Pathological nodal staging score for renal cell carcinoma: how to build reliable therapeutic choices basing on assumptions

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In the interesting article originally published in the *World Journal of Urology* at the end of 2018, Malte Rieken and eminent coauthors, from both American and European countries, proposed and externally validated a pathological nodal staging score (pNSS) for patients with clear cell renal cell carcinoma (ccRCC) (1). They developed such β-binomial model to estimate the probability that a ccRCC patient with pathologic node-negative status at radical nephrectomy (RN) and lymph node dissection (LND) truly has no lymph node metastases (LNM), with the aim to refine patient counseling, to improve decision-making about surveillance regimens and to possibly identify inclusion criteria for trials of adjuvant therapy.

The same methodology was previously applied to other cancer types, such as colon cancer, prostate carcinoma and bladder/urothelial tumors, with interesting results, potentially useful for clinical practice (2-5). Then, the pNSS was validated in the present work for ccRCC, since the LND is the most accurate procedure for nodal staging also in patients with localized renal cancer, despite the lack of indication to perform LND in absence of clinical N+ in such malignancy (differently from the others previously cited) (2-5).

The investigators used a development cohort of 1,389 patients treated with RN and LND, and they next compared the findings to those from a validation cohort from the Surveillance, Epidemiology and End Results (SEER) database (2,270 patients). They assessed the probability of LNM as a function of the number of lymph nodes (LNs) examined: in both populations, the probability of missing LNM decreased with an increasing number of LNs examined. Interestingly, in patients with pT1/T2 and Fuhrman grade (G)1–2 tumors, the examination of only one LN was sufficient to achieve a likelihood of more than 95% to predict correct pathological nodal status. On the other hand, three LNs were sufficient to achieve a likelihood of more than 95% to predict correct pathological nodal status in patients with pT3/4 and Fuhrman grade G1–2 tumors, whilst the number of LNs needed for appropriate nodal staging was higher in case of Fuhrman G3–4 tumors. Noteworthy, the Fuhrman grade seems to affect the prediction more than the tumor staging (T), needing at least eight LNs to achieve a likelihood of more than 95% to predict correct pathological nodal status in the case of low-T/high-G, not differently from the case of high-T/high-G.

This interesting association of the number of LNs and the histologic characteristics, already previously highlighted (6-8), is unfortunately limited by the hindsight, since the pathological tumor stage and the Fuhrman grade are unknown until the definitive histological report after surgery.

Beyond this main limitation, some peculiarities of this work may risk confining the proposed model to a merely

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scientific interest rather than a true clinical niche, at least in the case of ccRCC.

Notably, the study population was collected between 1970 and 2012. This long-time interval could represent a confounding factor for the analysis, due to the changes in the surgical approach and pathological assessment occurred in the last 40 years. Even if we understand that it is difficult to quantify the impact of such changes, a parameter "τ" related to the time variability in assessing LN positivity should have been considered in the assumption one that estimates the influence of false negatives (#FNk) as a function of the number of true positive LNs (#TPk).

Furthermore, T stages were divided into two subgroups, T1–2 and T3–4. This makes difficult the application of this model to identify patients who will benefit from adjuvant therapies, which was one of the goals proposed by the authors. Indeed, two studies ongoing in the adjuvant setting are enrolling only patients with T3–4 stage tumors (9,10), but most of the ongoing trials are including also patients with T2 but not T1 stage RCC (11-15). This suggests that dividing patients into two different subgroups, T1 and T2–4, could better reflect the inclusion criteria currently employed in research protocols.

Moreover, the Fuhrman grade will be no longer available in the future, since the ISUP grading system have been recently adopted and replaced the old standard for ccRCC (16). However, several validated models currently used in clinical practice and/or for stratification in recent adjuvant trials, still include the Fuhrman grading system as an independent factor to better define prognosis of RCC after nephrectomy (17-19).

Finally, since LND is not yet a standardized procedure for RCC patients and it is currently recommended only in case of clinical evidence of LNM or in patients with other adverse clinical features, a paradigm change should precede the actual application of the pNSS in such setting (20). To date, LND remains a controversial surgical option for patients with RCC (21). Renal lymphatic drainage is largely unpredictable. An EORTC randomized phase III trial in 2009 showed no survival advantage for clinically node negative patients treated with nephrectomy alone compared with nephrectomy with LND (22). This remained the only prospective evidence in the field. The application of the model to the current clinical practice, in many cases characterized by the anecdotal or even incidental dissection of a small number of LNs, would probably render less reliable the score's predictions. Indeed, as the model is based on the actual number of LNs removed in each given cohort of patients, the number of LNs to be examined will tend to be lower in cohorts of patients with lower number of LNs removed, possibly underestimating the need of wider dissections. Furthermore, despite the inclusion of only patients without clinical evidence of LNM, the number of LNs removed could have still been affected by the surgeon's experience and by its intraoperative findings, resulting in a wider dissection in case of intraoperative finding of LNs with suspicious appearance.

The use of a predictive score in the routine clinical practice may change the management of patients with RCC after surgery and potentially improve their oncological outcome. The opportunity to take advantage of a predictive score at diagnosis may be, indeed, of paramount importance. Unfortunately, the pNSS is directly correlated to LN status but not necessarily to the oncological outcome of patients diagnosed with RCC. A legitimate doubt about the suitability of the pNSS as a true surrogate of the oncological outcome may limit its usage in clinical practice. Nevertheless, even in the era of the new technologies for the detection of LN metastases, such as the position emission tomography with prostate specific membrane antigen tracer (PSMA-PET), possibly capable to improve the detection of metastatic disease also in RCC (23), the availability of a score for pathological nodal staging is still of great interest.

In their conclusions, the authors of this interesting work comment that their model is "built on assumptions", an element that, despite debatable, actually characterizes each single mathematical model used for prediction and prognostication in the field of cancer. Thus, the more the assumption are appropriate, the more the model can be reliable and maybe useful for clinical practice and patients' selection for clinical trials, allowing to fill another piece of the puzzle for an optimal management of the disease.

In this light, the possible evolution of the pNSS model could be represented by its application in the stratification of patients who are candidate to receive adjuvant therapy in future prospective clinical trials.

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Footnote

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

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