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Review Article

Small Renal Masses: Surgery or Surveillance

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The incidence of kidney cancer has been rising over the past two decades, especially in cases in which the disease is localized and small in size (< 4 cm). This rise is mainly due to the widespread use of routine abdominal imaging such as ultrasonography, computed tomography, and magnetic resonance imaging. Early detection was initially heralded as an opportunity to cure an otherwise lethal disease. However, despite increasing rates of renal surgery in parallel to this trend, mortality rates from renal cell carcinoma have remained relatively unchanged. Moreover, data suggest that a substantial proportion of small renal masses are benign. As a result, the management of small renal masses has continued to evolve along two basic themes: it has become less radical and less invasive. These shifts are in part a reflection of an improved understanding that the biology of incidentally discovered renal cell carcinoma may be more indolent than previously thought. However, not all small renal masses are indolent, and *de novo* metastatic disease can develop at the initial presentation. Therefore, it is with this background of clinical uncertainty and biological heterogeneity that clinicians must interpret the benefits and disadvantages of various clinical approaches to small renal masses.

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INTRODUCTION

Over 200,000 new cases of kidney cancer are diagnosed worldwide each year [1]. The number of cases has been growing in Korea as well as in Europe and in the United States. According to a report of the Korea National Cancer Information Center, 3,435 new cases occurred in 2009 [2]. This is largely the result of the increased detection of localized renal cell carcinoma (RCC) as small renal masses (SRMs) during medical evaluation for unrelated conditions and routine health checkups [3,4]. A SRM is generally defined as a solid renal tumor ≤4 cm that is enhanced on computed tomography (CT) and magnetic resonance imaging (MRI) and is suspected of being RCC [5]. The biological aggressiveness of SRMs varies. Several studies have shown that up to 20% of SRMs are benign, 55% to 60% are indolent RCC, and only 20% to 25% have potentially aggressive features defined by high nuclear grade or locally invasive characteristics [6-8]. Despite their increased detection, for which long-term survival following excision exceeds 95%, the mortality rate from RCC continues to increase, which is primarily attributed to larger renal tumors (greater than 7 cm) of higher grade or stage [9]. Earlier detection and treatment with paradoxical increases in kidney cancer-specific death rates suggests that the paradigm of treatments for all patients with a SRM must be reevaluated.

The standard treatment for clinically localized RCC remains surgical excision, resulting in excellent long-term, cancer-specific survival. Traditionally, SRMs have been treated by open radical nephrectomy (ORN) or, increasingly, partial nephrectomy (PN) [10]. In recent years, ORN has rapidly been replaced by laparoscopic radical nephrectomy (LRN), which is associated with less short-term morbidity than ORN but a similar impact on long-term renal function [11,12]. Recent data have shown that PN not only has an excellent oncologic outcome but also results in better long-term preservation of renal function, leading to better overall survival [13-16]. Ablative therapies (ATs) in the form of cryotherapy and radiofrequency ablation have

also emerged as potential treatment options for SRMs. Although early results assessing AT are promising, further validation and long-term follow-up are needed to generalize the results to a patient with SRM [17]. Finally, some have argued that incidentally discovered SRMs may not negatively impact survival because of the slow tumor growth and minimal risk of progression, particularly in patients with advanced age or medical comorbidities. As a result, active surveillance (AS) has been proposed as a treatment option [17]. Data are emerging, mostly from retrospective case series, on the safety of this approach in selected patients [18-20]. Based on this background, SRMs present an increasingly difficult clinical dilemma in determining the ideal treatment while balancing the risks of cancer-related progression and death against the potential advantages and disadvantages of each modality.

The aim of this article was to review the strategy of management of SRMs in terms of the rationale for surgery and for AS.

DEFINITIONS OF SRMs

Although modern imaging brings many blessings, it also brings a curse in the urologic field, the small renal lesion. A renal mass discovered by routine ultrasound, CT, or MRI indicated for another reason could be termed *incidental*. A significant number of SRMs are incidentally diagnosed [21]. Most studies agree that a SRM can be defined as a renal mass less than 4 cm in diameter [22-24]. Actually, 79% to 84% of SRMs are detected before genitourinary symptoms are present [25-27]. Although mean tumor size has decreased in the past years, recent reports indicate that this variable is one of the most important prognostic factors for RCC, and the latest modifications of RCC staging and treatment have been devoted to tumor size [28,29].

RATIONALE FOR SURGERY

Current clinical guidelines recommend surgical excision as the preferred management of SRMs in young, healthy patients [30-32]. In particular, PN remains the treatment of choice for those patients having SRMs amenable to resection on the basis of location and tumor size and who are healthy enough to tolerate surgery [33]. The oncologic and functional efficacy of PN was noted in contemporary series [33-35]. In the European Organisation for Research and Treatment of Cancer study, 541 patients with small ($\leq$5 cm) solitary tumors suspicious for RCC and a normal contralateral kidney were randomly assigned to PN or RN at several European and North American centers. Over a mean follow-up of 9.3 years, few RCC-related deaths were observed [33]. Lau et al. [34] demonstrated that in a matched analysis of patients surgically treated with RN and PN for unilateral RCC at the Mayo Clinic, the long-term outcomes at 15 years were similar for local and distant recurrence-free survival (99% vs. 95%, p=0.18, and 99% vs. 95%, p=0.18, respectively) and cancer-specific survival (96% vs. 91%, p=0.71). Also, Zini et al. [35] used a multi-institutional historical cohort to similarly demonstrate that PN and RN achieved equally low cancer-specific mortality at 5 years. In terms of renal function, recent population-based cohorts from Surveillance, Epidemiology and End Results (SEER)-Medicare demonstrated the benefits of PN in observing a 26% reduction in adverse renal outcomes (hazard ratio [HR], 0.74; $p<0.001$) [15]. A retrospective study by Huang et al. [12] analyzed 662 patients with normal serum creatinine levels and two normal kidneys who underwent PN or RN for renal tumors <4 cm. After surgery, the 3-year probability of freedom from new onset of an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 was 80% (95% confidence interval [CI], 73 to 85) after PN and 35% (95% CI, 28 to 43; $p<0.0001$) after RN. Likewise, a Canadian population-based study showed that RN was associated with an HR of 1.75 (95% CI, 1.02 to 2.99) compared with PN for the development of adverse renal outcomes [36]. In a recently published comprehensive assessment from a high-volume center evaluating PN risk stratified according to tumor complexity, the authors noted only a 6.4% perioperative risk of major complications for excision [37]. Furthermore, Thomas et al. [8] and Hillyer et al. [38] showed the safety of laparoscopic PN and robotic PN in octogenarian patients. Both studies revealed that the perioperative complication rates were not significantly different compared with those in young patients. Additionally, most complications were minor and were managed conservatively without significant sequelae.

The rationale for treatment at diagnosis is that tumor progression will be less likely and survival will improve. Although there are several good reasons for AS [5,19], the greatest risk of observing a SRM is the potential for progression to metastatic disease. This risk is especially relevant with the current lack of effective systemic therapies for the treatment of metastatic RCC as well as in an adjuvant setting [39,40]. RCC can be cured only when the tumor is organ-confined, and surgery is the only curable treatment modality.

The ability to identify tumors that are destined to grow or metastasize would be of great benefit when designing and implementing treatment plans for patients presenting with enhancing renal tumors. However, despite efforts to assess malignant potential, uncertainty exists in treatment planning because of the failure of current imaging and biopsy techniques to accurately distinguish various types of RCC from benign pathologic entities before surgical intervention [41].

The issue of percutaneous renal biopsy was recently readdressed in a comprehensive review [42]. This study revealed that in pooled data prior to 2001, renal biopsy exhibited an 81% accuracy rate with four of five biopsies correctly predicting the tumor's pathology. Pooled series after 2001 suggest that the accuracy rate has improved to 90%. This improvement may be the result of improved technical considerations when performing the biopsies as well as the

addition of immunohistochemical and molecular analyses of the tissue specimen. However, sometimes renal mass biopsies can be nondiagnostic. Tumor size was found to be a principal factor affecting the rate of a nondiagnostic biopsy. The accuracy decreases with decreasing tumor size; thus, for SRMs sized 3 cm or smaller, the corresponding results were only 84% and 60%, respectively [43]. Moreover, current radiological imaging modalities cannot definitely differentiate between a benign and a malignant tumor. According to Remzi et al. [44], 42% of patients with benign lesions that had been incorrectly identified as malignant by CT underwent RN. Therefore, until improved biopsy techniques or cancer-specific imaging modalities are readily available, the definitive pathologic characterization of renal masses by extirpation will remain the reference standard.

Not all SRMs are clinically insignificant. A recent analysis of the SEER database from 1998 to 2003 showed a 5.2% prevalence of metastasis at presentation among 8,792 patients with RCCs $\leq$4 cm, with an increase in metastasis by 3.5% for each 1-cm increase in tumor size [45]. Crispen et al. [46] reported that metastatic disease can develop in patients with a 2- to 3-cm SRM undergoing AS. In a study with only 2 years of follow-up, nearly 3% of patients already had *de novo* tumors and 1.4% had metastatic disease. Those authors concluded that no clinical predictors of tumor growth or disease progression have been identified, although the risk of developing progressive disease over the short term appears low. Also, a multinational retrospective study showed that among 1.208 patients with SRM who were treated by surgical removal, 88% of the cases were RCC and 7% presented with metastatic disease [47]. In that study, the majority of patients who died of RCC presented with concomitant synchronous metastatic disease; however, no significant correlation was observed between tumor size and metastatic disease. According to Kunkle et al. [29], the overall frequency of malignancy in SRM with available pathological findings did not differ significantly between the "grow" group and the "did not grow" group during surveillance (83% vs. 89%, p=0.56). Lee et al. [25] also showed that of 230 cases of SRM, 88% were malignant and 12% were benign. Furthermore, several studies have shown no significant relationship between tumor size and malignancy. Jeon et al. [48] reported that no significant association was found between tumor size and percentage of benign tumors. Similar results were demonstrated by Lee et al. [49]. In their study, no clear inverse relationship was found between tumor size and percentage of benign tumors. Pathological grade is another important predictor of the metastatic potential of RCC. A 2- to 3-cm RCC has a metastatic risk of 1.5% in grade I and 19.3% in grade IV [45]. However, the overall clinical ability of preoperative nomograms incorporating primarily patient characteristics (age, gender, smoking history, symptom classification, and tumor size) to predict high Fuhrman grade in SRM is quite limited. Jeldres et al. [50] and Lane et al. [51] incorporated the aforementioned factors into nomograms and found only 55.6% to 58% accuracy, which implies that tumors would be misclassified in over 40% of patients, which is clearly clinically inadequate.

Although these data imply that tumors that are small in size and do not demonstrate interval growth have a low stage, low grade, and low metastatic potential, this biological assumption remains unproven before surgical excision.

The indolent potential of enhancing SRMs may lead to a feeling of comfort; however, this potential never applies to all patients. As mentioned previously, the current guidelines apparently indicate that surgery remains the standard of treatment for a solid, enhancing SRM in a healthy patient with a good life expectancy.

RATIONALE FOR ACTIVE SURVEILLANCE

According to current clinical guidelines, although the mainstay treatment of SRM is surgical excision, AS is a reasonable treatment option for patients with old age, decreased life expectancy, or extensive comorbidities [30-32]. The idea of AS in urologic cancer has precedence. Increasing evidence has supported this approach in selected patients with prostate cancer on the basis of the belief that competing comorbidities have a greater threat to life expectancy than does the prostate cancer itself [52,53]. A comparable strategy has developed for selected patients with SRMs, because emerging data suggest that some SRMs may not significantly impact a patient's mortality [22].

To delineate the pathologic feature of SRMs, Frank et al. [6] evaluated the relationship between tumor size and RCC subtype in a cohort of 2,770 patients who underwent RN or PN. About 23% of tumors sized 4 cm or less were benign. As tumor diameter increased, the odds of having malignancy (odds ratio [OR], 1.17; 95% CI, 1.08 to 1.26), clear cell type (OR, 1.17; 95% CI, 1.11 to 1.23), and high-grade nuclear features (OR: 1.32; 95% CI: 1.27–1.37) were increased. Kunkle et al. [54] compared 110 patients with biopsy-proven synchronous metastatic RCC at presentation with 250 patients with clinically localized RCC. Their findings revealed that tumors with synchronous metastasis were significantly larger than were clinically localized tumors (median size, 8.0 cm vs. 4.5 cm; $p<0.001$), and the odds of synchronous metastasis increased by 22% for each 1-cm increase in tumor size ($p<0.001$). Interestingly, no patients with tumors 2 cm or smaller had metastatic disease, and less than 5% of all systemic metastases occurred in patients with tumors $<$3 cm. Lane et al. [55] retrospectively evaluated cancer-specific survival between treatment modalities. A total of 537 patients who had localized tumors $\leq$7 cm detected at age $\geq$75 years underwent RN (27%), nephron-sparing intervention (53%), or AS (20%). There was no significant difference in 5-year cancer-specific mortality among groups (9.3% for RN, 5.8% for PN, and 5.8% for AS, p=0.33). A multicenter, prospective phase 2 clinical trial of AS was conducted in 178 patients with 209 SRMs. Mean age was 74 years and median tumor

size was 2.1 cm. A mixed-model regression analysis demonstrated an average overall growth rate of 0.13 cm/y. Among them, the growth rate of biopsy-proven RCC was 0.14 cm/y and that of biopsy-proven benign tumors was 0.17 cm/y. This study concluded that even biopsy-proven RCC SRMs may not grow, the metastatic rate is low, and biopsy-proven benign tumors appear to grow at the same rate as malignant ones. Therefore, patients who do not have a long life expectancy can be initially managed conservatively [56]. A competing risk analysis of data from SEER-Medicare in 26,618 patients who underwent nephrectomy for RCC was performed to elucidate the relationships of age and primary renal tumor size with cancer-specific versus other-cause mortality after nephrectomy. Five-year cancer-specific mortality (5.3%; 95% CI, 4.6 to 6.1) was lowest in patients with SRMs ($\leq$4 cm) and varied inversely with tumor size in all age groups. However, competing-cause mortality rose with increasing patient age. The estimated 5-year competing-cause mortality for those aged 70 years and older was 28.2% (95% CI, 25.9 to 30.8). This result suggests that the relative benefits of surgical treatment are lowest among elderly patients ($\geq$70 years) with SRMs and significant concurrent comorbidity and that AS may thus be warranted [57].

Whether delayed intervention for SRMs increases the risk of stage progression or decreases recurrence-free survival rates was evaluated by Crispen et al. [20]. A total of 87 SRMs were treated with nephron-sparing intervention following a 14-month median AS period. Concordance of clinical T (cT) and pathologic T (pT) classification was identified in 51 of 54 RCCs (94%) after extirpative surgery. Among them, 3 tumors (6%) showed discordant cT and pT classifications, 2 tumors were upstaged to pT1b, and 1 tumor was upstaged to pT3a with pathologic review. The median tumor size was 2.0 cm at diagnosis, and the median growth rate was 0.19 cm/y (mean, 0.30 cm/y; range, -0.22 to 1.47 cm/y) in patients with RCC who had delayed surgery for 12 months or more. The estimated 1-year and 3-year cancer recurrence-free survival rates were 100% and 99%, respectively. Delayed management of SRMs was proposed cautiously without incurring a high risk of disease progression.

To identify the best candidates for AS, Jacobs et al. [58] retrospectively evaluated 204 consecutive patients with localized, clinical stage T1 renal masses (tumor size $\leq$4 cm) who underwent AS or treatment. Treatment included RN, PN, cryotherapy, and radiofrequency ablation. In their study, the "ideal" criteria for AS included tumor size $\leq$4 cm, Charlson comorbidity index (CCI) $\geq$2, Eastern Cooperative Oncology Group performance status (ECOG PS) $\geq$2, and eGFR $<$60 mL/min. After performing sensitivity analyses to identify the most predictive factors compared with the "ideal" criteria, neither the eGFR nor the CCI was a significant factor. The combination of tumor size $<$3 cm, ECOG PS $\geq$2, and an endophytic tumor were the most predictive for AS. Other factors that affected AS were long distance from the hospital ($>$99.6 km), multifocal lesions, and surgeon's preferred surgical methods (open surgery) [58].

Abouassaly et al. [59] evaluated the optimal treatment strategy for SRMs in patients with $\geq$60 years between LRN, PN, AT, and AS by using a decision-analytic Markov model. The mean life expectancy was 18.49, 18.09, 17.85, and 17.70 years for PN, LRN, AT, and AS, respectively. PN offered an incremental life expectancy gain of 9.5 months compared with AS. However, incremental life expectancy gain was different with aging. AS was preferred and offered a small advantage in life expectancy compared to PN in patients over 74 years. In these patients, the probability of systemic progression on AS was $<$1.3%/y or the hazard ratio of death with chronic renal insufficiency was $>$1.63. When quality-adjusted life expectancy was assessed, the age threshold at which AS was preferred over PN decreased to 66 years.

There are many significant limitations in the application of AS as an optimal treatment for SRMs. Most studies included a limited number of patients, retrospectively collected data, inherent selection bias, and relatively short follow-up periods. The quality of evidence in the existing data for AS is poor; all are under level III. A universal pathologic evaluation for SRMs is lacking. Benign tumors are included in SRMs and rapidly growing tumors are excluded from SRMs. This selection bias might reduce the exact observation of disease progression and metastasis. Because of heterogeneity across studies, risk of cancer-related deaths cannot be predicted accurately. Also, there was no consensus on how to monitor and when to perform a surgery or intervention during AS. A validated and standardized protocol on the monitoring and follow-up imaging should be established to avoid unwarranted radiation exposure and associated secondary malignancies. More high-quality evidence of AS compared with the different treatment options is needed. We anticipate further comprehensive studies, improved imaging techniques, and utilization of percutaneous biopsy and biomarkers for individualized treatment algorithms for SRM.

These published data suggest that the linear growth rate of SRM is the most accurate predictor of metastasis and that rapid growth of a SRM may proceed to intervention or surgery. Until level I evidence is forthcoming, AS for SRMs should be considered only in selected patients with old age, decreased life expectancy, or extensive comorbidities. Physicians and patients must fully discuss and consider the calculated risks of AS and the trade-off of AS against extirpative surgery.

CONCLUSIONS

The majority of SRMs are mostly low-grade, clear cell RCCs that grow at a slow rate and have a low rate of metastasis or cancer progression. Therefore, treatment decisions to determine whether to proceed with surgery (including ablation) or AS remain highly complex. Patient counseling is extremely important and renal biopsy can be considered.

Correct clinical judgments are needed regarding the risk of cancer-related factors, patient-related factors, and surgeon factors.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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