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Comparison of Immediate vs Deferred Cytoreductive Nephrectomy in Patients With Synchronous Metastatic Renal Cell Carcinoma Receiving Sunitinib
The SURTIME Randomized Clinical Trial

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Invited Commentary page 171

Supplemental content

IMPORTANCE In clinical practice, patients with primary metastatic renal cell carcinoma (mRCC) have been offered cytoreductive nephrectomy (CN) followed by targeted therapy, but the optimal sequence of surgery and systemic therapy is unknown.

OBJECTIVE To examine whether a period of sunitinib therapy before CN improves outcome compared with immediate CN followed by sunitinib.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial began as a phase 3 trial on July 14, 2010, and continued until March 24, 2016, with a median follow-up of 3.3 years and a clinical cutoff date for this report of May 5, 2017. Patients with mRCC of clear cell subtype, resectable primary tumor, and 3 or fewer surgical risk factors were studied.

INTERVENTIONS Immediate CN followed by sunitinib therapy vs treatment with 3 cycles of sunitinib followed by CN in the absence of progression followed by sunitinib therapy.

MAIN OUTCOMES AND MEASURES Progression-free survival was the primary end point, which needed a sample size of 458 patients. Because of poor accrual, the independent data monitoring committee endorsed reporting the intention-to-treat 28-week progression-free rate (PFR) instead. Overall survival (OS), adverse events, and postoperative progression were secondary end points.

RESULTS The study closed after 5.7 years with 99 patients (80 men and 19 women; mean [SD] age, 60 [8.5] years). The 28-week PFR was 42% in the immediate CN arm (n = 50) and 43% in the deferred CN arm (n = 49) (P = .61). The intention-to-treat OS hazard ratio of deferred vs immediate CN was 0.57 (95% CI, 0.34-0.95; P = .03), with a median OS of 32.4 months (95% CI, 14.5-65.3 months) in the deferred CN arm and 15.0 months (95% CI, 9.3-29.5 months) in the immediate CN arm. In the deferred CN arm, 48 of 49 patients (98%; 95% CI, 89%-100%) received sunitinib vs 40 of 50 (80%; 95% CI, 67%-89%) in the immediate arm. Systemic progression before planned CN in the deferred CN arm resulted in a per-protocol recommendation against nephrectomy in 14 patients (29%; 95% CI, 18%-43%).

CONCLUSIONS AND RELEVANCE Deferred CN did not improve the 28-week PFR. With the deferred approach, more patients received sunitinib and OS results were higher. Pretreatment with sunitinib may identify patients with inherent resistance to systemic therapy before planned CN. This evidence complements recent data from randomized clinical trials to inform treatment decisions in patients with primary clear cell mRCC requiring sunitinib.

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In the cytokine era, 2 randomized clinical trials[1,2] have shown a modest but statistically significant survival benefit of cytoreductive nephrectomy (CN) followed by interferon alfa vs interferon alfa alone in patients with primary metastatic renal cancer (mRCC). A combined analysis[3] of both studies demonstrated a significant median overall survival (OS) improvement of 5.8 months with CN and interferon compared with interferon alone. Since 2006, more effective vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) have been the standard of care for the treatment of mRCC.[4] Guidelines recommend CN in patients with good performance, absence of poor risk features, and solitary or oligometastatic disease,[5-7] but the role of CN for patients who require medical treatment in the targeted therapy era is unknown. Although multiple retrospective studies have reported a survival benefit with CN in combination with VEGFR-TKIs,[7] results were biased, and surgery-related morbidity may prevent delivering postoperative systemic therapy.[8,9] The Clinical Trial to Assess the Importance of Nephrectomy (CARMENA), a trial designed to answer the question of whether CN is still required in the era of targeted therapy in patients with primary mRCC, aimed to demonstrate noninferior survival with sunitinib alone compared with CN followed by sunitinib.[10] Parallel to CARMENA, the European Organisation for Research and Treatment of Cancer (EORTC) GenitoUrinary Cancer Group, the National Cancer Research Institute Renal Clinical Studies Group/Wales Cancer Trial Unit (United Kingdom), and the Canadian Uro-Oncology Group jointly conducted the Immediate Surgery or Surgery After Sunitinib Malate in Treating Patients With Metastatic Kidney Cancer (SURTIME) trial, a randomized clinical trial of immediate vs deferred CN in patients with synchronous mRCC treated with sunitinib. The objective of SURTIME was to investigate whether pretreatment before planned surgery improves outcome by identifying patients with inherent resistance to VEGFR-TKIs who are unlikely to benefit from CN. Prior single-arm phase 2 studies[11,12] of deferred CN after presurgical sunitinib demonstrated that the approach is safe and avoids CN in individuals with early resistance to VEGFR-TKIs while exposing patients with aggressive disease to immediate systemic therapy. In addition, a deferred approach may reduce cancer-related morbidity, primary tumor size, and neovascularization, which in turn may decrease surgical risk and morbidity.[13,14]

Key Points

Question Does a period of sunitinib therapy before cytoreductive nephrectomy improve outcomes in patients with renal cancer compared with immediate cytoreductive nephrectomy followed by sunitinib therapy?

Findings In this randomized clinical trial of 99 patients, the progression-free rate at 28 weeks did not improve when patients began sunitinib therapy before planned cytoreductive nephrectomy; however, more patients received systemic therapy, and cytoreductive nephrectomy could be avoided in those with progressive disease.

Meaning Pretreatment with sunitinib may identify patients with inherent resistance to systemic therapy before planned cytoreductive nephrectomy without inferior outcome.

Methods

Eligibility Criteria

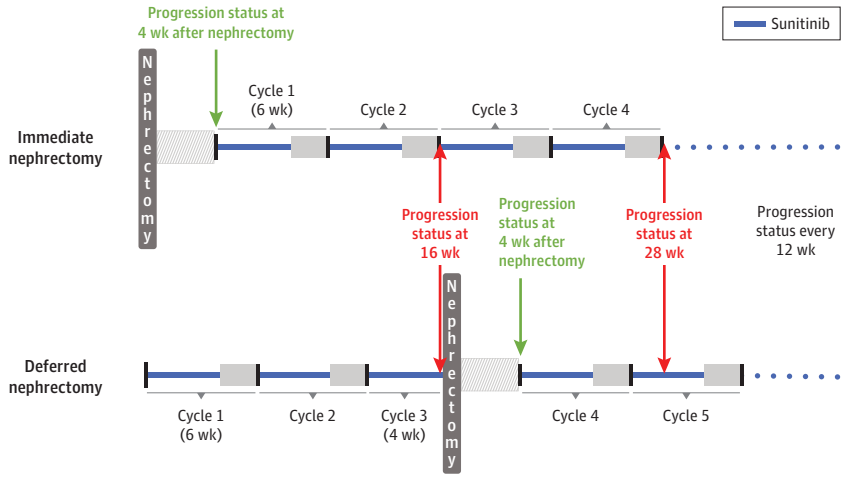
Eligible patients were 18 years or older and had histologically confirmed, previously untreated clear cell mRCC with a resectable asymptomatic primary tumor in situ and required therapy with sunitinib. Additional requirements included a World Health Organization (WHO) performance status of 0 or 1; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; no clinical signs of central nervous system involvement; a life expectancy greater than 3 months; adequate bone marrow, liver, cardiac, and renal function; and 3 or fewer surgical risk factors, including serum albumin *Common Terminology Criteria for Adverse Events,* version 4.0 grade 2 or higher, serum lactate dehydrogenase greater than 1.5 times the upper limit of normal, liver metastases, symptoms caused by metastases, retroperitoneal or supradiaphragmatic lymph node involvement, and stage cT3 to T4 disease.[15] Prior radiotherapy for bone lesions was allowed. Memorial Sloan Kettering Cancer Center (MSKCC) risk was assessed but not used for eligibility.[5] All patients signed written informed consent forms, and all data were deidentified. The study was approved by the institutional review board at each center (The Netherlands Cancer Institute, Radboud University Hospital, Princess Margaret Hospital, Cardiff Hospital, Institut Jules Bordet, Academic Medical Center, Queen Elizabeth II Health Sciences Center, Saint Antonius Hospital, Maastricht University Medical Center, University of Montreal Hospital Center, The Royal Free Hospital and Queen Mary University, University of Groningen, Gent University Hospital, and Cliniques Universitaires Saint-Luc) and complied with the Declaration of Helsinki,[16] Good Clinical Practice guidelines, and local laws and regulations. The trial protocol can be found in Supplement 1.

Study Design and Treatment

This open-label, multicenter randomized clinical trial was initially designed as phase 3. From July 14, 2010, to March 24, 2016, patients were included in the trial and were centrally randomized 1:1 at the EORTC between immediate CN followed by sunitinib therapy vs treatment with 3 cycles of sunitinib followed by CN and sunitinib by minimization (variance method),[17] with the following factors noted: institution, performance status (0 vs 1), and number of metastatic sites (1 vs ≥2). There was no masking in the study. Baseline computed tomography (CT) of the chest and abdomen was required within 4 weeks before randomization. Sunitinib was administered at 50 mg/d for 4 weeks followed by 2 weeks of rest. Dose reductions and modifications were allowed according to standard practice.[8]

In the deferred CN arm, sunitinib therapy was stopped the day before nephrectomy. In both arms, radiologic assessment was performed with CT (chest and abdomen) 16 weeks after the start of treatment, which was before planned CN in

Figure 1. Trial Design



Patients were randomized 1:1 to immediate or deferred nephrectomy. Blue bars indicate sunitinib therapy. Green arrows point to the progression status 4 weeks after nephrectomy.

the deferred arm. In case of systemic progressive disease (PD) in the deferred arm, nephrectomy was not recommended but left at the discretion of each investigator. In both arms, sunitinib was administered 4 weeks after surgery and given until progression of disease or toxic effects. To study risk of disease progression after sunitinib therapy interruption, a post-surgery CT (chest and abdomen) was performed at the end of the 4-week rest period in both arms; the scan was compared with the CT scan at week 16 in the deferred CN arm and the baseline CT scan in the immediate CN arm. This CT scan was not used to change treatment. From week 28, patients in both arms were followed up with CT every 12 weeks until progression. The study design is shown in **Figure 1**.

Outcomes

The primary end point was progression (by RECIST, version 1.1) assessed by a local investigator without central review. Progression-free survival (PFS) is the interval from randomization to first progression (local or distant) or death from any cause. To adjust for different timing of evaluations between the arms, all cases of disease progression that occurred in the interval from day 1 of treatment to the end of week 16 (±15 days) and those that occurred during the interval from day 1 of week 16 (±15 days) to the end of week 28 (±15 days) were counted as occurring at the end of the interval. Overall survival was counted from randomization to death from any cause. Patients without an event were censored at the last follow-up. Additional secondary end points included recording of all adverse events and surgical morbidity assessed by *Common Terminology Criteria for Adverse Events*, version 4.0; rate of RECIST, version 1.1 complete and partial response (PR) to sunitinib and rate of unresectable tumors in the deferred arm; the effect of nephrectomy on early progression (defined as PD within 4 weeks of surgery) in both arms; and comparison of the surgical intervention (approach and extent) between arms. The 28-week progression-free rate (PFR) was calculated as the binomial proportion of cases of disease progression documented before or at week 28 (eTable 1 in Supplement 2).

Statistical Analysis

The trial originally aimed to test for a hazard ratio (HR) of 0.75 on PFS with a 2-sided, 5%-level log-rank test with 80% power (380 events, 458 patients). An independent data monitoring committee oversaw the trial safety and progress.

After 3 years of recruitment, accrual indicated that the study would not reach its planned objective. On the basis of masked recruitment data and using results reported for the intermediate MSKCC risk group in the pivotal trial that suggested a 70% 28-week PFR among patients with nephrectomy,[8] the study was downsized to 98 patients. The revised objective was to show a 20% increase of the 28-week PFR in the deferred CN arm with a 1-sided, 5%-level Fisher exact test and 80% power in the intention-to-treat (ITT) population (all randomized patients). The modification was endorsed by the study independent data monitoring committee. The secondary end points of PFS and OS were estimated by Kaplan-Meier analysis and compared in the ITT population using a Cox proportional hazards regression model stratified by WHO performance status.[18] For all outcomes, 95% CIs are reported except for the 28-week PFR, for which a 2-sided 90% CI is reported, reflecting the 1-sided 5% significance level. Sensitivity analyses were conducted in the per-protocol population, excluding patients ineligible or not receiving the allocated treatment and, for the 28-week PFR end point only, patients not assessed at week 28 (eTable 1 in Supplement 2).

Results

The study closed after 5.7 years. A total of 99 patients (80 men and 19 women; mean [SD] age, 60 [8.5] years) were randomized by 19 institutions in the Netherlands, Belgium, the United Kingdom, and Canada: 50 in the immediate CN arm and 49 in the deferred CN arm (**Figure 2**). The clinical cutoff date for this trial was May 5, 2017. The median follow-up was 3.3 years (range, 0-6.2 years). Eighteen patients (18%) were clinically ineligible: 10 in the immediate CN arm and 8 in the deferred CN

arm (Figure 2). A total of 87 patients (88%) presented with MSKCC intermediate risk.[5] Baseline characteristics (eTable 2 in Supplement 2) were balanced between the immediate and deferred CN arms except for 3 surgical risk factors (12 [24%] vs 7 [14%]), cT3 to T4 tumors (26 [52%] vs 18 [37%]), and 2 or more metastatic sites (43 [86%] vs 46 [94%]).

Treatment and Safety

In the deferred arm, 48 of 49 patients (98%; 95% CI, 89%-100%) received presurgical sunitinib. One patient appeared to be ineligible for sunitinib and was not treated. Forty patients (83%) received 3 cycles of presurgical sunitinib; 8 patients did not complete the 3 cycles because of PD (n = 6) and/or sunitinib-related toxic effects (n = 4). Relative dose intensity and dose modifications are detailed in eTable 3 in Supplement 2 Of the 48 patients, 11 (23%; 95% CI, 12%-37%) had a PR and 14 (29%; 95%, CI 18%-43%) had PD before planned nephrectomy (eTable 3 in Supplement 2). The median reduction in primary tumor diameter during presurgical sunitinib compared with baseline was 13.8% (range, 95.5% reduction to 20.0% increase), with a decrease in 34 patients (71%). Of the 48 patients in the deferred CN arm, 34 patients had CN per protocol and 14 had a recommendation against CN because of progression at metastatic sites. Of those patients, 6 underwent surgery off protocol despite disease progression while taking sunitinib (40 CN cases in the ITT population). No patients were unable to undergo surgery as a result of primary tumor progression.

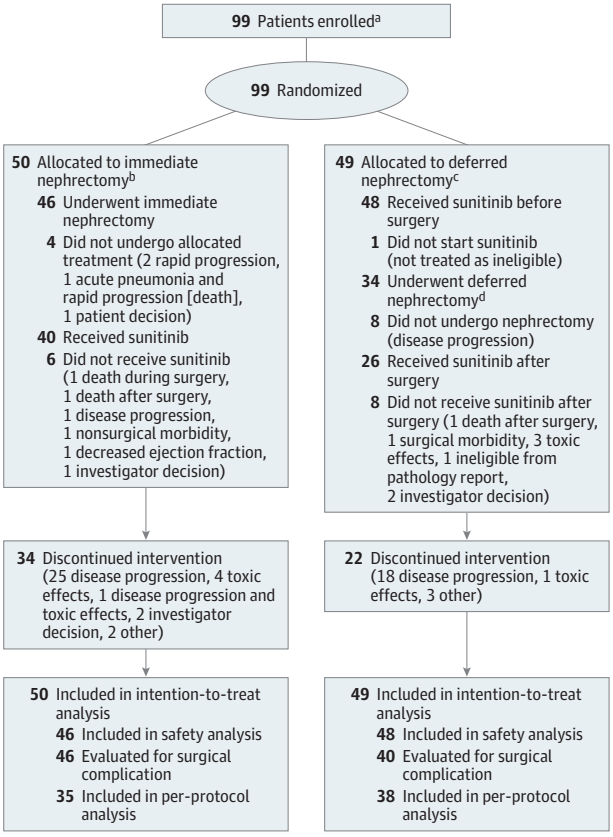
In the immediate CN arm, 46 of 50 patients (92%; 95% CI, 81%-97%) underwent nephrectomy, 2 had rapid PD, 1 refused surgery, and 1 developed acute pneumonia that prevented surgery, with subsequent PD and death (Figure 2). Forty of 50 patients (80%; 95% CI, 67%-89%) received sunitinib.

Surgical complications occurred in 24 of 46 patients (52%; 95% CI, 37%-67%) in the immediate arm and in 18 of 34 patients (53%; 95% CI, 35%-70%) in the deferred arm (eTable 4 in Supplement 2). One patient died during immediate CN of cardiac arrest caused by a caval vein tumor thrombus. Two other patients died 3 and 6 days after CN of myocardial infarction and pulmonary embolism (at autopsy) possibly related to surgery. At the 4-week postsurgery restaging, 9 of 46 patients (20%; 95% CI, 9%-33%) had confirmed PD in the immediate CN arm compared with 8 of 34 patients (24%; 95% CI, 11%-41%) in the deferred CN arm.

Postoperative sunitinib was given for the first time to 40 of the 46 patients in the immediate CN arm and continued in 26 of the 34 patients without PD before CN in the deferred arm. In addition to the 2 deaths described above, the reasons to not initiate sunitinib therapy after immediate CN were poor performance status attributable to rapid PD (n = 1), non-surgery-related morbidity (n = 1), decreased ejection fraction (n = 1), and investigator decision (n = 1). In the deferred arm, the reasons were postoperative death (n = 1), toxic effects caused by presurgical sunitinib (n = 3), surgical morbidity (n = 1), investigator decision (n = 2), and type 1 papillary renal cell carcinoma after CN (n = 1).

At the time of data analysis, postoperative sunitinib treatment was ongoing in 6 of 40 patients in the immediate CN arm and 4 of 26 patients in the deferred CN arm. Most patients stopped treatment because of PD (Figure 2).

Figure 2. CONSORT Flow Diagram



[a] The numbers of individuals screened for eligibility and the reasons for exclusion were not captured at all sites.

[b] Included 10 ineligible patients: no measurable lesion (n = 5), abnormal cardiac function (n = 3), symptomatic severe aortic valve stenosis (n = 1), and pneumonia (n = 1).

[c] Included 8 ineligible patients: no measurable lesion (n = 1), hypertension (n = 4), abnormal laboratory values (n = 2), and lung cancer (n = 1).

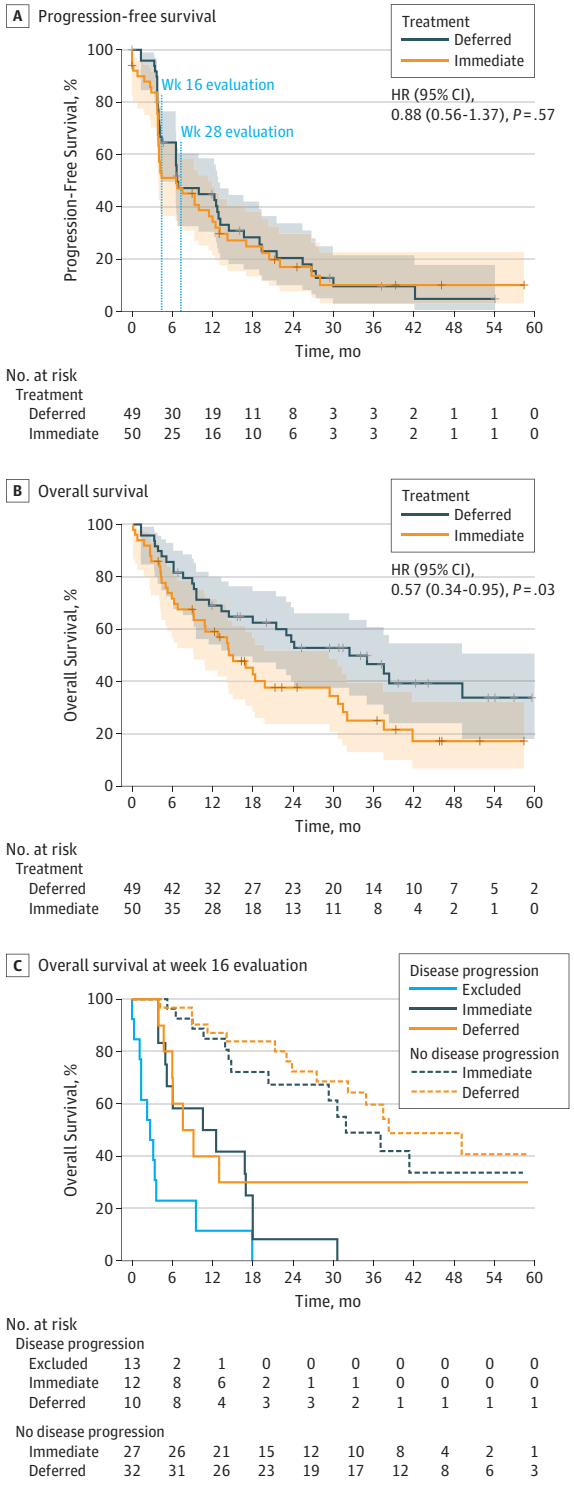
[d] Six patients underwent nephrectomy off protocol.

The rates of grade 3 or higher adverse events reported during the study were similar in the 2 arms: 52% in the immediate CN arm vs 58% in the deferred CN arm (eTable 5 in Supplement 2). The most common grade 1 or higher adverse events in both arms were fatigue, oral mucositis, nausea, diarrhea, dysgeusia, and constipation.

PFR, PFS, and OS

In the ITT population, the 28-week PFR was 42% (90% CI, 30%-55%) in the immediate CN arm and 43% (90% CI, 31%-56%) in the deferred CN arm (1-sided Fisher test, $P = .61$) (eTable 6 in Supplement 2). At the time of analysis, 35 of 50 patients in the immediate CN arm and 28 of 49 patients in the deferred CN arm died. The leading cause of death was PD in 30 patients (86%) in the immediate CN arm and 25 (89%) in the deferred CN arm. Forty-one patients in each arm had an event for the end point PFS. The PFS HR for deferred vs immediate CN was 0.88 (95% CI, 0.56-1.37; $P = .57$) (**Figure 3**A). For OS, the HR

Figure 3. Long-term Outcomes in All Randomized Patients in the Intention-to-Treat Population



HR indicates hazard ratio.

was 0.57 (95% CI, 0.34-0.95; P = .03) (Figure 3B), with a median OS of 32.4 months (95% CI, 14.5-65.3 months) in the deferred CN arm and 15.0 months (95% CI, 9.3-29.5 months) in the immediate CN arm. In the per-protocol population, OS was greater in the deferred CN group (HR, 0.71; 95% CI, 0.40-1.24), but the difference was no longer statistically significant (P = .23) (eFigure in Supplement 2). The exploratory landmark analysis at week 16 of OS according to treatment arm and progression status suggests that patients whose disease progressed in the deferred arm before planned surgery or within 16 weeks after immediate CN have similar poor survival prognosis (Figure 3C).

Discussion

In this randomized clinical trial, deferred CN in patients with primary clear cell mRCC did not improve the PFR at 28 weeks. Consistent with this finding, there was no improvement in median PFS. However, although not statistically significant, OS results were higher with the deferred CN approach. In addition, the surgical complication rate was similar in patients who underwent CN after 3 months of pretreatment with sunitinib compared with those who underwent immediate surgery. With the exception of 1 patient ineligible for treatment with sunitinib, all ITT patients in the deferred arm received systemic therapy compared with 40 of 46 patients (87%) who had an immediate CN. This finding suggests that delaying systemic therapy by performing CN first may be a risk for some patients. Recently, CARMENA, which investigated CN followed by sunitinib vs sunitinib alone, demonstrated noninferiority for systemic therapy alone in patients with MSKCC intermediate and poor risk and 2 or more metastatic sites.[10]

The results of SURTIME support data from CARMENA that showed that immediate CN does not result in additional benefit and may even be detrimental in patients with primary clear cell mRCC who require sunitinib. The findings in SURTIME suggest that a deferred approach to CN in which patients start treatment with sunitinib and are offered nephrectomy only if their disease does not progress might be superior to performing CN up front followed by sunitinib therapy. Although these results are only exploratory, deferred CN was not formally investigated in CARMENA, and it would be premature to reject this approach based on noninferiority of sunitinib alone. Of note, there is an element of deferred CN in the sunitinib-alone arm of CARMENA. Thirty-eight patients (17%) underwent secondary CN for acute symptoms or near-complete response. The median time from randomization to CN was 11.1 months, suggesting that the secondary nephrectomy rate was even higher (25%-30%) among patients who survived long enough; thus, there may be a role for CN after sunitinib therapy in selected patients. The median OS observed in SURTIME in the deferred arm (32.4 months; 95% CI, 14.5-65.3 months) is comparable to survival data of previous single-arm phase 2 studies of presurgical sunitinib (26.0 months; 95% CI, 13.6 months to not available) and pazopanib (22.7 months; 95% CI, 14.3 months to not estimable).[12,19] These data suggest that performing deferred CN in patients with nonprogressing disease may confer a survival benefit instead of limiting CN to only the few patients who need surgery after treatment with sunitinib alone.

Of note, a recent study[20] of clinically distinct metastatic phenotypes in clear cell mRCC provided a scientific rationale for CN in individuals in whom the evolutionary diversity of their primary tumors accounted for increased metastatic capacity. In addition, patients in SURTIME were of predominantly MSKCC intermediate risk and selected along surgical risk factors to identify the most suitable surgical candidates. By comparison, CARMENA had broad inclusion criteria, which allowed enrollment of 43% MSKCC poor-risk patients who had a short OS in the CN arm (median OS, 10.2 months; 95% CI, 9.0-14.0 months).[10] This finding confirms the results from large retrospective data sets that surgery is not beneficial in these patients[21] and affects the generalizability of the CARMENA results. Therefore, despite our results being exploratory, we believe that unless proven otherwise, deferred CN remains a valid treatment option for MSKCC intermediate-risk patients.

In an era of personalized therapy, the results of SURTIME also suggest a concept of patient selection based on early response to therapy. The exploratory landmark analysis (Figure 3C) suggests that progression before planned CN can be used to identify patients with inherent resistance to VEGFR-targeted therapy. In the deferred arm, 25% of the patients had documented RECIST progression at metastatic sites before planned surgery (eTable 3 in Supplement 2). This finding confirms data from the single-arm phase 2 studies of presurgical VEGFR-TKI therapy in which PD in patients treated with sunitinib or pazopanib before planned CN was associated with short survival.[12,19] From a clinical perspective, identification of patients with inherent resistance is meaningful because they are poor candidates for subsequent CN. Validated molecular markers or predictive risk models are not available, and progression during systemic therapy has been suggested as a marker to identify patients unlikely to benefit from surgery.

Contrary to previous retrospective studies,[22-26] SURTIME suggests that surgery after sunitinib is safe. The perioperative grade 3 or higher complication rate reported in SURTIME (eTable 4 in Supplement 2) is similar to the 22% to 26% rates in nonrandomized studies of presurgical sunitinib or pazopanib.[12,19,27] Of note, postoperative wound healing complications were low in SURTIME, in which treatment was interrupted 24 hours before surgery. Cytoreductive nephrectomy remains an intervention with a higher morbidity and mortality rate than nephrectomy in the curative setting. The surgical mortality rate after CN in SURTIME is comparable to reports in the literature (1.8%-3.6%), depending on the series and age at surgery.[28-30]

Limitations

This study has several limitations. Accrual was affected by several factors, including local regulatory decisions that prevented 2 European countries from participating, complexity of timing of surgery and systemic treatment, and the use of surgical risk factors for eligibility rather than WHO performance status. Although modifications were enforced, including a revised end point, the loss of sites had a profound effect on the accrual. In addition, 18% of patients were ineligible, although reasons were unrelated to performance, surgical risk factors, or oncologic eligibility criteria. With hindsight, PFS and PFR end points required complex timing, and OS as the primary end point would have been preferable. Finally, the superiority of nivolumab and ipilimumab over sunitinib in terms of survival and quality of life changes first-line treatment for patients with intermediate- and poor-risk mRCC and limits the applicability of the results of both CARMENA and this trial. Despite these limitations, our results may be meaningful, in conjunction with the results of CARMENA, for treatment decisions in patients with primary clear cell mRCC who require sunitinib.

Conclusions

Deferred CN did not improve the 28-week PFR. With the deferred approach, more patients received sunitinib and OS was higher (although this finding was not statistically significant). Pretreatment with sunitinib may identify patients with inherent resistance to systemic therapy before planned CN.

ARTICLE INFORMATION

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Correction: This article was corrected on February 14, 2019, to change the affiliation for Dr del Pilar Laguna.

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Author Contributions: Dr Bex had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bex, Mulders, Wagstaff, Powles, Tombal, Marreaud, S. Collette, Haanen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bex, Mulders, Wagstaff, S. Collette, L. Collette.
Critical revision of the manuscript for important intellectual content: Bex, Mulders, Jewett, Wagstaff, van Thienen, Blank, van Velthoven, del Pilar Laguna, Wood, van Melick, Aarts, Lattouf, Powles, de Jong, Rottey, Tombal, Marreaud, L. Collette, Haanen.
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Obtained funding: Bex, Jewett.
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Conflict of Interest Disclosures: Dr Bex reported receiving grants from Pfizer during the conduct of the study; receiving personal fees from Pfizer, Eisai Co., Ipsen, EUSA, and Bristol-Myers Squibb; and serving as a member of the steering committee of the IMMotion 010 adjuvant trial in renal cell carcinoma from Roche outside the submitted work. Dr de Jong reported receiving grants from Astellas Pharma and personal fees from Bayer Pharma outside the submitted work. Dr Jewett reported receiving honoraria from Pfizer, Ipsen, Olympus, and Theralase Therapeutics. Dr van Thienen reported receiving personal fees from Roche and fees to his institution for training (European Society for Medical Oncology 2017) from Novartis outside the submitted work. Dr Blank reported receiving personal fees for advisory roles for BMS, MSD, Roche, GlaxoSmithKline, Eli Lilly and Company, Novartis, and Pfizer and grants from Novartis and BMS outside the submitted work. Dr Lattouf reported receiving honoraria from Janssen and Bayer for participation in advisory boards outside the submitted work. Dr Powles reported receiving grants from AstraZeneca and Roche and personal fees from AstraZeneca, Roche, Pfizer, Novartis, Merck & Co, and BMS outside the submitted work. Dr Wood reported receiving research funding to her institution from Pfizer and clinical trial funding to her institution from Novartis, Merck & Co, Roche, AstraZeneca, and BMS outside the submitted work. No other disclosures were reported.

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Data Sharing Statement See Supplement 3.

REFERENCES

1. 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(23):1655-1659. doi:10.1056/NEJMoa003013

2. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa–based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet*. 2001;358 (9286):966-970. doi:10.1016/S0140-6736(01) 06103-7

3. 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(3): 1071-1076. doi:10.1097/01.ju.0000110610.61545.ae

4. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*. 2015;67(5):913-924. doi:10.1016/j.eururo.2015.01.005

5. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol*. 1999;17(8):2530-2540. doi:10.1200/JCO.1999.17.8.2530

6. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27(34):5794-5799. doi:10.1200/JCO.2008.21.4809

7. Bex A, Ljungberg B, van Poppel H, Powles T; European Association of Urology. The role of cytoreductive nephrectomy: European Association of Urology recommendations in 2016. *Eur Urol*. 2016;70(6):901-905. doi:10.1016/j.eururo.2016.07.005

8. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356(2):115-124. doi:10.1056/NEJMoa065044

9. Kutikov A, Uzzo RG, Caraway A, et al. Use of systemic therapy and factors affecting survival for patients undergoing cytoreductive nephrectomy. *BJU Int*. 2010;106(2):218-223. doi:10.1111/j.1464-410X.2009.09079.x

10. Méjean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med*. 2018;379(5):417-427. doi:10.1056/NEJMoa1803675

11. Powles T, Kayani I, Blank C, et al. The safety and efficacy of sunitinib before planned nephrectomy in metastatic clear cell renal cancer. *Ann Oncol*. 2011; 22(5):1041-1047. doi:10.1093/annonc/mdq564

12. Powles T, Blank C, Chowdhury S, et al. The outcome of patients treated with sunitinib prior to planned nephrectomy in metastatic clear cell renal cancer. *Eur Urol*. 2011;60(3):448-454. doi:10.1016/j.eururo.2011.05.028

13. Patard JJ, Thuret R, Raffi A, Laguerre B, Bensalah K, Culine S. Treatment with sunitinib enabled complete resection of massive lymphadenopathy not previously amenable to excision in a patient with renal cell carcinoma. *Eur Urol*. 2009;55(1):237-239. doi:10.1016/j.eururo.2008.09.006

14. Shuch B, Riggs SB, LaRochelle JC, et al. Neoadjuvant targeted therapy and advanced kidney cancer: observations and implications for a new treatment paradigm. *BJU Int*. 2008;102(6): 692-696. doi:10.1111/j.1464-410X.2008.07660.x

15. Culp SH, Tannir NM, Abel EJ, et al. Can we better select patients with metastatic renal cell carcinoma for cytoreductive nephrectomy? *Cancer*. 2010;116(14):3378-3388. doi:10.1002/cncr.25046

16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

17. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975;31(1): 103-115. doi:10.2307/2529712

18. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. 2nd ed. New York, NY: John Wiley; 2002. doi:10.1002/9781118032985

19. Powles T, Sarwar N, Stockdale A, et al. Safety and efficacy of pazopanib therapy prior to planned nephrectomy in metastatic clear cell renal cancer. *JAMA Oncol*. 2016;2(10):1303-1309. doi:10.1001/jamaoncol.2016.1197

20. Turajlic S, Xu H, Litchfield K, et al; PEACE; TRACERx Renal Consortium. Tracking cancer evolution reveals constrained routes to metastases: TRACERx Renal. *Cell*. 2018;173(3):581-594.e12. doi:10.1016/j.cell.2018.03.057

21. 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(4):704-710. doi:10.1016/j.eururo.2014.05.034

22. Harshman LC, Yu RJ, Allen GI, Srinivas S, Gill HS, Chung BI. Surgical outcomes and complications associated with presurgical tyrosine kinase inhibition for advanced renal cell carcinoma (RCC). *Urol Oncol*. 2013;31(3):379-385. doi:10.1016/j.urolonc.2011.01.005

23. Margulis V, Matin SF, Tannir N, et al. Surgical morbidity associated with administration of targeted molecular therapies before cytoreductive nephrectomy or resection of locally recurrent renal cell carcinoma. *J Urol*. 2008;180(1):94-98. doi:10.1016/j.juro.2008.03.047

24. Thomas AA, Rini BI, Stephenson AJ, et al. Surgical resection of renal cell carcinoma after targeted therapy. *J Urol*. 2009;182(3):881-886. doi:10.1016/j.juro.2009.05.014

25. Shaw GL, Hussain M, Nair R, et al. Performing cytoreductive nephrectomy following targeted sunitinib therapy for metastatic renal cell carcinoma: a surgical perspective. *Urol Int*. 2012;89 (1):83-88. doi:10.1159/000338057

26. Patel N, Woo J, Liss MA, et al. Does timing of targeted therapy for metastatic renal cell carcinoma impact treatment toxicity and surgical complications? a comparison of primary and adjuvant approaches. *Can J Urol*. 2016;23(2):8227-8233.

27. Hanna N, Sun M, Meyer CP, et al. Survival analyses of patients with metastatic renal cancer treated with targeted therapy with or without cytoreductive nephrectomy: a national cancer data base study. *J Clin Oncol*. 2016;34(27):3267-3275. doi:10.1200/JCO.2016.66.7931

28. Cloutier V, Capitanio U, Zini L, et al. Thirty-day mortality after nephrectomy: clinical implications for informed consent. *Eur Urol*. 2009;56(6):998-1003. doi:10.1016/j.eururo.2008.11.023

29. Jackson BL, Fowler S, Williams ST; British Association of Urological Surgeons (BAUS)–Section of Oncology. Perioperative outcomes of cytoreductive nephrectomy in the UK in 2012. *BJU Int*. 2015;116(6):905-910. doi:10.1111/bju.12890

30. Wallis CJ, Bjarnason G, Byrne J, et al. Morbidity and mortality of radical nephrectomy for patients with disseminated cancer: an analysis of the National Surgical Quality Improvement Program database. *Urology*. 2016;95:95-102. doi:10.1016/j.urology.2016.04.055