



Role of cytoreductive nephrectomy in metastatic renal cell carcinoma patients with tumor thrombus: does it change with development of systemic therapy?

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The role of cytoreductive nephrectomy (CN) is changing with improvement of systemic therapy for metastatic renal cell carcinoma (mRCC) patients. In the era of cytokine therapy, immediate CN prior to systemic therapy had been the standard of care for mRCC patients. Two randomized, phase 3 trials demonstrated survival advantages of CN plus interferon therapy over interferon alone with respective median overall survival (OS) of 11.1 versus 8.1 months (1) and 17 versus 7 months (2). However, the first-line treatments for mRCC patients have been replaced by molecular targeted agents in the first decade of the 21st century and are being taken over by immuno-oncology drugs and their combination with targeted agents in the second decade.

Recently, results of two randomized, phase 3 trials to assess the prognostic role of CN in mRCC patients treated with targeted therapy were published. The CARMENA (Cancer du Rein Metastatique Nephrectomie et Antiangiogéniques) trial compared survival between immediate CN followed by sunitinib versus sunitinib alone in mRCC patients at intermediate and poor risk according to the Memorial Sloan-Kettering Cancer Center risk criteria (3). The CARMENA study demonstrated that sunitinib alone was non-inferior to CN plus sunitinib with the median OS of 18.4 months [95% confidence interval (CI), 14.7 to 23.0 months] versus 13.9 months (95% CI, 11.8 to 18.3 months). Another study was the SURTIME trial, comparing survival between immediate CN followed by

sunitinib versus three cycles of sunitinib followed by CN in the absence of progression on sunitinib (4). Although the 28-week progression-free survival was comparable between the two arms, the intention-to-treat OS hazard ratio (HR) of deferred versus immediate CN was 0.57 (95% CI, 0.34 to 0.95; $P=0.03$) with respective median OS of 32.4 and 15.0 months. Results of these two studies do not support immediate CN in mRCC patients treated with targeted therapy.

Extension of tumor thrombus into the renal vein and the inferior vena cava (IVC) is one of characteristic features of locally advanced RCC. Although the role of radical nephrectomy with tumor thrombectomy is established in non-metastatic RCC patients, the prognostic impact of CN in mRCC patients with a tumor thrombus remains largely unknown. Lenis *et al.* retrospectively investigated the prognostic role of CN in these patients using a large cohort of 2,334 mRCC patients with a tumor thrombus derived from the National Cancer Database (NCD) from 2010 to 2013, the era of targeted therapy (5). During the study period, mRCC patients with a thrombus were more likely to undergo CN than those without a thrombus (78.6% versus 59.7%, $P<0.01$). In the mRCC patients with a thrombus, the CN group showed significantly more favorable OS than the no CN group for those with a renal vein thrombus and an infradiaphragmatic IVC thrombus but not for those with a supradiaphragmatic IVC thrombus with respective

HR of 0.43 ($P < 0.01$), 0.68 ($P = 0.03$), and 0.58 ($P = 0.33$) after propensity score matching mainly for socioeconomic variables. The median OS for the CN group versus no CN group was 24.0 versus 9.2 months for patients with a renal vein thrombus, 22.3 versus 11.5 months for those with an infradiaphragmatic thrombus, and 13.1 versus 10.3 months for those with a supradiaphragmatic thrombus. In this study, systemic therapy was given to 60% of patients undergoing CN, of whom 90% had received immediate CN.

Caution should be taken in interpreting the results of the study by Lenis *et al.* This was a retrospective study using a real-world nationwide patient cohort, which lacked information on important prognostic factors of mRCC such as performance status, hemoglobin, albumin and C-reactive protein. Patients at poor risk were unlikely to undergo CN and thus the results could be biased in favor of the CN group.

Should we avoid immediate CN for mRCC patients with a tumor thrombus in the situation where the prognostic role of CN remains uncertain? The answer would be “NO” because these patients always have a risk of sudden death from tumor thrombus-associated embolization unless they underwent CN with thrombectomy. In my opinion, it would be better to recommend these patients to undergo immediate CN with thrombectomy when they are medically feasible to the surgery to avoid the risk of sudden death, which is supported by the study by Lenis *et al.* (5). For patients who are not feasible to CN with thrombectomy due to tumor-related cachexia or symptomatic metastatic lesions, deferred CN would be considered when the patients' general condition improves by and their tumors respond to systemic therapy. Further studies using propensity score matching on multicentric large patient cohorts in which data on established prognostic factors are available are needed to explore the substantial prognostic impact of immediate CN with thrombectomy in mRCC patients with a tumor thrombus.

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Footnote

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