



# Surgical harm of cytoreductive nephrectomy in the era of targeted therapy

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In the September issue of *Urology*, Wallis *et al.* (1) examine the effect of disseminated cancer on perioperative outcomes in renal cell carcinoma (RCC) patients following radical nephrectomy. They utilized the National Surgical Quality Improvement Program (NSQIP), which is an American College of Surgeons initiative that supports the collection of risk-adjusted perioperative data to facilitate the assessment of surgical outcomes and complications in (within) 30 days of surgery. In contrast to previous studies that reported outcomes after cytoreductive nephrectomy, the strength of this study lies in the presence of a comparator group to merely assess the effect of “disseminated disease”. Wallis and colleagues therefore stratified the total of 7,800 NCC patients according to “disseminated” (8.4%) or “non-disseminated cancer” (91.6%) status. By relying on robust methodology the authors demonstrate a greater risk of major complications including mortality and reoperation [adjusted odds ratio (aOR) 2.04, 95% confidence interval (CI): 1.46–2.86], prolonged length of hospital stay (aOR 1.27, 95% CI: 1.06–1.53) and pulmonary (aOR 1.68, 95% CI: 1.09–2.59), venous thromboembolic (aOR 1.72, 95% CI: 1.01–2.96), as well as bleeding complications (aOR 2.12, 95% CI: 1.73–2.60) in the presence of disseminated cancer compared to non-disseminated status.

Careful patient selection for surgery is crucial with regard to balance the oncological benefit with perioperative risk in metastatic RCC patients. The higher rates of open surgery in these patients likely reflect the complexity of the cases. Further, patients with disseminated cancer more often underwent concurrent procedures. In the NSQIP, a

concomitant procedure is defined as additional operative procedure performed by a different surgical team under the same anesthetic. Concomitant procedures included bowel-related procedures, pancreatectomy, splenectomy, hepatectomy and major vascular repair. However reflecting meticulous patient selection prior cytoreductive nephrectomy, metastatic RCC patients in the current analysis were more likely to be younger, to have a lower body mass index, and less likely had received dialysis.

In 2001, two randomized trials (SWOG 8949 and EORTC 30947) provided level 1 evidence for the use of cytoreductive nephrectomy for the treatment of metastatic RCC (2,3). Survival advantage with cytoreductive nephrectomy has been most beneficial in patients with favorable or intermediate-risk disease and with low tumor burden. Unfortunately the authors of the current article were incapable accounting for these parameters using the NSQIP. While the NSQIP accurately provides patients characteristics such as preoperative laboratory values and comorbidities as well as perioperative outcomes such as operating time and surgical complications, tumor size, stage, grade and histological subtype, and radiology findings are not accounted for in the NSQIP. Clinical T stage has been demonstrated to be significantly associated with perioperative outcomes in metastatic RCC patients undergoing cytoreductive nephrectomy (4). Specifically T4 stage is associated with the highest odds of adverse events. Consequently certain findings warrant restrained interpretation using the NSQIP in oncological cohorts. Nevertheless the strength of the present study lies in the

large sample size and its population-based nature, with good-quality prospectively collected clinical information provided.

With the adoption of targeted therapies and checkpoint inhibition, the role of cytoreductive nephrectomy has become a matter of discussion. Uncertainties mainly concern the survival benefit and the timing of surgery. Until now there remains a lack of level 1 evidence for cytoreductive nephrectomy in metastatic RCC patients. A recent study suggests modest effectiveness of cytoreductive nephrectomy in primary metastatic RCC patients treated with first-line sunitinib (5). Unfortunately Wallis *et al.* did not include the NSQIP variable “chemotherapy within 30 days prior to surgery”, which might indicate neoadjuvant targeted therapy use, into the current analysis. Within this context an important issue includes the potential delay of receipt of targeted therapies due to perioperative complications. Though, a variable for postoperative administration of chemotherapy is not included in the NSQIP.

Two ongoing prospective clinical trials [CARMENA (NCT00930033) and SURTIME (NCT01099423)] may provide further important insights. Until then the decision to perform cytoreductive nephrectomy will individually base on patient and tumor characteristics. However, outcome prediction in metastatic RCC patients is always challenging. Preoperative nomograms may support patient stratification and consequent treatment choice. Finally, despite reports of declining use of cytoreductive nephrectomy observed in the Surveillance, Epidemiology and End Results registry [2001–2008], Tsao *et al.* observed an increase over the study period (5.0% in 2006 to 9.1% in 2014) (6).

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