Editorial Commentary

Predicting biological behaviour of newly diagnosed renal masses: a possible role of cell proliferation biomarkers?

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Due to the common use of axial imaging, a surge in renal cell carcinoma (RCC) incidence has been observed in the last decades, with cT1 tumors accounting for 40–50% of new diagnosis (1). Despite earlier detection, mortality remained stable, suggesting possible overdiagnosis and overtreatment (2). Actually, one out of three small renal masses (SRMs) are benign and most of the malignant ones (80%) are low-grade tumors, with a 5-year cancer specific survival (CSS) of 95–100% (2,3). Given these characteristics, lesions traditionally treated with surgery are increasingly managed with nephron sparing approaches (4).

To enhance patient-tailored treatment options, nomograms have been proposed to enhance risk prediction of non-RCC mortality (5) which are of utmost importance, especially among elderly comorbid patients (6).

Tumor size and sex are the strongest predictors of malignant pathology (7). Lane *et al.* developed a nomogram based on demographic (age and sex), clinical (smoking status) and radiographic (tumor size) parameters which achieved an index of concordance of 0.64 for benign pathology in cT1 masses (8). Kutikov and Uzzo, which initially developed a nephrometry score to standardize the assessment of renal tumor complexity, subsequently reported its association with the risk of malignancy and cancer aggressiveness (9).

To guide treatment selection (10,11) and prevent overtreatment of benign/low-grade lesions, international guidelines recommend to perform percutaneous renal tumor biopsy (RTB) (12). Its use has increased over time, especially in the field of thermal ablation or systemic therapy (13); though concerns remain over its diagnostic accuracy and safety profile. According to a recent meta-analysis, RTB sensitivity and specificity for the diagnosis of malignancy were 99.1% (95% CI: 96.4–99.8) and 99.7% (95% CI: 93.7–100), respectively. Up to 22% of core biopsies, however, were non-diagnostic (14). Despite the low complication rate [8.1% (IQR: 2.7–11.1%)], almost Clavien-Dindo grade <3), seven cases of tumor seeding have been recently reported, suggesting that this event is not anecdotal as acknowledged in the current guidelines (15).

As a fact, the significant incidence of non-diagnostic cores and concerns about oncologic safety have limited the use of RTBs outside academic and high-volume centres (13).

Within this context, there is a growing need for the identification of clinical tools that reliably predict tumor behaviour. *Ki67* (also known as *MIB-1*) is a biomarker of cell proliferation which is present in the G1, S, G2 and M-phase of all cycling human cells but it is remarkably overexpressed in cancer cells. It was widely investigated as a potential prognostic marker in retrospective studies of malignant diseases and appears as a promising tool for tumor diagnosis and a therapeutic target for cancer therapy (16). Zheng *et al.* already provided evidence that the joined assessment of p53 and Ki67 overcame any single marker in estimating RCC patients' prognosis (17). Tollefson *et al.* confirmed that patients with higher expression of MIB-1 are 68% more likely to die from the disease (18). Moreover, according to a recent meta-analysis, Ki67 expression predicts poor

CSS (HR =2.01; 95% CI: 1.66–2.44; P<0.001) and OS (HR =2.06; 95% CI: 1.64–2.57; P<0.001) probabilities but it also has a significant association with tumor stage (III/IV *vs.* I/II, OR =1.92; 95% CI: 1.61–2.28) and grade (3/4 *vs.* 1/2, OR =1.94; 95% CI: 1.21–3.10) (all P<0.001).

In this recently published study, Kikuchi *et al.* revealed an association between tumor proliferative activity and its surgical complexity (estimated by means of the R.E.N.A.L. score) (19), thus confirming the previous findings that anatomical features of SRMs are associated with their malignant potential.

The main limitation of this study is the assessment of MIB-1 index on surgical specimen, while a preoperative tool is advocated to better select patients for nephron sparing strategies, to assess the risk of malignancies of SRMs and finally to enhance prognosis estimation.

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Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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