Surgical safety of cytoreductive nephrectomy following sunitinib: Results from the multi-centre, randomized controlled trial of immediate versus deferred nephrectomy (SURTIME).

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Abstract

The EORTC SURTIME trial explored timing of sunitnib, a tyrosine kinase inhibitor (TKI) and cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma (mRCC). Previous retrospective studies suggest increased surgery related adverse events (AEs) after presurgical TKI. We report surgical safety from a randomized comparison of CN before or after sunitinib. In-hospital mortality, 30-day readmission rate and intra- and 30-day postoperative AEs according to CTCAE version 4 and Clavien-Dindo (CD) were analyzed. Patients were randomized 1:1 to immediate CN followed by sunitinib versus sunitinib followed by deferred CN 24 hours after the last dose and TT. None of the tumours in the deferred arm became irresectable and only 2 patients had a sunitinib-related delay of CN > 2 weeks. AEs related to surgery (all grades) in the immediate and deferred arm occurred in 52% and 53% after CN, respectively, although the number of intraoperative surgery

related AEs were higher in the immediate arm. Postoperative AEs CD >/= 3, 30-day readmission and in-hospital mortality rates were 6.5%, 13% and 4.3% in the immediate arm and 2.5%, 7.5% and 2.5% in the deferred arm, respectively. There were no differences for surgery time, blood loss and hospital stay.

Patient summary

Patients with metastatic kidney cancer do not have more surgical complications whether they are treated with systemic therapy before or after surgery.

Take Home Message

Sequence of targeted therapy does not affect surgical safety in metastatic renal cell cancer.

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Brief correspondence

CARMENA, a phase-3 trial investigated the role of cytoreductive nephrectomy (CN) in the era of targeted therapy and concluded that OS in patients treated with sunitinib alone is not inferior to CN followed by sunitinib. Of note, 17% of patients in the sunitinib only arm in CARMENA underwent secondary CN after having been exposed to sunitinib, mostly due to near-complete responses at metastatic sites [1].

The EORTC SURTIME trial explored a period of sunitinib prior to CN as an alternative approach to immediate CN. The sequence of CN and sunitinib did not affect the progression free rate (PFR) but a higher OS was seen for deferred CN [2].

Based on both trials the recently updated EAU guidelines recommend to consider CN in patients who respond to initial treatment with vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKI) [3]. The new paradigm in first-line therapy now includes a combination of immune checkpoint inhibitors with VEGFR-TKI for patients with metastatic clear-cell RCC. Therefore, information about the surgical safety of CN following VEGFR-TKI is relevant. Previous retrospective

studies of deferred CN reported that tumor shrinkage and reduction of neovascularization may be exploited to facilitate resection but also suggested increased surgery related adverse events (AEs) after presurgical VEGF-targeted therapy [4-6] when compared to untreated patients.

The surgical safety of CN following pretreatment with sunitinib, was a prespecified secondary endpoint from the EORTC 30073 SURTIME trial (NCT01099423), including in-hospital mortality, 30-day readmission rate and AEs related to surgery (intra- and 30-day postoperative AEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and Clavien-Dindo (CD). This provides for the first time data from a randomized controlled trial in which CN after pretreatment with TKI was compared to upfront CN. Design and methods of the SURTIME study are described in the online supplement (Supplement methods). Briefly, patients with mRCC and favourable surgical risk factors [7] were randomized 1:1 to immediate CN followed by sunitinib versus 3 cycles sunitinib followed by CN 24 hours after the last dose and sunitinib.

When SURTIME closed after 5.7 years with 99 patients entered, 46 of 50 patients in the immediate arm had CN. In the deferred CN arm, 40 of 48 had CN 24 hours after sunitinib. Six patients with progressive disease had CN off protocol. The majority of patients were MSKCC intermediate risk (Supplement table 1). Primary tumours in the deferred arm had a median reduction of the diameter of 13,8% (Supplement figure 1) and none became irresectable. Only 2 patients had a sunitinib-related delay of CN > 2 weeks. One patient required an embolization of the tumour bearing kidney due to hematuria during pretreatment.

AEs related to surgery (all grades) in the immediate and deferred arm (per protocol) occurred in 52% and 53% of patients who underwent CN, respectively (difference in rates 0.77, 95% Confidence Interval (CI) -20.4 to + 21.8), although the number of intraoperative surgery related AEs were higher in the immediate arm (Figure 1, Supplement table 2). Intraoperative grade 3-5 surgical AEs included bleeding, pancreatic and bowel damage, splenectomy and one death in the immediate arm due to cardiac arrest caused by a caval vein tumour thrombus.

Postoperative AEs by CD grade 3-4, 30-day readmission and in-hospital mortality were 17%, 9% and 2% in the immediate arm and 17.5%, 5% and 2.5% in the deferred arm, respectively (differences in rates 0.1 (95% CI -15.8 to + 16.8), 3.7 (95% CI -8.9 to + 15.9), 0.3 (95% CI -9.1 to +10.9), respectively). Postoperative CD grade 3-5 AE included pancreatic leakage, bowel obstruction,

bleeding and one postoperative death in the deferred arm due to pulmonary embolism. Wound healing problems occurred in 2 patients (1 in the immediate and 1 in the deferred arm). These were superficial and required no intervention (CD grade 1). There were no significant differences for surgery time, blood loss and hospital stay (Table 1). The observation of a numerically higher intraoperative and similar postoperative complication rate in the immediate CN arm in SURTIME compared to patients who had per-protocol CN in the deferred arm is unexpected. Previous retrospective studies reported intraoperative adhesions, difficulties with dissection, wound healing problems and a higher postoperative complication after presurgical VEGF-targeted therapy [4,5]. However, they did not use a classification to grade complications following pretreatment and used descriptive terms instead limiting direct comparison with the results from SURTIME.

Powles et al. demonstrated in a combined analysis of two prospective single-arm studies of presurgical sunitinib, postoperative complications according to CD occurred in 27% following CN. Four patients (11%) had CD grades 3-5, including one death (3%) [8]. Another prospective single-arm study of presurgical pazopanib reported a 22% perioperative grade 3-5 complication rate according to CTCAE v3.0 in the 63 patients who underwent CN. These included bleeding (8%), splenectomy (3%) and death (2%) [9].

These reported surgical AE rates are similar to the grade 3-5 perioperative CTCAE and postoperative CD rate reported in SURTIME. Surgery related intraoperative AEs were numerically higher in the immediate arm independent of T stage, MSKCC risk group, and number of surgical risk factors. Of note, postoperative wound healing complications were generally low in SURTIME in which sunitinib which may interfere with wound-healing was interrupted as early as 24-48 hours prior to surgery in the majority of patients in the deferred arm.

Under randomized controlled settings we did not see evidence of a difference in surgical side effects, blood loss, surgery time, readmissions and mortality between deferred CN following sunitinib and immediate CN. However, we cannot rule out a large increase in rates and the findings would need to be interpreted with caution and confirmed in further studies. CN remains an intervention with certain morbidity and mortality and the mortality rate in SURTIME is comparable to reports in the literature, which was 1.8-3.6 % after CN [10].

Although the study is limited by low numbers it provides the only randomized data in this setting that were controlled by well defined eligibility criteria and balanced surgical risk factors. Based on the

updated EAU guideline recommendations for CN and systemic therapy it is important to recognize surgical side effects that may be related to pretreatment with angiogenesis inhibitors.

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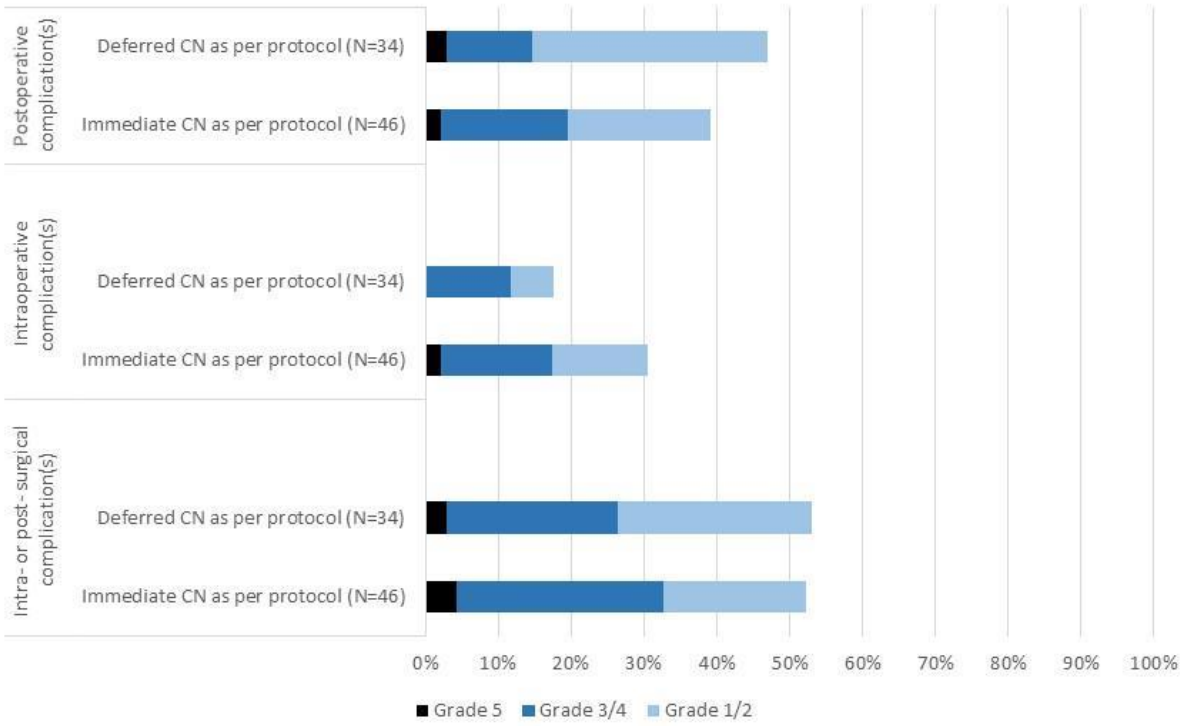
Figure 1



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172 Table 1

	Immediate CN (n=46)	Deferred CN (n=36)	Deferred CN -Off protocol- (n=6)
Duration of surgery (minutes) Mean (SD)	185 (72)	166 (65)	163 (62)
Estimated blood loss (ml) Mean (SD)	974 (1153)	1035 (1302)	1360 (1270)
Estimated blood loss (ml)			
<400ml	18 (39%)	10 (29%)	2 (33%)
400-1500ml	11 (24%)	9 (27%)	2 (33%)
>1500ml	7 (15%)	4 (12%)	1 (17%)
Unknown	10 (22%)	11 (32%)	1 (17%)
Duation of hospital stay (days) Mean (SD)	8 (7)	7 (3)	8 (3)

Prolongation of hospital stay >20days	3 (7%)	1 (3%)
Readmission within 30 days after CN	4 (9%)	2 (5%)

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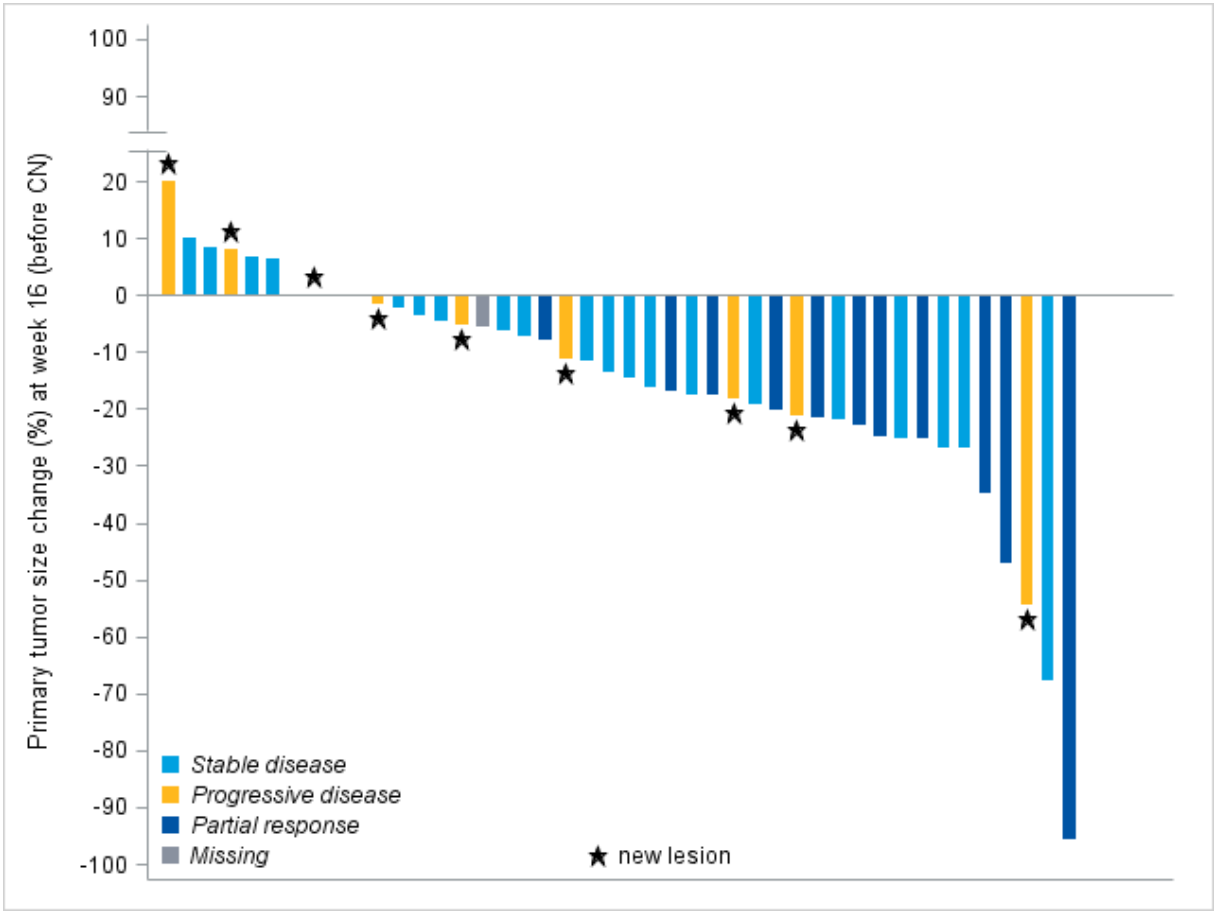
174 Suppl Table 1

	Assigned to Immediate CN (n=50)	Assigned to Deferred CN (n=49)
Age (years)		
Minimum age	39	43
First quartile (25% percentile)	53	52
Median (50% percentile)	60	58
Third quartile (75% percentile)	68	66
Maximum age	78	74
Sex:		
Male	41 (82%)	39 (80%)
Female	9 (18%)	10 (20%)
Number of surgical risk factors (Culp)		
0	8 (16%)	11 (22%)
1	14 (28%)	16 (33%)
2	16 (32%)	15 (31%)
3	12 (24%)	7 (14%)
MSKCC risk score:		
Intermediate risk (0-2 factors)	43 (86%)	44 (90%)
Poor risk (3 factors)	7 (14%)	5(10%)
Clinical T stage:		
T1	9 (18%)	8 (16%)
T2	15 (30%)	23 (47%)
T3	22 (44%)	15 (31%)
T4	4 (8%)	3 (6%)

Clinical N stage:		
N0	17 (34%)	20 (41%)
N1	15 (30%)	10 (20%)
N2	10 (20%)	8 (16%)
unknown	8 (16%)	11 (23%)
Number of metastatic site:		
1	7 (14%)	3 (6%)
≥2	43 (86%)	46 (94%)
Primary tumour size (mm):		
Minimum tumor size	13	33
First quartile (25% percentile)	82	87
Median (50% percentile)	91	96
Third quartile (75% percentile)	125	132
Maximum tumour size	200	180
Surgical approach:		
Transabdominal open	24 (52%)	20 (50%)
Retroperitoneal open	3 (7%)	1 (3%)
Transabdominal laparoscopic	13 (28%)	13 (33%)
Retroperitoneal laparoscopic	1 (2%)	3 (7%)
Missing	5 (11%)	3 (7%)

Suppl figure 1


Primary tumor size change (%) at week 16 (before CN)
100
90
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
Stable disease
Progressive disease
Partial response
Missing
new lesion

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