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A commentary on 'The role of cytoreductive nephrectomy in metastatic renal cell carcinoma in the targeted therapy and immunological therapy era: a systematic review and meta-analysis' [*Int J Surg* (2023) 109:982–994]

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Dear Editor,

Renal cell carcinoma (RCC) is a common urological tumor. About 30% of patients with RCC have distant metastases when first diagnosed, and among one-third of patients, recurrence or metastasis occurs even after radical surgery[1]. The 5-year survival rate of metastatic renal-cell carcinoma (mRCC) does not live up to our expectations the least. Therefore, improving the prognosis of mRCC is the focus of clinical research. Currently, with improvements in diagnosis and treatment, the treatment of mRCC has changed remarkably. Since the cytokine era, cytoreductive nephrectomy (CN) has significantly prolonged the overall survival of patients with mRCC receiving interferon therapy[2], making CN in combination with interferon the first-line treatment for mRCC. However, as we step into the era of molecular targeted therapy, the progression-free survival and median survival of mRCC patients have been prolonged, which has challenged the therapeutic status of CN[3]. Recently, Chen *et al.*[4] conducted a systematic review and meta-analysis to explore whether CN provides a survival benefit for patients with mRCC and how we should better treat mRCC patients with CN in clinical practice. The results showed, first, mRCC patients who received CN had better survival rates than those who did not, no matter what treatment strategies were used. Second, the combination of upfront CN and targeted therapy may result in better survival outcomes compared to targeted therapy alone. In addition, survival outcomes were similar in the upfront CN + systemic therapy (ST) group and the ST + deferred CN group.

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Although the role of CN in mRCC remains controversial, CN has been shown to result in a survival benefit while reducing the tumor burden, which may potentially enhance an immune-mediated systemic therapeutic response. Moreover, the removal of the tumor alternatively eliminates molecular components such as growth factors and immunosuppressive cytokines, etc[5]. By analogy, two clinical trials back in the cytokine era showed that CN did improve survival in mRCC patients. Even though CN utilization has declined in the era of targeted therapies, several retrospective studies have shown that it is still associated with improved survival[1]. However, the CARMENA trial demonstrated that in patients with mRCC who were in the MSKCC intermediate-risk or poor-risk groups, sunitinib alone is not inferior to CN followed by sunitinib, and thus CN prior to ST is not recommended[3]. Therefore, it is undeniable that the value of CN needs to be reassessed in the new era of combining targeted therapy with immunotherapy as first-line mRCC therapy.

Yet, as the ongoing prospective randomized controlled clinical studies are still incomplete, prospective randomized trials are needed to clarify the optimal management strategy of CN in patients with mRCC receiving novel targeted therapies. For example, patient selection; upfront or deferred CN; the potential risks of complications followed by CN. Therefore, for the time being, to maximize benefits for patients, CN intervention is generally recommended in clinical practice for patients with mRCC who are in good general condition (ECOG score <2, no or mild associated symptoms, and low metastatic load) and for whom surgery can significantly reduce the tumor burden[1]. Nevertheless, clinical practice requires comprehensive, individualized assessment and decision-making for each patient.

With the spread of minimally invasive surgery and the development of surgical techniques, CN treatment of mRCC has transitioned from open surgery to laparoscopic surgery and to robot-assisted surgery. Robot-assisted surgery has been shown to be safe and feasible in reducing morbidity and improving perioperative prognosis in patients with advanced RCC, especially in estimating blood loss, number of transfusions, and length of stay in the hospital. In addition, the study has shown that the robot-assisted CN does not appear to delay and may actually shorten the interval from the CN to the initial ST[6]. All these indicate that robotic technology provides a better choice for surgical treatment of mRCC patients due to its own advantages (clear surgical vision, dexterity, automatic filtering of tremors, less trauma, etc.). Although robot-assisted surgery is subject to expensive prices and

lengthy procedures, it is expected to bring more benefits to patients with mRCC as it becomes more widely available.

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