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Review Article

Current Status of Renal Biopsy for Small Renal Masses

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Small renal masses (SRMs) are defined as radiologically enhancing renal masses of less than 4 cm in maximal diameter. The incidence of renal cell carcinoma (RCC) has increased in recent years, which is mainly due to the rise in incidental detection of localized SRMs. However, the cancer-specific mortality rate is not increasing. This discrepancy may be dependent on the indolent nature of SRMs. About 20% of SRMs are benign, and smaller masses are likely to have pathologic characteristics of low Fuhrman grade and clear cell type. In addition, SRMs are increasingly detected in elderly patients who are likely to have comorbidities and are a high-risk group for active treatment like surgery. As the information about the nature of SRMs is improved and management options for SRMs are expanded, the current role of renal mass biopsy for SRMs is also expanding. Traditionally, renal mass biopsy has not been accepted as a standard diagnostic tool in the clinical scenario because of several issues about safety and accuracy. However, current series on SRM biopsy have reported high diagnostic accuracy with rare complications. Studies of modern SRM biopsy have reported diagnostic accuracy greater than 90% with very high specificity. Also, current series have shown very rare morbid cases caused by renal mass biopsy. Currently, renal biopsy of SRMs can be recommended in most cases except when patients have imaging or clinical characteristics indicative of pathology and in cases in which conservative management is not considered.

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INTRODUCTION

Unlike other urological malignancies, localized renal cell carcinoma (RCC) is treated by surgical extirpation only, without the undertaking of a preoperative renal mass biopsy, because radiologic studies including ultrasonography (US), contrast-enhanced computed tomography (CT), and magnetic resonance imaging (MRI) provide relatively sufficient information about the probability of malignancy of a renal mass [1]. In addition, renal tumor biopsies are considered to have certain limitations related to safety and accuracy [2]. Traditionally, renal mass biopsies have been used to make a pathologic diagnosis in the case of a renal mass with other primary malignancy, to confirm a case of suspected infection in a renal mass, and to find the proper targeting therapeutic agent in the case of metastatic RCC.

The incidence of RCC has increased in recent years, which is mainly due to the rise in the detection rate of localized, small renal masses (SRMs), a phenomenon attributable to the expanding use of cross-sectional imaging modalities [3]. Although surgical resection remains the first treatment option for SRMs suspected to be malignant, the treatment paradigm is gradually changing. In the era of increased detection of SRMs, the benign nature of SRMs has been extensively investigated. Although nephron-sparing surgery has remained the standard management option for SRMs suspected to be malignant, the spectrum of management options for SRMs has been expanding in recent years, ranging from minimally invasive modalities, including ablative therapy, to observation. In addition, the prevalence of chronic kidney disease (CKD) is increasing worldwide, and about 25% of patients who have SRMs are known to have stage 3 CKD or worse [4]. Furthermore, SRMs are commonly being detected in elderly patients who have vari-

ous medical comorbidities [5]. In these patients, a management option other than a surgical one may be appropriate, considering the risks and benefits of surgery. As the management options for SRMs have expanded, the current role of renal biopsy has also expanded compared with the traditional indications. In this article, we aim to review the current role, efficacy, and technique of SRM biopsy.

NATURE AND EXPANDING MANAGEMENT OPTIONS OF SMALL RENAL MASSES

The incidence of RCC, especially RCC in SRMs, has been increasing worldwide [6]. Although the definition of an SRM has not been definitively established, an SRM is generally considered to be a radiologically enhancing renal mass with a maximum diameter of less than 4 cm [7]. With increasing interest in this clinical field, information about SRMs, including their nature and pathology, has improved.

Chawla et al. [8] reported in a meta-analysis that the mean growth rate in SRMs with a mean size of 2.6 cm was 0.28 cm/y [8]. The initial tumor size did not correlate with the growth rate, and progression to metastatic disease occurred in 1% of cases (3 of 286 cases). Remzi et al. [9] reported in a study analyzing solid renal masses of 4 cm or less in diameter at diagnosis that 20% of SRMs are benign tumors [9]. Several other studies reported a higher percentage of benign findings [10,11]. Frank et al. [10] reported that 30% of tumors less than 2 cm, and 21% of those 2 to 4 cm in size, were nonmalignant. However, there may be aggressive disease in some small renal tumors. Metastasis at presentation was observed in 5.2% of 8,792 patients with RCC of less than 4 cm, and the rate of metastasis increased by 3.5% with an increase of 1 cm in the size of the renal mass in an analysis of the Surveillance, Epidemiology and End Results database from 1998 to 2003 [12]. The size of the SRM is known to be positively correlated with the likelihood of malignancy. In a retrospective study analyzing 2,935 renal tumors, 46.3% of renal masses less than 1 cm were benign tumors, whereas 6.3% of renal masses 7 cm or greater in diameter were benign [10]. In addition, as tumor size increased, there was a significant increase in the incidence of high-grade malignancy and the proportion of papillary RCC to clear cell carcinoma. Another study reported that a lower histological Fuhrman grade is seen with smaller masses [9]. In that study, which analyzed 287 renal tumors, 4.2%, 5%, and 25.5% of masses 2 cm or less, 2.1 to 3 cm, and 3.1 to 4 cm in diameter, respectively, were diagnosed as grade 3 or 4. In addition, two studies reported that SRMs in young women were more likely to be nonmalignant [13,14].

SRMs are composed of disease moieties that have heterogeneous pathologic and clinical features, and this should be considered when making a decision about the proper management of an SRM. In radiologically enhancing renal masses, surgical resection including partial or radical nephrectomy has remained the standard treatment option, resulting in excellent long-term oncologic outcomes. However, for SRMs or other types of tumors in specific cases, less invasive treatment modalities are now available, ranging from ablative therapy, including cryoablation and radiofrequency ablation, to active surveillance (AS).

Ablative therapy can be applied to patients with high surgical risk. Ablative therapy should be considered for patients with serious medical comorbidities or a tumor in a solitary kidney and in patients with CKD because surgical resection can cause substantial loss of renal function [15]. Selective arterial embolization combined with ablative therapy can be applied for the management of SRMs. Several studies have reported the feasibility and safety of selective arterial embolization in combination with thermal ablative therapy [16-19]. AS can be also considered as a treatment option for patients who have a limited life expectancy because of old age, patients who have high medical surgical risk or severe renal dysfunction, or for informed younger patients who refuse active treatment [20].

CURRENT STATUS OF SMALL RENAL MASS BIOPSY

1. Performance of small renal mass biopsy

The goals of biopsy are to determine the existence of a malignancy in a tumor and to make a pathologic diagnosis that includes determining the histology and grade of the renal mass to assist in decision making about the appropriate treatment [15]. In SRMs, the percentage of benign pathology is expected to be higher than in the overall population of renal tumors. SRMs are increasingly being detected in older patients who are likely to have comorbidities and poor performance status, which make them unfit candidates for surgery. In this population, an accurate pathologic diagnosis is important for making decisions about proper management; the age of the patient and any comorbidities should be taken into consideration.

Renal mass biopsy has not been accepted as a standard diagnostic tool in the clinical setting for several reasons. Traditionally, there have been concerns about the safety and accuracy of renal tumor biopsies [2]. However, in recent years, renal mass biopsy has shown safe and effective outcomes.

Achieving accuracy in diagnosing renal masses involves differentiating the malignancy from benign tissue, diagnosing the histological subtype, and grading the tumor. Of these, the ability to distinguish a malignant tumor from a benign mass can be crucial in the diagnosis of renal masses, as this affects management decisions. Some recently performed series have demonstrated high accuracy in the diagnosis of malignancy. In a review performed by Lane et al. [21] in which over 2,700 renal mass biopsies were reanalyzed, studies on renal mass biopsies in 2001 and thereafter showed a diagnostic accuracy for malignancies of between 92% and 100%. In that review, Lane et al. [21] analyzed 2,474 renal mass biopsies from studies that had been performed before 2001. The mean false-negative and

false-positive biopsy rates were reported to be 4.4% and 1.2%, respectively, of the total renal mass biopsies in the studies published before 2001. However, in 362 clinically diagnosed renal mass biopsies of the series performed in 2001 and later, the mean false-negative and false-positive results were 0.6% and 0%, respectively. Other studies evaluating the performance of biopsy in SRMs have also shown an accuracy rate of above 90% in discriminating malignancy [22-29].

Biopsy failure and indeterminate biopsy are the main concerns in SRM biopsy. Biopsy failure is defined as the inability to obtain sufficient tissue for pathological diagnosis, whereas in indeterminate biopsy, a definitive diagnosis cannot be made with the available tissue [21]. In a consensus meeting about renal mass biopsy held by Tsivian et al. [30], conception biopsy failures and indeterminate biopsies were integrated as nondiagnostic samples. Nondiagnostic results in renal mass biopsies seem to be more frequent for smaller masses and those of a cystic nature. In a study performed by Lechevallier et al. [31] that analyzed 73 CT-guided core biopsies, 37% of the biopsy failures occurred in tumors that were 3 cm or less in diameter, and 9% were found in tumors larger than 3 cm (p=0.006). In this study, the median size of tumors with biopsy failure was 3 cm, whereas the median size was 4.8 cm in the case of successful biopsies (p=0.03).

Leveridge et al. [32] also reported that a 1-cm increase in tumor size was a dependent predictor of successful biopsy in a multivariate analysis. Volpe et al. [33] reported that larger tumor size was a significant predictor of the diagnostic result in a retrospective study analyzing 100 SRM biopsies. In a review performed by Laguna et al. [34], it was suggested that the rate of nondiagnostic biopsies, including biopsy failure and indeterminate biopsies, seemed to be higher in studies that included only SRMs than in the general series reviewed by Lane et al. [21]. However, several reports have shown no difference in diagnostic yield or accuracy regarding tumor size [25,35], although one of these studies was performed with laparoscopy as the base mode of investigation [35].

SRMs are composed of various tumors that have heterogeneous radiologic characteristics. With cystic lesions, it is especially difficult to target the areas to be biopsied. Regarding complex cystic SRMs, the solid components are likely to be smaller in size than the cystic portions, and thus it becomes more difficult to obtain a precise sample [30]. In a retrospective study analyzing 345 SRM biopsies, a solid appearance on imaging was an independent predictor of successful biopsy on multivariate analysis [32]. However, there is evidence that repeated biopsy after an initial nondiagnostic biopsy results in a similar diagnostic rate as the initial one. For example, Leveridge et al. [32] reported a diagnostic rate of 83.3% in repeated biopsies compared with 80.6% in initial biopsies. In a retrospective study analyzing 268 biopsies of SRMs, repeated biopsy yielded a histological diagnosis rate of 94% [36].

RCCs may vary in prognosis according to the histological subtype. Histological subtyping of RCCs was shown in a recent literature review to have a diagnostic accuracy rate of 86% to 98% [21]. Also, in a recent study, it was shown that subtype determination in SRMs was possible in 93% of malignant renal masses by use of immunohistochemistry to make a correct identification of the type of RCC present [33]. Another study showed a high concordance rate (more than 91%) between the histological subtype of the biopsy and that of the final nephrectomy specimen for SRMs [22].

Determination of grading on SRM biopsies is challenging and its accuracy is considered to be not optimal (70%–83%) [22,32,33]. Furthermore, biopsy specimens are prone to underestimate the true nuclear grade of a specimen [37]. However, when classification of grade is simplified as low (Fuhrman I–II) or high (Fuhrman III–IV) grade, the diagnostic accuracy of grading is improved [38].

2. Technical issues with small renal mass biopsy

Fine needle aspiration (FNA) and core biopsy are currently the main methods of obtaining tissue from a renal mass during a biopsy. FNA has the advantage of allowing extensive sampling of a renal mass because of the multiple approaches to the tumor in the procedure. Contemporarily, FNA has been shown to have inferior diagnostic ability compared with core biopsy [29]. In a recent consensus meeting, Tsivian et al. [30] suggested that FNA alone should not be performed. However, FNA can be used as a complementary tool for core biopsy to increase diagnostic accuracy [39]. Also, the diagnostic accuracy of FNA has improved to an accuracy rate of 98% by use of improved agar microbiopsy techniques [40].

Choosing the type of radiological imaging modality to be used with renal mass biopsy is another technical issue. Currently, US and CT or MRI are commonly used for renal mass biopsy. There is no suggestion about the superiority of one specific imaging modality over another in the literature [32]. The choice is considered to be highly dependent on the operator [5]. In clinical practice, the operator must choose the most appropriate method according to the clinical situation.

3. Complications of renal mass biopsy

Although initial reports suggested substantial morbidity associated with renal mass biopsies, modern series report infrequent minor complications (4.7%), exceedingly rare severe complications (0.3%), and no cases of mortality [21]. In a review analyzing complications of needle core biopsies, a rate of 0% to 2% of significant complications requiring active treatment or hospital admission was reported in a recent series [41]. There are several major complications associated with renal mass biopsies. Bleeding is the most common complication encountered after a renal mass biopsy. Of 200 renal mass biopsies, a number of mild hematomas were identified on CT scans that had been performed immediately after the biopsy [42]. However, clinically significant renal hemorrhages resulting in hospitalization or blood transfusion were extremely rare (0%–1.3%). Track

seeding of the tumor is another complication that is highly feared by clinicians, although contemporary series have not reported this phenomenon yet [41]. Through 2001, only six cases of track seeding had been reported [29]. However, Tsivian et al. [30] suggested that the risk of track seeding may have been underestimated as a result of underreporting and the lack of long-term follow-up. Pneumothorax is another possible complication of renal mass biopsy, although clinically significant pneumothorax is uncommon, and the risk can be avoided by using a subcostal approach [43]. Overall, renal mass biopsy is considered to be safe, and the risk of over- and undertreatment, which can result from the absence of a pretreatment diagnosis, may overcome the risk of complications.

4. Current indications for renal mass biopsy in small renal masses

Traditionally, renal mass biopsy is recommended in the following situations: a renal mass with an extrarenal primary malignancy, an unresectable renal mass, a suspicious renal mass secondary to infection, and significant comorbidities occurring in a patient with a renal mass.

As the nature of SRMs has been extensively investigated and the spectrum of management for SRMs is expanding, the role of renal mass biopsy is currently also expanding. Thermal ablation therapy including radiofrequency ablation and cryoablation should be considered in the management of SRMs in patients who are unfit for surgery owing to comorbidities and poor performance. Before ablation of the renal mass, it is essential to histologically confirm the renal mass to identify optimal candidates for thermal ablation [15,44]. However, in special cases, postablative tissue can be obtained even when a biopsy of the treated mass has not been performed. Postablative biopsy has the advantage of minimal bleeding, although ablation is likely to alter the tissue architecture, increasing the difficulty of making a histological diagnosis. Margulis et al. [45] have suggested that acute radiofrequency ablation causes predictable histological changes without altering the architecture of the tissue.

Regarding cryoablation, there are conflicting reports about postprocedure biopsy. Truesdale et al. [46] have suggested that preablative sampling shows superior diagnostic accuracy, although Chen et al. [47] suggested that one cycle of cryoablation does not significantly alter the biopsy accuracy. Of note, confirming the tissue diagnosis for every case treated with ablative therapy is currently strongly recommended [30]. In addition, renal mass biopsy should be considered after ablation therapy when there is a suspicion of recurrence [44].

AS is defined as the monitoring of tumor size by routine imaging follow-up with delayed intervention for cases in which the SRMs show progression [48]. AS is currently considered a proper management option for elderly patients or patients with significant comorbidities who are at high risk during surgery [15,44]. The decision for AS should be made by taking into consideration the patient's characteristics and the nature of the renal mass. AS may be an appropriate strategy for patients who have benign renal masses and RCCs with low malignant potential. Renal mass biopsy can be used for obtaining information about patients with an SRM who are not fit for surgery because of their age and comorbidities. In the first prospective study on AS in 209 SRMs in elderly or infirm patients, renal tumor biopsy was proposed on enrolment, and in 48.3% of cases, renal mass biopsy was performed [49]. Among these cases, proven RCCs did not show a statistically significantly faster growth rate compared with histologically confirmed benign renal masses. Renal mass biopsies can be used as a helpful guide for surveillance strategies. RCCs proven to be high grade by renal mass biopsies may not be suitable for AS, whereas relatively indolent tumors can be checked with less strict imaging follow-up [20]. In a report from an international consensus panel, renal mass biopsy was recommended for AS but not for watchful waiting [30]. In recent years, renal mass biopsy has been recommended for all types of clinical situations except when patients have imaging or clinical characteristics indicative of pathology and in cases in which conservative management is not contemplated [30].

CONCLUSIONS

The value of renal biopsy in SRMs is considered to be good for a diagnostic method in a clinical setting. In most cases, renal mass biopsy can be used for diagnosis of SRMs to gather information for suggesting proper management options to patients.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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