Urinary Biomarkers for the Detection and Management of Localized Renal Cell Carcinoma

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The incidence of renal masses is increasing because of the widespread use of abdominal imaging. As a result, urologists are often faced with a dilemma in the diagnostic and therapeutic approach to these masses, which are typically small (diameter < 4 cm), asymptomatic, and often seen in patients with advanced age, comorbidities, or compromised renal function. Radiologic features can sometimes, but not always, differentiate benign from malignant tumors. Renal mass biopsy has recently been pursued more frequently with the hope of differentiating a benign or less aggressive mass, such as a chromophobe tumor or a low-grade clear cell tumor, from a malignant tumor. Indeed, there is a growing body of evidence supporting acceptable patient outcomes with active surveillance of such small renal masses (SRMs).2

In this context, Morrissey et al3 present data building on their prior publications regarding the potential clinical utility of urine markers, aquaporin-1 (AQP1) and perilipin-2 (PLIN2), as biomarkers to screen for renal cell carcinoma (RCC). AQP1 is a water-transport protein found in the glomerular capillary endothelium and apical membrane of the proximal tubule in normal kidneys.4 PLIN2 is an adipocyte differentiation-related protein whose transcriptional activation is mediated by hypoxia-inducible factor and is up-regulated in clear cell RCC.5 The authors measured AQP1 and PLIN2 levels in 3 distinct populations: 720 patients undergoing routine abdominal computed tomography (the screening population), 80

healthy RCC controls, and 19 patients with pathologically confirmed RCC. Patients with known RCC had significantly higher AQP1 and PLIN2 levels than the controls or the screening population, with sensitivities and specificities in the 90% range compared with the screening population and approaching 100% compared with healthy controls. Notably, the sensitivity and specificity of the combination of biomarkers was not different from those of the individual markers. In addition, 3 of the 720 screened patients had elevated AQP1 and PLIN2 levels and on computed tomography were found to have a renal mass, 2 of which were confirmed RCC.

Morrissey et al.2 are to be commended for their efforts to validate clinically meaningful biomarkers in this setting. There are 2 separate but equally important aspects to this work. The first is whether these biomarkers can be applied to a general population to screen for RCC, and the second is whether these biomarkers could be used in the management of SRMs. Regarding the first, the important question for any biomarker to be used in a screening setting is whether it can detect clinically meaningful cancers. Several decades after the introduction of prostate-specific antigen (PSA), the utility of this biomarker to detect lethal prostate cancer is still debated, and overtreatment of nonlethal prostate cancer is a significant clinical issue. Of note, of the 3 screening patients discovered to have a renal mass in the setting of high urinary biomarker levels, 2 had small, low-grade clear cell tumors (grade 2, pathologic stage T1a) and 1 patient died, presumably of non-RCC-related causes. Thus, the lethality of RCC tumors detected by these urinary biomarkers is not supported by the current data. Another overriding issue with any screening modality for RCC is the relatively low incidence in the general population (20-25 new cases per 100,000 population per year) and obligatory concerns about cost-effectiveness. In this setting, any proposed test must be almost 100% specific to avoid an unacceptably high false-positive rate, which would lead to unnecessary, expensive, and potentially harmful diagnostic or therapeutic procedures. The utility of these biomarkers may be enhanced by application to target populations at higher risk for RCC, such as those with a known or suspected inherited RCC syndromes, smokers, or patients with acquired renal cystic disease associated with end-stage renal failure. Renal ultrasonography could be complementary in these settings as a secondary screening modality for patients with elevated urinary biomarker levels.

The second and perhaps more immediately clinically relevant application of these urinary markers would be in the care of patients with known SRMs. Such patients can present a dilemma regarding which masses will be potentially lethal in the patient’s lifetime and which can be safely observed, since no current clinical features are associated with aggressive growth kinetics. Previous work from Morrissey and colleagues6 demonstrated that urinary AQP1 and PLIN2 levels were significantly higher in patients with clear cell and papillary RCC compared with benign renal tumors including oncocytoma and angiomyolipoma. However, while current and previous data show a correlation with renal tumor size, there is no association of these markers with tumor grade, which is equally if not more important in determining risk of progression and metastases.7 It is conceivable that information regarding 1 or both of these markers could be used in conjunction with imaging characteristics and potentially renal mass biopsy findings to guide SRM management. This will require prospective study but is potentially valuable, especially if AQP1 and PLIN2 measurement are able to obviate the need for biopsy or reduce the frequency of imaging in certain cohorts of patients.

In conclusion, elevated urinary AQP1 and PLIN2 levels are associated with the presence of RCC and have potential utility in both general population screening and SRM management settings. Further investigation, however, with more robust numbers of patients with SRMs and independent, prospective evaluation will be required to validate these findings and define the ultimate utility of these biomarkers.

REFERENCES