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Platinum Priority – Brief Correspondence

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Surgical Safety of Cytoreductive Nephrectomy Following Sunitinib: Results from the Multicentre, Randomised Controlled Trial of Immediate Versus Deferred Nephrectomy (SURTIME)

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Abstract

The European Organisation for Research and Treatment of Cancer SURTIME trial explored timing of sunitinib, a tyrosine kinase inhibitor (TKI), and cytoreductive nephrectomy (CN) in patients with metastatic renal cell carcinoma. Previous retrospective studies suggest increased surgery-related adverse events (AEs) after presurgical TKI. We report surgical safety from a randomised comparison of CN before or after sunitinib. In-hospital mortality, 30-d readmission rate, and intraoperative and 30-d postoperative AEs according to Common Terminology Criteria for Adverse Events version 4 and Clavien-Dindo (CD) were analysed. Patients were randomised 1:1 to immediate CN followed by sunitinib versus sunitinib followed by deferred CN 24 h after the last dose of sunitinib. None of the tumours in the deferred arm became unresectable, and only two patients had a sunitinib-related delay of CN of >2 wk. AEs related to surgery (all grades) in the immediate and deferred arms occurred in 52% and 53% after CN, respectively, although the number of intraoperative surgery-related AEs was higher in the immediate arm. Postoperative AEs (CD ≥3), 30-d 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 in surgery time, blood loss, and hospital stay.

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

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CARMENA, a phase 3 trial, investigated the role of cytoreductive nephrectomy (CN) in the era of targeted therapy and concluded that overall survival (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 European Organisation for Research and Treatment of Cancer (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, but higher OS was seen for deferred CN [2].

Based on both trials, the recently updated European Association of Urology (EAU) guidelines recommend considering CN in patients who respond to initial treatment with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) [3]. The new paradigm in first-line therapy now includes a combination of immune checkpoint inhibitors with VEGFR-TKIs for patients with metastatic clear-cell renal cell carcinoma. Therefore, information about the surgical safety of CN following a VEGFR-TKI is relevant. Previous retrospective studies of deferred CN reported that tumour shrinkage and reduction of neovascularisation may be exploited to facilitate resection, but also suggested increased surgery-related adverse events (AEs) after presurgical VEGF-targeted therapy [4–6] when compared with untreated patients.

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-d readmission rate, and AEs related to surgery (intraoperative and 30-d 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 randomised controlled trial in which CN after pretreatment with a TKI was compared with upfront CN. Design and methods of the SURTIME study are described in the Supplementary material. Briefly, patients with metastatic renal cell carcinoma and favourable surgical risk factors [7] were randomised 1:1 to immediate CN followed by sunitinib versus three cycles of sunitinib followed by CN 24 h after the last dose of sunitinib.

When SURTIME closed after 5.7 yr with 99 patients having been entered, 46 of 50 patients in the immediate arm had CN. In the deferred CN arm, 40 of 48 had CN 24 h after sunitinib. Six patients with progressive disease had CN off protocol. The majority of patients had Memorial Sloan Kettering Cancer Center (MSKCC) intermediate risk (Supplementary Table 1). Primary tumours in the deferred arm had a median reduction of the diameter of 13.8% (Supplementary Fig. 1) and none became unresectable. Only two patients had a sunitinib-related delay of CN of >2 wk. One patient required embolisation of the tumour-bearing kidney due to haematuria during pretreatment.

AEs related to surgery (all grades) in the immediate and deferred arms (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 was higher in the immediate arm (Fig. 1 and Supplementary Table 2). Intraoperative grade 3–5 surgical AEs included

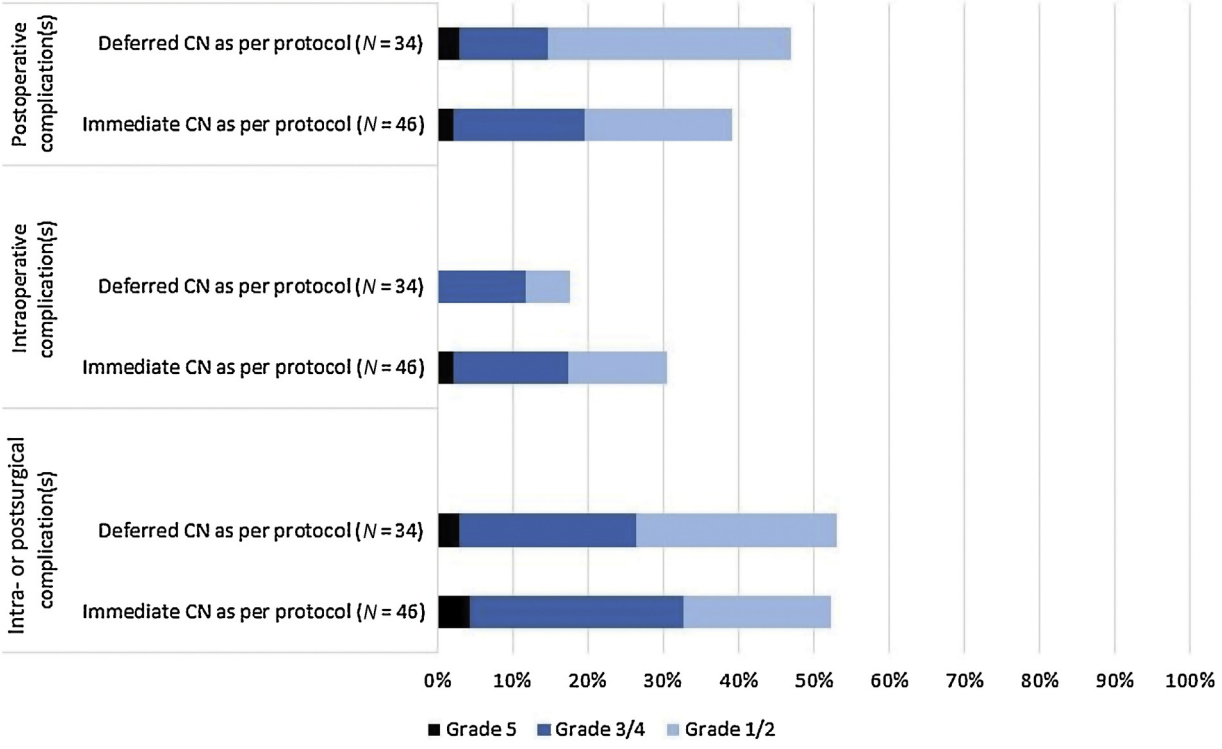

Fig. 1 – Postoperative, intraoperative, and all (either intra- or postsurgical) complication(s) related to surgery in the deferred and immediate cytoreductive nephrectomy (CN) arms, graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Table 1 – Duration of surgery, blood loss, and hospital stay

	Immediate CN (*n* = 46)	Deferred CN (*n* = 34)	Deferred CN off protocol (*n* = 6)
Duration of surgery (min), mean (SD)	185 (71)	166 (65)	164 (62)
Estimated blood loss (ml), mean (SD)	974 (1153)	1035 (1302)	1360 (1270)
Estimated blood loss (ml), *n* (%)			
<400	18 (39.1)	10 (29.4)	2 (33.3)
400–1500	11 (23.9)	9 (26.5)	2 (33.3)
>1500	7 (15.2)	4 (11.8)	1 (16.7)
Unknown	10 (21.7)	11 (32.3)	1 (16.7)
Duration of hospital stay (d), mean (SD)	8.4 (7.1)	7.4 (3.4)	7.8 (3.2)
Prolongation of hospital stay >20 d, *n* (%)	3 (6.5)	1 (2.5)	
Readmission within 30 d after CN, *n* (%)	2 (5.0)	4 (8.7)	

CN = cytoreductive nephrectomy; SD = standard deviation.

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-d 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], and 0.3 [95% CI −9.1 to +10.9], respectively). Postoperative CD grade 3–5 AEs included pancreatic leakage, bowel obstruction, bleeding, and one postoperative death in the deferred arm due to pulmonary embolism. Wound healing problems occurred in two patients (one in the immediate and one in the deferred arm). These were superficial and required no intervention (CD grade 1). There were no significant differences in 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 with 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 rate 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 a direct comparison with the results from SURTIME.

Powles et al. [8] demonstrated in a combined analysis of two prospective single-arm studies of presurgical sunitinib that postoperative complications according to CD occurred in 27% following CN. Four patients (11%) had CD grades 3–5, including one death (3%). 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 rates reported in SURTIME. Surgery-related intraoperative AEs were numerically higher in the immediate arm independent of the 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 24–48 h prior to surgery in the majority of patients in the deferred arm.

Under randomised 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 with reports in the literature, which was 1.8–3.6% after CN [10].

Although the study is limited by a small number of participants, it provides the only randomised 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 recognise surgical side effects that may be related to pretreatment with angiogenesis inhibitors.

Author contributions: Axel 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.

Study concept and design: De Bruijn, Mulders, Jewett, Wagstaff, Van Thienen, Blank, Van Velthoven, Wood, van Melick, Aarts, Lattouf, Powles, De Jong, Rottey, Tombal, Haanen, Bex.
Acquisition of data: De Bruijn, Mulders, Jewett, Wagstaff, Van Thienen, Blank, Van Velthoven, Wood, van Melick, Aarts, Lattouf, Powles, De Jong, Rottey, Tombal, Haanen, Bex.
Analysis and interpretation of data: De Bruijn, Mulders, Jewett, Wagstaff, Van Thienen, Blank, Van Velthoven, Wood.
Drafting of the manuscript: Bex, de Bruijn.
Critical revision of the manuscript for important intellectual content: Wood.
Statistical analysis: Bex, de Bruijn, Marreaud, S. Collette, L. Collette.
Obtaining funding: Bex, Haanen.
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Supervision: Bex.
Other: None.

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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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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2019.06.006.

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