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Sunitinib Alone or After Nephrectomy for Patients with Metastatic Renal Cell Carcinoma: Is There Still a Role for Cytoreductive Nephrectomy?

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Abstract

Background: The CARMENA trial in patients with metastatic renal cell carcinoma (mRCC) demonstrated that treatment with sunitinib alone was noninferior to cytoreductive nephrectomy (CN) followed by sunitinib (nephrectomy–sunitinib).

Objective: The objective of this study was to provide updated overall survival (OS) outcomes of CARMENA and assess whether some subgroups may still benefit from upfront CN.

Design, setting, and participants: CARMENA was a phase III trial in 450 patients with mRCC enrolled from 2009 to 2017.

Intervention: Patients in the intention-to-treat population received nephrectomy–sunitinib (standard of care [SOC]; $n = 226$) or sunitinib alone ($n = 224$).

Outcome measurements and statistical analysis: Primary endpoint was OS, assessed using an updated data cut-off (October 2018; median OS event-free follow-up, 36.6 mo). Patients were risk stratified using International Metastatic RCC Database Consortium (IMDC) criteria.

Results and limitations: Sunitinib alone was noninferior to nephrectomy–sunitinib (hazard ratio [HR], 0.97; 95% confidence interval, 0.79–1.19; $p = 0.8$) and demonstrated longer median OS (19.8 mo vs 15.6 mo, respectively). For patients with two or more IMDC risk factors, OS was significantly longer with sunitinib alone than with nephrectomy–sunitinib (31.2 mo vs 17.6 mo, respectively; HR, 0.65; $p = 0.03$). For patients with one IMDC risk factor, OS was longer for nephrectomy–sunitinib versus sunitinib alone although not significantly (31.4 mo vs 25.2 mo; HR, 1.30; $p = 0.2$). The post hoc nature of the subgroup analyses may limit their interpretation.

Conclusions: Sunitinib alone was noninferior compared with nephrectomy–sunitinib, suggesting that CN should not be considered SOC in patients with mRCC requiring systemic treatment. Certain subgroups, including patients with one IMDC risk factor, may still benefit from upfront CN.

Patient summary: We assessed the survival of patients with metastatic kidney cancer in a clinical trial. Patients treated with sunitinib on its own had the same survival as patients who

had surgery before sunitinib treatment. We conclude that surgery may not be necessary for some patients with metastatic kidney cancer.

1. Introduction

Cytoreductive nephrectomy (CN) has long been the standard of care (SOC) for patients who present with metastatic renal cell carcinoma (mRCC), based on data from randomized controlled trials where CN before treatment with interferons improved survival of patients with mRCC [1–3]. Recently, the phase III CARMENA trial demonstrated that treatment of patients with mRCC with sunitinib alone was noninferior to CN followed by sunitinib treatment for both intermediate- and poor-risk disease as classified by the Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model [4]. Median overall survival (OS) was 18.4 mo in the sunitinib alone group compared with 13.9 mo in the nephrectomy–sunitinib group (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.71–1.10; noninferiority limit, 1.20) [4].

While the CARMENA trial provided practice-changing evidence that patients with intermediate- or poor-risk disease should be not be given CN before starting systemic treatment [5], questions remained over the benefit for intermediate-risk patients, given the clinical evidence indicating that selected patients may still benefit from upfront CN [6,7].

The International Metastatic RCC Database Consortium (IMDC) risk classification system is a prognostic model for mRCC [8]. Unlike other risk classification systems such as the MSKCC prognostic model, it is based on outcomes across a wide range of settings (eg, clinical trials, community centers, different countries) in patients who received modern, targeted treatments for mRCC [9]. In a validation study, the IMDC prognostic model most accurately predicted the number of deaths at 2 yr compared with other widely used models (including the MSKCC criteria) [9]. Therefore, to better define the subgroups in this analysis, patients were reclassified by risk according to the IMDC criteria.

The objectives of this analysis were to report updated OS outcomes from the final data cut-off of the CARMENA trial and to assess whether some subgroups may benefit from CN before starting medical treatment. As the inclusion of patients with minimal tumor burden may also have affected trial outcomes, the effect of tumor burden (number of metastatic sites) was explored.

2. Patients and Methods

2.1. Study design

The full details of the CARMENA trial design have been published previously [4]. In brief, this was a prospective, multicenter, open-label, randomized, phase III trial in which patients were randomized 1:1 to undergo CN followed by sunitinib treatment or to receive sunitinib alone [4]. Patients were stratified by risk group according to the MSKCC prognostic model [4].

2.2. Study oversight

The trial protocol was approved by the French National Agency for the Safety of Medicines and Health Products (Agence Nationale de Sécurité du Médicament et des Produits de Santé). The conduct of the trial conformed with the International Conference on Harmonization E6 guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. All the patients provided written informed consent before undergoing any trial procedures.

2.3. Updated analysis

The updated data cut-off for final analysis was October 20, 2018, after 358 OS events had occurred (this was an amendment from the original planned number of events of 476 due to early termination of the study from insufficient recruitment). In this analysis, patients were reclassified by IMDC risk classification [8,9], in order to better define the different subgroups.

As by definition of the study, all patients had at least one risk factor (time from diagnosis to treatment <1 yr); patients were considered to be intermediate risk if they had one or two risk factors and poor risk if they had three to six risk factors (Supplementary Table 1).

OS was assessed in the overall study population and in subgroups of interest, including patients in the IMDC intermediate-risk group (both as a whole and stratified by number of risk factors), patients with one or two or more metastatic sites (tumor burden), and patients who underwent delayed CN. OS was defined as the time between date of randomization and date of death, irrespective of cause of death. Censoring was based on the date of the most recent patient update.

2.4. Statistical analysis

Per the statistical analysis plan, prespecified analyses of OS were performed using four study populations: intention-to-treat (ITT) and several per-protocol populations (PP1, PP2, and PP3). The ITT population consisted of two treatment arms: a nephrectomy–sunitinib group and a sunitinib only group. The subgroup analyses of patients stratified by IMDC risk factor, number of metastatic sites, and patients who underwent delayed CN were performed post hoc.

The PP1 population included patients in the nephrectomy–sunitinib group who had undergone CN only, and patients in the sunitinib alone group who had received sunitinib. The PP2 population included patients in the nephrectomy–sunitinib group who had undergone CN and subsequently received sunitinib, and patients in the sunitinib alone group who had received sunitinib. The PP3 population consisted of eligible patients (excluding patients with deviations from inclusion or exclusion criteria, wrongly included, not evaluated, or lost to follow-up) treated in accordance with the protocol (given CN followed by sunitinib in the nephrectomy–sunitinib group and given sunitinib without any CN in the sunitinib alone group).

The rates and 95% CIs for the OS analyses were estimated in the ITT, PP1, and PP2 populations using the Kaplan-Meier method. Treatment arms were compared using a log-rank test. The post hoc analyses for efficacy were carried out on the ITT population; safety was not re-evaluated at this time.

Treatment with sunitinib alone was considered to be noninferior to CN followed by sunitinib treatment if the upper bound of the 95% CI of the HR for death was ≤ 1.20 .

3. Results

3.1. Patient population

At final analysis, the ITT population ($n = 450$) included 226 patients in the nephrectomy–sunitinib group and 224 in the sunitinib alone group (Supplementary Fig. 1). The PP1 population included 203 patients who underwent CN and 221 patients who received sunitinib alone. The PP2 population included 183 patients in the nephrectomy–sunitinib group and 210 patients who received sunitinib alone. The PP3 population included 183 patients in the nephrectomy–sunitinib group and 172 patients who received sunitinib alone. Baseline demographics and disease characteristics for the ITT population are shown in Table 1.

3.2. Overall survival

OS with sunitinib alone at final analysis remained noninferior to nephrectomy–sunitinib in the ITT population (HR, 0.97; 95% CI, 0.79–1.19; $p = 0.8$; Supplementary Fig. 2). Median follow-up of OS event-free patients ($n = 92$) was 36.6 mo (95% CI, 29.6–50.0). Results from the per-protocol population analyses showed similar HRs, although noninferiority was not met (PP1: HR, 0.99; 95% CI, 0.80–1.24; PP2: HR, 1.06; 95% CI, 0.85–1.33; PP3: HR, 1.28; 95% CI, 1.00–1.62). There was a longer median OS in the sunitinib alone group compared with the nephrectomy–sunitinib group in all patient populations except the PP3 population (ITT, 19.8 mo vs 15.6 mo; PP1, 20.5 mo vs 17.3 mo; PP2, 20.5 mo vs 18.3 mo; PP3, 17.5 mo vs 18.3 mo).

3.3. Post hoc analysis of overall survival in the ITT population stratified by IMDC risk group classification

The numbers of patients in the IMDC intermediate- and poor-risk groups were 127/226 (56%) and 99/226 (44%), respectively, in the nephrectomy–sunitinib group, and 139/224 (62%) and 85/224 (38%), respectively, in the sunitinib alone group. Therefore, more patients in both the nephrectomy–sunitinib and sunitinib alone groups were considered to be intermediate risk (with one or two risk factors).

In the IMDC intermediate-risk group, 126 patients had one risk factor (time to systemic therapy <1 yr) and 140 patients had two risk factors. Of patients with two risk factors, the most common were hemoglobin below the lower limit of normal ($n = 47$, 34%), corrected

calcium above the upper limit of normal ($n = 45$, 32%), and neutrophils above the upper limit of normal ($n = 36$, 26%), in addition to time to systemic therapy <1 yr ($n = 140$, 100%).

In the IMDC intermediate-risk group, OS was numerically longer for sunitinib alone (27.9 mo; 95% CI, 21.1–34.7) than for nephrectomy–sunitinib (19.0 mo; 95% CI, 16.0–25.3), though noninferiority was not reached (HR, 0.94; 95% CI, 0.70–1.24; Table 2).

An OS analysis stratified by number of risk factors was also performed for the IMDC intermediate-risk group. For patients with one IMDC risk factor, OS was longer with nephrectomy–sunitinib than with sunitinib alone, although not significantly (31.4 mo vs 25.2 mo, respectively; HR, 1.30; 95% CI, 0.85–1.98; $p = 0.2$). For patients with two or more IMDC risk factors, OS was significantly longer with sunitinib alone (31.2 mo vs 17.6 mo; HR, 0.65; 95% CI, 0.44–0.97; $p = 0.03$). Among patients treated with sunitinib alone, OS was numerically longer for patients with two or more risk factors compared with one risk-factor (31.2 mo vs 25.2 mo, respectively; HR, 0.88; 95% CI, 0.59–1.30; $p = 0.5$). For patients with two or more risk factors as compared with one risk factor, nephrectomy–sunitinib was associated with a significantly lower OS (17.6 mo vs 31.4 mo, respectively; HR, 1.69; 95% CI, 1.11–2.57; $p = 0.02$; Fig. 1; Table 2).

3.4. Post hoc analysis of overall survival in the ITT population depending on number of metastatic sites (one vs two or more)

In patients with only one metastatic site, OS was similar for nephrectomy–sunitinib and sunitinib alone (23.2 mo vs 22.7 mo, respectively; HR, 1.09; 95% CI, 0.75–1.59; $p = 0.7$). For patients with two or more metastatic sites, OS was longer for sunitinib though this difference was also not significant (16.7 mo vs 14.4 mo, respectively; HR, 0.87; 95% CI, 0.68–1.12; $p = 0.3$; Fig. 2; Table 3). Within the nephrectomy–sunitinib group, the HR for OS significantly favored the one metastatic site group as compared with two or more metastatic sites (23.2 mo vs 14.4 mo, respectively; HR, 1.42; 95% CI, 1.03–1.96; $p = 0.03$). Within the sunitinib-alone group, OS was numerically longer for the one metastatic site group as compared with two or more metastatic sites, though this difference was not significant (22.7 mo vs 16.7 mo, respectively; HR, 1.19; 95% CI, 0.86–1.64; $p = 0.3$).

IMDC intermediate-risk patients with only lung metastases have a longer survival with nephrectomy–sunitinib compared with sunitinib alone (median [95% CI] OS 44 mo [23.2–64.6] vs 31.5 mo [14.7–64.4]; HR, 1.24; 95% CI, 0.62–2.47, respectively).

3.5. Post hoc analysis of overall survival in patients with secondary nephrectomy

A total of 40 (18%) patients in the sunitinib alone group ($n = 224$) underwent secondary CN, of which seven (18%) patients required secondary CN for emergency treatment of the primary tumor. The remaining 33 (83%) patients required secondary CN for cytoreduction in metastatic sites. Of these 40 patients, 31% resumed sunitinib treatment following the secondary CN. Patients with secondary CN had a significantly longer OS (median 48.5 mo; 154 events) than those who had no subsequent CN (median 15.7 mo; HR, 0.34; 95% CI, 0.22–0.54; 25 events; Fig. 3).

4. Discussion

In the current analysis of a longer follow-up period, treatment with sunitinib alone was not inferior to CN followed by sunitinib treatment in terms of survival of patients with mRCC. A similar trend was observed in the PP1, PP2, and PP3 populations, though noninferiority was not met in these groups. This supports the previously published findings of the CARMENA trial, and indicates that CN alone should not be considered the SOC for patients with mRCC [4]. Reclassification of patients initially stratified by MSKCC risk (as in the original trial design) into IMDC risk groups (as in the current analysis) showed consistent OS findings.

Although the preliminary findings of the CARMENA trial suggested that certain intermediate-risk patients may still benefit from upfront CN, the optimal treatment for intermediate-risk patients remains controversial. To address this, we tried to analyze this subgroup of patients (representing 59% of the overall patients enrolled in the trial) better by focusing on the number of IMDC risk factors and number of metastatic sites, which have demonstrated value as independent prognostic factors [9,10].

Overall, patients classed as IMDC intermediate risk demonstrated a notably higher OS with sunitinib alone compared with CN followed by sunitinib. However, in patients with only one risk factor, we observed a longer OS in the nephrectomy–sunitinib group compared with the sunitinib alone group (HR, 1.30). Although this difference was not statistically significant, it suggests that this subgroup of patients might still benefit from CN. By contrast, patients with two risk factors showed a longer OS in the sunitinib alone group. The number of metastatic sites had a prognostic implication in both groups, but neither subgroup showed a trend for longer OS in the nephrectomy–sunitinib arm. Interestingly, in those patients with lung metastases only, there was a trend for longer OS in the nephrectomy–sunitinib arm (although this observation was limited by the low number of patients).

Overall, these observations confirm that immediate CN is not beneficial to poor- or intermediate-risk patients [11], although intermediate-risk patients with only one IMDC risk factor can benefit from this approach. However, this post hoc subgroup analysis was not statistically significant and was based on a relatively small number of patients, so this finding should be interpreted with caution. Although the number of metastatic sites alone was not sufficient as a prognostic factor to identify patients who would benefit from surgery, there is a trend suggesting that patients with lung metastases only could be the best candidates for immediate CN, as previously reported [2].

In the present analysis, patients who underwent delayed CN after initial systemic treatment showed a longer OS compared with patients who received sunitinib alone. This finding is supported by the outcomes of the SURTIME trial, where patients who received sunitinib therapy prior to CN showed a longer median OS compared with patients who underwent immediate CN (32.4 mo vs 15.0 mo; HR, 0.57; 95% CI, 0.34–0.95) [12]. Together, these findings suggest that deferring CN in patients with a response to medical treatment may be of clinical benefit [11], although the ideal timing for such a delayed surgery remains uncertain. As the present findings may have been subject to selection or immortal time bias (e.g., patients selected for delayed CN may represent those with more indolent biology), prospective studies should be conducted to further validate the potential benefit of delayed CN in these patients.

To optimize patient outcomes, it is important to define predictive markers that identify patients who would benefit from local control with CN versus those who will likely experience rapid disease progression and who would benefit from prompt systemic therapy. Recent updates to clinical guidelines following results from trials of immune checkpoint inhibitors in mRCC recommend nivolumab plus ipilimumab or pembrolizumab plus axitinib as first-line therapy for intermediate- or poor-risk patients with clear cell mRCC [13]. It remains unclear whether the current results can be used with these new first-line treatments. However, it seems acceptable to suggest that the more potent the medical treatment indicated, the less reason there is to start with surgery in patients who require medical treatment.

The original analysis of CARMENA was limited by use of the MSKCC criteria, which are less relevant than the IMDC criteria in the current era of targeted therapy [4]. This limitation was addressed in the current analysis through reclassifying patients per the IMDC criteria. However, as patients in the updated analysis were required to have a time from diagnosis to treatment of less than 1 yr, it is possible that the patient population may be skewed toward those with poorer prognosis. In addition, as the subgroup analyses were not prespecified, these findings should be interpreted with caution. Furthermore, having a lower than anticipated number of OS events (due to early termination of the study from insufficient recruitment) reduced the statistical power for detecting noninferiority in the OS analysis.

5. Conclusions

In summary, these further analyses from the CARMENA trial confirm that CN should not be considered as SOC in patients with synchronous mRCC who require systemic treatment. In addition, these findings will help to guide treatment decisions for certain patient subgroups (especially patients with only one IMDC risk factor) for whom upfront CN may still be beneficial.

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Study concept and design: Méjean, Ravaud, Colas, Escudier.

Acquisition of data: All authors.

Analysis and interpretation of data: Thezenas, Colas, Méjean, Escudier, Laguerre, Geoffrois, Thiery-Vuillemin, Albiges, Lebret.

Drafting of the manuscript: Méjean, Ravaud, Thezenas, Escudier, Colas.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Thezenas.

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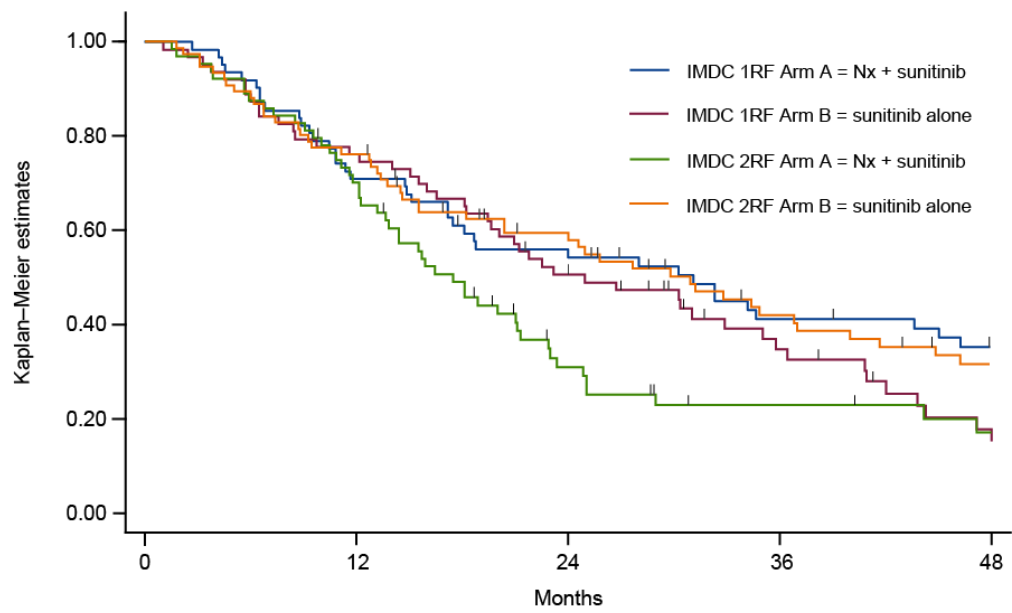
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Fig. 1 – Overall survival in patients with intermediate IMDC risk score (ITT population), stratified by one versus two risk factors. The x-axis was truncated at the final timepoint where all treatment groups had at least five patients at risk. IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intent to treat; Nx = nephrectomy; RF = risk factor.

Fig. 2 – Overall survival in patients (ITT population), stratified by one metastatic site versus two or more metastatic sites. The x-axis was truncated at the final timepoint where all treatment groups had at least five patients at risk. ITT = intention to treat; Nx = nephrectomy.

Fig. 3 – Overall survival in patients with secondary nephrectomy in arm B (ITT population). The x-axis was truncated at the final timepoint where all treatment groups had at least five patients at risk. ITT = intention to treat.

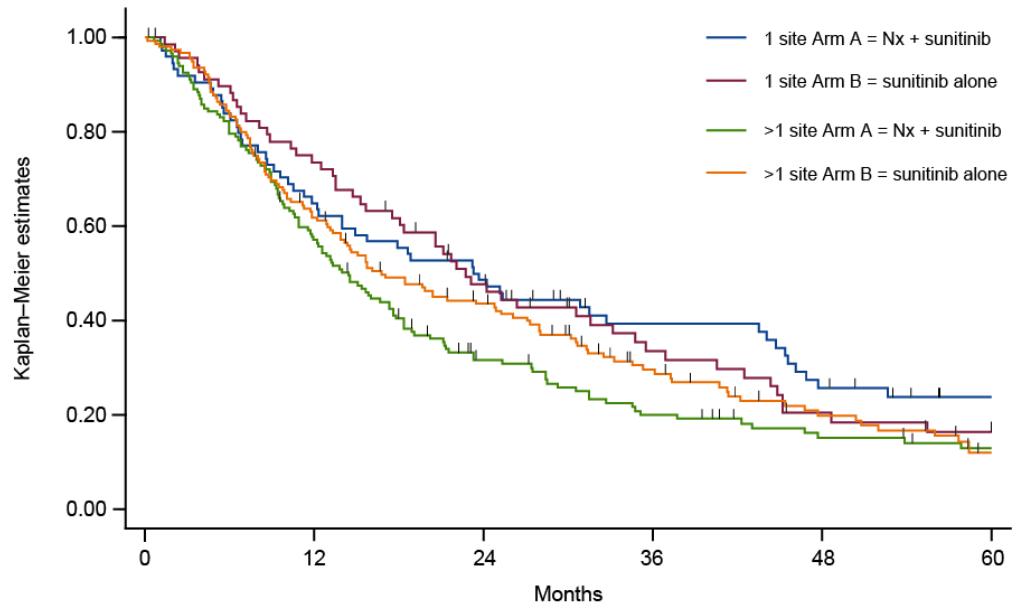
Fig. 1



Number at risk

IMDC 1RF Arm A = Nx + sunitinib	63	44	33	22	18
IMDC 1RF Arm B = sunitinib alone	63	48	31	17	7
IMDC 2RF Arm A = Nx + sunitinib	64	44	16	9	6
IMDC 2RF Arm B = sunitinib alone	76	57	39	25	17

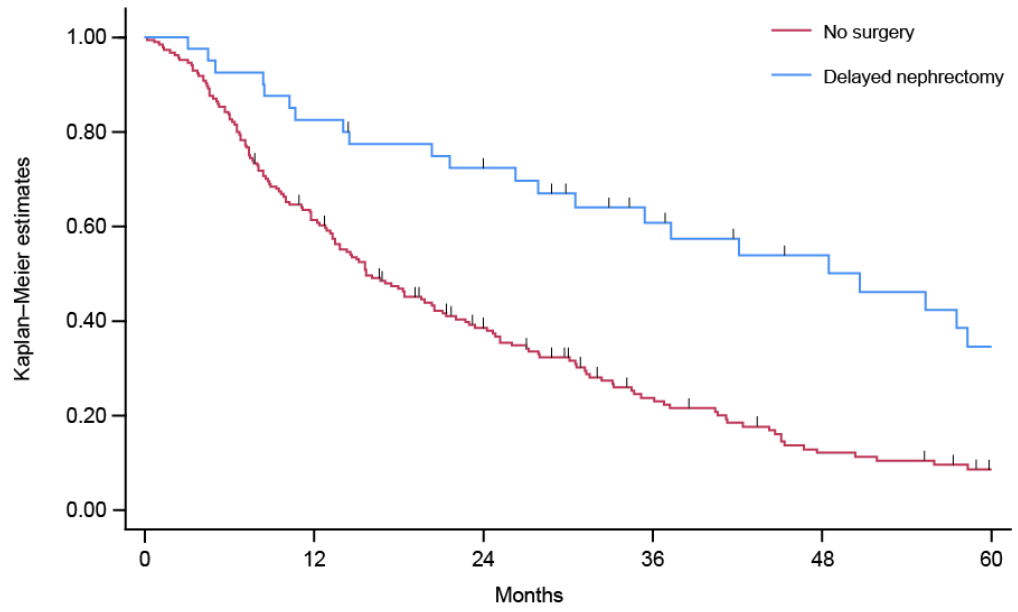
Fig. 2



Number at risk

1 site Arm A = Nx + sunitinib	75	48	35	23	15	8
1 site Arm B = sunitinib alone	68	50	29	18	10	7
>1 site Arm A = Nx + sunitinib	148	83	39	24	15	10
>1 site Arm B = sunitinib alone	155	94	61	33	19	9

Fig. 3



Number at risk

No surgery	184	111	63	32	15	7
Delayed nephrectomy	40	33	27	19	14	9

Table 1 – Patient demographics and disease characteristics (ITT population) [4]

Characteristic	Arm A: nephrectomy + sunitinib (<i>n</i> = 226)	Arm B: sunitinib alone (<i>n</i> = 224)
Median age (IQR), yr	63 (56–69)	62 (56–68)
Male sex, <i>n</i> (%)	169 (75)	167 (75)
MSKCC score, <i>n</i> (%)		
Intermediate	125 (56)	131 (59)
Poor	100 (44)	93 (42)
Missing	1 (0.4)	0 (0)
IMDC score, <i>n</i> (%)		
Intermediate	127 (56)	139 (62)
Poor	99 (44)	85 (38)
Missing	0 (0)	0 (0)
ECOG PS, <i>n</i> (%)		
0	130 (58)	122 (55)
1	96 (43)	102 (46)

ECOG PS = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic RCC Database Consortium; IQR = interquartile range; ITT = intent to treat; MSKCC = Memorial Sloan Kettering Cancer Center.

Table 2 – Overall survival in patients (ITT population) of IMDC intermediate risk, stratified by one versus two risk factors

	Median OS, mo (95% CI)			
	Arm A: nephrectomy + sunitinib (<i>n</i> = 127)	Arm B: sunitinib alone (<i>n</i> = 139)	HR (95% CI)	<i>p</i>
Overall	19.0 (16.0–25.3) 91 events	27.9 (21.1–34.7) 102 events	0.94 (0.70–1.24)	–
One IMDC risk factor	(<i>n</i> = 63) 31.4 (17.3–45.5) 41 events	(<i>n</i> = 63) 25.2 (19.6–35.4) 47 events	1.30 (0.85–1.98)	0.2
Two IMDC risk factors	(<i>n</i> = 64) 17.6 (13.7–21.5) 50 events	(<i>n</i> = 76) 31.2 (20.5–40.4) 55 events	0.65 (0.44–0.97)	0.03
HR (95% CI)	1.69 (1.11–2.57)	0.88 (0.59–1.30)		
<i>p</i>	0.02	0.5		

CI = confidence interval; HR = hazard ratio; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; ITT = intent to treat; OS = overall survival.

Table 3 – Overall survival in patients (ITT population) with one metastatic site versus two or more metastatic sites

	Median OS, mo (95% CI)			
	Arm A: nephrectomy + sunitinib (<i>n</i> = 226)	Arm B: sunitinib alone (<i>n</i> = 224)	HR (95% CI)	<i>p</i>
One site	(<i>n</i> = 75) 23.2 (13.9–43.4) 55 events	(<i>n</i> = 68) 22.7 (17.5–33.1) 54 events	1.09 (0.75–1.59)	0.7
Two or more sites	(<i>n</i> = 148) 14.4 (11.8–17.6) 122 events	(<i>n</i> = 155) 16.7 (13.8–24.8) 124 events	0.87 (0.68–1.12)	0.3
HR (95% CI)	1.42 (1.03–1.96)	1.19 (0.86–1.64)		
<i>p</i>	0.03	0.3		

CI = confidence interval; HR = hazard ratio; ITT = intent to treat; OS = overall survival.