in the interferon alfa (IFNα) era (1992–2005) solidified the role of CN in mRCC by demonstrating a 5.8-month overall survival (OS) benefit of CN plus IFNα over IFNα alone [3,4]. However, the use of IFNα has drastically declined since the introduction of targeted therapies such as the monoclonal vascular endothelial growth factor (VEGF) antibody bevacizumab and VEGF-receptor tyrosine kinase inhibitors (VEGFR-TKIs), such as sunitinib, sorafenib, pazopanib, axitinib, cabozantinib and tivozanib, that became the standard of care [5]. Only recently, these VEGF-targeted therapies were superseded by immune checkpoint inhibitors after showing excellent results in phase III trials [6–8].

The role and timing of CN in upfront mRCC in the VEGF-targeted therapy era has recently been investigated. Retrospective data consistently report a survival benefit for CN plus VEGFR-TKI over VEGFR-TKI alone [9,10]. In the largest retrospective series, Heng et al. [11] suggested that patients may benefit from CN, except those with a life expectancy <12 months or at least four unfavorable International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. However, outcome in these retrospective series can be biased by patient selection, patients with aggressive disease being less considered for CN compared to patients with more indolent disease. Therefore, a prospective randomized controlled trial was set up to provide evidence on the continued use of CN in the VEGFR-TKI era. The CARMENA trial randomized upfront metastatic clear cell RCC (m-ccRCC) patients in two treatment arms, CN plus sunitinib versus

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sunitinib only, in an intention-to-treat non-inferiority design evaluating OS as primary endpoint. This trial reported somewhat surprisingly non-inferiority of the sunitinib-only arm [12]. These results challenged the role of CN in upfront m-ccRCC in the VEGFR-TKI era and have shifted treatment paradigms away from surgery. However, it is believed that some patients would benefit from the continued use of CN.

Our hypothesis was that the surprising CARMENA results were influenced by the fact that all the included patients in this trial were in need for immediate systemic therapy and that CN could still be useful in patients in whom systemic therapy can be delayed after CN. Thus, the first critical question to answer is whether the patient is in urgent need for systemic therapy.

In order to test this hypothesis, we retrospectively analyzed the records of all the patients who were diagnosed in our hospital with upfront m-ccRCC in order to (a) test the CARMENA-findings in our patient series, (b) describe the subgroup of upfront m-ccRCC patients in whom CN can lead to a long period of active surveillance (AS) before the start of systemic therapies and (c) search for prognostic factors associated with long periods of AS in order to select these patients for CN.

Materials and methods

Following approval by the local ethical committee (MP001780), we retrospectively identified upfront m-ccRCC patients treated with CN (defined as nephrectomy in any metastatic case) and/or VEGF-targeted therapies. Within this cohort, three subgroups were defined: patients immediately starting VEGFR-TKI treatment after diagnosis without CN (TKI only), patients undergoing CN followed by immediate (within 6 months after CN) VEGFR-TKI treatment (CN > TKI) and patients undergoing CN followed by a therapy-free interval of minimum 6 months prior to starting VEGFR-TKIs (CN > AS) [13]. The first two subgroups corresponded to the two arms in the CARMENA trial, whereas the third subgroup of patients was not represented in this trial. All patients who underwent surgery did so within 3 months of diagnosis.

Patients were treated with first-line VEGFR-TKIs at the usual starting dose. Response evaluation was done with thoracic and abdominal computed tomography (CT) scan each two to three treatment cycles by the investigator with the response evaluation criteria in solid tumors (RECIST). During AS, patients underwent thoracic and abdominal CT scans each 3–4 months, with longer intervals of up to 6 months in indolent tumors.

Outcome parameters were systemic therapy free survival (STFS), progression free survival (PFS), overall survival (OS) and response rate (RR). STFS was defined as the time between initial diagnosis and start of first line VEGFR-TKI.

The following criteria, presumably associated with STFS, were extracted from electronic patient records at initial diagnosis of upfront m-ccRCC: age, gender, baseline hemoglobin, neutrophil count, platelet count, corrected calcium, Karnofsky performance score, C-reactive protein (CRP), number of metastatic sites, number of metastases, the organs hosting the metastases, cT-stage and cN-stage [14–18]. Oligometastatic disease was defined as ≤3 synchronous metastases [19]. It is important to note that the IMDC risk factor 'time between initial diagnosis and start of systemic therapy' is not evaluable at initial diagnosis of upfront m-ccRCC patients in whom a considerable interval of AS after CN could be expected, since the start of systemic therapy has not yet occurred. Therefore, we could only consider the five other IMDC risk factors for the prediction of STFS. These were called the 'evaluable IMDC risk factors'. Sarcomatoid dedifferentiation in the primary tumor, an unfavorable prognostic feature, was not included in our analysis since it is impossible to assess this feature on a pre-operative biopsy due to the considerable intratumoral heterogeneity in RCC [20].

Survival was assessed via Kaplan-Meier and Cox proportional hazards regression analyses. Subgroups were compared using the Fisher's exact *t*-test. A two-sided *p*-value <0.05 was considered statistically significant. Factors with a *p*-value <0.2 on univariate analysis were subsequently included in the multivariate model. Data analysis was carried out using R (version 3.6.2).

Results

Included patients

One hundred and nineteen upfront m-ccRCC patients were included between June 2004 and November 2018: 26 were immediately started on TKI without CN (TKI only), 44 underwent CN immediately followed by TKI (CN > TKI) and 49 underwent CN followed by a therapy-free interval of at least 6 months (CN > AS). Median follow-up was 22 months and at the time of analysis 100 patients (84.0%) had died. Table 1 shows the baseline characteristics for the entire study population.

Validation of the CARMENA findings

Table 2 shows the baseline characteristics stratified per subgroup. In the CN > TKI and TKI only subgroup all patients were IMDC intermediate (55.9%) or poor risk (44.1%). There were no IMDC good risk patients, due to the fact that all patients had at least one unfavorable IMDC risk factor, namely that they all were started on systemic therapy within 12 months after first diagnosis. The patient and tumor characteristics were not statistically significant for the CN > TKI and TKI only subgroups with the exception of the proportion of oligometastatic patients (29.5% vs 7.7% for the CN > TKI and TKI only subgroup, respectively).

The CN > TKI and the TKI only group showed overlapping OS curves. Median OS was 17 and 13 months for the CN > TKI and TKI only group, respectively ($p = 0.38$) (Figure 1). Median PFS on first-line VEGFR-TKI did not differ in the CN > TKI group vs TKI only group (5 months for both groups, $p = 0.44$). Although RR on first-line VEGFR-TKIs was 36.1% and 13.0% for the CN > TKI and TKI only group, respectively ($p = 0.04$), this did not affect survival outcomes.

Table 1. Patient characteristics at inclusion.

Patient characteristics at inclusion	Total cohort
Number of patients	$n = 119$
Age, years*	63.2 (57.1–69.5)
Gender, *n* (%)	
Male	76 (63.9)
Female	43 (36.1)
Evaluable IMDC prognostic criteria at inclusion, *n* (%)	
Hemoglobin < LLN	66 (55.5)
Platelet count > ULN	24 (20.2)
Neutrophils > ULN	16 (14.3)
Serum corrected calcium > ULN	18 (21.4)
KPS < 80%	25 (21.6)
CRP > ULN, *n* (%)	82 (68.9)
Clinical tumor stage, *n* (%)	
cT1	16 (14.4)
cT2	16 (14.4)
cT3	65 (58.6)
cT4	14 (12.6)
cN0	50 (50.0)
cN+	50 (50.0)
Number of metastases, *n* (%)	
1–3	46 (38.6)
3+	73 (61.4)
Patients with a single metastatic site	67 (56.3)
Mean number of metastatic sites per patient	1.7
Site of metastases	
Lung	83 (69.7)
Mediastinal nodes	21 (17.6)
Bone	43 (36.1)
Liver	16 (13.5)
Other	23 (19.3)
Patients with lung as only metastatic site	44 (37.0)
Patients with bone as only metastatic site	15 (12.6)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance score; LLN, lower limit of normal; ULN, upper limit of normal; CRP, C-reactive protein.
*Data are shown as median (interquartile range).
Note: We used the term 'evaluable IMDC criteria' since the criterion 'time to systemic treatment < 12 months' is not evaluable at the time of initial diagnosis for patients in whom CN could be considered.
Hemoglobin LLN: Female: 12.0 g/dL; Male: 14.0 g/dL. Platelet count ULN: 450 *10^9/L. Neutrophils ULN: 7.0 *10^9/L. Serum corrected calcium 2.55 mmol/L.

Description of the subgroup of upfront m-ccRCC patients that could benefit from AS after CN

In the CN > AS subgroup, VEGFR-TKIs were eventually started in 36 out of 49 (73.5%) patients. However, in as many as 13 out of 49 (26.5%) patients, there was still no indication to start with systemic therapy at last follow-up. Median time to start of VEGFR-TKIs after CN was even 23 months, meaning that in these 49 patients, adverse events of systemic therapies could be avoided during almost 2 years. Table 2 shows that patient and tumor characteristics of the CN > AS group were, as expected, very different as compared to the characteristics in the CN > TKI and TKI only subgroups who correspond to the patients included in the CARMENA trial and were in need of immediate systemic treatment. Patients in the CN > AS subgroup had significantly less anemia ($p = 0.009$), lower CRP ($p = 0.009$), fewer bone metastases ($p = 0.001$), fewer liver metastases ($p = 0.002$), more oligometastatic disease ($p < 0.0001$) and more single site metastases ($p = 0.0007$). Of note, of the 14 patients (11.8%) in our cohort who harbored only one metastasis, eight were in the CN > AS group, of whom four have undergone metastasectomy at some point. Triggers for the start of systemic therapy after AS were in most cases acceleration of tumor growth or development of symptoms.

Median OS after inclusion in the study was substantially longer in the CN > AS subgroup compared to the CN > TKI and TKI only subgroups (56 vs 17 and 13 months, respectively, $p < 0.001$) (Figure 1). Median PFS after the start of first-line VEGFR-TKI was also longer in the CN > AS subgroup compared to the CN > TKI and TKI only subgroups (19 vs 5 vs 5 months, respectively, $p = 0.04$). RR was 48.2% in the CN > AS subgroup compared to 27.1% in the pooled CN > TKI + TKI only group, $p = 0.08$).

Identification of criteria associated with duration of AS after CN

We calculated STFS in the entire population and within the CN > AS subgroup to identify criteria correlated with a long STFS. The criteria considered were the following: 'lung as only metastatic site', 'bone as only metastatic site', number of metastases ('oligometastatic' or not), number of 'evaluable IMDC criteria', 'baseline CRP-levels', 'cT-stage' and 'cN-stage'. Note that there were few patients with metastases confined to a single host organ except lung or bone.

STFS was longer in patients with 'oligometastatic disease' (median 20.5 vs 3 months, HR = 0.41, 95% CI = 0.27–0.62, $p < 0.0001$), 'lung as only metastatic site' (median 8 vs 3 months, HR = 0.54, 95% CI = 0.36–0.81, $p = 0.002$), 'oligometastatic disease and lung or bone as single metastatic site' (median 29 vs 3 months, HR = 0.39, 95% CI = 0.26–0.58) as well as '$\leq$ 2 evaluable IMDC factors' (median 5 vs 2 months, HR = 0.42, 95% CI = 0.19–0.93, $p = 0.03$) (Figure 2). Subsequent multivariate Cox proportional hazards regression revealed 'oligometastatic disease', 'lung as only metastatic site' and '$\leq$ 2 evaluable IMDC criteria' to remain significant predictors for STFS (Table 3).

Within the CN > AS subgroup itself, 'oligometastatic disease and bone or lung as single metastatic site' was also associated with a longer STFS (median 64 vs 19 months, HR = 0.34, 95% CI = 0.16–0.72).

'Oligometastatic disease', 'bone as only metastatic site' and '$\leq$ 2 evaluable IMDC criteria' were also associated with better OS on univariate analysis. On multivariate analysis, 'oligometastatic disease' remained a significant predictor for OS (Supplementary data).

Discussion

In our patient series, we corroborate the findings of the CARMENA trial: patients who are in need of immediate systemic therapy do not appear to benefit from CN in terms of survival: PFS and OS were similar in upfront m-ccRCC patients treated with CN immediately followed by VEGFR-TKIs and patients treated with VEGFR-TKIs only. However, we also identified an unneglectable subgroup of patients (49/119, 41%), with baseline clinical characteristics that are clearly different from the CARMENA patients, in whom the start of systemic therapy with VEGFR-TKIs could be delayed for at least 6 months after CN. Median STFS was even as

Table 2. Patient characteristics for the three individual subgroups.

Patient characteristics	CN > TKI	TKI only	CN > AS	*p*-value (comparing CN > TKI + TKI only) groups to CN > AS group)
Number of patients, *n* (%)	44 (37.0)	26 (21.8)	49 (41.2)	
Characteristics at inclusion				
Age, years*	62 (56–68)	65 (58–71)	63 (58–71)	0.41
Gender, *n* (%)				
Male	31 (70.5)	13 (50.0	32 (65.3)	0.85
Female	13 (29.5)	13 (50.0)	17 (34.7)	0.85
Evaluable IMDC prognostic criteria at inclusion, *n* (%)				
Hemoglobin < LLN	28 (63.6)	18 (72.0)	20 (41.7)	**0.009**
Platelet count > ULN	9 (20.5)	7 (29.2)	8 (16.3)	0.49
Neutrophils > ULN, *n* (%)	7 (16.3)	6 (25.0)	5 (11.1)	0.58
Serum corrected calcium > ULN	10 (30.3)	3 (13.0)	5 (17.9)	0.78
KPS < 80%	11 (25.0)	7 (29.2)	7 (14.6)	0.17
CRP > ULN, *n* (%)	34 (79.1)	22 (91.7)	28 (63.6)	**0.009**
Clinical tumor stage, *n* (%)				
cT1	4 (9.1)	4 (22.2)	8 (16.3)	0.59
cT2	5 (11.4)	3 (16.7)	8 (16.3)	0.59
cT3	29 (65.9)	7 (38.9)	29 (59.2)	0.46
cT4	6 (13.6)	4 (22.2)	4 (8.2)	0.39
cN0	19 (47.5)	5 (35.7)	26 (56.5)	0.32
cN+	21 (52.5)	9 (64.3)	20 (43.5)	0.32
Number of metastases, *n* (%)				
1–3	13 (29.5)	2 (7.7)	31 (63.3)	**<0.0001**
3+	31 (70.5)	24 (92.3)	18 (36.7)	**<0.0001**
Patients with a single metastatic site	22 (50.0)	8 (30.8)	37 (75.5)	**0.0007**
Mean number of metastatic sites	1.8	2.3	1.3	0.11
Site of metastases				
Lung	33 (75.0)	16 (61.5)	34 (69.4)	>0.99
Mediastinal nodes	5 (11.4)	1 (3.9)	15 (30.6)	**0.003**
Bone	15 (34.1)	13 (50.0)	6 (12.3)	**0.001**
Liver	6 (13.6)	9 (34.6)	1 (2.0)	**0.002**
	15 (34.1)	11 (42.3)	5 (10.2)	**0.001**
Patients with lung as only metastatic site	15 (34.1)	4 (15.4)	25 (51.0)	**0.01**
Patients with bone as only metastatic site	3 (6.8)	2 (7.7)	10 (20.4)	**0.048**
Characteristics at start of systemic therapy				
First-line VEGFR-TKI	44 (100)	26 (100)	36 (73.5)	**<0.0001**
Sunitinib	26 (59.1)	16 (61.5)	21/36 (58.3)	>0.99
Pazopanib	15 (34.1)	7 (26.9)	12/36 (33.3)	0.83
Sorafinib	3 (6.8)	3 (11.6)	3/36 (8.4)	>0.99
None			13 (26.5)	**<0.0001**
IMDC at start of systemic therapy				
Good	0	0	11/36 (30.6)	**<0.0001**
Intermediate	25 (56.8)	13 (54.2)	22/36 (61.1)	0.68
Poor	19 (43.2)	11 (45.8)	3/36 (8.3)	**0.0001**

p-values compare the pooled CN > TKI and TKI only groups to the CN > AS group.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance score; LLN, lower limit of normal; ULN, upper limit of normal; CRP, C-reactive protein; VEGFR-TKI, Vascular endothelial growth factor receptor tyrosine kinase inhibitor.
*Data are shown as median (interquartile range).
Note: We used the term 'evaluable IMDC criteria' since the criterion 'time to systemic treatment < 12 months' is not evaluable at the time of initial diagnosis for patients in whom CN could be considered.
Hemoglobin LLN: Female: 12.0 g/dL; Male: 14.0 g/dL. Platelet count ULN: 450 *10^9/L. Neutrophils ULN: 7.0 *10^9/L. Serum corrected calcium 2.55 mmol/L.
Significant *p*-values (<0.05) are displayed in bold.

high as 23 months in this subgroup. Thus, despite the results of the CARMENA trial, there is a subgroup of patients that continue to benefit from CN, at least in terms of delay of systemic therapy and the concomitant decrease in quality-of-life. Additionally, these patients are spared from the potential local complications of their tumor. Finally, we describe several criteria that allow to expect a long period of AS following CN. Therefore, the question of whether immediate systemic therapy at diagnosis is needed (with or without CN) or if a period of AS after CN can be expected is essential. This is also the first consideration in a recently proposed treatment algorithm for upfront mRCC patients by Kuusk et al. [21] to select patients for CN and is considered a crucial criterion to individualize indications for CN [22].

In fact, the CARMENA trial only included patients who were in need for systemic treatment, with or without CN. This population consisted of patients with poor prognostic markers: more than 50% of the patients were intermediate risk and more than 40% poor risk in both arms [23]. Good risk patients were not included due to the fact that the criterion 'interval between primary diagnosis and start of systemic therapy less than 12 months' was always met. Additionally, the CARMENA patients had a median of two metastatic sites [12]. Patients with a low metastatic load, slow growing metastases and small impact on their general health were probably not included in this trial as the clinician would not want to expose these patients to sunitinib toxicity in this stage of the disease. In our study, patient

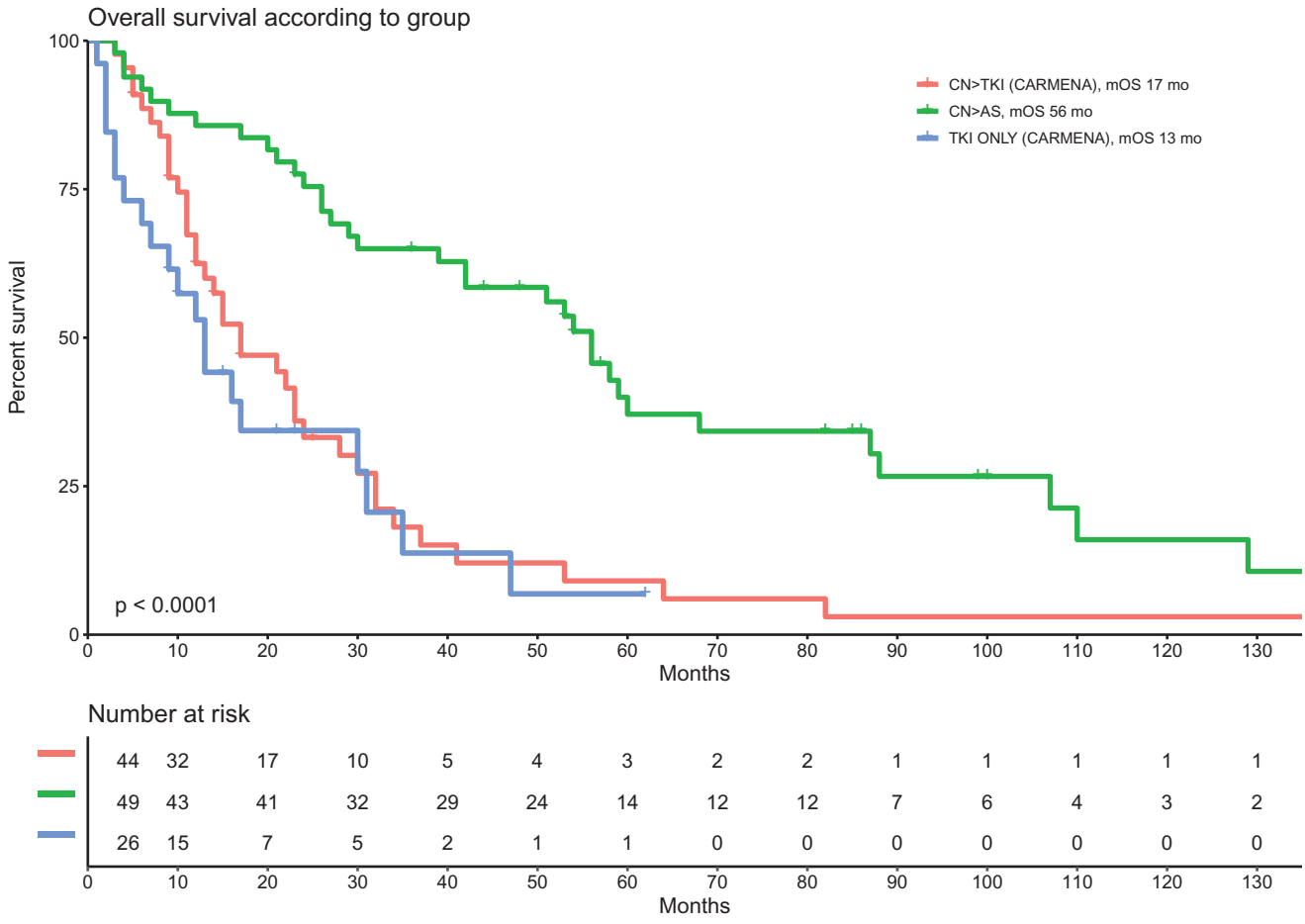

Figure 1. Kaplan-Meier curve depicting the overall survival (OS) of patients with metastatic renal cell carcinoma by group. Green: cytoreductive nephrectomy without immediate systemic treatment, red: cytoreductive nephrectomy followed by immediate systemic treatment, blue: no cytoreductive nephrectomy and immediate systemic treatment.

characteristics in the CN > TKI and TKI Only subgroups were similar to the CARMENA population. Contrarily, the CN > AS subgroup is a highly selected subpopulation, strikingly different from the CARMENA cohort: it harbors a larger amount of patients with favorable prognostic features such as single site and low volume disease, with lower incidence of bone and liver metastases, less patients with multiple metastatic sites, less cN1-stage and less IMDC risk factors such as anemia, neutrophilia, thrombocytosis and low Karnofsky score.

In order to select patients in advance who will benefit from an AS period after CN, we studied various possible criteria associated with STFS. Multivariate analysis revealed that 'oligometastatic disease', 'lung as only metastatic site' and '≤ 2 evaluable IMDC criteria' were associated with longer STFS. Patients with 'oligometastatic disease only present in lung or bone as single metastatic site' were also strongly associated with better STFS. As expected, OS was significantly and substantially longer in this subgroup of patients (CN > AS) compared to the two subgroups of patients who were in need of immediate systemic treatment (CN > TKI and TKI only). This is probably mostly due to the more indolent disease evolution in these patients. In the absence of a control group of patients in whom AS was observed without CN, it is difficult to prove that there has been an OS advantage due to the CN itself, although this is at least hypothesis generating.

In our series, 'oligometastatic disease' was also associated with longer OS. However, the proportion of oligometastatic patients was higher in the CN > TKI arm compared to the TKI only arm but this did not influence survival outcomes. Additionally, the updated CARMENA results do not show an impact of number of metastases and our findings are thus probably driven by the CN > AS cohort, as these patients were not well represented in the CARMENA trial population [12].

Our results are in coherence with the largest retrospective study on the impact of CN in upfront mRCC by Heng et al. [11]. They showed an OS benefit in patients undergoing CN compared to those starting immediately with systemic therapy without CN. However, in the group of patients that underwent CN, some started with systemic therapies immediately after this procedure, whereas in others the start of systemic therapies was delayed after CN. The study by Heng et al. [11] does not stratify outcomes for these two separate subgroups. Thus, the group that underwent CN in their study corresponds to the pooled CN > TKI and CN > AS subgroups in our study. As a consequence, the OS benefit for the CN group observed in the study by Heng et al. [11] is probably

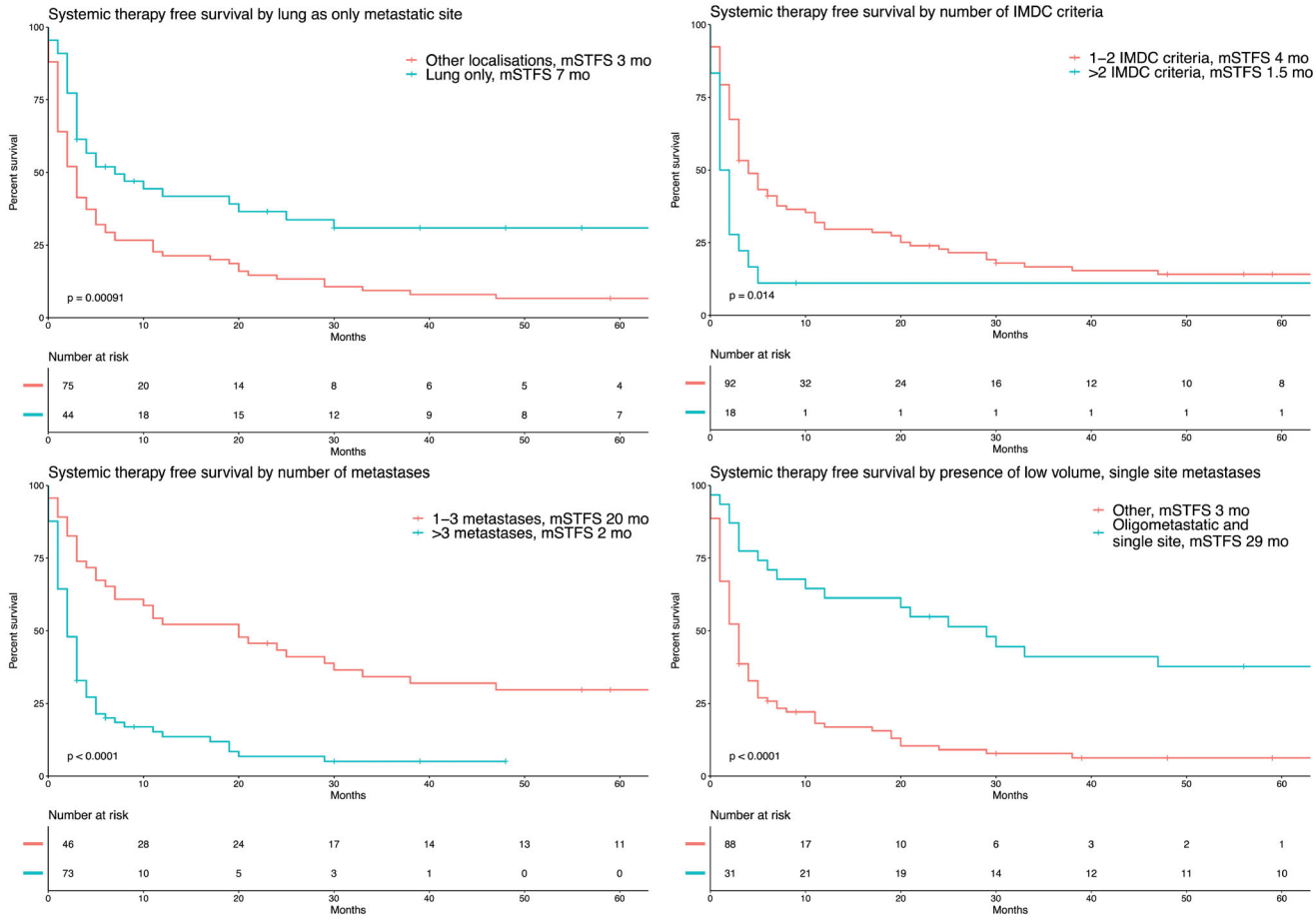

Figure 2. Kaplan-Meier curves depicting the systemic therapy free survival (STFS) of patients with metastatic renal cell carcinoma. Upper left panel: lung as only metastatic site, upper right panel: ≤2 evaluable IMDC criteria, lower left panel: number of metastases, lower right panel: number of metastases and lung or bone as single metastatic site.

Table 3. Univariate and multivariate Cox proportional hazards regression analyses for systemic therapy free survival.

Variable	HR	95% CI of HR	*p*-value
Univariate Cox proportional hazards regression			
cT-stage (1 vs 2 vs 3 vs 4)	0.99	0.79–1.25	0.96
cN-stage (0 vs 1)	0.83	0.54–1.28	0.40
Oligometastatic (max 3)	0.34	0.22–0.53	**<0.0001**
Lung only	0.52	0.34–0.79	**0.002**
Bone only	0.63	0.35–1.13	0.12
Oligometastatic (max 3) and Bone or Lung only	0.30	0.18–0.51	**<0.0001**
≤2 Evaluable IMDC criteria	0.53	0.31–0.92	**0.02**
Normal baseline CRP	0.68	0.43–1.06	0.09
Multivariate Cox proportional hazards regression			
Oligometastatic (max 3)	0.33	0.21–0.54	**<0.0001**
Lung only	0.48	0.31–0.76	**0.001**
≤2 Evaluable IMDC criteria	0.56	0.32–0.98	**0.04**

HR, Hazard Ratio; CI, Confidence Interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; CRP, C-Reactive Protein.
Significant *p*-values (<0.05) are displayed in bold.

largely driven by the subgroup of patients who did not immediately start with systemic therapy after CN.

Additionally, even in the group of patients who need upfront systemic therapies, there possibly still exist some reasons to perform CN. First, a considerable number of patients will need a CN for local complications. Additionally, one could argue that, unlike biopsies, CN provides a complete specimen of the very heterogeneous tumors that RCCs are. This could be of great significance in the era in which prognostic or even predictive tissue biomarkers will gain more and more importance in everyday practice. Moreover, CN can also be performed after induction therapy with VEGFR-TKIs. In the CARMENA trial, 40 out of 224 patients (17.9%) in the sunitinib only arm underwent a secondary CN after induction therapy with sunitinib [12]. Furthermore, the SURTIME trial concluded that surgery after upfront sunitinib appears to be safe: PFS on sunitinib and complication rates were similar in both subgroups. An OS signal favoring deferred CN was observed [24]. There were no patients in our cohort who underwent surgery after initial systemic treatment.

This study is limited by its single-center, retrospective design and relatively small sample size. Additionally, we did not have the exact number of patients available who did not meet inclusion criteria for this study readily available. However, it benefits from its real-world setting and clinical patient selection. Another limitation is that the results of the CARMENA trial and of the present study are possibly outdated due to the fact that immune checkpoint inhibitors with or without VEGFR-TKIs have now become the backbone of first-line m-ccRCC treatment, superseding VEGFR-TKI monotherapy.

Conclusions

The results of the CARMENA trial, that have in part shifted treatment paradigms away from CN in upfront m-ccRCC, are

largely influenced by patient selection criteria, namely the fact that all the included patients were in need for systemic therapy without delay. However, in daily practice, a long interval of AS prior to the start of systemic therapy can be observed in a considerable subgroup of upfront m-ccRCC patients, thus making it unwise to completely abandon CN. These patients are characterized by oligometastatic disease, $\leq$2 evaluable IMDC prognostic criteria and lung metastases as unique metastatic site and could be good candidates for CN followed by AS rather than immediately starting systemic therapy.

Ethical approval

Ethical board approval was obtained prior to this study (MP001780) for retrospective chart review. This study did not involve active participation by human participants nor animals.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

E. Roussel: Data collection, Data analysis, Manuscript writing; A. Verbiest: Data analysis, Manuscript editing; U. Milenkovic: Manuscript editing; B. Van Cleynenbreugel: Manuscript editing; H. Van Poppel: Manuscript editing; S. Joniau: Manuscript editing; B. Beuselinck: Project development, Data analysis, Manuscript editing; M. Albersen: Project development, Data analysis, Manuscript editing.

Informed consent

All authors have given their explicit informed consent to submit this work.

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