An important step in establishing a treatment strategy for small renal masses of clear cell renal cell carcinoma based on the significance of adverse histopathologic features on tumor needle biopsy

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Renal cell carcinoma (RCC) accounts for 3–4% of all adult cancer cases in the United States, and is divided into two groups: clear cell RCC (CCRCC) and non-CCRCC (1,2). CCRCC is the most dominant histological phenotype that accounts for 70–80% of all RCC cases. A total of 20–40% of patients with RCC experience metastatic or recurrent disease after a primary surgery [nephrectomy or partial nephrectomy (PN)], and approximately 50% of patients with RCC eventually receive systemic medication during their disease course (2). Patients with CCRCCs presenting with small renal masses (SRMs), defined as contrast-enhancing kidney tumor with a maximum diameter of ≤4 cm, generally show long-term survival with indolent and dormant features (3). Recently, the number of incidentally diagnosed SRMs without any symptoms and metastases has increased because of the widespread use of imaging examinations and technological development of diagnostic imaging (4). Therefore, various treatment options have been available for patients with CCRCC and SRMs, including active surveillance (AS); ablative therapies such as cryoablation, radiofrequency ablation, and high-intensity focused ultrasound; PN with minimum incision, endoscopic, laparoscopic, and robot-assisted laparoscopic surgery; and radical nephrectomy (RN) (5). Optimal management is required in such cases with the consideration of oncologic outcomes, such as tumor volume control, disease-free survival (DFS), disease-specific survival (DSS), and overall survival (OS), and potential adverse events associated with each treatment option. A study evaluating RCC patients aged ≥75 years showed that SRM interventions were unassociated with OS improvement (6). Increasing age and comorbidity were associated with death from any cause with cardiovascular disorders as the most common (6). Patel *et al.* reported that differences in OS and DSS were statistically insignificant among RN, PN, and AS for SRMs with a median follow-up of 34 months (7). A recent multi-institutional study enrolling 497 patients with SRMs who selected either primary active intervention or AS reported that OS for surgical intervention and AS was 98% and 96% at 2 years and 92% and 75% at 5 years, respectively (P=0.06), and DSS for primary intervention and AS at 5 years was 99% and 100%, respectively (P=0.3) (8). AS was not predictive of OS or DSS in regression modeling with a relatively short follow-up. Based on these results, AS could be considered as a safe management option for select patients with SRMs.

Hence, AS has been widely recommended for renal tumors with diameter ≤3 cm, increasing diameter <5 mm yearly, no infiltration, low complexity, and favorable histopathology (including chromophobe type RCC and oncocytoma) per the American Urological Association guideline. AS is being recognized as a standard of care for the management of SRMs (9). However, histology-based studies that stratify the prognosis of patients with SRMs have been limited, in addition to the lack of prospective and long-term outcomes; furthermore, existing studies have been largely limited to the grade and histologic subtype. An accurate detection system is required for aggressive CCRCCs because some SRMs show a highly aggressive disposition resulting in local invasion and distant metastasis during AS.

Therefore, Yang *et al.* conducted a study for determination of the extent and frequency of adverse histopathologic features in CCRCCs of ≤4 cm in size and their relevance to patient outcomes (10). They reviewed the pathological archives of RCC patients in their hospital for identification of radical and partial nephrectomies carried out and found 631 consecutive cases of nephrectomies (10). Adverse histopathologic characteristics were identified because they are known to correlate with the prognosis of patients with RCC. They were necrosis, high nuclear grade defined as International Society of Urological Pathology (ISUP)/World Health Organization (WHO) grades 3 and 4, lymphovascular invasion, sarcomatoid, and rhabdoid histology defined as >5% of sarcomatoid or rhabdoid morphological tumor cells. However, information on SRM is still lacking (11). Their study indicated that tumor size is strongly correlated with both the presence and percentage of high nuclear grade (10). Additionally, patients with at least one adverse histologic finding patients had a 84.7% 5-year DFS and 82.9% 10-year DFS, in contrast to the 5-year DFS of 95.3% and 10-year DFS of 95.3% in patients without adverse histology (P=0.0043) (10). The 5- and 10-year OS for patients with at least one adverse histologic finding were 90.2% and 90.2%, respectively, whereas for those without adverse histology were 97.8% and 91.1%, respectively (10). Although the difference in OS was insignificant between patients with and without any adverse histology, a marginally significant difference was observed (P=0.0554) (10). These data indicate that a specific subpopulation of patients with CCRCC and SRM requires invasive treatment options, such as ablative therapies, PN, and RN in some cases.

As mentioned by the authors in the paper, adverse histopathologic characteristics should be accurately diagnosed before deciding the course of treatment. Tumor needle biopsy seems to be the only method for histopathologic diagnosis at pretreatment. Nondiagnostic biopsies have been reported to be 0–21%, and the coincidence between diagnosis based on biopsy and nephrectomy pathology was 86.7–100% (12-15). A recent systematic review summarizing the current outcomes of tumor needle biopsy reported a median overall diagnostic rate of 92%, and sensitivity and specificity of tumor needle biopsy against surgical pathology were 99.1% and 93.2%, respectively (16). Moreover, in another systematic review, core biopsy showed high sensitivity [97.5%, 95% confidence interval (CI), 96.5–98.5] and specificity (96.2%; 95% CI, 90.7–100) when a pathological diagnosis was obtained; however, the overall nondiagnostic rate was 14.1%. Importantly, Fuhrman upgrading in surgical pathology was notable (16%) from low [1–2] to high grade [3–4] (17). The tumor grade differences between biopsy and surgical pathology results may be considered when performing tumor needle biopsy. Although the most controversial complication of tumor needle biopsy may be the potential risk of tumor seeding along the needle tract, the overall estimated risk was reported to be <0.01% (18). A most recent study reported that tumor needle biopsy was strongly and independently associated with reduced surgery for SRMs, especially with increasing age and comorbidity (19). Based on these results, tumor needle biopsy may be a reasonable diagnostic method before treatment for SRMs. However, the tumor needle biopsy procedure should be appropriately performed to obtain adequate amount of tissue. Wunderlich *et al.* recommended that one central and one peripheral biopsy specimen should be obtained from tumors <4 cm and two peripheral specimens from larger tumors (20). It is especially challenging to detect the presence of necrosis, lymphovascular invasion, and rhabdoid or sarcomatoid component because these pathologic findings are usually observed in small limited areas.

Objective scoring methods without tumor needle biopsy to differentiate patients with SRMs are most suitable for AS, such as the delayed intervention and surveillance for small renal mass (DISSRM) score (age, ECOG performance status, highest tumor diameter, RENAL nephrometry score, dementia, or cardiovascular index), has been reportedly useful for guiding the management selection (21). As an additional workup such as confirmatory biopsy should be

performed to achieve an accurate treatment decision, tumor needle biopsy may be replaced with these scoring methods in the future.

The present study is expected to be an important step in establishing a treatment strategy for SRMs of CCRCC based on the significance of adverse histopathologic features on tumor needle biopsy. Further investigations with a large sized, prospective, and randomized design must confirm the importance of adverse histopathologic characteristics in patients with SRMs and their association with long-term outcomes.

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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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