Editorial on "Risk prediction models for cancer-specific survival following cytoreductive nephrectomy in the contemporary era"

Yasmin Abu-Ghanem[1,2], Jacob Ramon[1,2]

[1]Department of Urology, Sheba Medical Center, Tel Hashomer, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Correspondence to: Yasmin Abu-Ghanem, MD, MSc., Med. Department of Urology, Chaim Sheba Medical Centre, Tel-Hashomer, Ramat-Gan 52621, Israel. Email: ag.yasmin@gmail.com.

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During the immunotherapy era, cytoreductive nephrectomy (CN) has been the standard of care in the treatment of metastatic renal cell carcinoma (mRCC). This practice was supported by randomized trials and large, retrospective studies (1-3). However, the low response rate and high toxicity associated with high-dose regimens as well as the wide-ranging spectrum of response to treatment have clearly demonstrated the need for further research and for standardized determination of patient and disease characteristics to predict clinical outcomes.

To date, several prognostic models have been suggested to help distinguish between poor and favorable risk patients. The Memorial Sloan Kettering Cancer Center (MSKCC) score (4) was the first model for predicting survival and stratifying patient risk (favorable, intermediate and poor) based on pre-treatment factors.

With the advent of targeted therapy, the MSKCC model has been revised, and other models have been developed based on similar factors or other independent predictors such as high neutrophil to lymphocyte ratio (NLR), thrombocytosis, lymph node metastases, sarcomatoid features and histologic subtype (5-7). The relevance of these variables in the era of targeted therapies is still a matter of debate and investigation. Moreover, with the substantial benefit of the vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs), such as sunitinib, the value of CN in patients with mRCC was questioned (8,9). The recently published CARMENA trial (Clinical Trial to Assess the Importance of Nephrectomy) (10) was designed to answer this question. In this trial, patients were randomized for treatment with either sunitinib alone or CN followed by sunitinib. Ultimately, median overall survival (OS) with sunitinib alone was noted to be non-inferior to CN followed by sunitinib group. In an exploratory subgroup analysis, based on the MSKCC model, CARMENA demonstrates that poor-risk patients derive no benefit from CN and are potentially harmed by surgical intervention. Nevertheless, MSKCC intermediate-risk patients were found to benefit from CN, when performed after medical treatment (differed), in the absence of disease progression.

Despite study limitations, the results of the CARMENA trial were substantial and shortly after its publication, the European Association of Urology (EAU) Renal Cell Cancer Guidelines Panel updated their recommendations for CN. The EAU guidelines stated that immediate CN should no longer be considered the standard of care in patients diagnosed with intermediate and poor risk mRCC when systemic therapy with VEGRFR-TKI is required (1). In view of the recent results, it remains paramount to identify prognostic factors that enable risk stratification prior to consideration of CN.

The trial by Lyon *et al.* (11) recently published in 'Urologic Oncology: Seminars and Original Investigations' was designed to develop a risk-stratification model for cancer-specific survival (CSS) following CN in the era of TKIs. The authors' objective was to develop an up to date preoperative risk prediction model for CSS in the era of targeted therapy, to better stratify patients prior to

consideration of CN. The authors retrospectively analyzed 313 patients who underwent CN for metastatic RCC from 1990 to 2010; patients were categorized by treatment era (cytokine *vs.* contemporary era) based on Food and Drug Administration (FDA) approval date for sorafenib. To establish the role of risk stratification for mRCC patients, two multivariable models were conducted. One limited to preoperative features, and the second using all features. The authors found on preoperative multivariable analysis that age ≥75, female sex, constitutional symptoms, lymphadenopathy and inferior vena cava (IVC) tumor thrombus were significantly associated with worse CSS. On the second multivariable analysis (including pathologic features); all variables above, as well as coagulative necrosis and sarcomatoid differentiation, were found significantly associated with CSS. Next, a risk score was developed based on the parameter estimates from each model to predict CSS according to an era. The aim of these scores was to construct a model that would help identify high-risk patients prior to starting any treatment. The authors also demonstrated the application of the preoperative model using decision curve analysis with 1-year CSM as the landmark time and demonstrated that applying the preoperative risk score would confer a net benefit beyond a threshold probability of 25%.

Notably, there are limitations to this study, including selection bias, retrospective design and the lack of other potential prognostic factors including lactate dehydrogenase, NLR, etc. Nevertheless, the authors add a new risk prognostic model that may be used to refine the eligibility criteria for CN, which is especially relevant in the 'post-CARMENA' era. The question remains whether these risk prediction models be applicable in the era of immune checkpoint inhibitors.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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