The best of uro-oncology in 2016 - Kidney cancer

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Organ-confined disease - Renal function preservation

Most renal cell carcinoma (RCC) patients are currently diagnosed with small masses confined to the kidney and often eligible for nephron sparing surgery (NSS)[1]. In this context, many efforts have been made to clarify the pathophysiology and the mechanism behind the development of chronic kidney disease (CKD) after surgery. Beyond the surgical aspects, much more emphasis has been attributed to the general health status of the patient and to his specific comorbidities. Tourojman et al. [2] evaluated the impact of preoperative proteinuria on long-term survival in patients treated with nephrectomy. In their cohort, 20% of patients had proteinuria before surgery. Longitudinal analysis revealed that the preoperative glomerular filtration rate, proteinuria and CKD risk group were independent predictors of poor overall survival[2]. Larcher et al. [3] relied on a collaborative multi-institutional database, including more than 1,700 cT1-2N0M0 patients, without baseline CKD, to assess the impact of surgery type (NSS vs. radical nephrectomy, RN) on mortality due to cause other than cancer mortality (OCM). In the overall population RN was not associated with an increased risk of OCM compared to NSS (HR 0.91, p=0.6), after adjustment for patient and cancer characteristics. However, RN increased the risk of OCM in patients with increased Charlson comorbidity index (interaction test p=0.0008), implying that RCC patients who are more fragile due to relevant comorbidities are probably those who benefit the most from NSS in terms of OCM.

Of interest, Zhang et al. proposed in this specific setting a spectrum score to reflect the degree of ischemic insult in the ipsilateral kidney and its relationship to subsequent functional recovery [4]. Based on split function and percent parenchymal mass preserved in the ipsilateral kidney, they calculated for each patient the individual functional recovery, defined as the ratio between the percent of function preserved and the percent of renal mass saved. Increased spectrum score (<25%, 25–50%, 50–75%, and >75% quartiles) showed decreased functional recovery (98%, 94%, 90%, and 89%, respectively, p<0.001) but not in the specific subgroup of patients treated with renal hypothermia[4]. On multivariable analysis spectrum score and ischemia type resulted significantly associated with functional recovery (both p<0.01), while age and comorbidities did not.

Locally advanced disease

The role of lymph node dissection (LND) in patients elected for radical nephrectomy (RN) for non-metastatic RCC has been further clarified by Gershman et al. [5]. The associations of LND with the development of distant metastases, cancer-specific mortality (CSM), and all-cause mortality (ACM) were evaluated using a 1:1 propensity score matching, adjustment for stratification and inverse probability weighting. LND was not significantly associated with a reduced risk of distant metastases, CSM or ACM, even among patients at increased risk of pN1 disease. Notably, such results were confirmed also in sub-analyses focusing on cases with preoperative radiographic lymphadenopathy, or across a wide range (0.05 to 0.50) of increasing threshold probabilities of pN1 disease[5].

In the setting of adjuvant therapy after nephrectomy, debatable results from two randomized clinical trials (RCT) have been reported. Ravaud et al. published a randomized, double-blind, phase 3 trial (S-TRAC) of 615 patients with loco-regional, high-risk clear-cell RCC receiving either sunitinib (50 mg per day) or placebo on a 4-weeks-on, 2-weeks-off schedule for 1 year or

until disease recurrence, unacceptable toxicity, or consent withdrawal[6]. The median duration of disease-free survival was 6.8 years in the sunitinib group and 5.6 years in the placebo group (HR 0.76, p=0.03) while overall survival data could not be evaluated due to limited follow-up. Dose reductions because of adverse events were more frequent in the sunitinib group than in the placebo group (34% vs. 2%), as were dose interruptions (46% vs. 13%) and discontinuations (28% vs. 5.6%). Grade 3 or 4 adverse events were more frequent in the sunitinib group (48% for grade 3 events and 12% for grade 4 events) than in the placebo group (16% and 3.6%, respectively). Conversely, Haas et al. reported a negative RCT including 1,943 patients randomly assigned (1:1:1) to receive 54 weeks of sunitinib 50 mg per day orally throughout the first 4 weeks of each 6 week cycle, sorafenib 400 mg twice per day orally throughout each cycle, or placebo [7]. The primary analysis showed no significant differences in disease-free survival. Median disease-free survival was 5.8 years for sunitinib (HR 1.0, p=0.8), 6.1 years for sorafenib (HR 0.9, p=0.7) and 6.6 years for placebo. Substantial treatment discontinuation occurred because of excessive toxicity, despite dose reductions.

Follow-up after treatment

Follow-up protocols after renal surgery are mostly empirical, due to lack of high-level evidence. In this scenario, Sohn et al. [8] tested the impact of surveillance imaging intensity and CSM. Using SEER-Medicare data they identified 7,603 men with RCC. Surprisingly, more than 30% of patients underwent neither chest or abdominal imaging[8]. Overall, more stringent follow-up imaging did result into lower CSM, raising important questions regarding the link between post-treatment imaging surveillance and patient prognosis.

With respect to emerging imaging modalities for the detection of RCC recurrence after surgery, Gorin et al. [9], confirmed that prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) might have potential implications in the future in the detection of RCC recurrence after surgery or clinically occult metastatic RCC, as well. This is particularly relevant in RCC since PSMA is expressed in the neo-vasculature and many of the commonly used drugs for this disease target angiogenesis. A diagnostic trial (ClinicalTrials.gov identifier NCT02687139) is ongoing to define the diagnostic accuracy of PSMA-targeted PET/CT across the various stages of RCC and to explore this novel imaging test in patients with non-clear cell variants of RCC.

Metastatic RCC

In the setting of metastatic RCC (mRCC), Hanna et colleagues sought to evaluate contemporary utilization rates and the survival benefit of cytoreductive nephrectomy (CN) compared with non-CN counterparts treated with targeted therapies (TT)[10]. Of note, among >15,000 patients treated with TT, only 35% underwent CN in the last decade. The median OS of CN versus non-CN patients was 17.1 versus 7.7 months (p<0.001). In sensitivity analyses using propensity scores adjustment in addition to other available covariates, CN patients showed a lower risk of any death (HR 0.45, p<0.001). Moreover, Davis et al. hypothesized that worsening in International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic category at start of second-line therapy (2L) for metastatic renal cell carcinoma (mRCC) might predict poorer response[11]. They performed a retrospective review of the IMDC database for mRCC patients who received first-line (1L) VEGF inhibitors (VEGF-i) and then 2L with VEGF-i or mTOR inhibitors (mTOR-i). IMDC prognostic categories were defined before each line of therapy (favorable, F; intermediate, I; poor, P). Data were analyzed for 1,516 patients, of whom 89% had clear cell histology. At start of 2L, 60% of patients remained in the same prognostic category; 9.0% improved (3% I → F; 6% P → I); 31% deteriorated (15% F → I or P; 16% I → P). Patients with