



## Platinum Priority – Editorial

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# Surgical Safety of Cytoreductive Nephrectomy Following Systemic Therapy: What Should We Look For?

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In this issue of *European Urology*, De Bruijn et al [1] report on safety outcomes with a focus on adverse events (AEs) caused by surgery or systemic therapy in the SURTIME trial [2]. The European Organisation for Research and Treatment of Cancer 30073 SURTIME trial was an open-label, multi-centre, randomised controlled study conducted at 19 centres in the Netherlands, Belgium, UK, and Canada. Eligible patients had histologically confirmed, previously untreated, metastatic renal cell carcinoma (mRCC) of the clear cell subtype with a resectable asymptomatic primary tumour in situ and required systemic therapy with sunitinib. Once enrolled, patients were randomised 1:1 to immediate cytoreductive nephrectomy followed by sunitinib (immediate nephrectomy, IN) or to three cycles of sunitinib followed by nephrectomy and sunitinib (deferred nephrectomy, DN) [2].

AEs related to surgery (all grades) occurred in 52% and 53% of the IN ( $n=46$ ) and DN ( $n=36$ ) patients, respectively, although the number of intraoperative surgery-related AEs was higher in the IN arm. Postoperative AEs, 30-d readmission, and in-hospital mortality rates were 6.5%, 13%, and 4.3% in the IN arm and 2.5%, 7.5%, and 2.5% in the DN arm, respectively. There were no differences regarding surgery time, blood loss, and hospital stay between the groups [1].

The findings from this investigation are severalfold. The SURTIME trial represents the first evidence of equal morbidity after the alternative sequences of surgery followed by systemic therapy versus systemic therapy followed by surgery (IN + sunitinib vs sunitinib + DN) in a prospective experimental setting. It thus addresses the risk of biased conclusions that affected all previous observa-

tional investigations [3–6] and assures high quality for data collection and complication classification. Second, although systemic progression after sunitinib in the DN arm resulted in a per-protocol recommendation against nephrectomy for 14 patients (29%; 95% confidence interval 18–43%), no patient treated with upfront sunitinib lost eligibility for surgery owing to local progression to an unresectable primary tumour and only two patients had a sunitinib-related delay in DN of >2 wk. Of note, for the six patients who underwent off-protocol DN, surgical, intra-operative, and postoperative AE rates were remarkably high at 100%, 50%, and 83%, respectively (Supplementary Table 2 [1]).

How can we incorporate the findings into the clinical management of patients diagnosed with mRCC? It is important to acknowledge that the post hoc analysis by De Bruijn et al could not address many important surgical issues for a proper interpretation of the safety data recorded in the SURTIME trial. For instance, no consideration was given to multiple major drivers of perioperative outcomes in kidney cancer surgery, such as caseload at the treating institution [7,8], individual experience of the treating surgeon [9,10], and specific surgical strategies [11,12]. Surgical proficiency was not recorded and cytoreductive surgery in the trial was performed using several different approaches (transabdominal open [50–52%], retroperitoneal open [3–7%], transperitoneal laparoscopic [28–33%], and retroperitoneal laparoscopic [2–7%]). It is unclear whether robot-assisted cases were categorised together with the laparoscopic cases or if there were none.

Another controversial aspect is the applicability of the study findings to contemporary patients. When SURTIME

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was designed, sunitinib represented the standard of care. However, this treatment is no longer the standard of care for mRCC patients, at least in the first-line setting [13].

Finally, the number of patients enrolled in the trial deserves special consideration. Owing to the relatively small sample size, consisting of 46 patients treated with IN, 36 treated with DN, and six patients who received an off-protocol nephrectomy, it was not possible to run specific subanalyses aimed at improving patient selection to decrease the risk of complications and unfavourable outcomes.

In conclusion, the current post hoc analysis provides useful insight into the safety of surgery after systemic therapy. However, we definitely need further data from retrospective population-based cohorts and post hoc analyses for prospective immunotherapy trials to better understand how to select patients with metastatic disease who might benefit from a particular surgical approach and how to decrease the morbidity and complication rates associated with such a multidisciplinary approach.

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